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Stereospecific Hydrogenation of (*Z*)-α-Benzoylamino-*o*-benzyloxy-[β-^{2}H]cinnamic Acid

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Photoisomerisation of (*Z*)-4-(2-acetoxybenzylidene)-2-phenyloxazolin-5-one gave the *E*-isomer. The stereochemistry of each form was established by successive treatment with alkali and acid: the former gave an *o*-hydroxycinnamic acid and the latter a coumarin. Catalytic (10% palladium–carbon) hydrogenation of (*Z*)-α-benzoylamino-*o*-benzyloxy[β-^{2}H]cinnamic acid and cyclisation (dicyclohexylcarbodi-imide) of the resulting phenolic acid gave 3-benzoylamino-3,4-dihydro[4-^{2}H]coumarin. The *trans*-orientation of the hydrogen atoms in this product, revealed by n.m.r. spectroscopy, showed that hydrogenation of the cinnamic acid had occurred in a *cis* manner with high stereoselectivity.

In developing a synthetic route [1] to aromatic amino-acids labelled [as in (1)] stereospecifically with deuterium or tritium in the β-methylene group, we required to know the steric course of reduction of acylaminocinnamic acids [as (2)]. To this end, we have studied *o*-hydroxycinnamic derivatives in the expectation that the phenolic hydroxy-group might be used to establish both the geometrical configuration of the cinnamic acid (2) and the orientation of deuterium in the reduction product (1).

o-Acetoxybenzaldehyde and benzoylglycine are reported [2] to condense in acetic anhydride containing a

[1] K. R. Hanson, R. H. Wightman, J. Staunton, and A. R. Battersby, *Chem. Comm.*, **1971**, 185; G. W. Kirby and J. Michael, *ibid.*, pp. 187 and 415.

[2] I. E. Erlenmeyer and W. Stadlin, *Annalen*, 1904, **337**, 283; A. Neuberger, *Biochem. J.*, 1948, **43**, 600.

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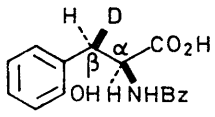
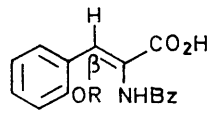
base to give a mixture of an oxazolinone (3; R = Ac) and a coumarin (4). The geometrical configuration of the oxazolinone was not explicity stated, but treatment with alkali, followed by acidification, gave a cinnamic acid (2; R = H) which did not spontaneously cyclise to the coumarin (4). We have found, in contrast, that ring-opening of the coumarin (4) with


(1)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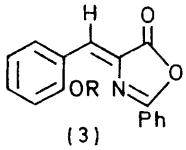
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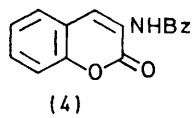
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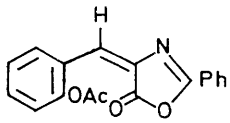
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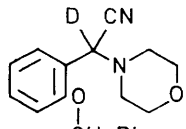
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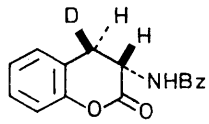
(7)

alkali, followed by acidification, regenerates the coumarin. It appeared likely, therefore, that the oxazolinone (3; R = Ac) and the cinnamic acid (2; R = H) both had the *trans*-cinnamoyl or *Z*-configuration. To confirm this point, a route to the unknown, isomeric oxazolinone (5) was sought. Baumann *et al.* have reported [3] that irradiation of the stable geometrical isomer of 4-benzylidene-2-phenyloxazolin-5-one gave a photostationary mixture of both geometrical isomers. Using this method, we converted the oxazolinone (3; R = Ac) into a mixture of isomers (3; R = Ac) (*ca.* 80%) and (5) (*ca.* 20%) separable by preparative t.l.c. on silica gel. Treatment of the new isomer (5) successively with alkali and acid gave the coumarin (4) rather than the geometrical isomer of (2; R = H). The configuration of compounds (2), (3), and (5) was thus placed beyond doubt.*

The stereochemistry of reduction of acylaminocinnamic acids was investigated as follows. *o*-Benzyloxybenz[^{2}H]aldehyde, prepared [6] by hydrolysis of the deuteriated morpholinonitrile (6), was converted *via* the corresponding oxazolinone [7] (3; R = CH_2Ph, D for H at benzylic position) into the β-deuteriocinnamic acid (2; R = CH_2Ph, D for β-H). The stereochemistry of compound (2; R = CH_2Ph) followed from the observation that the same isomer was formed from the phenol (2; R = H) on treatment with benzyl chloride and ethanolic potassium hydroxide.

Catalytic hydrogenation of β-deuterio-(2; R = CH_2-Ph) over 10% palladium–carbon gave the acid (1). Hydrogenation occurred in two stages, reduction of the double bond preceding hydrogenolysis of the benzyloxy-group. The relative configuration of the two chiral centres † in (1) was determined by cyclisation to the lactone (7). Cyclisation occurred readily at the m.p. of compound (1), but the n.m.r. spectrum of the product (see later) revealed that epimerisation of the α-centre had also taken place. However, treatment of (1) with dicyclohexylcarbodi-imide in dioxan gave the lactone (7) without epimerisation. The n.m.r. spectrum of unlabelled lactone (7) showed an ABX ($|J_{AB}|$ 14·7, $|J_{AX}|$ 5·8, and $|J_{BX}|$ 14·8 Hz) pattern for the aliphatic protons, after conversion of NH into ND. The large (14·8 Hz) vicinal coupling constant must be assigned to hydrogens *trans*-orientated about the six-membered lactone ring. This coupling persisted in the spectrum of the deuteriated compound (7; ND for NH), which must therefore have the relative configuration shown. No significant amounts of the other possible diastereoisomer were revealed by the n.m.r. spectrum of compound (7), and we conclude that hydrogenation of the double bond of (2; R = CH_2Ph) had occurred with at least 90% *cis*-stereospecificity.

These results formally provide a route to stereospecifically labelled *o*-tyrosine and, more importantly, when taken with two related examples,[1] show that catalytic hydrogenation of α-acyl aminocinnamic acids may be used generally to prepare aromatic amino-acids labelled stereospecifically in the β-methylene group.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were measured at 60 MHz. Light petroleum refers to the fraction, b.p. 40—60°.

(Z)-4-(2-*Acetoxybenzylidene*)-2-*phenyloxazolin*-5-*one* (3; R = Ac) *and* 3-*Benzoylaminocoumarin* (4).—Condensation [2] of 2-acetoxybenzaldehyde and benzoylglycine in acetic anhydride in the presence of potassium carbonate or sodium acetate gave a crystalline mixture of oxazolinone and coumarin. Recrystallisation from benzene–ethanol gave the oxazolinone. Chromatography of the mother liquors on neutral, grade III alumina and elution with benzene–chloroform gave, in the early fractions, the coumarin, which was crystallised from ether (*ca.* 7% yield).

(Z)-α-*Benzoylamino*-o-*hydroxycinnamic Acid* (2; R = H). —The (*Z*)-oxazolinone (3; R = Ac) was heated in aqueous

* The geometrical configuration of several other aralkylideneoxazolinones has recently been established.[1,4] Earlier work has been reviewed.[5]

† All chiral compounds reported in this paper were racemic.

[3] N. Baumann, M. Sung, and E. F. Ullman, *J. Amer. Chem. Soc.*, 1968, **90**, 4157.

[4] A. P. Morgenstern, C. Schutij, and W. Th. Nauta, *Chem. Comm.*, 1969, 321; A. E. A. Porter and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 2530; K. Brocklehurst, R. P. Bywater, R. A. Palmer, and R. Patrick, *Chem. Comm.*, 1971, 632.

[5] W. Steglich, *Fortschr. chem. Forsch.*, 1969, **12**, 77.

[6] D. J. Bennett, G. W. Kirby, and V. A. Moss, *J. Chem. Soc.* (*C*), 1970, 2049.

[7] F. Bergel, J. W. Haworth, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 1944, 261.

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methanol with an excess of sodium hydroxide. Acidification of the mixture gave the acid (2; R = H). Treatment of the coumarin (4) under the same conditions, followed by acidification, yielded unchanged coumarin.

(E)-4-(2-*Acetoxybenzylidene*)-2-*phenyloxazolin*-5-*one* (5).—The (*Z*)-oxazolinone (3; R = Ac) (500 mg) in dry, degassed propan-2-ol (500 ml), was irradiated with u.v. light through Pyrex for 5 h under nitrogen. The solution was concentrated at 20 °C to 200 ml and the precipitated (*Z*)-oxazolinone (193 mg) was filtered off. The filtrate was evaporated to dryness and the resulting mixture of (*Z*)- and (*E*)-oxazolinones was separated on silica plates (Merck PF_{254}), developed with chloroform–benzene (1 : 1). Each component was eluted immediately from the silica with chloroform. The component of lower R_F, the (E)-*oxazolinone* (89 mg), had m.p. 124° (from chloroform–light petroleum) (Found: C, 70·1; H, 4·5; N, 4·5. $C_{18}H_{13}NO_4$ requires C, 70·4; H, 4·3; N, 4·6%). The other component was the (*Z*)-oxazolinone (170 mg). The n.m.r. spectrum ($CDCl_3$) of the (*E*)-oxazolinone showed signals at τ ($CDCl_3$) 1·40 (m, 6-H) and 2·36 (s, benzylic H). The corresponding values for the other isomer were 1·05 and 2·65, in accord with earlier predictions [4] that protons *cis* to the carbonyl group of oxazolinones absorb at higher field than those *cis* to the ring nitrogen atom.

The (*E*)-oxazolinone (32 mg) was shaken overnight at room temperature in ethanol (3 ml) containing 0·5N-sodium hydroxide (1 ml). 3-Benzoylaminocoumarin (23 mg) was obtained from the mixture.

α-2-*Benzyloxyphenyl*-α-*morpholinoacetonitrile*.—2-Benzyloxybenzaldehyde (10·1 g) and morpholine perchlorate (10·2 g) were heated at 60 °C in morpholine for 1 h. Sodium cyanide (2·65 g) in the minimum quantity of water was added, and the mixture was heated for 1 h at 90 °C. Dilution with water (200 ml) precipitated the *morpholinoacetonitrile* (15 g), m.p. 97° (from light petroleum) (Found: C, 74·1; H, 6·6; N, 9·4. $C_{19}H_{20}N_2O_2$ requires C, 74·0; H, 6·5; N, 9·1%).

Conversion into the α-deuterio-derivative was effected [6] by treatment with sodium hydride in dimethylformamide followed by acidification with thionyl chloride–deuterium oxide.

2-*Benzyloxybenz*[^{2}H]*aldehyde*.—The deuteriated morpholinoacetonitrile (6) (3·09 g) was heated under reflux in 2N-hydrochloric acid (50 ml) for 1 h. Extraction with dichloromethane gave the product (1·26 g), which was crystallised from ether–light petroleum.

(Z)-α-*Benzoylamino*-o-*benzyloxycinnamic Acid*.—The appropriate oxazolinone [7] (0·71 g) was heated under reflux in methanol (7 ml) containing aqueous 2% sodium hydroxide (14 ml) for 3 h. Evaporation of the bulk of the methanol and acidification gave the *cinnamic acid* (0·63 g), m.p. 240° (from ethyl acetate–light petroleum) (Found: C, 74·2; H, 5·0; N, 3·8. $C_{23}H_{19}NO_4$ requires C, 74·0; H, 5·1; N, 3·8%). Deuteriated material was made in the same way from the oxazolinone prepared from 2-benzyloxybenz[^{2}H]aldehyde.

2-*Benzoylamino*-3-o-*hydroxyphenyl*[3-^{2}H]*propionic Acid* (1).—The appropriate deuteriated cinnamic acid (500 mg) in ethanol (20 ml) was hydrogenated over 10% palladium–carbon (50 mg) for 30 h. The product (306 mg) had m.p. 176° (lit.,[8] 176° for non-deuteriated material) (from ethyl acetate–light petroleum).

3-*Benzoylamino*-3,4-*dihydrocoumarin*.—The appropriate dihydrocinnamic acid, (150 mg) prepared in the manner described above for deuteriated material, in dry dioxan (6 ml) was treated with dicyclohexylcarbodi-imide (103 mg). After 2 h at room temperature the precipitated dicyclohexylurea was filtered off and the filtrate was evaporated. The residue was extracted with benzene and the extract evaporated to give the *dihydrocoumarin* (93 mg), m.p. 189° (from aqueous ethanol) (Found: C, 71·9; H, 4·8; N, 5·3. $C_{16}H_{13}NO_3$ requires C, 71·9; H, 4·9; N, 5·2%). The n.m.r. spectrum of the alicyclic protons (after conversion of NH into ND; $|J_{NH}|$ 6·0 Hz) was analysed as an ABX system: τ ($CDCl_3$) 5·03 (X), 6·38 (A), and 6·98 (B) ($|J_{AB}|$ 14·7, $|J_{AX}|$ 5·8, $|J_{BX}|$ 14·8 Hz). The high-field signals due to the axial methylene proton were broadened, presumably by coupling to aryl hydrogen. For the deuterio-derivative (7), vicinal coupling constants of 13·7 and 14·0 Hz were observed for two different specimens.

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[8] L. Blum, *Arch. exp. Path. Pharmak.*, 1908, **59**, 273.