Heterocyclic Imines and Amines. Part 18.[1] Conversion of *o*-Cyanobenzyl Cyanide into Isoquinoline, Benzylisoquinoline, and Azachrysene Products

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With sodamide in formamide, *o*-cyanobenzyl cyanide dimerises in the two ways possible: it also adds formamide to yield 1-amino-3-formamidoisoquinoline (2). Each dimer undergoes cycloisomerisation: thus 1-amino-3-*o*-cyanobenzyl-4-cyanoisoquinoline (5a) and 6,11-diamino-12-cyanobenzo[*c*]phenanthridine (9) were isolated. *o*-Cyanobenzyl cyanide with sodium methoxide afforded (5a) very slowly in methanol but much more rapidly in dimethyl sulphoxide–methanol.

o-Cyanobenzyl cyanide (1) was treated with sodamide in formamide in a further attempt to prepare the imidine, 1,3-di-imino-1,2,3,4-tetrahydroisoquinoline.[2] Besides 1-amino-3-formamidoisoquinoline (2), a product of cycloaddition of formamide to (1), we isolated two *dimeric* cyclisation products. One was the 3-benzylisoquinoline (5a) and the other was the azachrysene (9), the reactions involved providing new routes to these two ring systems.

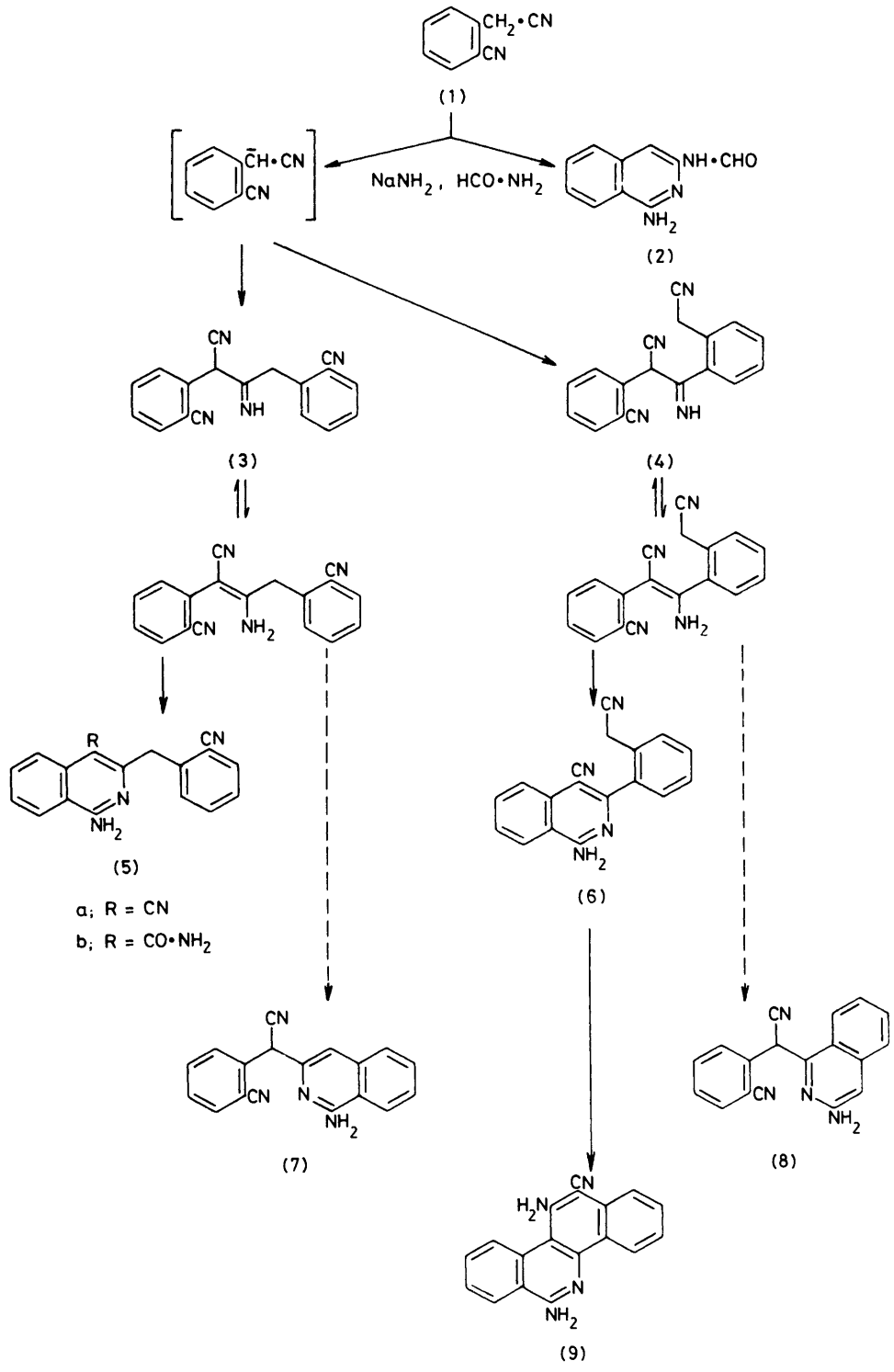
Previously we found that hydroxylamine would add to *o*-cyanobenzyl cyanide (1) to give either the imidine derivative, homophthalimide dioxime,[3] or the aromatised product, 1-amino-3-hydroxyaminoisoquinoline.[2,3] Ammonia addition required vigorous conditions and gave only 1,3-diaminoisoquinoline.[2,4] Ammonium salts could offer no advantage [5] but sodamide in formamide can add ammonia to simple dinitriles under very mild conditions.[6] *o*-Cyanobenzyl cyanide (1), however, has an active methylene group. The reagent could therefore generate the methylene carbanion which would add to a nitrile group in a second molecule of (1), as when (1) is treated with ethoxide.[7] Experiment showed that with sodamide such dimerisation, and subsequent cyclisations, predominated over the intended simple cycloaddition of ammonia to (1). Evidently in this case, the last-named process was the slowest.

o-Cyanobenzyl cyanide (1) with sodamide in formamide solution soon deposited a product, shown to be a dimer $C_{18}H_{12}N_4$ by mass spectrometry and combustion analysis. The u.v. light absorption curve from the product was very broad, showing maxima near 250 and 315 nm and extending to beyond 360 nm so suggesting an aminoheteroaromatic condensed ring system.[2,8] The i.r. spectrum indicated the presence of a primary amino group, a typical aryl cyano group (2 226 cm^{-1}), and a cyano group (2 206 cm^{-1}) conjugated to an amino group.[9] These observations precluded both of the simple dimeric tautomeric structures (3) and (4), but showed that further cycloisomerisation must have occurred. Excluding the formation of four-membered rings, and reactions involving carbanions derived from (3) and (4) (as being relatively much less likely), each dimer (3) and (4) could in principle cyclise in two ways, by addition of the amino or imino group anion on to one or other of the further cyano groups (Scheme). Of the four possible products (5)—(8), only (5a) and (6) have a cyano group conjugated to an amino group, as required by the low frequency CN stretch, and of these two, only (5a) has the additionally required aryl cyano group. The ^1H n.m.r. spectrum supported structure (5a) by showing a methylene singlet at δ 4.42, too low a chemical shift for the methylene protons in a cyanobenzyl group (δ 4.02) as in (6) or (1).[2] This new 1-amino-3-*o*-cyanobenzyl-4-cyanoisoquinoline (5a) was additionally characterised as its 4-*N*-acetyl derivative which had the expected i.r. and ^1H n.m.r. spectra. On one occasion, addition of water to the reaction filtrate from (5a) caused the separation some 12 h later of the monoamide (5b), presumably as a result of hydrolysis of nitrile (5a) which remained in solution. The u.v. absorption of the product (5b) was similar to that of the nitrile (5a), and the i.r. absorption showed that it was the aryl cyano group which persisted. A signal at δ 4.44 in the ^1H n.m.r. spectrum demonstrated the presence of the bridging methylene group and so helped to confirm the structure (5b).

On all other occasions, addition of water to the reaction filtrate from product (5a) caused crystallisation of an isomeric yellow compound, $C_{18}H_{12}N_4$, the ^1H n.m.r. spectrum of which showed the absence of benzylic methylene protons and the presence of two amino groups and eight aromatic protons. The i.r. spectrum indicated two primary amino groups, plus a single cyano group at an exceptionally low wavenumber (2 189 cm^{-1}), suggesting it was conjugated to *both* of the amino groups. A further cycloisomerisation must therefore have occurred. Again excluding formation of four-membered rings, cycloisomerisation was not feasible with compounds (5a), (7), and (8), but only with (6). With that compound, cycloaddition of the methylene carbanion on to the cyano group of the adjacent pyridyl ring provides 6,11-diamino-12-cyanobenzo[*c*]phenanthridine (9), a structure consistent with the observed properties. Added support came from the u.v. light absorption curve (extending to 425 nm) which is similar to that of 6-acetyl-12-aminochrysene,[10] a close benzo-analogue of (9). The absorption envelope resembled in shape that from benzo[*c*]phenanthridine [11] but was shifted bathochromically, as expected in the presence of the amino groups in (9). Both this 5-azachrysene and the route to it are novel: it may be possible to improve the yield and extend the reaction to other derivatives.

The unusually low CN stretching frequency in conjugated cyanoenamines $\geq N-(C=C)_n-CN$, both alkenyl and aryl, was attributed by Baldwin [9] to lowering of the CN bond order by resonance contributors of the type $\geq \overset{+}{N}=(C-\overset{-}{C})_n=C=\overset{-}{N}$. These last contributors would be expected to increase the reactivity of the cyano group towards nucleophiles. A possible explanation thus emerges of the selective hydrolysis (5a) ⟶ (5b) and of the cyclisation of the tentative intermediate (6) to give (9).

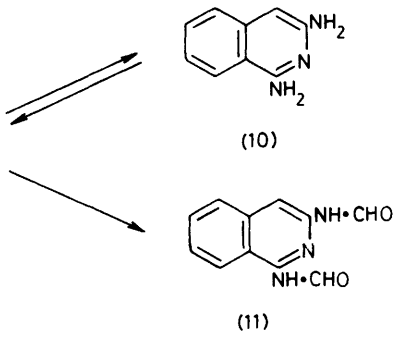
After isolation of the 5-azachrysene (9), addition of more water to the reaction filtrate slowly precipitated monoformylated 1,3-diaminiosoquinoline, $C_{10}H_9N_3O$. This was easily hydrolysed by alkali to 1,3-diaminoisoquinoline (10) and was identical with the product of formylation of 1,3-diaminoiso-



Scheme.

quinoline with acetic formic anhydride at 0 °C: formylation at 20 °C gave the 1,3-diformamido compound (11). This last-named compound had complicated i.r. and ^{1}H n.m.r. spectra, consistent with it being a mixture of the four possible *E*- and *Z*-amide forms (*cf.* ref. 12).

The identity of the two preparations of the monoformyl derivative, from (1) and from (10), was shown by the i.r. spectra, which also suggested that each preparation was a mixture. Seen under the hot-stage microscope, each preparation consisted of small needle clusters and long splinters, with m.p. 207—208 °C and 217 °C, respectively, but the possible deduction that the preparations were mixtures of the two positional isomers, 1(3)-amino-3(1)-formamidoisoquinoline, was militated against by the ^{1}H n.m.r. spectrum (see Table). This indicated two NH and two CHO proton chemical shifts, but with the intensities consistent with *one*



formamido group in *E*- and *Z*-amide forms, as in formanilide where, also, the NH to CHO coupling constant ($^3J_{HH}$) is large (11 Hz) in the *E*- and small in the *Z*-amide form.[12] The relevant amino and amido proton signals were identified partly from the chemical shifts (*i.e.* comparison with the ^1H spectra of 1,3-diaminoisoquinoline, its diacetyl derivative, and 1-amino-3-hydroxyaminoisoquinoline),[2] partly from the splittings, and partly through reductions in signal intensity effected by exchange with added deuterium oxide. It thus became clear that the monoformyl derivative was 1-amino-3-formamidoisoquinoline (2), present as its *E*- and *Z*-amide forms in the ratio *ca.* 60 : 40.

The formation of the product (2) presumably arose through addition of formamide anion to the aliphatic cyano group in *o*-cyanobenzyl cyanide (1), followed by cycloaddition to the aryl cyano group. That the product (2) was not formed by attack of the first-formed 1,3-diaminoisoquinoline (10) or its anion upon formamide under the basic conditions was demonstrated by the recovery of (10) after treatment with sodamide in formamide for 6 h. One other example of the addition of formamide, rather than ammonia, to a dinitrile is known.[6] In these cases and in the various additions of amines and ammonia to dinitriles,[13] as with the reactions (1) ⟶ (5) and (1) ⟶ (9) now described, it seems likely that the additions involved are essentially reversible, so that the products actually isolated are those which happen to be the least soluble.

Finally in this paper we describe the action on *o*-cyanobenzyl cyanide (1) of sodium methoxide, a possible alternative to sodamide, although a less powerful base. Atkinson and Thorpe [14] had obtained, from benzyl cyanide and sodium methoxide, the sodio derivative of the imine dimer, 3-imino-2,4-diphenylbutyronitrile, which slowly gave 4-amino-2,6-dibenzyl-5-phenylpyrimidine through further addition of benzyl cyanide and cyclisation. By treating *o*-cyanobenzyl cyanide (1) with sodium ethoxide in boiling ethanol for 3 h, Johnson and Nasutavicus [7] obtained a dimer which was thought to have structure (4),[15] together with a minor product, m.p. 225 °C, which they suggested [7] might be 2,4-diamino-1-cyano-3-*o*-cyanophenylnaphthalene from i.r. results. By heating *o*-cyanobenzyl cyanide (1) with sodium methoxide in boiling methanol for 8 h, we obtained the isoquinoline dimeric product (5a), but only in 9% yield. By increasing the effective basicity of the medium through addition of dimethyl sulphoxide [16] and excluding air, the yield of the isoquinoline (5a) was increased five-fold in a third of the time.

Experimental

U.v. data were obtained for solutions in 96% ethanol, unless otherwise stated, using a Unicam SP 800 B spectrophotometer. I.r. maxima were taken from spectra recorded for Nujol mulls with a Grubb Parsons Spectromaster. ^1H N.m.r. spectra were recorded at 90 MHz and 25 °C with a Bruker WH 90 Fourier Transform spectrometer or at 60 MHz and 35 °C with a Perkin-Elmer R12 instrument, using solutions in $(CD_3)_2SO$ containing $SiMe_4$ as internal reference.

Table. ^1H N.m.r. data at 60 MHz for compound (2) in $(CD_3)_2SO$ containing $SiMe_4$

δ	Multiplicity (*J*/Hz)	Relative intensity	Assignment *E*-Amide	Assignment *Z*-Amide
6.77	br s	0.8		1-NH_2
6.95	br s	1.0	1-NH_2	
6.33	s	0.6	4-H	
7.1—7.7	Complex	3.6	5-, 6-, 7-H	4-H + 5-, 6-, 7-H
8.11	*ca.* dd (8.5)	1.0	8-H	8-H
8.26 [a]	br (unresolved d)	0.4		CHO
9.24 [a]	d (11.2)	0.7	CHO	
9.87 [b]	br s	0.4		3-NH
10.22 [b]	br d (11.2)	0.5	3-NH	

[a] Collapsed to s on addition of D_2O. [b] Disappeared on addition of D_2O.

1-Amino-4-cyano-3-(o-cyanobenzyl)isoquinoline (5a).—A solution of *o*-cyanobenzyl cyanide (8.25 g) in hot formamide (80 ml; deoxygenated by passage of dry N_2) was cooled to 15 °C and an ice-cold solution of sodamide (6 g) in formamide (100 ml; deoxygenated) was added in portions, with stirring under nitrogen. Solid began to separate after 1 h. After 2 h, the product was collected, washed (formamide), extracted briefly with boiling ethanol, and recrystallised from tetrahydrofuran (THF) (purified) to yield prisms of *1-amino-4-cyano-3-(o-cyanobenzyl)isoquinoline* (1.57 g, 18%), m.p. 223—224 °C (Found: C, 76.1; H, 4.2; N, 19.6. $C_{18}H_{12}N_4$ requires C, 76.1; H, 4.2; N, 19.7%), *m/z* 284 (M^+); $\nu_{max.}$ 3 448 and 3 328 (NH_2), 3 190br (bonded NH), 2 226 (aryl CN), 2 206 (CN conjugated to N), 1 653s, 1 619, 1 580, 1 558, 1 511, 1 491, 1 408, 1 195, 788, 775, and 682 cm^{-1}; $\lambda_{max.}$ (THF) 247, 276, 284, 315, and 335 nm (10^{-3} ε 20.0, 3.6, 4.6, 12.0, and 9.0, respectively); δ 4.42 (s, 2 H, CH_2), 7.2—8.1 (c, 7 H, aryl Hs), 7.87 (br s, 2 H, NH_2; removed by D_2O), and 8.36 (*ca.* dd, 1 H, 5-H, J_o 8.5 Hz, *peri* to CN).

The finely powdered amine (5a) (0.71 g) was heated with acetic anhydride (5 ml) and acetic acid (5 ml) under reflux for 35 min. Pouring the hot solution on to ice (30 g) gave an oil which soon solidified. Crystallisation from THF afforded *1-acetamido-4-cyano-3-(o-cyanobenzyl)isoquinoline* (0.74 g, 91%) as prisms, m.p. 233—235 °C (decomp.) (Found: C, 73.8; H, 4.3; N, 17.3. $C_{20}H_{14}N_4O$ requires C, 73.6; H, 4.3; N, 17.2%), *m/z* 326 (M^+); $\nu_{max.}$ 3 268 (NH), 2 222 (aryl CN), 2 212 (CN conjugated to N), 1 674, 1 663s, 1 573, 1 523 cm^{-1}, *etc.*; $\lambda_{max.}$ 240, 279infl., 285, 294, 306, 335, and 349sh nm ($10^{-3} \times$ ε 35.2, 6.9, 8.1, 8.8, 10.6, 10.6, and 7.5); δ 2.06 (s, 3 H, Me·CO), 4.64 (s, 2 H, CH_2), 7.2—8.2 (c, 7 H, aryl H's), 8.35 (*ca.* dd, 1 H, 5-H, J_o *ca.* 8.5 Hz), and 10.8 (br s, 1 H, NH; removed by D_2O).

6,11-Diamino-12-cyanobenzo[c]phenanthridine (9).—To the reaction filtrate from (5a), water (*ca.* 300 ml) was added to cause turbidity. The greenish solid which slowly separated was collected after 1 h, washed (EtOH), and recrystallised (EtOH; charcoal) to give pale yellow needles (0.25 g, 3%), m.p. 285 °C (decomp.), of *6,11-diamino-12-cyanobenzo[c]phenanthridine* (Found: C, 76.6; H, 4.2; N, 20.1. $C_{18}H_{12}N_4$ requires C, 76.1; H, 4.2; N, 19.7%), *m/z* 284 (M^+); $\nu_{max.}$

3 448 and 3 356 (NH_2), 3 426 and 3 344 (NH_2), 2 189 (CN conjugated to N), 1 620, 1 570, 1 560, 1 523, 1 507, 1 409, and 768 cm^{-1}; $\lambda_{max.}$ 220, 234, 254, 271, 293, 303infl., 319, 360, and 394sh nm (10^{-3} ε 23.3, 23.0, 32.4, 35.2, 19.8, 19.0, 17.2, 14.0, and 6.2, respectively); δ 6.40 (br s, 2 H, 11-NH_2; removed by D_2O), 7.2—8.0 [c, 7 H, 2-, 3-, 7-, 8-, 9-H + 6-NH_2; 2 H (NH_2) removed by D_2O], 8.45 (dd, 1 H, 1-H, J_o *ca.* 8.5, J_m *ca.* 3 Hz), 8.96 (*ca.* dd, 1 H, 10-H, J_o *ca.* 8.5 Hz), and 9.07 (dd, 1 H, 4-H, J_o *ca.* 8.5, J_m *ca.* 3 Hz) (*cf.* ref. 17).

1-*Amino*-3-*formamidoisoquinoline* (2).—The reaction filtrate from (9) was made turbid by addition of water (*ca.* 300 ml) and the discoloured product which slowly separated was collected and recrystallised (EtOH; charcoal) to yield 1-*amino*-3-*formamidoisoquinoline* (1.54 g, 14%) as a mixture of needle clusters, m.p. 207—208 °C, and splinters, m.p. 217 °C (unchanged by repeated crystallisation from EtOH) (Found: C, 64.5; H, 4.9; N, 23.1. $C_{10}H_9N_3O$ requires C, 64.2; H, 4.8; N, 22.5%), *m/z* 187 (M^+); $\nu_{max.}$ 3 475 and 3 388 (NH_2), 3 260s (amide NH), 3 160br (bonded NH), 1 675s and 1 650s (Amide I), 1 619s, 1 602, 1 562, 1 523, 1 510, 1 408, 1 327, 1 290s, 1 199, 995, 795s, 787s, 739, and 678 cm^{-1}; $\lambda_{max.}$ 220, 249, 310, and 340infl. nm (10^{-3} ε 33.0, 19.6, 12.8, and 4.8, respectively).

The formamido compound (2) (0.1 g) in ethanol (5 ml) was heated with sodium hydroxide (20 ml; *ca.* 2M) under reflux for 1 h. Evaporation under reduced pressure caused precipitation of a yellow solid which was washed (H_2O) and recrystallised (MeOH–H_2O) to yield yellow prisms of 1,3-diaminoisoquinoline (10) (0.06 g, 71%), m.p. 232—233 °C, undepressed in admixture with authentic material (lit.,[2] m.p. 231.5—232.5 °C) and having the same i.r. spectrum.

To 1,3-diaminoisoquinoline [2] (0.24 g) in formic acid (5 ml) at 0 °C was added, dropwise, cold acetic formic anhydride [3 ml; prepared by adding formic acid (1 ml) to acetic anhydride (2 ml) at 0 °C, heating at 50 °C for 15 min and at once cooling in ice]. After the reaction solution had been stirred at 0 °C for 2 h, water (20 ml) was added and the solution neutralised (aqueous Na_2CO_3). The product which separated was recrystallised (EtOH; charcoal) to afford crystalline 1-amino-3-formamidoisoquinoline (0.22 g, 79%), m.p. 207—208 °C and 217 °C, with i.r. absorption identical with that of the foregoing preparation from (1).

Repetition of this formylation of 1,3-diaminoisoquinoline (0.24 g) for 6 h at 20 °C gave a product which began to separate after 4.5 h. Addition of water (10 ml) to the filtrate afforded a second crop. Recrystallisation of the product (THF–EtOH; charcoal) provided fine needles of 1,3-*bis*-*formamidoisoquinoline* (11) (0.2 g, 62%), m.p. 262—263 °C (decomp.) (Found: C, 61.4; H, 4.1; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%), *m/z* 215 (M^+); $\nu_{max.}$ 3 220br, 3 140br, and 3 080br (NH), 1 690s and 1 670s (Amide I), 1 633, 1 525, 1 460s, 1 430, 1 406, 1 380, 1 365, 1 340s, 1 280, 1 259s, 1 235, 1 150, 1 128, 810br, 750, 707, 689, and 660 cm^{-1}; $\lambda_{max.}$ 240, 277sh, 290, 301, and 347 (10^{-3} ε 37.9, 7.0, 11.6, 12.1, and 6.1, respectively).

1-*Amino*-4-*carbamoyl*-3-o-*cyanobenzylisoquinoline* (5b).—On one occasion, reaction of *o*-cyanobenzyl cyanide (1) with sodamide in formamide, as described above, again gave the isoquinoline (5a) (0.77 g, 9%), m.p. and physical properties as before. Addition of water (*ca.* 300 ml) failed to precipitate compound (9) during 1 h. Next day, the creamy product which had separated was recrystallised (EtOH; charcoal) to give 1-*amino*-4-*carbamoyl*-3-o-*cyanobenzylisoquinoline* (5b) (0.92 g, 10%) as plates, decomp. 256 °C (Found: C, 71.6; H, 4.6; N, 18.5. $C_{18}H_{14}N_4O$ requires C, 71.5; H, 4.6; N, 18.5%), *m/z* 302 (M^+); $\nu_{max.}$ 3 472 and 3 381 (NH_2), 3 196br (amide NH), 2 224 (aryl CN), 1 685s (Amide I), 1 620, 1 605, 1 572, 1 524, 1 414, 1 361, 1 332, 1 299, 1 266s, 1 250, 1 156, 799, 763, 746, and 678 cm^{-1}; $\lambda_{max.}$ 222, 252, 277sh, 285sh, 312, and 342infl. nm (10^{-3} ε 42.0, 16.2, 3.8, 5.8, 12.6, and 6.0, respectively); δ 4.44 (s, 2 H, CH_2), 6.76 (*ca.* dd, 1 H, *o*-H to CH_2), 7.04 (s, 2 H, NH_2; removed with D_2O), 7.2—7.7 (c, 5 H, aryl H's), 7.84 (dd, 1 H, 8-H), 8.24 (*ca.* dd, 1 H, 5-H, J_o *ca.* 8.5 Hz, *peri* to $CONH_2$), 9.35 (br, s, 1 H, *E*-N*H*; diminished by D_2O), and 10.18 (br, s, 1 H, *Z*-N*H*; removed by D_2O).

Treatment of o-*Cyanobenzyl Cyanide with Sodium Methoxide*.—To *o*-cyanobenzyl cyanide (1.42 g) dissolved in methanol (20 ml), sodium methoxide (from 50 mg Na) in methanol (5 ml) was added. The solution was refluxed (N_2) for 8 h and then cooled in ice to give 1-amino-4-cyano-3-*o*-cyanobenzylisoquinoline (0.13 g, 9%) (THF; charcoal), identical with authentic material (m.p., mixed m.p., i.r. spectrum).

To *o*-cyanobenzyl cyanide (0.5 g) in dimethyl sulphoxide (5 ml, air-free), sodium methoxide (from 50 mg Na) in methanol (5 ml) was added, and the solution refluxed under N_2 for 2 h. Cooling and addition of water gave 1-amino-4-cyano-3-*o*-cyanobenzylisoquinoline (0.22 g, 44%) as prisms, m.p. and mixed m.p. 223 °C, *m/z* 284.

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