Further Observations on the Cyclisation of 2-Benzamido-1-phenylpropan-1-ol

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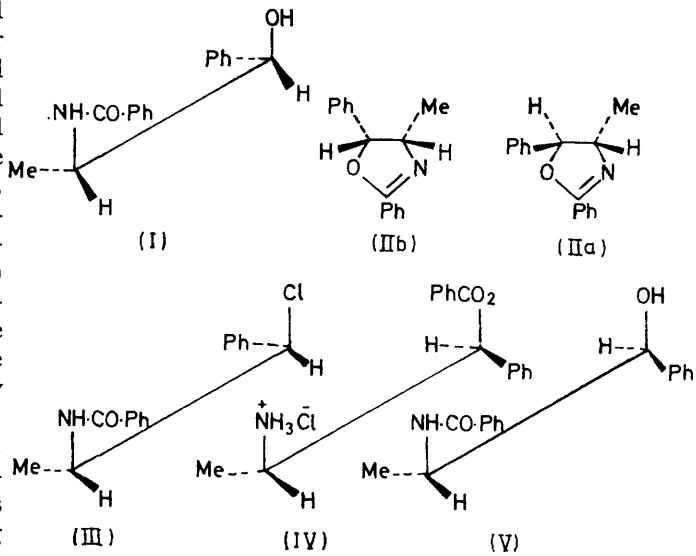
The formation of *threo*-2-benzamido-1-phenylpropan-1-ol from attempted cyclisation of its *erythro*-isomer is explained. In place of the expected 3-methyl-1-phenylisoquinoline, cyclisation yields 4-methyl-2,5-diphenyl-Δ^2-oxazoline. Attempted isolation of the product *via* hydrochloride salt formation results in ring opening and eventual formation of *threo*-2-benzamido-1-phenylpropan-1-ol *via* a three-stage process.

Goszczyński and Kopczyński have recently shown [1] that the cyclisation of *erythro*-2-benzamido-1-phenylpropan-1-ol to 3-methyl-1-phenylisoquinoline can be effected by phosphorus pentoxide in boiling decalin. An earlier procedure using phosphorus pentoxide and phosphoryl chloride in boiling xylene described by Whaley and Hartung [2] and since published by one of us [3] as a standard preparation was shown not to have given the isoquinoline but the *threo*-isomer (V) of the original *erythro*-amide (I). It was suggested that in the Whaley and Hartung reaction, the *threo*-amide could have resulted from *threo*-2-amino-1-benzoyloxy-1-phenylpropane hydrochloride (IV) and that the latter was derived from *trans*-4-methyl-2,5-diphenyl-Δ^2-oxazoline (IIa) although surprisingly, the isolation and identification of these intermediates were not attempted, and no real evidence for this pathway was presented.

Work carried out simultaneously has confirmed that the Whaley and Hartung product is *threo*-2-benzamido-1-phenylpropan-1-ol (V), but that its mode of formation is somewhat different to that suggested in the foregoing scheme.

A careful examination of the Whaley and Hartung reaction showed that treatment of the *erythro*-amide (I) with phosphorus pentoxide and phosphoryl chloride in



boiling xylene leads to a high yield (80%) of a *trans–cis* mixture (90 : 10 from n.m.r.) [4] of 4-methyl-2,5-diphenyl-Δ^2-oxazoline (IIa and b) (plus a trace of isoquinoline),

[1] S. Goszczyński and T. Kopczyński, *J. Org. Chem.*, 1973, **38**, 1245.

[2] W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, 1949, **14**, 650.

[3] A. O. Fitton and R. K. Smalley, 'Practical Heterocyclic Chemistry,' Academic Press, London, 1968, p. 79.

[4] E. Ghera and S. Shouha, *J.C.S. Chem. Comm.*, 1972, 639.

and that complications then arise during the attempted isolation of the product *via* its hydrochloride. Thus, treatment of the oxazoline mixture with dry hydrogen chloride in dry benzene gave 2-benzamido-1-chloro-1-phenylpropane from which on crystallisation, using dry propan-2-ol–light petroleum, the *erythro*-form (III), m.p. 109—111° (lit.,[5] 112—113°) was isolated. The presence of traces of moisture during the crystallisation (and of D_2O during n.m.r. measurement) was shown to be responsible for the conversion of this compound into *threo*-2-amino-1-benzoyloxy-1-phenylpropane hydrochloride (IV), presumably by hydrolysis and benzoyl migration. Thus (IV) is the compound suspected by Whaley and Hartung to be 3-methyl-1-phenylisoquinoline hydrochloride. Basification of this hydrochloride with aqueous sodium hydrogen carbonate then leads to a second benzoyl migration [6] with formation of the *threo*-amide (V).

The *erythro* nature of the original amide presumably arises because the reduction of α-nitrosopropiophenone involves the intermediacy of α-aminopropiophenone [7] which on further reduction selectively forms the *erythro*-isomer.[8] The formation of *trans*- and *cis*-oxazolines from the pure *erythro*-amide indicates that two cyclisation mechanisms are operative, and the predominance of the *trans*-form has been explained in related reactions on steric grounds.[9] However, the isomer ratio also depends on the cyclisation catalyst since polyphosphoric acid produced a relatively lower proportion of the *trans*-isomer (80 : 20). Cyclisation of the *threo*-amide (V) in polyphosphoric acid gave *trans*- and *cis*-oxazolines in the ratio 86 : 14 respectively.

EXPERIMENTAL

N.m.r. spectra were determined at 60 MHz for carbon tetrachloride solutions (unless otherwise stated) with tetramethylsilane as internal reference. I.r. spectra were determined for Nujol mulls.

erythro-2-*Benzamido*-1-*phenylpropan*-1-*ol* (I) was obtained by the method described by Fitton and Smalley [3] and had m.p. 143—144°.

4-*Methyl*-2,5-*diphenyl*-Δ²-*oxazoline* (II).—To an intimate mixture of *erythro*-2-benzamido-1-phenylpropan-1-ol (10 g) and phosphorus pentoxide (100 g) was added phosphoryl chloride (60 ml) and dry xylene (250 ml). The mixture was heated under reflux for 2·5 h, then cooled, and ice–water (250 ml) was added dropwise. The resulting two-phase system was separated and the xylene layer was extracted with water (100 ml). The combined aqueous solution was washed with ether, then made basic with 30% aqueous sodium hydroxide. The liberated oil was extracted with ether and after drying ($MgSO_4$), the ethereal solution was evaporated to yield *trans–cis*(90 : 10)-4-methyl-2,5-diphenyl-Δ²-oxazoline (7·5 g) as a pale yellow oil. Distillation gave a colourless liquid, b.p. 170—173° at 2 mmHg of similar isomeric composition; *trans*-isomer, τ 8·58 (d, *J* 6·5 Hz, Me), 5·88 (m, $CH_3CH{\cdot}N$), 5·00 (d, *J* 8 Hz, $PhCH{\cdot}O$), and 2·65—1·84 (m, ArH); *cis*-isomer, τ 9·20 (d, *J* 7 Hz, Me) and 4·35 (d, *J* 10 Hz, $PhCH{\cdot}O$) (remaining signals obscured by *trans*-isomer), $\nu_{max.}$ 1665 cm^{-1} (C=N–).

When the cyclisation was effected by polyphosphoric acid (200 g) at 100° the amide (12·7 g) gave *trans–cis*(80 : 20)-4-methyl-2,5-diphenyl-Δ²-oxazoline (8·4 g).

erythro-2-*Benzamido*-1-*chloro*-1-*phenylpropane* (III).—Through a solution of *trans–cis*-4-methyl-2,5-diphenyl-Δ²-oxazoline (2 g) in dry benzene (25 ml) was bubbled dry hydrogen chloride for 45 min. The solvent was evaporated off and the residue was dissolved in a hot mixture of propan-2-ol (5 ml) and light petroleum (b.p. 60—80°) (11 ml). The mixture was left at 0° for 24 h, then filtered. The residue gave *erythro*-2-benzamido-1-chloro-1-phenylpropane (2 g), as needles, m.p. 109—111° (lit.,[5] 112—113°), τ [$(CD_3)_2SO$] 8·58 (d, *J* 6·5 Hz, Me), 5·62—5·00 (m, $MeCH{\cdot}N$), 4·58 (d, *J* 8 Hz, $PhCH{\cdot}Cl$), 2·70—1·60 (m, ArH), and 1·28 (d, *J* 8 Hz, exchangeable, NH). Addition of D_2O caused signals due to (IV) to increase at expense of those due to (III), $\nu_{max.}$ 3320 (NH) and 1645 cm^{-1} (C=O).

threo-2-*Amino*-1-*benzoyloxy*-1-*phenylpropane Hydrochloride* (IV).—A solution of *erythro*-2-benzamido-1-chloro-1-phenylpropane (1·5 g) in ethanol (5 ml) containing traces of moisture was heated under reflux for 5 min. After cooling, filtration gave *threo*-2-amino-1-benzoyloxy-1-phenylpropane hydrochloride (1·25 g) as needles, m.p. 220° (lit.,[10] 220°), τ [$(CD_3)_2SO$] 8·87 (d, *J* 6·5 Hz, Me), 6·5—6·0 (m, $CH_3CH{\cdot}N$), 4·04 (d, *J* 9 Hz, $PhCH{\cdot}O{\cdot}CO-$), 2·70—1·60 (m, ArH), and 1·25 (s, $-NH_3^+$, exchangeable), $\nu_{max.}$ 1720 cm^{-1} (C=O).

threo-2-*Benzamido*-1-*phenylpropan*-1-*ol* (V).—Finely divided *threo*-2-amino-1-benzoyloxy-1-phenylpropane hydrochloride (1 g) was well stirred for 1 h with saturated aqueous sodium hydrogen carbonate (25 ml). The precipitate gave *threo*-2-benzamido-1-phenylpropan-1-ol (0·77 g) as needles (from benzene), m.p. 128° (lit.,[10] 128°), τ ($CDCl_3$) 8·76 (d, *J* 6·5 Hz, Me), 6·43 (s, OH, exchangeable), 6·00—5·23 (m, $CH_3CH{\cdot}N$), 5·20 (d, *J* 5·5 Hz, $PhCH{\cdot}O$), 3·45 (d, NH, exchangeable), and 2·65—2·16 (m, ArH), $\nu_{max.}$ 3315 (NH,OH) and 1645 cm^{-1} (C=O).

Using polyphosphoric acid as cyclising agent the *threo*-amide (V) yielded *trans–cis*-4-methyl-2,5-diphenyl-Δ²-oxazoline (98%) in the ratio 86 : 14.

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