Tetrahedron Letters No. 51, pp 4543 - 4544, 1977. Pergamon Press. Printed in Great Britain.

A TOTAL SYNTHESIS OF (±)-ISO-OCHRACINIC ACID, A HYDROXY PHTHALIDE FROM ALTERNARIA KIKUCHIANA

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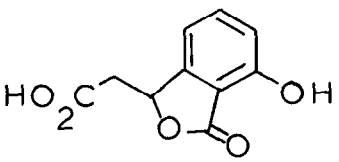
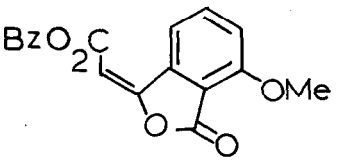
(Received in UK 14 October 1977; accepted for publication 27 October 1977)

Iso-ochracinic acid (1) has recently been isolated[1] from Alternaria kikuchiana, a parasitic fungus which causes black spot disease in Japanese pears. The occurrence of such phthalides in nature is rare[2] and little is known of their biological role. We now wish to report a total synthesis of (1).



(1)



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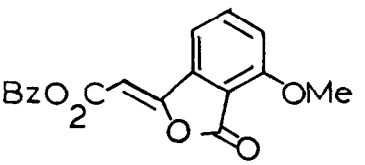
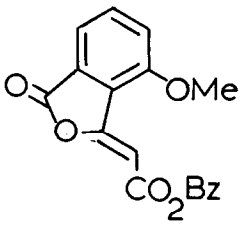


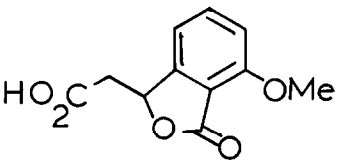
(4)

In earlier studies,[3,4] it has been shown that alkoxycarbonylmethylidene phthalides and butenolides are readily available in high yield by a Wittig reaction between carboxymethylenetriphenylphosphoranes and anhydrides and this suggested a route to (1) employing 3-methoxyphthalic anhydride (2). It was anticipated on steric and electronic grounds that the presence of the 3-methoxy substituent could result in a largely regioselective attack by the phosphorane on the 7-carbonyl of the anhydride. Hydrogenation and deprotection of the resulting ylidenephthalide would then lead to iso-ochracinic acid. In fact, reaction between (2) and benzyloxycarbonylmethylenetriphenylphosphorane in boiling chloroform resulted in the formation of three isomeric benzyloxycarbonylmethylidenephthalides, in an overall yield of 87%, which were separated by chromatography over silica gel eluted with chloroform. The structures were assigned as follows:- The least polar isomer (A) (24%), m.p. 94-95°, showed ν_{max} ($CHC\ell_3$) 1774, 1700 and 1640 cm^{-1}, τ ($CDC\ell_3$) 1.36 (d, J = 8.5Hz), 2.30 (t, J = 8.5Hz), 2.60 (s, C_6H_5), 2.88 (d, J = 8.5Hz), 3.88 (:$CH.CO_2Bz$), 5.75 (CH_2Ph) and 6.01 (OMe). These data, particularly the low-field doublet at τ 1.36, lead to the conclusion that this isomer is the 3-(E)-7-methoxyphthalide (3). It has previously been shown[3] that in compounds such as (3), the near-by ester carbonyl group deshields the 4-H to an extent of ca. 1τ. The most polar isomer C(14%), m.p. 134.5-135°, showed ν_{max} ($CHC\ell_3$) 1798, 1710 and 1670 cm^{-1}., τ ($CDC\ell_3$) 2.30 (t, J = 8.5Hz), 2.6 (m, C_6H_5), 2.74 (d, J = 8.5Hz), 2.92 (d, J = 8.5Hz),

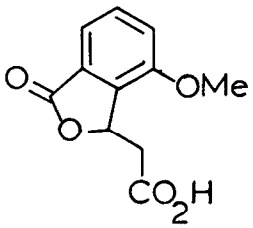
4.12 (:$CHCO_2Bz$), 4.72 (.CH_2Ph) and 6.00 (OMe). Although an unambiguous assignment of structure was not possible from these data, it was suspected that this was the 3-(Z)-7-methoxyphthalide (4) on the grounds of the close similarity of its n.m.r. spectrum to isomer (3), and by contrast to the third isomer B, (49%), which had m.p. 138-139°, ν_{max} ($CHCl_3$) 1778, 1738 and 1660 cm^{-1}, τ ($CDCl_3$) 2.38-2.74 (m, 7H), 2.84 (dd, J = 8.5 and ca 1Hz), 3.78 (:CH CO_2B_z), 4.75 (CH_2Ph) and 6.08 (OMe). The latter isomer was tentatively assumed to be the 3-(Z)-4-methoxy isomer (5); presumably the fourth possible isomer, the 3-(E)-4-methoxy-, is not formed due to excessive steric interaction with the methoxy group.



(5)



(6)



(7)

Each isomer was then hydrogenated (10% Pd-C; MeOH) until two equivalents of hydrogen were adsorbed. Isomers A and C gave the same compound, (6), (90%) m.p. 197-198°, ν_{max} ($CHCl_3$) 1760 and 1720 cm^{-1}, which had τ ($CDCl_3$-$(CD_3)_2CO$) 2.32 (t, J = 8Hz), 2.86 (d, J = 8Hz), 2.97 (d, J = 8Hz), 4.20 (t, J = 7Hz), 6.01 (OMe) and 7.14 (d, J = 7Hz), thus confirming the structure of C as (4). These data are closely similar to those reported for iso-ochracinic acid.[1] By contrast, hydrogenation of isomer B(5) gave a compound which was clearly different; it had m.p. 209-210°, ν_{max} ($CHCl_3$) 1778, and 1726 cm^{-1}, τ($CDCl_3$-$(CD_3)_2CO$) 2.30-2.85 (m, 3H), 4.15 (dd, J = 8 and 3Hz), 6.06 (OMe), 6.70 (dd, J = 17 and 3Hz) and 7.45 (dd, J = 17 and 8Hz). These data confirm structure (7) for this compound, the n.m.r. data indicating that free rotation of the carboxylic acid side chain is hindered by the proximity of the 4-methoxy group.

Final conversion of (6) to iso-ochracinic acid was achieved in moderate yield by demethylation with boron tribromide at -70°, to give (1), m.p. 159-160°, identical (m.p., u.v., n.m.r.) to the data recorded[1] for (1).

It is interesting to note that the reaction between phthalic anhydride itself and alkoxycarbonylmethylenetriphenylphosphoranes leads exclusively to the (E) isomer[3]. It has been proposed[3] that this is due to a favourable interaction between the ester carbonyl group and the aromatic ring. Presumably, with 3-methoxyphthalic anhydride, this is less favourable due to the greater electron density caused by the methoxy substituent. Furthermore, the 3-methoxy substituent induces attack by the phosphorane predominantly (ca 5:4) at the more hindered carbonyl of the anhydride. This could possibly be due to an attractive interaction between the phosphonium cation and the π-electrons of the aromatic methoxyl group. The factors governing the site of attack and the product stereochemistry are at present under investigation.

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