Tetrahedron Letters No.52, pp. 4797-4801, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF ANISATIN

Kiyoyuki Yamada, Susumu Takada, Shiro Nakamura and
Yoshimasa Hirata

Chemical Institute, Faculty of Science, Nagoya University
Nagoya, Japan

(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.). The intraperitoneal dose for the mouse is 1γ/g. of the body weight. Pure crystals of anisatin ($C_{15}H_{20}O_8$, m.p. 215-220°, $[\alpha]_D^{25}$ -27° (c 2, dioxane)) were first obtained by Lane and his co-workers and the partial structure shown below was reported (1).

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

In this communication, we wish to report the structure of anisatin (I).

The properties of anisatin (I) is as follows. Anisatin (I)** : $C_{15}H_{20}O_8$, m.p. 227-228°***; $\nu_{max.}$, 1826, 1739 cm^{-1} in $CHCl_3$; transparent in the U.V. region (no end absorption); diacetate (II) (m.p. 225-227° (sublimation)) and triacetate (III) (m.p. 230-234° (sublimation)) were already reported by Lane et al. (1); on acetylation by acetic anhydride - pyridine at room temperature for 20 hr. gave monoacetate (IV) ($C_{17}H_{22}O_9$, m.p. 173-174°);

---

* Japanese name, " Shikimi ".

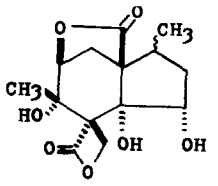
** Satisfactory analyses were obtained for all new compounds. Melting points were not corrected.

*** Anisatin was recrystallized from water. Anisatin recrystallized from ethyl acetate shows melting point (215-220°) reported by Lane et al.

monobenzoate (V) ($C_{22}H_{24}O_9$, m.p. 229-231°) with benzoyl chloride - pyridine at room temperature for 2 days; monotosylate (VI) ($C_{22}H_{26}O_{10}S$, m.p. 188-190°) with tosyl chloride - pyridine at room temperature; carbonate (VII) ($C_{16}H_{18}O_9$, m.p. 218-220°) with phosgene in tetrahydrofuran and pyridine; one mole of periodic acid (or lead tetraacetate) was consumed.

From the properties of anisatin (I), a vic-glycol is evidently present. Anisatin (I) is isomerized to a monobasic acid, anisatinic acid (VIII) ($C_{15}H_{20}O_8$, m.p. 216-218°) on treatment with alkali (1). This transformation is not a simple hydrolysis of a lactone, but a complex reaction.*

In a preceding paper (2) from our laboratory, the structure (IXa) was presented for noranisatin (IX), an oxidation product of anisatin (I).



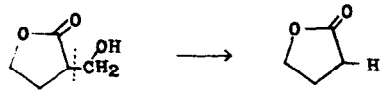
(IXa)

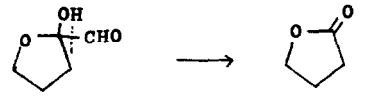
It is secured that the carbon skeleton is intact during the oxidation of I to IX from the following findings: anisatin carbonate (VII), on oxidation with potassium permanganate gave a product which is identical with noranisatin carbonate (X) ($C_{15}H_{16}O_8$) (2), prepared from noranisatin (IX) with phosgene in tetrahydrofuran - pyridine. Of the two carbonyl bands (1826, 1739 cm^{-1}) in I, a band at 1826 cm^{-1} appears at nearly the same position after oxidation of I to IX ($\nu_{max.}$ 1832 cm^{-1} in IX), whereas the second carbonyl band at 1739 cm^{-1} in I appears at 1778 cm^{-1} (γ-lactone) in IX. A difference of molecular formulas between I and IX is CH_2O, which is associated with the γ-lactone moiety of IX.

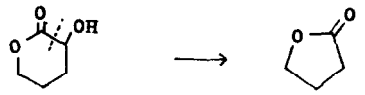
---

* The structure and the mode of formation on anisatinic acid (VIII) will be reported in a separate paper.

From these results, the following three possibilities are conceivable for the transformation, I → IX.

(Ia) 

(Ib) 

(Ic) 

The possibility (Ia) can be excluded because an α-carbon of the γ-lacton carbonyl has no hydrogen in IX. In the N.M.R. spectrum of I, an aldehyde hydrogen is not observed, excluding the formulation (Ib). The third possibility (Ic) remains, a positive evidence of which is obtained from the N.M.R. spectrum of triacetate (III), (Fig. 1).

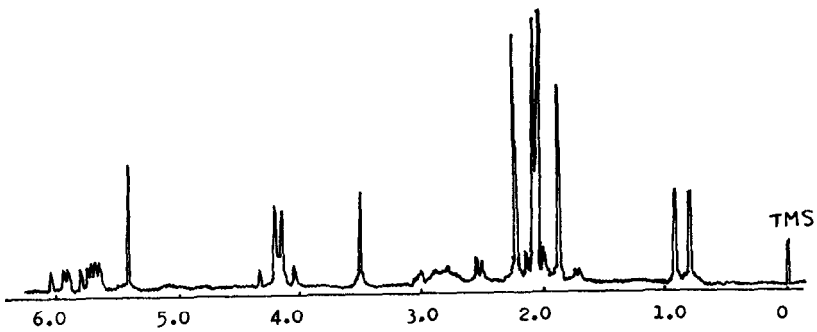
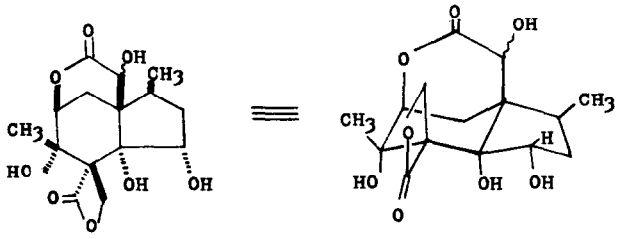


FIG. 1.

The N.M.R. spectrum of anisatin triacetate (III) at 60 Mc in $CDCl_3$

Prominent signals at higher field are a secondary methyl (3 H, 0.87 ppm, doublet, J = 7.0 cps), a tertiary methyl (3 H, 1.87 ppm, singlet) and three acetate methyls (2.06 ppm, 2.09 ppm, 2.26 ppm, singlet, respectively). A signal at 5.40 ppm (1 H, singlet) is due to a hydroxyl hydrogen, because it disappears on addition of D_2O. Four hydroxyl groups are therefore present in anisatin (I). The presence of a group, $-CH_2-O-CO-$ is indicated by a quartet at 4.17 ppm (2 H, J_{AB}= 7.0 cps). A signal at 5.88 ppm (1 H, quartet, J_{AX}= 6.5 cps, J_{BX}= 8.0 cps) can be assigned to a hydrogen on the carbon carrying a secondary hydroxyl group of a vic-glycol. A signal at 5.66 ppm (1 H, quartet, J_{AX}= 2.0 cps, J_{BX}= 4.0 cps) corresponds to that of a hydrogen on carbon carrying a γ-lactone oxygen in IX.

Thus, the N.M.R. spectrum of triacetate (III) corresponds well to that of noranisatin (IX) except a signal at 5.40 ppm (1 H, singlet) in III. This signal, considering its chemical shift is presumably due to a hydrogen of the type $-\overset{|}{C}H-O-$. The presence of a secondary hydroxyl group, $>CH-OH$ is indicated from the above finding, coupled with the fact that anisatin (I) has one more hydroxyl group than noranisatin (IX). The deduced structure (Ic) satisfactorily accounts for the observed change of the carbonyl band from I to IX. Anisatin (I) is therefore represented as (Id).*



(Id)

* The configuration of the secondary methyl group was determined by the X-ray analysis (3) of norbromoanisatinone, a derivative of noranisatin (IX).

Acknowledgements: The authors' thanks are due 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.

REFERENCES

1. J.F. Lane, W.T. Koch, N.S. Leeds and G. Gorin, J. Amer. Chem. Soc. 74, 3211 (1952).
2. K. Yamada, S. Takada, S. Nakamura and Y. Hirata, Tetrahedron Letters, 52, 4785 (1965).
3. N. Sakabe, Y. Hirata, A. Furusaki, Y. Tomiie and I. Nitta, Tetrahedron Letters, 52, 4795 (1965).