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A NEW SYNTHESIS OF HYDROXYPHTHALIDES

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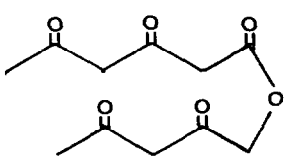
Summary: Cyclization of suitable enamino ketones can produce hydroxyphthalides.

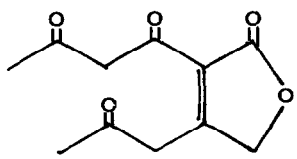
Several natural products with a hydroxyphthalide structure have been isolated from mould cultures[1]. Because of their pharmacological properties the synthesis of the above compounds is receiving current attention by many authors[2].

We here report on a new synthetic approach to the hydroxyphthalide system based on the use as starting material of an acyclic framework containing all the atoms of the target product.

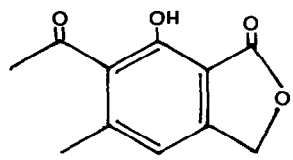
Taking into account the hypothesis that the hydroxyphthalide system can arise by cyclization of a β-polyketide chain, our synthetic strategy is illustrated in the following scheme:



I



II



III

Compounds like (I) can be obtained as the isoxazole derivatives (VII) and (VIII) wich are expected to behave as "masked" β-polyketonic systems[3].

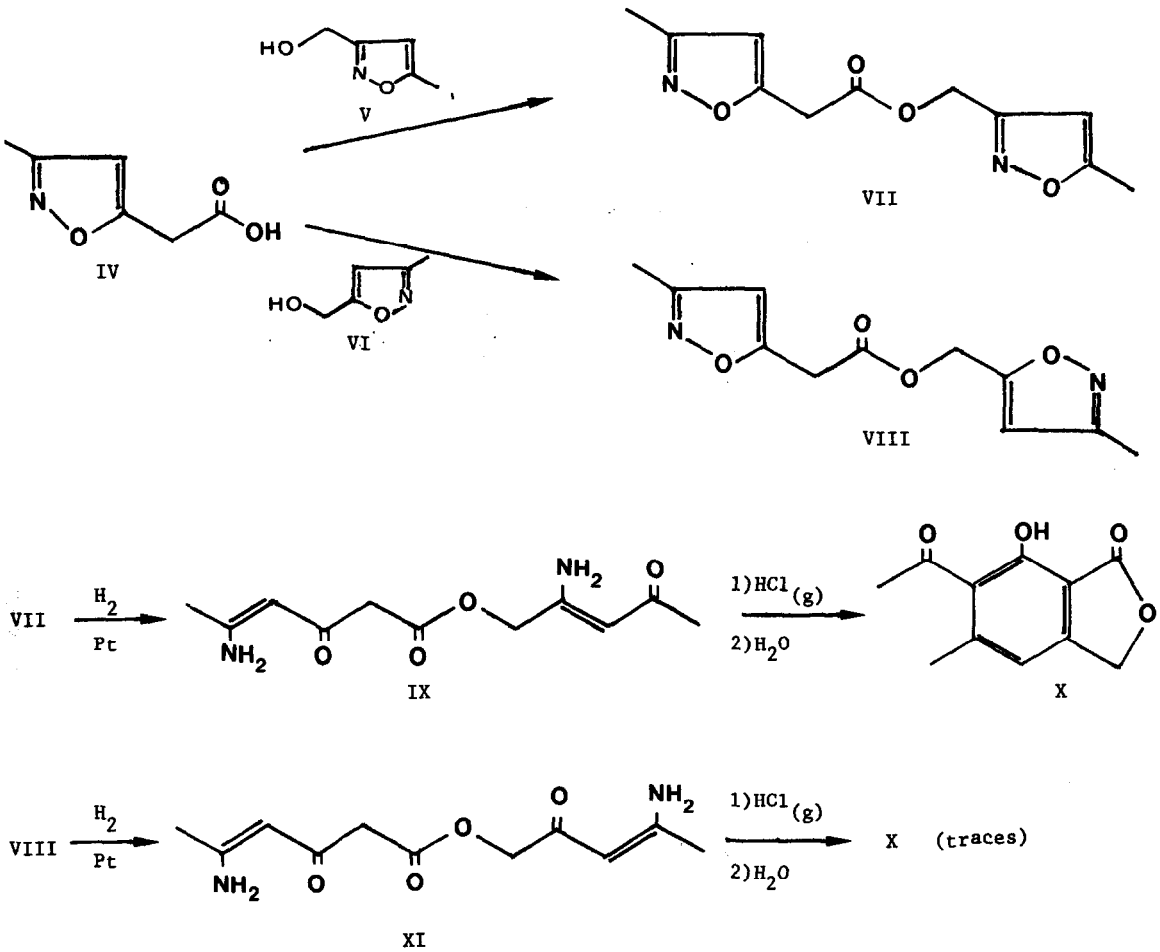
To this end, we synthesized the isomeric isoxazole esters (VII) and (VIII) by esterification of the isoxazolic acid (IV) with the isoxazolylcarbinols (V) and (VI), respectively.

Compound (VII), once hydrogenated, gave the dienamino derivative of a tetraketo esters(IX), which, upon treatment with dry HCl in anhydrous non-polar solvents, followed by aqueous work-up, yielded (X). The structure of this compound is based on analytical and spectroscopic data.

However, when compound (VIII) was hydrogenated, the dienamino derivative (XI) was obtained, in the form of a high melting and very stable compound. This material, when treated under the experimental condition which gave from (IX) the disired hydroxyphthalide (X), remained mainly unaltered. Only traces of compound (X) were isolated from the reaction mixture.

The obtainment of hydroxyphthalide (X) from the isoxazole esters (VII) represents a further example of the synthetic utility of the isoxazole nucleous as "masked" β-polyketide system.

Furthermore, the above evidence indicates, as already shown by us[4], that the position of the enamino groups in the developing polyketonic chain is crucial for the mode of the subsequent cyclization.



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2) A.J. Birch, J.J. Wright, Chemical Comm. 788 (1969); L. Canonica, E. Rindone, E. Santaniello and C. Scolastico, Tetrahedron Letters 2691 (1971).

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