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BENZOHETEROCYCLES VIA ARYNE C–C CYCLISATION

INITIAL APPROACHES

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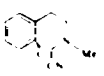
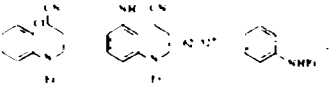
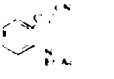
Abstract—The preparation of some benzo-4,5 and 6-membered mononitrogen heterocycles by cyclisation of an aryne with a side chain carbanion α to a cyanide group has been investigated: Thus 1-cyano-2-methyl-1,2,3,4-tetrahydroisoquinoline, (50%); 4-cyano-1-ethyl-1,2,3,4-tetrahydroquinoline, (11%); 2-methylisoindole, (89%) have been prepared. Attempts to prepare an N-acetyl indoline gave 2-methylbenzoxazole, and a benzazetine approach gave predominantly amination products.

The formation of benzocyclic systems by aryne cyclisation is well documented. Both carbocyclic and heterocyclic compounds have been prepared by the reaction of a side chain nucleophile with the aryne function.[1-3] In the formation of a heterocycle in this manner a hetero-atom may be the nucleophile, acting directly, as in the preparation of 1 - methyl - 1,2,3,4 - tetrahydroquinoline[4] and 2-phenylbenzoxazole.[5] Alternatively a carbon nucleophile may be produced and the hetero-atom not be directly involved in ring closure, as in the preparation of a variety of oxindoles in which a nucleophile is formed from the methyl of an acetamido group,[2] serving as precedent for formation of a 3-isoquinolone.[6] Examples of ambident nucleophilicity are seen in the preparation of a spirobenzopyrrolidone[7] and a dibenzopiperidone,[8] phenanthridines and diazaphenanthrenes.[9] Our initial investigations are concerned with approaches to benzomononitrogen heterocycles by reactions not involving the nitrogen function as a nucleophile, thus:

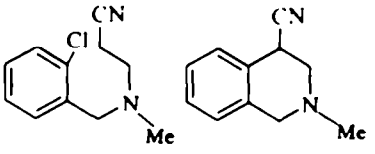
(a) Where the nitrogen could not be directly employed as a nucleophile since it is not attached to the benzene ring in the product. Cyclisation was envisaged as reaction of an aryne function, produced from a chlorobenzene, with a carbanionic site obtained by deprotonation of a CH group α to a cyanide function.[10] The nucleophile activating function would then be exocyclic in the product and could serve as a point of elaboration. The syntheses of 2-methylisoindole and related compounds by an extension of this principle have been achieved.[11,12]

(b) Where the nitrogen function is attached to the benzene ring in the product, requiring aryne production from a suitably N-substituted halogenoaniline in which

Table 1. Potassamide–liquid ammonia cyclisations.

Objective	Yield %	Precursor	Other identified products, %
			
a 1,2,3,4-tetrahydro-isoquinoline, **4**	50	**3**	
			
an isoindole, **8**	89	**7**	
			
a 1,2,3,4-tetrahydro-quinoline, **15**	11,9*	**14**, R=Et	**16**, 62,52*; *N*-ethylaniline, 1.
			
an indoline, **19**, R=Et	nil	**18**, R=Et	*N*-ethylchloroaniline, 84; *N*-ethylaniline, 8
an indoline, **19**, R=Ac	nil	**18**, R=Ac	2-methylbenzoxazole, 64,50*
			
a benzazetine, **26**	?,0.2	**21**	

*sodamide/liquid ammonia.
†from analogous bromo precursor.

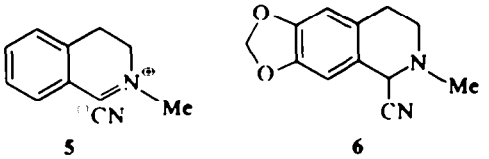


1 2

the side chain bore a cyano group to serve as a nucleophile activator as above.

Type a: *a tetrahydroisoquinoline.* Shortly after this work was initiated Julia *et al.* reported[13] the cyclisation of N - 2 - chlorobenzyl - 3 - methylaminopropionitrile (1) to 4 - cyano - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline (2) by the action of sodamide in liquid ammonia, a model system serving the synthesis of compounds related to lysergic acid.[14] This is one of the two ways by which this type of tetrahydroisoquinoline can be prepared in this context and we here present an account of the alternative route, cyclisation of an aminoacetonitrile (3) to the tetrahydroisoquinoline (4). The amino function of the starting material is made tertiary to forestall nucleophilic competition and/or cyanide elimination which might occur if a nitrogen anion was produced by the action of the base upon a secondary amine.

Reaction of the nitrile with potassamide in liquid ammonia gave 1 - cyano - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline (4), identified by its PMR spectrum (Experimental) and corresponding to material previously reported.[15] It could conceivably exist as an equilibrating mixture of two forms, 4 and 5, analogous to a pseudo-base equilibrium.[16] This situation is also found in the cotarnine derivative (6).[15,17] Only faint positives were



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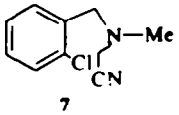
obtained when a methanolic solution of the material was tested for ionic cyanide with the ferric thiocyanate test,[18] although the colour intensity was considerably increased after the solution had stood in contact with silica gel GF_{254} for some time. The PMR spectrum had a signal at 5.37τ attributed to the Ar·CH(CN)N proton and no detectable signal in the region 2–2.25τ attributable to Ar·CH=N.[19] Accordingly there would seem to be an insignificant proportion of the ionic form at equilibrium under normal conditions. Aminated material was not analysed in detail, the PMR spectrum of the eluted mixture being consistent with both *ortho* and *meta* amination. Minor products in mixture lacked a cyano group (IR) but possessed primary aromatic amine and amide functions. These products could arise during workup following amide attack upon the cyano group of starting material and major products.

Type a: *an isoindole.* The preparation of 2-methylisoindole as under has been the subject of a preliminary communication.[11]

Thus the starting material 7, analogous in principle to 3,



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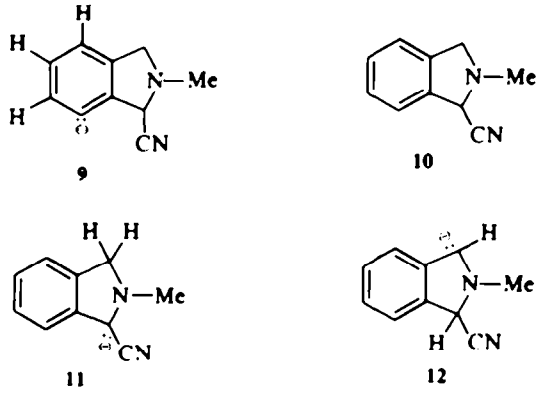
on treatment with potassamide in liquid ammonia gave an unstable brown solid from which 2-methylisoindole, 8, was obtained by sublimation. The spectroscopic properties of the product were consistent with its suggested structure, the UV and IR absorption spectra of 2-methylisoindole having been published.[20] The PMR spectrum confirms its aromatic nature and is very similar to those of isoindole and 2-butylisoindole[21] in that the 1 and 3 protons resonate as a singlet, and the 4 and 7, and 5 and 6, protons as multiplets. Absorption by the 1 and 3 and N-Me protons appears to be concentration dependent in a non-polar solvent (CCl_4) but not so much in a polar solvent $(CD_3)_2CO$ (Experimental). It would seem that self association at increasing concentration in CCl_4 affects the pyrrole ring.

It is very likely that the methylisoindoline nitrile anion, 9, is first formed by cyclisation of the aryne ion. Protonation by solvent to the isoindoline 10 and deprotonation, or proton shift, can give rise to 11 and 12, subsequent loss of cyanide ion from 12 leading to the



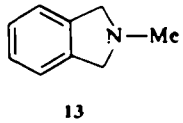
9 10

11 12

isoindole 8. It is possible that cyanide may be lost from the isoindoline, 10, to give an isoindolium ion which subsequently loses a proton. There is some spectroscopic evidence for the presence of the isoindoline 10 in the crude reaction product, minor peaks in the PMR spectrum at 5.40, 6.12 and 7.43τ are consistent with this compound (the C_1 proton of 4 absorbs at 5.37τ). Also seen are peaks attributable to hydrogenolysed starting material, aminated product(s) and products of oxidation of 2-methylisoindole.

The rapid decomposition of 2-methylisoindole has been noted previously[22,23] and the autoxidation of 2-butylisoindole produces the relevant hydroxyphthalimidine, phthalimidine and phthalimide.[24] Solutions of 2-methylisoindole in carbon tetrachloride exposed to the air seemed to oxidise in a similar fashion. The PMR absorption of the product of oxidation of solid 2-methylisoindole indicates that a different reaction is involved, possibly similar to that reported for some other isoindoles.[25]

Reduction of 2-methylisoindole with W4 Raney nickel in n-butanol[23] gave a mixture of starting material and 2-methylisoindoline, 13. Complete reduction was readily achieved using sodium borohydride in ethanol in acid conditions. Sodium borohydride in ethanol had little effect



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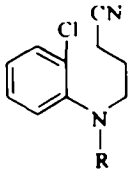
upon the isoindole and with an alkaline (ammonia) workup only a little reduced product was obtained. Working up with acid (HCl), gave a high yield of 2-methylisoindoline independent of borohydride contact time, suggesting that reduction may involve a cation. 2-Methylisoindole does react readily with acids as shown by the rapid resinification that occurs when it is treated with ethanolic HCl. Attempts to form a picrate similarly result in destruction of the compound. However a stable 1,3,5-trinitrobenzene adduct is readily prepared.[26]

Type **b**: *a tetrahydroquinoline*. Generation of arynes from halogenobenzenes bearing an otherwise unstabilised α anion is generally unsuccessful.[2,4,9] Thus a tertiary amine, **14** (R=Me or Et) appeared to be a suitable substrate



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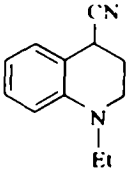
but several attempts at substitutive alkylation of 2-chloroaniline, its anion and the anion of the N-ethyl amine were unsuccessful.

Attention turned to alkylation by addition of the acetanilide ion to an α,β-unsaturated system. The amide failed to react with acrylaldehyde but reacted slowly with methyl acrylate in dichloromethane in the presence of benzyltrimethylammonium hydroxide. The reaction never went to completion and the addition product was not amenable to distillation, undergoing a retro-Michael reaction, but the crude product could be readily reduced by LAH. Conversion of the alcohol via the chloride to the nitrile, **14** (R=Et), was accomplished in high yield.

Reaction of 4 - (2 - chloro - N - ethylanilino)butyronitrile, **14**, with potassamide in liquid ammonia and chromatography of the residue gave 4 - cyano - 1 - ethyl - 1,2,3,4 - tetrahydroquinoline, **15**, (11%) and 4 - (3 - amino - N - ethylanilino)butyronitrile (40–62%), **16**, as the major products, both of which were identified by their spectroscopic properties (Experimental).



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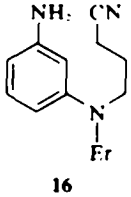

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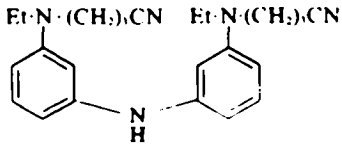
An interesting minor product was N-ethylaniline (*ca.* 1% isolated) for the starting material contained none of this compound and the 2 - chloro - compound was barely detectable (G.L.C). The hydrogenolysis of *ar*-chloro compounds by amide ion in liquid ammonia is known[29,30] and in two cases it appears that an intramolecular hydride transfer occurs from a side-chain to the aryne moiety.[31,32] In this case formation of N-ethylaniline can be rationalised by transfer of hydride from the methylene α to the aniline nitrogen and subsequent hydrolysis of the imine. Another minor product, not obtained pure, which appeared to possess NH and CN groups (IR) may arise from an analogous reaction involving the methylene of the N-Et group. Alternatively or additionally these properties would be satisfied by a secondary amination product such as **17**, and this type of compound has been found in other reactions (see below).



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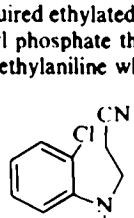
The formation of *meta* aminated products is as expected from the observations of Roberts[33] and de Graaff[34] in their amination studies.

Whilst this work was in progress Julia[13] reported that sodamide was a better cyclising agent than potassamide in the formation of the tetrahydroisoquinoline, **2**, from the precursor **1**. Using sodamide our chloronitrile, **14**, gave the tetrahydroquinoline **15** in 9% yield co-eluting with starting material (11%), thus giving no improvement in cyclisation and surprisingly sparing some precursor although the contact time was longer than for potassamide.

The proportion of aminated material (52%) was not significantly different from that when potassamide was used but additional material (10%) was obtained which was not investigated in detail but whose spectroscopic properties are consistent with compounds produced by the intermolecular attack of a sidechain carbanion upon an aryne.

Julia[13] obtained the highest yield of **2** by carrying out the reaction with sodamide in hexamethylphosphorous-triamide (HMPT) at room temperature, 63% against 46% with $NaNH_2/NH_3$. Under these conditions our nitrile produced a red coloured solution suggesting that an anion had formed[35] but only starting material was recovered after 19 hr. Under the same conditions 2 - chloro - N,N - diethylaniline did not produce a colour and was recovered unchanged while a number of alkyl nitriles with α hydrogens did produce coloured solutions. It would thus seem that although the nitrile **14** produced a sidechain anion, deprotonation of the aromatic ring and subsequent aryne generation did not proceed. When the reaction was attempted at 120° the cyanide-group was destroyed but aromatic chlorine remained.

Type **b**, *an indoline*. Cyclisation of a precursor such as **18** should produce an indoline. As before the anilino nitrogen function must be made aprotic. N - Ethyl - 2 - chloroaniline did not cyanoethylate[36] in the presence of cupric acetate,[37] acetic acid,[38] diethylamine[39] or Triton B. Attempts to alkylate 3 - 2' - chloroanilinopropionitrile, **18** (R=H) with ethyl iodide/potassium carbonate/DMF, diethyl sulphate, and triethyl phosphate resulted in retro-Michael reactions of the starting material and apparently of the required ethylated compound. Certainly in the case of triethyl phosphate the sole amine product was 2 - chloro - N - ethylaniline whereas 2-chloroaniline

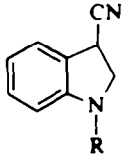


18

gave the diethyl compound under the same conditions. Eventually the required compound, **18** (R=Et) was obtained in low yield by reaction of N-ethyl-2-chloroaniline with acrylonitrile, and zinc chloride under pressure.[40]

Concurrently our attention was with the cyanoethylation of 2-chloroacetanilide, a reaction analogous to the carbomethoxyethylation used above. Under similar conditions, Triton B catalyst in dichloromethane, reaction was essentially complete in 1 h at room temperature and the product, **18** (R = Ac) obtained pure in high yield.

The amine, in liquid ammonia with potassamide, underwent a retro-Michael reaction so that the major product was 2 - chloro - N - ethylaniline. There was no evidence of formation of the indoline, **19** (R = Et) or more



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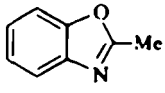
than a trace of amination products, the latter case illustrating the resistance of the derived anion of the chloroaniline to aryne generation. N-Ethylaniline was isolated and not being present in the starting material may have been produced by hydrogenolysis via the side chain anion. The higher yield of this product compared to its formation from 4 - (2 - chloro - N - ethylanilino) butanonitrile, **14**, would be consistent with the better driving force of the carbanion here compared to the nitrogen of the latter compound.

The amide, **18** (R = Ac) also underwent a retro-Michael reaction in the potassamide-liquid ammonia system. In this case however the product is able to produce an aryne since the anion is delocalised in the side chain. The cyclisation of 2 - halo - N - acylanilines has been studied[2,5] and mono-substituted amides afford 2-substituted benzoxazoles. The formation here of 2-methylbenzoxazole, **20**, in 64% yield may thus be rationalised by the eliminated acetanilide ion reacting in this fashion.



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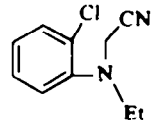
In the hope that if the rate of aryne generation in the starting material could be increased the required carbanion would react before a retro-Michael reaction occurred the 2-bromo compound was investigated. The relative rate of bromide/chloride loss in aryne generation is suggested to be at least of the order of 20/1.[1] If the cyanoindoline, **19** (R = Ac) was formed it could conceivably eliminate the elements of HCN under the basic conditions, as with the isoindole preparation, and possibly de-acylate producing indole. 3 - (N - Acetyl - 2 - bromoanilino)propionitrile was prepared as for the chloro analogue. However it also gave 2-methylbenzoxazole, with *ca* 20% of amination products.

Type b, *a benzazetine*. Although the benzazetine system is of interest only one account of the synthesis of a simple example appears to have been made. N-Phenylbenzazetine has been prepared in good yield by the photolysis of 3 - phenyl - 4H - benzo - 1,2,3 - triazine.[41] The formation of benzocyclobutenes by aryne cyclisation is successful[10,42–46] and suggested investigation of N - ethyl - 2 - chloroanilinoacetonitrile, **21**. Reaction with potas-



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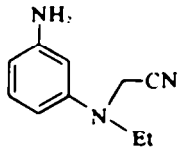
samide in liquid ammonia gave predominantly 3 - amino - N - ethylanilinoacetonitrile, **22**, with two secondary amination products, **23** and **24**. The bis-amination product was identified by comparison of its spectra with those of bis - 3 - diethylaminophenylamine, **25**, produced under similar conditions from 2 - chloro - N,N - diethylaniline. The other aminated product is assigned the amide structure, **24**, upon spectroscopic grounds, it is feasible that such a compound could be produced during workup from an amidine resulting from amide ion attack upon the nitrile function.[48]



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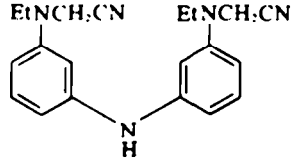

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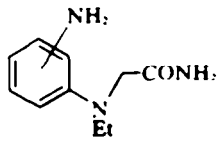

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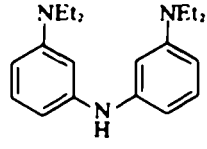

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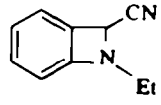
A very small quantity of a compound which could be the desired 2 - cyano - 1 - ethylbenzazetine, **26**, was isolated but unequivocal proof of its structure was not obtained. Its NMR spectrum (CCl_4, τ) showed absorption



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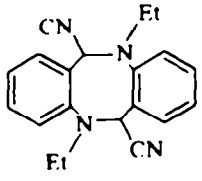
attributable to an Et group (8.64, t, 3; 6.73, q, 2), a methine (5.02, s, 1) and four aromatic hydrogens (multiplet, 2.4–3.4). The methylene absorption of N-phenylbenzazetine[41] occurs at 5.22τ, the difference of 0.2 ppm is consistent with the absence of N-phenyl and the presence of the nitrile group but these features would also be consistent with the intermolecularly produced compound **27**.

The low yield of this material which may be the benzazetine compared to yields of up to 70% of benzocyclobutenes obtained under similar conditions,[9,43] would suggest that cyclisation is unfavourable despite the potential stability which would be derived by formation of

the aromatic ion. Thus it would appear that the critical phase of the reaction is competitive formation of the ions **28** and **29**, whether or not ionised to the cyanide-group.

It is possible that some of the benzazetine is lost after formation, by nucleophilic attack of ammonia and/or amide ion, since N-phenylbenzazetine is opened by aniline.[41] It is anticipated that the use of a non-aminating aryne generation system would improve the yield of benzazetine by eliminating these two factors.



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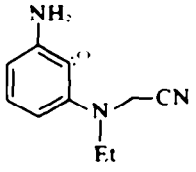

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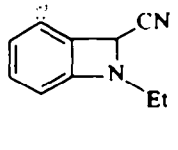

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EXPERIMENTAL

Unless specified otherwise elemental analyses, were consistent with the proposed structures of critical compounds.

2-Chlorophenylacetonitrile. Addition of redistilled 2-chlorobenzyl chloride (88.5 g, 0.55 mole) to a soln/suspension of NaCN (53.9 g, 1.10 mole) in dry DMF (500 ml) with stirring caused a slow exothermic reaction (52° after 1 hr at ambient r.t.). Four hr later (tlc, no starting material) water was added and the product extracted with ether. Purification by distillation gave the nitrile 75.7 g (91%) $b_{0.005mm}$ 62–64° (lit.,[42] b_{4mm} 101–104,[43] b_{2mm} 106–111), 99% purity (GLC, 5% carbowax 20M terminated with terephthalic acid on Chromosorb G AW-DMCS, 173° oven).

2-Chlorophenethylamine. Aluminium chloride (85.4 g, 0.64 mole) in dry ether (500 ml) was added to a stirred suspension of LAH (24.3 g, 0.64 mole) in dry ether (1 l.) over 15 min. After a further 10 min 2-chlorophenylacetonitrile (68.2 g, 0.45 mole) in dry ether (500 ml) was added dropwise over 2.25 hr at a rate sufficient to maintain reflux. The mixture was heated under reflux for a further 1.5 hr, cooled in ice and, in order, water (24.5 ml), 15% NaOHaq (24.5 ml), water (24.5 ml), NaOH (102.8 g) in water (120 ml), water (150 ml) added. The filtrate and ether washings (by continuous extraction) combined, dried and distilled gave the amine, 66.8 g, 95%, $b_{0.007mm}$ 56–58, lit.[44] $b_{0.8}$ 77–80, 99.5% purity (GLC, as above). It rapidly formed a white solid on exposure to the atmospbere. B · HCl 141–141.5°, lit.[31] 139–140°, 141–142°.[32]

N-2-Chlorophenethylformamide. Method of Blicke and Chi-Jung Lu,[33] in which freshly distilled chloral (14.7 g, 0.1 mole) was added to the amine (15.6 g, 0.1 mole) at 0°, stood overnight at ambient r.t. and distilled, 14.8 g, 81%. $b_{0.01mm}$, 114–116°, lit.[34] $b_{0.005mm}$ 124–127°.

N - Methyl - 2 - chlorophenethylamine. LAH (13.1 g, 0.35 mole)/ether (1 l.) reduction of the formamide (42.4 g, 0.23 mole) in ether (500 ml) in the normal fashion gave the secondary amine 34 g, 87%, $b_{0.02mm}$ 49–52°, lit.[34] b_{12mm} 109–112°, 96% purity, (GLC, as above). The amine formed a white solid on exposure to the atmosphere. B · HCl 137.5–138°. N' - 1 - naphthylcarbamide derivative; 113–113.5°.

N - 2 - Chlorophenethyl - N - methylaminoacetonitrile, 3. Formalin (10.8 ml, 0.14 mole) was added to a swirled mixture of N - methyl - 2 - chlorophenethylamine (20.4 g, 0.12 mole) and water (50 ml). After 5 min sodium metabisulphite (15.21 g, equivalent to 0.14 mole bisulphite at min 90% purity) was added and a second mildly exothermic reaction ensued. Upon warming a soln was obtained which was heated at 80–105° for 2 hr before adding KCN (9.8 g, 0.15 mole) in water (25 ml). The mixture was heated under reflux for 8 hr, cooled and extracted with ether. The crude product distilled gave s.m. (1.9 g), mixture (1.3 g) and the aminonitrile (19 g), 76%, $b_{0.01mm}$, 92–94°, 99% purity (GLC, as above).

IR (film): 2805*s* (NCH_3), 2235*w* (CN), 1053*s* (ar-Cl). PMR (τ, CCl_4): 2.5–2.95 (*m* with sharp signal at 2.79, 4H, ar), 6.52 (*s*, 2H, $\underline{CH_2}$-CN), 6.9–7.55 (14 line *m*. of AA'BB' system, 4H-Ar·$\underline{CH_2}$·$\underline{CH_2}$·N), 7.61 (*s*, 3H, N-$\underline{CH_3}$). UV (λ_{max} nm, log ε, 95% EtOH): 252 sh, 259.5 (2.27), 266 (2.37), 273.5 (2.28). *hydrochloride*, m.p. 104.5–105.5°.

Potassamide/liquid ammonia reaction. Based upon the procedure of Bunnett and Skorcz.[10] N - 2 - Chlorophenethyl - N - methylaminoacetonitrile (5 g, 23.4 millimole) in ether (15 ml) was added to KNH_2, from K (3.75 g, 95.8 milliequiv), in liquid ammonia (600 ml). After 30 min ammonium nitrate (12 g) was cautiously added to quench the reaction and the ammonia allowed to evaporate. Water and ether extraction of the residue gave a yellow oil (3.4 g) which was applied to a basic alumina (100–120 mesh) column (150 g).

Elution with ether gave 1 - cyano - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline, 4, (2.06 g, 50%) as a pale yellow oil which solidified on standing. TLC indicated only a trace of impurity. Several crystallisations (petrol 40–60) gave needles m.p. 76.5–77°, sublimed at 0.03 mm, 70° to give analytical sample, m.p. 77–77.5° (lit.[14] m.p. 77–78°, 76–78°). IR (cm $^{-1}$, melt): 2835 (s) and 2810(m) (NCH_3), 2220 (CN). pmr (τ, CCl_4): 2.81 (s, 4H Ar), 5.37 (s, 1H arCH(CN)N), 7.00–7.22 (m, 4H, distorted AA'BB', sharp signal at 7.14, $ArCH_2\underline{CH_2}$-N), 7.45 (s, 3H-N$\underline{CH_3}$). (τ, CD_3OD): 5.01 singlet, 1H, slowly decreasing in intensity with time, (ArCH(CN)N). UV (λ_{max} nm, log ε, 95% EtOH): 251 sh, 257 sh, 265 (2.31), 272 (2.35).

Elution with increasing proportion of ether in hexane gave small quantities of impure tetrahydroisoquinoline. Methanol elution gave a mixture (0.43 g) of aminated materials (IR). The aqueous phase left from extraction of the crude product was extracted with chloroform to give 0.48 g of a three component mixture. It could be acetylated but no detailed investigation was made.

N - 2 - Chlorobenzyl - N - methylaminoacetonitrile, 7. Redistilled 2-chlorobenzyl chloride (17.39 g, 0.108 mole) and N-methylaminoacetonitrile (15.14 g, 0.216 mole; b.p. 64–65°/15 mm, from the commercially available hydrochloride) were heated under reflux in dry toluene (90 ml) for 18 hr. Basic material was extracted with 2N HCl (4 × 50 ml). The acidic extract, washed with ether, was made basic (pH 11) and extracted with ether (6 × 50 ml) from which the product was isolated by distillation, $b_{0.01mm}$ 76–78°, 11.71 g (56%) 96% pure by GLC (as above). In another preparation a spinning band column gave material $b_{0.005mm}$ 67–69°, 97% pure. IR (cm^{-1}, film): 2800 (N-Me), 2230w (CN), 1057*s* (Ar-Cl). PMR (τ, CCl_4): 2.35–2.85 (m, pk at 2.64, 4Ar H), 6.27 (s, Ar-$\underline{CH_2}$), 6.54 (s, -$\underline{CH_2}$C), 7.55 (s, -N$\underline{CH_3}$). UV (nm, 95% EtOH; λ_{max} log ε): 262.5 sh, 266.5 (2.31), 274 (2.18); λ_{min}: 272 (2.13), *hydrochloride*: ppted from ether m.p. 122–128°, finally liquefying 132.5°, recrystallisation or sublimation lowers m.p.t.

Potassamide-liquid ammonia reaction. N - 2 - Chlorobenzyl - N - methylaminoacetonitrile (5.00 g, 0.0257 mole), in ether (15 ml)

PMR (τ)	Multiplet 4 and 7H	Singlet 1 and 3H	Multiplet 5 and 6H	N-Me
CCl_4,	2.50, 2.55,	3.13	3.09, —,	6.20
100 mg/ml	2.61, 2.67		3.20, 3.25	
50 mg/ml	"	3.09	—, 3.14,	6.15
			3.20, 3.25	
25 mg/ml	"	3.06	3.09, 3.14,	6.06
			3.20, 3.25	
12.5 mg/ml	"	3.03	3.20, 3.25	6.02
$(CD_3)_2CO$	2.37, 2.42,	2.84	3.04, 3.08,	6.06
100 mg/ml	2.48, 2.53		3.15, 3.20	
25 and	2.39, 2.44,	2.81	3.05, 3.10,	6.01
50 mg/ml	2.49, 2.55		3.17, 3.21	

was added to KNH_2, from K (4.02 g, 0.1027 g-atom) in liquid ammonia (600 ml). After 33 min ammonium nitrate (12 g) was added to quench the reaction and the ammonia allowed to evaporate. Water and ether extraction gave a brown solid which was sublimed twice at 62°/1.5 mm to give 2-methylisoindole (3.01 g, 89%). m.p. 83–86° as white needles: Resublimation at 35°/0.009 mm gave material melting at 87–89°, stored in N_2. IR (cm $^{-1}$, CCl_4): 3060, 3025, 2940, 2850, 1479, 1412, 1364, 1332, 1158, 1134, (cm $^{-1}$, KBr): 762, 753. UV (nm, 95% EtOH, λ_{max}, log ϵ): 224.5 (4.62), 266 (3.16), 276 (3.12), 277 (3.19), 289 (3.20), 326 (3.64). (λ_{max}, log ϵ): 263.5 (3.11), 268.5 (3.10), 274 (3.05) 284 (3.00), 290.5 (3.11). MS (*m/e*): 131 (M^+, 100%), 130, 116, 104, 103, 90, 89, 77.

1,3,5 - *Trinitrobenzene* derivative: deep maroon needles from EtOH, m.p. 139.5–140.5° (dec, sublimes), lit.,[25] m.p. 145–146°. Repeated recrystallisation did not raise the m.p. IR (cm $^{-1}$, $CHCl_3$): 3105, 1624, 1548, 1341. PMR (τ, $CDCl_3$): 0.85 (s, trinitrobenzene Ar-H), 2.55, 2.61, 2.65, 2.71 (intenser peaks of multiplet, 4 & 7H); 3.04 (s, 1 & 3H); 3.12, 3.19, 3.23 (clear peaks of multiplet 5 & 6H); 6.02 (s, N-Me). Trinitrobenzene itself; 0.46 (s).

2-*Methylisoindoline*, **13**, 2-Methylisoindole (0.284 g, 0.002 mole) was added to $NaBH_4$ (0.151 g, 0.004 mole) in dry EtOH (10 ml) and the mixture stirred. When all solids had dissolved sufficient 10% HCl was added to make the soln acidic and then NaOH aq added to make the soln alkaline. Dilution with water and ether extraction gave a light yellow oil, distillation in a microbulb gave colourless 2-methylisoindoline, 95° (bath), 19 mm.

IR (cm $^{-1}$, film): 3030, 2940, 2840, 2765, 1468, 1362, 1279, 1207, 1152, 1116, 1029, 867, 743. PMR (τ, CCl_4): 2.91 (s, Ar-H), 6.18 (s, 2 × Ar-CH_2-N), 7.51 (s, N-CH_3). *Methiodide* derivative: silvery plates from ethanol, m.p. 262.5–263.5°, lit.[22] 245–246°,[23] 252–253°,[24,26] 253–255°. PMR (τ, D_2O): 2.52 (s in m Ar-H), 5.10 (s, 2 × Ar-CH_2-N), 6.62 (s, 2 × N-CH_3).

Methyl 3 - (N - *acetyl* - 2 - *chloroanilino*)*propionate*. Methyl acrylate (32.28 g, 0.375 mole) was added to 2-chloroacetanilide (42.40 g, 0.250 mole) dissolved in dry dichloromethane (500 ml), followed by a 40% soln in MeOH of benzyltrimethylammonium hydroxide (2 ml) and the soln stirred and set aside at r.t. Further quantities of base were added as the reaction progressed: 5.5 hr, 2 ml; 70 hr, 1 ml; 96 hr, 1 ml. The reaction was terminated by the addition of glacial AcOH (0.54 ml) after 141 hr when TLC showed no apparent further increase in intensity of "product" spot. Removal of solvent under reduced pressure gave a crude adduct (66.9 g, stoichiometry requires 63.9 g) which was used for the subsequent reduction.

A small quantity was purified by evaporative distillation and column chromatography. It gave a satisfactory elemental analysis and had IR (cm^{-1}, film): 3450, 1738s, 1666s (split), 1196, 1174, 1049. PMR (τ, CCl_4): 2.2–2.7 (m, 4 arH), 5.74 (quin, 1H of N-CH_2CH_2), 6.19–6.66 (m, peak at 6.36, CO_2CH_3 and 1H of -N-CH_2-CH_2), 7.40 (t, CH_3·CO_2Me), 8.27 (s, CH_3CON), cf.[23]

3 - (N - *Ethyl* - 2 - *chloroanilino*)*propanol*. Crude methyl 3 - (N - acetyl - 2 - chloroanilino)propionate (66.9 g, considered to be 0.25 mole) in dry ether (300 ml) was added over 1½ hr to a stirred soln/suspension of LAH (21.5 g, 0.57 mole) in dry ether (1200 ml) at a rate sufficient to maintain reflux. Heating at reflux was maintained for a further 1.5 hr before the mixture was cooled and worked up using the water/NaOHaq method. Fractional distillation of the product gave N - ethyl - 2 - chloroaniline followed by the desired alcohol b.p. 0.4 mm, 120–123°. IR (cm^{-1}, film): 3360s (bd), 1053s. PMR (τ, CCl_4): 2.5–3.2 (m, peak at 2.83, 4 × arH), 6.27 (t, -CH_2OH), 6.35 (bd, D_2O exch., -OH), 6.78 and 6.89 (t and q -N-CH_2 and CH_3·CH_2-N-), 8.31 (quin, -CH_2-CH_2-CH_2), 8.99 (t, CH_3-CH_2-). 1-*Naphthylurethane* derivative, m.p. 62–63°.

3 - (N - *Ethyl* - 2 - *chloroanilino*)*propyl chloride*. The alcohol (20.0 g, 0.094 mole) was added to triphenylphosphine (32.73 g, 0.125 mole) dissolved in CCl_4 (120 ml) and the mixture heated to reflux for 2 hr after the initial reaction had subsided. Solid was removed by filtration and ether washed. The combined filtrate was concentrated to afford the chloride as an oil which was purified by distillation, b.p. 92–94°/0.18–0.28 mm. IR (cm $^{-1}$, film): 1055s, 651 w. PMR (τ, $CDCl_3$): 6.40 (t, -CH_2Cl), relevant remainder similar to that of the alcohol precursor.

4 - (N - *Ethyl* - 2 - *chloroanilino*)*butyronitrile*, **14**, R = Et. The chloride (20.0 g, 0.086 mole) and NaCN (8.45 g, 0.172 mole) in dry DMF (150 ml) were stirred and heated at 60–65° for 24 hr. Dilution with water and ether extraction gave the nitrile, purified by distillation, b.p. 104–106°/0.05–0.08 mm. IR (cm $^{-1}$, film): 2245m, 1053s. PMR (τ, $CDCl_3$): 7.57 (t, -CH_2·CN), relevant remainder similar to that of the alcohol precursor.

Potassamide-liquid ammonia reaction. 4 - (N - Ethyl - 2 - chloroanilino)butyronitrile, (5.00 g, 0.0224 mole) in dry ether (10 ml) was added to KNH_2 (from K, 3.51 g, 0.0898 g atom) in liquid ammonia (600 ml). After 45 min ammonium nitrate (12 g) was added and the ammonia allowed to evaporate. Water was added to the residue and the whole thoroughly extracted with ether to give a brown oil (4.9 g) which was applied to a basic alumina column (150 g, 100–200 mesh) in chloroform. Elution with ether/petrol, 1:1, gave N-ethylaniline (1%) followed by **15**, (11%) eluted with ether as pale-yellow liquid, homogeneous on TLC. 5% EtOH in ether eluted **16** (40%).

4 - *Cyano* - 1 - *ethyl* - 1,2,3,4 - *tetrahydroquinoline*, **15**. Sample purified by evaporative distillation. IR (cm $^{-1}$, film): 2970, 2940, 2870, 2240, 1604, 1503, 1454, 1343, 1272, 1195, 746. PMR (τ, $CDCl_3$): 2.70–3.15 (m, arH 5 & 7), 3.25–3.60 (m, peak at 3.37, arH, 6 & 8), 6.14 (t, -CHCN), 6.68 and 6.4–6.9 (q and m, CH_3·CH_2N and N-CH_2-), 7.83 (q, -CH_2-CH-CH-), 8.89 (t, CH_3·CH_2-). UV (nm, 95% EtOH, λ_{max}, log ϵ): 263 (4.46), 310.5 (3.36). λ_{min}, 285.5 (3.08). MS *m/e*: 186 (M^+), 172, 171 (100%), 144, 134, 130, 116, 106, 77, 51, 28.

4 - (N - *Ethyl* - 3 - *aminoanilino*)*butyronitrile*, **16**. b.p. 147–148°/0.007 mm. IR (cm $^{-1}$, film): 3450, 3370, 3325, 2970, 2930, 2870, 2245, 1612, 1583, 1505, 1374, 1168, 756, 689. PMR (τ, $CDCl_3$): 3.01 (t, arC-H), 3.7–4.05 (m, peak at 3.98, 3 × arH), 6.51, 6.67 and 6.69 (bd, s, t and q; ar-NH_2, N-CH, CH_3-CH_2-N), 7.66 (t, -CH-CN), 8.12 (quin., -CH_2-CH_2-CH_2-), 8.88 (t, CH_3-CH_2-).

In another experiment the cyclic product (11%) was followed by a several-component mixture whose IR spectrum showed a single absorption above 3100 cm^{-1}, at 3400 cm^{-1}, and absorption at 2245 cm^{-1} attributable to -CN.

Sodamide in hexamethylphosphorous triamide (Method of Julia *et al.*[11])

(a) Sodamide (80%) min, 1.05 g, 0.0337 mole), 4 - (N - ethyl - 2 - chloroanilino)butyronitrile (2.50 g, 0.0112 mole), dry HMPT (80 ml), stirred at r.t. for 19 hr during which time a bright red colour developed. Addition of ammonium nitrate (4.5 g) discharged the red colour. Water and ether workup gave starting material, 96% recovery.

(b) Repeated, after 30 min at r.t. the mixture was heated at 120–125° for 114 hr. Workup as before gave an oil whose IR spectrum showed very weak CN absorption (2220 cm^{-1}), strong absorption at 3540–3140 and ca. 1670 cm^{-1}.

3 - (N - *Ethyl* - 2 - *chloroanilino*)*propionitrile*, **18** (R = Et). N - Ethyl - 2 - chloroaniline (46.65 g, 0.3 mole), (LAH reduction of N - acetyl - 2 - chloroaniline), acrylonitrile (18 g, 0.339 mole), $ZnCl_2$ (3.14 g, freshly fused and powdered), glacial AcOH (3.90 g), and hydroquinone (0.12 g) were stirred and heated together in a 1 litre autoclave[46] at 110–135° for 2 hr and allowed to cool overnight. Water and ether workup gave an oil, fractionally distilled into s.m. and a mixture of s.m. and title compound. Column chromatography (silica gel, CH_2Cl_2) gave the required compound (3.7 g, 6%, 25% on s.m. consumed), b.p.$_{0.14mm}$ 92–94°. IR (cm $^{-1}$, film): 2245m, (CN) 1057 m, (Ar-Cl). PMR (τ, CCl_4): 2.5–3.2 (m, peak at 2.89, 4 arH), 6.61 and 6.82 (t and q, N-CH_2 and CH_3-CH_2-N), 7.64 (t, -CH_2CN), 8.95 (t, CH_3-CH_2).

3 - (N - *Acetyl* - 2 - *chloroanilino*)*propionitrile*, **18** (R = Ac). Acrylonitrile (3.98 g, 0.075 mole) was added to benzyltrimethylammonium hydroxide (from 0.5 ml of a 40% aqueous solution, dried azeotropically with EtOH) and 2-chloroacetanilide (8.48 g, 0.05 mole) in dichloromethane (110 ml) and the mixture stirred at r.t. for 1.5 hr. Glacial AcOH (one drop) was added and the solvent evaporated to give an oil, which solidified on standing. Purification by passage through neutral alumina (200 g; 100–240 mesh) (ether/dichloromethane, 1:1) gave the adduct (11.12 g, 100%), crystallised from 1,2-dimethoxyethane/petrol (40–60°), m.p. 62.5°. IR (cm $^{-1}$, CCl_4): 2250w, (CN) 1689s, and 1682s (CO) 1047m (ArCl). PMR (τ, $CDCl_3$): 2.3–2.75 (m, peak at 2.53, 4 arH), 5.74 (quin, 1H of N-CH_2), 6.43 (quin, 1H of NCH_2), 6.8, 6.92, 7.03, 7.09, 7.20, 7.32, 7.43, 7.49, 7.60, 7.72 (10 line symmetric multiplet,[27] -CH_2·CN),

8.17 (s, CH₃·CO·N). The corresponding 2-bromo compound was prepared in the same fashion, m.p. 59.5°.

Potassamide-liquid ammonia reactions

3 - (N - *Ethyl* - 2 - *chloroanilino)propionitrile*, (2.5 g, 0.0120 mole), potassium (1.87 g, 0.0429 g-atom), liquid ammonia (300 ml). The reaction product, applied to a silica gel column (90 g; 60–120 mesh) and eluted with ether/petrol (40–60°), 3:7 gave: N - ethyl - 2 - chloroaniline (1.48 g, 79%), N-ethylaniline (0.12 g, *ca* 8%) and an intervening mixture (0.11 g, 23:2 by GLC) of these.

3 - (N - *Acetyl* - 2 - *chloroanilino)propionitrile* (5 g, 0.0225 mole), K (3.51 g, 0.0898 g-atom), liquid ammonia (600 ml). Chromatography of the product (acidic alumina, 100 g; 100–200 mesh) with ether/petrol (40–60°), 1:3 gave 2-methylbenzoxazole (1.90 g, 64%), identical with an authentic sample prepared from 2-chloroacetanilide in the same manner.[2]

The corresponding 2-bromo compound (4 g, 0.015 mole) gave 2-methylbenzoxazole (0.8 g, 40%) in the same fashion. Additionally, ether and MeOH eluted 0.63 g aminated material [IR (cm⁻¹, film): 3500–3100 absorption] which was not investigated further.

2 - (N - *Ethyl* - 2 - *chloroanilino)acetonitrile*, 21. N - Ethyl - 2 - chloroaniline (44.52 g, 0.286 mole) and cyanomethyl benzenesulphonate[36] (25.88 g, 0.131 mole) were slowly heated together under N_2.[37] The mixture began to darken at *ca.* 90°, becoming dark red at 122°. The temp. was gradually increased and held at 145° for 15 min then allowed to cool to 60°. Dichloromethane (20 ml) was added and the mixture heated to reflux for 5 min. Dichloromethane, ether/water workup gave an orange oil, fractionally distilled to give starting amine (35%) and 2-(N-ethyl-2-chloroanilino)acetonitrile (12.39 g, 66%), b.p. 72–74°/0.008 mm (96% purity, GLC). Further purification on a spinning band column gave material b.p. 79.5–80.5°/0.025 mm, 98.5% pure. IR (cm⁻¹, film: 2235w, 1056s. PMR (τ, CCl_4): 2.35–3.0 (m, peak at 2.61, 4 arH), 5.95 (s, –CH₂CN), 6.73 (q, CH₃·CH₂–N), 8.85 (t, CH₃–CH₂–). UV (nm, 95% EtOH, λ_{max}, log ε): 245 (3.73), 282 sh.

Reaction with potassamide in liquid ammonia. To KNH_2, from K (4.02 g, 0.1027 g.atom), in liquid ammonia (600 ml) was added 2-(N-ethyl-2-chloroanilino) acetonitrile (5.0 g, 0.0257 mole) in dry ether (15 ml). After 30 min ammonium nitrate (12 g) was added, the ammonia allowed to evaporate and the residue worked up as before to give a dark green oil (5.38 g) applied in ether/hexane to a neutral alumina column (150 g, 100–120 mesh). Elution gave (a) 10% ether/hexane, N-ethyl-2-chloroaniline, 38 mg, (present in starting material); (b) 20% ether/hexane, postulated 2 - cyano - 1 - ethylbenzazetine, **26**, 10 mg, (see discussion for spectra), further development gave mixtures of this material with other compounds; (c) ether, *bis* - 3 - N' - *cyanomethylethyl* - *aminophenylamine*, **23**, *ca.* 90 mg in mixture, purified by prep TLC. IR (cm⁻¹, film): 3375m, 2240w. PMR (τ, $CDCl_3$): 2.69 (t, 5 & 5' arH), 3.21, 3.34 and 3.53 (m, 6 × arH), *ca.* 4.14 (bd, NH), 5.85 (s, 2 × CH₂CN), 6.55 (q, 2 × CH₃·CH₂N), 8.77 (t, 2 × CH₃CH₂–); (d) ether. 2-(N-*ethyl*-3-*aminoanilino)acetonitrile*, **22**, *ca.* 2.5 g, contaminated but purified by distillation, b.p. 142–144°/0.009 mm, darkening quickly. IR (cm⁻¹, film): 3450m, 3370s, 3220w, 2240w. PMR (τ, $CDCl_3$): 2.83 (t, C, arH), 3.5–3.85 (m, peaks at 3.62, 3.77, 3 × arH), 5.91 (s, CH₂–CN), 6.35 (s, D_2O exch, NH_2), 6.62 (q, CH₃–CH₂–N), 8.82 (t, CH₃–CH₂).

The base, in ether, formed a *hydrochloride*, m.p. 163–167° (d), softens 153.5°. Repeated crystallisation did not improve the m.p., the salt appeared to decompose. *Picrate*, sublimed 85–120°/0.05 mm, m.p. 137–138° (d); (e), MeOH, viscous purple oil, 0.72 g, predominantly one component (TLC) but not identified. IR similar to the simple amination product but with relatively stronger absorption in 3500–3100 cm⁻¹ region, no absorption 2500–2000 cm⁻¹, strong absorption *ca.* 1670 cm⁻¹; PMR, D_2O exch. absorptions 6.25–6.5τ.

Potassamide in liquid ammonia with N,N - *diethyl* - 2 - *chloroaniline*

N,N - *Diethyl* - 2 - *chloroaniline*, (5.0 g, 0.0272 mole) prepared by the alkylation of 2-chloroaniline with triethyl phosphate,[37] in ether (15 ml) was reacted with KNH_2, from K (4.26 g, 0.1089 gatom), in liquid ammonia (600 ml) in the standard method.

Chromatography of the product on neutral alumina (150 g, 100–200 mesh) gave **25**, *ca.* 9%, a pure (TLC) sample had IR (cm⁻¹, film): 3395m. PMR (τ, CCl_4): 2.91 (t, 5 & 5' arH), 3.4–3.9 (m, peaks at 3.54, 3.57, 3.64, 3.81, 6 × arH), 4.49 (bd, D_2O exch., NH), 6.65 (q, 4 × CH_3CH_2N), 8.86 (t, 4 × CH₃–CH₂–), MS (*m/e*): 311 (M^+), 297, 296 (100%), 282, 266, 252, 224, 167, 140.5, 112.5, 77.

Elemental analysis was unsatisfactory. Subsequently N,N - diethyl - 3 - aminoaniline was eluted, b.p. 90–92°/0.006 mm, lit.[38] b.p. 127°/25 mm, picrate (EtOH), m.p. 151.5–152.5°, lit.,[38] m.p. 152°.

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