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

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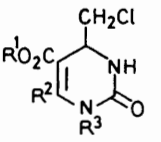
Reactions of 4-chloromethyl-2-oxotetrahydropyrimidines with various nucleophiles give derivatives of 1,3-diazepin-2-one. In contrast, reactions with amines give rise to α-aminopyrrolines, and a controlled reaction with hydroxide gave an α-hydroxypyrroline. A general conversion of these chloromethylpyrimidines into *N*-substituted pyrroles is described.

THE preparation of several 4-chloromethyl-1,4-dihydropyridines and their reactions with various nucleophiles were first described in 1918.[2,3] A reinvestigation of the reactions of these dihydropyridines in 1967 [4] revealed that under the action of basic nucleophiles ring expansion occurred, yielding derivatives of dihydro- and tetrahydro-azepine.

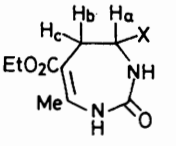
The formation and ring expansion of the analogous 4-chloromethyltetrahydropyrimidines to derivatives of 1,3-diazepine is the subject of the present paper. Recently, Gregory *et al.*[5] briefly described the formation of such a 4-chloromethyltetrahydropyrimidine (1b) and its ring expansion with cyanide or methoxide to give 7-cyano- or 7-methoxy-1,3-diazepin-2-ones. Spectral confirmation of ring expansion had been obtained but was not described. The present work was carried out with the corresponding ethyl esters.

The reaction of urea with ethyl acetoacetate and αβ-dichloroethyl ethyl ether in ethanol containing a trace of hydrochloric acid gave the 4-chloromethyl-1,2,3,4-tetrahydropyrimidine (1a).† The methyl ester (1b) was similarly prepared from methyl acetoacetate, and the 6-phenyl analogue (1c), in low yield, from ethyl benzoylacetate. The structures of all three products were confirmed by analysis of their ^{1}H n.m.r. spectra, each of which showed the expected ABX pattern for the CH·CH$_2$Cl region along with two discrete NH resonances; the NH signal at higher field was noticeably broadened due to coupling with the C-4 proton. The mass spectra showed very weak molecular ion peaks, the ion corresponding to the base peak arising in each case *via* loss of CH$_2$Cl.

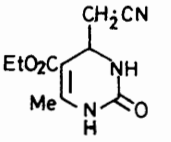
Replacement of urea with *N*-methylurea in the synthesis of (1a) gave a single product formulated as (1d) on the basis of its n.m.r. spectrum. This exhibited a broad singlet at δ 6·38 for the N(3)H resonance due to coupling with the C-4 proton, which gave rise to a five-line first-order double double doublet at δ 4·5 (J_{CH,CH_2} 7 and 4; $J_{CH,NH}$ 4 Hz). Upon deuteriation this collapsed to a sharp double doublet, thus confirming the presence of an adjacent NH group. Again, the mass spectrum



(1) a; R^1=Et, R^2=Me, R^3=H
b; R^1=Me, R^2=Me, R^3=H
c; R^1=Et, R^2=Ph, R^3=H
d; R^1=Et, R^2=Me, R^3=Me
e; R^1=Et, R^2=CH_2Br, R^3=H



(2) a; X=CN
b; X=SH
c; X=NR^1R^2
d; X=OEt
e; X=OMe
f; X=SO_2H
g; X=H



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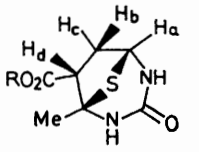
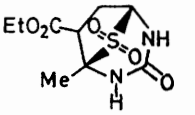


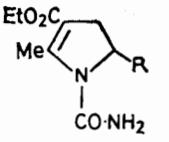
(4) a; R=Et
b; R=H



(5)

Approximate torsion angles for H_{a-d} (Dreiding models) in (4a):

H_aCCH_b	30°
H_aCCH_c	85°
H_cCCH_d	130°
H_bCCH_d	0°



(6) a; R=NEt_2
b; R=piperidin-1-yl
c; R=pyrrolidin-1-yl
d; R=morpholin-1-yl
e; R=4-(*p*-methoxyphenyl)piperazin-1-yl
f; R=4-(*o*-methoxyphenyl)piperazin-1-yl
g; R=HO·NMe

of (1d) showed a weak parent ion peak and a very strong peak at $M - CH_2Cl$.

† Separate formation of the ureidocrotonate as described in ref. 5 is not necessary.

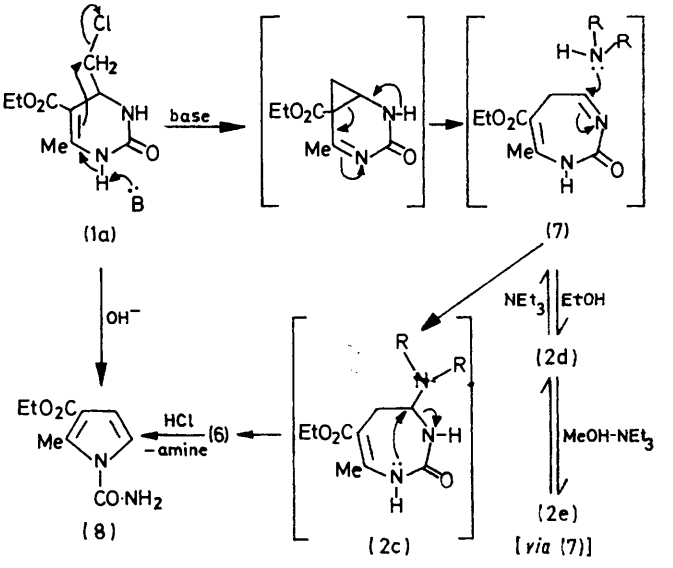
[1] Preliminary account, J. Ashby and D. Griffiths, *J.C.S. Chem. Comm.*, 1974, 607.
[2] E. Benary, *Ber.*, 1918, **51**, 567.
[3] E. Benary, *Ber.*, 1920, **53**, 2218.
[4] J. Ashby, L. Cort, J. Elvidge, and U. Eisner, *J. Chem. Soc.* (*C*), 1968, 2311, and references cited therein.
[5] E. Bullock, R. A. Carter, B. Gregory, and D. C. Shields, *J.C.S. Chem. Comm.*, 1972, 97.

Reaction of compound (1a) in dimethyl sulphoxide with potassium cyanide gave the 7-cyano-1,3-diazepine (2a) (88%). The n.m.r. spectrum of (2a) showed the N(1)H resonance as a doublet (J 6 Hz) at δ 7·75 and the N(3)H signal as a singlet at δ 8·6. The resonances of H_a, H_b, and H_c formed a clearly resolved ABX pattern (J_{ac} 6, J_{ab} 2·5, J_{bc} 14 Hz). The H_a resonance at δ 4·7 was further split by the N-1 proton (J 6 Hz) thus forming a six-line system. The double doublet associated with H_b at δ 2·6 appeared broadened owing to further homoallylic coupling with the C-4 methyl group (J *ca.* 1 Hz). The C-4 methyl resonance gave a sharp doublet at δ 2·2 (J *ca.* 1 Hz). The chemical shift and primary splitting pattern of the resonance at δ 2·6 clearly define it as due to part of the CH_2 group; therefore the presence of homoallylic coupling with the methyl group rules out the alternative formulation of the product as (3). The mass spectrum of (2a) showed a strong molecular ion peak (*m/e* 223) which was also the base peak. Further strong peaks were associated with M — HCN and M — $EtO_2C{\cdot}CH{:}CH_2$. The loss of ethyl acrylate is a known feature of the mass spectra of the related 4-substituted 3,4-dihydroazepines [4] and is absent in compounds (1a—c). The absence of an M — CH_2CN peak again confirms structure (2a).

Brief treatment of compound (1a) with potassium hydrogen sulphide in aqueous ethanol under reflux gave the sulphur-bridged diazepine (4a) (90%), whereas prolonged refluxing resulted in complete ester hydrolysis giving the corresponding acid (4b) (69%). Oxidation of (4a) with *m*-chloroperoxybenzoic acid gave the sulphone (5).

The formation of the sulphur compound (4a) is envisaged as proceeding *via* formation of the ring-expanded mercapto-compound (2b) followed by internal Michael addition to the β-ureidocrotonate system. A mechanism for the formation of both compounds (2a) and (4a) is suggested in Scheme 1. All spectral data are consistent with our formulation of (4a). The i.r. spectrum shows a saturated ester carbonyl absorption at 1740 cm^{-1} and a ring carbonyl absorption at 1690 cm^{-1}. The stereochemistry shown for (4a) is supported by its n.m.r. spectrum. The signals due to H_{a-d} form a first-order ABXY pattern the details of which appear in the Experimental section. If we assume the stereochemistry shown for (4a) the torsion angles between the various pairs of C–H bonds would be as indicated [see structure (4)]. The bridgehead proton H_a is assumed to be responsible for the low-field double doublet on the basis of the deshielding effect of the adjacent ureido-function and its collapse to a doublet upon deuteriation. The fact that the torsion angle H_aCCH_c is slightly less than 90° results in a slight broadening of the resonances of H_a and H_c, and this serves to distinguish the H_c signal from that of H_b. With the chemical shift of H_c thus established its coupling constant with H_d (4 Hz) is consistent with a torsion angle H_cCCH_d of *ca.* 130°. With the ester group in the opposite configuration the angle H_cCCH_d would be *ca.* 0°, with an expected coupling constant greater than 10 Hz. The n.m.r. spectrum of the derived sulphone (5) was essentially similar to that of (4a) with the exceptions that the resonances associated with H_a and the C-5 methyl group were both substantially shifted owing to the anisotropic effect of the sulphone group, thus further confirming the assignment of the H_a resonance.

Treatment of compound (1a) with solutions in ethanol of various secondary amines of $pK_a > 10$ resulted in ring expansion and addition of the amine to give the



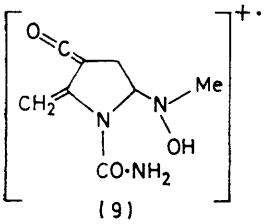
SCHEME 1

intermediate adducts of type (2c). The products isolated were, however, the ring-contracted aminopyrrolines (6a—c). Morpholine (pK_a 8·4) failed to react under these conditions and the starting pyrimidine (1a) was recovered, indicating that ring expansion is initiated by the removal of the N-1 proton by a base of $pK_a > 10$ (Scheme 1). In view of this observation the aminopyrrolines (6d—g) were readily prepared by treatment of a mixture of the starting materials in ethanol with guanidine free base (strong base; weak nucleophile). Repeating this reaction in the absence of amine resulted in the isolation of the 7-ethoxy-compound (2d). The ethoxy-compound (2d) reacted readily with the above weakly basic amines to give the same products (6d—g), indicating the existence of an equilibrium between (2d) and (7) which was confirmed by refluxing a solution of (2d) in methanol containing triethylamine: a solid was obtained shown by n.m.r. to consist of a mixture of (2d and e). The importance of the N-1 proton in the ring-expansion step is underlined by the failure of (1d) to react with a solution of either potassium cyanide or piperidine.

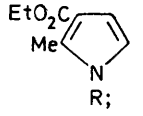
Elimination of piperidine from (6b) was rapidly accomplished by treatment with warm ethanolic hydrogen chloride, yielding the *N*-carbamoylpyrrole (8). This compound was also obtained by Gregory [5] *via* acidic hydrolysis of (2a) (in the methyl ester series). Prolonged reflux periods in the preparation of any of the

amine adducts (6) resulted in increasing formation of the pyrrole (10a) (as shown by t.l.c.), and in the case of (6g) even if the reaction time was reduced to only 0·5 h a small amount of (10a) was still obtained. The unsubstituted pyrrole (10a) obviously arises *via* the amide (8) and in fact separate treatment of (8) with base, for example ethanolic potassium cyanide, gave (10a) in good yield.

Formulation of the amino-adducts as (6a—g) rather than the isomeric form (2c) was based equally upon analysis of their n.m.r. and mass spectra. A characteristic feature of the 7-substituted 1,3-diazepines described above [(2a and d), (4a and b), and (5)] was the presence of well separated NH resonances in their n.m.r. spectra, one of which showed coupling to the C-7 proton. None of the amino-adducts showed such separation. Instead a very broad NH_2 resonance was observed and in some cases even this was not discernible. Further, the methine proton adjacent to the amine substituent always gave rise to a sharp double doublet which was unaffected by deuteriation. A feature common to the 1,3-diazepin-2-ones was the long-range homoallylic coupling between the ring methyl group and either one or both of the ring methylene protons. The mass spectra of the amino-adducts all showed strong molecular ion peaks with primary decomposition involving the loss of the amine substituent giving in each case a strong peak (usually the base peak) at *m/e* 196 corresponding to the ion of (8). Below *m/e* 196 the spectra were identical with that of the *N*-carbamoylpyrrole (8). In addition, the loss of ammonia from the molecular ions of (6a—f) was observed in each case and argues strongly in favour of their formulation as (6). The mass spectrum of (6g) was different from the rest, the base peak being formed by the cyclic loss of ethanol giving the ion *m/e* 197 (9), followed by loss of CONH (*m/e* 154) and then elimination of HNMeOH (*m/e* 108).



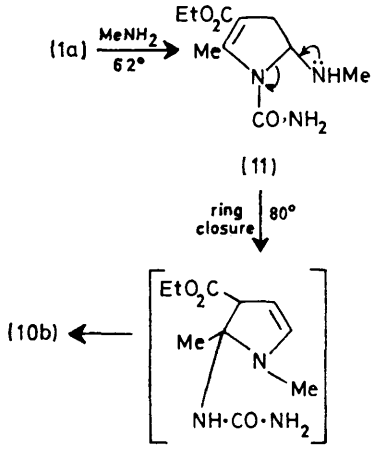
(9)



(10) a; R = H
b; R = Me
c; R = $CH_2CH(OH)\cdot CH_2OPh$

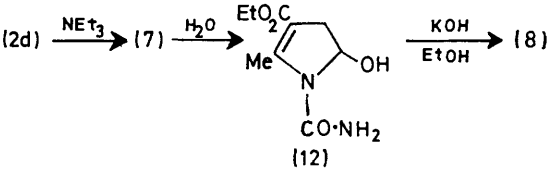
Reaction of compound (1a) with ethanolic methylamine under reflux gave the *N*-methylpyrrole (10b) as sole product, although t.l.c. indicated the presence of an intermediate which later disappeared. By conducting the reaction at 62° the analogous aminopyrroline (11) was formed; this was separated by fractional crystallization from the small amount of (10b) also present.

The thermal transformation of (11) to (10b) rather than to (8) and ultimately (10a), as observed earlier, must involve ring opening of (11) followed by reclosure involving the $N\cdot CH_3$ group (Scheme 2). To check the generality of this reaction the 1-amino-3-phenoxypropan-2-ol [6] was treated with (1a) resulting in the formation of the pyrrole (10c).



SCHEME 2

Ethanolic potassium hydroxide smoothly converted compound (1a), at room temperature, into the *N*-carbamoylpyrrole (8) (61%). Based on the assumption that this reaction had taken a similar course to that with the secondary amines, attempts were made to isolate the intermediate hydroxypyrroline (12). Reaction of



SCHEME 3

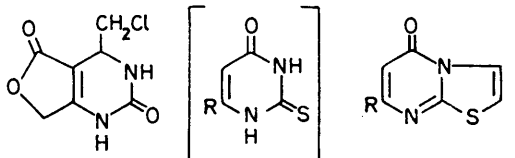
the 7-ethoxy-compound (2d) with triethylamine in aqueous acetone gave (8) along with a low yield of the hydroxy-amide (12) (15%). The n.m.r. spectrum of (12) was very similar to those of (6) and the mass spectrum showed a molecular ion at *m/e* 214. Primary loss of H_2O gave (8) (*m/e* 196), and thereafter the spectrum was identical with that of (8).

Pyrolysis of the sulphone (5) resulted in loss of SO_2 and concomitant oxidation giving finally the *N*-carbamoylpyrrole (8). This reaction presumably proceeds *via* formation of the ring-opened sulphinic acid (2f), followed by ring contraction and elimination of H_2SO_2 [the formation of (8) is also observed in the mass spectrum of (5)].

Bromination of compound (1a) yielded the bromomethyl compound (1e), which upon pyrolysis at 160° gave the lactone (13) by elimination of ethyl bromide. Similar reactions have been observed previously.[7] The

[6] R. Oda and M. Hata, *Nippon Kagaku Zasshi*, 1961, **82**, 1426.
[7] G. Zigeuner, H. Hamberger, H. Blaschke, and H. Sterk, *Monatsh.*, 1966, **97**, 1408.

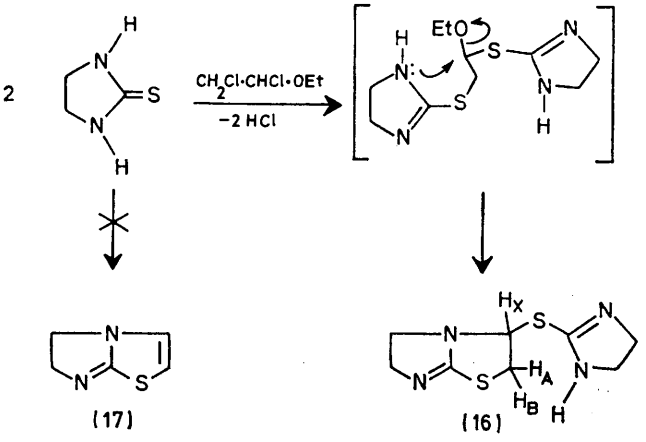
lactone (13) did not react with either potassium cyanide or ethanolic piperidine.



(13) (14) a; R = Me b; R = Ph (15) a; R = Me b; R = Ph

Ring expansion of compound (1a) with guanidine followed by addition of an excess of sodium borohydride gave the tetrahydrodiazepine (2g). The symmetrical multiplets for the C-6 and -7 methylene protons at δ 2·65 and 3·25 in the n.m.r. spectrum of (2g) are consistent only with the ring-expanded formulation shown.

Attempts to condense ethyl acetoacetate and αβ-dichloroethyl ethyl ether with guanidine or *S*-methylisothiouronium iodide failed. Reaction with thiourea gave the thiazolopyrimidine (15a), presumably formed *via* annulation of the pyrimidine (14a) by the chloro-ether Ethyl benzoylacetate likewise gave the phenyl analogue (15b). In an attempt to investigate the proposed annulation of (14), imidazoline-2-thione was treated with the chloro-ether in ethanol. The product isolated (24%) is formulated as (16) (Scheme 4) on the basis of its



(17) (16)

SCHEME 4

spectral properties (see Experimental section), in particular an isolated double doublet in its n.m.r. spectrum associated with H_X of the expected ABX pattern. Modification of the reactant molar ratios did not give any of the expected 1 : 1 product (17).

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian A60A, HA100, or HA100D spectrometer (Me_4Si internal standard); unless stated otherwise data are quoted for 100 MHz spectra. The spectra for compounds (1) and (6) are available as Supplementary Publication No. SUP 21269 (6 pp.),† as are the i.r. spectra of all compounds prepared. Mass spectra were measured with a Hitachi RMU 6E or A.E.I. MS9 spectrometer and i.r. spectra with a Perkin-Elmer 157 spectrometer (for Nujol mulls). M.p.s were determined with a Buchi oil-bath apparatus. Results of elemental analyses were within 0·4% of the calculated values.

4-Chloromethyl-3,4-dihydropyrimidin-2(1H)-ones. General.—A mixture of the urea (0·05 mol), the β-keto-ester (0·072 mol), 1,2-dichloroethyl ethyl ether (0·048 mol), and hydrochloric acid (11N; 0·4 ml) was refluxed in absolute ethanol (20 ml). Removal of the solvent and washing with light petroleum gave the crude product (Table 1).

*Ethyl 7-Cyano-2,3,6,7-tetrahydro-4-methyl-2-oxo-*1H*-1,3-diazepine-5-carboxylate* (2a).—Potassium cyanide (1·8 g, 0·033 mol) was added to a solution of the pyrimidine (1a) (1·2 g, 0·0055 mol) in dimethyl sulphoxide (20 ml); the pink solution was stirred (72 h) and added to water (200 ml). Filtration gave the *product* (1·1 g, 88%), m.p. 250—252°, unchanged by crystallization from aqueous dimethyl sulphoxide, δ [$(CD_3)_2SO$] 8·6 (s, 3-H), 7·75 (d, *J* 6 Hz, 1-H), 4·7 (ddd, J_{ac} 6, J_{ab} 2·5, $J_{a,NH}$ 6 Hz, H_a), 4·15 (q, ester CH_2), 3·24 (dd, J_{cb} 14, J_{ca} 6 Hz, H_c), 2·6br (dd, J_{ba} 2·5, J_{bc} 14, J_{b,CH_3} 1 Hz, H_b), 2·2 (d, $J_{b,Me}$ 1 Hz, Me), and 1·2 (t, ester Me); *m/e* 223 (M^+, base), 208w ($M^+ - CH_3$), 196 ($M^+ - HCN$), 177 ($M^+ - EtOH$), and 123 (M^+ — ethyl acrylate) (Found: C, 53·5; H, 5·9; N, 18·5%).

Ethyl 5c-*Methyl-3-oxo-8-thia-2,4-diazabicyclo*[3.2.1]*octane-*6r-*carboxylate* (4a).—A mixture of the pyrimidine (1a) (2·0 g, 0·0086 mol) in ethanol (80 ml) and aqueous potassium hydrogen sulphide [8] (8 ml) was refluxed for 15 min, cooled, and evaporated (<40 °C). The residual solid was extracted with ethyl acetate (2 × 50 ml) and the extracts were evaporated giving the crude *product* (1·8 g, 90%), m.p. 188—190°. Recrystallization (EtOAc) gave material with m.p. 200—202° (1·6 g); δ [$(CD_3)_2SO$] 7·44 (d, $J_{NH,a}$ 6 Hz, 1-H), 7·32 (s, 3-H), 4·98 (dd, J_{ab} 5, $J_{a,NH}$ 6 Hz, H_a), 4·1 (dq, *J* 7 Hz, further split by 2 Hz due to asymmetry of CH_2, ester CH_2), 3·18 (dd, J_{db} 11, J_{dc} 4 Hz, H_d), 2·76 [dd, J_{cd} 4, J_{cb} 13 Hz, H_c (resonance slightly broadened)], 2·4 (ddd, J_{bd} 11, J_{bc} 13, J_{ba} 5 Hz, H_b), 1·83 (s, CH_3), and 1·22 (t, *J* 7 Hz, ester CH_3); *m/e* 230 (M^+), 197 ($M^+ - HS$), 185 ($M^+ - EtO$), 151 (197 — EtOH), and 130 (base, M^+ — ethyl acrylate) (Found: C, 47·1; H, 6·2; N, 12·0%).

If the above reaction mixture was refluxed for 26 h a crystalline deposit of the potassium salt of (4b) was obtained (1·6 g); m.p. 240°. Treatment of an aqueous solution of this salt with hydrochloric acid (2N) gave the corresponding free acid (4b) (1·2 g, 69%), m.p. 240° (decomp.) (from Me_2SO–H_2O), *m/e* 202 (M^+), 169 ($M^+ - HS$), 130 (M^+ — acrylic acid, base) (Found: C, 41·5; H, 4·9; N, 14·0%).

Formation and Pyrolysis of Ethyl 5c-*Methyl-3-oxo-8-thia-2,4-diazabicyclo*[3.2.1]*octane-*6r-*carboxylate* 8,8-*Dioxide* (5).—A solution of *m*-chloroperoxybenzoic acid (1·75 g, 0·01 mol) in AnalaR chloroform (25 ml) at 0° was added to a solution of (4a) (1·15 g, 0·005 mol) in AnalaR chloroform (25 ml) at 0° and the mixture was kept at room temperature for 72 h. The *product* (5) was filtered off; yield 0·3 g (23%), m.p. 158—160° (decomp.) (from ethanol); δ [$(CD_3)_2SO$] 7·8 (s, 3-H), 7·6 (d, *J* 6 Hz, 1-H), 7·52 (dd, J_{ab} 5, $J_{a,NH}$ 6 Hz, H_a), 4·15 (dq, ester CH_2), 3·26 (m, H_d), 2·8 (m, H_c), 2·5 (m, H_b), 1·48 (s, ring CH_3), and 1·22 (t, ester CH_3, *J* 7 Hz); *m/e* 262w (M^+), 230 ($M^+ - O_2$), 198 ($M^+ - SO_2$), 197 ($M^+ - HSO_2$), and 196 ($M^+ - H_2SO_2$) [the remainder of the spectrum was identical with that of (8)] (Found: C, 41·1; H, 5·3; N,

† For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

[8] J. Ashby and U. Eisner, *J. Chem. Soc.* (*C*), 1967, 1706.

10·3%). Upon heating (5), under nitrogen, at 158 °C for 30 s the melt became deep green in colour. Cooling and crystallization from ethanol gave the amide (8) (47%), m.p. 178—182°, identical with an authentic sample.

The Aminopyrrolines (6) *and* (11).—*Method A*. A solution of the pyrimidine (1a) (0·006 mol) and the appropriate amine (pK_a > 10; 0·06 mol) in absolute ethanol (75 ml) was refluxed for 7 h. Removal of the solvent gave the crude product (Table 2).

Method B. To a hot solution of the pyrimidine (1a) (0·012 mol) in absolute ethanol (150 ml) was added the appropriate amine (0·12 mol) followed by a solution of guanidine (0·015 mol) in absolute ethanol (30 ml). [The guanidine solution was formed by the addition of guanidine hydrochloride (0·015 mol) to a solution of sodium (0·015 mol) in ethanol (30 ml).] The solution was refluxed for 18 h; filtration and evaporation then gave the crude product (Table 2).

Method C. A solution of the diazepine (2d) (0·005 mol) and the appropriate amine (0·05 mol) in absolute ethanol (25 ml) was refluxed for 18 h. Evaporation gave the crude product, which was washed with water prior to crystallization.

Ethyl 1-(2-*Hydroxy*-3-*phenoxypropyl*)-2-*methylpyrrole*-3-*carboxylate* (10c).—Treatment of the pyrimidine (1a) (1·4 g, 0·006 mol) with 1-amino-3-phenoxypropan-2-ol [6] (1·7 g, 0·006 mol) as described for compounds (6) (method B) gave an oil upon work-up (1·6 g). This oil (1 g) in methanol was chromatographed on preparative thick-layer plates (Merck GF 2 mm; eluant 10% MeOH–$CHCl_3$). Extraction of the

TABLE 1

4-Chloromethyl-3,4-dihydropyrimidin-2(1*H*)-ones (1)

Reactants	Reaction time (h)	Purification solvent [a]	Yield [b] (%)	Product	M.p. (°C)	Found (%) C	H	N	Mass spectral fragments
$(NH_2)_2CO$; $AcCH_2·CO_2Et$	4	A	32	(1a)	175—176	46·3	5·6	12·0	$M^+ - CH_2Cl$
$(NH_2)_2CO$; $AcCH_2·CO_2Me$	4	B	17	(1b)	202	44·2	5·1	12·6	M^+ (w), $M^+ - CH_2Cl$
$(NH_2)_2CO$; $BzCH_2·CO_2Et$	18	C	2	(1c)	192—194	57·4	5·1	9·2	M^+ (w), $M^+ - CH_2Cl$
$MeNH·CO·NH_2$; $AcCH_2·CO_2Et$	6	A	30	(1d)	121—123	48·4	6·1	11·3	M^+, $M^+ - CH_2Cl$
c	*c*	C	79	(1e)	155—156 (decomp.) (270) [d]	35·1	4·0	8·9	$M^+ - CH_2Cl$
e	*e*	D	55	(13)	282	41·3	3·7	13·5	M^+, $M^+ - CH_2Cl$

[a] A, abs EtOH; B, MeOH; C, 90% EtOH–H_2O; D, Me_2SO–H_2O. [b] After crystallization. [c] Compound (1e) obtained by treatment of (1a) (0·043 mol) in acetic acid (250 ml) with Br_2 (0·043 mol) in acetic acid (50 ml), dropwise during 1·5 h below 15 °C, followed by addition of H_2O; the resulting oil solidified when washed with H_2O. [d] With slow heating conversion into (13) occurs. [e] Compound (13) obtained by pyrolysis of (1e) (0·013 mol), dry, at 130° (½ h) and then at 160° (¼ h).

TABLE 2

Aminopyrrolines (6) and (11)

Starting amine	Method [a]	Yield (%)	Purification [b] solvent [c]	Product	M.p. (°C)	Found (%) C	H	N	Mass spectral fragments
$HNEt_2$	A	52	B	(6a)	147—148	58·0	8·6	15·4	M^+, $M^+ - NH_3$ (*m** 236·0), M^+ — CONH, M^+ — amine, then as for (8)
	B	63							
Piperidine	A	62	A	(6b)	148—149	59·5	8·2	14·7	M^+, $M^+ - NH_3$ (*m** 248·0), M^+ — CONH, M^+ — amine, then as for (8)
	C	79							
Pyrrolidine	A	15	B	(6c)	125—126	58·2	8·1	15·9	M^+, $M^+ - NH_3$ (*m** 234·0), M^+ — amine, then as for (8)
Morpholine	B	70	A	(6d)	128—129	54·9	7·7	15·0	M^+, $M^+ - NH_3$ (*m** 250·0), M^+ — CONH, M^+ — amine, then as for (8)
1(*p*-Methoxyphenyl)piperazine	B	17	A	(6e)	169	61·6	7·2	14·5	M^+, $M^+ - NH_3$, M^+ — amine, then as for (8)
1-(*o*-Methoxy phenylpiperazine	B	24	A	(6f)	210—212	61·6	7·2	14·5	M^+, $M^+ - NH_3$, M^+ — amine, then as for (8) + starting amine
	C	50							
MeNH·OH	B [d]	62	C	(6g)	162	49·3	7·0	17·3	M^+, M^+ — EtOH (9), (9) — CONH (*m** 120·4), (9) — CO (*m** 103·1), (9) — amine
$MeNH_2$	A [e]	17	*e*	(11)	146—148	52·4	7·2	18·3	M^+, $M^+ - NH_3$, M^+ — amine, then as for (8); also rearrangement to (10b) as in pyrolysis

[a] See text. [b] After crystallization. [c] A, EtOH; B, light petroleum (b.p. 60—80°); C, EtOAc. [d] Reaction time 0·5 h. Extraction of the crude product with petroleum yielded a solid, m.p. 78° identified as (10a) by comparison with an authentic sample [lit. m.p. 78° (E. Benary, *Ber.*, 1911, **44**, 495)]. [e] Conducted at 62° for 2 h; crude material crystallized cold from ethanol–petroleum by freezing. Conducting the reaction as in method A gave (10b), m.p. 21° [lit., 24° (H. Shinohara, S. Misaki, and E. Imoti, *Nippon Kagaku Zasshi*, 1962, **83**, 637)], which was also fully characterized.

band at R_F 0·75 with hot methanol gave an oil, which was dissolved in chloroform and washed with water to remove residual binding agent. The resultant chloroform extract was dried and evaporated yielding the *product* as an oil (71 mg), δ ($CDCl_3$) 7·2 and 6·9 (m, Ph), 6·49 (s, pyrrole 4- and 5-H), 4·2 (q, *J* 7 Hz, ester CH_2), 3·95 (m, side-chain CH_2·CHOH·CH_2), 2·49 (s, pyrrole CH_3), and 1·3 (t, *J* 7 Hz, ester CH_3) (Found: C, 66·3; H, 7·0; N, 4·7%; M^+, 303. $C_{17}H_{21}NO_4$,0·25H_2O requires C, 66·3; H, 7·0; N, 4·55%; *M*, 303).

Ethyl 1-*Carbamoyl*-2-*methylpyrrole*-3-*carboxylate* (8).—To a solution of the pyrimidine (1a) (0·5 g, 0·0025 mol) in ethanol (20 ml) at 0 °C was added a solution of potassium hydroxide (1 g) in water (4 ml) at 0 °C and the resultant solution was allowed to warm to room temperature. After 1·5 h the mixture was poured into water (60 ml), acidified with hydrochloric acid (2N), and cooled. Filtration gave the *product* (0·3 g, 61%), m.p. 184—186°, raised to 186—187° by recrystallization from ethanol; δ [$(CD_3)_2SO$; 60 MHz] 9·24 (s, NH_2), 8·52 (d, $J_{2,3}$ 3 Hz, 2-H), 7·7 (d, $J_{3,2}$ 3 Hz, 3-H), 5·0 (q, ester CH_2), 3·17 (s, 5-CH_3), and 1·48 (t, *J* 6 Hz, ester CH_3); *m/e* 196 (M^+) and 153 (M^+ — CONH; *m** 119·4) [thereafter as for (10a)] (Found: C, 55·1; H, 6·2; N, 14·3%).

Ethyl 7-*Ethoxy*-2,3,6,7-*tetrahydro*-4-*methyl*-2-*oxo*-1H-1,3-*diazepine*-5-*carboxylate* (2d).—The reaction was conducted as for (6) (method B) with no amine present. After refluxing for 1 h the solution was evaporated to yield the *product* as a solid which was triturated with water and collected (75%); m.p. 164—166°; δ ($CDCl_3$) 7·5 (s, 3-H), 6·5br (s, 1-H), 4·55 (m, 7-H), 4·14 (q, ester CH_2), 3·5 (m, C-7 ethoxy CH_2), 2·8 (m, 6-H_2), 2·26 (s, 4-CH_3), and 1·2 (qq, ester and C-7 ethoxy CH_3); *m/e* 242 (M^+), 197 (M^+ — EtO), 196 (M^+ — EtOH), and 142 (M^+ — ethyl acrylate) (Found: C, 54·1; H, 7·5; N, 11·8%).

Ethyl 2,3,6,7-*Tetrahydro*-4-*methyl*-2-*oxo*-1H-1,3-*diazepine*-5-*carboxylate* (2g).—The reaction was conducted as for (6) (method B) with no amine present. After adding the guanidine solution a large excess of sodium borohydride was added. The mixture was refluxed for 90 min with the addition of further borohydride at 15 min intervals. The mixture was poured into water (200 ml), left overnight, and extracted with chloroform (5 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated giving the product as a solid [0·8 g from 1·4 g of (1a)]. Crystallization from ethanol gave the pure material (0·7 g, 60%), m.p. 171·0895) [thereafter as for (8)] (Found: C, 50·2; H, 6·6; N, 12·7%).

TABLE 3

The thiazolopyrimidines (15) and the imidazothiazole (16)

Reactants	Reaction time (h)	Yield [a] (%)	Product	M.p. (°C)	Found (%) C	H	N	Mass spectral fragments
$(NH_2)_2CS$; $AcCH_2·CO_2Et$	3	8	(15a)	Hydrochloride, 256—258° Base, [c] 130—132° [b]	41·5	3·4	14·0	M^+, M^+ — CO, M^+ — (CH_3C=C–CO)
$(NH_2)_2CS$; $BzCH_2·CO_2Et$	6	1·4	(15b)	168° [d]	63·2	3·7	12·1	M^+, M^+ — CO, M^+ — (PhC=C–CO)
Imidazoline-2-thione	2	24	(16)	Hydrochloride, 228—230° Base, [c] 246°	36·1 42·0	4·8 5·4	20·8 24·3	M^+, M^+ — (imidazolinethione)

[a] After crystallization from ethanol. [b] Lit., 132—134° [D. W. Dunwell and D. Evans, *J. Chem. Soc.* (*C*), 1971, 2094]. [c] By treatment of hydrochloride with 2N-NaOH and crystallization from EtOH. [d] Lit., 175° [S. Minami, M. Tomita, and K. Kanaguchi, *Chem. and Pharm. Bull.* (*Japan*), 1972, **20**, 1716]; the n.m.r. spectrum of (15b) also agrees with the published spectrum.

Ethyl 2-*Methylpyrrole*-3-*carboxylate* (10a).—To a warm solution of the amide (8) (1 g, 0·0054 mol) in ethanol (50 ml) was added potassium cyanide (0·2 g) in water (2 ml), and the mixture was refluxed for 4·5 h. After cooling and filtration from the inorganic salts the product was obtained by evaporation (0·6 g, 72%), m.p. 78—79° (lit., 78°; see Table 2, footnote *d*).

Ethyl 1-*Carbamoyl*-5-*hydroxy*-2-*methyl*-Δ²-*pyrroline*-3-*carboxylate* (12).—A solution of the diazepine (2d) (0·5 g, 0·002 mol) in 50% aqueous acetone containing a few drops of triethylamine was refluxed for 24 h. Upon cooling a solid separated (0·25 g, 48%), m.p. 184°, identified as (8) by comparison with an authentic sample. Evaporation of the mother liquors gave an oil which was purified by preparative thick-layer chromatography (Merck silica GF plates; eluant 10% MeOH–$CHCl_3$). Extraction of the band at R_F 0·5 with hot methanol and evaporation gave the *product* as a solid (0·1 g, 15%), m.p. 159°, raised to 164° by recrystallization from ethyl acetate: δ [$CDCl_3$–$(CD_3)_2SO$] 5·7 (s, NH_2), 5·4 (dd, $J_{5,4}$ 3, $J_{5,4'}$ 8 Hz), 4·15 (q, *J* 6 Hz, ester CH_2), 2·8 (m, 4-H_2), 2·6 (t, J <1 Hz, ring CH_3), and 1·28 (t, ester CH_3); *m/e* 214 (M^+), 196·0852 (M^+ — H_2O requires 196·0848), 171·0884 (M^+ — HCNO requires 192—193°, δ [$CDCl_3$–$(CD_3)_2SO$] 7·5 (s, 1-H), 6·8br (s, 3-H), 4·12 (q, *J* 7 Hz, ester CH_2), 3·25 and 2·65 (m, 7- and 6-H_2, symmetrical pattern), 2·24 (s, 4-CH_3), and 1·27 (t, ester CH_3); *m/e* 198 (M^+) (Found: C, 54·7; H, 7·1; N, 14·2%).

The Thiazolo[3,2-a]*pyrimidin*-5-*ones* (15).—A mixture of thiourea (0·05 mol), the β-keto-ester (0·072 mol), 1,2-dichloroethyl ethyl ether (0·048 mol), and hydrochloric acid (11N; 0·4 ml) was refluxed in absolute ethanol (20 ml) for the required time. Cooling gave the crude product which was filtered off and crystallized (see Table 3).

2,3,5,6-*Tetrahydro*-3-(Δ²-*imidazolin*-2-*ylthio*)*imidazo*-[2,1-b]*thiazole* (16).—A mixture of imidazoline-2-thione (0·047 mol), 1,2-dichloroethyl ethyl ether (0·047 mol), and hydrochloric acid (11N; 0·4 ml) was refluxed in ethanol (20 ml). Complete dissolution had occurred after 10 min, and the product then began to precipitate out. Heating was continued for 2 h, and the *product* was then filtered off (see Table 3); δ ($CDCl_3$) 6·2 (dd, J_{AX} 4, J_{BX} 7 Hz, H_X) and 4·4 (11H, m).

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