Protection of Primary Amines as *N*-Substituted 2,5-Dimethylpyrroles

Stephen P. Bruekelman, (Miss) Susan E. Leach, G. Denis Meakins,* and Malcolm D. Tirel
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QY

Protection of a primary amine group is achieved by incorporating it into an *N*-substituted 2,5-dimethylpyrrole system. The method affords protection against strong bases and nucleophiles, heating with concentrated alkali, standard mineral acid work-up conditions, and various other reagents.

Phenyl-, pyridyl-, thiazolyl-, and alkyl-amines have been studied. All give trisubstituted pyrroles in high yield (>80%) by reaction with hexane-2,5-dione. The pyrroles from the first three types are stable to storage; even the *N*-alkyl compounds can be used without difficulty. Regeneration of the amine group, by treatment with hydroxylamine hydrochloride, is efficient (*ca.* 80% yield) with the phenyl, pyridyl, and alkyl compounds but less satisfactory (60—65% generally but down to 25% in two cases) with the thiazolyl derivatives.

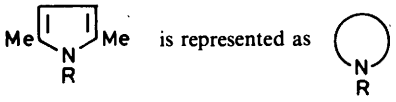
Work up to 1981 on protection of primary amines has been comprehensively reviewed.[1] More recent methods include the use of an arylmethanesulphonyl group (removed photochemically)[2] and the 1,3-dithian-2-ylmethoxycarbonyl group (removed by peroxy acids),[3] and conversion of the amino group into a tetramethyldisilylazacyclopentane system (which regenerates the amine on treatment with aqueous methanol)[4] or the derived *N*,*N*-diallylamine (from which the amine is reformed by isomerisation using Wilkinson's catalyst followed by hydrolysis).[5] During the syntheses of 4- and 5-aryl-4,5-dihydropyridazin-3(2*H*)-ones[6] and other heterocyclic systems[7] we wished to protect the primary amino-group of certain substrates in such a way that strong bases (*e.g.*, Bu^nLi, Pr^i_2NLi) could be used to give carbanions suitable for the attachment of electrophiles. Further, the protected group was required to be stable to several strong nucleophiles (*e.g.* RMgHal), to heating with concentrated alkali (*e.g.* 5M-KOH), and to standard mineral acid work-up conditions (*e.g.* 2M-HCl at 20 °C for *ca.* 1 h). These requirements clearly excluded most of the previous approaches. For example, while replacement of N–H by N–Si[4,8] affords protection against strong bases and nucleophiles in non-polar solvents the protecting groups are unstable in hydroxylic media. Conversion into *N*,*N*-diallylamines appeared to be suitable in most respects, but the possibility that the deprotection stage (involving prolonged heating in the presence of the catalyst) might lead to undesired isomerisation of double bonds elsewhere in the substrates could not be excluded.

For the present purposes it was planned to substitute both NH_2 protons by carbon atoms to give a system not containing a C=O group and with hydrogen atoms of only very low acidity. The possibility of converting primary amines into *N*-substituted 2,5-dimethylpyrroles as a method of amine protection was based on work dating from the 1880s: several amines had been condensed with hexane-2,5-dione to give *N*-substituted 2,5-dimethylpyrroles,[9] and the product formed by heating pyrrole with hydroxylamine hydrochloride and sodium carbonate had been identified as the dioxime of succinaldehyde.[10] Subsequently both reactions were reinvestigated. Standard conditions for the condensation were established,[11] and the yield of the dioxime from pyrrole (and that of the corresponding product from 2,5-dimethylpyrrole) was shown to depend on the pH of the medium.[12] For the applications envisaged here blocking of the weakly acidic 2- and 5-positions of the pyrrole ring was essential, but it was hoped that the 3- and 4-positions, with hydrogens of lower acidity, could be left unsubstituted; the general instability of tetra-alkylpyrroles also militated against the possibility of more extensive substitution. Although no *N*-substituted pyrrole appeared to have been treated with hydroxylamine it seemed likely that a primary amine would accompany the dioxime in such a reaction and thereby afford a means of deprotection.

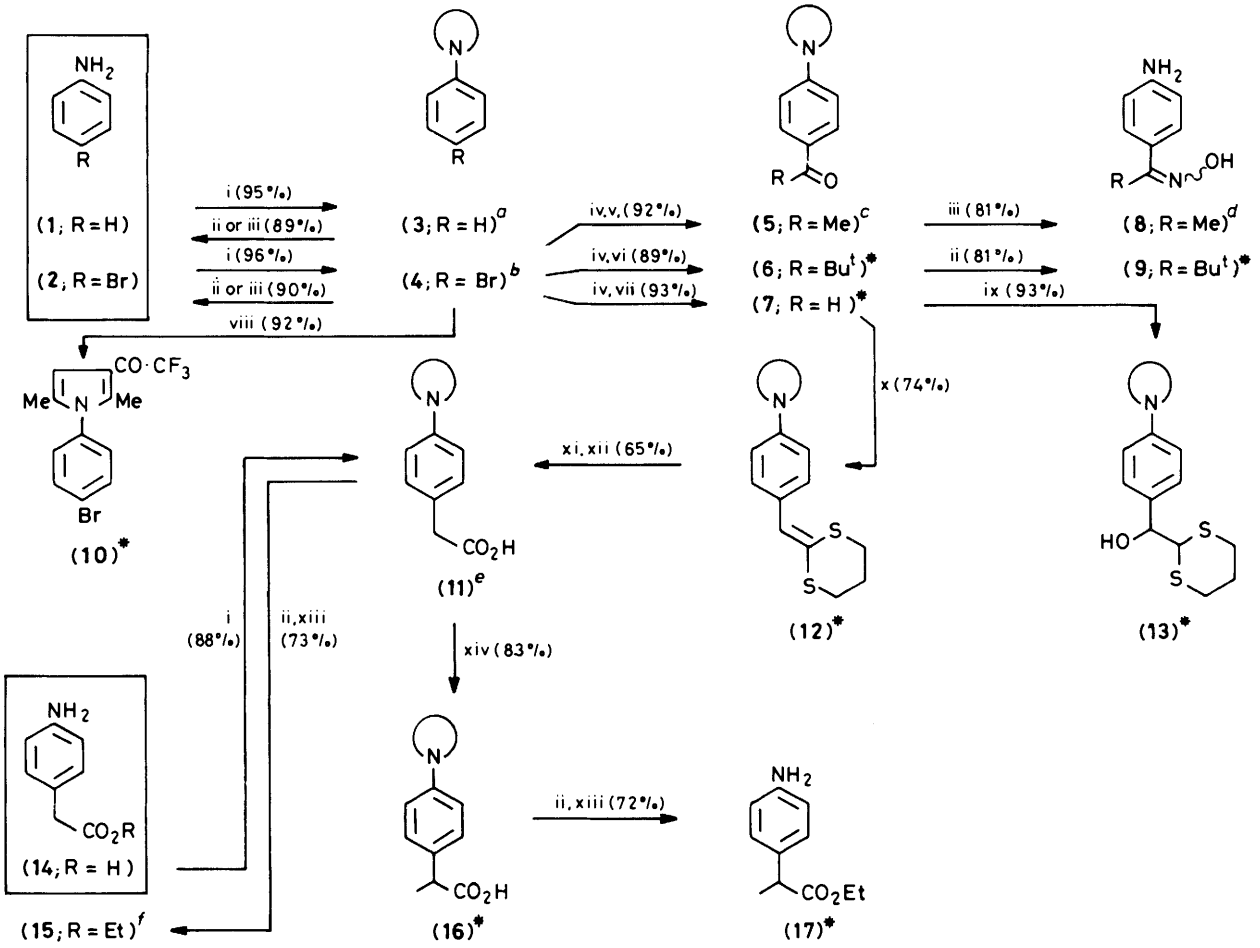
The results with derivatives of benzene, pyridine, and thiazole, and with aliphatic compounds (outlined earlier[13]) are presented in Schemes 1—4; since most of the work is straightforward only brief commentaries on the individual sections are required. Consideration of the collected results leads to the following conclusions. (i) Conversion of primary amines into *N*-substituted 2,5-dimethylpyrroles proceeds in uniformly high yield (>80%). (ii) The trisubstituted pyrroles with phenyl, pyridyl, or thiazolyl groups as the *N*-substituents are stable to storage for long periods; even the *N*-alkyl compounds, which are the least stable, can be stored at 0 °C for 2 days without appreciable decomposition. (An exception is mentioned later.) (iii) The protecting group is unaffected by a variety of reagents which do not involve prolonged contact with acidic media. (iv) Deprotection is efficient (*ca.* 80% yield) with the *N*-phenyl-, *N*-pyridyl-, and *N*-alkyl-pyrroles, but less satisfactory with the *N*-thiazolyl derivatives (65—25% yield).

The pyrroles (**3**)[14] and (**4**)[15] (Scheme 1) were used for exploratory work. Findlay[12] found that whereas treatment of pyrrole (1 equiv.) with hydroxylamine hydrochloride (2 equiv.) led to dark polymeric material, treatment with hydroxylamine hydrochloride (2.6 equiv.) and potassium hydroxide (1.6 equiv.) afforded succinaldehyde dioxime in 61% yield. With the pyrroles (**3**) and (**4**) hydroxylamine hydrochloride alone or in the presence of potassium hydroxide gave similar high yields of the amines (**1**) and (**2**), and the simpler procedure (without potassium hydroxide) was used for most of the deprotections reported here. An unexpected feature, very useful in the dihydropyridazinone preparations,[6] is that the protecting group is not removed by hydrazine under comparable conditions. Experiments in which the *N*-phenyl compound (**3**) was recovered unchanged after treatment with Bu^nLi or Pr^i_2NLi at −30 °C followed by work-up with D_2O established the very low acidity of the protons in the protecting group. Reactions between the lithio-derivative of the *N*-4-bromophenyl compound (**4**) and *N*,*N*-dimethylamides led conveniently to the aldehyde (**7**), the methyl ketone (**5**), and the t-butyl ketone (**6**). The last of these exemplifies a simple preparation of t-butyl ketones which has been applied to several aromatic and heterocyclic systems.[7,16] [Other methods employed for similar transformations of 4-bromoaniline include protection as the *N*,*N*-bis(trimethylsilyl)amine[17] and direct use of the 4,*N*,*N*-

In the Schemes starting materials are shown in boxes, references are given to known compounds which are not commercially available, new compounds are marked with an asterisk, and yields (%) of stages (or of sequences of stages) are shown with the reagent numbers.



Scheme 1. Benzene derivatives



Reagents: i, $MeCO[CH_2]_2COMe$–AcOH (small quantity)–C_6H_6, heat; ii, H_2NOH·HCl (4—5 equiv.)–EtOH–H_2O, heat; iii, H_2NOH·HCl (4.6 equiv.)–KOH (2.7 equiv.)–EtOH–H_2O, heat; iv, Bu^nLi; v, $MeCONMe_2$; vi, Bu^tCONMe_2; vii, $HCONMe_2$; viii, $(CF_3CO)_2O$; ix, $S(CH_2)_3SCHLi$; x, $S[CH_2]_3SC(SiMe_3)Li$; xi, $HgCl_2$–MeOH; xii, KOH–EtOH; xiii, EtOH–H_2SO_4; xiv, $LiNPr^i_2$ (2 equiv.), then MeI (1 equiv.).

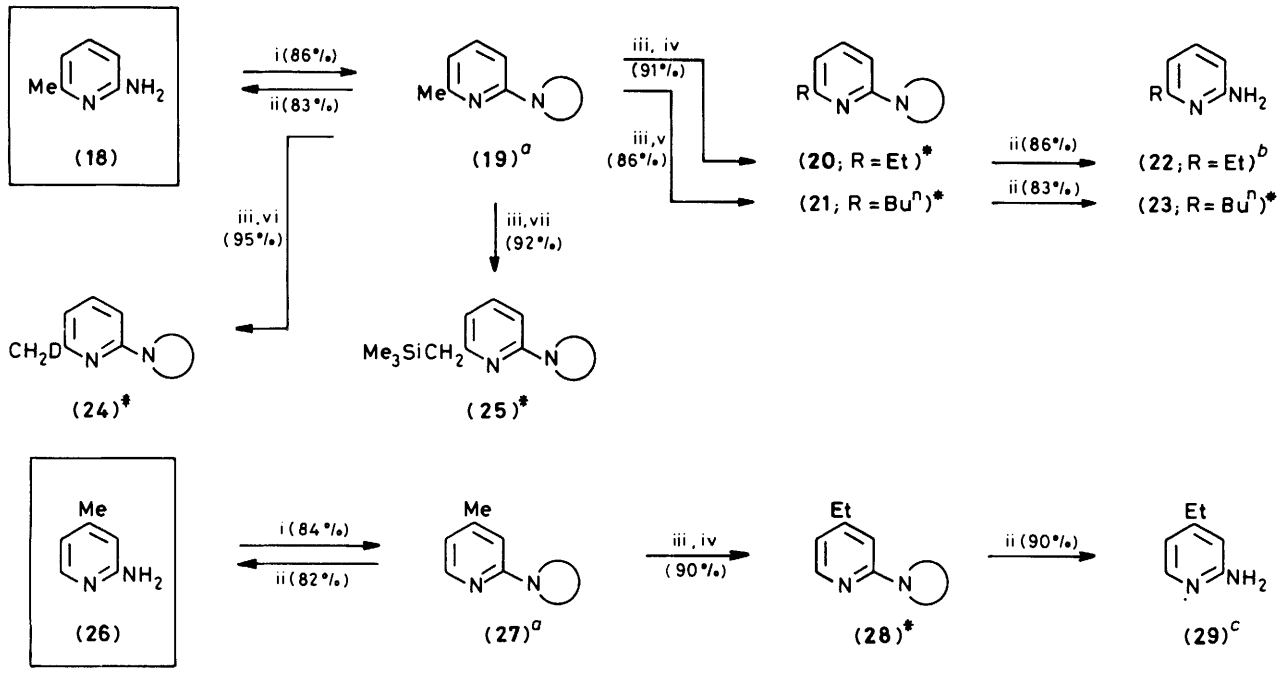
References: [a] 14, [b] 15, [c] 11, [d] 27, [e] 6, [f] 26.

trilithio-derivative.[18]] Elaboration of the aldehyde (**7**) to the esters (**15**) and (**17**) illustrates the possible application to the synthesis of amino acids.

In the pyridine series (Scheme 2) the intention was to use the protecting group as a means of directing alkylation to the methyl rather than the amino groups of the 6- and 4-methyl 2-amines (**18**) and (**26**). The three-stage homologations shown afforded the 6- and 4-ethyl-2-amines (**22**)[19] and (**29**)[20] in overall yields of 67 and 68% respectively. Where the appropriate alkylpyridine is readily available the 2-amino-group may be introduced by nucleophilic substitution,[21] but the present route provides more convenient access to products such as 2-amino-6-butylpyridine (**23**).

Most of the thiazole work involved transformations of the pyrrole (**34**) derived from 2-amino-4-methylthiazole (**30**)[22] which were intended to give 2-amines with various substituents at position 5. Clean formation of the 5-lithio derivative was demonstrated by preparing the 5-deuterio and 5-trimethylsilyl compounds (**40**) and (**42**). Although attempts to introduce the 5-pivaloyl group by treating the 5-lithio derivative with *N*,*N*-dimethylpivalamide were unsuccessful the low reactivity of this thiazolyl-lithium was overcome by using the more reactive *N*-methoxy-*N*-methylamide (a new compound), the approach being based on previous acylations with this type of reagent.[23] Alternative routes to 5-acyl compounds are illustrated by the two-stage preparation of the t-butyl ketone (**36**), which establishes the stability of the protecting group to Moffatt-Pfitzner oxidation,[24] and the preparation of the phenyl ketone (**37**) involving addition of the 5-lithio-derivative to benzoyl chloride in tetrahydrofuran at low temperature. Alkylation at position 5 of the amino-protected 4-methyl and 4-phenyl compounds led to the 4,5-disubstituted 2-aminothiazoles (**45**), (**46**), and (**49**). This approach is useful in situations where the Hantzsch condensation requires an α-bromo-ketone (for

Scheme 2. Pyridine derivatives



Reagents: i, ii as Scheme 1; iii, Pr^i_2NLi; iv, MeI; v, Pr^nI; vi, D_2O; vii, Me_3SiCl.
References, [a] 27, [b] 19, [c] 20.

condensation with thiourea) which is not the predominant product obtained by brominating an unsymmetrical ketone. Deprotonation of the 5-methyl group in compound (**48**), as evidenced by formation of the deuterio-derivative (**47**), could be used for homologation at the 5-position.

The 4-methylthiazole derivative (**34**) was largely unchanged by treatment with hydroxylamine hydrochloride and the standard amount of potassium hydroxide, presumably because the thiazole's basicity reduces the proton concentration to such a low level that very little protonation of the pyrrole system occurs. (There is evidence[12] that protonation precedes nucleophilic attack by hydroxylamine in the pyrrole ring-opening.) Deprotection of all the thiazoles occurred with hydroxylamine hydrochloride alone, but the yields were disappointing in general (*ca.* 60—65%) and especially so (25%) with compounds (**36**) and (**37**) having electron-withdrawing groups at position 5. The situation was not improved by the obvious variations (changing the ratios of the reactants, the concentrations of the solutions and the reaction times, and by excluding oxygen). It may be that there is competition between ring-opening of the pyrrole system and nucleophilic addition at the thiazole 2-position; the latter would be encouraged by the presence of 5-acyl groups.

The work with the salt of an aliphatic bromo-amine (**50**) (Scheme 4) was designed to test the suitability of the protecting group for widely used operations involving halogen substituents. Protection, reaction with 1,3-dithian-2-yl-lithium, and methylation led to the intermediate (**56**) containing protected amine and carbonyl groups. These were exposed selectively giving (**55**) and (**57**), the singly protected derivatives of an amino-ketone. The oxo-pyrrole (**55**) is markedly the least stable of the products reported here; it darkens rapidly at 20 °C but may be distilled at low pressure and stored at −70 °C under reduced pressure.

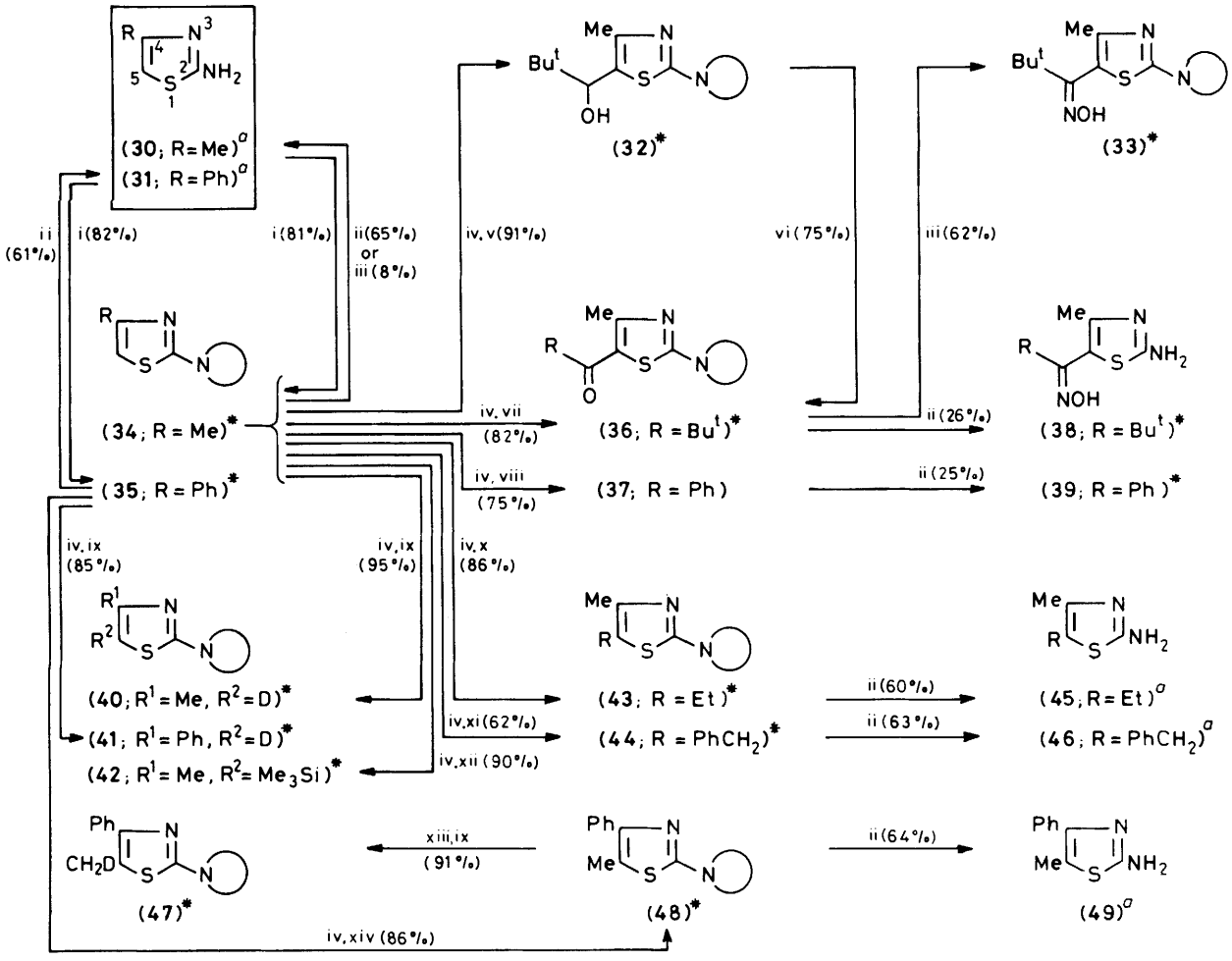
Experimental

Unless stated otherwise ^1H n.m.r., i.r., and u.v. spectra were recorded using Perkin-Elmer R32 (90 MHz), 297, and 555 spectrometers with solutions in $CDCl_3$, CCl_4, and EtOH respectively. General procedures are described where they are first used and then identified by capital letters. Petroleum refers to light petroleum, b.p. 40—60 °C, and THF to tetrahydrofuran. The characterisation of new compounds is shown in the Table; complete accounts of their spectrometric characteristics are given elsewhere.[7] The constants of known compounds agreed with those recorded in the literature cited in the Schemes.

Scheme 1: Products from 4-Bromoaniline (**2**) *and Aniline* (**1**).—Procedure A. A solution of 4-bromoaniline (14 g), hexane-2,5-dione (9.4 g), and AcOH (1 ml) in benzene (70 ml) was boiled under reflux for 4 h while water was removed in a Dean-Stark head. The solution was diluted with Et_2O, washed with 2M-HCl, brine, M-$NaHCO_3$, and brine, and dried ($MgSO_4$). Removal of the solvents gave crystals (19.3 g), m.p. 69—71 °C. Recrystallisation of a portion afforded 1-(4-bromophenyl)-2,5-dimethylpyrrole (**4**), m.p. 74—75 °C (lit.,[15] 74—75 °C), δ 2.00 (6 H, s, Me_2), 5.85 (2 H, s, pyrrole-H_2), and 7.02 and 7.53 (4 H, two d with *J* 9 Hz, C_6H_4). Aniline (5.1 g) similarly gave 2,5-dimethyl-1-phenylpyrrole (**3**) (9.0 g), m.p. 50—51.5 °C (lit.,[14] 51—52 °C). Apart from compound (**51**), described later, all the *N*-substituted 2,5-dimethylpyrroles were prepared by procedure A; the yields are given in Schemes 1—4.

A solution of 1-(4-bromophenyl)-2,5-dimethylpyrrole (**4**) (1.1 g) and trifluoroacetic anhydride (2 ml) in dry benzene (8 ml) was boiled under reflux for 4 h. Dilution with water and extraction with CH_2Cl_2 gave material which was sublimed at 100 °C (bath-temp.)/0.1 mmHg. Recrystallisation from petroleum afforded the *trifluoroacetylpyrrole* (**10**) (1.4 g), δ 1.99 (3 H, s, 5-Me), 2.34

Scheme 3. Thiazole derivatives



Reagents: i, ii, iii as Scheme 1; iv, Bu^{n}Li; v, Bu^{t}CHO; vi, Ac_2O–Me_2SO; vii, Bu^{t}CON(OMe)Me;* viii, PhCOCl; ix, D_2O; x, EtI; xi, $PhCH_2Br$; xii, Me_3SiCl; xiii, Pr^i_2NLi; xiv, MeI.

[a] Ref. 22.

(3 H, s, 2-Me), 6.43 (1 H, br s, pyrrole 4-H), and 7.05 and 7.66 (4 H, two d, C_6H_4); *m/z* 347, 345 (M^+, 53%), and 276 (100).

Procedure B. 1-(4-Bromophenyl)-2,5-dimethylpyrrole (**4**) (1.48 g) was added to a solution of H_2NOH·HCl (2.06 g) in EtOH (16 ml)–H_2O (6 ml). The solution was boiled under reflux for 1 d, poured into 2M-HCl, washed with Et_2O, and basified with 2M-NaOH. Extraction with Et_2O afforded 4-bromoaniline (0.90 g) identified by comparison (^{1}H n.m.r., t.l.c.) with an authentic specimen. Most of the deprotections were carried out by this procedure; the yields of the amines are given in the Schemes.

Procedure C. 1-(4-Bromophenyl)-2,5-dimethylpyrrole (**4**) (1.56 g) was added to a solution of H_2NOH·HCl (2.0 g) and KOH (0.96 g) in EtOH (16 ml)–H_2O (6 ml). Continuation as in the foregoing experiment gave 4-bromoaniline (0.96 g). The deprotections carried out in this way are specified in the Schemes.

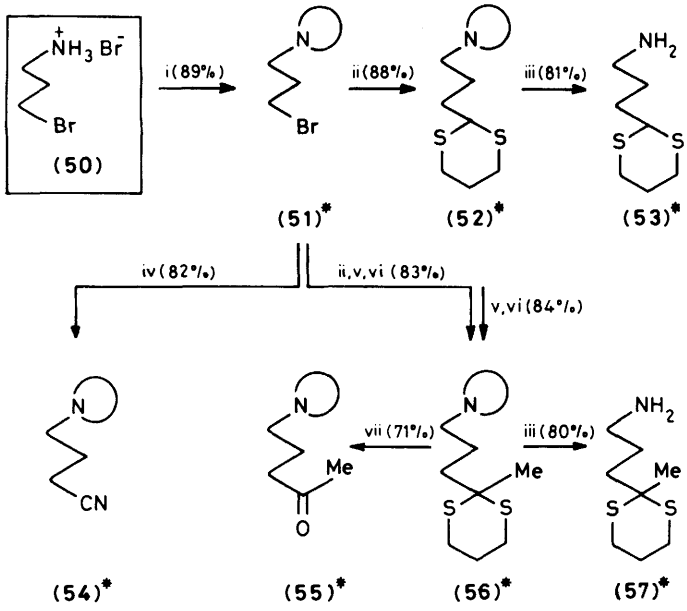
The substituted pyrrole (**4**) was not affected by being boiled with PhNH·NH_2 and with H_2NCO·NH·NH_3Cl^- in EtOH–H_2O. Procedures B and C with 2,5-dimethyl-1-phenylpyrrole (**3**) gave aniline in yields of 90 and 91% respectively. The substituted pyrrole (**3**) was not affected by being boiled with N_2H_4·H_2O in EtOH–H_2O or EtOH–AcOH–H_2O; treatment with various combinations of N_2H_4·2HCl and N_2H_4·H_2O in boiling EtOH–H_2O gave small amounts (less than 15% yield) of aniline.

Procedure D. A 1.55M-solution of Bu^{n}Li in hexane (39 ml) was added during 5 min to a solution of 1-(4-bromophenyl)-2,5-dimethylpyrrole (**4**) (14.4 g) in dry Et_2O (80 ml) which was stirred at −20 °C under N_2 during the addition and for a further 45 min. A solution of $HCONMe_2$ (freshly distilled; 5.1 g) in Et_2O (10 ml) was added during 5 min, and stirring was continued for a further 1 h. The cooling bath was removed, and after 2 h the solution was poured into ice–H_2O (100 ml) containing $NaHCO_3$ (3 g), and extracted with Et_2O. The Et_2O solution was washed (2M-HCl, brine, M-$NaHCO_3$, and brine), dried, and evaporated, and the residue crystallised from hexane to give the *aldehyde* (**7**) (10.7 g), δ 10.04 (1 H, s, CHO); $\nu_{max.}$ 1 707 cm^{-1}; *m/z* 199 (M^+, 100%).

Procedure E. Treatment of 1-(4-bromophenyl)-2,5-dimethylpyrrole (**4**) (4.1 g) with 1.55M-Bu^{n}Li (11.1 ml) and then with $MeCONMe_2$ (1.6 g) as in procedure D gave 1-(4-acetylphenyl)-2,5-dimethylpyrrole (**5**) (3.2 g), m.p. 112—113 °C (lit.,[11] 110—111 °C); δ 2.6 (3 H, s, MeCO).

Procedure F. Treatment of 1-(4-bromophenyl)-2,5-dimethylpyrrole (**4**) (6.15 g) with 1.55M-Bu^{n}Li (16.7 ml) and then with

Scheme 4. Aliphatic compounds



Reagents: i, $MeCO[CH_2]_2COMe$–MeOH, heat, slow addition of KOH; ii, $S[CH_2]_3SCHLi$; iii, $H_2NOH{\cdot}HCl$–KOH–EtOH–H_2O, heat; iv, NaCN–Me_2SO; v, Bu^nLi; vi, MeI; vii, $HgCl_2$–$CaCO_3$–H_2O–MeCN.

Bu^tCONMe_2 (3.5 g) as in procedure D gave the *t-butyl ketone* (**6**) (5.6 g), δ 1.38 (9 H, s, Bu^tCO); $\nu_{max.}$ 1 677 cm^{-1}; *m/z* 255 (M^+, 54%) and 198 (100).

Procedure G. A 1.5M-solution of Bu^nLi in hexane (3.8 ml) was added during 5 min to a solution of 1,3-dithiane (0.65 g) in dry THF (20 ml) which was stirred at −20 °C under N_2. After 15 min the solution was cooled to −40 °C and a solution of 4-(2,5-dimethylpyrrol-1-yl)benzaldehyde (**7**) (1.1 g) in THF (12 ml) was added during 5 min. The cooling bath was removed, and after 1 h the solution was poured into ice–water (80 ml). The material isolated with Et_2O crystallised from CH_2Cl_2–pentane to give the *alcohol* (**13**) (1.6 g), $\nu_{max.}$($CHCl_3$) 3 590 and 3 450 cm^{-1}; *m/z* 319 (*M*, 8%) and 119 (100). A solution of this alcohol when heated with *p*-Me·C_6H_4·SO_3H in C_6H_6 gave dark amorphous material.

A 1.5M-solution of Bu^nLi in hexane (19.3 ml) was added during 5 min to a solution of 2-trimethylsilyl-1,3-dithiane[25] (5.3 g) in THF (60 ml) which was stirred at −20 °C under N_2. The temperature of the solution was allowed to reach 0 °C during 45 min. The solution was cooled to −20 °C, and a solution of the aldehyde (**7**) (5.5 g) in THF (15 ml) was added during 5 min. The cooling bath was removed, and after 12 h the solution was poured into M-HCl. The material isolated with CH_2Cl_2 crystallised from CH_2Cl_2–pentane to give the *alkene* (**12**) (9.8 g), δ 6.86 (1 H, s, CH); *m/z* 301 (M^+, 100%).

The foregoing alkene (1.45 g) was added to a solution of $HgCl_2$ (2.9 g) in MeOH (72 ml)–water (8 ml) under N_2, and the mixture was boiled under reflux for 4 h. The mixture was filtered, and the precipitate washed with CH_2Cl_2. The filtrate and washings were combined and washed with 5M-NH_4OAc and water. The solution was dried, treated with activated charcoal, filtered, and evaporated. The residue was dissolved in MeOH (6 ml) containing KOH (0.4 g), and the solution was boiled under reflux for 2 h. Acidification with 2M-HCl and isolation with CH_2Cl_2 gave 2-[4-(2,5-dimethylpyrrol-1-yl)-phenyl]ethanoic acid[6] (**11**) (0.72 g), m.p. and mixed m.p. 115—117 °C.

A solution of the foregoing acid (2.5 g) and $H_2NOH{\cdot}HCl$ (3.7 g) in EtOH (30 ml)–H_2O (9 ml) was boiled under reflux for 1 d, and the solvents were evaporated at 100 °C/15 mmHg. EtOH (50 ml) containing H_2SO_4 (1.6 ml) was added. The solution was boiled under reflux for 3 h, concentrated to *ca.* 30 ml at 80 °C/15 mmHg, cooled, poured into 2M-HCl, washed with Et_2O, and basified at 5 °C with M-NaOH. The material isolated with Et_2O was purified by flash chromatography on SiO_2 to give ethyl (4-aminophenyl)ethanoate (**15**) (1.43 g), eluted with Et_2O–petroleum (1:1), m.p. 49—50 °C (lit.,[26] 49.5 °C).

Procedure H. A 1.55M-solution of Bu^nLi in hexane (5.9 ml) was added during 5 min to a solution of Pr^i_2NH (922 mg) in dry THF (10 ml) which was stirred under N_2 at −40 °C during the addition and at −25 °C for a further 20 min. A solution of the ethanoic acid (**11**) (953 mg) in THF (10 ml) was added. After 20 min a solution of MeI (611 mg) in THF (4 ml) was added, and stirring was continued for 30 min. The cooling bath was removed, and after 2 h the solution was poured into 2M-NaOH, washed with Et_2O, and acidified with 2M-HCl. The material isolated with Et_2O crystallised from Et_2O–petroleum to give the *acid* (**16**) (842 mg) and 3.76 (1 H, quart, *J* 8 Hz, MeC*H*); *m/z* 243 (M^+, 100%). Deprotection of the acid (**16**) (820 mg) followed by esterification [as described for conversion of the acid (**11**) into the ester (**15**)] gave the *ester* (**17**) (472 mg), $\nu_{max.}$ 1 736 cm^{-1}; *m/z* 193 (M^+, 14%) and 120 (100).

Scheme 2: Products from the 2-Aminopyridines (**18**) *and* (**26**).—The protected amine (**19**)[27] (3.8 g) was treated with Pr^i_2NLi [from Pr^i_2NH (2.2 g)] and then MeI (3.05 g) as in procedure H. Dilution with water, extraction with Et_2O, and distillation of the product gave the *6-ethyl compound* (**20**) (3.72 g), δ 2.79 (2 H, quart, *J* 7 Hz, MeCH_2), *m/z* 200 (M^+, 100%). Similar treatment of the protected amine (**19**) (1.6 g) with Pr^i_2NLi and then with Pr^nI (1.55 g) followed by purification of the product using flash chromatography on SiO_2 with pentane–Et_2O (3:1) as eluant gave the *6-butyl compound* (**21**) (1.7 g), δ 2.78 (2 H, t, *J* 8 Hz, PrCH_2), *m/z* 228 (M^+, 100%). Similar treatment of the protected amine (**19**) (1.1 g) with Pr^i_2NLi and then with D_2O (2 ml) gave the *deuterio compound* (**24**) (1.05 g), δ 2.52 (2 H, br s, CH_2D); *m/z* 187 (M^+, 100%). Similar treatment of the protected amine (**19**) (3.3 g) with Pr^i_2NLi and then with Me_3SiCl (2.3 g) gave the *silyl compound* (**25**) (4.2 g); δ 0.08 (9 H, s, Me_3Si); *m/z* 258 (M^+, 87%) and 73 (100).

The protected amine (**27**)[28] (2.85 g) was treated with Pr^i_2NLi [from Pr_2NH (1.65 g)] and then MeI (2.3 g) as in procedure H. Dilution with water, extraction with Et_2O, and distillation of the product gave the *4-ethyl compound* (**28**) (2.75 g), δ 2.66 (2 H, quart, *J* 8 Hz, MeCH_2); *m/z* 200 (M^+, 100%).

Scheme 3: Products from the 2-Aminothiazoles (**30**) *and* (**31**).—Procedure I. A 1.55M-solution of Bu^nLi in hexane (12.2 ml) was added during 5 min to a solution of the protected amine (**34**) (3.4 g) in dry THF (30 ml) which was stirred at −30 °C under N_2 during the addition and for a further 45 min. A solution of Bu^tCHO (1.65 g) in THF (4 ml) was added during 5 min, and stirring was continued for a further 1 h. The cooling bath was removed, and after 2 h the solution was poured into ice–water. Isolation with Et_2O, and crystallisation of the product from Et_2O–petroleum gave the *alcohol* (**32**) (4.5 g), δ 4.71 (1 H, d, *J* 3 Hz, C*H*OH); *m/z* 278 (M^+, 18%) and 221 (100). The protected amine (**34**) (685 mg) was treated with 1.5M-Bu^nLi (2.5 ml) and then with D_2O (2 ml) as in procedure I to give the *deuterio derivative* (**40**) (654 mg), *m/z* 193 (M^+, 100%), lacking the signal at δ 6.84 (1 H, s, 5-H) of the starting material (**34**). The protected amine (**34**) (2.1 g) was treated with 1.5M-Bu^nLi (7.7 ml) and then with Me_3SiCl (1.3 g) as in procedure I, and the product was

Table. Characterisation of new compounds

Compound	M.p. (°C)	B.p. [bath temp. (°C)/ mmHg]	Found (%)			Molecular formula	Requires (%)		
			C	H	N		C	H	N
2,5-Dimethyl-1-(4-pivaloylphenyl)pyrrole (**6**)	80—80.5		79.8	8.3	5.5	$C_{17}H_{21}NO$	80.0	8.3	5.5
4-(2,5-Dimethylpyrrol-1-yl)benzaldehyde (**7**)	79—80.5		78.5	6.5	7.0	$C_{13}H_{13}NO$	78.4	6.6	7.0
4-(1-Hydroxyimino-2,2-dimethylpropyl)-phenylamine (**9**)	212—215 (decomp.)		68.5	8.5	14.4	$C_{11}H_{16}N_2O$	68.7	8.4	14.6
1-(4-Bromophenyl)-2,5-dimethyl-3-trifluoroacetylpyrrole (**10**)	77.5—79		48.7	3.1	4.1	$C_{14}H_{11}BrF_3NO$	48.6	3.2	4.0
2-[4-(2,5-Dimethylpyrrol-1-yl)benzylidene]-1,3-dithian (**12**)	94—95		67.9	6.3	4.5	$C_{17}H_{19}NS_2$	67.7	6.3	4.6
1,3-Dithian-2-yl-[4-(2,5-dimethylpyrrol-1-yl)-phenyl]methanol (**13**)	123—130		64.0	6.5	4.5	$C_{17}H_{21}NOS_2$	63.9	6.6	4.4
2-[4-(2,5-Dimethylpyrrol-1-yl)phenyl]propanoic acid (**16**)	134—135 (decomp.)		73.9	7.0	5.9	$C_{15}H_{17}NO_2$	74.0	7.0	5.8
Ethyl 2-(4-aminophenyl)propanoate (**17**)	34—36		68.5	7.8	7.2	$C_{11}H_{15}NO_2$	68.4	7.8	7.25
2-(2,5-Dimethylpyrrol-1-yl)-6-ethyl pyridine (**20**)		84—86/0.04	77.9	8.0	14.1	$C_{13}H_{16}N_2$	78.0	8.05	14.0
6-Butyl-2-(2,5-dimethylpyrrol-1-yl)-pyridine (**21**)		93—95/0.03	*m/z* 228.1625			$C_{15}H_{20}N_2$	M^+, 228.1625		
2-Amino-6-butylpyridine (**23**)		156—158/15	71.8	9.3	18.5	$C_9H_{14}N_2$	71.95	9.4	18.65
6-(Deuteriomethyl)-2-(2,5-dimethyl-pyrrol-1-yl)pyridine (**24**)		76—78/0.04	*m/z* 187.1220			$C_{12}H_{13}DN_2$	M^+, 187.1220		
2-(2,5-Dimethylpyrrol-1-yl)-6-trimethyl-silylmethylpyridine (**25**)		97—99/0.03	*m/z* 258.1553			$C_{15}H_{22}N_2Si$	M^+, 258.1552		
2-(2,5-Dimethylpyrrol-1-yl)-4-ethylpyridine (**28**)		85—87/0.03	78.1	7.9	13.9	$C_{13}H_{16}N_2$	78.0	8.05	14.0
N-Methoxy-*N*-methyl-2,2-dimethylpropanamide		74—74/16	57.8	10.5	9.5	$C_7H_{15}NO_2$	57.9	10.4	9.65
1-[5-(1-Hydroxy-2,2-dimethylpropyl)-4-methyl-thiazol-2-yl]-2,5-dimethylpyrrole (**32**)	142—143		64.8	7.9	10.1	$C_{15}H_{22}N_2OS$	64.7	8.0	10.1
1-[5-(1-Hydroximino-2,2-dimethylpropyl)-4-methylthiazol-2-yl]-2,5-dimethylpyrrole (**33**)	121—122		61.7	7.3	14.3	$C_{15}H_{21}N_3OS$	61.8	7.3	14.4
2,5-Dimethyl-1-(4-methylthiazol-2-yl)pyrrole (**34**)		75—78/0.03	*m/z* 192.0721			$C_{10}H_{12}N_2S$	M^+, 192.0721		
2,5-Dimethyl-1-(4-phenylthiazol-2-yl)pyrrole (**35**)	52.5—53.5		71.0	5.6	10.9	$C_{15}H_{14}N_2S$	70.8	5.6	11.0
2,5-Dimethyl-1-[4-methyl-5-(2,2-dimethyl-1-oxopropyl)thiazol-2-yl]pyrrole (**36**)	72—73		65.4	7.1	10.1	$C_{15}H_{20}N_2OS$	65.2	7.3	10.1
1-(5-Benzoyl-4-methylthiazol-2-yl)-2,5-dimethylpyrrole (**37**)	77—78		68.7	5.6	9.6	$C_{17}H_{16}N_2OS$	68.9	5.4	9.5
2-Amino-5-(1-hydroxyimono-2,2-dimethylpropyl)-4-methylthiazole (**38**)	170—172 (decomp.)		50.5	7.1	19.7	$C_9H_{15}N_3OS$	50.7	7.1	19.7
2-Amino-5-(1-hydroximinobenzyl)-4-methylthiazole (**39**)	171—173		56.5	5.0	17.9	$C_{11}H_{11}N_3OS$	56.6	4.8	18.0
1-(5-Deuterio-4-methylthiazol-2-yl)-2,5-dimethylpyrrole (**40**)		76—78/0.04	*m/z* 193.0784			$C_{10}H_{11}DN_2S$	M^+, 193.0783		
1-(5-Deuterio-4-phenylthiazol-2-yl)-2,5-dimethylpyrrole (**41**)	51—52		*m/z* 255.0940			$C_{15}H_{13}DN_2S$	M^+, 255.0940		
2,5-Dimethyl-1-(4-methyl-5-trimethylsilylthiazol-2-yl)pyrrole (**42**)		93—95/0.04	*m/z* 264.1116			$C_{13}H_{20}N_2SSi$	M^+, 264.1116		
1-(5-Ethyl-4-methylthiazol-2-yl)-2,5-dimethyl-pyrrole (**43**)		80—82/0.003	65.5	7.2	12.7	$C_{12}H_{16}N_2S$	65.4	7.3	12.7
1-(5-Benzyl-4-methylthiazol-2-yl)-2,5-dimethyl-pyrrole (**44**)		64—66/0.005	72.1	6.2	10.0	$C_{17}H_{18}N_2S$	72.3	6.4	9.9
1-[5-(Deuteriomethyl)-4-phenylthiazol-2-yl]-2,5-dimethylpyrrole (**47**)	72—73		*m/z* 269.1097			$C_{16}H_{15}DN_2S$	M^+, 269.1097		
2,5-Dimethyl-1-(5-methyl-4-phenylthiazol-2-yl)-pyrrole (**48**)	73.5—75		71.6	5.9	10.4	$C_{16}H_{16}N_2S$	71.6	6.0	10.4
1-(3-Bromopropyl)-2,5-dimethylpyrrole (**51**)		82—83/0.05	49.8	6.4	6.5	$C_9H_{14}BrN$	50.0	6.5	6.5
2-[3-(2,5-Dimethylpyrrol-1-yl)propyl]-1,3-dithiane (**52**)		130—132/0.01	61.1	8.4	5.3	$C_{13}H_{21}NS_2$	61.15	8.3	5.5
2-(3-Aminopropyl)-1,3-dithiane (**53**)	95—96		*m/z* 177.0646			$C_7H_5NS_2$	M^+ 177.0646		
1-(3-Cyanopropyl)-2,5-dimethylpyrrole (**54**)		82—83/0.03				$C_{10}H_{14}N_2$	74.0	8.7	17.3
2,5-Dimethyl-1-(4-oxopentyl)pyrrole (**55**)		111—114/0.03	*m/z* 179.1309			$C_{11}H_{17}NO$	M^+ 179.1309		
2-[3-(2,5-Dimethylpyrrol-1-yl)propyl]-2-methyl-1,3-dithiane (**56**)		129—131/0.01	*m/z* 269.1271			$C_{14}H_{23}NS_2$	M^+ 269.1272		
2-(3-Aminopropyl)-2-methyl-1,3-dithiane (**57**)	59—60.5		50.1	9.0	7.4	$C_8H_{17}NS_2$	50.2	9.0	7.3

distilled to give the *trimethylsilyl derivative* (**42**) (2.6 g); *m/z* 264 (M^+, 100%).

N,O-Dimethylhydroxylamine hydrochloride (2.6 g) was added in portions during 5 min to a solution of Bu^{t}COCl (freshly distilled; 3 ml) in $CHCl_3$ (freed from EtOH by passage through dry Al_2O_3; 30 ml) which was stirred at 0 °C. C_5H_5N (distilled, then stored over KOH; 4.3 ml) was added, stirring was continued for 1 h at 0 °C, and the solution was poured into brine. Isolation with Et_2O–CH_2Cl_2 (3:1) and distillation of the product gave N-*methoxy*-N-*methyl*-2,2-*dimethylpropanamide*

(3.2 g), $\nu_{max.}$ 1 655 cm^{-1}; *m/z* 145 (M^+, 2%) and 57 (100). The protected amine (**34**) (740 mg) was treated with 1.5M-Bu^{n}Li (2.7 ml) and then with Bu^{t}CON(OMe)Me (587 mg) as in procedure I. Crystallisation of the product from pentane gave the *t-butyl ketone* (**36**) (872 mg), $\nu_{max.}$ 1 664 cm^{-1}; *m/z* 276 (M^+, 43%) and 219 (100). A solution of the alcohol (**32**) (2.3 g) in Ac_2O (freshly distilled; 4 ml)– Me_2SO (distilled, and stored over CaH_2; 15 ml) was kept at 20 °C for 1 d. The mixture was diluted with Et_2O, washed repeatedly with brine, dried, and evaporated. The residue was purified by flash chromatography on SiO_2 with Et_2O as eluant to give the t-butyl ketone (**36**) (1.7 g). Treatment of the ketone (**36**) (710 mg) with H_2NOH·HCl (880 mg) and KOH (530 mg) by procedure C gave the *hydroximino-compound* (**33**) (464 mg), *m/z* 291 (M^+, 100%); treatment of the ketone (**36**) (880 mg) with H_2NOH·HCl (1.04 g) by procedure B and purification of the product by flash chromatography on SiO_2 with Et_2O as eluant gave the *hydroximino-amine* (**38**) (177 mg); *m/z* 213 (M^+, 3%) and 114 (100).

A 1.55M-solution of Bu^{n}Li in hexane (5.2 ml) was added to a solution of the protected amine (**34**) (1.55 g) in dry THF (20 ml) which was stirred at −30 °C under N_2 during the addition and for a further 45 min. The solution was cooled to −70 °C, and added *via* a metal cannula during 15 min to a stirred solution of PhCOCl (1.36 g) in THF (5 ml) at −70 °C under N_2. The cooling bath was removed, and after 4 h the solution poured into 2M-NaOH. Extraction with Et_2O and purification of the product by flash chromatography on SiO_2 using petroleum–Et_2O (4:1) as eluant followed by crystallisation from Et_2O–hexane (*ca.* 1:5) gave the *phenyl ketone* (**37**) (1.8 g), $\nu_{max.}$ 1 648 cm^{-1}; *m/z* 296 (M^+, 100%).

The protected amine (**34**) (2.75 g) was treated with 1.55M-Bu^{n}Li (9.7 ml) and then with EtI (2.5 g) as in procedure I, and the product was distilled to give the *ethyl derivative* (**43**) (2.7 g), δ 1.24 (3 H, t, *J* 8 Hz, CH_3CH_2); *m/z* 220 (M^+, 100%). Similarly, the protected amine (**34**) (960 mg), 1.55M-Bu^{n}Li (3.4 ml), and $PhCH_2Br$ (940 mg) gave the *benzyl derivative* (**44**) (874 mg), *m/z* 282 (100%); the protected amine (**35**) (460 mg), 1.45M-Bu^{n}Li (1.3 ml), and D_2O (2 ml) gave the *deuterio derivative* (**41**) (393 mg), *m/z* 255 (M^+, 100%); and the protected amine (**35**) (1.1 g), 1.45M-Bu^{n}Li (3.15 ml), and MeI (0.71 g) gave the *methyl derivative* (**48**) (1.0 g), 2.51 (3 H, s, thiazole 5-Me), *m/z* 268 (M^+, 100%). The methyl derivative (**48**) (780 mg) was treated with Pr_2NLi [from Pr_2NH (320 mg)] and then with D_2O (2 ml) as in procedure H to give the *deuteriomethyl derivative* (**47**) (712 mg); *m/z* 269 (M^+, 100%).

Scheme 4: Products from 3-Bromopropylammonium Bromide (**50**).—A solution of KOH (2.5 g) in MeOH (20 ml)–H_2O (1 ml) was added during 1 h to a mixture of the salt (**18**) (10 g), hexane-2,5-dione (5 ml), and MeOH (20 ml) which was boiling under reflux. The mixture was boiled for a further 2 h, cooled, diluted with Et_2O, and washed with brine, 2M-HCl, M-$NaHCO_3$, and brine. Evaporation of the solvent, and distillation of the residue gave 1-(3-*bromopropyl*)-2,5-*dimethylpyrrole* (**51**) (8.8 g), δ 2.16 (2 H, m, $CH_2CH_2CH_2$), 2.21 (6 H, s, Me_2), 3.34 (2 H, t, *J* 7 Hz, CH_2Br), 3.87 (2 H, t, *J* 7 Hz, CH_2N), and 5.92 (2 H, s, pyrrole-H_2); *m/z* 217 (M^+, 35%) and 108 (100).

A solution of the bromide (**51**) (4.3 g) in THF (10 ml) and a solution prepared from 1.5M-Bu^{n}Li (14.5 ml) and 1,3-dithane (2.6 g) in THF (30 ml) were used as in procedure G but at a temperature of −10 °C. Distillation of the product gave the *monosubstituted dithiane* (**52**) (4.45 g), δ 3.91 (1 H, t, *J* 6 Hz, SCHS); *m/z* 255 (M^+, 100%). The dithiane (**52**) (3.6 g) was treated with 1.45M-Bu^{n}Li (10.2 ml) and then with MeI (2.3 g) as in procedure I. Distillation of the product gave the *disubstituted dithiane* (**56**) (3.2 g) δ 1.57 [3 H, s, SC(Me)S]; *m/z* 269 (M^+, 60%) and 148 (100). Procedure G (without work-up) followed by procedure I with the bromide (**51**) (3.5 g) gave the dithane (**56**) (3.6 g).

A mixture of the disubstituted dithiane (**56**) (948 mg), $CaCO_3$ (770 mg), $HgCl_2$ (2.1 g), water (6 ml), and MeCN (24 ml) was boiled under reflux for 6 h under N_2. The mixture was filtered, the precipitate was washed with CH_2Cl_2–pentane (1:1), and the washings were combined with the filtrate. The solution was washed (5M-NH_4OAc, water, and brine), and dried. Evaporation of the solvent and distillation of the residue gave the *ketone* (**55**) (448 mg), δ 2.07 (3 H, s, MeCO); $\nu_{max.}$ 1 717 cm^{-1}; *m/z* 179 (M^+, 61%) and 108 (100).

NaCN (210 mg) was dissolved in Me_2SO (dried over CaH_2; 4 ml) at 90 °C. A solution of the bromide (**51**) (795 mg) in Me_2SO (1.5 ml) was added, the heating bath was removed, and after 30 min the solution was poured into water. The mixture was extracted with Et_2O, and the extract was washed with brine and evaporated; distillation of the residue gave the *nitrile* (**54**) (487 mg), δ 3.78 (2 H, t, *J* 7 Hz, CH_2N); $\nu_{max.}$ 2 255 cm^{-1}; *m/z* 162 (M^+, 56%) and 108 (100).

Acknowledgements.
We thank the S.R.C. for studentships (to S. P. B. and M. D. T.).

References

1 T. W. Greene, 'Protective Groups in Organic Synthesis,' John Wiley and Sons, New York, 1981, ch. 7.
2 G. A. Epling and M. E. Walker, *Tetrahedron Lett.*, 1982, **23**, 3843.
3 R. Bathels and H. Kunz, *Chem. Ber.*, 1982, **115**, 833; *Angew. Chem.*, 1982, **94**, 302.
4 S. Duric, J. Venit, and P. Magnus, *Tetrahedron Lett.*, 1981, **22**, 1787.
5 B. C. Laguzza and B. Ganem, *Tetrahedron Lett.*, 1981, **22**, 1486.
6 S. P. Breukelman, G. D. Meakins, and A. M. Roe, unpublished work.
7 D.Phil. Theses, Oxford, of M. D. Tirel, 1984, and S. P. Breukelman, 1979.
7 J. R. Pratt, W. D. Massey, F. H. Pinkerton, and S. F. Thames, *J. Org. Chem.*, 1975, **40**, 1090.
9 C. Paal and C. W. T. Schneider, *Chem. Ber.*, 1886, **19**, 558, 3157; L. Knorr, *ibid.*, 1889, **22**, 168.
10 G. Ciamician and C. U. Zanetti, *Chem. Ber.*, 1889, **22**, 1968.
11 W. S. Bishop, *J. Am. Chem. Soc.*, 1945, **67**, 2261.
12 A. P. Findlay, *J. Org. Chem.*, 1956, **21**, 644.
13 S. P. Breukelman, G. D. Meakins, and M. D. Tirel, *J. Chem. Soc., Chem. Commun.*, 1982, 801.
14 A. C. Haley and P. Maitland, *J. Chem. Soc.*, 1951, 3155.
15 S. J. Hazlewood, G. K. Hughes, F. Lions, K. J. Baldick, J. W. Cornforth. J. N. Graves, J. J. Maunsell, T. Wilkinson, A. J. Birch, R. H. Harradence, S. S. Gilchrist, F. H. Monaghan, and L. E. Wright, *J. Proc. Roy. Soc. New South Wales*, 1937, **71**, 92.
16 S. E. Leach, Part II Thesis, Oxford, 1983.
17 D. R. M. Walton, *J. Chem. Soc. C*, 1966, 1706.
18 H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, 1941, **63**, 2844.
19 S. J. Childress and J. V. Scudi, *J. Org. Chem.*, 1958, **23**, 67.
20 A. Horters and E. Dohrn, *Ger. Pat.*, 398, 204/1924 (*Chem. Zentr.*, 1924, **II**, 1409.
21 M. T. Leffler, *Org. React.*, 1942, **1**, 91.
22 References to the 2-aminothiazoles (**30**), (**31**), (**45**), (**46**), and (**49**) are given by R. Barone, M. Chanon, and R. Gallo in 'Thiazole and Its Derivatives,' ed. J. V. Metzger, Wiley, New York, 1979, Part 2, ch. VI.
23 S. Nahm and S. M. Weinreib, *Tetrahedron Lett.*, 1981, 3815.
24 J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, 1965, **87**, 4214.
25 A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Am. Chem. Soc.*, 1967, **89**, 431.
26 H. Salkowski, *Chem. Ber.*, 1895, **28**, 1917.
27 N. Buu-Hoi, *J. Chem. Soc.*, 1949, 2882.

Received 16 *April* 1984; *Paper* 4/620