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SYNTHESIS OF ASPERENONE, A NEW PIGMENT FROM ASPERGILLUS NIGER AND ASPERGILLUS AWAMORI

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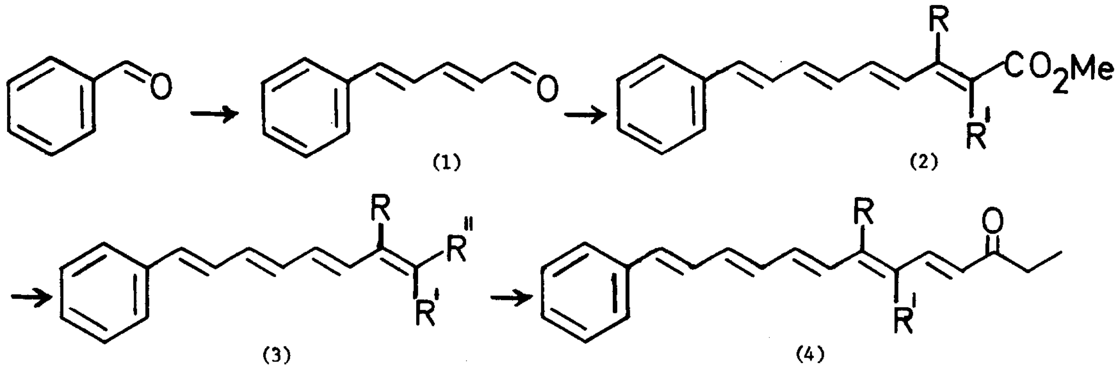
Asperenone is the name proposed[1] ('asperyellone' has also been suggested[2]) for a new yellow pigment isolated from Aspergillus niger and Aspergillus awamori. The pigment was isolated and characterised independently in two laboratories.[1,2] Chemical and spectroscopic studies indicate that the pigment is a methyl derivative of 13-phenyltrideca-4,6,8,10,12-pentaen-3-one, with the methyl group located somewhere on the side chain. The exact location of the methyl group is not known, but n.m.r. deuteration[1] and decoupling[2] experiments on the decahydro derivative show that it is not located on carbon atoms 4,5,12 or 13. Examination of the relative abundances of hydrocarbon fragments in the mass spectrum of asperenone led Yu *et al.*[2] to assign two structures for the pigment, the methyl group being located on either C-7 (4a) or C-6 (4b); of these two structures the Japanese authors favour (4a). Jefferson,[1] however, on the basis of similar mass spectral analysis, suggests the methyl group is most likely located on C-8 (10). This communication describes unambiguous syntheses of the three structures (4a), (4b) and (10) put forward for asperenone. Comparison with the natural material confirms structure (10) for asperenone.

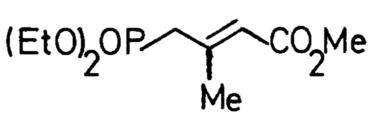
Reaction of benzaldehyde with the Grignard reagent derived from 1-methoxybut-1-en-3-yne followed by reduction ($LiAlH_4$) of the resulting acetylenic alcohol, and acid work up, gave the diene-aldehyde (1).[3] Condensation of (1) with a *cis*-*trans* mixture of the phosphonate ester (5)[4] derived from methyl 3-bromomethylcrotonate, in the presence of sodium methoxide, gave a mixture of isomers of (2a) from which the all-*trans*-(*E*) ester (2a), m.p. 100-101°; $\lambda_{max.}$(EtOH) 272 (15.6), 345 (52.8), 361.5 (65.3), 377 (57.6) mμ.[5], $\nu_{max.}$($CHCl_3$) 1705, 1615, 1600, 1585, 1000 $cm.^{-1}$, τ 2.4-2.8 (5H,m), 3.0-3.6 (6H,m), 4.18 (:C$\underline{H}$.CO_2Me), 6.28 (OMe), 7.67 (:C.Me), was isolated by chromatography and crystallisation. Reduction of (2a) with lithium aluminium hydride gave the alcohol (3a, R"= CH_2OH), m.p. 123-124°; $\lambda_{max.}$(EtOH) 328, 342, 362 mμ., $\nu_{max.}$($CHCl_3$) 3400, 1600, 1590, 1070, 995 $cm.^{-1}$, τ 2.5-3.0 (5H,m), 3.1-3.8 (6H,m), 4.3 (t,*J* 7, :C$\underline{H}$-CH_2), 5.71 (d,*J* 7,-CH_2-), 8.18 (:C.Me), ~8.3 (OH), which gave the corresponding aldehyde



(1) (2) (3) (4)

a R = Me; R' = H *b* R = H; R' = Me.

(3a, R" = -CHO), m.p. 126-127°; $\lambda_{max.}$(CHCl$_3$) 281 (6.6), 386 (60.6) mμ.[5], $\nu_{max.}$(Nujol) 2710, 1645, 1590, 1570, 995, 746, 688 cm.$^{-1}$, τ -0.14 (d,*J* 7.5,-C*H*O) 2.4-2.8 (5H,m), 3.0-3.8 (6H,m), 4.0 (d,*J* 7.5, :C*H*.CHO), 7.7 (:C.Me), on oxidation with manganese dioxide. Wittig reaction between (3a, R" = CHO) and phosphorane (7)[6] in refluxing di-n-butyl ether, followed by chromatography and crystallisation, gave the all-*trans*-(*E*) ketone (4a), m.p. 150-152° (natural asperenone has m.p. 128-130°); $\lambda_{max.}$ 412 (80.2), 390 (98.0), 372 (73.0), 295 (8.8), 285 (8.0) mμ.[5], $\nu_{max.}$(Nujol) 1655, 1610, 1596, 1572, 1560, 1005, 980, 750, 690 cm.$^{-1}$, τ 2.35 (dd,*J* 11.5 and 15.5, C-5-H), 2.4-2.8 (∿5H,m), 3.0-3.6 (∿7H,m), 3.79 (d,*J* 15.5, C-4-H), 7.4(q,*J* 7.5,-CH_2-), 7.98 (:C.Me), 8.87 (t,*J* 7.5, CH_3).



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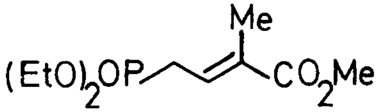

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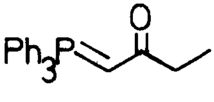
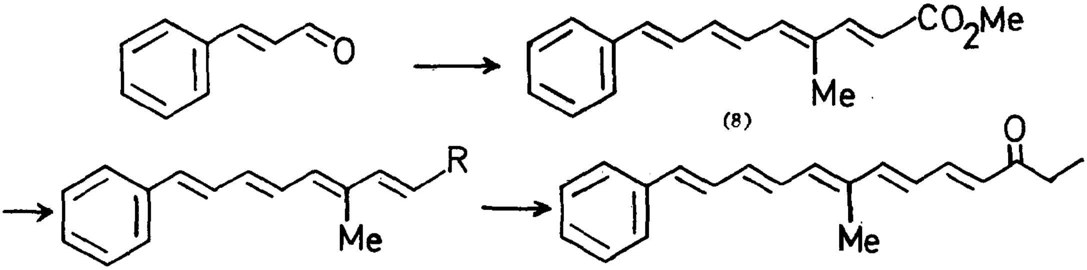


(7)

By a similar series of transformations, but using phosphonate ester (6)[4] in place of (5), the all-*trans*-(*E*)-6-methyl ketone (4b) was obtained having m.p. 127-129° (depressed to m.p. 110-114° on admixture with natural asperenone, m.p. 128-130°); $\lambda_{max.}$ 414.5 (92.7), 391.5 (105), 371 (74.2) mμ.[5], $\nu_{max.}$(Nujol) 1680, 1603, 1590, 1572, 1555, 995, 748, 690 cm.$^{-1}$; τ 2.35-2.8 (∿6H,m), 3.0-3.6 (∿7H,m), 3.78 (d,*J* 15.5, C-4-H), 7.38 (q,*J* 7.5, -CH_2-), 8.07 (:C.Me), 8.87 (t,*J* 7.5, -CH_3). The mass spectra of the synthetic 7-methyl-(4a) and 6-methyl-ketones (4b) were closely similar with that of natural asperenone (determined under the same conditions) but their n.m.r. (notably the τ 2-4 region) and i.r. spectral data were quite different from the data given for the natural material.

Condensation between cinnamaldehyde and the trans-(E)-2, trans-(E)-4 phosphorane (15), gave a mixture of isomers of ester (8) from which the all-trans-(E) tetraene (8), m.p. 105-107°; $\lambda_{max.}$ 272.5 (10.2), 347.5 (48.1), 367 (64.1), 382 (55.9) mμ.^{5}, $\nu_{max.}$ 1700, 1615, 1590, 1575, 995 cm.$^{-1}$, τ 2.4-2.75 (6H,m), 3.0-3.6 (5H,m), 4.05 (d,J 15.5, :CH.CO_2Me), 6.21 (OMe), 8.05 (:C.Me), was separated by chromatography and crystallisation. Phosphorane (15) was obtained from methyl 3,3'-dimethylacrylate (11, R = Me) as follows^7: Reaction with NBS gave a mixture of cis-, and trans-isomers of bromide (11, R = CH_2Br), which, during a Kröhnke reaction yielded the trans-(E)-aldehydo-ester (11, R = CHO) exclusively. The latter was converted into the corresponding acetal (12, R = CO_2Me) which was then reduced ($LiAlH_4$) to the hydroxy-acetal (12, R = CH_2OH). Treatment of (12, R = CH_2OH) with Ac_2O/C_5H_5N gave the trans-(E)-acetoxy-aldehyde (13) directly, and Wittig condensation between (13) and phosphorane (16) furnished the trans-(E)-2, trans-(E)-4-acetoxy ester (14). Reaction of (14) with triphenylphosphonium bromide, and treatment of the phosphonium salt thus formed with base, gave the corresponding phosphorane (15). Reduction ($LiAlH_4$) of ester (8) gave alcohol (9, R = CH_2OH), which was oxidised (MnO_2) to the corresponding aldehyde (9, R = CHO). Condensation between (9, R = CHO) and (7), followed by chromatography and crystallisation of the product, gave all-trans-(E)-8-



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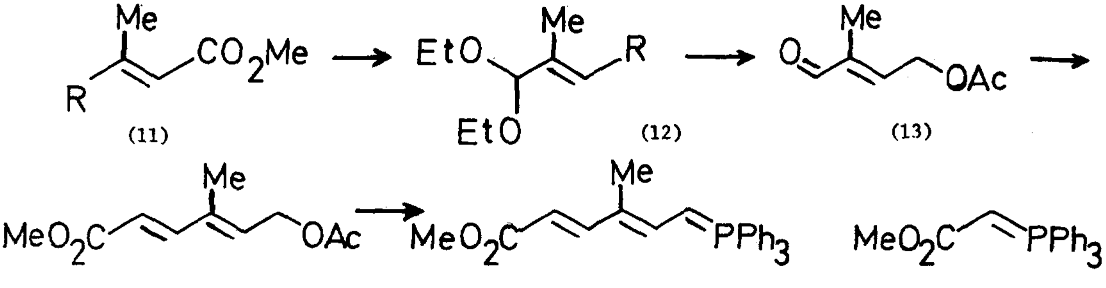
(10)



(11) (12) (13)

(14) (15) (16)

-methyl ketone (10), m.p. 128-130° (undepressed on admixture with natural asperenone, m.p. 128-130°); $\lambda_{max.}$ 415 (81.0), 392 (94,8), 371.5 (70.5) mμ.[5], $\nu_{max.}$ (KBr) 1673, 1590, 1574, 1560, 1550, 1224, 1143, 1035, 1005, 990, 983, 880, 868, 848, 833, 752, 698 cm.$^{-1}$, τ 2.4-2.8 (∿6H,m), 3.0-3.6 (∿7H,m), 3.78 (d,*J* 15.5, C-4-H), 7.4 (q,*J* 7.5,-CH_2-), 8.02 (:C.Me), 8.87 (t,*J* 7.5, CH_3). *A mass spectrum was identical with that of natural asperenone (determined under the same* conditions) and the visible and i.r. light absorption, and n.m.r. data were closely similar with those reported for the natural pigment.

I thank Dr. W.E. Jefferson, Jnr., fot supplying a sample of natural asperenone, and Professor L. Crombie for his interest.

REFERENCES.

1. W.E. Jefferson, *Biochemistry*, *6*, 3479, (1967).
2. J. Yu, G. Tamura, N. Takahashi and K. Arima, *Agr. Biol. Chem.*, *31*, 831, (1967).
3. D. Marshall and M.C. Whiting, *J. Chem. Soc.*, 4082, (1956).
4. G. Pattenden and B.C.L. Weedon, *J. Chem. Soc.(C)*, 1984, 1997, (1968).
5. Visible and ultraviolet light absorption data were determined for light petroleum (b.p. 60-80°) solutions unless indicated otherwise; ε x 10^{-3} in parentheses.
6. K. Fujiwara, H. Takahashi and M. Ohta, *Bull. Chem. Soc. Japan*, *35*, 2042, (1962).
7. G. Pattenden, J.E. Way and B.C.L. Weedon, *J. Chem. Soc.(C)*, In the press.