Tetrahedron. Vol. 33, pp. 673 to 680. Pergamon Press 1977 Printed in Great Britain

# NAPHTO- AND ANTHRAQUINONES OF *STREPTOMYCES THERMOVIOLACEUS* WR-141. STRUCTURES AND MODEL SYNTHESES†

J. ST. PYREK,* O. ACHMATOWICZ, JR. and A. ZAMOJSKI
Instytut Chemii Organicznej PAN, 00 961 Warszawa, Polska

(*Received in UK* 3 *August* 1976; *Accepted for publication* 28 *September* 1976)

**Abstract**—In addition to previously identified antibiotic granaticin **1** *Streptomyces thermoviolaceus* WR-141 was shown to produce dihydrogranaticin **2**, and anthraquinone pigments **5**, and **6**. Model synthesis of the chromophore and dihydropyran part of these antibiotic pigments are described.

The main component of the mixture of antibiotic pigments produced by the thermophilic mould *Streptomyces thermoviolaceus* subsp. pigens var. WR-141 was identified as the known antibiotic granaticin.[1] The structure **1**, and the absolute configuration of granaticin molecule was determined by degradation and spectral methods including X-ray analysis.[2] Granaticin is produced also by few other strains of Streptomyces besides the above mentioned and *Str. olivaceus*, from which it was isolated for the first time.[3] Recently in addition to its antibacterial and antiprotozoal activities found before,[4] an antileucemic activity was also detected.[5]

In the present paper the isolation and structure determination of three other pigments from the same strain is reported, namely dihydrogranaticin **2**, the direct granaticin **1** precursor, and two structuraly related quinizarin derivatives **5** and **6**. Model reactions leading to the chromophore part and the dihydropyran part of the above quinones are also described.

## RESULTS

*Dihydrogranaticin* **2**. According to pigments composition, followed by TLC during the growth of Str. WR-141, the production of granaticin **1** is preceded by the secretion of the more polar, more acidic compound having the same UV spectrum as **1**. Its IR spectrum showed the presence of free carboxyl group ($\nu_{max}$ 1725 $cm^{-1}$) apart of chelated quinone carbonyl groups (1610, 1570 $cm^{-1}$). The presence of the former was confirmed by the formation of methyl ester **3** (1757 $cm^{-1}$) on treatment with MeOH/HCl. The elemental analysis of the crystalline sample combined with the presence of the molecular ion in the mass spectrum (446 1% of base peak 384) pointed to a molecular formula $C_{22}H_{22}O_{10}$, i.e. the dihydro derivative of granaticin **1**. The anticipated structure **2**, for the new pigment, was confirmed by the following $^1H$ NMR data of the chloroform soluble methyl ester **3**. The three signals of TFA exchangable protons located at 12.73 sharp, 13.15 broad, and 3.05 broad, (two protons), correspond to OH group protons; the signals of bicyclo octane fragment, similar to those of **1**, are located at 0.98 doublet of 22-$CH_3$, 3.75 quartet of H-21 J 6.5 Hz, 4.00 double doublet of H-19 with J 8 and 1 Hz, 2.7 and 1.4 complex partially overlapped multiplets of $CH_2$-18, 5.19 double doublet of H-17 with J 2 and 1 Hz. Also analogous to those of **1** are signals of $CH_3$-16 at 1.57, doublet, and H-15, quartet at 5.02 with J 6.5 Hz. The remaining resonances form a strongly coupled pattern which were assigned as follows: 2.66 doublet with J 6.2 Hz $CH_2$-2, 4.30 broad H-3, 2.34 and 2.99 AB part of ABX system $CH_2$-4, $J_{4a,4e}$ 19, $J_{4a,3a}$ 10 and $J_{4e,3a}$ 3 Hz. Three protons singlet at 3.84 was assigned to the OMe group.

These data are in full accordance with those obtained for the model synthetic quinone **27** with the *trans* configuration at C-3 and C-15, as well as with those reported for analogous natural quinones like actinorodin[6] and nanaomycin A.[7]

The forgoing sturctural assignment was additionally confirmed by the direct, both ways transformation of **1** to **2**, and **2** to **1**. Granaticin **1** hydrogenated over platinum absorbed two moles of hydrogen with the formation of yellow quinol which was easily reoxidized by air to a pigment identical with **2**. This reaction is obviously the consequence of the hydrogenolysis of the γ-lactone closed onto the benzylic position. The reverse reaction was accomplished by the slow air oxidation of dihydrogranaticin **2** absorbed on $KH_2PO_4$ buffered silica gel. The analogous transformation was recently described for nanaomycin A which was oxidized to nanaomycin D in methanol solution.[8]

$^{13}C$ NMR *data of dihydrogranaticin* **2** *and its methyl ester* **3**. The extensive examination of $^{13}C$ NMR spectra of **2** and **3** was done as a part of a larger program devoted to natural and model quinones.[9] The data were obtained in FT mode at 25.2 MHz using noise and selective proton decoupling, as well as undecoupled spectrum in the case of **3**, Table 1.

The assignment of three Me groups quartets was straightforward. The OMe group gives the sharpest lines with the highest $^1J_{CH}$ and characteristic chemical shift. Two other Me groups differ in chemical shift value both in $^{13}C$ and $^1H$ spectra thus allowing the use of selective decoupling and residual coupling for the assignment. The irradiation at 2.66 ppm was used for the differentiation of three methylene group carbon triplets, and led to the total decoupling of C-2 signal, whereas C-4 triplet had residual coupling 23 Hz (the corresponding proton signals lie at 2.8 and 4.4 ppm), and C-18 triplet changed to the double doublet with residual couplings 47 and 12 Hz (proton signals lie at 2.7 and 1.4 ppm). The residual couplings and selective decoupling was also used for the assignment of five CH doublets. For the quaternary C atoms, with an exception of C-14 broad signal and C-1 multiplet,

†J. St. Pyrek, Thesis (1971); reported in part: IUPAC 7th Int. Symp. Chem. Nat. Prod. Riga, 1970.

Table 1. $^{13}C$ NMR spectral data of dihydrogranaticin 2 and dihydrogrananticin methyl ester 3

| C no. | 2 DMSO $d_6$, TFA | | 3 $CDCl_3$ | | | | |
|---|---|---|---|---|---|---|---|
| | δ | a | δ | b | $J_{CH}$ | $d_{1/2}$ | d |
| 21 | 16.78 | q | 16.53 | q | 128 | | 66 |
| 16 | 18.88 | q | 19.16 | q | 128 | | 16 |
| 4 | 27.07 | t | 27.70 | t | 131 | | 4 |
| 18 | 36.83 | t | 35.88 | tt | 131<br>2 | | 47<br>12 |
| 2 | 40.18 | t | 40.44 | t | 129 | | e |
| OMe | - | - | 51.83 | q | 149 | | 54 |
| 17 | 61.37 | d | 61.95 | d | 161 | | 106 |
| 3 | 63.01 | d | 63.16 | dt | 143<br>4 | | 73 |
| 15 | 66.45 | d | 67.53 | bd | 150 | | 96 |
| 19 | 70.53 | d | 70.87 | d | 152 | | 68 |
| 21 | 71.76 | d | 72.72 | dt | 152<br>6 | | 57 |
| 20 | 79.88[f] | s | 80.54[f] | bs | | 14 | |
| 7 | 109.99[f] | s | 110.15[f] | bs | | 15 | |
| 12 | 110.31[f] | s | 110.40[f] | bs | | | |
| 5 | 137.76[g] | s | 136.32[g] | bs | | 25 | |
| 14 | 140.15 | s | 140.32 | bs | | 20 | e |
| 9 | 140.38[g] | s | 142.23[g] | bs | | 18 | |
| 10 | 144.82[g] | s | 144.67[g] | bs | | 15 | |
| 8 | 158.40[h] | s | 162.88[h] | s | | 9 | |
| 11 | 164.54 | s | 168.44[h] | s | | 8 | |
| 1 | 171.87[i] | s | 170.88[i] | m | | 20 | |
| 6 | 177.54[i] | s | 175.11[i] | s | | | |
| 8 | 178.19[i] | s | 175.18[i] | s | | | |

[a] off resonance multiplicity; [b] undecoupled spectrum multiplicity; [c] undecoupled spectrum half-width; [d] selective decoupling at 2.66 ppm downfield from $^1H$ TMS signal; [e] decoupled signal; [f,g,h,i] these assignments might be reversed.

reversible assignments were based on chemical shift values.[9]

*Quinizarin derived compounds* Zgg **5**, *and* Zg **6**. The extensive column and preparative TLC of the crude granaticin preparation give two red pigments Zgg and Zg† in the yield of about 1% each. The analytical and mass spectral data indicated the formula $C_{22}H_{16}O_8$ and $C_{22}H_{18}O_8$ for Zgg and Zg respectively. The substituted quinizarin chrompohore in both compounds was easily recognized by their UV spectra (Table 2) and was supported by the presence of chelated CO band in IR spectrum (1620 $cm^{-1}$) and two signals of chelated phenol groups in $^1H$ NMR spectrum (Table 3). For both compounds IR spectrum showed also the γ-lactone band (1790 $cm^{-1}$). In the case of Zgg an additional CO band (1700 $cm^{-1}$) was also apparent, which correspond to the aromatic acetyl group as was shown by $^1H$ NMR. On the other hand in the $^1H$ NMR spectrum of Zg pigment the signal of COMe was replaced by the $AX_3$ system of $CH(OH)CH_3$ group. The presence of the latter was additionally confirmed by the spectrum of Zg triacetate **7** (Table 3). The upper field part of spectra of both pigmants are nearly identical and resemble that of "dihydropyran - γ - lactone" fragment of granaticin **1**. The spectra showed also three proton aromatic resonance, which in the case of Zgg formed a clear AMX system of adjacent protons. The presence of 5-acetyl quinizarin, as chromophore of Zgg pigment, was confirmed by comparison of spectral data with those of the former (Tables 2 and 3). Therefore pigments Zgg and Zg should have structures **5** and **6** respectively, and their relation was confirmed by the Jones oxidation of Zg to Zgg. The choice of C-20 position for the substituent was based mainly on the structural analogy with granaticin **1** since pigment Zgg is formally bisanhydrogranaticin. The small deshielding effect of H-13 and $CH_3$-14, in the case of

†These abbreviations correspond to Polish "yellow-upper-upper", and "yellow-upper" spot.

Table 2. UV spectral data $\lambda_{max}$ nm (1 g ε) of anthraquinones Zgg **5**, Zg **6**, quinizarin and 5-acetylquinizarin **41**

| Quinizarin | 41 | | 5 | | 6 | |
|---|---|---|---|---|---|---|
| EtOH | EtOH/HCl | EtOH/NaOH | EtOH/HCl | EtOH/NaOH | EtOH/HCl | EtOH/NaOH |
| | 228 (4.29) | | 228 (4.39) | | 228 (4.40) | 231 (4.39) |
| 248 (4.43) | 249 (4.45) | 250[i] (4.40) | 252 (4.54) | 253[i] (4.39) | 254 (4.54) | 256 (4.52) |
| 254 (4.26) | | 256 (4.41) | | 258 (4.40) | | |
| 279 (3.95) | 280 (3.99) | | 282 (3.98) | | 285 (3.93) | |
| 452[i] (3.87) | 463[i] (3.88) | | | | 465 (4.01) | |
| 480 (3.91) | 483 (3.92) | | 483 (3.99) | | 485 (4.01) | |
| 500 (3.76) | 515 (3.66) | | 515[i] (3.81) | | 515[i] (3.96) | |
| 512 (3.67) | | | | | | |
| | | 565 (4.13) | | 566 (4.11) | | 555 (4.08) |
| | | 602 (4.18) | | 603 (4.17) | | 595 (4.07) |

[i] inflection.

Table 3. $^1$H NMR spectral data ($\delta$, J Hz) of anthraquinones Zgg **5**, Zg **6**, Zg triacetate **7** and 5-acetylquinizarin **41**

| | 5 | | 41 | | 6 | | 7 |
|---|---|---|---|---|---|---|---|
| | TFA | $CDCl_3$ | TFA | $CDCl_3$ | TFA | $CDCl_3$ | $CDCl_3$ |
| 2-$H_2$ | 3.33 dd (19, 4) | 3.07 dd (17, 3.5) | | | 3.38 dd (19, 4) | 3.06 dd (17, 4) | 2.94 dd (18, 4) |
| | 3.06 bd (19) | 2.72 bd (17) | | | 3.05 bd (19) | 2.75 bd (17) | 2.64 bd (18) |
| 3-H | 5.08 t (3) | 4.80 t (3.5) | | | 5.08 t (3) | 4.77 t (3.5) | 4.75 t (3.5) |
| 4-H | 5.77 d (2.7) | 5.42 d (2.7) | | | 5.74 d (2.8) | 5.42 d (2.8) | 5.22 d (3) |
| 15-H | 5.45 q (6.7) | 5.24 q (6.7) | | | 5.40 q (6.8) | 5.25 q (6.7) | 5.15 q (6.7) |
| 16-$H_3$ | 1.72 d (6.7) | 1.56 d (6.7) | | | 1.68 d (6.8) | 1.54 d (6.7) | 1.50 d (6.7) |
| 17-H | 8.50 bd (7.7) | 8.37 dd (7.5, 1) | 8.55 dd[a] (7.7, 2) | 8.42 dd[a] (7.3, 2) | 8.34 dd (7.7, 2) | (8.22) | 8.07 dd (7.0, 2) |
| 18-H | 8.02 t (7.7) | 7.89 t (7.5) | 8.02 t[b] (7.7) | 7.88 t[b] (7.3) | 7.87 t (7.7) | 7.72 dd | 7.70 t (7.5) |
| 19-H | 7.70 bd (7.7) | 7.54 dd (7.5, 1) | 7.70 dd[c] (7.7, 2) | 7.55 dd[c] (7.3, 2) | 8.22 dd (7.7, 2) | (8.22) | 7.87 dd (8, 2) |
| | | | 7.45 s[d] | 7.32 s[d] | | | |
| 21-H | | | | | 6.15 q (6.3) | 5.97 q (6.3) | 6.85 q (6.3) |
| 22- | 2.80 s | 2.56 s | 2.80 s | 2.58 s | 1.77 d (6.3) | 1.52 d (6.3) | 1.58 d (6.3) |
| OH | | 12.62 s 13.19 s | | 12.35 bs 12.72 s | | 13.03 s 13.22 s | |
| Ac | | | | | | | 2.47 s 2.47 s 2.06 s |

[a,b,c,d] according to anthraquinone numbering H-8, H-7, H-6 and $H_2$-2,3 resp.

**5**, presumably due to the CO group anizotropy might be taken as a further indication of their relative location.

The trace amount of two other orange pigments (Zdd and Zd, having lower $R_f$ value comparing to **1**) was also detected among pigments produced by Str. WR-141. They were isolated as a mixture and according to its IR spectrum (1730, 1700, 1620 and 1580 $cm^{-1}$) they are presumed to be dihydroanalogs of **5** and **6** with the opened $\gamma$-lactone.

*The synthesis of* 1 - *methyl* - 3 - *carbomethoxymethyl* - 1,3,4,5,10 - *pentahydro* - 5,10 - *dioxonaphto* - (2,3-c) - *pyran* cis **26** *and* trans **27**. The aim of the synthesis described below was twofold, first to obtain model compounds for reliable $^1$H NMR data comparison of *cis* and *trans* isomers, analogous to those obtained for eleutherin and isoeleutherin,[10] second to elaborate a simple approach to the dihydropyran fragment of granaticin and related compounds, in particular more simple quinones kalafungin,[11] actinorhodin,[6] and recently described nanaomycin A,[7] B,[7] C[12] and D.[8] Our synthetic plan was based on similar idea as used for the synthesis of eleutherins,[13] i.e. the introduction of C-2 naphthalene substituent by the allylic ether rearrangement. The dihydropyran fragment was built up on the simplest starting substrate, 1 - hydroxy - 2 - allylnaphtalene **8**, protected in the form of benzyl ether **14**.† The epoxidation with pertrifluroacetic acid gave good yield of epoxide **15**, in which spliting of the oxirane ring furnished the expected nitrile **16** in an excelent yield. The protection of the OH group was necessary because epoxide **9** or its acetate **10** on treatment with cyanide or any base formed cyclic ether **11**. The regioselectivity opposite to normal one for the opening of the terminal epoxide by an internal phenolate is highly favored. Also in the case of chlorhydrine **13** the reaction with potasium cyanide formed only ether **11** with conceivable participation of terminal epoxide.

The nitrile **16** is formed by the normal opening of the epoxide ring from the less substituted terminal. Its structure was confirmed by the $^1$H NMR spectrum showing quintet of CHOH group at 3.91, shifted downfield in the spectrum of its acetate **17** to 5.25. Both $^1$H NMR spectrum and TLC of the crude hydroxynitrile did not show the presence of an appreciable amount of isomeric compound with the primary OH group. The hydrolysis of hydroxynitrile **16** with alkaly gave hydroxy acid **18**, and unsaturated acid **20** as a side product, which were separated as methyl esters **19** and **21** by column chromatography. The removal of benzylic ether by hydrogenolysis resulted in the formation of naphthol **22**, which subjected to the Fremy's salt oxidation yielded quinone **23**. Attempts of the direct cyclization of the latter with acetaldehyde and phosphoric acid, according to the procedure used for eleutherin synthesis,[13] gave a complicated mixture. The clean cyclization was effected when the quinone **23** was reduced in two phase system ether/HCl aq with zinc powder, and the resulting hydroquinone **24** without purification was subsequently treated with an excess of acetaldehyde in ethyl ether in the presence of hydrochloric acid. After short reaction time a good yield of *cis* hydroquinone **25** was obtained, whereas due to the air oxidation, longer reaction time led to *cis* quinone **26** along with only trace of more thermodynamicaly stable *trans* quinone **27**. Compound **26**

†Attempted etherification with $CH_2N_2$ led to coupling.[14]

was isomerized to **27** by dissolution in sulfuric acid similarly as was done for eleutherin isomerization.[13]

The relative configuration of the dihydropyran ring in quinones **26** and **27** follows from the analysis of their $^1$H NMR spectra (Table 4), in particular the long range coupling constants between allylic protons. For both isomers large $J_{3a,4a}$ values indicate the equatorial position of C-3 substituent, therefore relatively high homoallylic couplings for H-15 in the spectrum of **26** unequivocaly show its pseudoaxial position and consequently *cis* configuration of the dihydropyran substituents. These values are comparable to those found for eleutherin (3.5 and 2.9 Hz).[10] On the other hand smaller values of H-15 homoallylic couplings observed for the second isomer **27** prove its *trans* configuration, these values are exactly as reported for isoeleutherin.[10] The differential solvent shift $\delta_{CDCl_3}-\delta_{C_6H_6}$ for the 16 Me group signal is close to the observed for eleutherin (0.10 ppm)[15] in the case of **27**, but differs for *cis* isomer **26** and eleutherin (0.02 and −0.09 ppm resp.).

The foregoing sequence of reactions is directly applicable to the total synthesis of nanaomycin A, and this work is now in progress.

*Synthesis of 5-acetylquinizarin* **41** *and 1-hydroxy-5-acetyl- and 1-hydroxy-8-acetylanthraquinones* **34**, and **36**. 5-Acetyquinizarin **41** was synthesized in order to confirm on spectral ground its existence as the chromophore of the quinone Zgg **5**. Two isomeric quinones **34** and **36** were designed as starting substrates for the synthesis of both possible isomers of Zgg on the route described for quinone **27**.

Quinones **34** and **36** were obtained by two independent ways from 5-acetylnaphtoquinone-1,4 (to our knowledge the compound not described so far in literature). Its direct condensation with 3-hydroxy-α-pyrone (isopyromucic acid) formed the mixture of both desired anthraquinones as result of nonregioselective diene reaction with subsequent carbon dioxide elimination.†

Due to difficulties in separation and unambigous structure assignment we looked for the clean and selective way. This was achieved by the use of Diels-Alder condensation of 5-acetylnaphtoquinone-1,4 **28** with methoxycyclohexadiene-1,3 according to the known procedure.[16] This condensation yielded two possible adducts **29** and **30**, however, their separation after transformation to hydroquinones **31** and **32** was simple, and the spectral properties led unambigously to structure assignment. For the acetone insoluble, less polar product the IR spectrum in $CCl_4$ indicated an intramolecular H–bond for both OH groups (3378 cm$^{-1}$), therefore pointing to "1,5" structure **31**. The second product, purified by recrystallization from alcohol, showed the presence of the free and bonded OH group (3617 and 3360 cm$^{-1}$) and was identified as "1,8" isomer **32**, other spectral data were consistent with assigned structures. Both hydroquinones **31** and **32** were oxidized with silver oxide in boiling xylene with the concomitant retrodiene elimination of the ethylene bridge to give anthraquinones **33** and **35**. The usual air oxidation in alkaline medium was not applicable in this case since products of the the acetyl group condensation were formed. The additional proof for the relative orientation of the substituents was obtained from their $^1$H NMR and IR spectra. For "1,5" isomer **33** the chemical shift of OMe group was found to be identical with that of 1-methoxyanthraquinone-9,10, whereas in the case of "1,8" isomer **35** this signal was shifted upfield by 0.04 ppm due to the shielding effect of acetyl group (spectra were measured in the same molar concentration). The IR data comparison of **33–36** with mono and disubstituted anthraquinones (Table 5) allowed for the assignment of the characteristic for 1,5 and 1,8 substitution C–H out-of-plane vibrations. Diacetyl anthraquinones **37** and **38**, used for that comparison, were obtained from appropriate antracene derivatives by the known method.[18] The $^1$H NMR data of these anthracenes unambigously confirmed substitution pattern, corroborating previous correlations (two signals of H-9 and H-10 for 1,8 and one for 1,5-isomer).

Anthraquinone **36** was transformed by the normal procedure, i.e. nitration to **39**, followed by reduction with $Na_2S$ to **40**, and acid hydrolysis to 5-acetyl-quinizarin **41**. Its spectral comparison with quinone Zgg is given in Tables 2 and 3.

†Recently the obvious dienophilic reactivity of isopyromucic acid was exemplified in literature.[17]

Table 4. $^1$H NMR data of dihydropyran fragment of dihydrogranaticin **2**, dihydrogranaticin methyl ester **3** and model naphtoquinones **26** and **27**

| | 2 | 3 | 26 | 27 |
|---|---|---|---|---|
| | TFA | $CDCl_3$ | $CDCl_3$ | $CDCl_3$ |
| 2-$H_2$ | 2.98 d (6) | 2.66 d (6.2) | 2.62 dd[a] (4.0, 2.9) | 2.63 d (6.5) |
| 3a-H | 4.67 m | 4.30 m | 3.90 m | 4.29 m |
| 4a'-H | 2.64[b] (19, 2) | 2.34 ddd (19, 10, 2) | 2.30 ddd (19.5, 10.5, 3.8) | 2.35 ddd (19.0, 11.0, 2) |
| 4e'-H | 3.1 | 2.99 dd[c] (19, 3) | 2.82 dt (19.5, 2.5) | 2.79 dd[c] (19.0, 4) |
| 15-H | 5.32 bq (6.5) | 5.02 bq (6.5) | 4.82 m | 4.95 bq (6.9) |
| 16-$H_3$ | 1.73 d (6.5) | 1.57 d (6.5) | 1.52 d (6.8) | 1.54 d (6.9) |
| OMe | | 3.84 s | 3.72 s | 3.72 s |

[a] center lines position of AB part of ABX system; [b] overlapped, [c] additional coupling ~1 Hz.

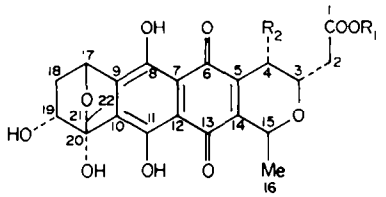
Table 5. IR spectral data (out-of-plane C-H vibrations) for 1,5- and 1,8-disubstituted and 1-monosubstituted anthraquinones

| substituents | | $\nu_{max}$ (KBr) $cm^{-1}$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1-acetyl | | | | | | | | 702 s | | |
| 1-hydroxy | | | | | 770 s | | | 700 s | | |
| 1-methoxy | | | | | | | | 700 s | | |
| 1,5-diacetyl | 37 | | 820 s | | | | | 705 s | | |
| 1-hydroxy-5-acetyl | 34 | | 822 m | | 775 s | | | 702 s | | |
| 1-methoxy-5-acetyl | 33 | | 820 s | | | | | 705 s | | |
| 1,8-diacetyl | 38 | 850 s | | | | 740 m | | | | 670 m |
| 1-hydroxy-8-acetyl | 36 | 845 s | | | 780 s | 740 s | | | | 670 m |
| 1-methoxy-8-acetyl | 35 | 850 m | | | | 740 s | | | | 670 m |

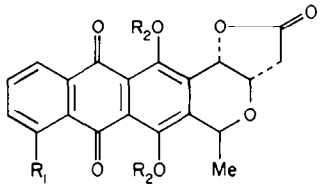
## DISCUSSION

The right hand fragment of granaticin **1**, dihydrogranaticin **2**, and anthraquinones **5** and **6** molecules, i.e. the substituted 3,4 - dihydro - 1H - naphto - (2,3-c) - pyran (benzoisochromane) is encountered in few other quinone antibiotics with juglone or naphthazarin chromophores as actinorhodin,[6] kalafungin[11] and nanaomycins A-D.[7,8,12] For the latter compounds the structural analogy is evidently due to biogenetic reason. $C_{16}$ polyketide chain should operate as a precursor in all cases as it was shown for nanoamycin A.[7]

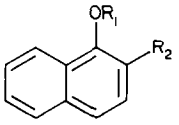
Biogenetic origin of the whole molecule, in cases of **1**, **2**, **5** and **6** is not so obvious. Our speculative assumption is that the analogous fragment of all these quinones is derived from the same polyketide, but the additional ring C atoms are of sugar origin, dideoxysugar is connected in later step to form C-glycoside **42**, the hypothetic precursor analogous to the known compound aquayamcine.[19] Further cyclization of **42** should form dihydrogranaticin **2**, which one is evidently the direct precursor of **1**, or on alternate route should form quinizarin derivatives **5** and **6**.



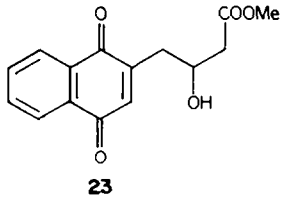
**1** $R_1$——$R_2$
**2** —H —H
**3** —Me —H
**4** —H —OH



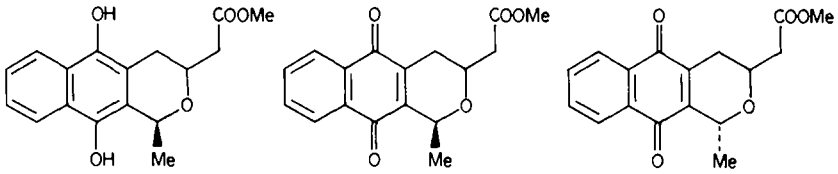
**5** $R_1$—$COCH_3$ $R_2$—H
**6** —$CHOHCH_3$ —H
**7** —$CHOAcCH_3$ —Ac

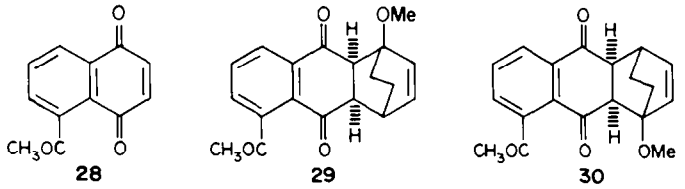


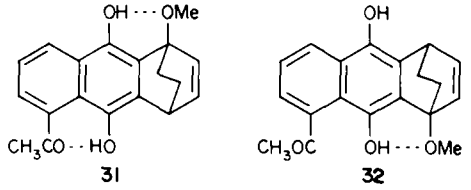
| | $R_1$ | $R_2$ |
|---|---|---|
| **8** | —H | —$CH_2$—CH=$CH_2$ |
| **9** | —H | —$CH_2$—CH—$CH_2$ (O) |
| **10** | —Ac | —$CH_2$—CH—$CH_2$ (O) |
| **11** | —$CH(CH_2OH)$—$CH_2$— | |
| **12** | —$CH(CH_2OAc)$—$CH_2$— | |
| **13** | —Ac | —$CH_2$—$CHOHCH_2Cl$ |
| **14** | —$CH_2C_6H_5$ | —$CH_2$—CH=$CH_2$ |
| **15** | —$CH_2C_6H_5$ | —$CH_2$—CH—$CH_2$ (O) |
| **16** | —$CH_2C_6H_5$ | —$CH_2$—$CHOHCH_2CN$ |
| **17** | —$CH_2C_6H_5$ | —$CH_2$—$CHOAcCH_2CN$ |
| **18** | —$CH_2C_6H_5$ | —$CH_2$—$CHOHCH_2COOH$ |
| **19** | —$CH_2C_6H_5$ | —$CH_2$—$CHOHCH_2COOMe$ |
| **20** | —$CH_2C_6H_5$ | —CH=$CHCH_2COOH$ |
| **21** | —$CH_2C_6H_5$ | —CH'=$CHCH_2COOMe$ |
| **22** | —H | —$CH_2$—$CHOHCH_2COOMe$ |

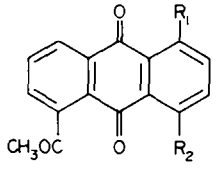


**23** **24**

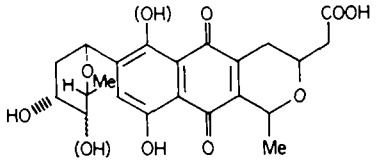



| | $R_1$ | $R_2$ |
|---|---|---|
| **33** | $-OCH_3$ | —H |
| **34** | —OH | —H |
| **35** | —H | $-OCH_3$ |
| **36** | —H | —OH |
| **37** | $-COCH_3$ | —H |
| **38** | —H | $-COCH_3$ |
| **39** | $-NO_2$ | —OH |
| **40** | $-NH_2$ | —OH |
| **41** | —OH | —OH |




**42**

## EXPERIMENTAL

*Dihydrogranaticin* **2**. The crude preparation of granaticin produced by *Streptomyces thermoviolaceus* subsp. pigens var. WR-141 was separated by means of preparative TLC on silicagel impregnated with 1% of $KH_2PO_4$ with $CHCl_3$:MeOH 9:1 as solvent, to give dihydrogranaticin **2**, m.p. 191° (from EtOH). Its yield depended on the growth phase being higher than that of **1** in early stages. On the end of growth, when pH falls down, granaticin **1** was hydrolysed to **4**. $R_f$ values in the above mentioned system were **1** 0.50, **2** 0.35 and **4** 0.10.

Granaticin **1**, in EtOAc, was hydrogenated over Pt to give yellow soln with the $H_2$ consumption 2.0–2.2 moles/mol **1**. On air oxidation red colour was restored, and on repeated hydrogenation one mole of $H_2$ was absorbed. The single product **2** was in all respect identical with the described above.

$\lambda_{max}$ (EtOH/HCl) 212, 289, 495, 521, 559 infl., $\lambda_{max}$ (EtOH/NaOH) 279, 311, 588, 625, $\lambda_{max}$ ($CHCl_3$/TFA) 286 (3.89), 469 (3.90), 516 (3.91) nm (1 g $\epsilon$). $\nu_{max}$ (KBr) 1725, 1610, 1570 $cm^{-1}$. *m/e* (70 eV): 446 (1), 414 (7), 410 (53), 402 (8), 400 (12), 396 (15), 392 (6), 384 (100), 369 (13), 366 (20), ... 335 (16), 323 (27), 309 (35), 295 (17), ... 44 (66), 43 (90). (Found: C, 59.57; H, 5.69. Calc. for $C_{22}H_{22}O_{10}$: C, 59.19; H, 5.11%).

*Dihydrogranaticin methyl ester* **3**. Dihydrogranaticin **2** was dissolved in MeOH cont. 1% of HCl. The product **3** was formed quantitatively (TLC), m.p. 191°, from EtOH. $\lambda_{max}$ (EtOH) 287, 495, 521 nm: $\nu_{max}$ (KBr) 1757, 1620 $cm^{-1}$. (Found: C, 59.6; H, 5.7. Calc. for $C_{23}H_{24}O_{10}$: C, 59.99, H, 5.38%).

*Granaticin* **1** *from dihydrogranaticin* **2**. Dihydrogranaticin **2** (39 mg) was absorbed on the start line of the preparative TLC plate (20, 20, 0.1 cm silicagel impregnated with $KH_2PO_4$). The development after one week yielded **1** (4 mg) identical with the original sample by $R_f$ value and IR comparison. In the analogous experiment, after 3 months of oxidation, up to 50% of **1** was formed along with polar deep brown product.

*Anthraquinones* **Zgg 5** *and* **Zg 6**. From the crude preparation of granaticin (2.0 g) less polar pigments were separated by column chromatography on silicagel containing 1% of $KH_2PO_4$ with $CHCl_3$:AcOH 100:1 and increasing concentration of EtOH. The final purification was achieved by the multiple TLC as described before. $R_f$ values were **5** 0.80 and **6** 0.65. **Zgg 5** was purified by recrystallization from acetone (24 mg) m.p.230–234°; $\nu_{max}$ (KBr) 1790, 1705, 1640, 1580 $cm^{-1}$; *m/e*: 408 (100), 393 (51), 365 (29), 364 (27), 362 (12), 349 (39), 347 (22), 321 (19), ... 44 (72), 43 (85). (Found: C, 65.3; H, 5.44. Calc. for $C_{22}H_{16}O_8$: C, 64.70; H, 3.95%).**Zg 6** was purified by crystallization from acetone (27 mg) m.p. 241–248°; $\nu_{max}$ (KBr) 1790, 1640, 1580 $cm^{-1}$; *m/e*: 410 (84), 392 (98), 377 (12), 349 (65), 333 (61), 305 (27), .. 43 (100); (Found: C, 64.75; H, 4.88. Calc. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42%). The small sample of **6** was oxidized quantitatively to **5** by Jones reagent in acetone ($R_f$ value, IR comparison). The following concentrations ($\mu$g/ml) were found to inhibit growth of *Bacillus cereus*: **1** 0.04, **2** 0.3, **3** 0.3, **4** 1.0, **5** 1.3 and **6** 5.

*2-Allyl-1-hydroxynaphthalene* **8**. The thermal rearragement of 1-allyoxynaphthalene (neat, 130°) yielded **8** as a single product;

m.p. 34–36° (from petr. ether), b.p. 114–119°/0.5, $d_4^{16}$ 1.0880, $[n]_D^{16}$ 1.6269; acetate b.p. 200–210/30 (corrected analytical data and expected spectral properties were obtained).

2 - (2',3' - *Epoxypropyl*) - 1 - *acetoxynaphthalene* **10**. 2-Allyl-1-acetoxynaphtalene (12 g) was dissolved in peracetic acid prepared from $Ac_2O$ and 30% $H_2O_2$, and left for 4 days at room temp. Dilution with water, petrol ether extraction and chromatography on silicagel column regenerated substrate (5.6 g) and gave epoxide **10** (4.4 g) m.p. 68–76° (from EtOH-water); $\nu_{max}$ 1750, 1600, 1380, 1210 $cm^{-1}$. 2 - hydroxymethyl - 2,3 - dihydro - naphto - (1,2-b) - furan **11**. The epoxide **10** treated with an excess of NaCN in EtOH-water yielded as the sole produce **11** as oil; $\nu_{max}$ 3400, 1600, 1570, 1050 $cm^{-1}$; $\delta$ 3.56 d J = 5.5 Hz ($CH_2OH$), acetate **12**: 4.15 d ($CH_2$–OAc). The same product was obtained on analogous treatment with KOH and $Na_2CO_3$, or by transformation to chlorohydrine **13** (with HCl) and further cyanide treatment.

2 - *Allyl* - 1 - *benzyloxynaphthalene* **14**. 2 - Allyl - 1 - hydroxynaththalene **8** (4.25 g) was refluxed for 2 hr in acetone (50 ml) with benzyl chloride (4 g) and an excess of $K_2CO_3$. After filtration solvent was removed and the product washed with conc NaOH aq. Distillation (160°/0.4) gave **14** (4.4 g); $\nu_{max}$ 3100, 1640, 1600, 1580, 1080 $cm^{-1}$; $\delta$ ($CCl_4$): 4.88 s ($CH_2C_6H_5$) complex allyl and aromatic protons signals.

2 - (2',3' - *Epoxypropyl*) - 1 - *benzyoxynaphthalene* **15**. The benzyl ether **14** (16.9 g) in $CH_2Cl_2$ (150 ml), in the presence of a large excess of $Na_2CO_3$ was treated with the solution of pertrifluoracetic acid prepared from trifluoracetic acid anhydride (18.5 ml) and 80% $H_2O_2$ (4.5 ml). After 0.5 hr reflux time the salts were filtered off and the mixture chromatographed on silicagel column to give pure epoxide **15** (9.6 g) as an oil, also nonreacted ether **14** (4.9 g) was regenerated. $\nu_{max}$ 1600, 1585, 1505, 820, 750, 730, 690 $cm^{-1}$; $\delta$ ($CCl_4$): 2.3–3.1 m (3'-$H_2$, 2'-H), 2.97 bs (1'-$H_2$), 4.98 s ($CH_2C_6H_5$), 7.1–8.1 (11 H). (Found: C, 82.13; H, 6.15. Calc. for $C_{20}H_{18}O_2$: C, 82.73, H, 6.25%).

2 - (3' - *Cyano* - 2' - *hydroxypropyl*) - 1 - *benzyloxynaphthalene* **16**. The epoxide **15** (9.6 g) in EtOH (300 ml) was treated with the soln of KCN (10 g) in water (60 ml). After 3 days at room temp the solvent was evaporated, the residue washed with water and chromatographed on silicagel column. Pure **16** (8.4 g) was obtained as an oil; $\nu_{max}$ 3450, 2240, 1600, 1570 $cm^{-1}$; $\delta$ ($CDCl_3$) 2.37 d J = 5.5 Hz (3'-$H_2$), 2.95 d J = 6.0 Hz (1'-$H_2$), 4.15 quintet J = 6.0 Hz (2'-H), 5.02 s ($CH_2C_6H_5$), 7.2–8.2 (11 H). (Found: C, 79.56; H, 6.16; N, 4.48. Calc. for $C_{21}H_{19}O_2N$: C, 79.47; H, 6.03, N, 4.41%). Acetate **17**, $\delta$ ($CDCl_3$): 2.02 s (AcO), 2.52 center of an AB part of ABX system $J_{AB}$ 17 Hz, $J_{AX} = J_{BX} = 5.5$ Hz (3'-$H_2$), 3.10 d J = 7 Hz (1'-$H_2$), 5.05 s ($CH_2C_6H_5$), 5.25 broad quintet (2'-H), 7.2–8.2 (11 H).

2 - (3' - *Carboxymethyl* - 2' - *hydroxypropyl*) - 1 - *benzyloxynaphthalene* **19**. Cyanide **16** (6.0 g) was refluxed with 2N NaOH aq (100 ml) for 20 hr. Products recovered by ether extraction of the acidified soln were treated with an excess of etheral diazomethane, and separated on silicagel column to give **19** (3.45 g) as an oil; $\nu_{max}$ 3500, 1730, 1575, 815, 750, 735, 690, 680 $cm^{-1}$; $\delta$ ($CCl_4$): 2.31 d J = 6.5 Hz (3'-$H_2$), 2.87 d J = 6.0 Hz (1'-$H_2$), 3.24 bs (OH), 3.45 s (OMe), 4.21 quintet J = 6.0 Hz (2'-H), 4.92 s ($CH_2C_6H_5$). (Found: C, 75.25; H, 6.45. Calc. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.85%).

Ester **21** was obtained as a by product (2.22 g), $\nu_{max}$ 1730, 970, 805, 750, 720, 690 $cm^{-1}$; $\delta$ ($CCl_4$): 3.52 s (OMe), 4.84 s ($CH_2C_6H_5$), 6.84, 6.16, 3.02 $ABX_2$ system of 1'-H, 2'-H and 3'-$H_2$ resp. $J_{1'2'} = 16$ Hz, $J_{2'3'} = 6.7$ Hz, $J_{1'3'} = 0$ Hz. (Found: C, 78.81; H, 6.07. Calc. for $C_{22}H_{22}O_3$: C, 79.01; H 6.63%).

2 - (3' - *Carboxymethyl* - 2' - *hydroxypropyl*) - 1 - *hydroxynaphthalene* **22**. The methyl ester **19** (3.05 g) in MeOH (50 ml) was hydrogenated over 10% Pd/C (2 g) to give pure **22** (1.94 g); $\nu_{max}$ 3450, 3300, 1730, 1630, 1610, 1580, 815, 763 $cm^{-1}$.

2 - (3' - *Carboxymethyl* - 2' - *hydroxypropyl*) - *naphthoquinone* - 1,4 **23**. The phenol **22** (1.94 g) was dissolved in ether and shaken with Fremy's salt (potasium nitrozodisulphonate, prepared according to,[20] 6.0 g) in phosphate buffer pH 11.1 (0.1 M, 400 ml). After ether extraction, **23** (1.91 g) was crystallized from ether-petroleum ether m.p. 60–62°; $\nu_{max}$ (Nujol) 3500, 1730, 1660, 1360, 1590, 795, 787, 780, 735, 710 $cm^{-1}$; $\lambda_{max}$ (MeOH): 245, 251, 262, 334 nm; ($CDCl_3$): 3.0–2.4 m (3'-$H_2$ and 1'-$H_2$), 3.25 bs (OH), 3.71 s (OMe), 4.31 m (2'-H), 6.95 t J = 1 Hz (3-H). (Found: C, 65.50; H, 5.24. Calc. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14%).

cis - 1 - *Methyl* - 3 - *carbomethoxymethyl* - 5,10 - *dihydroxy* - 1,3,4 - *trihydronaphtho* - (2,3-c) - *pyran* **25**. The naphthoquinone **23** (0.63 g) in ethyl ether (100 ml) was reduced with an excess on zinc powder and conc HCl aq (4 ml). The ether phase was separated and treated with acetaldehyde (11 ml). After 1 hr the mixture washed with water, evaporated and crystallized from ether–hexane to give **25** (0.425 g) m.p. 146–151°; $\nu_{max}$ (Nujol) 3400, 1725, 1635, 1600, 775, 750 $cm^{-1}$; $\lambda_{max}$ (MeOH): 211, 241, 310, 318, 333 nm; $\delta$ ($CDCl_3$): 1.61 d J = 5 Hz (1-Me) 2.2–3.5 m (4H), 3.90 m (3-H), 4.67 q J = 5 Hz (1-H), 6.40 (2 OH) br, 7.3–8.2 m (4H). Chromatographic separation of the mother liquor yielded **26** (94 mg) and **27** (10 mg) identical with compounds described later.

cis - 1 - *Methyl* - 3 - *carbomethoxymethyl* - 5,10 - *dioxo* - 1,3,4,5,10 - *pentahydronaphtho* - (2,3-c) - *pyran* **26**. The cyclization of **23** (0.212 g) according the above procedure was stopped after 20 hr giving **26** (52 mg) purified by recrystallization from MeOH (3-times) m.p. 146-149°; $\lambda_{max}$ (EtOH): 210 (4.30), 246 (4.35), 274 (4.00), 332 (3.52), 435 (0.72). (Found: C, 68.01; H, 5.39. Calc. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37).

trans - 1 - *Methyl* - 3 - *carbomethoxymethyl* - 5,10 - *dioxo* - 1,3,4,5,10 - *pentahydronaphtho* - (2.3-c) - *pyran* **27**. The naphthoquinone **26** (41 mg) was dissolved in $H_2SO_4$ (2 ml), and after 2 hr the product was precipitated with the addition of ice. Purification by recrystallization from MeOH yielded **27** (25 mg) m.p. 185–187°; $\nu_{max}$ (KBr) 1740, 1660, 1620, 1595 $cm^{-1}$; $\lambda_{max}$ (EtOH) 245 (4.22), 267 (4.11), 332 (3.52), 435 (2.72) nm (1 g $\epsilon$). (Found: C, 67.76; H, 5.50, (compare above)).

5 - *Acetylnaphthoquinone* - 1,4 **28**. 1-acetylnaphthalene (80%, 50 ml) in AcOH (1 l) was treated with the soln of $CrO_3$ (200 g) in water (200 ml). The crude product recovered by dilution with water and ether extraction was crystallized from MeOH to give **28** (8.0 g) m.p. 134–139.5°. Additional crystallization improved the m.p. to 140–141.5°, $\nu_{max}$ (Nujol) 1700, 1660, 1615, 1585, 765 $cm^{-1}$; $\lambda_{max}$ ($C_7H_{16}$) 198 (4.27), 245 (4.30), 332 (3.38); $\delta$ ($CDCl_3$): 2.50 s (Me), 6.95 s (2, 3 $H_2$), 7.44 dd J = 7.3 and 2.0 Hz (6-H), 7.75 t J = 7.3 Hz (7-H), 8.10 dd J = 7.3 and 2.0 Hz (8-H).

*Condensation of* 5-*acetylnaphthoquinone* **28** *with* 3-*hydroxy* - $\alpha$ - *pyrone*. Quinone **28** (57.4 mg) and 3-hydroxy-$\alpha$-pyrone (60 mg) prepared according to the original method,[21]† was refluxed for 48 hr in xylene (10 ml). Chromatography and crystallization from MeOH afforded mixture of **34** and **36** (20 mg) identified by TLC and IR comparison with compounds with described later.

*Condensation of* 5 - *acetyl* - *naphthoquinone* **28** *with methoxycyclohexadiene*-1,3. Quinone **28** (7.5 g) and methoxycyclohexadiene-1,3 (70%, 10 ml),[23] was refluxed in benzene (50 ml) for 15 min. The solvent was evaporated and the residue was crystallized from MeOH to give 3 crops of mixed adducts **29** and **30** (6.9 g, m.p. 135–154°, 3.6 g, m.p. 130–146°, and 0.8 g, m.p. 128–145°); $\nu_{max}$ 1700, 1680, 1570 $cm^{-1}$; $\lambda_{max}$ (EtOH) 227 (4.45) nm (1 g $\epsilon$). (Found: C, 73.84; H, 6.08. Calc. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85%).

1,4 - *Dihydro* - 1,4 - *ethane* - 1 - *methoxy* - 9,10 - *dihydroxy* - 5 - *acethylanthracene* **31** *and* 1,4 - *dihydro* - 1,4 - *ethane* - 1 - *methoxy* - 9,10 - *dihydroxy* - 8 - *acetylanthracene* **32**. The mixture of **29** and **30** (11.3 g) in MeOH (150 ml) was added to the soln of NaOMe (from 4 g of Na and 100 ml of MeOH) under $N_2$. The red soln was acidified with AcOH, diluted with water and extracted with ethyl ether to give the mixture of **31** and **32** (11.2 g). TLC in benzene : ether 5 : 1 showed two spots with $R_f$ 0.37 and 0.20. The mixture was disolved in boiling acetone (250 ml) to give on cooling to −10° **31** (2.73 g) as white crystals m.p. 220–222° (in vac.) $R_f$ 0.37; $\nu_{max}$ (KBr) 3380, 1685, 1645, 1599 $cm^{-1}$; $\nu_{max}$ ($CCl_4$) 3378 $cm^{-1}$; $\lambda_{max}$ (EtOH) 216 (4.36), 254 (4.38), 345 (3.85) nm (1 g $\epsilon$). (Found: C, 73.71; H, 6.07. Calc. for $C_{19}H_{18}O_4$; C, 73.53; H, 5.85%). The filtrate of the above crystallization was evaporated and recrystallized from EtOH to give **32** (4.85 g) as yellow crystals, m.p. 218–220° (in vac.) $R_f$ 0.20; $\nu_{max}$ (KBr) 3500, 3350, 1690, 1640, 1595 $cm^{-1}$; $\nu_{max}$ ($CCl_4$) 3617, 3360 $cm^{-1}$. (Found: C, 73.40; H, 6.05% (compare above)).

†The original method [21] was reported to fail.[22]

1 - *Methoxy* - 5 - *acetylanthraquinone* **33**. Hydroquinone **31** (2.65 g) was refluxed in xylene (70 ml) with $Ag_2O$ (12 g) for 30 min. The hot soln was filtered to give on cooling yellow **33** (2.30 g), m.p. 187.5–189.5°; $\nu_{max}$ (KBr) 1700, 1670, 1660, 1585, 820, 705 $cm^{-1}$, $\lambda_{max}$ (EtOH) 218 (4.35), 253 (4.44), 333 (3.43), 387 (3.74) nm (1 g $\epsilon$), ($CDCl_3$) 4.025 s (OMe), 2.56 s (COMe). (Found: C, 73.05; H, 4.37. Calc. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32%).

1 - *Methoxy* - 8 - *acetylanthraquinone* **35**. The analogous reaction performed on **32** (4.28 g) yielded yellow **35** (3.79 g), m.p. 221–222.5°; $\nu_{max}$ (KBr) 1697, 1681, 1674, 1592, 1580, 850, 740, 670 $cm^{-1}$; $\lambda_{max}$ (EtOH) 218 (4.27), 253 (4.44), 333 (3.43), 387 (3.74) nm (1 g), $\delta$ ($CDCl_3$) 3.98 s (OMe), 2.58 s (COMe). (Found: C, 73.2; H, 4.22, Calc. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32%).

1 - *Hydroxy* - 5 - *acetylanthraquinone* **34**. Methyl ether **33** (0.24 g) in AcOH (2 ml) and 40% HBr aq (2 ml) was refluxed for 1 hr, dilution with water and crystallization of the ppt from methylcelosolve yielded orange **34** (0.17 g), m.p. 183–186°; $\nu_{max}$ (KBr) 1705, 1669, 1636, 1599, 1575, 822, 775, 702 $cm^{-1}$. (Found: C, 72.24; H, 4.21, Calc. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79%).

1 - *Hydroxy* - 8 - *acetylanthraquinone* **36**. The analogous hydrolysis of **35** (0.22 g) yielded orange **36** (0.18 g), m.p. 196–197°; $\nu_{max}$ (KBr) 1702, 1670, 1633, 1602, 1575, 845, 780, 740, 640 $cm^{-1}$. (Found: C, 72.41; H, 3.97% (compare above)).

5 - *Acetyl* - 1,4 - *dihydroxyanthraquinone* (5 - *acetylquinizarin*) **41**. To the soln of **36** (0.107 g) in $H_2SO_4$ (5 ml) 1N $HNO_3$ in $H_2SO_4$ (0.45 ml) was added. After 30 min, the mixture was poured on ice and the ppt crystallized from methylcelosolve to give crude **39** (0.102 g), $\nu_{max}$ 1700, 1680, 1640, 1580, 1540 $cm^{-1}$, which was refluxed with $Na_2S$ solution to give **40** (0.10 g) $\nu_{max}$ 1690, 1670, 1610–1600, 1585 $cm^{-1}$. This aminoanthraquinone (0.080 g) was heated in $H_2SO_4$ 1:20 at 160° for 24 hr. The product was purified by chromatography on silicagel and sublimation at 220° to give **41** (10 mg); $\nu_{max}$ 1695, 1620, 1565 $cm^{-1}$; *m/e* 282 (60), 267 (100), 264 (5), 256 (6), 240 (3), 239 (3), 236 (2), 211 (6), 183 (7), 155 (4), 127 (7). (Found: C, 68.54; H, 3.55. Calc. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57%).

*Additional Note*: The cyclization of epoxide **9** or **10** to cyclic ether **11** is an example of the favoured 5-*Exo*-*Tet* cyclization process. The alternative one -6-*Enolo*-*Tet* is disfavoured according to *Rule* 1 of J. E. Baldwin (*J. Chem. Soc. Chem. Commun.* 735 (1976)).

## REFERENCES


[1]J. St. Pyrek, M. Mordarski and A. Zamojksi, *Arch. Immun. Therap. Exper.* **17**, 827 (1969).

[2]W. Keller-Schierlein, M. Brufani and S. Barcza, *Helv. Chim. Acta* **51**, 1256 (1968); M. Brufani and M. Dobler, *Ibid.* **51**, 1269 (1968).

[3]R. Corbaz, L. Ettlinger, E. Gaumann, J. Kalvoda, W. Keller-Schierlein, F. Kraddofer, B. K. Manukian, L. Neipp, V. Prelog, P. Reusser and H. Zahner, *Ibid.* **41**, 205 (1957).

[4]T. Krzywy, M. Mordarski, B. Orlowska and A. Tkaczowa, *Arch. Immun. Therap. Exper.* **17**, 54, 63 (1969).

[5]Ghing Jer Chang, H. G. Floss, P. Soong and Ching-te-Chang, *J. Atibiotics Tokyo* **28** 156 (1975).

[6]H. Brockmann, A. Zeeck, Kirsten van der Merwe and W. Muller, *Liebigs Ann*, **698**, 209 (1966).

[7]H. Tanaka, Y. Koyama, J. Awaya, H. Marumo, R. Oiwa, M. Katagiri, T. Nagai and S. Ōmura, *J. Antibiotics Tokyo* **28**, 860 (1975); H. Tanaka, Y. Koyama, T. Nagai, H. Marumo and S. Ōmura, *Ibid.* **28**, 868 (1975).

[8]S. Ōmura, H. Tanaka, Y. Okada and H. Marumo, *J. Chem. Soc. Chem. Commun.* 320 (1976).

[9]A. Arnone, G. Fronza, R. Mondelli and J. St. Pyrek, in prep.

[10]D. W. Cameron, D. G. I. Kingston, N. Sheppard and Lord Todd, *J. Chem. Soc.* 98 (1964),

[11]M. E. Bergy *J. Antibiotics Tokyo* **21**, 454 (1968).

[12]H. Tanaka, H. Marumo, T. Nagai, M. Okada, K. Taniguchi and S. Ōmura, *J. Antibiotics Tokyo* **28**, 925 (1975).

[13]W. Eisenhuth and H. Schmid, *Helv. Chim. Acta* **41**, 2021 (1958).

[14]J. St. Pyrek and O. Achmatowicz, Jr., *Tetrahedron Letters* 2651 (1970).

[15]J. H. Bowie, D. W. Cameron, P. E. Schutz, D. W. Williams and N. S. Bhacca, *Tetrahedron* **22**, 1771 (1966).

[16]A. J. Birch and V. H. Powell, *Tetrahedron Letters* 3467 (1970).

[17]E. J. Corey and A. P. Kozikowski, *Ibid.* 2389 (1975).

[18]H. F. Bassilios, M. Shawky and A. Y. Salem, *Rec. Trav. Chim.* **81**, 679 (1962).

[19]N. Tanaka, U. Ogata, K. Ushiyama and U. Ono, *Japan J. Antibiotics* **24**, 222 (1971).

[20]R. F. Singh, *Can. J. Chem.* **44**, 1994 (1966).

[21]E. E. Blaize and H. Goult, *Bull. Soc. Chem. Fr.* **9**, 588 (1909), *C.R. Acad. Sci., Paris* **148**, 177 (1909).

[22]R. H. Wiley and C. H. Jorboe, *J. Am. Chem. Soc.* **78**, 2398 (1956).

[23]A. J. Birch and G. S. R. Subba Rao, *Aust. J. Chem.* **33**, 2020 (1968).