Heteroanthracyclines. 1. 4-Demethoxyxanthodaunomycinone (6,7,9,11-tetrahydroxy-9-acetyl-7,8,9,10-tetrahydrobenzo(*B*)xanthen-12-one)[1]

CHIU-MING WONG,[2] WASIMUL HAQUE, HING-YAT LAM,[3] KIRK MARAT, AND E. BOCK
Department of Chemistry, University of Manitoba, Winnipeg, Man., Canada R3T 2N2

AND

AI-QIAO MI
Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, People's Republic of China

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Two heteroanthracyclinones, namely 4-demethoxyxanthodaunomycinone (**29**) and its epimer 4-demethoxy-7-epixanthodaunomycinone (**30**), were synthesized using 2-acetyl-5,8-dimethoxytetralin (**12**) as starting material. Condensation of **12** with 2-methoxybenzoic acid followed by hydrolysis and oxidative cyclization gave xanthones **17** and **18** which were converted to **19** and **20** for the purpose of separation and structure assignment by dipole moment. Hydrolysis of **19** followed by alkylation with chloromethyl methyl ether and oxidation with molecular oxygen gave **26** and **27**, which on acid hydrolysis gave 4-demethoxyxanthodaunomycinone (**29**) and 4-demethoxy-7-epixanthodaunomycinone (**30**). Preliminary biological assays with MCF-7, a human breast cancer cell line, showed that both **29** and **30** were weakly active while daunomycinone, the aglycone of **2**, showed no activity under similar conditions.

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On a synthétisé deux hétéroanthracyclinones: la déméthoxy-4 xanthodaumycinone (**29**) et son épimère la déméthoxy-4 épi-7 xanthodaumycinone (**30**) en partant de l'acétyl-2 diméthoxy-5,8 tétraline (**12**). La condensation du composé **12** sur l'acide méthoxy-2 benzoïque, suivie d'une hydrolyse et d'une cyclisation oxydante conduit aux xanthones **17** et **18** que l'on transforme en composés **19** et **20** pour les besoins de séparation et d'identification de structure par le moment dipolaire. L'hydrolyse du composé **19** suivie de l'alkylation avec l'éther chlorométhyle méthyle et de l'oxydation subséquente du produit obtenu avec l'oxygène moléculaire donne les composés **26** et **27** qui par hydrolyse acide donnent accès à la déméthoxy-4 xanthodaunomycinone (**29**) et à la déméthoxy-4 épi-7 xanthodaunomycinone (**29**) et à la déméthoxy-4 épi-7 xanthodaunomycinone (**30**). Un essaie biologique préliminaire avec le MCF-7, une des cellules du cancer du sein, montre que les deux composés **29** et **30** sont faiblement actifs tandis que la daunomycinone, l'aglycone du composé **2** dans les mêmes conditions n'a aucune activité.

[Traduit par le journal]

Introduction

The rewarding results of clinical application of some antitumor anthracyclines such as adriamycin (**1**), daunomycin (**2**), and carminomycin (**3**) and their simple derivatives are well documented (1). Efforts to improve the potency and efficacy of these first generation anthracycline antitumor drugs also met with encouraging results. Synthetic analogues such as 4-demethoxydaunomycin (**4**), 4-demethoxy-4′-deoxyadriamycin (**5**), and 4-demethoxy-11-deoxydaunomycin (**6**) are much more potent than the first generation natural anthracyclines (2, 3). However, both the synthetic and natural products are cardiotoxic and prolonged administration invariably leads to congestive heart failure (3).

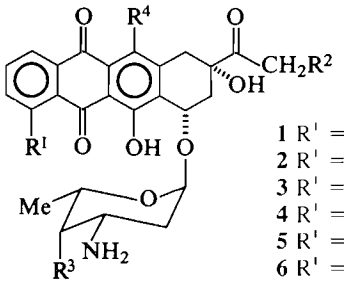
Adriamycin and daunomycin bind strongly to chromosomal DNA (4), inhibiting its template function and mitotic process, causing the degeneration and destruction of cells. X-ray crystallography indicated that daunomycin molecules sit in the major groove of the DNA double helix intercalating successive base-pairs. The basic nitrogen atom of daunosamine together with the chromophore of the aglycone are involved in intercalation (5). The C-9 hydroxy and the acetyl groups are implicated to help stabilize the intercalation, possibly through hydrogen bonding, and inversion at C-7 prevents intercalation (6).

It was proposed that adriamycin stimulated the generation of superoxide in the heart cells, which have low superoxide dismutase activity. Accumulation of the highly toxic superoxide and hydrogen peroxide is responsible for the cardiotoxicity (7).

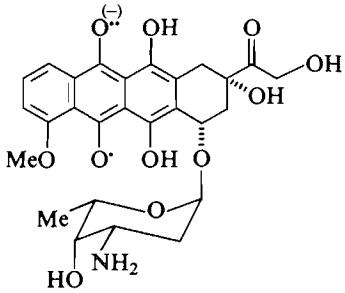
A reasonable suggestion linking the adriamycin molecule with the superoxide formation is that the quinone moiety of adriamycin may function as an electron acceptor, taking electrons from a specific site of the NADH dehydrogenase. The resulting semiquinone **7** then participates in a nonenzymatic redox reaction with molecular oxygen leading to superoxide and subsequent hydrogen peroxide formation (8). In addition, it is also possible that **7** may become an active precursor of the quinone methide (**8**) which is less likely to form when the quinone is strongly hydrogen-bonded with the C-6 phenolic function. Quinone methides are powerful alkylating and cytotoxic agents (9).

It is therefore reasonable to speculate that cardiotoxicity and intercalating and alkylating properties are three different characters of antitumor anthracycline antibiotics. Recently, adriamycin was found to exert its cytotoxic action by interaction with cell membrane (10). The mechanism of interaction is not known. Lipid peroxidation triggered by the formation of **7**, as suggested by Bachur (11), Hochstein (12), and Myres (13), could be responsible for the membrane damage. In this case, the quinone chromophore becomes responsible for the superoxide formation which in turn becomes responsible for both

[1]Presented at the 63rd CIC Conference, Ottawa, June 1980.
[2]Author to whom all correspondence should be addressed.
[3]American Leukemia Society Scholar, Department of Medicine, University of Manitoba, Winnipeg, Manitoba.



1 $R^1 = OCH_3$, $R^2 = R^3 = R^4 = OH$
2 $R^1 = OCH_3$, $R^2 = H$, $R^3 = R^4 = OH$
3 $R^1 = R^3 = R^4 = OH$, $R^2 = H$
4 $R^1 = R^2 = H$, $R^3 = R^4 = OH$
5 $R^1 = R^3 = H$, $R^2 = R^4 = OH$
6 $R^1 = R^2 = R^4 = H$, $R^3 = OH$



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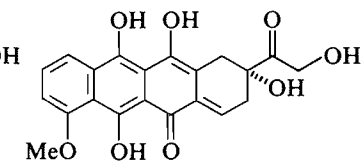

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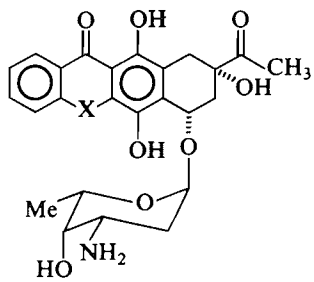
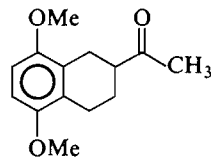


9 X = O
10 X = S
11 X = SO



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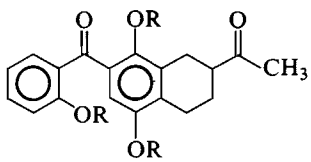
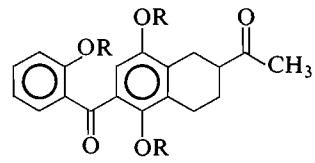


13 R = CH_3
15 R = H

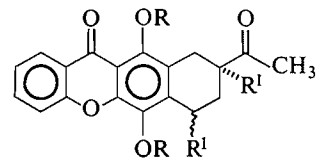
cytoxicity and cardiotoxicity. Making heteroanthracyclines, such as 4-demethoxyxanthodaunomycin (**9**), 4-demethoxythioxanthodaunomycin (**10**), and 4-demethoxy-5-sulfoxodaunomycin (**11**), available could help clarify the origin of cardiotoxicity and cytotoxicity of anthracyclines.

Results and discussion

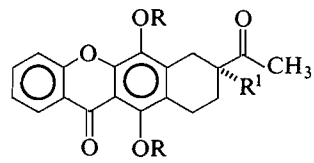
The tetracyclic xanthone skeleton of **9** was constructed using the versatile 2-acetyl-5,8-dimethoxy tetralin (**12**) (14) as starting compound. Condensation of the tetralin (**12**) with 2-methoxybenzoic acid in trifluoroacetic acid solution gave a mixture of two isomers **13** and **14**. The reaction temperature was maintained at 20–24°C. Below 15°C, the reaction was very slow and at 40°C, trifluoroacetylation of the tetralin (**12**) was a major reaction. The two isomers were separated by high performance liquid chromatography on silica and were characterized by ir, ^{1}Hmr, and ms. However, separation at this stage for preparative purposes is not practical. The isomeric mixture (**13** and **14**) was hydrolysed by aluminium chloride to the



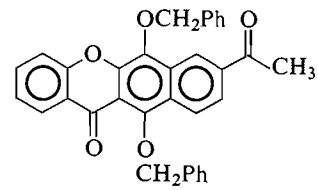
14 R = CH_3
16 R = H



17 R = R' = H
19 R = CH_2—Ph, R' = H
21 R = CH_2—Ph, R' = OH
25 R = CH_2—OCH_3, R' = H



18 R = R' = H
20 R = CH_2Ph, R' = H
24 R = CH_2Ph, R' = OH



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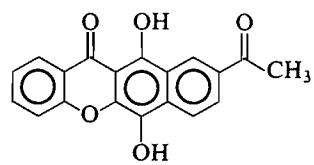

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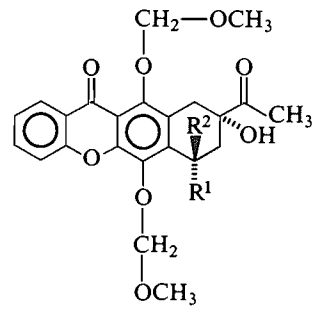


26 R' = OH, R^2 = H
27 R' = H, R^2 = OH

phenols **15** and **16**; hydrolysis by trimethyl chlorosilane (15) or potassium cyanide in dimethylsulfoxide (16) gave only a mixture of partially demethylated products.

Oxidative cyclization of **15** and **16** by lead tetracetate gave the tetracyclic xanthones **17** and **18** in excellent yield. Large scale separation of **17** and **18** was accomplished easily by column chromatography of their corresponding dibenzyl ethers **19** and **20** on silica, followed by acid hydrolysis. Structure assignment to **19** and **20** based on spectroscopic data was inconclusive. However, the first isomer collected had a dipole moment of 3.5 D and was assigned structure **20**, the calculated value of which was 3.48 D. The second isomer collected from the column had a dipole moment of 4.1 D and was assigned structure **19**, the calculated value of which was 4.9 D. Dipole moments of **19** and **20** were calculated using the reported dipole moment of xanthone, 3.14 D (17), and published values for benzene solution group moments (18).

Oxidation of **19** by molecular oxygen in the presence of potassium *tert*-butoxide in *N*,*N*-dimethylformamide solution gave a good yield of the dihydroxyxanthone **21** (19). Attempts to form an isopropylidene derivative of, or to debenzylate **21** invariably led to aromatization of ring D (**23**). Oxidation of isomer **20** under similar conditions yielded the monohydroxylated xanthone (**24**) or the aromatized product (**22**) depending on the length of the oxidation process. However, methoxymethylation of **17** with chloromethyl methyl ether under proper conditions gave an excellent yield of **25** which, under similar oxidation conditions, gave **26** as the major product and **27** as the minor product. The *cis*-geometry of the C-7

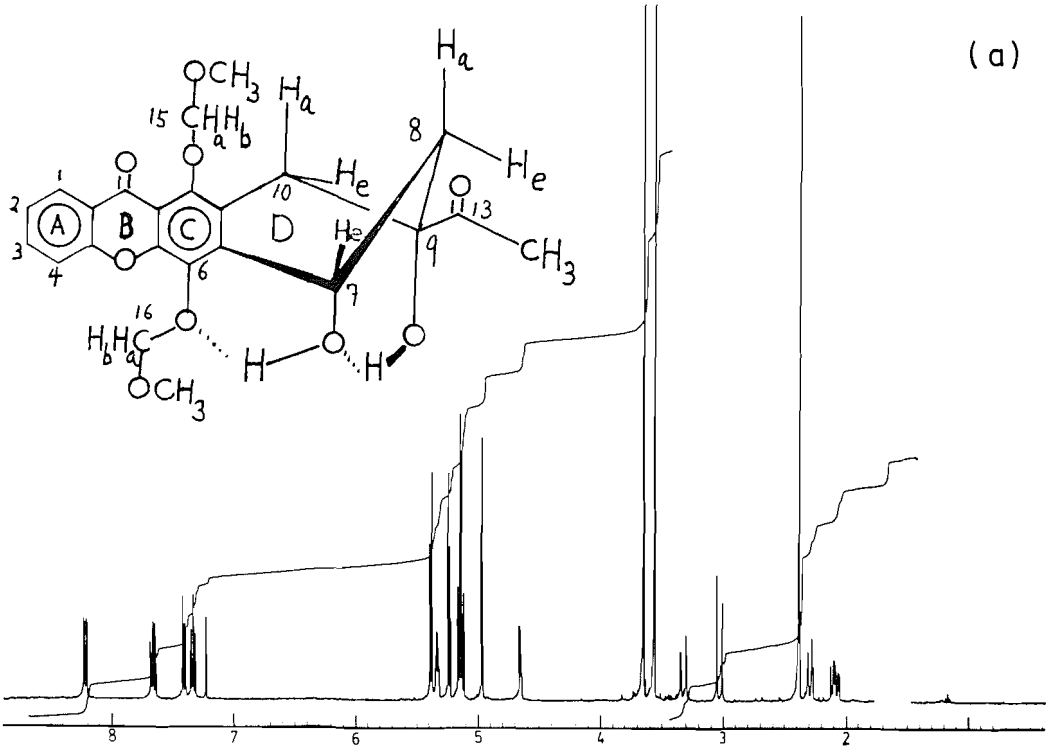


FIG. 1. (a)–(d) Bruker WH-400 ^{1}Hmr spectrum of **26** and the first order analysis of C_{15}, C_{16}, and D-ring protons. (a) Complete spectrum of **26** in $CDCl_3$.

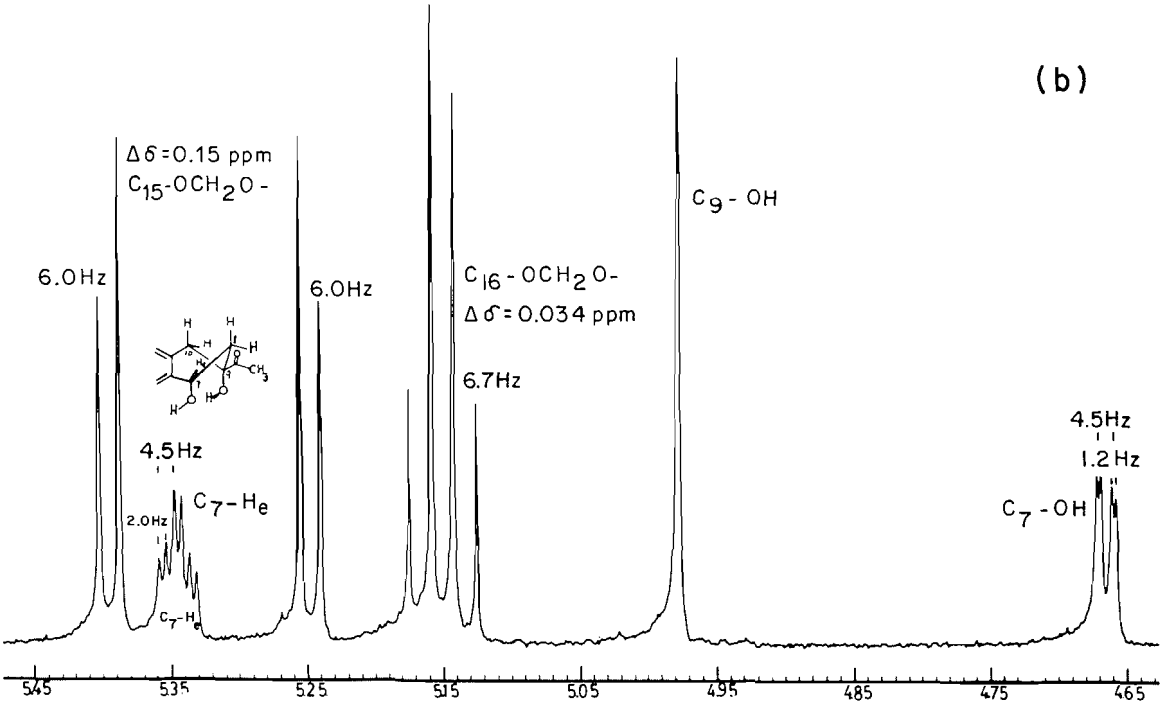


FIG. 1. (b) Expanded area between 4.65–5.45 ppm corresponding to C_7—H_e, C_7—OH, C_{15}—OCH_2O—, and C_{16}—OCH_2O—.

and C-9 hydroxy functions of **26** was established by detailed analysis of the high field ^{1}Hmr spectrum and computer simulated ^{1}Hmr spectrum of the D-ring of **26** (Figs. 1(a)–1(d) and 2).

The C_7—H_e appears as doublets of a triplet at 5.343 ppm. Its quasi-equatorial position is locked by the hydrogen-bond formation between the C_7—OH proton and the C_6-phenolic oxygen and revealed by the coupling constants. The $J_{7e,8a} = 4.5$ Hz corresponds to a dihedral angle of 45° and $J_{7e,8e} = 2.1$ Hz corresponds to a dihedral angle of 60°. The $J_{7e,7OH} = 4.6$ Hz corresponds to a dihedral angle of 40°, which agrees well with the H—O—C_7—H angle when the hydroxy proton hydrogen-bonds the C_6 oxygen. The C_7—OH appears as a quartet at 4.665 ppm due to coupling with C_7—H_e ($J_{7e,7OH} = 4.6$ Hz) and

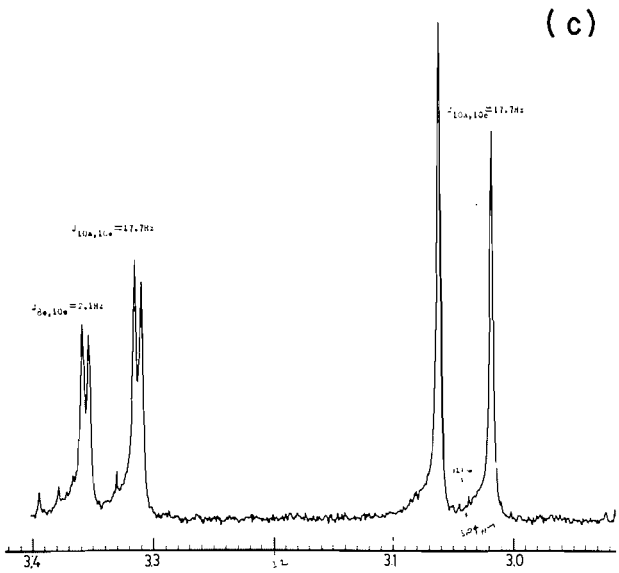


FIG. 1. (c) Expanded area between 3.0–3.4 ppm corresponding to C_{10}—H_aH_e.

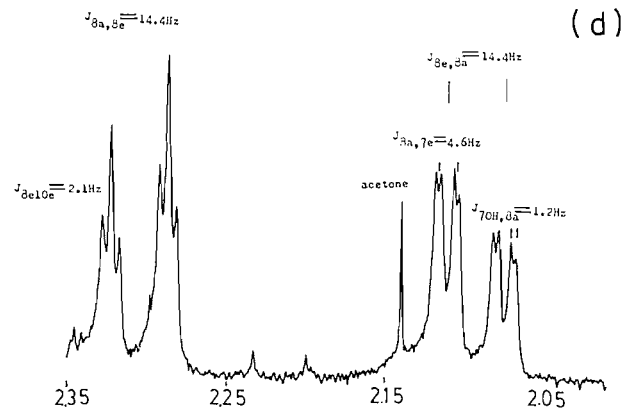
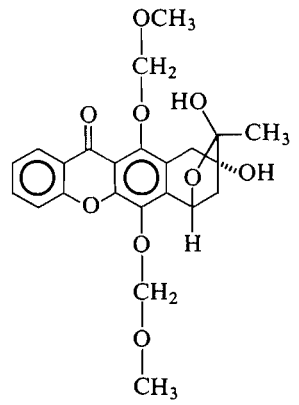


FIG. 1. (d) Expanded area between 2.05–2.35 ppm corresponding to C_8—H_aH_e.

C_8—H_a ($J_{7OH,8a}$ = 1.2 Hz). The latter is a four-bond coupling which is discernible only if the C_7—OH is locked by hydrogen bonding as suggested. The C_8—H_e appears as triplets of a doublet at 2.305. Its geminal coupling is $J_{8a,8e}$ = 14.4 Hz and its vicinal coupling is $J_{8e,7e}$ = 4.5 Hz and its four-bond coupling is $J_{8e,10e}$ = 2.1 Hz. The C_8—H_a appears at 2.092 as doublets of a quartet due to couplings with C_8—H_e ($J_{8a,8e}$ = 14.4 Hz), C_7—H_e ($J_{8a,7e}$ = 4.5 Hz), and C_7—OH ($J_{8a,7OH}$ = 1.2 Hz). The C_{10}—H_e appearing at 3.335 ppm as a quartet couples with C_{10}—H_a ($J_{10e,10a}$ = 17.7 Hz) and C_8—H_e ($J_{10e,8e}$ = 2.1 Hz). The C_{10}—H_a at 3.04 ppm appearing as a doublet couples to C_{10}—H_e only ($J_{10a,10e}$ = 17.7 Hz). Figures 1 and Fig. 2 show the ^{1}Hmr spectrum, including the conformation of the D-ring, and the computer simulated spectrum of the D-ring of **26**, respectively. The complete analysis of the ^{1}Hmr spectrum of **27** is difficult due to the presence of a slow equilibrium between **27** and **28**. The infrared spectrum shows a weak absorption at 1715 cm^{-1}; two methyl peaks at 2.39 ppm and 1.36 ppm integrated for 3 protons correspond to the C_{13}—CH_3 of **27** and **28**; two peaks at 3.60 ppm and 3.66 ppm integrated for 3 protons are tentatively assigned to C_{16}—O—CH_3 and two peaks at 3.703 and 3.708 ppm integrated for 3 protons are tentatively assigned to C_{15}—O—CH_3 of **27** and **28**; a quartet at



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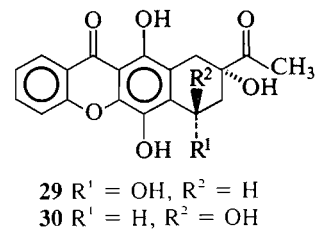
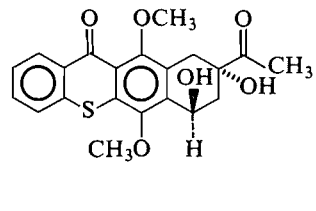


29 R^1 = OH, R^2 = H
30 R^1 = H, R^2 = OH



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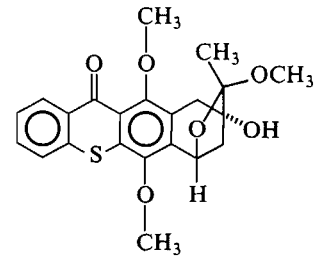

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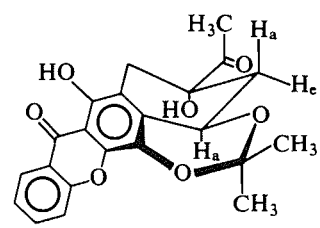

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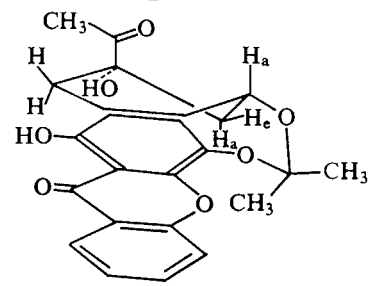

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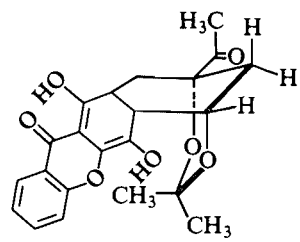

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5.324 ppm ($J_{15a,15b}$ = 6.1 Hz, $\Delta\delta_{Ha,Hb}$ = 0.152 ppm) and a singlet at 5.211 ppm, together integrated for 2 protons, are assigned to the C_{15}—H_2 of **27** and **28**, respectively; a quartet at 5.159 ppm ($J_{16a,16b}$ = 6.2 Hz, $\Delta\delta_{Ha,Hb}$ = 0.034 ppm) and a singlet at 5.169 ppm, together integrated for 2 protons, are assigned to the C_{16}—H_2; a doublet at 5.475 ppm ($J_{7OH,7H}$ = 5.8 Hz) and a singlet at 4.16 ppm, together integrated for one proton, are assigned to the C_7—OH of **27** and **28**; a broad doublet of a triplet at 5.432 ppm integrated for one proton is assigned to the C_7—H which is spin–spin coupled to C_7—OH ($J_{7H,7OH}$ = 5.8 Hz), C_8—H_a ($J_{7H,8a}$ = 6.3 Hz), and C_8—H_e ($J_{7H,8e}$ = 2.0 Hz). The C_9—OH appears as two singlets at 3.0 and 3.10 ppm, integrated for one proton. Similar equilibrium also exists in the thioxanthodaunomycinone derivative (**31**) which reacts with excess 2,2-dimethoxypropane in the pres-

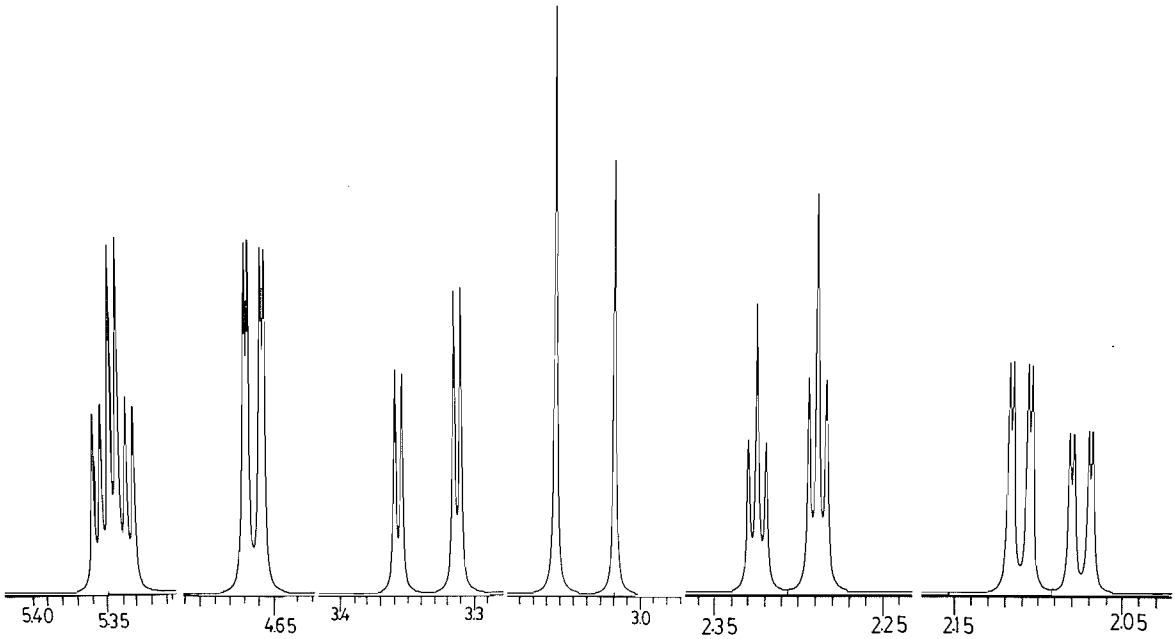

FIG. 2. Computer simulated spectrum of C_7—H_e, C_7—OH, C_8—H_aH_e, and C_{10}—H_aH_e.

ence of anhydrous *p*-toluenesulfonic acid to give exclusively **32**.[4]

Hydrolysis of **26** in dilute hydrochloric acid – acetone solution gave **29**, while **27** under similar conditions gave **30**. Both **26** and **27**, upon dissolving in trifluoroacetic acid followed by the addition of water, could be converted to a mixture of **29** and **30**. Reaction of **29** or **30** with dimethoxypropane in the presence of *p*-toluene sulfonic acid gave two isopropylidene derivatives, **33** and **34**, instead of **35**. This conclusion was arrived at solely on the basis of the coupling constants of the C_7—H of **33** and **34**. A Dreiding model of **33** shows that the H_7—C_7—C_8—H_{8a} extends a dihedral angle of about 180° and H_7—C_7—C_8—H_{8e} extends a dihedral angle of 60°, while **34** has the two corresponding dihedral angles of 160° and 40°. Thus, it is possible to come to a conclusion, according to the Karplus approximation, that the C_7—H spin–spin coupling constants of **33** and **34** will not differ greatly. However, in the case of **35**, the H_7—C_7—C_8—H_{8a} and H_7—C_7—C_8—H_{8e} can each extend a dihedral angle of about 60° and the C_7—H is likely to appear as a triplet (J = 2 Hz approximately) rather than as a quartet, in the case of **33** at 4.88 ppm ($J_{7a,8a}$ = 11 Hz, $J_{7a,8e}$ = 5.5 Hz) and in the case of **34** at 5.26 ppm ($J_{7a,8e}$ = 7 Hz). The isopropylidene methyl groups of **33** seem to be equivalent and appear as a 6-proton singlet while the isopropylidene methyl groups of **34** are nonequivalent. One methyl group appears at 1.72 ppm and the other is moved upfield to 1.63 ppm due to the shielding effect of the C-ring.

Preliminary in vitro cytotoxicity assays done in our laboratory using tumor cells MCF-7, a human breast cancer cell line, as indicator showed that both 34-demethoxyxanthodaunomycinone (**29**) and 4-demethoxy-7-epixanthodaunomycinone (**30**) were weakly cytotoxic. Daunomycinone, the aglycone of daunomycin (**2**), showed no cytotoxicity under similar conditions.

A more detailed study of the biological properties of 4-demethoxyxanthodaunomycin (**9**), 4-demethoxythioxanthodaunomycin (**10**), and 4-demethoxy-5-sulfoxodaunomycin (**11**) will be reported in later communications.

[4]Unpublished work by the authors; see also ref. 19*b*.

Experimental

All melting points were recorded on a Fischer–Johns apparatus and were uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian spectrometer A56/60A or a HA 100, Bruker WH-90, or Bruker WH-400 spectrometer, using tetramethylsilane as internal standard unless otherwise specified. Infrared spectra were recorded on a Perkin–Elmer 710 infracord and dipole moments were taken on a DM01 Kahl dipolometer. Mass spectra were recorded on a Finnigan 1015 or a A.E.I. MS-50. Elemental analyses were performed by C. Daessle or Geller Laboratories.

*Preparation of 2-acetyl-5,8-dimethoxy-7-(2-methoxybenzoyl)tetralin (**13**) and 2-acetyl-5,8-dimethoxy-6-(2-methoxybenzoyl)tetralin (**14**)*

To a solution of trifluoracetic anhydride (38 mL) and 2-methoxybenzoic acid (40 g) was added 2-acetyl-5,8-dimethoxytetralin (12 g) followed by trifluoracetic acid (5 mL), keeping the temperature of the solution at 18–20°C. A second portion of trifluoroacetic acid (10 mL) was added after the solution was stirred for 1 h and stirring was continued for a total of 9 h. The trifluoroacetic acid was removed under reduced pressure and the residue was dissolved in chloroform (300 mL). The chloroform solution, washed with water, saturated sodium bicarbonate solution (3 × 100 mL), and dried over magnesium sulfate, was evaporated under reduced pressure to give a tinted clear residue (23 g); ir (cm^{-1}): 1710 ($COCH_3$), 1660 (phenone); ^{1}Hmr (δ): 7.6–7.35 (m, 2H, aromatic), 7.15–6.83 (m, 2H, aromatic), 6.90 (s, 1H, aromatic), 3.77 (s, 3H, —OCH_3), 3.70 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.22 (s, 3H, $COCH_3$); ms: 368 (M^+), 353, 325. *Mol. Wt.* (high resolution ms) calcd. for $C_{22}H_{24}O_5$: 368.1624; found: 368.1630.

*2-acetyl-5,8-dihydroxy-7-(2-hydroxybenzoyl)tetralin (**15**) and 2-acetyl-5,8-dihydroxy-6-(2-hydroxybenzoyl)tetralin (**16**)*

Aluminium chloride (40 g) was added to a chloroform solution (400 mL) of **13** and **14** (13 g) and stirred mechanically at room temperature for 25 h. The excess of aluminium chloride was decomposed by water and the chloroform solution washed with saturated oxalic acid solu-

tion, water, and saturated sodium bicarbonate solution and dried over magnesium sulfate, then evaporated under reduced pressure. The residue was dissolved in methylene chloride (20 mL) and ether (20 mL) from which a yellow crystalline product (3 g) was collected. The mother liquor was subjected to column chromatography on silica and an additional amount of yellow crystalline product (1.5 g) was isolated. Isomer **15** could be isolated after tedious recrystallizations (5×) from acetone, mp 224–227°C; ir(cm^{-1}): 3570 (phenol —OH), 3600–2900 (chelated phenolic H), 1705 (—$COCH_3$), 1620 (phenone), 1600, 1580 (aromatic); ^{1}Hmr (δ): 11.5 (chelated OH), 9.60 (br s, chelated OH), 8.05 (br s, nonchelated OH), 7.7–7.3 (m, 2H, aromatic), 7.15–7.85 (m, 3H, aromatic), 2.24 (s, 3H, $COCH_3$), ms: 326 (M^+), 309, 279, 232. *Mol. Wt.* (high resolution ms) calcd. for $C_{19}H_{18}O_5$: 326.1153; found: 326.1154. *Anal.* calcd. for $C_{19}H_{18}O_5$: C 69.93, H 5.52; found: C 70.11, H 5.44. The combined mother liquor was evaporated to dryness and some of the solid residue was subjected to high pressure liquid chromatographic separation on a silica column. The first isomer (**16**) collected was recrystallized from acetone, mp 208–211°C. Spectroscopic properties are similar to those of **15**. Structures were established by comparing the oxidative cyclization products with those obtained from the hydrolysis of **19** and **20** (*vide infra*).

7,8,9,10-Tetrahydro-6,11-dihydroxy-9-acetylxanthen-12-one (17) and 7,8,9,10-tetrahydro-6,11-dihydroxy-9-acetylxanthen-5-one (18)

The isomeric mixture of **15** and **16** (3 g) together with lead tetracetate (4.4 g) in glacial acetic acid (8 mL) was ground in a mortar for 20 min at ambient temperature. The acidic slurry was washed into a separatory funnel and extracted with ethyl acetate (4 × 200 mL). The combined ethyl acetate solution was stirred with sodium thiosulfate solution (10%, 100 mL) for 2 h at room temperature, washed with water, and dried over magnesium sulfate. Evaporation of the solvent to dryness gave a yellow solid residue (2.6 g) which was purified by recrystallization from acetone, mp 219–225°C; separation could be done easily via the dibenzyl derivatives **19** and **20**.

Separation of 17 and 18

The isomeric mixture of **17** and **18** (4 g), benzyl bromide (8 mL), and pulverized anhydrous potassium carbonate (20 g) in acetone (300 mL) was heated under reflux for 14 h in a nitrogen atmosphere. The acetone solution was cooled, filtered, and evaporated to give an oily residue which was subjected to further evacuation and heating to remove the excess benzyl bromide and acetone dimer. The residue, which could be easily crystallized from ether on standing, was separated by column chromatography on silica (DSF-256 Merck) into its components (**19** and **20**) using toluene as eluent. Isomer **20** (2.6 g) was recrystallized from methylene chloride – ether, mp 119–120°C; ir (cm^{-1}): 1710 ($COCH_3$), 1660 (phenone), 1600 (aromatic); ^{1}Hmr (δ): 8.35 (dd, 1H, C_1—H, $J_{1,2}$ = 7 Hz, $J_{1,3}$ = 2 Hz, aromatic), 7.78–7.33 (m, 14H, aromatic), 5.17 (s, 2H, C_6—O—CH_2Ph), 5.09 (q, 2H, C_{12}—O—CH_2Ph, J_{gem} = 10 Hz, Δδ = 0.14 ppm), 2.18 (s, 3H, $COCH_3$); ms: 504, 413, 323. *Mol. Wt.* (high resolution ms) calcd. for $C_{33}H_{28}O_5$: 504.1937; found 504.1942; dipole moment estimated for **20**: 3.5 D; found: 3.48 D.

Heating **20** (2.2 g) in an acidic methanolic solution (concentrated hydrochloric acid 25 mL, methanol 50 mL) under reflux for 16 h gave the xanthone **18** (1.4 g) which was purified by recrystallization from acetone, mp 239–242°C; ir (cm^{-1}): 3650 (OH), 3400–2900 (chelated phenolic H), 1705 ($COCH_3$), 1650, 1630 (phenone), 1610 (aromatic); ^{1}Hmr (δ): 12.10 (s, 1H, chelated, OH), 8.26 (d,d 1H, $J_{3,4}$ = 7 Hz, $J_{2,4}$ = 1.8 Hz, aromatic), 7.30–7.80 (m, 3H, aromatic), 5.25 (br s, 1H, —OH), 2.31 (s, 3H, $COCH_3$); ms: 324 (M^+), 309, 281. *Mol. Wt.* (high resolution ms) calcd. for $C_{19}H_{16}O_5$: 324.0998; found: 324.1002.

Isomer **19** (2 g) was recrystallized from methylene chloride – ether, mp 138–140°C; estimated dipole moment for **19**: 4.9 D, found: 4.19 D. Spectroscopic data are similar ro those of **20** above. *Anal.* calcd. for $C_{33}H_{28}O_5$: C 78.57, H 5.56; found: C 78.47, H 5.65. Debenzylation as in the case of **20** gave **17** (1.2 g), which was also purified by recrystallization from acetone, mp 264–267°C; spectroscopic data are similar to those of **18**.

7,8,9,10-Tetrahydro-9-acetyl-6,11-dimethoxymethylenoxyxanthen-12-one (25)

Chloromethyl methyl ether (5 mL), freshly prepared by passing distilled chloromethyl methyl ether through an alumina column (G-1, neutral), was added dropwise under a nitrogen atmosphere to an anhydrous acetone solution (200 mL) containing freshly baked pulverized potassium carbonate (20 g) and **17** (1.2 g). The solution was heated under reflux for 4 h, cooled, filtered, and concentrated. Methylene chloride was added to the residue and the solution was filtered to remove the potassium carbonate, evaporated under reduced pressure, and finally subjected to further evacuation and heating to remove the acetone dimer. The clear residue (1.48 g), upon addition of ether, crystallized and was recrystallized from methylene chloride – ether, mp 152–154°C; ir (cm^{-1}): 1710 ($COCH_3$), 1660 (phenone), 1605 (aromatic); ^{1}Hmr (δ): 8.27 (dd, 1H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 2 Hz, C_1—H), 8.0–7.33 (m, 3H, aromatic), 5.22 (s, 2H, —O—CH_2—O—), 5.20 (s, 2H, —OCH_2—O—), 3.70 (s, 3H, —OCH_3), 3.66 (s, 3H, OCH_3), 2.28 (s, 3H, $COCH_3$); ms: 412 (M^+), 381, 367, 337. *Mol. Wt.* (high resolution ms) calcd. for $C_{23}H_{24}O_7$: 412.1515; found: 412.1519.

*4-Demethoxy-bis-*O*-methoxymethylxanthodaunomycinone (26) and 4-demethoxy-bis-*O*-methoxymethyl-7-epixanthodaunomycinone (27)*

Potassium *tert*-butoxide (850 mg) was added to a solution of anhydrous dimethylformamide (150 mL) and *tert*-butyl alcohol (20 mL). The solution was stirred with occasional warming until the solid material was completely dissolved and then cooled in a −25°C cold bath. Trimethyl phosphite (2.7 mL) was added, followed by the xanthone (**25**) (900 mg). Dry oxygen was introduced into the solution through a gas-dispersion tube, keeping the cold bath between −25°C and −15°C for 1.5 h. Cold dilute hydrochloric acid (0.1 *M*) was added to the solution, with vigorous stirring, until the pH = 8.

Water (300 mL) was added to the solution which was exhaustively extracted with chloroform (3 × 200 mL). The combined chloroform extracts, washed with water and dried over magnesium sulfate, were concentrated under reduced pressure to give a residue which was subjected to further heating under vacuum until it was free of dimethyl formamide. The semi-solid residue was subjected to preparative thin-layer chromatographic separation and **26** (420 mg) was isolated and recrystallized from acetone–ether, mp 162–164°C; ir (cm^{-1}): 3430 (OH), 1715 ($COCH_3$), 1660 (phenone), 1605 (aromatic); ^{1}Hmr (δ): 8.236 (dd, C_1—H, $J_{1,2}$ = 7.8 Hz, $J_{1,3}$ = 2.0 Hz), 7.70–7.33 (m, 3H, aromatic), 5.324 (q, 2H, J_{gem} = 6.1 Hz, Δδ = 0.148 ppm, C_{11}—O—CH_2—O—), 5.345 (dt, 1H, C_7—He, $J_{7e,7OH}$ = 4.6 He, $J_{7e,8a}$ = 4.5 Hz, $J_{7e,8e}$ = 2.1 Hz), 5.151 (q, 2H, C_6—OCH_2O—, J_{gem} = 6.7 Hz, Δδ = 0.034 ppm), 4.98 (s, 1H, C_9—OH), 4.665 (q, 1H, C_7—OH, $J_{7e,OH}$ = 4.6 Hz, $J_{7OH,8a}$ = 1.2 Hz), 3.66 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3) 3.335 (q, 1H, C_{10}—H_e, $J_{10a,10e}$ = 17.7 Hz, $J_{10e,8e}$ = 2.1 Hz), 3.04 (d, 1H, C_{10}—H_a, $J_{10a,10e}$ = 17.7 Hz), 2.38 (s, 3H, $COCH_3$), 2.305 (td, 1H, C_8—H_e, $J_{8a,8e}$ = 14.4 Hz, $J_{8e,7e}$ = 2.1 Hz, $J_{8e,10e}$ = 2.1 Hz), 2.092 (dq, 1H, C_8—H_a, $J_{8a,8e}$ = 14.4 Hz, $J_{8a,7e}$ = 4.5 Hz, $J_{8a,7OH}$ = 1.2 Hz) (Fig. 1); ms: 444 (M^+), 414, 426, 382. *Mol. Wt.* (high resolution ms) calcd. for $C_{23}H_{24}O_9$: 444.1413; found: 444.1411.

The minor isomeric product (**27**) (140 mg) was isolated and purified by recrystallization from acetone–ether, mp. 156–158°C; ir (cm^{-1}): 3560 (OH), 3470 (OH), 1715 ($COCH_2$, weak), 1660 (phenone), 1605 (aromatic); ms: 444 (M^+), 414, 382; ^{1}Hmr: the presence of a slow equilibrium between **27** and **28** makes the complete analysis of the ^{1}Hmr spectrum difficult. Reaction of **26** and **27** with trifluoroacetic acid followed by water led to the formation of both **29** and **30** in the same ratio.

4-Demethoxyxanthodaunomycinone (29) and 4-demethoxy-7-epixanthodaunomycinone (30)

To a stirred solution of acetone (20 mL) containing **26** (180 mg) was added dropwise concentrated hydrochloric acid (1/2 mL) at room temperature and the stirring was continued for 6 h. The solution, diluted with water (50 mL), was extracted with ethyl acetate (3 × 100 mL). The combined extracts, washed with saturated sodium bicar-

bonate solution and dried over magnesium sulfate, were evaporated to dryness to give the yellow crystalline 4-demethoxyxanthodaunomycinone **29** (130 mg) which was purified by recrystallization from acetone, mp 216–218°C; ir (cm^{-1}): 3550–2900 (OH), 1710 ($COCH_3$), 1660 (weak), 1635 (strong) (hydrogen-bonded phenone), 1615, 1600 (aromatic); ^{1}Hmr (δ) (DMSO-d_6): 12.17 (s, 1H, hydrogen-bonded C_{11}—OH), 9.24 (br s, 1H, C_6—OH), 8.20 (dd 1H, C_1—H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 1.5 Hz), 8.02–7.41 (m, 3H, aromatic), 5.97 (s, 1H, C_9—OH), 5.63 (br s, 1H, C_7—OH), 5.13 (br t, 1H, C_7—H, J = 5 Hz), 2.87 (q, 2H, C_{10}—H_aH_e, J_{gem} = 8 Hz, Δδ = 0.12 ppm), 2.26 (s, 3H, $COCH_3$), 2.12 (br d, 2H, C_8—H_aH_e, J_{gem} = 5 Hz); ms: 356 (M^+), 338, 320, 305, 295. *Anal.* calcd. for $C_{19}H_{16}O_7$: C 64.05, H 4.53; found: C 64.09, H 4.51.

Hydrolysis of **27** to 4-demethoxy-7-epixanthodaunomycinone (**30**) was done similarly; mp 199–202°C. *Mol. Wt.* (high resolution ms) calcd. for $C_{19}H_{16}O_7$: 356.0891; found: 356.0893.

*Isopropylidenes **33** and **34***

The xanthone **30** (15 mg) was added to an anhydrous benzene solution (20 mL) containing toluenesulfonic acid (10 mg) and freshly distilled 2,2-dimethoxypropane (0.1 mL). The solution was stirred for 5 h at room temperature, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. Two crystalline products **33** (3 mg) and **34** (4 mg) in addition to two other minor compounds were isolated by tlc on silica. The isopropylidene (**33**) was recrystallized from methylene chloride and ether, mp 204–206°C; ir (cm^{-1}): 3550 (C_6—OH), 3550–2900 (C_{11}—OH), 1710 ($COCH_3$), 1650 (weak), 1630 (strong) (phenone), 1610, 1600 (aromatic); ^{1}Hmr (δ): 12.39 (s, 1H, C_{11}—OH), 8.28 (dd, 1H, C_1—H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 2 Hz), 7.86–7.30 (m, 3H, aromatic), 5.25 (dd, 1H, C_7—H, $J_{7e,8e}$ = 11 Hz, $J_{7e,8a}$ = 6 Hz), 4.28 (s, 1H, C_6—OH), 3.01 (q, 2H, C_{10}—H_eH_a, $J_{10e,10a}$ = 18 Hz, Δδ = 0.55 ppm), 2.26 (s, 3H, $COCH_3$), 2.12 (dq, 2H, $J_{7e,8e}$ = 11 HZ, $J_{7e,8a}$ = 6 HZ, $J_{8a,8e}$ = 18 Hz, Δδ = 0.33 ppm), 1.71 (s, 6H, CH_3—C—CH_3); ms: 396 (M^+), 338, 320, 277. *Mol. Wt.* (high resolution ms) calcd. for $C_{22}H_{20}O_7$: 396.1203; found: 396.1208.

The isopropylidene **34** was recrystallized from methylene chloride – ether, mp 193–195°C; ir (cm^{-1}): 3480 (C_9—OH), 3500–2900 (C_{11}—OH), 1710 ($COCH_3$), 1650, 1630 (hydrogen-bonded phenone), 1610, 1600 (aromatic); ^{1}Hmr (δ): 12.42 (s, 1H, C_{11}—OH), 8.29 (dd, 1H, C_1—H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 2 Hz), 7.88–7.31 (m, 3H, aromatic), 4.88 (dd, 1H, C_7—H, $J_{7e,8e}$ = 10 Hz, $J_{7e,8a}$ = 7 Hz), 3.01 (s, 1H, C_9—OH), 2.93 (q, 2H, C_{10}—H_aH_e, $J_{10a,10e}$ = 16 Hz, Δδ = 0.50 ppm), 2.41 (s, 3H, $COCH_3$), 2.27 (dq, 2H, C_8—H_aH_e, $J_{7e,8a}$ = 7 Hz, $J_{7e,8e}$ = 10 Hz, $J_{8e,8a}$ = 15 Hz, Δδ = 1.0 ppm), 1.70 (s, 3H, C—CH_3), 1.61 (s, 3H, C—CH_3); ms: 396 (M^+), 338, 320, 295, 277. *Mol. Wt.* (high resolution ms) calcd. for $C_{22}H_{20}O_7$: 396.1203: found, 396.1206.

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