Some Ring Expansion–Ring Contraction Reactions of Ethyl 4-Chloromethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate

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Summary Reaction of the title chloromethylpyrimidine with potassium hydrosulphide yields a sulphur-bridged 1,3-diazepin-2-one; in contrast, reaction with various amines give rise to α-aminopyrrolines and controlled reaction with hydroxide an α-hydroxypyrroline.

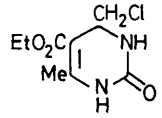
IT has been demonstrated that treatment of the 4-chloromethyltetrahydropyrimidine (**1**) with NaCN or NaOMe results in ring expansion and addition of nucleophile yielding the 1,3-diazepines (**2a,b**). Further, treatment of (**2b**) with acid gave the ring-contracted 1-carbamoylpyrrole (**3a**).[1] These reactions are closely allied to those of the corresponding 4-chloromethyldihydropyridine.[2,3] We now report some reactions of (**1**), some of which deviate substantially from this parallel.

Brief treatment of (**1**) with aqueous KSH gave the sulphur-bridged diazepine (**4a**), m.p. 200—202°, while prolonged treatment resulted in ester hydrolysis giving (**4b**).† Oxidation of (**4a**) with *m*-chloroperoxybenzoic acid gave the corresponding sulphone (**5**). Pyrolysis of (**5**) results in oxidative elimination of SO_2 yielding the 1-carbamoylpyrrole (**3a**) along with a small amount of the derived ethyl 2-methylpyrrole-3-carboxylate. The formation of (**4a**) is envisaged as proceeding *via* the ring-expanded thiol (**2**; R = SH) which undergoes rapid intramolecular Michael addition to the acrylic double bond. Spectral data are fully consistent with the formulation and stereochemistry of (**4a**) shown.

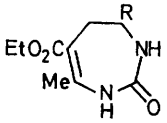
Treatment of (**1**) with solutions of various amines in hot ethanol followed a different course. With secondary amines of $pK_a > 10$ (*e.g.* diethylamine, piperidine, or pyrrolidine) ring expansion occurred to give (**6**) (not isolated) followed by addition of the amine yielding the intermediate amino-compounds (**2c**). The products isolated were, however, the ring contracted amino-pyrrolines (**7a—c**) (Scheme 1). Treatment of (**1**) with amines of $pK_a < 10$ (*e.g.* morpholine, *N*-methylhydroxylamine, *etc.*) gave slow reactions resulting in many products. This is consistent with the first step in all the above reactions of (**1**) being base-catalysed removal of N^1–H leading to ring expansion. To overcome these difficulties the chloromethyl compound (**1**) was pretreated with guanidine free base (strong base, weak nucleophile) in ethanol thus generating the intermediate (**6**) which reacted rapidly with the appropriate

† All new compounds gave satisfactory elemental analyses.

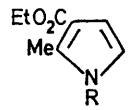
amines to give (**7d**, **e**). The amine adducts (**7**) were formulated as such by comparison of their n.m.r. and mass spectra with those of compounds of type (**2a**,**b**) and (**4a**).



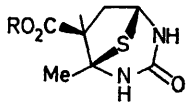
(1)



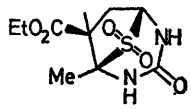
(2) a; R = CN
b; R = OMe
c; R = NR^1R^2
d; R = OEt
e; R = H



(3) a; R = $CONH_2$
b; R = Me

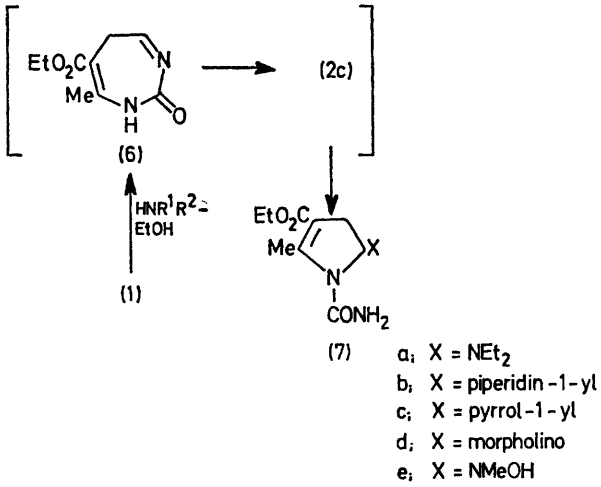


(4) a; R = Et
b; R = H



(5)

Brief treatment of (**7b**), m.p. 146°, with HCl or prolonged reflux in ethanolic piperidine resulted in elimination of piperidine giving (**3a**) and ultimately ethyl 2-methylpyrrole-3-carboxylate.

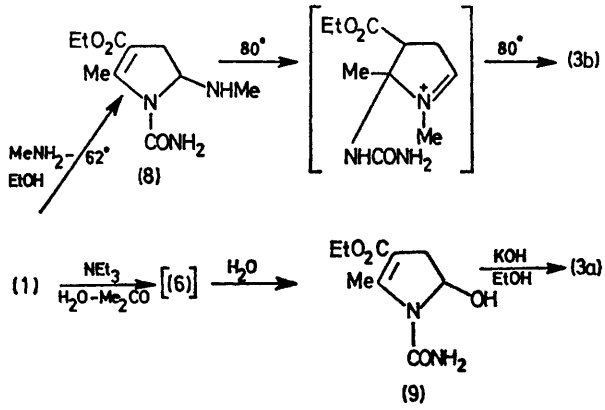


(7) a; X = NEt_2
b; X = piperidin-1-yl
c; X = pyrrol-1-yl
d; X = morpholino
e; X = NMeOH

SCHEME 1

Attempts to isolate the reactive intermediate (**6**) after treatment of (**1**) with guanidine were unsuccessful, the corresponding ethanol addition product (**2d**) being isolated, m.p. 164—166°.

Treatment of (**1**) with ethanolic $MeNH_2$ under reflux gave the *N*-methylpyrrole (**3b**) as sole product. However, t.l.c. indicated the presence of an intermediate compound and by conducting the reaction at 62° the analogous aminopyrroline (**8**) was isolated. In this case ring opening of (**8**) followed by ring closure and elimination of urea must be favoured over the simple elimination of methylamine (Scheme 2). This reaction of (**1**) with primary amines to give the corresponding *N*-substituted pyrroles is general.



SCHEME 2

Treatment of (**1**) with ethanolic KOH at room temperature gave a high yield of the 1-carbamoylpyrrole (**3a**). By using water as the nucleophile in place of the strongly basic hydroxide ion the intermediate α-hydroxypyrroline (**9**) was isolated, m.p. 159°. Further treatment of (**9**) with ethanolic KOH again gave (**3a**) (Scheme 2).

Treatment of (**1**) with guanidine in EtOH followed by the addition of excess of $NaBH_4$ gave the diazepine (**2e**), m.p. 192—193°. The absence of a methyl doublet in the n.m.r. spectrum of (**2e**), a resonance expected had simple nucleophilic replacement of chlorine in (**1**) occurred, conclusively proves that ring expansion of (**1**) in the above reactions has taken place.

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[1] E. Bullock, R. A. Carter, B. Gregory, and D. C. Shields, *J.C.S. Chem. Comm.*, 1972, 97.
[2] P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson, and H. Williams, *J. Chem. Soc.*, 1963, 4819.
[3] J. Ashby, L. A. Cort, J. A. Elvidge, and U. Eisner, *J. Chem. Soc.* (C), 1968, 1706, and refs. therein.