Synthetic Studies of Hydronaphthacenic Antibiotics. I. The Synthesis of 4-Demethoxy-7-*O*-methyl Daunomycinone

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Daunomycin is a new and very promising antitumor antibiotic. This communication reports the synthesis of (*dl*)-4-demethoxy-7-*O*-methyl daunomycinone as part of a scheme toward the total synthesis of daunomycin.

La daunomycine est un antibiotique nouveau et prometteur contre les tumeurs. Cette communication relate la synthèse du *dl* déméthoxy-4 *O*-méthyl-7 daunomycinone en tant qu'étape en vue de la synthèse totale de la daunomycine.

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Introduction

In the last two decades numerous antibiotics with a linear tetracyclic skeleton have been isolated from different kinds of bacterial cultures (1). The tetracyclines attracted the attention of many organic chemists due to their very complicated structures and their potent antibacterial properties. Thus the syntheses of tetracyclines have been reported by many research groups since 1962 (2). Rhodomycins (3) are another group of antibiotics having a linear tetracyclic skeleton but which are not as potent against bacteria as the tetracyclines. However, two members recently isolated, daunomycin (rubidomycin) (**1**) and adriamycin (**2**) (5), have shown very high activity against tumors (4) and have been used successfully in treating acute lymphomas.

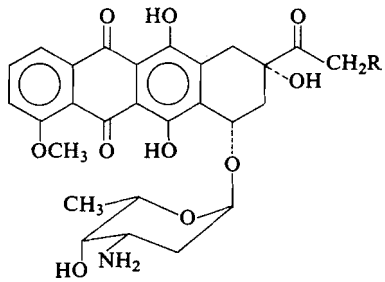
Daunomycin under mild acid hydrolysis gives an amino-sugar daunosamine (**3**) and a tetracyclic hydronaphthacenequinone aglycone daunomycinone (**4**). The synthesis of **3** and its derivatives was reported recently (6). A synthesis of the tetracyclic system **5** and the condensation of **5** with glucose was also reported (7). However, the synthesis of the tetracyclic aglycone **4** has not been reported and we are reporting our synthesis of 4-demethoxy-7-*O*-methyl daunomycinone (**6**) as a working model toward the total synthesis of daunomycin and adriamycin.

Results and Discussion

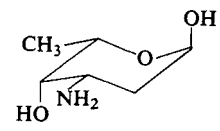
Condensing 2,5-dimethoxybenzaldehyde with 2,4-pentanedione in benzene solution in the presence of piperidine and acetic acid gave almost quantitatively the diketone **7**, which upon hydrogenation in ethanol using 5% Pd/C as catalyst, gave the diketone **8**. This compound, when freshly distilled, existed in an equilibrium between the keto and the enol form. This was evident from the n.m.r. spectrum which showed a small peak at $-6.50\ \tau$ corresponding to the enol proton with an area integrated to about one-third of a hydrogen; a singlet at $6.58\ \tau$ corresponding to the benzylic hydrogens of the enol-form and a doublet at $7.06\ \tau$ corresponding to the benzylic hydrogens of the keto-form. On standing, the diketone **8** crystallized entirely in the enol-form; this was shown by the n.m.r. spectrum which now had a singlet at $-6.63\ \tau$ for the enol proton integrating to exactly one hydrogen.

The diketone **8** was then alkylated with ethyl-bromoacetate and sodium hydride in anhydrous tetrahydrofuran to give the keto-ester **9** which on treatment with aqueous sodium hydroxide solution underwent a reversed Claisen followed by the hydrolysis of the ester to give the keto-acid **10**. Cyclization of **10** in the presence of hydrofluoric acid gave the tetralone **11** or the lactone **12** depending on the concentration and the reaction temperature. At 35 °C and low concentration of **10**, the tetralone **11** was isolated in 72% yield together with the lactone **12** in about 5% yield. At 0 °C and high concentration of **10**, the lactone **12** was isolated as the major product.

Hydrogenolysis of **11** in acidic ethanolic solution in the presence of 5% Pd/C gave the tetralin **13**, which upon oxidation in *t*-butyl alcohol with potassium *t*-butoxide and oxygen followed by reduction with zinc gave the hydroxyketone **14** in



1 R = H
2 R = OH



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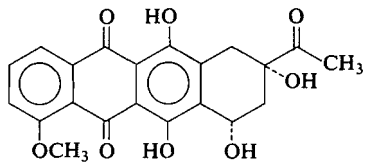

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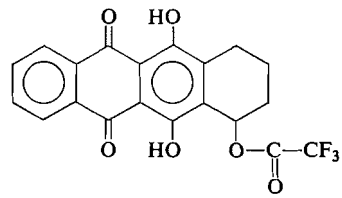

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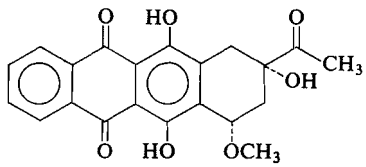

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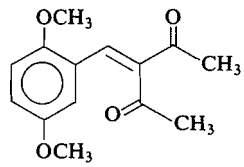

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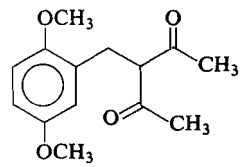

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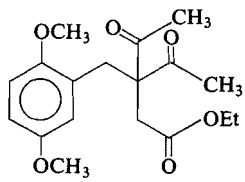

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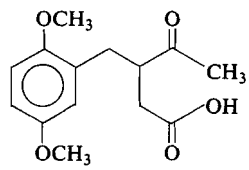

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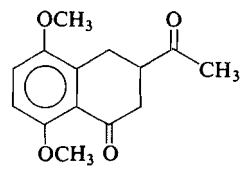
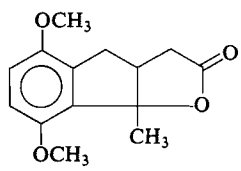


11

excellent yield. The use of sodium *t*-butoxide however, gave less than 5% yield, possibly due to the low solubility of the sodium salt at the reaction temperature.

In order to ascertain that the hydroxy group is in the tertiary position, the tetralin **13** was reduced with sodium borohydride to the corresponding alcohol and eventually converted to the olefinic mixture **15** by tosyl chloride and pyridine. Osmium tetroxide oxidation of **15** to the diol **16** followed by oxidation with dicyclohexylcarbodiimide and dimethylsulfoxide gave the identical hydroxyketone **14**.

Condensing **14** with phthalic acid monomethyl ester in trifluoroacetic anhydride solution followed by basic hydrolysis and then cyclization with hydrofluoric acid gave the tetracyclic hydroxyketone **17**. This was then converted to



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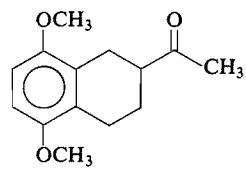

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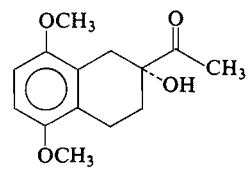

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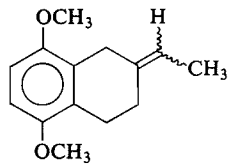

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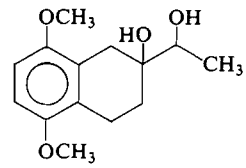

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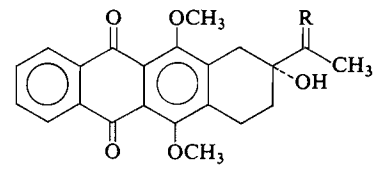
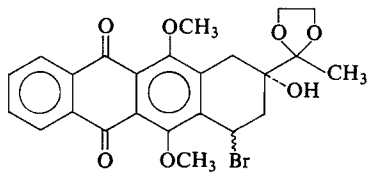


17 R = O
18 R = O—CH_2
O—CH_2



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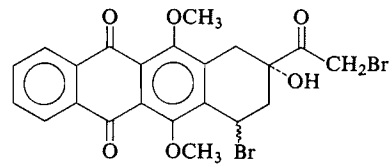

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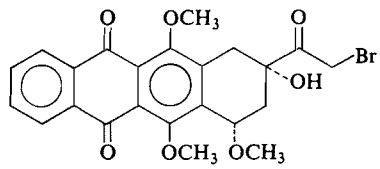

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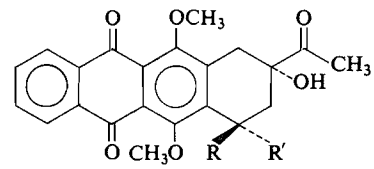
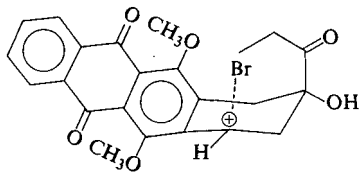


22 R = OCH_3; R′ = H
23 R = H; R′ = OCH_3

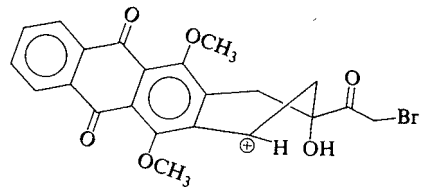
the ketal **18** making the two benzylic positions different enough to be selectively attacked by *N*-bromosuccinimide on the less hindered position. Thus refluxing the ketal **18** with *N*-bromosuccinimide in carbon tetrachloride in the presence of a trace of benzoyl peroxide gave the unstable bromoketal **19** and the dibromide **20**. This mixture, without purification, was then refluxed in anhydrous methanol to give **21**, **22**, and **23** which were separated from each other by t.l.c. on silica.

The stereochemistry of **21**, **22**, and **23** was assigned mainly on the basis of the n.m.r. spectra of **14**, **17**, **18**, **21**, **22**, and **23**. Under identical conditions, the hydroxy protons of **14**, **17**, **18**, and **22** had chemical shifts higher than 6 τ while those of **21** and **23** were lower than 5 τ. The chemical shift differences are interpreted as being a result of the existence of hydrogen bonding between the hydroxy proton and the C_7—OCH_3 groups in **21** and **23**.

The fact that the C_7-isomer of **21** was not observed and that there was twice as much of **23** produced as **22** would indicate that the conversion



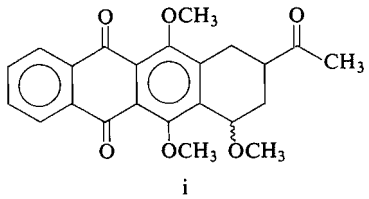
24
26 Br replaced by H



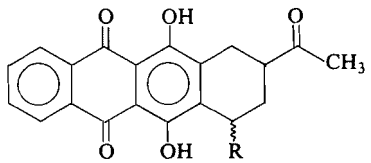
25
27 Br replaced by H

of **19** and **20** to **21**, **22**, and **23** went through a partially stereospecific S_N1 process.[1] The C_7-carbonium ion formed when **20** is refluxed in methanol exists mainly in the conformation **24** which is more stable than the other conformation **25** due to the presence of a bridging between the bromine atom and the carbonium ion.[2] Thus methanol can only come from the α-side giving the C_7-*O*-methyl group *cis* to the C_9-hydroxy group. On the other hand, the carbonium ions **26** and **27** are very similar energetically. In the former case methanol will come mainly from the α-side due to the steric effect of the axial C_9-acetyl group while in the latter case, approach of methanol from the β-side is slightly favored.

[1]In another series of investigations, the conversion of **i** to **ii** by aluminum chloride in refluxing benzene was accompanied by the formation of **iii**, also dissolving **ii** in chloroform in the presence of trifluoroacetic acid gave the corresponding trifluoroacetate **iv**. These results would indicate that the formation of a carbonium ion was very easy.



i



ii R = OCH_3
iii R = C_6H_5
iv R = $O-\overset{O}{\overset{\|}{C}}-CF_3$

[2]This will be proven further in the synthetic approach to adriamycin.

The hydroxyketone **23** was then hydrolyzed to the red crystalline 4-demethoxy-7-*O*-methyl daunomycinone (6) in benzene solution in the presence of aluminum chloride (5*b*).

Experimental

Melting points and boiling points are uncorrected. The i.r. spectra (cm^{-1}) were recorded on a Perkin–Elmer model 700 spectrophotometer using methylene chloride as solvent or as otherwise specified. The n.m.r. spectra (τ) were recorded on a Varian Model A56/60A MHz spectrometer using deuterated chloroform as solvent and tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi Perkin–Elmer Model RMU-6D or a Finnigan Model 1015 mass-spectrometer. High resolution mass spectra were recorded on the MS9 mass-spectrometer of the Chemistry Department, University of Alberta, Edmonton, Alberta. Microanalyses were performed by Dr. Daesslé of Montreal and Dr. Yates of Arizona.

Preparation of 3-Acetyl-4-(2′,5′-dimethoxyphenyl) 3-Buten-2-one (7)

A benzene solution (500 ml) containing 2,5-dimethoxybenzaldehyde (100 g), 2,4-pentanedione (80 g), piperidine (4 ml), and acetic acid (12 ml) was refluxed in a 1 l flask equipped with a condenser and a water separator, for 2 h. The benzene was then removed under reduced pressure and the residue which crystallized on standing (148 g) could be purified by recrystallization from methanol; m.p. 65–66 °C; i.r. 1710 and 1700 (ketones), 1665 (C=C), 1620 and 1595 (aromatic); n.m.r. 2.51 (s, 1H, olefinic), 3.33 (s, 3H, aromatic), 6.33 (s, 3H, OCH_3), 6.45 (s, 3H, OCH_3), 7.82 (s, 3H, $COCH_3$), 8.00 (s, 3H, $COCH_3$).

Preparation of 3-Acetyl-4-(2′,5′-dimethoxyphenyl) 2-Butanone (8)

The crude product **7** above was dissolved in 200 ml of distilled ethanol and filtered into a 3 l flask containing Pd/C (5%, 13 g) and distilled ethanol (1.3 l). The solution was then hydrogenated at atmospheric pressure until the uptake of hydrogen ceased. The catalyst was removed by filtration and the ethanol evaporated under reduced pressure. The residue was purified by distillation (b.p. 150–155 °C at 0.5 mm Hg) (133 g). The distillate crystallized on standing and was recrystallized from carbon tetrachloride and petroleum ether; m.p. 63–68 °C; i.r. 1600 (broad); n.m.r. −6.63 (s, 1H, enol), 3.17–3.58 (m, 3H, aromatic), 6.24 (s, 3H, OCH_3), 6.34 (s, 3H, OCH_3), 6.47 (s, 2H, benzylic), 8.00 (s, 6H, $C-CH_3$).

*Preparation of 3-Acetyl-4-(2',5'-dimethoxyphenyl) Butanoic Acid (**10**)*

To a 1 l flask equipped with a mechanical stirrer, a condenser, and a dropping funnel, freshly distilled dry tetrahydrofuran (600 ml), the diketone **8** (30 g), and sodium hydride (6 g 50% mineral oil suspension) in small portions were added. The tetrahydrofuran solution was heated to a gentle reflux and ethyl bromoacetate (21 g) in dry tetrahydrofuran (50 ml) was added through the dropping funnel over a period of 15 min. After refluxing for 1 h, most of the tetrahydrofuran was distilled off and water (100 ml) was added to the residue. The aqueous solution was extracted exhaustively with benzene. The benzene solution was dried over magnesium sulfate, and evaporated under reduced pressure to give the crude crystalline keto-ester **9** (40 g) which could be recrystallized from methanol; m.p. 66–67 °C; i.r. 1735 (ester), 1700 (ketone), 1600 (aromatic); n.m.r. 3.35 (m, 3H, aromatic), 5.86 (q, 2H, $COOCH_2$—CH_3), 6.30 (s, 3H, OCH_3), 6.37 (s, 3H, OCH_3), 6.58 (s, 2H, benzylic), 7.18 (s, 2H, CH_2—$COOC_2H_5$), 7.80 (s, 6H, $COCH_3$), 8.75 (t, 3H, $COOCH_2CH_3$).

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.11; H, 6.99.

The keto-ester **9** was then hydrolyzed by heating in a sodium hydroxide solution (8%, 250 ml) at 65 °C for 3 h. The basic solution was then washed with benzene and acidified with cold concentrated hydrochloric acid. The keto-acid precipitate **10** was filtered and dried in a desiccator to give 27 g of white solid which was further purified by recrystallization from methanol, m.p. 106–107 °C; i.r. 1740 (acid), 1700 (ketone); n.m.r. −2.10 (s, 1H, COOH), 2.70 (m, 3H, aromatic), 5.97 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.13; H, 6.76. Found: C, 63.30; H, 6.58.

*Cyclization of Keto-acid **10***

The keto-acid **10** (10 g) was added with stirring into a polyethylene reaction flask containing hydrofluoric acid (100 ml). After stirring for 3 h in a water bath at 20 °C, the temperature was raised to 40 °C to evaporate the remaining hydrofluoric acid. The residue was diluted with water and extracted exhaustively with chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried, and then evaporated to dryness under reduced pressure. Upon addition of methanol to the residue, the tetralone **11** crystallized and was then collected by filtration. The mother liquor was evaporated to dryness and the residue was dissolved in benzene. After stirring the benzene solution with sodium hydroxide solution (25 ml, 8%) for 2 h, the benzene layer was separated, washed with water, and dried over magnesium sulfate and evaporated to dryness. Upon addition of methanol and ether, another crop of tetralone **11** crystallized and was collected as before. The combined tetralone **11** (6.7 g) was further purified by recrystallization from methanol ether; m.p. 123–125 °C; i.r. 1710 (ketone), 1685 (conjugated ketone), 1590 (aromatic); n.m.r. 3.20 (q, 2H, aromatic), 6.20 (s, 3H, OCH_3), 6.23 (s, 3H, OCH_3), 7.97 (s, 3H, $COCH_3$); mass spectrum 248 (m^+/e), 205 (M-$COCH_3$).

The aqueous sodium hydroxide solution was acidified with concentrated hydrochloric acid and then extracted with chloroform. Evaporating the chloroform solution to dryness gave lactone **12** (450 mg) which was purified by recrystallization from methanol; m.p. 137–138 °C; i.r. 1765 (lactone), 1610 (aromatic); n.m.r. 3.38 (s, 3H, aromatic), 6.26 (s, 3H, OCH_3), 6.30 (s, 3H, OCH_3), 8.21 (s, 3H, t-CH_3); mass spectrum 248 (m^+/e), 233 (M-CH_3), 190 (2-methyl, 4,7-dimethoxyindene cation).

*Preparation of 1,4-Dimethoxy-6-hydroxy-6-acetyl Tetralin (**14**)*

A solution of the tetralone **11** (10 g), distilled ethanol (400 ml), concentrated hydrochloric acid (10 ml), water (40 ml), and 5% Pd/C (2 g) was hydrogenated at atmospheric pressure and room temperature for 6 h with mechanical shaking. After filtering the catalyst, the alcoholic solution was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol and petroleum ether to give the crystalline monoketone **13** (8.4 g); m.p. 81–82 °C; i.r. 1715 (ketone), 1610 (aromatic); n.m.r. 3.41 (s, 2H, aromatic), 6.26 (s, 6H, OCH_3), 7.80 (s, 3H, $COCH_3$).

The monoketone **13** (5.7 g) dissolved in dry t-butyl alcohol (50 ml) was added to an oxygen-saturated t-butyl alcohol solution (400 ml) in a 1 l flask containing potassium t-butoxide prepared by dissolving freshly cut potassium (8 g) in the t-butyl alcohol. Dry oxygen was bubbled through a gas dispersion tube into the solution for exactly 5 min keeping the reaction temperature at 35 °C. The solution was then cooled in an ice bath and glacial acetic acid was added until the solution became acidic. Zinc dust (20 g) was added immediately and the solution was then stirred at room temperature for 6 h. The zinc was then removed by filtration and the filtrate was evaporated to a syrupy residue at 50 °C under reduced pressure. The residue was diluted with water and extracted exhaustively with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated to dryness to give the crude crystalline hydroxyketone **14** (5.5 g) which was purified by recrystallization from methanol and ether; m.p. 100–102 °C; i.r. 3525 (OH), 1705 (ketone), 1600 (aromatic); n.m.r. 3.40 (s, 2H, aromatic), 6.26 (s, 3H, OCH_3), 6.30 (s, 3H, OCH_3), 6.42 (s, 1H, OH), 7.75 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.12; H, 7.20. Found: C, 67.18; H, 7.20.

*Preparation of the Tetracyclic Hydroxyketone **17***

Trifluoroacetic anhydride (10 ml) was added to a mixture of the hydroxyketone **14** (2 g) and the phthalic acid monomethyl ester (4 g). The solution was refluxed under dry nitrogen atmosphere overnight. After removing the trifluoroacetic anhydride under reduced pressure, the residue was hydrolyzed by 8% sodium hydroxide solution (30 ml) at 65 °C. The basic aqueous solution was washed with chloroform and then acidified by concentrated hydrochloric acid. The acidic solution was then extracted exhaustively with chloroform. Evaporating the chloroform solution to dryness as usual gave a dark brown residue which, without purification, was then dissolved in hydrofluoric acid (10 ml) in a polyethylene flask and then worked-up as described in the preparation of the tetralone **11**. The dark yellow residue was purified by preparative t.l.c. on alumina to give the yellow crystalline tetracyclic hydroxyketone **17** (700 mg) which could be recrystallized

from methanol; m.p. 184–186 °C; i.r. 3510 (OH), 1710 (ketone), 1670 (quinone), 1600 and 1560 (aromatic); n.m.r. 1.73–2.34 (m, 4H, aromatic), 6.10 (s, 3H, OCH_3), 6.15 (s, 3H, OCH_3), 6.20 (s, 1H, OH), 6.91 (broad s, 4H, benzylic); mass spectrum 380 (m^+/e), 362 (M-H_2O), 337 (M-$COCH_3$).

Anal. Calcd. for $C_{22}H_{20}O_6$: C, 69.49; H, 5.29. Found: C, 69.55; H, 5.13.

Preparation of 4-Demethoxy Daunomycinone Trimethyl Ether (23)

A benzene solution (60 ml) of the hydroxyketone **17** (600 mg), ethylene glycol (1 ml), and anhydrous *p*-toluenesulfonic acid (50 mg) was distilled at a very slow rate. After about 30 ml of benzene was collected, the residual benzene was washed with sodium carbonate solution and then evaporated to dryness under reduced pressure to give quantitatively the crystalline ketal **18** which could be recrystallized from benzene, m.p. 185–186 °C; i.r. showed the absence of 1710 peak. The ketal **18** was then refluxed in carbon tetrachloride solution (50 ml) containing *N*-bromosuccinimide (290 mg) and a trace of benzoylperoxide for 45 min under dry nitrogen atmosphere. The solution was then evaporated under reduced pressure at room temperature to about 10 ml and the succinimide was then removed by filtration. The orange solution, without further purification, was refluxed in anhydrous methanol (50 ml) overnight under dry nitrogen. After evaporating the methanolic solution to dryness under reduced pressure, concentrated hydrochloric acid (3 ml) and water (10 ml) in 30 ml of tetrahydrofuran were added and the solution was stirred at room temperature for 4 days. After most of the tetrahydrofuran was removed under reduced pressure, the residue was diluted with water and extracted by chloroform exhaustively. Washing the chloroform solution with dilute sodium bicarbonate solution and evaporating the chloroform solution to dryness gave a dark orange residue which was separated by t.l.c. on silica into three major fractions corresponding to compounds **21**, **22**, and **23**.

The bromoketone **21** (95 mg) was further purified by recrystallization from methanol; m.p. 176–178 °C; i.r. 3475 (OH), 1735 (ketone), 1670 (quinone), 1595 and 1560 (aromatic); n.m.r. 1.74–2.35 (m, 4H, aromatic), 4.81 (s, 1H, OH), 5.08 (t, 1H, C_7—H), 5.20 (s, 2H, $CO\mathit{CH}_2Br$), 6.04 (s, 3H, OCH_3), 6.13 (s, 3H, OCH_3), 6.43 (s, 3H, C_7—OCH_3); mass spectrum 490 (m^+/e Br-81), 488 (m^+/e Br-79), 367 (M-$COCH_2Br$), 359 (M-H_2O, CH_3OH, Br), 335 (M-CH_3OH, $COCH_2Br$). This bromoketone was converted to **23** via zinc and acetic acid.

The crude hydroxyketone **22** (110 mg) was further purified by t.l.c. on silica followed by recrystallization from methanol; m.p. 192–193 °C; i.r. 3525 (OH), 1715 (ketone), 1675 (quinone), 1600 and 1575 (aromatic); n.m.r. 1.70–2.33 (m, 4H, aromatic), 4.95 (q, 1H, $J = 2$, $J = 4.5$ Hz, C_7—H), 6.03 (s, 3H, OCH_3), 6.08 (s, 3H, OCH_3), 6.14 (s, 1H, OH), 6.50–7.12 (q, 2H, $J = 15$ Hz, C_{10}—H_2), 6.65 (s, 3H, C_7—OCH_3), 7.29 (d of d, 1H, $J = 2$, $J = 15$ Hz, C_8—H), 8.04 (d of d, 1H, $J = 4.5$, $J = 15$ Hz, C_8—H); mass spectrum 410 (m^+/e), 392 (M-H_2O), 335 (M-CH_3OH, $COCH_3$), 307 (M-$COCH_3$, CH_3OH, CO).

The hydroxyketone **23** (220 mg) was recrystallized from methanol; m.p. 194–195 °C; i.r. 3475 (OH), 1710 (ketone), 1670 (quinone), 1595 and 1560 (aromatic); n.m.r. 1.70–2.33 (m, 4H, aromatic), 4.96 (s, 1H, OH), 5.04 (d of d, 1H, $J = 2$, $J = 4$ Hz, C_7—H), 6.01 (s, 3H, OCH_3), 6.10 (s, 3H, OCH_3), 6.42 (s, 3H, C_7—OCH_3), 6.70–6.85 (m, 2H, C_{10}—H_2), 7.35–7.67 (m, 1H, C_8—H), 7.93–8.24 (d of d, 1H, $J = 4$, $J = 15$ Hz, C_8—H); mass spectrum 410 (m^+/e), 392 (M-H_2O), 360 (M-H_2O, CH_3OH), 335 (M-CH_3OH, $COCH_3$), and 307 (M-CH_3OH, $COCH_3$, CO).

Anal. Calcd. for $C_{23}H_{22}O_7$ (mol. ion 410.1365): C, 67.31; H, 5.36. Found (410.1360 (high resolution mass spectrum)): C, 67.30; H, 5.33.

Preparation of 4-Demethoxy-7-O-methyl Daunomycinone (6)

The hydroxyketone **23** (140 mg) and aluminum chloride (300 mg) in benzene solution (20 ml) were stirred together with sea sand at 50 °C overnight under dry nitrogen atmosphere. The benzene solution was then extracted twice with an aqueous oxalic acid solution (20 ml, 5%) and the combined oxalic acid solution was extracted with chloroform. The combined benzene and chloroform solutions were then dried over sodium sulfate and evaporated to dryness under reduced pressure giving a red solid residue. The residue was then purified by t.l.c. on silica to give the red crystalline 4-demethoxy-7-*O*-methyl daunomycinone (**6**) (96 mg) which was recrystallized from a large volume of chloroform; m.p. 250–254 °C; i.r. ($CHCl_3$) 3400 (OH), 3400–2700 (phenols), 1715 (ketone), 1625 (quinone), 1595 (aromatic); n.m.r.[3] −3.50 (s, 1H, phenol), −3.20 (s, 1H, phenol), 1.50–2.03 (m, 4H, aromatic), 4.80 (s, 1H, C_9—OH), 4.92 (d of d, 1H, C_7—H), 6.20 (s, 3H, OCH_3), 6.64 (q, 2H, C_{10}—H_2), 7.37 (s, 3H, $COCH_3$); mass spectrum 382 (m^+/e), 332 (M-H_2O, CH_3OH), 307 (M-$COCH_3$, CH_3OH), 289 (M-$COCH_3$, H_2O, CH_3OH).

Mol. Ion Calcd. for $C_{21}H_{18}O_7$: 382.1053. Found (high resolution mass spectrum): 382.1050.

The synthesis toward daunomycin and adriamycin is progressing and results will be reported later.

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