

Isamic Acid: an Azomethine Imine

By P. DE MAYO and J. J. RYAN

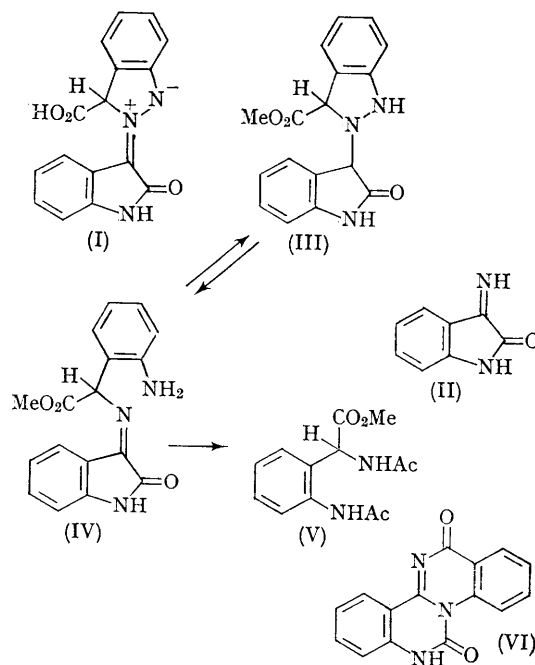
(University of Western Ontario, London, Canada)

In a recent Paper the first deliberate synthesis of an azomethine imine ($\text{>C}=\overset{+}{\text{N}}-\overset{-}{\text{N}}$), a previously unknown class of compound, was reported.¹ We now show that isamic acid, first prepared by Laurent in 1842,² and later studied by Reissert³ and Jacini,⁴ is a venerable member of this class of substances.

Isamic acid, (I) $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_3 \cdot \text{H}_2\text{O}$, is prepared as red crystals by the action of ammonia (1 mole) on isatin (2 moles) or of sodium isoatoate on β -isatin-imide (II). Hydrolysis of the acid with 0.1N-hydrochloric acid regenerates the isatin and ammonia quantitatively. The acid ($\text{p}K_a$ 4.85*) is esterified with diazomethane and the ester is readily hydrolysed with base to the parent acid. The ester has no detectable basic function.†

Evidence, chemical and spectroscopic, is available to show that one of the oxindole moieties is present intact in isamic acid and has a site of unsaturation at the β -position (λ_{max} 417 m μ : isatin, λ_{max} 415 m μ). The ester, for instance, undergoes the acetylation-methanolysis sequence known for isatin and for (II).⁶ The other moiety does not have a free amidic hydrogen since an *N*-methylisamic acid may be prepared from *N*-methylisatinimide and sodium isoatoate, but not from (II) and sodium *N*-methylisoatoate. The correctness of the structure (I) is shown by, amongst other evidence, the following sequence of reactions.

Hydrogenation of methyl isamate (uptake of 1 mole of hydrogen) gives a colourless product consisting of two diastereoisomers (III). The ultraviolet spectrum is compatible with that expected by addition of the separate chromophores.



* Determined in Methylcellosolve-water (4:1).

† Determined in Methylcellosolve-water. Titration in acetic acid solution with perchloric acid showed the presence of a base comparable in strength with urea.

In the presence of a trace of acid each is converted into (IV). Neutralisation with sodium hydrogen carbonate reverses the process and regenerates both isomers. The structure of (IV), isolated as the *N*-acetylated product, is shown by hydrolysis and acetylation, which gives isatin and (V), and by the ultraviolet absorption (λ_{\max} 412 m μ).

The generation of (IV) from a system lacking extended conjugation requires that a ready elimination take place. From the structure of (IV), and the spectroscopic properties of (III), only the amino-function is available to act as an

ejectable group: the presence of the essential feature of (I), the N-N bond, is thus established.

The genesis of such a bizarre product as (I) by such simple means, although at first surprising, can be rationalised by a sequence of known, or quite unexceptional, steps. The transformation, by oxidation with alkaline peroxide, of (I) into (VI)^{4,6} may also be explained as may other reported transformations.^{3,4,7} The existence of a species prior to its later deliberate confection has already received comment.⁸

(Received, October 27th, 1966; Com. 826.)

¹ R. Huisgen, R. Fleischmann, and A. Eckell, *Tetrahedron Letters*, 1960, 1.

² A. Laurent, *J. prakt. Chem.*, 1842, **25**, 456.

³ A. Reissert and H. Hoppmann, *Ber.*, 1924, **57**, 972.

⁴ G. Jacini, *Gazzetta*, 1943, **73**, 306; 1947, **77**, 295.

⁵ F. Meyer, *Ber.*, 1966, **99**, 3061.

⁶ J. J. Ryan, unpublished work.

⁷ These will be discussed in detail in the full Paper to be submitted to the *Canad. J. Chem.*

⁸ Koheleth, *Ecclesiastes*, **1**, 9.