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THE CYANIDE-CATALYZED CONVERSION OF β-FORMYLMUCONATES INTO TRIGLOCHINATES: A USEFUL BIOMIMETIC SYNTHESIS

by

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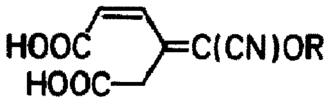
*Upon treatment with cyanide under slightly basic conditions, β-formyl-*cis,cis*-muconic acid and esters, prepared from vanillin, undergo a sequence of prototropic shifts equivalent to an internal redox process in which 1,4-reduction of the diene system is balanced by oxidation of the formyl group.*

Triglochinin[1-3] (1, R = β-D-glucopyranosyl), unusual in being an enol glucoside, is one of the most widely distributed cyanogenic principles of flowering plants.[4] The presumed immediate forerunners[2] of triglochinin are the unknown protriglochinins[5] (2, R = β-D-glucopyranosyl), epimeric cyanohydrin glucosides derived from β-formyl-*cis,cis*-muconic acid, from which triglochinin would result by double-bond shift. The prior stages of triglochinin biosynthesis appear to consist in formation from tyrosine[2,6,7] of a glucoside (3, R = β-D-glucopyranosyl) of an enantiomer of 3,4-dihydroxymandelonitrile, followed by oxidative cleavage of the aromatic ring.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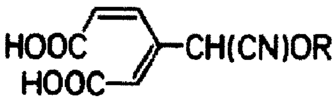
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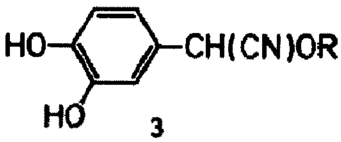
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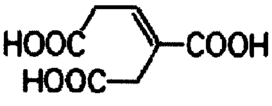
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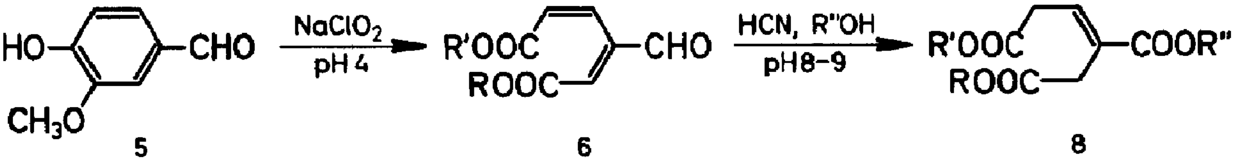
Hydrolysis of triglochinin with β-glucosidase yields glucose, hydrogen cyanide, and triglochinic [(E)-2-butene-1,2,4-tricarboxylic] acid (4).^{1,2,8} Since the reaction is initiated by glucosyl-oxygen cleavage, the enol 1 (R = H) is the first intermediate on the path to 4, and 4 should result when the enol is generated in aqueous medium from any precursor. An evident likely source of 1 (R = H) is the cyanohydrin 2 (R = H), the aglucone of the protriglochinins. Accordingly, a two-step synthesis of triglochinic acid and esters from vanillin (5) was realized. Oxidation of 5 with chlorite^{9} at pH 4 affords a means of opening the aromatic ring without oxidation of the aldehyde group,^{10} the product,$^{9-11}$ monomethyl β-formyl-*cis,cis*-muconate (6, R = CH_3, R' = H), being stabilized by existing predominantly as the lactol 7 (R = CH_3) in acidic aqueous solution,^{12} as well as in the solid state and aprotic media.^{11} The monomethyl ester was hydrolyzed with base to give 7 (R = H; equivalent to 6, R = R' = H), m.p. 154 °C (dec.),^{13} or converted^{14} to 6 (R = R' = CH_3), m.p. 63-64 °C.^{13} Heating (water bath) equimolar amounts of 7 (R = CH_3) and sodium bicarbonate in 2 M aqueous hydrogen cyanide for 15 min and fractionation of the product by anion-exchange chromatography (Amberlite CG-400, acetate form) gave the monomethyl triglochinate 8 (R = CH_3, R' = R'' = H), m.p. 161-162 °C,^{13} in 40-50% yield. Similarly, 7 (R = H) and 6 (R = R' = CH_3) yielded respectively triglochinic acid (8, R = R' = R'' = H, equals 4), m.p. 175 °C (dec.; lit.^{8} m.p. 167-168 °C), and 8 (R = R' = CH_3, R'' = H), m.p. 117-118 °C.^{13} When methanol was the solvent, 7 (R = CH_3) was transformed to 8 (R = R'' = CH_3, R' = H), m.p. 70-71 °C.^{13}



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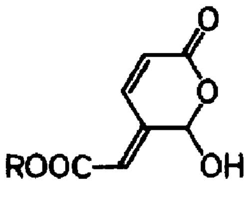

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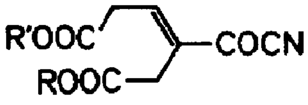

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After conversion of the β-formylmuconates (6) to cyanohydrins [2 (R = H) or its esters], a base-catalyzed double-bond shift will give enols such as 1 (R = H). The remaining steps to triglochinates can be formulated in a variety of ways,[15] of which ketonization to acyl cyanides (9) corresponding to 8, followed by solvolysis, appears most straightforward at present. This synthesis, a model for the formation and hydrolysis of triglochinin, is simpler than the earlier synthesis[8] of 4 and allows preparation of triglochinic mono- and diesters of precisely determined structure. Thus the hydrolysis product 8 (R,R' = CH_3,H, R'' = H) of a monomethyl ester of triglochinin, which by one report may occur in *Thalictrum aquilegiifolium* (Ranunculaceae),[6,16] can now be identified. The readily available, highly reactive polyfunctional intermediate 7 (R = CH_3) will be the subject of further papers.

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REFERENCES AND NOTES

1. R. Eyjólfsson, Phytochemistry 9, 845 (1970).
2. M. Ettlinger and R. Eyjólfsson, J.C.S. Chem. Comm., 572 (1972).
3. Notwithstanding some statements in the literature [ref. 6; D.S. Seigler, Phytochemistry 14, 9 (1975); Progr. Phytochem. 4, 83 (1977)] about triglochinin and derivatives, the coupling constant between the olefinic hydrogens (^3J 12.5 Hz, as against 15.5 Hz for isotriglochinin[2]) requires that the configuration of the disubstituted double bond be *cis*.[17] The configuration of the tetrasubstituted double bond is left unspecified for the purpose of this communication.
4. Species of the following plant families are known to contain triglochinin: Scheuchzeriaceae, Juncaginaceae, Poaceae, Araceae (monocots); Magnoliaceae, Ranunculaceae, Papaveraceae, Euphorbiaceae, Platanaceae, Campanulaceae (dicots).
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6. D. Sharples, M.S. Spring, and J.R. Stoker, Phytochemistry 11, 2999, 3069 (1972).
7. J.W. Jaroszewski and M.G. Ettlinger, to be published.
8. R. Eyjólfsson, Acta Chem. Scand. 24, 3075 (1970).
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11. A.T. Ainsworth and G.W. Kirby, J. Chem. Soc. C, 1483 (1968); *cf.* also T. Ishikawa, M. Sumimoto, and T. Kondo, Kami-pa Gikyoshi (J. Japanese Tappi) 23, 117 (1969).
12. The apparent spectrophotometric acidity constant of 7 (R = CH_3) was found to be 5.6, at least two units above what might be expected for the open-chain form 6 (R = CH_3, R' = H), which hence cyclizes to the extent of at least 99% in aqueous solution. In acidic solution (pH < 4) the cyclic form exhibits an absorption maximum at 265 nm (ε 19000). In alkaline solution (pH > 8) the corresponding open-chain (*cf.* 6) anion has ε 7500 at 265 nm. Ring-chain equilibria of the anion will be discussed elsewhere.
13. Consistent analytical and spectroscopic (^{1}H-NMR, IR, UV) data were obtained for all new compounds. Melting points are corrected.
14. The dimethyl ester 6 (R = R' = CH_3) is best obtained from 7 (R = CH_3) by prolonged reflux in CH_3OH-$(CH_3O)_3CH$-HCl and hydrolysis of the resulting oily dimethyl acetal[13] of 6 (R = R' = CH_3) with 0.01 M HCl (6 hours, room temp.). The yield exceeds 90%.
15. For model reactions see K. Shakhidayatov, L.A. Yanovskaya, and V.F. Kucherov, Bull. Acad. Sci. USSR, Div. Chem. Sci., 535 (1970); J.S. Walia, D.H. Rao, M. Singh, and G.R. Nath, Chem. Ind. (London), 583 (1967); L.C. Vishwakarma and J.S. Walia, Indian J. Chem. 14B, 692, 696 (1976); V. Franzen and L. Fikentscher, Liebigs Ann. Chem. 623, 68 (1959).
16. *Cf.* ref. 3. In other investigations [ref. 7; L. Tjon Sie Fat, Proc. Koninkl. Nederl. Akad. Wetensch. 82c, 197 (1979)] *T. aquilegiifolium* has been found to contain only unesterified triglochinin.
17. The cinnamic acids, ^3J 12.3 (*cis*) and 15.8 (*trans*) Hz [E.O. Bishop and R.E. Richards, Mol. Phys. 3, 114 (1960)], are simple and appropriate models.

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