

A New Synthetic Route to 2-Dialkylaminopteridin-7(8H)-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(8H)-one 5-N-oxides, whereas under reflux, the products are the corresponding pteridin-6(5H),7(8H)-diones or their 5-N-hydroxy derivatives.

CURRENT interest in pteridine *N*-oxides may be attributed to their potential biological activity¹ and their utility as intermediates for the synthesis² 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 oxidation⁵ of the parent heterocycles. The base-catalysed cyclisation of

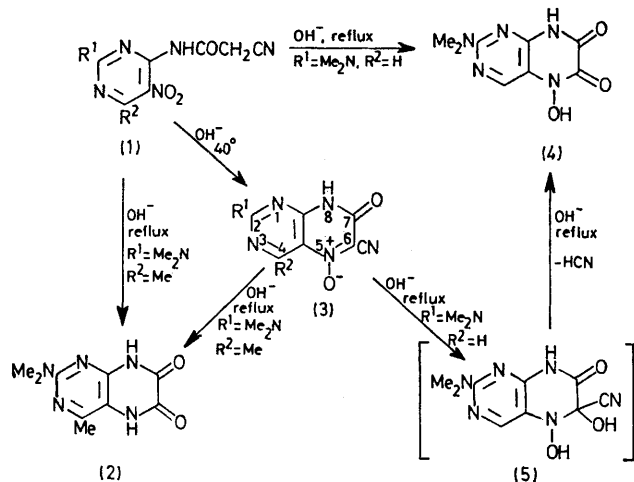
readily accessible 4-(2-cyanoacetamido)-5-nitropyrimidines now reported, is a new approach to the synthesis of pteridine *N*-oxides.†

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**; R¹ = NMe₂, R² = H or Me) heated briefly (15 min) at 40 °C with aqueous 2.5M sodium hydroxide gave the *N*-oxides (**3**; R¹ = NMe₂, R² = H) (55%), m.p. 268 °C and (**3**; R¹ = NMe₂, R² = 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(8H)-one 5-N-oxides (**3**; R¹ = dialkylamino, R² = H or Me) (70–90%). In contrast, different products

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

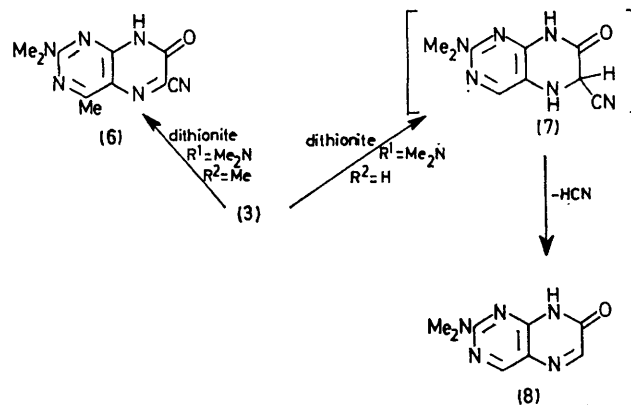
result when the amides (**1**) are briefly (15 min) heated under reflux in aqueous 2.5M sodium hydroxide. Under these conditions the amide (**1**; R¹ = NMe₂, R² = Me) gave the pteridinedione (**2**) (77%), m.p. > 320 °C which was also the product (93%) when the *N*-oxide (**3**; R¹ = NMe₂, R² = Me) was heated under reflux in aqueous alkali. On the other



hand, similar treatment of the amide (**1**; R¹ = NMe₂, R² = H) or the derived *N*-oxide (**3**; R¹ = NMe₂, R² = 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**; R¹ = NMe₂, R² = H) or (**1**; R¹ = NMe₂, R² = H) is readily explained by hydration of the 5,6-double bond and ensuing loss of hydrogen cyanide [(**3**; R¹ = NMe₂, R² = H) → (**5**) → (**4**)]. The mode of formation of (**2**) from (**3**; R¹ = NMe₂, R² = Me) or (**1**; R¹ = NMe₂, R² = 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**; R¹ = NMe₂, R² = Me) → (**2**)] involving the thermal reduction of the 4-methyl analogue of (**4**) which would be analogous to the known⁶ thermal reduction of a quinoxaline hydroxamic acid.

Dichotomy was also observed in the dithionite reduction of the *N*-oxides. The methyl derivative (**3**; R¹ = NMe₂, R² = Me) yielded the anticipated 6-cyanopteridin-7(8*H*)-one (**6**) (86%), m.p. 312 °C, but reduction of the *N*-oxide (**3**; R¹ = NMe₂, R² = H) resulted in the loss of the cyano-



group and the formation of the pteridinedione (**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**; R¹ = NMe₂, R² = 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. Pfeiderer, *Chem. Ber.*, 1973, **106**, 3203 and previous papers in the series.

⁶ G. Tennant and K. Vaughan, *J. Chem. Soc. (C)*, 1966, 2287.