Tetrahedron Letters No. 23, pp. 1035-1039, 1962. Pergamon Press Ltd.
Printed in Great Britain.

ON THE BIOSYNTHESIS OF 2,3-DIHYDROXY-4-PHENYL-QUINOLINE (VIRIDICATIN)[1]

Martin Luckner

Pharmakognostisches Institut der Universität Halle

Halle (Saale), DDR

and

Kurt Mothes

Institut für Biochemie der Pflanzen der DAW zu Berlin

Halle (Saale), DDR

(Received 30 July, 1962)

Viridicatin, 2,3-dihydroxy-4-phenyl-quinoline was first isolated from the mycelium of Penicillium viridicatum Westling[2] and later on various strains of Penicillium cyclopium Westling[3]. RAISTRICK et al.[3] have elucidated the constitution of this alkaloid. In the meantime we found three other alkaloids in the culture growth and in the mycelium of Penicillium viridicatum (cyclopenin A, cyclopenin B and alkaloid X). In

---

[1] A more detailed paper will be published in the journal "Archiv der Pharmazie".

[2] CUNNINGHAM, K.G. and G.G. FREEMAN, Biochem. J. 53, 328 (1953)

[3] BRACKEN, A., A. POCKER and H. RAISTRICK, Biochem. J. 57, 587 (1954)

the near future together with J.H. BIRKINSHAW et al.[4] a report on the chemical structure of the compounds will be published.

The strain of Penicillium viridicatum we used, forms alkaloids in surface cultures only. The formation of alkaloids begins at the 4^{th} day of culture and we found the highest incorporation of precursors into the alkaloid viridicatin if the substances were added in minor amounts over a period of three days beginning with the 3^{rd} day of culture.

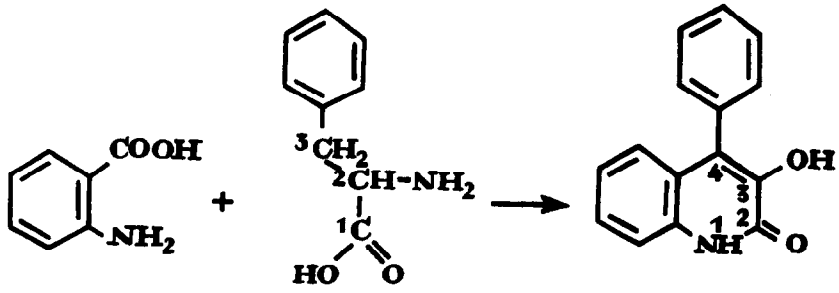
Anthranilic acid-U-^{3}H was incorporated into the viridicatin with a specific rate of 3%, whereas the radioactivity of anthranilic acid-$^{14}COOH$ was not recovered in the viridicatin molecule. Therefore we suppose that the carboxylic group of anthranilic acid is lost by the incorporation of anthranilic acid into the viridicatin.

Phenylalanine-U-^{14}C was incorporated into the alkaloid with a specific rate of up to 80%. After decomposition of the radioactively labelled viridicatin formed in this reaction to 2-aminobenzophenon and oxalic acid(measured as CO_2) 79,4% of the total incorporated radioactivity was found in the 2-aminobenzophenon and 18,8% in the oxalic acid. This distribution can be expected if the whole C-skeleton of phenylalanine is incorporated into the viridicatin and the C-atoms 2 and 3 of the quinolinic ring system of viridicatin are both labelled. In this case 7/9 (77,8%) of the total

[4] J.H. BIRKINSHAW, London School of Hygiene and Tropical Medicine, London. We wish to thank professor BIRKINSHAW for sending us a strain of Penicillium viridicatum.

radioactivity of the viridicatin should be found in the 2-aminobenzophenon and 2/9 (22,2%) in the oxalic acid. Phenylalanine-2-^{14}C under favourable conditions also is incorporated with a specific incorporation rate of 8o%. After decomposition of the viridicatin formed in this reaction all the radioactivity was found in the oxalic acid, that is at the positions 2 or 3 of the quinolinic nucleus. Phenylalanine-3-^{14}C was incorporated with a specific rate of 15%. In this case all the radioactivity after decomposition was found in the 2-aminobenzophenon.

From these experiments it can be concluded that the ring system of viridicatin is formed by the reaction of a phenylpropane derivative (possibly phenylalanine itself) with anthranilic acid, the carboxylic group of anthranilic acid being split off.



ANTHRANILIC ACID PHENYLALANINE VIRIDICATIN

This reaction sequence is a way not yet described in the literature which leads in vivo to the quinoline ring system. The lower incorporation rate of anthranilic acid into the viridicatin we may explain by the faster metabolism of the

compound and the possibility of its dilution with endogenous anthranilic acid formed by the decomposition of tryptophan[5] The formation of the quinolinic ring system of viridicatin seems to be in some way similar to the formation of the indol nucleus of tryptophan[6]. In both cases anthranilic acid is a precursor and the carboxylic group of the anthranilic acid is lost. For this reason we have proposed a mechanism of ring closure for the formation of viridicatin like that of the indol ring of tryptophan, that means first the formation of the anthranilid of a phenylpropionic acid and secondly the formation of an enol-configuration at the ß-C-atom of the phenylpropionic acid. Closely related to this postulated enol is ß-phenylserine. ß-phenylserine forms ß-phenyl-ß-hydroxy-acrylic acid if oxydatively deaminated and enolised. The specific incorporation rate of ß-phenylserine into the

---

5 LUCKNER, M., Z.allgem. Mikrobiol. in the press.

6 NYC, J.F., H.K. MITCHELL, E. LEIFER and W.H. LANGHAM, J. biol. Chemistry 179, 783 (1949)

BONNER, D.M. and C.W.H. PARTRIDGE, Federat. Proc. 9, 154 (1950)

PARTRIDGE, C.W.H. and D.M. BONNER, J. biol. Chemistry 194, 269 (1952)

PARTRIDGE, C.W.H., D.M. BONNER and C. YANOFSKY, J. biol. Chemistry 194, 269 (1952)

YANOFSKY, C., Biochim. biophysica Acta (Amsterdam) 16, 594 (1955), J.biol. Chemistry 223, 171 (1956); Biochim.biophysica Acta (Amsterdam) 20, 438 (1956)

GIBSON, F., C.H. DOY and S.B.SEGALL, Nature (London) 181, 549 (1958)

DOY, C.H. and F. GIBSON, Biochem. J. 72, 586 (1959)

SMITH, O.H. and C. YANOFSKY, J.biol.Chemistry 235, 2051 (1960)

DOY, C.H., A. RIVERA and P.R. SRINIVASAN, Biochem.biophysic. Res.Commun. 4.83 (1961)

DOY, C.H., P.R. SRINIVASAN and A. RIVERA, Federat.Proc. 20, 10 (1961)

viridicatin, however, was only 6-9%. Therefore it is possible that ß-phenyl-ß-hydroxy-acrylic acid is not closely related to viridicatin and the incorporation of ß-phenylserine takes place via phenylalanine. On the other hand ß-phenylserine is not a physiological compound and therefore it may not be oxydatively deaminated or may not be carried quickly to the place of formation of viridicatin.