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THE STRUCTURE OF NORANISATIN, AN OXIDATION PRODUCT OF ANISATIN

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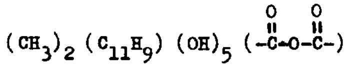
ANISATIN is a toxic compound obtained from the seeds of Japanese star anise*, <u>Illicium religiosum</u> Sieb. et Zucc.(<u>Illicium Anisatum</u> L.).

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.

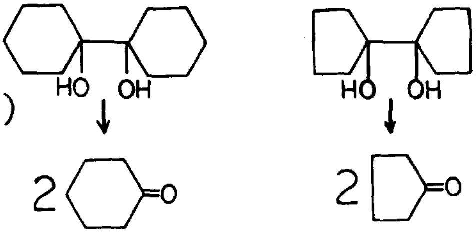
frequently been characterized[4,6] by a transition state having the appearance of the carbonyl product.

In support of their postulate Roček and Westheimer have gathered calculations and rate data (see Table IV ref. (2)) purporting to demonstrate a good correlation of the cleavage rates of substituted glycols and the enthalpy differences between the ground states of the glycol reactants and the carbonyl products. However, as admitted by these authors,[2] some of the relative rates of fission in their comparisons are extremely approximate; the degree of correspondence of $\Delta(\Delta H)$ and relative rates is often quite poor; and, the fact that some of the compounds in the series considered can undergo oxidation without fission does not afford great confidence in applying the data for support of their postulate.

Since these considerations currently constitute the <u>only</u> basis for their proposing an activated complex of glycol cleavage that resembles the product structure, we have sought to carry out a direct test of the R and W proposal. We have chosen to compare the rates of cleavage of two pinacols whose reaction enthalpy differences, ($\Delta(\Delta H)$), could be readily estimated to be of significant magnitude and where experimental heats of combustion data are available to provide some security in these calculations. Furthermore, both the direction and magnitude of the relative cleavage rates (to be compared) could be unequivocally anticipated on the basis of the R and W transition state.[2] The oxidation of (bicyclohexyl)-1,1'-diol(I) and (cicyclopentyl)-1,1'-diol,(II), affords two moles (each) of the corresponding cleavage ketones under experimental conditions employed by Roček and Westheimer[2] for their studies of the rates of cleavage of cis and trans 1,2-dimethyl-1,2-cyclopentanediols.

Results of Calculations of the
Enthalpies of Fission

(I)



(II)

Calculated by-	ΔH,Fission Kcal/mole the Klages Method[a]	ΔH, Fission -the Franklin Method[a]
Cyclohexyl Pinacol(I)	-33.3	-35.0
Cyclopentyl Pinacol(II)	-38.1	-41.8
Δ(ΔH)	4.8	6.8

[a] See (2) for details and references to these calculation methods.

The most probable value of $\Delta(\Delta H)$ may be assumed to lie somewhere between the extremes arrived at by applying (respectively) the methods of Klages and Franklin, (see Table of Results); let us say $\Delta(\Delta H) \cong 5.8$ Kcal/mole. This may be deduced as a plausible value for $\Delta(\Delta H)$ on the assumption made by R and W[2] that the energetics of the fission of glycols is to be compared to that of secondary alcohol oxidation. Thus we may compute from available experimental data:[7]

ΔH(cyclohexanol-cyclohexanone)-ΔH(cyclopentanol-cyclopentanone)=3.1 Kcal.

Because we form two moles of ketone per mole of pinacol cleaved, the $\Delta(\Delta H)$ for the corresponding pinacol fission reactions = 2 x 3.1 = 6.2 Kcal/mole, (compared to the median value (5.8) computed above). These computations suggest that, if the R and W transition state proposal[2] is correct, cyclopentyl pinacol, (II), should experience cleavage approximately 10^4 times as readily as cyclohexyl pinacol, (I).

In a 30% acetic acid solution that was 0.25M in $HClO_4$ and 0.15 M in $NaClO_4$ (ionic strength = 0.4) the rate of oxidation of I was almost 120 times greater[8] than that of II. Thus, the experimental relative rates are exactly opposite in direction and are more than 6 orders of magnitude different from what could be expected on the basis of the energetics of reaction calculated in accordance with the R and W postulate.[2] We have no alternative, therefore, but to reject the product-like structure of the chromic acid cleavage transition state. By the same token, as we have suggested previously,[3,5] a carbonyl-structured transition state of secondary alcohol oxidation, which has been so often advanced[4,6] to account for the rate acceleration effects noted in sterically hindered alcohols, must also be rejected.

An attractive possibility for explaining the greater cleavage rate of I arises from the fact that the formation of the cyclic ester tends to arrest the psuedo rotation of the cyclopentane rings in II (through which non-bonded interactions of vicinal groups are normally relieved). This effect, of course, is not a factor in the stability of the puckered cyclohexane rings in I. Consequently the cleavage rate differences observed may be attributed to a rate determining formation of the cyclic chromate ester rather than (as supposed by R and W[2]) its decomposition.

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3. H. Kwart, J. A. Ford, Jr. and G. C. Corey, ibid., 84, 1252 (1962).
4. The most recent discussion of this proposal has been presented by J. Roček, F. H. Westheimer, A. Eschenmoser, L. Moldovanyi and J. Schreiber, Helv. Chem. Acta., 45, 2554 (1962). See, however, reference (5) for evidence and discussion in support of an alternative interpretation.
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   b. ibid, Chem. and Ind., 610 (1962).
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8. This is minimum figure for the relative rates after correcting for some acid-catalyzed pinacol rearrangement observed to take place under these reaction conditions. A full report on the relative rates of chromic acid cleavage and pinacol rearrangement measured under a variety of conditions will be rendered in a future publication from these laboratories.