Tetrahedron Letters No.52, pp. 4785–4794, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF NORANISATIN, AN OXIDATION PRODUCT OF ANISATIN

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(Received 1 November 1965)

ANISATIN is a toxic compound obtained from the seeds of Japanese star anise*, Illicium religiosum Sieb. et Zucc.(Illicium Anisatum L.).

In 1952, Lane and his co-workers (1) isolated anisatin in a pure crystalline form (m.p. 215-220°, $[\alpha]_{25}^{D}$ -27°(c 2, dioxane)) and gave a molecular formula, $C_{15}H_{20}O_8$ together with the partial structure shown below.

$$(CH_3)_2\,(C_{11}H_9)\,(OH)_5\,(-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-)$$

The molecular formula by Lar group was confirmed in the present study: molecular weight, 328 (mass spectrum), $C_{15}H_{20}O_8$ **, m.p. 227-228°. In this communication, we wish to report the structure of noranisatin (I), an important oxidation product of anisatin.

Anisatin, on oxidation with potassium permanganate in acetic acid at room temperature for 20 hr. gave two neutral compounds, noranisatin (I) ($C_{14}H_{18}O_7$, m.p. 162-163°) and noranisatinone (II) ($C_{14}H_{16}O_7$, m.p. 213-215°, $\nu_{max.}$, 1831, 1789, 1754 cm^{-1} in $CHCl_3$).
II was also obtained by chromic acid oxidation of I in acetic acid.
The properties of I are as follows.

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* Japanese name, " Shikimi ".

** Satisfactory analyses were obtained for all new compounds. Melting points were not corrected.

Noranisatin (I) : two carbonyl groups ($\nu_{max.}$, 1832, 1778 cm^{-1} in $CHCl_3$); no double bonds (no end absorption); information from the N.M.R. spectrum,* a secondary methyl group (CH_3-CH< , 1.03 ppm, doublet, J = 6.5 cps), a tertiary methyl group (CH_3-C≤ , 1.50 ppm, singlet), three hydroxyl groups (detected by H-D exchange on addition of D_2O); one mole of periodic acid in aqueous methanol is consumed slowly, whereas that of lead tetraacetate in acetic acid rapidly; formation of acetate (III) ($C_{16}H_{20}O_8$, m.p. 186-188°) with acetic anhydride and pyridine at 20°; formation of carbonate (IV) ($C_{15}H_{16}O_8$, m.p. 236-238°, $\nu_{max.}$, 1830, 1798 (five-membered ring carbonate), 1770 cm^{-1} KBr) with phosgene in tetrahydrofuran-pyridine.

From the properties above, a vic-glycol group is present in I. Lead tetraacetate oxidation of I afforded seconoranisatin ketoaldehyde (V) ($C_{14}H_{16}O_7$, m.p. 191-192°, $\nu_{max.}$, 1845, 1768, 1717, 1700 cm^{-1}, KBr) which in turn was led to seconoranisatin ketoacid (VI) ($C_{14}H_{16}O_8$, m.p. 152-154, pKa', 3.8 in H_2O) on potassium permanganate oxidation in diluted sulfuric acid-acetic acid. Formation of ketoacid (VI) from I via V, thus indicates that hydroxyl groups of the vic-glycol are secondary and tertiary. The acetate (III) is resistant to lead tetraacetate oxidation, indicating that the secondary hydroxyl group of the vic-glycol is acetylated.
In the N.M.R. spectra, a singnal at 4.60 ppm (1 H, quartet, J = 5.5, 8.5 cps) of I corresponds to a signal at 5.67 ppm (1 H, quartet, J = 7.0, 9.5 cps) of acetate (III). This signal is assigned to a hydrogen on carbon bearing the acetoxyl group in III, and the shape (quartet) of this signal shows the presence of two hydrogens on carbon adjacent to the carbon atom bearing the acetoxyl group.
From the above findings, the partial structure of I is represented by (Ia).

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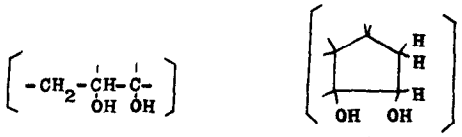
* Tetramethylsilane was used as the internal standard and deuterochloroform was the solvent unless otherwise stated.



(Ia) (Ib)

The ketoacid (VI), prepared from I via ketoaldehyde (V) was also obtained by periodic acid oxidation of noranisatinone (II), showing that the secondary hydroxyl group of the vic-glycol in I is oxidized to become a ketone group in II. From the carbonyl band position (1754 cm^{-1}) of this ketone, the vic-glycol is attached to a five-membered ring and the partial structure of I is represented by (Ib).

Bromination of noranisatinone (II) in acetic acid gave bromonoranisatinone (VII) ($C_{14}H_{15}O_7Br$, m.p. 207-211° , $\nu_{max.}$, 1833, 1778, 1770 cm^{-1} in $CHCl_3$). The shift of carbonyl band of the ketone to the higher frequency (1754 cm^{-1} in II, 1770 cm^{-1} in VII) suggests that bromination took place at an α-carbon of the ketone group, which was confirmed by regeneration of II on treatment of VII with zinc and acetic acid. All the hydrogens of VII were well analyzed from the N.M.R. spectrum (Fig. 1), as follows.

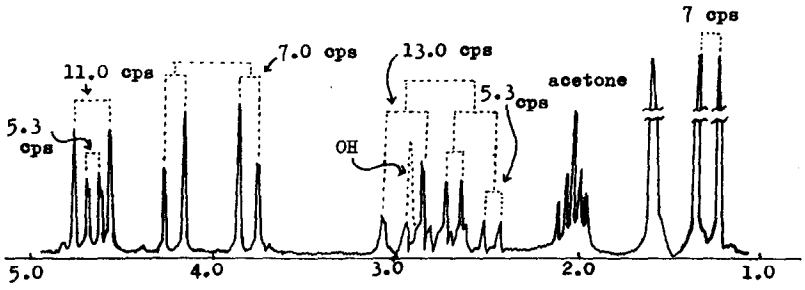


FIG. 1.

The N.M.R. spectrum of bromonoranisatinone (VII) at 60 Mc in CD_3COCD_3

The presence of a secondary methyl group (3 H, 1.25 ppm, doublet, J = 7.0 cps) and a tertiary methyl group (3 H, 1.60 ppm, singlet) is indicated. Two signals at 2.90 ppm (1 H, singlet) and 5.80 ppm (1 H, broad), which disappeared on addition of D_2O, are assigned to two hydroxyl groups. A signal at 4.02 ppm (2 H, AB-type, quartet, J = 7.0 cps) is due to hydrogens on carbon bearing an oxygen atom. Two possible groupings, $-CH_2-O-$ and $-O-CH-CH-O-$ are conceivable for this signal, but the former seems to be the actual one*, because this signal appears as a sharp singlet in the N.M.R. spectra of I and III. Signals at 2.4-3.1 ppm (2 H, multiplet) and at 4.65 ppm (1 H, quartet) constitute a typical ABX pattern (J_{AB} = 13.0 cps, J_{AX} = 0.8 cps, J_{BX} = 5.3 cps) and are due to a $-CH_2-CH-O-$ group**. A signal at 4.75 ppm (1 H, doublet, J = 11.0 cps), not observed in the N.M.R. spectrum of I, is due to a hydrogen on carbon with a bromine. Thus, fourteen among fifteen hydrogens of VII are assigned and characterized. The shape (doublet) of the signal at 4.75 ppm shows that a hydrogen is present on a carbon next to the carbon with a bromine. And this hydrogen, last one to be analyzed, must be attached to the carbon carrying a secondary methyl group***.

Partial structure of bromoketone (VII) is shown as (VIIa) from its N.M.R. spectral analysis. Consequently, I and its oxidation products (II), (IV) and (V) are represented by partial structure (Ic), (IIa), (IVa) and (Va) respectively.

Noranisatin (I) can be represented by (Id) or (Ie) from the N.M.R. analysis of bromoketone (VII) and the positions of two carbonyl bands of I, coupled with the fact that noranisatin consumes two moles of alkali.

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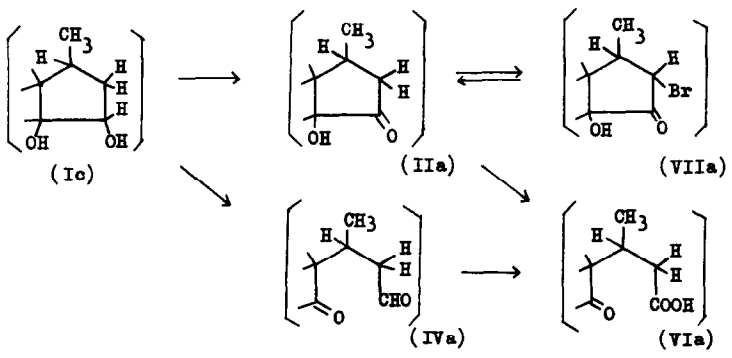
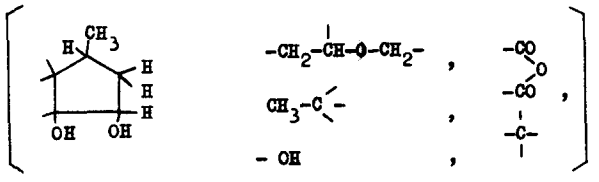
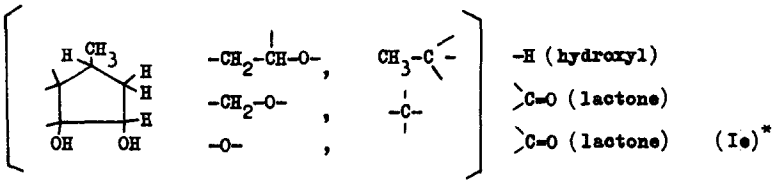
* This signal appears as a quartet with the coupling constant of 13.5 cps in methyl noranisatinate acetate (XIII), supporting a $-CH_2-O-$ group strongly.

A decoupling experiment on noranisatin (I) confirmed this view.

*** None of fourteen among fifteen hydrogens already assigned, are entitled to couple to a secondary methyl group. The remaining hydrogen in question is the sole and very one that can couple to a secondary methyl group.







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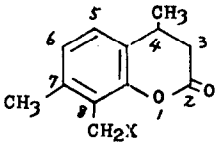
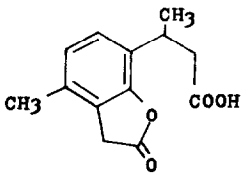
* The possibilities that a tertiary methyl group is attached at one of the carbons forming a five-membered ring must be considered but are excluded from the formation of dihydrocoumarins (VIII) and (IX) mentioned later.

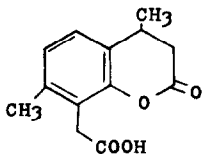
On treatment with hydriodic acid under reflux for 20 hr., ketoacid (VI) afforded a colorless liquid, which was identified as 4,7,8-trimethyldihydrocoumarin (VIII) ($C_{12}H_{14}O_2$, b.p. 114-115° (2 mmHg)) by spectral (I.R., U.V., N.M.R. and Mass) and v.p.c. comparison with the synthetic compound.*



X=H (VIII)
X=Cl (IX)

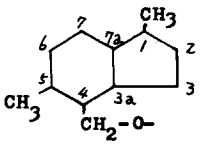


(X)



(XI)

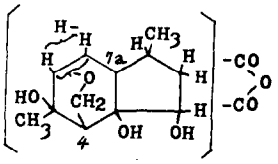
A dihydrocoumarin derivative (IX) ($C_{12}H_{13}O_2Cl$, m.p. 83°, $\nu_{max.}$,1770 cm^{-1} in $CHCl_3$) was obtained by treatment of ketoacid (VI) with acetic acid - hydrogen chloride in a sealed tube at 140° for 3 hr. Catalytic hydrogenation of IX with platinum in acetic acid gave VIII. Evidence was obtained that a chloromethyl group in IX is attached to C_8-position as follows: sodium cyanide and IX were refluxed in aqueous ethanol for 3 hr. to produce a nitrile, which was subsequently hydrolyzed with diluted hydrochloric acid. The products consisted of X and XI, the former of which showed a band at 1800 cm^{-1} (five-membered phenol lactone). Dihydrocoumarins, (VIII) and (IX) were formed from ketoacid (VI) with loss of two carboxyl carbons. The carbon skeleton of noranisatin (I) is, thus represented as (If).



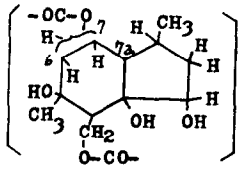
(If)

* Ethyl acetoacetate was condensed with 2,3-dimethylxylenol in conc. sulfuric acid to give 4,7,8-trimethylcoumarin, which upon catalytic reduction with platinum in acetic acid afforded a desired product in a pure state.

In noranisatin (I), two of the three hydroxyls constitute a vic-glycol, while the properties of the third hydroxyl group remains unknown. Of the possible two formulations (Id) and (Ie) for noranisatin (I), this hydroxyl is evidently tertiary in (Id), whereas in (Ie) the hydroxyl group is one of the three possibilities, $-CH_2OH$, $-CH_2-\overset{|}{C}H-OH$, $-\overset{|}{\underset{|}{C}}-OH$. From the following evidence, the hydroxyl is tertiary also in (Ie): the hydroxyl group in carbonate (IV) is not acetylated under forcing conditions and is resistant to vigorous oxidations (chromic acid and permanganate). The position of the tertiary hydroxyl group in the carbon skeleton (If) is deduced as follows: ketoacid (VI) containing the tertiary hydroxyl in question is quite stable to periodic acid in aqueous methanol and lead tetraacetate in acetic acid, excluding the possibility that the hydroxyl is on C_4 or C_{7a} position in (If). Since a $-CH_2-\overset{|}{C}H-O-$ group present in I occupies C_6-C_7 in (If), the only available position for the tertiary hydroxyl is C_5, which carries a tertiary methyl.*
From the above result, in conjunction with the skeleton (If), noranisatin (I) is represented as (Ig) or (Ih).



(Ig)



(Ih)

The possibility (Ig) is excluded: in this case, two carbons of the anhydride group are necessarily combined with C_4 and C_{7a} of skeleton (If), and this is sterically impossible. Another evidence excluding (Ig) is formation of a monobasic acid, noranisatinic acid acetate (XII) ($C_{16}H_{22}O_9$, m.p. 192-194°, pKá, 3.6 in H_2O) from acetate (III) on treatment with potassium bicarbonate in aqueous methanol.

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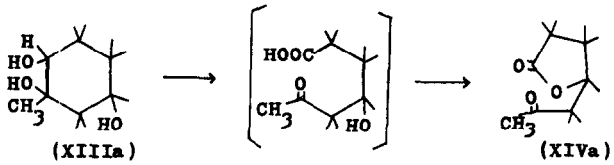
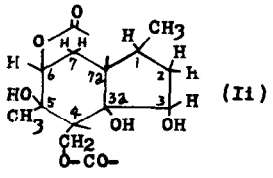
* A supporting evidence for this conclusion is a chemical shift (1.50 ppm) of a tertiary methyl group of noranisatin (I).

The molecular formula of XII is increased by H_2O in comparison with that of III, which is incompatible with the anhydride structure (Ig).* Therefore, noranisatin (I) is shown as a dilactone structure (Ih). Methylation of XII with diazomethane gave methyl noranisatinate acetate (XIII) ($C_{17}H_{24}O_9$, m.p. 190-191°, $\nu_{max.}$ 1732 cm^{-1}(broad) in $CHCl_3$). The ester (XIII) lacks two lactone carbonyl bands present in III, exhibits a new δ-lactone ($\nu_{max.}$ 1732 cm^{-1}) of a $-CH_2-O-CO-$ type (4.60 ppm, AB-type, J = 13.5 cps) and has a secondary hydroxyl. Oxidation of the ester (XIII) with chromic acid - acetic acid or chromic anhydride - pyridine gave a neutral compound, ketolactone (XIV) ($C_{17}H_{20}O_9$, m.p. 235-240° (sublimation), $\nu_{max.}$ 1785 (γ-lactone), 1751 (δ-lactone), 1737 (methyl ester and acetate), 1706 (ketone), no hydroxyl, in KBr). The transformation (XIII → XIV) with an oxidative fission of a C-C bond is shown below.

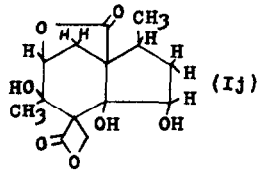


(XIVa)

The lactone oxygen is thus attached to C_6-position** in (Ih), and noranisatin (I) is represented as (Ii).



(Ii)



(Ij)

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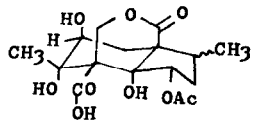
* In addition to the hydrolysis of the anhydride group, hydrolytic cleavage is necessary, in order to account for the transformation.

** Apart from the oxidation result (XIII → XIV), the possible two structures with a lactone oxygen at C_7 in (Ih) are clearly excluded; one contains two β-lactone rings, which is inconsistent with the infrared evidence; the other is sterically impossible.

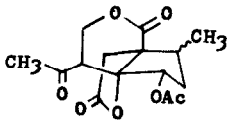
Since lactone carbonyl carbons in (Ii) are bonded to C_4 and C_{7a}, two structures are conceivable, one of which can not be constructed on steric ground. The only possible structure for noranisatin (I) is (Ij) which accounts for all the properties and reactions.

Stereochemistry of noranisatin (I)

Formation of carbonate (IV) indicates cis-relationship of the vic-glycol. The properties of XII and XIII show presence of a δ-lactone and a secondary hydroxyl, indicating the 1,3-diaxial relation of a $-CH_2-$ group of a β-lactone and $\rangle C{=}O$ of a γ-lactone in noranisatin (I). The structure of XII is represented as (XIIa). Formation of ketolactone (XIV), the structure of which is shown in (XIVb) indicates that the vic-glycol and a γ-lactone carbonyl are trans.

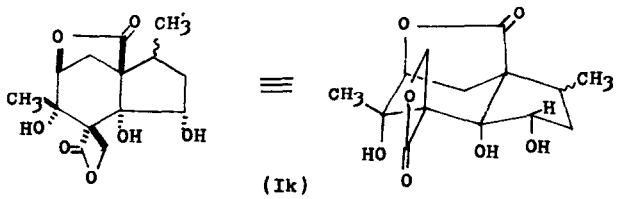


(XIIa)



(XIVb)

The methyl ester (XIII) consumed one mole of lead tetraacetate slowly, suggesting trans-relationship (as indicated in XIIa) of the vic-glycol in a six-membered ring. From the evidence mentioned above, noranisatin (I) is represented as (Ik).



(Ik)

Acknowledgements: The authors are grateful to the Public Health Service, National Institute of Health, U. S. A. for support of this work under Research Grant GM-7969, to the Toyo Rayon Science Foundation for purchasing a mass spectrometer and to Parke, Davis and Co., Ann Arbor, Mich. U.S.A. for fellowship.

REFERENCE

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