Palladium-catalysed Ring Opening of Oxazines: a Means of Stereospecific Isotopic Labelling at Benzylic Carbon

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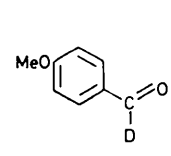
Summary The synthesis is reported of 3-(4-methoxyphenyl)propionic acid (**11**) asymmetrically labelled at C-3 with deuterium by a procedure which involves as key step the palladium-catalysed ring opening of the optically active oxazine (**6**).

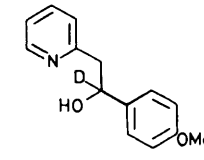
THE synthesis of phenylpropanoid, C_6—C_3, units stereospecifically labelled at the benzylic position with deuterium or tritium has recently received much attention in biosynthetic investigations.[1] We now report the synthesis of 3-(4-methoxyphenyl)propionic acid (**11**), a versatile intermediate in the synthesis of biologically active compounds, stereospecifically labelled at C-3 with deuterium by a route which involves ring opening of the optically active oxazine (**6**).

The products formed and the stereochemistry of this palladium-catalysed, formal disproportion of substituted cyclic amino-acetals to amides has been previously investigated in the oxazolidine system.[2] Although there is not yet unequivocal evidence for any particular mechanism, the present work establishes unequivocally that oxygen removal from C-6 of (**6**) occurs with inversion of configuration, because in the amide (**7**) the hydrogen enters with opposite configuration to that of the hydroxy-group in the parent amino-alcohol (**3**), and, further, offers an alternative synthetic approach to stereospecifically labelled phenylpropanoid units with high optical purity.

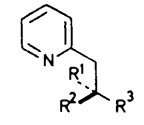
4-Methoxy[*formyl*-^{2}H]benzaldehyde (**1**) (96% $^2H_1$) was converted into the pyridine derivative (**2**)[3] which was resolved *via* the camphosulphonate and (−)-dibenzoyltartrate salts. Hydrogenation of the (+)-isomer (**3**) led to a separable mixture of diastereoisomeric piperidines (**5**) without deuterium loss. Mixture (**5**) was converted into the oxazine (**6**) by treatment with formaldehyde in aqueous ethanol. The oxazine (**6**) was heated for 0·5 h with 20% w/w 10% Pd/C in refluxing ethanol to yield the amide (**7**) (> 90%), with no deuterium loss. Reduction ($LiAlH_4$) of (**7**) gave the amine (**8**). Hoffman degradation of the



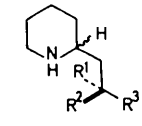
(1)



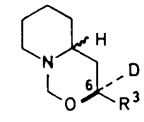
(2)



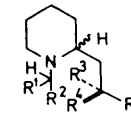
(3) R^1 = D; R^2 = OH; R^3 = *p*-MeO·C_6H_4
(4) R^1 = OH, R^2 = D; R^3 = *p*-MeO·C_6H_4



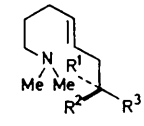
(5) R^1 = D; R^2 = OH; R^3 = *p*-MeO·C_6H_4



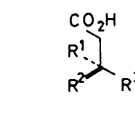
(6) R^3 = *p*-MeO·C_6H_4



(7) R^1,R^2=O; R^3=H; R^4=D; R^5= *p*-MeO·C_6H_4
(8) R^1=R^2=R^3=H; R^4=D R^5= *p*-MeO·C_6H_4



(9) R^1=H; R^2=D; R^3=*p*-MeO·C_6H_4
(10) R^1=H; R^2=OH; R^3=*p*-MeO·C_6H_4



(11) R^1 = H; R^2 = D; R^3 = *p*-MeO·C_6H_4
(12) R^1 = H; R^2 = D; R^3 = CO_2H
(13) R^1 = H; R^2 = OH; R^3 = *p*-MeO·C_6H_4
(14) R^1 = H; R^2 = OH; R^3 = CO_2H

methiodide of (**8**) gave a mixture of olefins, from which the compound (**9**) was isolated by chromatography (70% yield; 95% $^2H_1$). Careful ozonolysis of (**9**), followed by oxidative work up, yielded the required 3-(4-methoxyphenyl) [3-^{2}H]-propionic acid (**11**), which, on further ozonolysis in MeOH–$CHCl_3$ at room temperature gave [2-^{2}H]succinic acid in nearly quantitative yield. The latter sample was shown by o.r.d. comparison with reference samples[4] to contain 98 ± 10% of the (2*S*)-isomer (**12**).

The absolute configuration of the starting hydroxy-compound (**3**) was determined by degradation to malic acid, characterized as diamide,[5] by a route similar to that used in the conversion of (**8**) into succinic acid. Thus, the undeuteriated amino-alcohol (**3**) was converted into the methyltoluene-*p*-sulphonate by treatment with methyltoluene-*p*-sulphonate and hydrogenated[6] to a compound which, under Hoffman conditions, was cleaved to the olefin (**10**). Ozonolysis of (**10**) gave the propionic acid (**13**) {methyl ester showed $[\alpha]^{589}$ + 2 (*c* 0·21 in MeOH)}. Further exhaustive ozonolysis of (**13**) yielded (*S*)-malic acid (**14**), purified as the diamide.

Complementary evidence for the stereochemical course of the reaction was achieved starting from the (−)-isomer (**4**). As expected, from the (*R*)-alcohol through the aforementioned sequence, (*R*)-deuteriosuccinic acid was eventually isolated (optical purity > 97%). The overall yield of (**13**) from unresolved (**2**) was *ca.* 25%.

We have therefore established that the ring opening of the optically active oxazine (**6**) proceeds with inversion of configuration at C-6, and suggests an alternative synthesis of asymmetrically labelled precursors. The use of this method for the synthesis of tritiated materials is under investigation.

We thank Professor P. Salvadori, Università di Pisa, for the o.r.d. measurements on a Cary 60 spectrometer.

(*Received, 7th August* 1972; *Com.* 1376.)

[1] A. R. Battersby, J. Kelsey, and J. Staunton, *Chem. Comm.*, 1971, 183; K. H. Hanson, R. H. Wightman, J. Staunton, and A. R. Battersby, *ibid.*, p. 185; G. W. Kirby and J. Michael, *ibid.*, p. 187.

[2] D. Ghiringhelli and L. Bernardi, *Tetrahedron Letters*, 1967, 1039; L. Bernardi, C. Fuganti, and D. Ghiringhelli, *Gazetta*, 1968, **98**, 836.

[3] E. Profft and F. Schneider, *J. prakt. Chem.*, 1955, [4] **2**, 316.

[4] J. W. Cornforth, G. Ryback, G. Popjak, C. Donninger, and G. Schroepfer, *Biochem. Biophys. Res. Comm.*, 1962, **9**, 371; J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popják, G. Ryback, and G. J. Schroepfer, jun., *Proc. Roy. Soc.*, 1966, **163**, *B*, 436.

[5] H. Arakawa and M. Nakasaki, *Chem. and Ind.*, 1960, 73.

[6] C. Schöpf, G. Dummer, and W. Wüst, *Annalen*, 1959, **626**, 134.