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ISOLATION AND STRUCTURE OF NEOANISATIN

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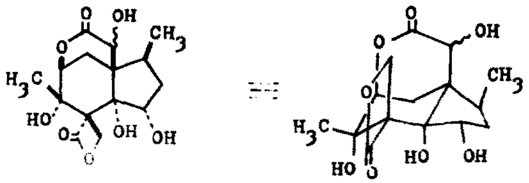
From the seeds of Japanese star anise*, *Illicium religiosum* Sieb. et Zucc. (*Illicium anisatum* L.), Lane and his co-workers isolated a toxic compound "anisatin", and described its partial structure(1). Recently we reported the whole structure of anisatin(I) as shown below(2).



(I)

In this communication, we wish to report the isolation and the structure of a new toxic compound for which the name "neoanisatin" is proposed.

Neoanisatin was obtained by the modified Lane's method(1) from the seeds of Japanese star anise together with anisatin. Chromatographic separation (alumina) and recrystallization from ethyl acetate gave crystalline complexes ($C_{15}H_{20}O_7 \cdot CH_3COOC_2H_5$, m.p. ca. 220° (dec.))**. Recrystallization of the complexes from water gave pure neoanisatin(II). The intraperitoneal dose for the mouse is ca. 1γ/g. of the body weight. The properties of

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* Japanese name, "Shikimi".
** Satisfactory analyses were obtained for all new compounds. Melting points were not corrected.

this compound are as follows.

Neoanisatin(II): $C_{15}H_{20}O_7$; m.p. 237-238°; $[\alpha]^{25}_{546}$ -25°(c 1, dioxane); νmax. 1823, 1733 cm^{-1} in $CHCl_3$; transparent in the U.V. region (no end absorption); no consumption of periodic acid and lead tetraacetate.

Neoanisatin(II) was isomerized to a monobasic acid, neoanisatinic acid(III) ($C_{15}H_{20}O_7$, m.p. 229-231°) on treatment with alkali similarly to isomerization of anisatin(I) to anisatinic acid(IV)*(1). The infrared spectrum of neoanisatin(II)

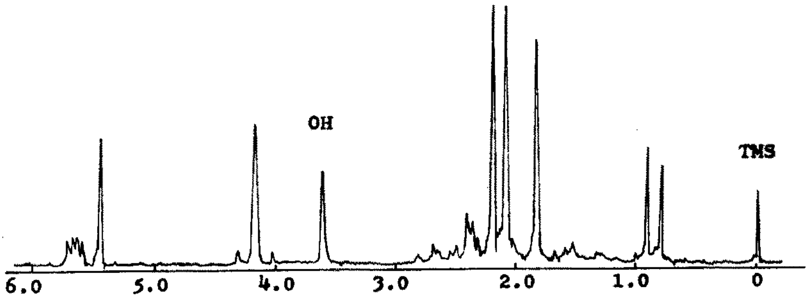

FIG. 1

The n.m.r. spectrum of neoanisatin diacetate(V) at 60 Mc in $CDCl_3$

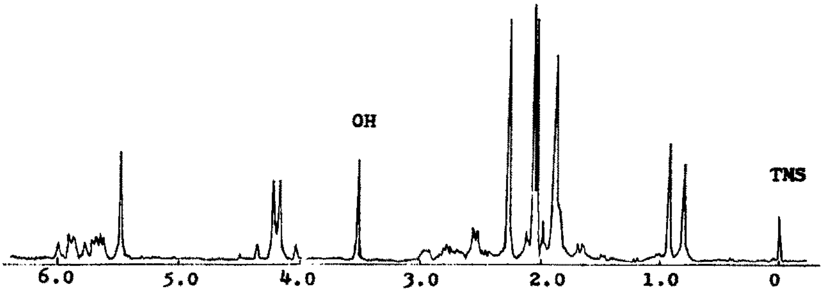

FIG. 2

The n.m.r. spectrum of anisatin triacetate(VI) at 60 Mc in $CDCl_3$

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* The structures and the mode of formations on anisatinic acid (IV) and neoanisatinic acid(III) will be reported in a separate paper.

resembles to that of anisatin(I) (νmax. 1826, 1739 cm^{-1} in $CHCl_3$), and the n.m.r. spectrum of neoanisatin diacetate(V) ($C_{19}H_{24}O_9$, m.p. 194-195°) also corresponds well to that of anisatin triacetate(VI) (FIG. 1 and 2).

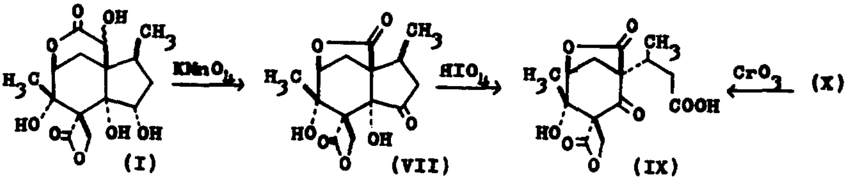
In the n.m.r. spectrum of neoanisatin diacetate(V), a signal at 3.68 ppm*(1 proton, singlet) which disappears on addition of deuterium oxide, is assigned to a hydroxyl group. From this result, neoanisatin(II) has three hydroxyl groups.

Neoanisatin(II) gave no benzoate by treating with benzoyl chloride - pyridine at room temperature, and no carbonate on treatment with phosgene in tetrahydrofuran - pyridine, whereas anisatin(I) gives a monobenzoate and a carbonate under the same conditions(2).

From these findings, II is expected to have the same structure of I, except that the secondary hydroxyl group of the *vic*- glycol in I is replaced by the hydrogen atom in II.

Norneoanisatin

Permanganate oxidation of anisatin(I) gave ketonoranisatin (VII) ($C_{14}H_{16}O_7$), together with noranisatin(VIII) ($C_{14}H_{18}O_7$) (3). In this oxidation the δ-lactone was changed into a γ-lactone by fission of a carbon-carbon bond and the secondary hydroxyl group of the *vic*-glycol became a carbonyl group. VII gave a ketoacid(IX) ($C_{14}H_{16}O_8$, m.p. 152-154°) on treatment with periodic acid in aqueous methanol.



Permanganate oxidation of neoanisatin(II) also gave norneoanisatin(X) ($C_{14}H_{18}O_6$, m.p. 155-156°, νmax. 1832, 1776 cm^{-1} in $CHCl_3$; information from the n.m.r. spectrum: a secondary

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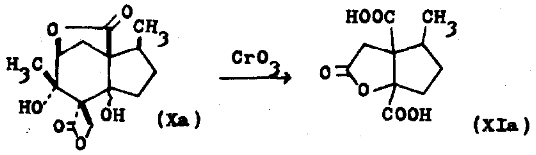
* tetramethylsilane was used as the internal standard.

methyl group(1.01 ppm, doublet, J=6.5 cps), a tertiary methyl group(1.55 ppm, singlet), $-CH_2-O-$ (4.20 ppm, singlet), $>CH-O-$ (4.22 ppm, doublet, J=5 cps), two hydroxyl groups (detected by H-D exchange on addition of D_2O)).
The n.m.r. spectrum and infrared spectrum of this compound are very similar to that of noranisatin(VIII). Chromium trioxide oxidation of X in acetic acid at 60-70° gave a ketoacid in good yield, which was identified with the ketoacid (IX) obtained from VII by infrared spectra and the mixed melting point. Since X does not have a <u>vic</u>-glycol, this evidence shows that X has the structure Xa, in which the configuration of the angular hydroxyl group is unknown.

On the other hand, chromium trioxide oxidation of norneoanisatin(X) in aqueous sulfuric acid at 80-85° gave a lactonic diacid(XI) ($C_{10}H_{12}O_6$, m.p. 201-203°; νmax. 1803, 1700 cm^{-1} in KBr; pKa' in H_2O 3.6, 4.8).

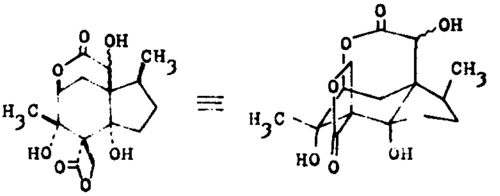


The n.m.r. spectrum of XI in $(CD_3)_2CO$ shows a doublet at 1.08 ppm(3 protons, J=6.5 cps) due to a secondary methyl group and multiplets near 2.2 ppm(5 protons measured in pyridine) due to methine and methylene protons. There appear an AB spectrum centered at 2.86 ppm(2 protons, J_{AB}=18 cps) and a singlet at 9.3 ppm(2 protons), the former being due to an additional methylene group and the latter due to carboxylic groups. In the infrared spectrum of XI, there is an absorption at 1803 cm^{-1}, which was shifted around 1600 cm^{-1} in the sodium salt prepared by treatment with sodium hydroxide. This band was regenerated on acidification of the sodium salt. These observations show the presence of a γ-lactone in XI. These findings coupled with the structure Xa show that XI has the structure XIa.

The carboxylic groups of XI form a five-membered anhydride (νC=O, 1865, 1800 cm^{-1}) by treating with acetic anhydride. The formation of the anhydride and the presence of a γ-lactone ring show the <u>cis</u> relation between the angular hydroxyl group and the methylene of the six-membered ring in the structure Xa, namely the <u>trans</u> fusion of two carbocyclic rings in norneoanisatin(X) similar to that in noranisatin(VIII).

Neoanisatin

The conversion of neoanisatin(II) to norneoanisatin(X) is the same as that of anisatin(I) to noranisatin(VIII)(2). Of the two carbonyl bands (1823, 1733 cm^{-1}) in the infrared spectrum of II a band at 1823 cm^{-1} appears at nearly the same position after oxidation of II to X, whereas the second carbonyl band at 1733 cm^{-1} in II appears at 1776 cm^{-1} (γ-lactone) in X. A difference of the molecular formula between II and X is CH_2O, which is associated with the γ-lactone moiety of X. Neoanisatin(II) has three hydroxyl groups, whereas norneoanisatin(X) has two hydroxyl groups. The extra hydroxyl group of II is secondary, because the signal at 5.42 ppm (1 proton, singlet) in the n.m.r. spectrum of neoanisatin diacetate(V) is due to a hydrogen of the type $\supset$CH-OAc. These findings indicate that II has an α-hydroxy(secondary)-δ-lactone in place of a γ-lactone in X. Neoanisatin(II) is therefore represented as shown below.



(II)

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3. K. Yamada, S. Takada, S. Nakamura and Y. Hirata, *Tetrahedron Letters*, **52**, 4785 (1965).