

## The Structure of Isamic Acid

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**Summary** Isamic acid is shown to be the 1,2-dihydroquinazoline derivative (II).

RECENTLY an unusual structure (I) was suggested<sup>1</sup> for isamic acid, which was first prepared in 1842.<sup>2</sup> Structure (II), which may be derived by combination of two moles of isatin with ammonia in an entirely straightforward manner, is fully in accord with the properties of isamic acid.

The sequence of transformations reported by De Mayo

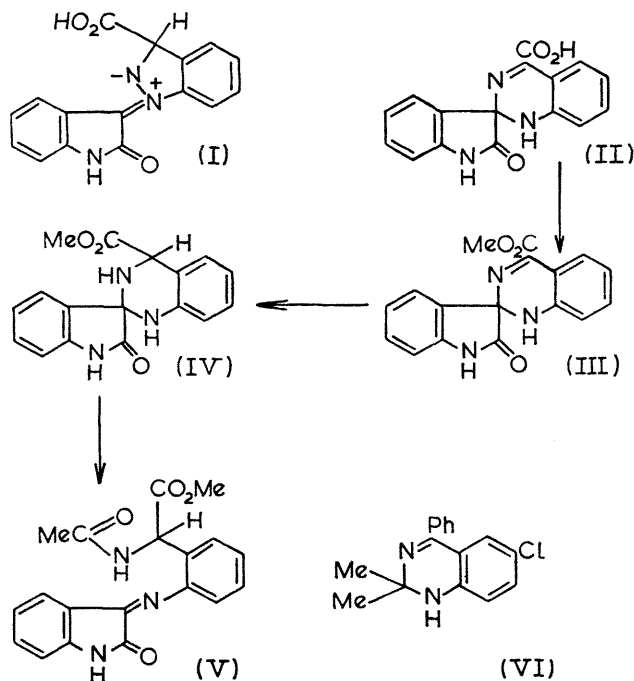
and Ryan<sup>1</sup> should be reformulated as shown. Reduction of methyl isamate (III) gives the dihydro-derivative (IV) as a mixture of diastereomers which, on acetylation, gives (V). The structure of (V) was shown to be correct by further transformations, if one ignores the possibility of ring-chain tautomers. Further, the other reported transformations of isamic acid are in accord with formulation (II).<sup>1,3</sup>

Comparison of the physical properties of isamic acid with the model 1,2-dihydroquinazoline (VI) also supports formulation (II). Compound (VI) shows a long-wavelength maximum at 400 nm. in the u.v. spectrum which is not far removed from the long-wavelength maximum at 417 nm. in the spectrum of isamic acid. Furthermore, the spectrum of (VI) in acid<sup>4</sup> showed a peak at 460 nm. The lack of basicity of methyl isamate is also in accord with structure (II). The  $pK_a$  of (VI) is about 5.9 in 12% propan-2-ol-water. The basicity of aliphatic amines is reported to drop about 2.8  $pK_a$  units on addition of an  $\alpha$ -carbonyl group.<sup>5</sup> Application of this factor twice to the  $pK_a$  of (VI) results in the prediction that the methyl ester of (II) should be a very weak base, as is the case for methyl isamate.

Methyl isamate was reported to contain only one exchangeable proton in the n.m.r. spectrum;<sup>1</sup> however we believe this report to be in error since methyl mono-*N*-methylisamate still showed an exchangeable proton.<sup>1</sup> We have re-determined the spectrum of methyl isamate in dimethyl sulphoxide, and the integral of the aromatic region is decreased on addition of deuterium oxide, as would be expected if this area contained a signal due to the missing NH.

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<sup>1</sup> P. De Mayo and J. J. Ryan, *Chem. Comm.*, 1967, 88; *Canad. J. Chem.*, 1967, **45**, 2177.

<sup>2</sup> A. Laurent, *J. prakt. Chem.*, 1842, **25**, 456; 1845, **35**, 108.

<sup>3</sup> P. De Mayo and J. J. Ryan, *Tetrahedron Letters*, 1967, 827; G. Jacini, *Gazzetta*, 1941, **71**, 532; 1942, **72**, 510; 1943, **73**, 85, 306; 1944, **74**, 3; 1947, **77**, 295; A. Reissert and H. Hoppmann, *Ber.*, 1924, **57**, 972; E. Sommaruga and E. Reichardt, *ibid.*, 1877, **10**, 432.

<sup>4</sup> G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, 1965, **30**, 3957.

<sup>5</sup> J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.