A New Synthetic Route to 2-Dialkylaminopteridin-7(8*H*)-ones and their 5-*N*-Oxides

By GEORGE TENNANT* and CHARLES W. YACOMENI
(*Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh* EH9 3JJ)

Summary 4-(2-Cyanoacetamido)-5-nitropyrimidines cyclise smoothly in aqueous dilute sodium hydroxide at 40 °C to give high yields of the hitherto unknown 6-cyanopteridin-7(8*H*)-one 5-*N*-oxides, whereas under reflux, the products are the corresponding pteridin-6(5*H*),7(8*H*)-diones or their 5-*N*-hydroxy derivatives.

CURRENT interest in pteridine *N*-oxides may be attributed to their potential biological activity[1] and their utility as intermediates for the synthesis[2] of biologically significant pteridines. To date, syntheses of pteridine *N*-oxides have been largely based on annelation procedures employing nitrosopyrimidines,[3] *N*-oxygenated pyrazines,[2] or *N*-oxygenated pyrimidines,[1,4] or on peracid oxidation[5] of the parent heterocycles. The base-catalysed cyclisation of readily accessible 4-(2-cyanoacetamido)-5-nitropyrimidines now reported, is a new approach to the synthesis of pteridine *N*-oxides.†

The 4-(2-cyanoacetamido)-5-nitropyrimidines (**1**) studied were readily synthesised in high yield (60—90%) by condensing a 2-substituted 4-amino-5-nitropyrimidine with cyanoacetyl chloride. The amides (**1**; $R^1 = NMe_2$, R^2 = H or Me) heated briefly (15 min) at 40 °C with aqueous 2·5M sodium hydroxide gave the *N*-oxides (**3**; $R^1 = NMe_2$, R^2 = H) (55%), m.p. 268 °C and (**3**; $R^1 = NMe_2$, R^2 = Me) (79%), m.p. 283 °C.

Cyclisations of the type [(**1**) → (**3**)] were readily extendable to the general synthesis of 6-cyano-2-dialkylaminopteridin-7(8*H*)-one 5-*N*-oxides (**3**; R^1 = dialkylamino, R^2 = H or Me) (70—90%). In contrast, different products

† Satisfactory elemental analyses and spectral data were obtained for all new compounds.

result when the amides (**1**) are briefly (15 min) heated under reflux in aqueous 2·5M sodium hydroxide. Under these conditions the amide (**1**; $R^1 = NMe_2$, $R^2 = Me$) gave the pteridinedione (**2**) (77%), m.p. > 320 °C which was also the product (93%) when the *N*-oxide (**3**; $R^1 = NMe_2$, $R^2 = Me$) was heated under reflux in aqueous alkali. On the other hand, similar treatment of the amide (**1**; $R^1 = NMe_2$, $R^2 = H$) or the derived *N*-oxide (**3**; $R^1 = NMe_2$, $R^2 = H$) gave the cyclic hydroxamic acid (**4**) (74—93%), m.p. >330 °C, whose structure follows from its dithionite reduction to the pteridinedione (**2**; H for Me) (80%), m.p. > 300 °C. The formation of (**4**) from (**3**; $R^1 = NMe_2$, $R^2 = H$) or (**1**; $R^1 = NMe_2$, $R^2 = H$) is readily explained by hydration of the 5,6-double bond and ensuing loss of hydrogen cyanide [(**3**; $R^1 = NMe_2$, $R^2 = H$) → (**5**) → (**4**)]. The mode of formation of (**2**) from (**3**; $R^1 = NMe_2$, $R^2 = Me$) or (**1**; $R^1 = NMe_2$, $R^2 = Me$) is not so clear. The stability of the cyclic hydroxamic acid (**4**) to heating under reflux in aqueous alkali appears to exclude the transformation [(**3**; $R^1 = NMe_2$, $R^2 = Me$) → (**2**)] involving the thermal reduction of the 4-methyl analogue of (**4**) which would be analogous to the known[6] thermal reduction of a quinoxaline hydroxamic acid.

Dichotomy was also observed in the dithionite reduction of the *N*-oxides. The methyl derivative (**3**; $R^1 = NMe_2$, $R^2 = Me$) yielded the anticipated 6-cyanopteridin-7(8*H*)-one (**6**) (86%), m.p. 312 °C, but reduction of the *N*-oxide (**3**; $R^1 = NMe_2$, $R^2 = H$) resulted in the loss of the cyano-group and the formation of the pteridinone (**8**) (68%), m.p. 262 °C. The formation of (**8**) possibly involves reduction to the 5,6-dihydro compound (**7**), and subsequent loss of hydrogen cyanide. The reason for the dichotomy in the reactions of (**3**; $R^1 = NMe_2$, $R^2 = H$ or Me) with alkali and with dithionite is not clear, but may be due to a steric effect at C-4 associated with the presence or absence of an alkyl group.

We thank the S.R.C. for a research studentship (to C.W.Y.) and Allen and Hanburys Research Limited for financial support.

(*Received, 8th August* 1975; *Com.* 919.)

[1] T. C. Lee, *J. Org. Chem.*, 1973, **38**, 703.
[2] E. C. Taylor, K. L. Perlman, Y. H. Kim, I. P. Sword, and P. A. Jacobi, *J. Amer. Chem. Soc.*, 1973, **95**, 6413 and references therein.
[3] I. J. Pachter, P. E. Nemeth, and A. J. Villani, *J. Org. Chem.*, 1963, **28**, 1197.
[4] R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.*, 1965, **30**, 408.
[5] H. Zondler, H. S. Forrest, and J. M. Lagowski, *J. Heterocyclic Chem.*, 1967, **4**, 124; W. Hutzenlaub, H. Yamamoto, G. B. Barlin, and W. Pfleiderer, *Chem. Ber.*, 1973, **106**, 3203 and previous papers in the series.
[6] G. Tennant and K. Vaughan, *J. Chem. Soc.* (*C*), 1966, 2287.