Synthesis of Isoquinolines from Benzylaminoacetonitriles. Part I. Compounds prepared from Veratrylamine [1]

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3,4-Dimethoxybenzylaminoacetonitriles cyclise in concentrated sulphuric acid to give, after hydrolysis, 1,2-dihydroisoquinolin-4(3*H*)-ones, in excellent yield. 3,3-Disubstituted 1,2-dihydroisoquinolin-4(3*H*)-ones are stable as the free base, in contrast to the 3-unsubstituted and 3-monosubstituted analogues. 1,2-Dihydro-6,7-dimethoxy-3-phenylisoquinolin-4(3*H*)-one as the free base underwent aerial oxidation to give 6,7-dimethoxy-3-phenylisoquinolin-4-ol, and could also be converted by a series of reactions into 6,7-dimethoxy-3-phenylisoquinoline in good yield.

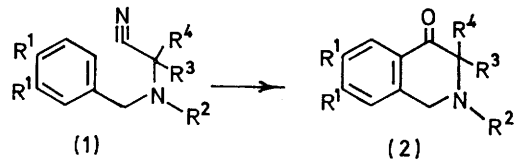
A MUCH-QUOTED review of twenty years ago [2] placed emphasis on the difficulty of synthesis of isoquinolines by routes analogous to the Pomeranz–Fritsch reaction. Many failures were reported,[3] and an attempt was made to rationalise the situation in general terms.[4]

Since then, the work of several groups [5–8] has altered the picture fundamentally. It is now apparent that the benzylamine route has no inherent theoretical barriers, but that the primary product is often difficult to isolate. The 1,2-dihydro-, 4-hydroxytetrahydro-, and 4-oxotetrahydro-isoquinolines, usual products of this kind of reaction, are all now known [7,9,10] to be relatively unstable. Thus the reduction of a reactive isoquinoline intermediate, without isolation, dramatically increased the yield of the corresponding tetrahydroisoquinoline.[6]

In view of the natural advantages of this approach to isoquinolines, particularly regarding the availability of starting materials, we were attracted to a reappraisal of one of the past unsuccessful routes. It was reported [3] that internal Hoesch reaction of the benzylaminonitrile (1a) with zinc chloride and dry hydrogen chloride in dry ether failed to give the required isoquinolinone (2a); other failures with similar systems under similar conditions were reported by other workers.[11] However, since α-aminonitriles are readily available,[12] this route potentially possesses great flexibility with respect to the 3-position of the isoquinoline (Scheme 1).

With a view to later extension to alkaloid syntheses, and in connection with other synthetic work,[13] we first studied the aminonitrile (1b), which would give a 3-phenylisoquinoline. Unfortunately, this compound and the corresponding tertiary base (1c) gave only the amide, formed by normal hydrolysis.

With the 'activated' analogue (1d) we were at first unsuccessful with a variety of acid treatments. We eventually succeeded in effecting cyclisation to compound (2d) by use of concentrated sulphuric acid, at first overnight at room temperature, and later, more conveniently,



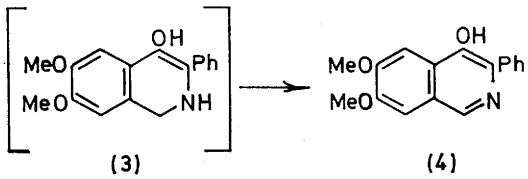
SCHEME 1

	R^1	R^2	R^3	R^4
a;	OMe	H	H	H
b;	H	H	Ph	H
c;	H	Me	Ph	H
d;	OMe	H	Ph	H
e;	OMe	H	Me	Me
f;	OMe	H	$[CH_2]_5$	
g;	OMe	H	Ph	Me
h;	OMe	H	DMP	H

DMP = 3,4-$(MeO)_2C_6H_3$

at 50 °C for 3·5—4 h. I.r., n.m.r., and analytical data for the product were unambiguous.

While the salts of the isoquinolinone produced were apparently stable indefinitely, in agreement with a previous report,[10] the free base underwent aerial oxidation on exposure to the air for several days, giving the aromatic isoquinolin-4-ol (4), possibly *via* the enolic form (3) (Scheme 2).



SCHEME 2

To test both the enolisation hypothesis and the flexibility of our route, we attempted cyclisation of the

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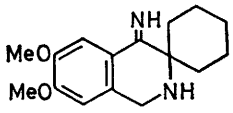
aminonitrile (1e). The expected product is incapable of enolisation, and was in fact found to be stable under all the conditions employed, being obtained crystalline from hot, strong sodium hydroxide solution.

In the case of the cyclohexanone derivative (1f) the initial product of the reaction, obtained by dilution of the concentrated sulphuric acid solution by direct addition to cold 5N-sodium hydroxide solution, was not the pure isoquinolinone (2f). The major component of the mixture gave an elemental analysis closer to that calculated for the imine (5); however it was not obtained



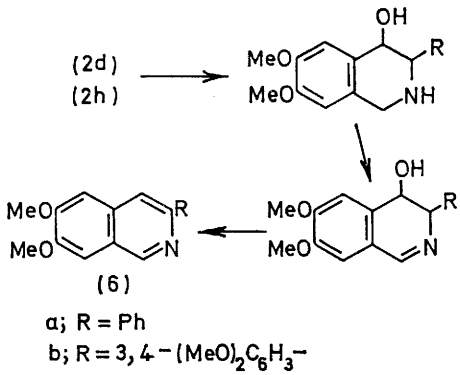
(5)

analytically pure. The i.r. and n.m.r. data of the mixture were ambiguous, but accurate mass measurement of the parent ion in the mass spectrum (*m/e* 274) indicated the molecular formula to be $C_{16}H_{22}N_2O_2$, consistent with the imine structure. Treatment of the imine with aqueous acid generated the expected ketone quickly and quantitatively. Similar experiences with imines from nitrile cyclisations have been recorded.[14] Another 3,3-disubstituted isoquinolinone (2g) was obtained in excellent yield, without difficulty.

With the 3-unsubstituted isoquinoline (2a), using direct basification of the sulphuric acid cyclisation medium without a preliminary dilution stage, we at first could obtain no product whatever. Presumably the intermediate imine is subject to attack by hydroxide, giving highly acid-, base-, and water-soluble product(s). However, when the concentrated acid was added carefully to ice–water, and set aside before basifying, the isoquinolinone could be isolated as the hydrochloride, after extraction with chloroform. The 30—50% yield represents a substantial improvement over that obtained by Grethe and his co-workers,[8] from cyclisation of the analogous glycine ester.

In order to investigate further the applicability of the route to alkaloid synthesis, we studied the cyclisation of the aminonitrile (1h). The expected product is potentially an intermediate for both benzo[*c*]phenanthridine and protoberberine types of ring system. Although the cyclisation succeeded, the low solubility of the product and by-product hydrochlorides in most solvents reduced the yield of pure material to 24%. No doubt this could be increased by improvements in the work-up technique.

The recent publication [15] of a simple synthesis of norcoralydine from 3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline has anticipated our own scheme. In order to realise the synthesis from our intermediate, it would be necesary to convert the dihydroisoquinolin-4-one (2h) into the corresponding aromatic isoquinoline (6b). As a model, we had chosen to convert the isoquinolinone (2d) (Scheme 3) into the aromatic isoquinoline (6a). Each of the stages is well established in principle,[16,17] and in fact the conversion was achieved in 44% overall yield.



(6)

a; R = Ph

b; R = 3,4-$(MeO)_2C_6H_3$–

SCHEME 3

We hope shortly to publish the results of cyclisations of other aminonitriles, including several with *N*-alkyl substituents, which have given different results.

EXPERIMENTAL

M.p.s of bases were taken with a Kofler hot-stage apparatus, and are corrected. M.p.s of salts (not corrected) were taken for samples in capillary tubes with a Gallenkamp apparatus; the tube was inserted 15—20° below the m.p. and heated at 5—7° per min. I.r. spectra were obtained with a Unicam SP 200 instrument for potassium bromide discs or liquid films. N.m.r. spectra were recorded with a Varian A60 instrument (tetramethylsilane as internal reference). Organic solutions were dried over anhydrous magnesium sulphate. Hydrochlorides were prepared by addition of hydrogen chloride in ether to an organic solution of the base.

Preparation of Aminonitriles.—General method. A solution of 3,4-dimethoxybenzylamine (0·1 mol) in water (200 ml) was made just acid with dilute hydrochloric acid. The aldehyde or ketone (0·1 mol), dissolved in ethanol (100 ml) if necessary, was added with stirring. Potassium cyanide (10 g) in water (50 ml) was added during 10 min with vigorous stirring; the solution was then stirred for 1 h and set aside overnight. The product was filtered off or extracted with ether or chloroform as appropriate, the solid or solution being washed thoroughly with water. Crystallisation, if necessary, or evaporation followed by crystallisation, gave the *aminonitrile* (see Tables 1 and 2). Where the m.p. and i.r. spectrum indicated a satisfactory degree of purity, the crude aminonitrile was used for cyclisation.

1,2-Dihydro-6,7-dimethoxyisoquinolin-4(3H)-ones.—General method. The aminonitrile (2 g) was dissolved with care in concentrated sulphuric acid (10 ml), so as to avoid excessive heating and consequent charring. The solution

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was heated at 50° for 4 h; slight variations in time had little effect. No systematic effort was made to discover the best reaction conditions. Cyclisation overnight at room temperature gave slightly lower yields. The chilled solution was added cautiously to ice–water; more ice was added as necessary to maintain the temperature below 5°. The final volume was about 200 ml. This solution was set aside for 30 min, and then basified carefully with 5N-sodium hydroxide or concentrated ammonium hydroxide, the addition of ice being continued as before. The *isoquinolinone* was filtered off or extracted with chloroform, and washed with water, before evaporating, if necessary, and drying. At this stage the isoquinolinones (2a) and 2(h) were converted into the hydrochlorides, since the free bases are unstable. The need for such a procedure was indicated with the isoquinoline (2d), but it was more convenient to avoid basification of the diluted acid solution, since on prolonged refrigeration the solution deposited microcrystalline 1,2-*dihydro*-6,7-*dimethoxy*-3-*phenyliscquinolin*-4(3H)-*one* (2d) *hydrogen sulphate*, which was stable and could be recrystallised from methanol–ether to give grey-green rods, m.p. 132—135° (decomp.), $\nu_{max.}$ 1680 cm^{-1} (Found: C, 54·0; H, 5·2; N, 3·55. $C_{17}H_{19}NO_7S$ requires C, 53·5; H, 5·0; N, 3·7%); yield 67%, after filtration from the mother liquor, washing with water, and drying.

1,2,3,4-*Tetrahydro*-4-*imino*-6,7-*dimethoxyisoquinoline*-3-*spirocyclohexane* (5).—The procedure adopted was as for the preparation of the isoquinolin-4-ones, except that the concentrated sulphuric acid solution after cyclisation was added, with caution, directly to ice–cold 10% sodium hydroxide. The white precipitate was filtered off, washed, and dried thoroughly (1·1 g; m.p. 123°). [This solid could be converted quantitatively into 1,2-dihydro-6,7-dimethoxyisoquinolin-4(3*H*)-one-3-spirocyclohexane, m.p. 148°, identical with that obtained previously, by dissolution in dilute hydrochloric acid and rebasification with sodium hydroxide.] After repeated crystallisation from petroleum (b.p. 80—100°) the solid had m.p. 125—126°, and probably contained about 20% of the isoquinolin-4-one (i.r. spectrum and elemental analysis). The major component was identified by accurate mass measurement of the parent ion in the mass spectrum (Found: M^+, 274·1682. $C_{16}H_{22}N_2O_2$ requires M, 274·1681).

6,7-*Dimethoxy*-3-*phenylisoquinolin*-4-*ol* (4).—1,2-Dihydro-6,7-dimethoxy-3-phenylisoquinolin-4(3*H*)-one (2d) (1·5 g) dissolved in 50% ether–chloroform (300 ml) was set aside for 3 days. Evaporation gave a pale brown gum, which on trituration with ether containing a little ethanol gave the *isoquinolin*-4-*ol* (0·55 g, 37%) as a pale yellow powder, m.p. 220°. A sample crystallised twice from aqueous ethanol as pale yellow plates had m.p. *ca.* 240°; final crystallisation from chloroform–petroleum (b.p. 40—60°) gave white microcrystals, m.p. 249°, $\nu_{max.}$ 3250 and 1625 cm^{-1}, δ (CF_3·CO_2H) 8·7 (1H), 7·5 (7H), and 4·1 (6H, d) p.p.m. (Found: C, 72·6; H, 5·5; N, 5·1. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·4; N, 5·0%).

6,7-*Dimethoxy*-3-*phenylisoquinoline* (6a).—1,2-Dihydro-6,7-dimethoxy-3-phenylisoquinolin-4(3*H*)-one (2d) hydrogen sulphate (30 g) dissolved in ethanol (300 ml) was basified carefully with sodium hydroxide, and sodium borohydride (10 g) was added. Next day the excess of borohydride was destroyed with dilute acetic acid, and the solution was rebasified with sodium hydroxide and extracted with chloroform. Drying and evaporation of the extract yielded a

TABLE 1

Spectroscopic data for benzylaminoacetonitriles (1)

	$\nu_{max.}$/cm^{-1} (NH)	$\nu_{max.}$/cm^{-1} (C≡N)	^{1}H N.m.r. (δ values in p.p.m.; solvent $CDCl_3$)
a	3350	2230	
b	3350	2230	7 (10H, m), 4·3 (1H), 3·6 (2H), 1·8br (1H) *†
d	3340	2220	7·15 (5H, m), 6·7 (3H, m), 4·5 (1H), 3·7 (2H), 3·65 (6H), 1·9br (1H) †
e	3330	2230	6·9 (3H, m), 3·85 (8H, d), 1·5 (7H) †
f	3325	2225	6·9 (3H, m), 3·85 (8H, d), 1·65br (11H) †
g	3300	2230	7·5 (5H, m), 6·85 (3H, m), 3·75 (8H), 2·7br, (1H) † 1·75 (3H)
h	3350	2220	

* In CCl_4. † 1H exchangeable.

TABLE 2

Benzylaminoacetonitriles (1)

	Yield (%)	M.p. *T*/°C	Found (%) C	H	N	Required (%) C	H	N
a	66	181—185 *[a] (decomp.)	54·2	6·3	11·1	54·4	6·2	11·5
d	93	65 [b]	72·3	6·4	9·8	72·3	6·4	9·9
e	100	53 [c]	66·5	7·8	11·95	66·1	7·9	12·2
f	80	88 [c]	70·4	7·7	10·3	70·0	8·1	10·2
g	53	72—74 [c]	73·1	6·7	9·4	72·9	6·8	9·45
h	98	60—61 [c]	67·1	6·6	7·8	66·65	6·5	8·2

* Hydrochloride (lit.,[3] 188°). The free base had m.p. 58—62° (lit.,[3] 64°), after crystallisation from ether–petroleum (b.p. 40—60°) and m.p. 98—100° after crystallisation from benzene–petroleum (b.p. 60—80°).

[a] From ethanol. [b] From ether–petroleum (b.p. 80—100°). [c] From petroleum (b.p. 80—100°).

TABLE 3

Spectroscopic data for 1,2-dihydro-6,7-dimethoxyisoquinolin-4(3*H*)-ones (2)

	$\nu_{max.}$/cm^{-1} (NH)	$\nu_{max.}$/cm^{-1} (C=O)	^{1}H N.m.r. (δ values in p.p.m.; solvent $CDCl_3$)
a	3350	1660	7·5 (1H), 6·65 (1H), 4·05 (2H), 3·9 (6H,d), 3·5 (2H), 3·0br (1H) *
d	3350	1665	7·3 (1H), 7·1 (5H), 6·4 (1H), 4·4 (1H), 3·95 (2H), 3·8 (6H), 2·1br (1H) *
e	3340	1655	7·5 (1H), 6·6 (1H), 4·1 (2H), 3·9 (6H), 2·3 (6H), 2·3br (1H),* 1·3 (6H)
f	3300	1650	7·5 (1H), 6·55 (1H), 4·0 (2H), 3·9 (6H), 1·65 (10H, m) †
g	3300	1650	7·7 (1H), 7·4 (5H, m), 3·95 (5H), 3·85 (3H), 2·7br (1H),* 1·6 (3H)
h	2750 ‡	1680 ‡	

* 1H exchangeable. † Integral trace indicated 1H between 2·2 and 3·2 p.p.m. before shaking with deuterium oxide, but not afterwards. ‡ Hydrochloride.

TABLE 4

1,2-Dihydro-6,7-dimethoxyisoquinolin-4(3*H*)-ones (2)

	Yield (%)	M.p. *T*/°C	Found (%) C	H	N	Required (%) C	H	N
a	30—50	235—236° * [a]						
d	60	138—139 [b]	71·8	6·2	4·8	72·0	6·05	4·9
e	53	135 [c]	66·4	7·3	6·1	66·4	7·3	5·95
f	80	147 [d]	70·0	7·8	5·3	69·8	7·7	5·1
g	83	150 [d]	72·8	6·3	4·7	72·8	6·45	4·7
h	24	255—256 †[e]	59·7	5·8	3·3	60·0	5·8	3·7

* Hydrochloride (lit.,[8] 236—237°). † Hydrochloride.

[a] From methanol. [b] From ether. [c] From benzene–petroleum (b.p. 80—100°). [d] From petroleum (b.p. 80—100°). [e] From water.

brown glass, which on trituration with ethanol–ether gave a yellow solid (19 g), m.p. 134—144°, clearly a mixture of bases, presumably the diastereoisomers of the tetrahydroisoquinolin-4-ol and their dehydration product.

The mixed bases (16·5 g) were dissolved in chloroform (200 ml) and *N*-bromosuccinimide (10·7 g) was added with swirling. After 2 h the solution was diluted with ether (800 ml.), and the green amorphous precipitate (23 g.) was filtered off and washed with ether. The green solid was suspended in concentrated hydrochloric acid (100 ml) and heated on a boiling water bath for 30 min. The cooled solution was diluted with water (400 ml) and the solid was filtered off, suspended in water, and treated with sodium hydroxide and ethanol, to give 6,7-*dimethoxy*-3-*phenylisoquinoline* (6a) as a brown crystalline solid, m.p. 127° (8 g, 44% based on isoquinolinone hydrogen sulphate), $\nu_{max.}$ 1620 cm^{-1}, δ ($CDCl_3$) 9 (1H), 8·1 (2H, m), 7·8 (1H), 7·4 (3H, m), 7 (1H), 6·9 (1H), and 3·9 (6H) p.p.m., which was crystallised from petroleum (b.p. 80—100°) to give elongated prisms, m.p. 131—132° (Found: C, 76·8; H, 5·8; N, 5·4. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%).

The *methiodide hemihydrate*, obtained by use of dimethyl sulphate followed by ion exchange in potassium iodide solution, had m.p. 219—225° (decomp.) (from ethanol), $\nu_{max.}$ 1635 and 1615 cm^{-1}, δ [$(CD_3)_2SO$] 9·9 (1H), 8·3 (1H), 7·8 (7H, m), 4·2 (3H), and 4·05 (6H, d) p.p.m. (Found: C, 52·1; H, 4·45; N, 3·0. $C_{18}H_{18}INO_2,0{\cdot}5H_2O$ requires C, 51·9; H, 4·6; N, 3·4%).

2-*Benzylamino*-2-*phenylacetamide*.— Benzylidenebenzylamine (49 g) was treated with an excess of concentrated sodium disulphite solution, giving a slurry which was washed with ether. Excess of concentrated potassium cyanide solution was added, giving a clear solution with an oil, which was extracted with ether. Drying and evaporation gave 2-benzylamino-2-phenylacetonitrile (1b) (51 g, 91%). A solution of the aminonitrile (2·2 g) in concentrated sulphuric acid (20 ml) was heated on a boiling water bath for 3 h, cooled, and added carefully to water (200 ml); the resulting solution was washed with ether, basified with sodium hydrogen carbonate, and extracted with ether. Drying and evaporation of the extract gave the *aminoacetamide* as a white powder (1·34 g, 56%), which crystallised from aqueous ethanol as leaflets, m.p. 106—107°, and was recrystallised from ethyl acetate–petroleum (b.p. 80—100°) to give white rosettes, m.p. 116—117°, $\nu_{max.}$ 1690 and 3300 cm^{-1}, δ($CDCl_3$) 7·0 (10H, d), 6·35br (2H, d, exchangeable), 4·0 (1H), 3·6 (2H), and 2·0 (1H, exchangeable) p.p.m. (Found: C, 74·9; H, 6·7; N, 11·4. $C_{15}H_{16}N_2O$ requires C, 75·0; H, 6·7; N, 11·7%).

2-(N-*Benzylmethylamino*)-2-*phenylacetamide*.— 2-(*N*-benzylmethylamino)-2-phenylacetonitrile (1c) was prepared by the general method, from *N*-methylbenzylamine in place of 3,4-dimethoxybenzylamine, in 88% yield; it crystallised slowly, m.p. 45—47°, $\nu_{max.}$ 2230 cm^{-1}. The amino-nitrile (5 g) was treated as if for cyclisation with concentrated sulphuric acid; work-up in the usual way gave the *aminoacetamide* as a white solid, m.p. 124° (2·95 g, 55%), which was recrystallised from aqueous ethanol; m.p. 135°, $\nu_{max.}$ 1670, 3450, and 3200 cm^{-1}, δ ($CDCl_3$) 7·1 (10H, d), 6·5br (2H, d, exchangeable), 3·9 (1H), 3·35 (2H, d), and 2·0 (3H) p.p.m. (Found: C, 75·5; H, 6·9; N, 11·2. $C_{16}H_{18}N_2O$ requires C, 75·6; H, 7·1; N, 11·0%).

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