A Novel Synthesis of Dihydropyrimidines

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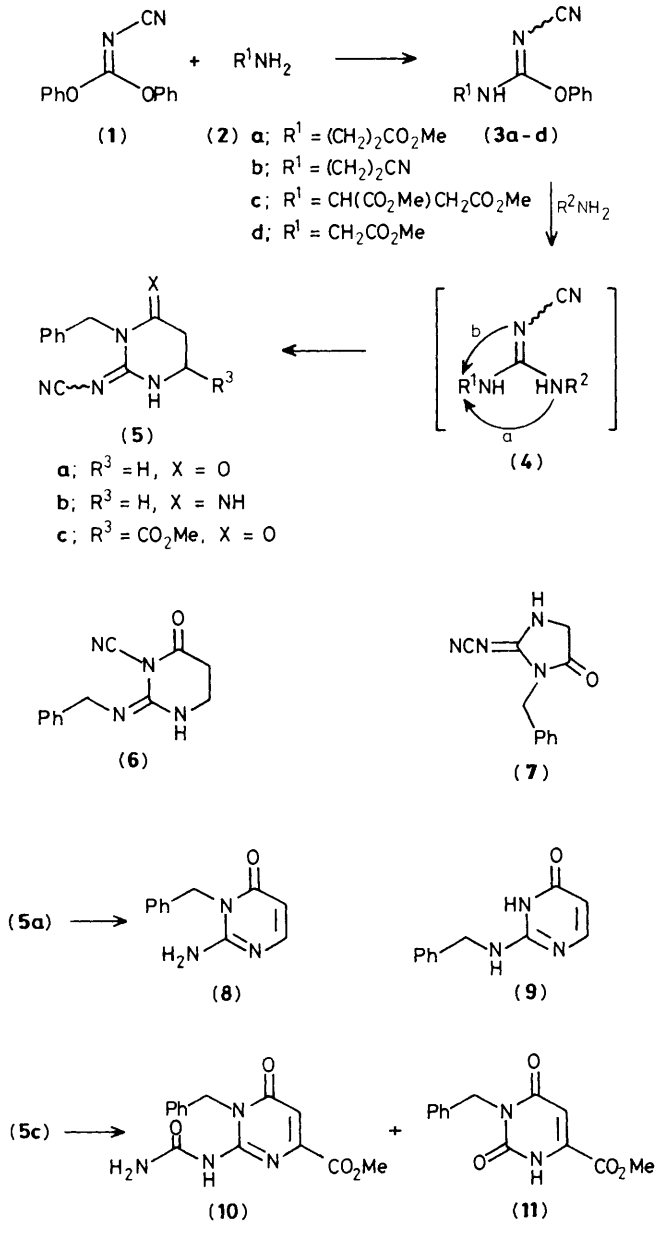
A new and potentially general synthesis of 5,6-dihydro-2,4-disubstituted pyrimidines is described.

2,4-Disubstituted pyrimidines are compounds of considerable pharmaceutical importance[1] and have consequently been a prime synthetic goal.[2] The synthetic approach almost universally adopted has been to join an N–C–N fragment to a C–C–C fragment by forming the 3,4- and 1,6-bonds. We now report a new method involving the sequential addition to a C fragment of a N–C–C–C fragment and an N fragment by forming the 1,2-, 2,3-, and 3,4-bonds, a route with close analogies to the biosynthetic formation of orotic acid.[3] This method leads to 5,6-dihydropyrimidines, themselves of considerable intrinsic



interest, and these can be readily dehydrogenated to form pyrimidines.

The cyano-imine (**1**) is known to react in a sequential manner with nucleophiles.[4] Treatment of (**1**) with methyl 3-aminopropionate (**2a**) at room temperature for 90 min gave the derivative (**3a**) in 72% yield.† Similar reaction of (**2b—d**) gave the corresponding products (**3b—d**), all in >60% yield.

† Satisfactory analytical and/or mass spectral data were obtained for all new compounds. The assigned structures are based on the spectral properties.

Treatment of (**3a**) with benzylamine in boiling propan-2-ol for 4 h gave the cyclic derivative (**5a**) in 61% yield, presumably *via* the intermediate (**4**). The mass spectrum, elemental analysis, and spectral properties were in accord with a cyclic structure of the general type shown. Decoupling experiments on the ^{1}H n.m.r. spectrum [δ 7.98 (br.s, 1H) 7.3 (m, 5H), 5.02 (s, 2H), 3.50 (A_2X, 2H, *J* 2.6, 7.0 Hz), 2.76 (t, 2H, *J* 7.0 Hz)] showed that N-1 must be protonated and that the double bond is exocyclic. We could not, however, find any means to determine whether cyclisation had occurred by path a [see structure (**4a**)], to give structure (**5a**), or path b, to give (**6**), in which the position of the CN and $PhCH_2$ groups is reversed. Treatment of (**3b** and **c**) with benzylamine in a similar manner gave the analogous products (**5b** and **c**). Similarly, when (**3a**) was treated with butylamine as the second nucleophile the cyclic derivative corresponding to (**5a**) was obtained. In the reaction of benzylamine with (**3d**) the 5-membered imidazolone (**7**) was formed.†

Treatment of (**5a**) with excess of Br_2 in boiling HOAc for 3 h, removal of the solvent, addition of pyridine, and boiling gave (**8**) (72%). Again it was not immediately clear that the spectral properties would distinguish between (**8**) and its positional isomer (**9**). The pyrimidine (**9**) was synthesised by a conventional route and its properties were compared with those of (**8**); besides the difference in melting point, the spectral properties (^{1}H, ^{13}C n.m.r., i.r., u.v.) were dissimilar. Diagnostically, the NH_2 protons of (**8**) appear in the ^{1}H n.m.r. spectrum (Me_2SO) as a broad singlet at δ 7.13, whereas in (**9**) the 3-NH is at δ 10.80 and the 7-NH is at 6.90.

Reaction of (**5c**) with Br_2 in HOAc gave (**10**) and (**11**). The formation of the uracil derivative (**11**) clearly substantiates the direction of cyclisation and both (**10**) and (**11**) could be hydrolysed under basic conditions to 3-benzylorotic acid.[5]

The mode of cyclisation in both cases is the same, pathway a on structure (**4**). We are currently investigating the factors that control this mode of cyclisation in order to determine whether conditions may be found under which pathway b would be favoured.

This synthetic route promises to be of general use for the preparation of a variety of 5,6-dihydropyrimidines and the corresponding pyrimidines. The use of other hetero and carbon nucleophiles would, if successful, extend the synthesis to a wide range of systems, and the observation that a 5-membered heterocycle can be formed, consistent with previous findings,[4] indicates that the method is not restricted to 6-membered rings.

Received, 30th December 1986; Com. 1843

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