Ring Expansion of a Chloromethyl-1,2,3,4-tetrahydropyrimidin-2-one

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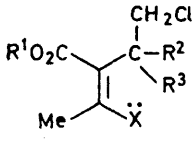
Summary Methyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate has been prepared and rearranged to give methoxy- and cyano- derivatives of methyl 2-oxo-2,3,4,5-tetrahydro-1*H*-1,3-diazepine-6-carboxylate, which undergo acid-catalysed ring contraction to give methyl 1-carbamoyl-2-methylpyrrole-3-carboxylate.

EARLIER work[1] on the nucleophile-induced ring expansion of 4-chloromethyl-1,4-dihydropyridines suggested that other heterocyclic homoallylic halides containing the structural entity (**1**) might behave in a similar manner. We now report the synthesis of methyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**) and its use in a new synthesis of the 1,3-diazepine ring system.

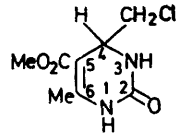
The reaction of methyl 3-ureidocrotonate with 1,2-dichloroethyl ethyl ether yielded a product† (**2**) which was characterised spectroscopically (u.v. and n.m.r.). The mass spectrum was dominated by a fragmentation pathway involving sequential loss of $ClCH_2\cdot$ and methanol to give ions (**3**) and (**4**) respectively.

Treatment of the chloromethyl compound (**2**) with sodium methoxide in methanol gave a 1,3-diazepine (**5**), which was characterised spectroscopically (u.v. and n.m.r. spectra and double irradiation experiments). When treated

† Satisfactory elemental analyses have been obtained for all new compounds.



(1)



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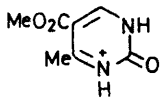

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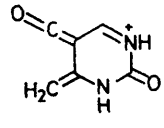

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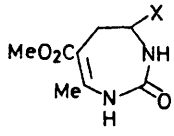
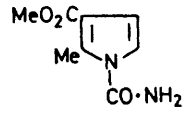
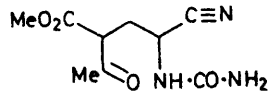


(5) X = OMe
(6) X = C≡N



(7)



(8)

with sodium cyanide in dimethyl sulphoxide, the chloromethyl compound (**2**) yielded the cyano-ester (**6**). The n.m.r. spectrum of (**6**) was similar to that of (**5**), but the i.r. spectrum showed a weak C≡N stretching band at 2240 cm^{-1}.

When dissolved in methanolic hydrogen chloride, the diazepine (**5**) was converted rapidly at room temperature into the 1-carbamoylpyrrole (**7**), m.p. 210—211°, also characterised spectroscopically (i.r., u.v., and n.m.r.). The 1-carbamoylpyrrole structure (**7**) was confirmed when reaction with potassium hydroxide in methanol gave methyl 2-methylpyrrole-3-carboxylate. The corresponding cyano-compound (**6**) was resistant to treatment with methanolic hydrogen chloride but was converted into the 1-carbamoylpyrrole (**7**) on heating with hydrochloric acid.

The mechanism of ring contraction of (**5**) is envisaged as proceeding *via* protonation at N-3 with subsequent methoxy-assisted cleavage between N-3 and C-4 (reminiscent of acetal hydrolysis), cyclisation to N-1, and elimination of methanol. The rearrangement of the cyano-compound (**6**), which proceeds only in the presence of water, may involve hydrolysis to the ureido-ester (**8**) followed by cyclisation and elimination of hydrogen cyanide.

A parallel investigation with ethyl esters revealed similar results.

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[1] P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson, and H. Williams, *J. Chem. Soc.*, 1963, 4819.