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REARRANGEMENTS IN THE PICTET-GAMS ISOQUINOLINE SYNTHESIS

Nasser Ardabilchi, Alan O. Fitton*, Jonathan R. Frost and Francis Oppong-Boachie

(The Ramage Laboratories, Department of Chemistry and Applied Chemistry,

University of Salford, Salford M5 4WT, England)

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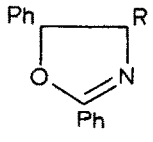
We have shown[1,2] that the conditions classically accepted to effect the cyclisation of 2-acylamino-1-arylalkan-1-ols (e.g. 1) to isoquinolines (the Pictet-Gams synthesis) are unreliable, and usually give Δ^2-oxazolines which ring-open during the normal isolation procedure. Under more severe cyclisation conditions (e.g. phosphorus pentoxide in boiling decalin), both the starting amides and oxazolines yield isoquinolines, and it was postulated[3] that oxazolines are intermediates in the reaction rather than side-products from it.

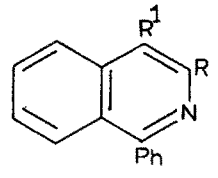
Reinvestigation of other[4] typical Pictet-Gams cyclisations involving 2-benzoylamino-1-arylalkan-1-ols has revealed[2] further incorrect formulations due to the formation of oxazolines rather than isoquinolines, but we now report several cases of rearranged isoquinolines being formed when the amides were cyclised using phosphorus pentoxide and boiling decalin. Thus, whereas the benzoyl derivatives (1a, b) gave the expected 3-substituted-1-phenylisoquinolines (3a, b), (1c) yielded a mixture of the 3- and 4-substituted-1-phenylisoquinolines (3c, f) and (1d, e) gave only the 4-substituted-1-phenylisoquinolines (3g, h).

PhCH(OH)CH(R)NHCOPh

(1)



(2)

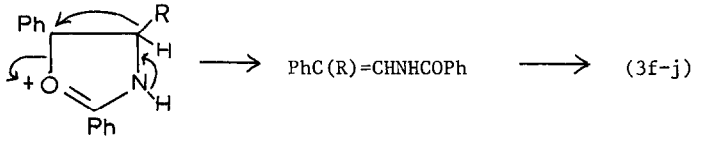


(3)

(a) R=Me
(b) R=Et
(c) R=Pr^n
(d) R=Bu^n
(e) R=Ph
(f) R=CH_2Ph
(g) R=p-C_6H_4OMe

(a) R=Me, R^1=H
(b) R=Et, R^1=H
(c) R=Pr^n, R^1=H
(d) R=Bu^n, R^1=H
(e) R=CH_2Ph, R^1=H
(f) R^1=Pr^n, R=H
(g) R^1=Bu^n, R=H
(h) R^1=Ph, R=H
(i) R^1=CH_2Ph, R=H
(j) R^1=p-C_6H_4OMe, R=H

When milder cyclising conditions[3] were employed, oxazolines were the main products and these (e.g. 2a, c, d) on treatment with phosphorus pentoxide in boiling decalin yielded the corresponding 3-, 3- and 4-, and 4-substituted isoquinolines. The 3-substituted isoquinolines (e.g. 3d, e), unambiguously synthesised[5] via the Bischler-Napieralski reaction were shown not to rearrange in the presence of phosphorus pentoxide and boiling decalin, and these results therefore provide further support for the theory of oxazoline intermediacy in Pictet-Gams cyclisations.



(4)

Scheme

The likely route to the rearranged isoquinolines from the oxazolinium salt intermediates (4) is shown in the Scheme. This pathway differs from the one[3] leading to the 3-substituted isoquinolines because of the migratory aptitude of the group R, and in salts derived from (2c-g), it is sufficiently high to cause at least partial rearrangement during ring-opening. This reasoning is supported by the fact that cyclisations of other amides (e.g. 1f, g) which possess better migrating groups gave only the 4-substituted isoquinolines (3i, j), (again, non-rearranged oxazolines could be isolated and then transformed into the rearranged isoquinolines).

All new compounds gave satisfactory analyses and the isoquinolines were identified by their p.m.r. spectra. The proportions of 4- and 3-substituted isoquinolines (3c, f) were determined from the integration of their 3- and 4-protons, respectively.

References

1. A.O. Fitton and J.R. Frost, J.C.S. Perkin I, 1974, 1153.
2. A.O. Fitton and F. Oppong-Boachie, unpublished results.
3. A.O. Fitton, J.R. Frost, M.M. Zakaria and G. Andrew, J.C.S. Chem. Comm., 1973, 889.
4. W.M. Whaley and W.H. Hartung, J. Org. Chem., 1949, 14, 650.
5. B.B. Dey and V.S. Ramanathan, Proc. Nat. Inst. Sci. India, 1943, 9, 214.