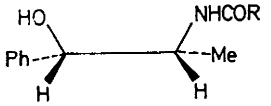
Observations on the Mechanism of the Pictet–Gams Reaction

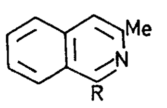
By Alan O. Fitton,* Jonathan R. Frost, Marwan M. Zakaria, and (in part) Graham Andrew
(*The Ramage Laboratories, University of Salford, Salford* M5 4WT)

Summary *N*-Acyl derivatives of 2-amino-1-phenylpropan-1-ol cyclise either to oxazolines or isoquinolines and since the oxazolines are readily converted into isoquinolines, their intermediacy in the Pictet–Gams reaction is postulated.

It was recently shown[1] that the cyclisation of *erythro*-2-benzamido-1-phenylpropan-1-ol (Ia) to 3-methyl-1-phenylisoquinoline (IIa) can be effected by phosphorus pentoxide in boiling decalin, but not by a mixture of phosphorus pentoxide and phosphorus oxychloride in boiling xylene as previously reported.[2,3] The latter reaction gave only the *threo*-isomer of the original *erythro*-amide.

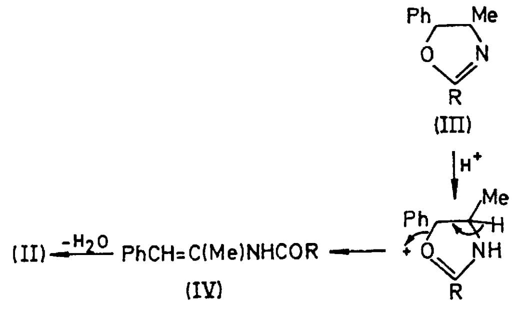


(I)



(II)

a; R = Ph d; R = Me
b; R = *m*-Tolyl e; R = Et
c; R = *p*-Tolyl f; R = CH_2Ph



Table

Amide (I)	Reaction conditions	Oxazoline (III) % from (I)	Isoquinoline (II) % from (I)	% from (III)
a	C	80	—	—
a	B	91·5	—	—
a	D	—	70	60
b	A	5	—	—
b	B	69	—	—
b	D	—	56	60
c	A	9	—	—
c	B	74	—	—
c	D	—	65	54
d	B	77	—	—
d	D	—	50	35
e	A	87	—	—
e	D	—	73	95
f	B	12	—	—
f	D	—	22	58

A = Phosphorus pentoxide/toluene/100°/3h. B = Polyphosphoric acid/100°/3h. C = Phosphorus pentoxide/phosphorus oxychloride/xylene/140°/3 h. D = Phosphorus pentoxide/decalin/192°/3 h.

A detailed examination of this reaction has now shown that cyclisation of (Ia) in fact leads to a high yield (80%) of a *trans–cis* mixture (90:10 from n.m.r.[4]) of 4-methyl-2,5-diphenyloxazoline (IIIa) and that treatment of this product with moist hydrogen chloride (as used originally[2] during attempted isolation of the isoquinoline) leads to ring opening with the eventual formation of *threo*-2-benzamido-1 phenylpropan-1-ol.

When the oxazoline was heated with phosphorus pentoxide in boiling decalin, it was converted into (IIa) and this suggests that the Pictet–Gams cyclisation of (Ia) could *proceed through* the oxazoline (IIIa). Further evidence for this was obtained from the cyclisation of (Ia) by phosphorus pentoxide in boiling decalin which was reported[1] to have given only the isoquinoline. When this reaction was stopped after 10 min, the basic product contained a mixture of oxazoline and isoquinoline in the ratio 86 : 14 respectively, compared with 28 : 72 after 30 min.

Although it has been mentioned[5] that the Pictet–Gams reaction occasionally suffers from a side-reaction leading to oxazoline, the intermediacy of the latter has not been appreciated, nor has the ability of 5-phenyloxazolines to "rearrange" into isoquinolines. It is commonly accepted that the Pictet–Gams modification of the Bischler–Napieralski synthesis allows for side-chain dehydration prior to cyclisation, and the isolation of unsaturated amides from the reaction has been cited[5] as evidence for this process. Such compounds, *e.g.* (IV), could, however, arise from the intermediate oxazoline.

In order to examine the generality or otherwise of the oxazoline mechanism, several *N*-acyl derivatives of 2-amino-1-phenylpropan-1-ol were prepared and cyclised under typical Pictet–Gams conditions (see Table).

Using phosphorus pentoxide in boiling toluene, the products were *cis-trans* oxazoline mixtures although higher yields were obtained when the cyclisations wer carried out in polyphosphoric acid at 100°. At the higher temperature of boiling decalin for 3 h, isoquinolines resulted. In each case, phosphorus pentoxide in boiling decalin converted the oxazoline into the corresponding isoquinoline, generally in high yield.

All the compounds were identified by their n.m.r. and i.r. spectra.

(*Received*, 18*th September* 1973; *Com.* 1307.)

---

[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.

[5] W. Krabbe, W. Eisenlohr, and H. G. Schöne, *Ber.*, 1940, **73**, 656; W. Krabbe, E. Polzin, and K. Culemeyer, *ibid.*, p. 652.