The Cyclisation of Benzylaminonitriles. Part 6.[1] Evidence for Exclusive Participation of a Spirocyclic Intermediate

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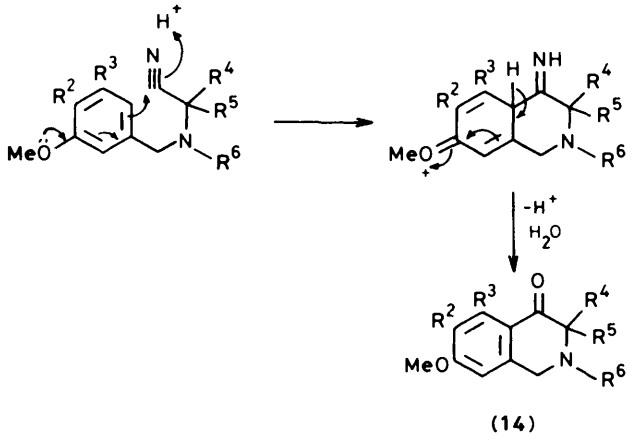
Cyclisation of 3,4-dialkoxybenzylaminoacetonitriles to 6,7-dialkoxy-1,2-dihydroisoquinolin-4(3*H*)-ones can occur by two mechanisms. The first involves electrophilic attack *para* to the 3-alkoxy substituent, and the second proceeds *via* formation of a spirocyclic intermediate with the participation of the 4-alkoxy group. In order to assess the relative contribution of these two mechanisms the cyclisation of 1-(4-ethoxy-3-methoxybenzylamino)cyclohexanecarbonitrile (**12**) and the isomer with the reverse orientation of alkoxy substituents (**13**) was studied. The benzylamino nitrile (**12**) on treatment with concentrated sulphuric acid at −10 °C, room temperature, and 50 °C gave a mixture of the 7-ethoxy-6-methoxyisoquinolinone (**27**) and the 7-hydroxy-6-methoxyisoquinolinone (**26**). Identical treatment of the isomeric 3-ethoxy-4-methoxybenzylamino nitrile (**13**) produced the 6-ethoxy-7-methoxyisoquinolinone (**28**), the 6-hydroxy-7-methoxyisoquinolinone (**29**), and the 6-ethoxy-7-hydroxyisoquinolinone (**30**). The relative proportion of phenolic products increased with rise in temperature of cyclisation.

The profile of *O*-dealkylation that occurred during cyclisation differed from that of the 6,7-dialkoxyisoquinolinones under identical conditions, and a case is argued that cyclisation proceeds no further than the spirocyclic intermediate in concentrated acid. Rearrangement to the iminium ion and conversion of the latter into the isoquinolinone *via* a Pictet-Spengler reaction therefore occur during subsequent stages in dilute aqueous conditions.

Previous publications in this series have described the sulphuric acid treatment of benzylaminoacetonitriles and offer evidence that two mechanisms of cyclisation may operate. The alternative mechanisms involve a classical cyclisation *via* electrophilic attack *para* to a 3-alkoxy substituent (Scheme 1);

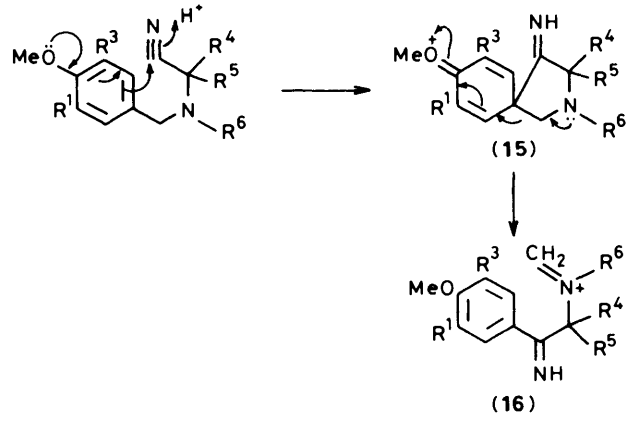


Scheme 1.

and secondly, a non-classical cyclisation in which a 4-alkoxy substituent participates in the formation of a spiro intermediate (**15**) (Scheme 2) which in turn rearranges to an iminium ion (**16**) (Scheme 2).

The cyclisation of benzylamino nitriles having a 3-alkoxy substituent only, necessarily follows the path of classical cyclisation. Thus the nitriles (**1**) and (**2**) (Table 1) are reported[2,3] to give the corresponding 7-methoxyisoquinolinones (**14**), although yields are relatively low. The analogous nitrile (**3**) failed to cyclise and gave an uncharacterised sulphonic acid.[2]

Where the benzylamino ring bears a 4-alkoxy substituent



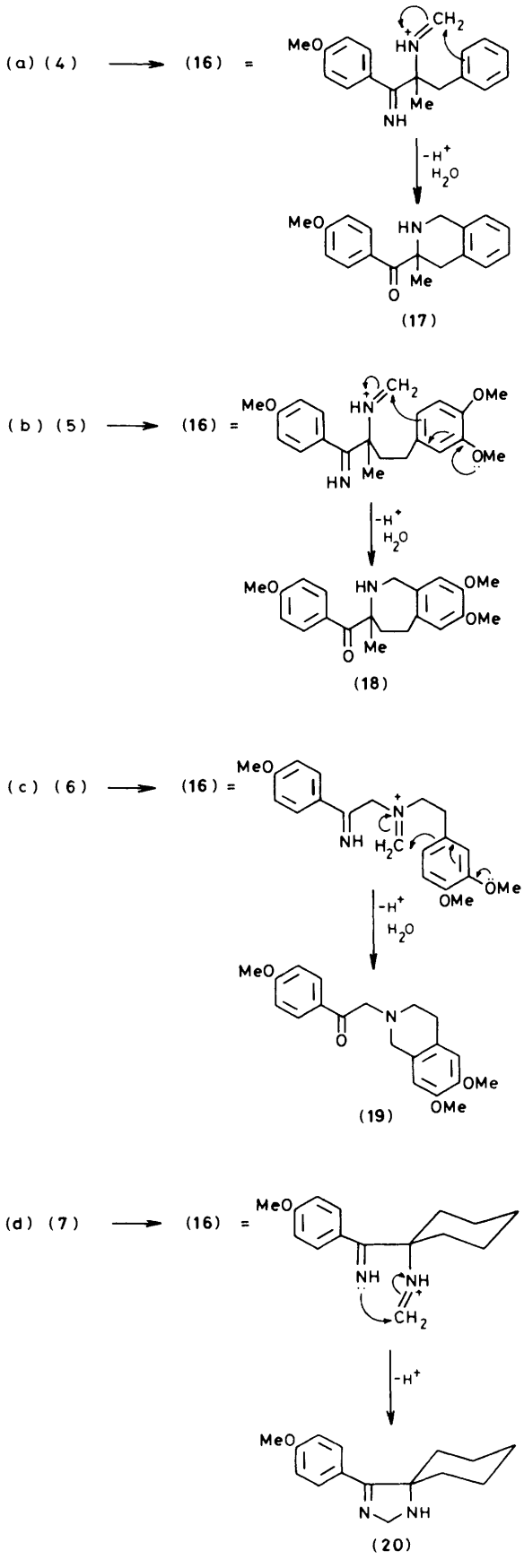
Scheme 2.

only (**4**)—(**7**) (Table 1), the spiro intermediate (**15**) is produced. The fate of the subsequent iminium ion (**16**) is dependent upon the nature of the substituents on the aminonitrile moiety. Thus the presence of a benzyl substituent (**4**) permits the iminium ion to undergo Pictet-Spengler cyclisation yielding the 3-benzoyl-1,2,3,4-tetrahydroisoquinoline[4] (**17**) (Scheme 3a).

The presence of a similarly disposed 3,4-dimethoxyphenethyl substituent (**5**) results in formation of the 2-benzazepine[2] (**18**) (Scheme 3b). An *N*-phenethyl substituent also allows for Pictet-Spengler cyclisation of the iminium ion. For example, the amino nitrile (**6**) gave the *N*-phenacyltetrahydroisoquinoline[2] (**19**) (Scheme 3c).

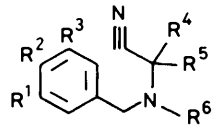
In the absence of suitably orientated nucleophilic sites, *e.g.* (**7**), the intermediate iminium ion underwent attack by the imino group to produce a 3-imidazoline[5] (20) (Scheme 3d).

Where the benzylaminonitrile possesses 3,4-dialkoxy substitution, the course of cyclisation is more complicated since either (or both) mechanisms can occur. The 3,4,5-trimethoxybenzyl-



Scheme 3.

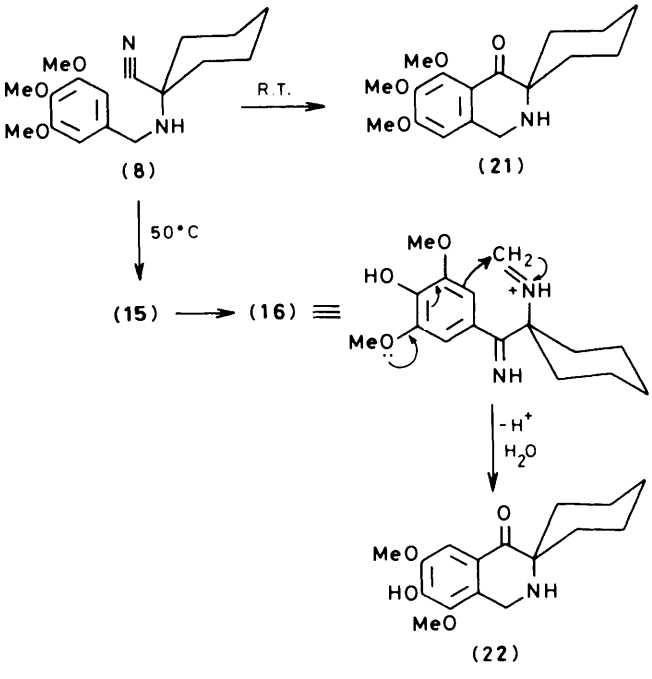
Table 1. Benzylamino nitriles



	R^1	R^2	R^3	R^4	R^5	R^6
(1)	MeO	H	H	H	H	H
(2)	MeO	H	H	H	Ph	Me
(3)	MeO	H	H	$CH_2(CH_2)_3CH_2$		H
(4)	H	MeO	H	Me	CH_2Ph	H
(5)	H	MeO	H	Me	DMP†	H
(6)	H	MeO	H	H	H	DMP†
(7)	H	MeO	H	$CH_2(CH_2)_3CH_2$		H
(8)	MeO	MeO	MeO	$CH_2(CH_2)_3CH_2$		H
(9)	MeO	MeO	H	H	CH_2Ph	H
(10)	MeO	MeO	H	Me	CH_2Ph	H
(11)	MeO	MeO	H	$CH_2(CH_2)_3CH_2$		H
(12)	MeO	EtO	H	$CH_2(CH_2)_3CH_2$		H
(13)	EtO	MeO	H	$CH_2(CH_2)_3CH_2$		H

[a] † DMP = 3,4-dimethoxyphenethyl.

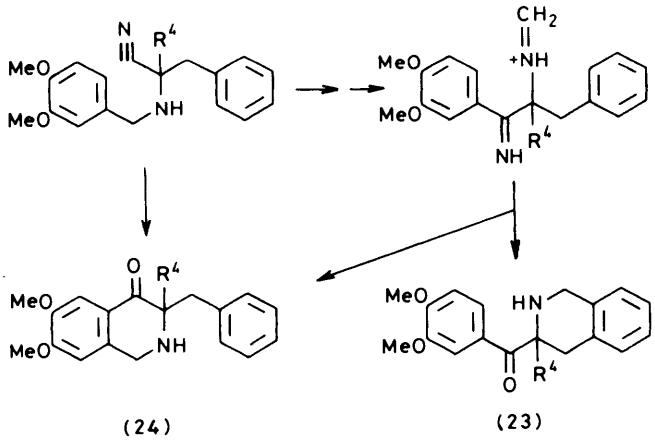
amino nitrile (**8**) produced the 5,6,7-trimethoxyisoquinolinone (**21**) when cyclisation was effected at room temperature, and is clearly the result of a classical mechanism (Scheme 1). At 50 °C however, the main product isolated was the 7-hydroxy-6,8-dimethoxyisoquinolinone (**22**) which would arise *via* the spiro intermediate (**15**) and the iminium ion (**16**). The increased nucleophilic character of the aromatic ring conferred by the suitably orientated 3-methoxy group, resulted in formation of the isoquinolinone (**22**) (Scheme 4).[2]



Scheme 4.

A 3,4-dimethoxy analogue (**9**) of the benzyl substituted nitrile (**4**) is reported[4] to yield an equimolecular mixture of the 3-(3,4-dimethoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (**23**; R^4 = H) and the 3-benzyl-6,7-dimethoxyisoquinolinone (**24**; R^4 = H) on treatment with sulphuric acid (Scheme 5).

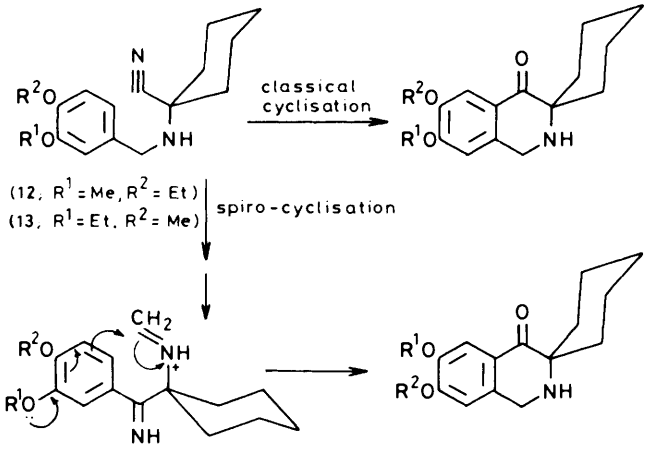
Here, production of the former was rationalised on the basis



Scheme 5.

of the spiro- and iminium ion-intermediates (*cf.* Scheme 3a). The isoquinolinone however, could be produced by a classical cyclisation (Scheme 1) or by a Pictet-Spengler cyclisation of the iminium ion involving the dimethoxy substituted ring (Scheme 5). Curiously, the close homologue (**10**) gave only the 3-(3,4-dimethoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (**23**; R^4 = Me). The origin of the isoquinolinone in the cyclisation of benzyl substituted nitriles is the subject of a paper in preparation.[6]

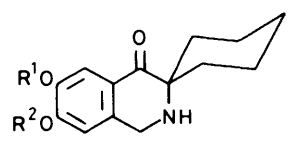
In the present work we have addressed our attention to the cyclisation of simple 3,4-dialkoxybenzylaminonitriles of the type exemplified by (**11**). Obviously, with two identical alkoxy substituents, the 6,7-dialkoxy isoquinolinone produced will be the same whether cyclisation proceeds *via* the classical route or by means of the spiro intermediate. In the case of the ethoxymethoxybenzylamino nitrile (**12**) and its reverse isomer (**13**), the orientation of 6,7-disubstitution in the resulting isoquinolinone will directly reflect the mode of cyclisation (Scheme 6).



Scheme 6.

The nitriles (**11**)—(**13**) were treated with concentrated sulphuric acid at −10 °C, room temperature, and 50 °C for 4 h. The reaction mixture was poured into iced water and stirred for a further 45 min. After basification with 20% (w/v) aqueous sodium hydroxide, extraction with chloroform gave the crude dialkoxyisoquinolinone. Reacidification followed by basification with potassium hydrogen carbonate and extraction with chloroform gave the crude phenolic isoquinolinone. Routine t.l.c. analysis was followed by fractional crystallisation or chromatographic techniques in order to separate mixtures, as indicated in the Experimental section. Results are summarised in Table 2.

Table 2. Isoquinolinones from cyclisation of the nitriles (**11**)—(**13**)

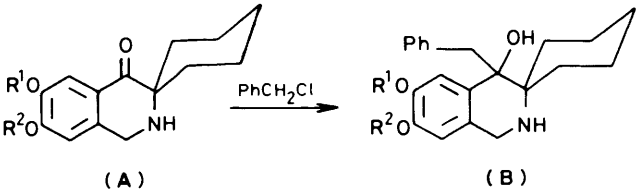


(**25**) R^1 = R^2 = Me
(**26**) R^1 = Me, R^2 = H
(**27**) R^1 = Me, R^2 = Et
(**28**) R^1 = Et, R^2 = Me
(**29**) R^1 = H, R^2 = Me
(**30**) R^1 = Et, R^2 = H

		Yield (%)		
		−10 °C	R.t.	50 °C
(**11**) →	(**25**)	65	60	15
	(**26**)	10	21	65
(**12**)* →	(**27**)	72	62	2.6
	(**26**)	15	22	65
(**13**) →	(**28**)	58	20	8
	(**29**)	0	25	48
	(**30**)	32	35	0

* The amino nitrile (**12**) also gave a minor phenolic product (**31**) in yields of 3.8, 3.9, and 2.2%, for cyclisation at −10 °C, room temp; and 50 °C respectively.

Table 3. Shielding coefficients reflecting introduction of a 4-benzyl substituent (abstracted from data in Tables 6 and 8)



(**A**) (**B**)

Isoquinolinone (A)	4-Benzyl derivative (B)	δ_H(A) − δ_H(B) (p.p.m.) 5-H	OMe	OCH_2Me
(**25**)	(**32**)*	0.22	0.06	—
(**25**)	(**33**)	1.28	0.16, 0.62	—
(**26**)†	(**34**)†	1.40	0.65	—
(**27**)	(**35**)	1.48	0.54	0.03
(**28**)	(**36**)	1.45	0.14	0.67
(**29**)†	(**37**)†	1.09	0.10	—
(**30**)†	(**38**)†	1.31	—	0.79

* 4-Ethyl-4-hydroxy derivative. † Me_2SO as solvent.

Orientation of the 6- *and* 7-*Substituents.*—^{1}H N.m.r. data. The orientation of alkoxy substituents in the isoquinolinones (**27**) and (**28**) could not be determined directly, their spectroscopic data being virtually identical. The method developed by Waigh [7] was adopted, this permitting assignments to be made with complete unambiguity. The procedure involved reaction of the isoquinolinone with benzylmagnesium chloride to give the corresponding 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines. In the presence of substituents at C-3, the benzyl group is forced into a conformation in which its aromatic ring exerts a strong shielding influence on 5-H and the 6-alkoxy group. The shielding effects noted by Waigh on converting a 6,7-dimethoxy-3,3-dimethylisoquinolinone into the 4-benzyl derivative were of the following magnitude: 1.4 p.p.m. (5-H), 0.51 p.p.m. (6-OMe), and 0.06 p.p.m. (7-OMe).

Table 3 shows the shielding effect upon the 5-H and alkoxy substituents on conversion of the isoquinolinones (**25**)—(**30**) into the corresponding 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**33**)—(**38**). The 4-ethyl-4-hydroxy analogue (**32**)

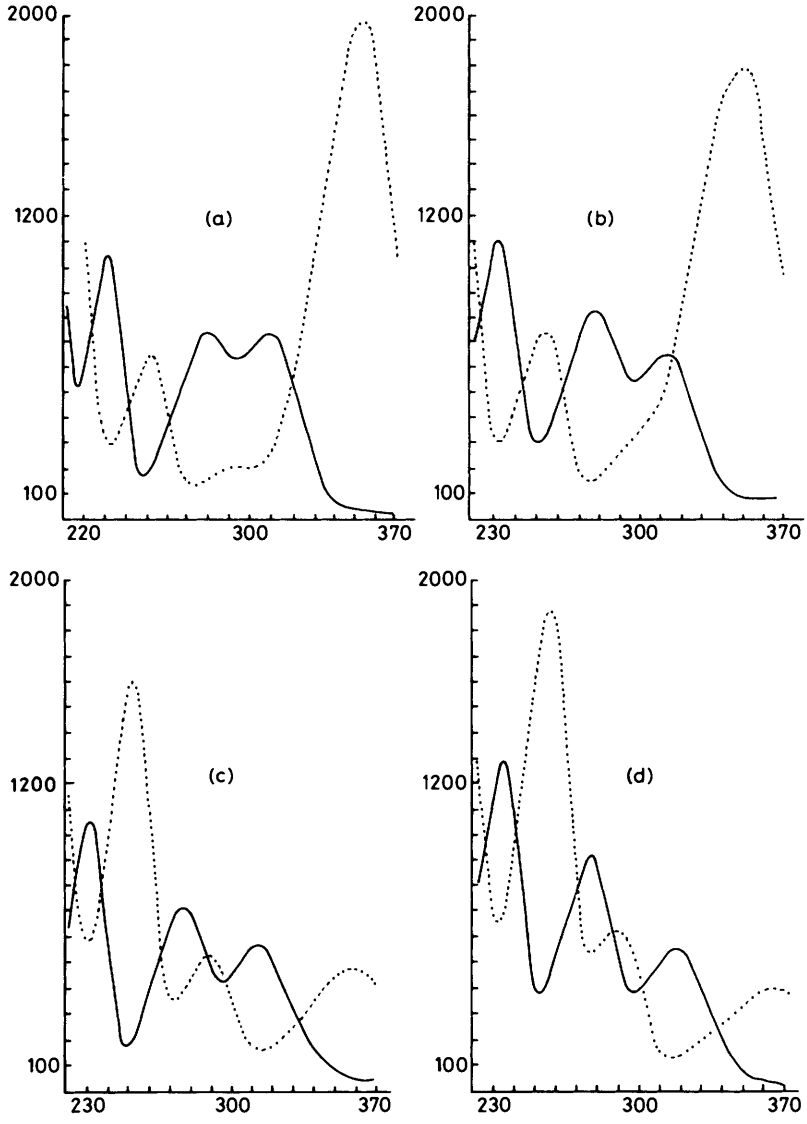


Figure. U.v. spectra ($\lambda_{max.}$/nm *vs.* $E^{1\%}_{1cm}$) taken in 95% EtOH for neutral (——) and 0.01M-KOH (· · ·) solutions: (*a*) vanillin (0.5 mg/100 ml), (*b*) compound (**26**) (1 mg/100 ml); (*c*) isovanillin (0.5 mg/100 ml), and (*d*) compound (**29**) (1 mg/100 ml).

was prepared to assess the effect of the loss of the anisotropic deshielding influence of the 4-carbonyl group.

In the ^{1}H n.m.r. spectra of all the 6,7-disubstituted isoquinolinones the two singlets for the 5-H and 8-H differ in appearance. The signal for the latter shows slight broadening, probably due to long-range coupling with the benzylic methylene protons. In the 4-benzyl derivatives, the sharper signal for 5-H appears at even higher field than the 8-H signal, indicating the powerful shielding effect of the benzyl substituent.

The data show a clear differentiation between the 6-OMe and 7-OMe in the 4-benzyl derivative (**33**) of the 6,7-dimethoxyisoquinolinone (**25**). The data for the derivatives (**34**) to (**38**) clearly establish the orientation of 6,7-disubstitution in the isoquinolinones (**26**) to (**30**).

Thus cyclisation of the 3,4-dimethoxybenzylaminonitrile (**11**) gave a mixture of the 6,7-dimethoxyisoquinolinone (**25**) and a phenolic isoquinolinone, the proportion of the latter increasing with rise in temperature.

The ^{1}H n.m.r. data show that this phenolic product is the 7-hydroxy-6-methoxyisoquinolinone (**26**) which could arise by either of the proposed mechanisms of cyclisation. The extensive *O*-demethylation experienced on cyclisation at 50 °C is not in accord with our previously published work,[8] which quotes yields of 80% for the dialkoxyisoquinolinone (**25**) in cyclisation at room temperature (r.t.) and 50 °C. The reason for this discrepancy probably lies in the quality of the sulphuric acid used. We have found that, provided acid is used that has a minimum content of 98% (w/w) H_2SO_4, dealkylation occurs to a significant extent at temperatures above ambient.

The cyclisation of the 4-ethoxy-3-methoxybenzylamino nitrile (**12**) follows a similar pattern to that of the dimethoxy analogue, the major product at −10 °C and room temperature being a dialkoxyisoquinolinone. The pertinent ^{1}H n.m.r. data (Table 3) confirm that this is the 7-ethoxy-6-methoxyisoquinolinone (**27**). The phenolic product which predominated at 50 °C, is the 7-hydroxy-6-methoxyisoquinolinone (**26**), and was separated by preparative t.l.c. from a minor phenolic product, the spectroscopic data for which are consistent with the 7-hydroxy-8-methoxyisoquinolinone (**31**) (Table 6). This minor product is evidently the result of an atypical Pictet-Spengler cyclisation of the iminium ion *ortho*, rather than *para*, to the alkoxy substituent.

Cyclisations of the isomeric 3-ethoxy-4-methoxybenzylamino

nitrile (**13**) followed a rather more complex course (Table 2). At −10 °C the dialkoxyisoquinolinone (**28**) was the major product. Conversion of the isoquinolinone into the 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**36**) resulted in a marked shielding of the ethoxy group (Table 3), which therefore locates this group at C-6. A single phenolic product was also produced at −10 °C, the data showing that this is the 6-ethoxy-7-hydroxyisoquinolinone (**30**). At 50 °C, cyclisation produced little of the dialkoxyisoquinolinone (**28**), the major product being the 6-hydroxy-7-methoxyisoquinolinone (**29**). At the intermediate temperature the products consisted of a mixture of the dialkoxyisoquinolinone (**28**) and both phenolic isoquinolinones (**29**) and (**30**). The significance of the ratio of dialkoxyisoquinolinone to phenolic products, and the more complex behaviour of the nitrile (**13**) are discussed later.

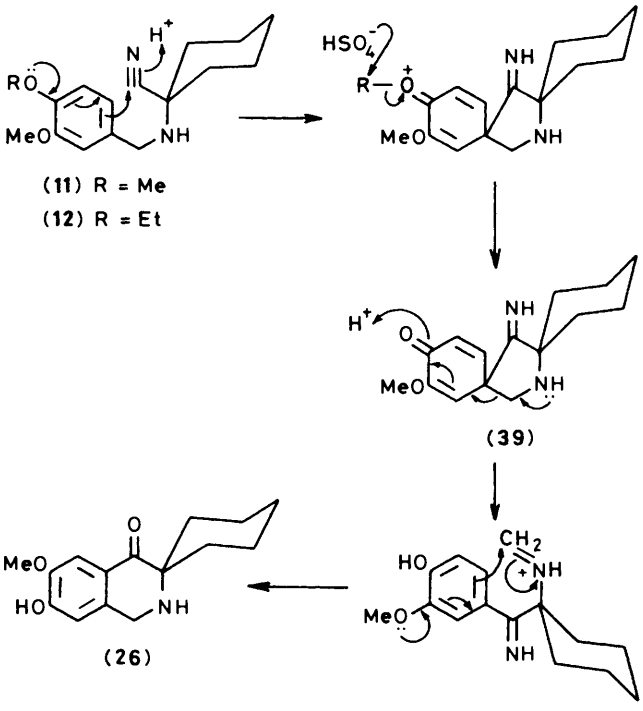
The orientation of the phenolic hydroxy group can be determined by a more direct method involving comparison of the ^{1}H n.m.r. spectra of the isoquinolinones (in Me_2SO) before and after addition of NaOD in D_2O. Conversion of a phenol into its anion results in an increased shielding of the aromatic protons, which is greatest at the position *ortho* to the phenoxide ion and least at the *meta* position. This technique has been used routinely in natural product chemistry as an aid to the orientation of phenolic groups.[9] The ^{1}H n.m.r. data for the phenolic isoquinolinones in Table 6 confirm the structures assigned. In the case of the 6,7-disubstituted isoquinolinones (**26**) and (**30**) the greater shielding effect is reserved for 8-H, showing that the hydroxy group is located at C-7. With the isoquinolinone (**29**) the shift experienced by the aromatic protons is less marked, but indicates the presence of a 6-OH group. The minor phenolic product (**31**), which is a 7,8-disubstituted isoquinolinone, possesses a 7-OH group.

U.v. Spectroscopy.—The u.v. absorption spectra of hydroxybenzaldehydes and hydroxyacetophenones show significant changes on conversion of the undissociated phenol into the phenoxide ion.[10] Lemon[11] has reported the effect of alkali on the u.v. spectra of a number of phenolic aldehydes and ketones and has shown that there is a bathochromic shift of the absorption bands in alkaline conditions. The intensity of absorption of the long-wave bands is increased when the phenolic hydroxy group and the carbonyl function are conjugated, the effects being most marked when the substitutents bear the *para* relationship. Grethe and co-workers[12] have used this principle to determine the orientation of substitution of hydroxy(methoxy)isoquinolinones produced by the selective *O*-demethylation of 6,7- and 7,8-dimethoxyisoquinolinones.

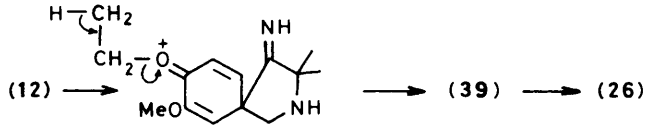
In the present work, u.v. spectra of phenolic isoquinolinones were recorded in 95% ethanol and in 0.01M-KOH in 95% ethanol (Table 6). The Figure shows the u.v. spectra of the isomeric phenolic isoquinolinones (**26**) and (**29**), with those of 4-hydroxy-3-methoxybenzaldehyde (vanillin) and isovanillin for reference purposes. The data are in agreement with those quoted by Grethe for 7-hydroxy and 6-hydroxyisoquinolin-4-ones, and clearly confirm the orientations established earlier by ^{1}H n.m.r. spectroscopy.

O-Dealkylation.—We believe that dealkylation most likely occurs in the concentrated sulphuric acid solution, with loss of the alkyl group from that alkoxy substituent which participates in formation of the spiro-intermediate. Thus the dimethoxybenzylamino nitrile (**11**) and the 4-ethoxy-3-methoxy analogue (**12**) give the dienone (**39**) (Scheme 7) which rearranges to the 7-hydroxy-6-methoxyisoquinolinone (**26**). The de-ethylation which occurs on cyclisation of the nitrile (**12**) more probably proceeds by elimination of ethene at the spiro-intermediate stage (Scheme 8).

Both processes occur very readily at 50 °C, giving the phenol



Scheme 7.



Scheme 8.

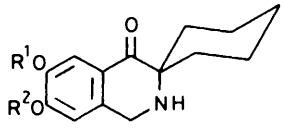
(**26**) in high yield in each instance. The dealkylation occurring during the cyclisation of the 3-ethoxy-4-methoxybenzylamino nitrile (**13**) follows a more complicated course. At −10 °C, the usual dealkylation of the spiro-intermediate occurs to a significant extent giving 32% of the 6-ethoxy-7-hydroxyisoquinolinone (**30**) and 58% of the 6-ethoxy-7-methoxyisoquinolinone (**28**). It is difficult to find a convincing explanation for the greater yield of phenol obtained here, compared with that obtained from nitriles (**11**) and (**12**) under the same conditions.

At room temperature, dealkylation of the nitrile (**13**) during cyclisation is more extensive than for the reverse isomer. The demethylated product (**30**) was obtained (35% yield) presumably as described above. However, the 6-hydroxy-7-methoxyisoquinolinone (**29**) is also produced (25% yield), and in cyclisations conducted at 50 °C, the latter is the sole phenolic isoquinolinone isolated.

Before attempting to rationalise these observations, it is helpful to consider the behaviour of the 6,7-dialkoxyisoquinolinones (**25**), (**27**), and (**28**) in concentrated sulphuric acid under conditions identical with those used for cyclisation of the nitriles (Table 4).

The isoquinolinones (**25**) and (**28**) underwent no dealkylation at −10 °C, while at 50 °C dealkylation at C-6 was extensive giving the 6-hydroxy-7-methoxyisoquinolinone (**29**). This is in accord with the observations of Brossi and co-workers[13] who studied the selective demethylation of 3,4-dimethoxy substituted aromatic aldehydes and ketones using concentrated sulphuric acid at 65 °C. Here the methoxy substituent that is not conjugated with the carbonyl function, and which is therefore more readily protonated, undergoes selective demethylation.

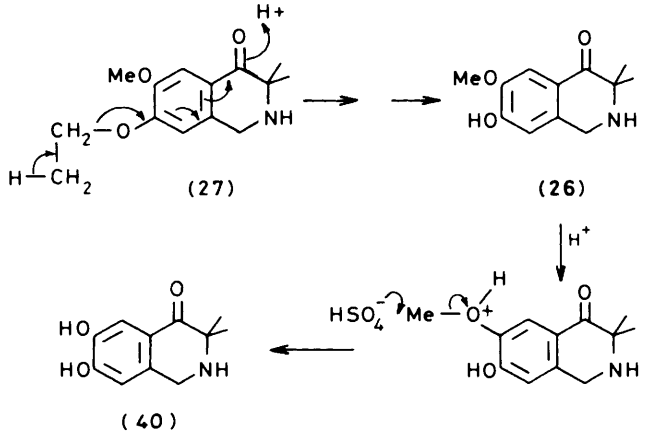
Table 4. *O*-Dealkylation of 6,7-dialkoxy-1,2-dihydroisoquinolin-4-(3*H*)-ones (**25**), (**27**), and (**28**)



Dialkoxyisoquinolinone	Phenolic product	Yield (%)			Total recovery (%) of phenolic + parent isoquinolinones		
		−10 °C	R.t.	50 °C	−10 °C	R.t.	50 °C
(**25**; $R^1 = R^2 =$ Me)	(**29**; R^1 = H, R^2 = Me)	0	20	78	78	81	81
(**27**; R^1 = Me, R^2 = Et)	(**26**, R^1 = Me, R^2 = H)	3	29	26	85	68	28
(**28**; R^1 = Et, R^2 = Me)	(**29**)	0	43	85	76	70	85

The same behaviour was observed by Grethe[12] on the treatment of 6,7- and 7,8-dimethoxy-1,2-dihydroisoquinolin-4(3*H*)-ones with 48% aqueous HBr–glacial acetic acid (1:1) at 115 °C, leading to selective dealkylation at C-6 and C-8 respectively. Our observation of the significantly greater yield of the phenol (**29**) on treatment of the 6-ethoxy-7-methoxyisoquinolinone (**28**) with sulphuric acid is presumably a reflection of the alternative process of dealkylation where an ethoxy group is involved (*i.e.* loss of ethene), which is related to temperature.

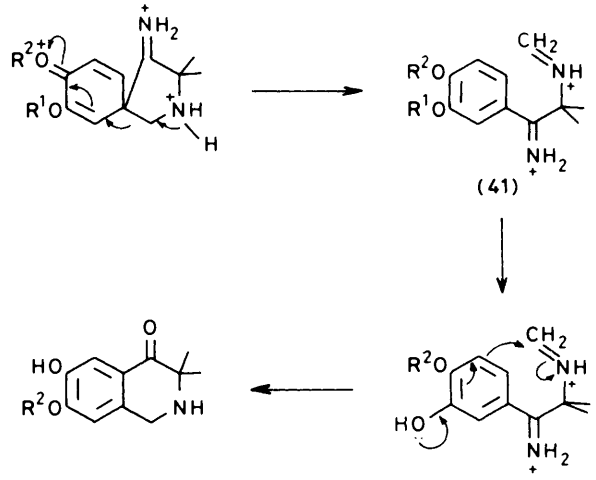
The 7-ethoxy-6-methoxyisoquinolinone (**27**) similarly underwent insignificant dealkylation at −10 °C; at room temperature and at 50 °C the 7-hydroxy-6-methoxyisoquinolinone (**26**) was the sole phenolic product. Of particular significance is the low yield (26%) of this product at 50 °C, which reflects the lability of the ethoxy group even when 'protected' from protonation by the conjugated carbonyl function. Indeed, such conjugation could assist elimination of ethene and, with concomitant *O*-demethylation at C-6, the major product at 50 °C may well be the pyrocatechol (**40**) which presumably is sufficiently polar to remain in the aqueous phase during subsequent solvent extraction (Scheme 9).



Scheme 9.

The most important observation is the ease with which dealkylation of the isoquinolinones at C-6 occurs. This implies that cyclisation of the amino nitriles does *not* proceed to the isoquinolinone stage in concentrated sulphuric acid, since it would then be impossible to rationalise the formation of the 7-hydroxy-6-methoxyisoquinolinone (**26**) in 65% yield in cyclisations of the nitriles (**11**) and (**12**) at 50 °C.

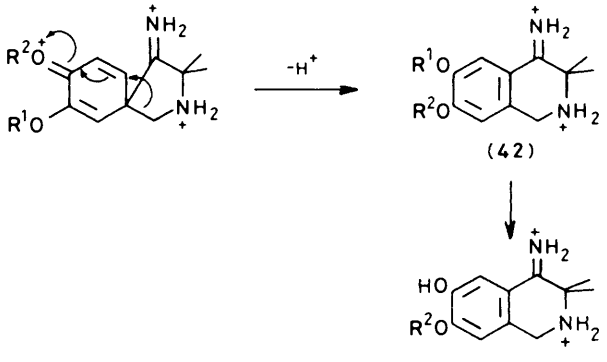
The observations of Bruderer and Brossi[14] regarding the selective demethylation of 6,7-dimethoxy-3,4-dihydroisoquinolines are also pertinent. Under a variety of acid conditions (including concentrated sulphuric acid), the unconjugated alkoxy group at C-7 underwent demethylation. By analogy, this suggests that in the nitrile cyclisations the iminium ion (**41**) is not produced in concentrated acid conditions (Scheme 10),



Scheme 10.

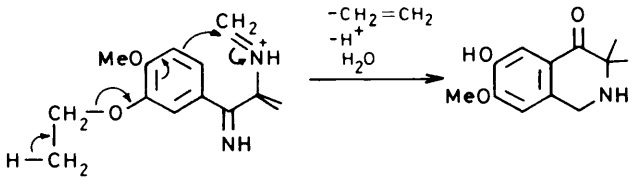
since the protonated imino group would protect the conjugated alkoxy substituent from dealkylation. The resulting selective dealkylation of the unprotected alkoxy group would result in formation of a 6-hydroxy-7-alkoxyisoquinolinone, which is not observed in the cyclisation of the amino nitriles (**11**) and (**12**).

By the same argument, the direct formation of the 4-iminoisoquinoline (**42**) in concentrated acid by means of a 1,2-migration appears unlikely (Scheme 11).



Scheme 11.

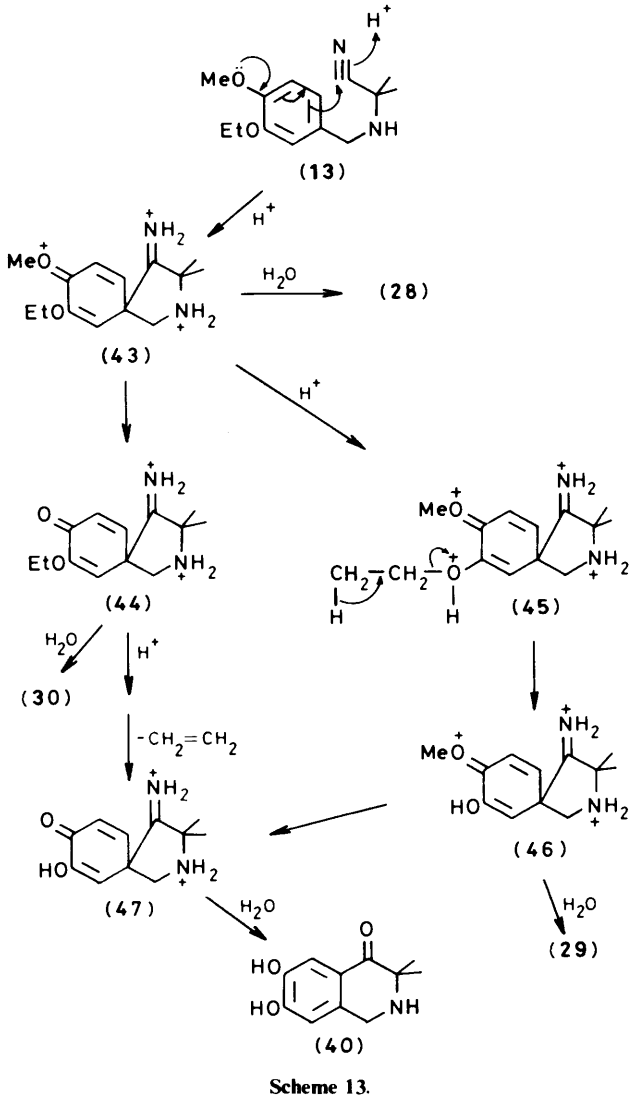
Returning to the cyclisation of the 3-ethoxy-4-methoxybenzylamino nitrile (**13**), it is possible that the de-ethylation that is observed could occur during the subsequent Pictet-Spengler cyclisation (Scheme 12). However, reference to Table 2



Scheme 12.

clearly indicates a relationship between temperature of the concentrated sulphuric acid and dealkylation. Having argued that formation of the iminium ion is unlikely to occur in the concentrated acid and is delayed until the subsequent stages of dilution (where the same temperature conditions apply for all cyclisations), any loss of ethene at this stage is a constant contribution irrespective of the temperature of cyclisation in sulphuric acid.

On the evidence available, we consider that the cyclisation of this nitrile (**13**) and the concomitant dealkylations occur in the following manner (Scheme 13). The initially formed spiro



Scheme 13.

intermediate (**43**) can undergo demethylation in the usual manner to yield the ethoxy dienone (**44**). Alternatively, the protonated form (**45**) loses ethene to produce the hydroxy methoxy spiro intermediate (**46**). Loss of ethene from the protonated ethoxy-dienone (**44**) or demethylation of the spiro intermediate (**46**) yields the hydroxy dienone (**47**). The intermediates (**43**), (**44**), (**46**), and (**47**) undergo rearrangement to their corresponding iminium ions after dilution of the concentrated acid, which is followed by Pictet-Spengler cyclisation to yield the 6-ethoxy-7-methoxyisoquinolinone (**28**), the 6-ethoxy-7-hydroxyisoquinolinone (**30**), the 6-hydroxy-7-methoxyisoquinolinone (**29**), and the 6,7-dihydroxyisoquinolinone (**40**) respectively. The relative yields of products are dependent on the reaction rates of the dealkylation processes involved at the different temperatures of cyclisation. The 6,7-dihydroxyisoquinolinone (**40**) was not isolated probably due to its high polarity, but its formation is implied in the relatively low overall recovery of products in the cyclisation of the nitrile (**13**) at 50 °C.

In this study of the cyclisation of the isomeric ethoxymethoxybenzylamino nitriles, the structures of all products isolated were consistent with the involvement of a spirocyclic intermediate. We believe that in those nitrile cyclisations where a choice exists between classical cyclisation and formation of a spiro intermediate, the latter should be regarded as the normal mechanism. The behaviour of the 3,4,5-trimethoxybenzylamino nitrile (**8**) at room temperature is an anomaly. The classical cyclisation observed in this instance is probably due to the fact that the central 4-methoxy group lacks co-planarity with the ring[15] due to steric crowding, and hence cannot participate in formation of the spiro-intermediate. At 50 °C, when the spiro-intermediate is produced, presumably coplanarity is achieved at the higher temperature or, more likely,[16] demethylation rapidly occurs and the species undergoing cyclisation is the 4-hydroxy-3,5-dimethoxybenzylamino nitrile.

The great majority of isoquinoline syntheses may be placed into one of two general categories: the cyclisation of a benzylamine derivative (*e.g.* the Pomeranz-Fritsch synthesis and its numerous modifications), or the cyclisation of a 2-phenylethylamine derivative (the Pictet-Spengler and Bischler-Napieralski routes). Paradoxically, the nitrile route falls into both categories, commencing as the former but ultimately achieving its objective *via* the latter.

Experimental

M.p.s were taken on a Gallenkamp melting point apparatus and are corrected. U.v. absorption spectra were recorded on a Perkin-Elmer 124 double beam spectrophotometer, and i.r. spectra recorded on a Unicam S.P. 200 spectrophotometer as potassium bromide discs unless otherwise stated. ^{1}H N.m.r. spectra were recorded on a JEOL PS 100 MHz instrument with $CDCl_3$ as solvent and $SiMe_4$ as internal standard unless otherwise specified. Electron impact mass spectra were obtained using an AEI MS12 mass spectrometer.

1-(4-*Ethoxy*-3-*methoxybenzylamino*)*cyclohexanecarbonitrile* (**12**).—4-Ethoxy-3-methoxybenzylamine (27.15 g, 0.15 mol) was suspended in water (100 ml) and hydrochloric acid (2M) added with stirring until dissolution was complete and the solution just acidic to litmus. Cyclohexanone (14.7 g, 0.15 mol) was added, followed by 95% ethanol (100 ml). A solution of potassium cyanide (15 g, 0.23 mol) in water (100 ml) was added to the stirred solution over a period of 30 min and the reaction mixture was then stirred overnight. The crude product was filtered, washed thoroughly with water, dried, and recrystallised from light petroleum (b.p. 60—80 °C) to give the amino nitrile (**12**) (38 g, 88%), m.p. 82 °C (Found: C, 70.5; H, 8.4; N, 9.6. $C_{17}H_{24}N_2O_2$ requires C, 70.8; H, 8.3; N, 9.7%); $\nu_{max.}$ 3 450 (NH)

Table 5. Analytical data for the 1,2-dihydroisoquinolin-4(3*H*)-ones (**25**)—(**31**).

Compd. (formula)	Solvent*	M.p. (°C)	Found (%) (Required) C	H	N
(**25**)	a:b	147—148			
($C_{16}H_{21}NO_3$)	(3:1)	(lit.[8], 147)			
(**26**)	a:b	161—162	68.8	7.45	5.3
($C_{15}H_{19}NO_3$)	(1:2)		(68.95)	(7.3)	(5.35)
(**27**)	a:b	114—115	71.0	8.2	5.1
($C_{17}H_{23}NO_3$)	(1:1)		(70.6)	(7.95)	(4.85)
(**28**)	a	164—165	70.45	8.1	5.1
($C_{17}H_{23}NO_3$)			(70.6)	(7.95)	(4.85)
(**29**)	a:b	208—209	69.05	7.4	5.3
($C_{15}H_{19}NO_3$)	(1:1)		(68.95)	(7.3)	(5.35)
(**30**)	a:b	152—153	70.2	7.85	(5.4)
($C_{16}H_{21}NO_3$)	(3:1)		(69.8)	(7.6)	(5.1)
(**31**)	a:b	202—203	68.85	7.35	5.75
($C_{15}H_{19}NO_3$)	(1:1)		(68.95)	(7.3)	(5.35)

* a = light petroleum (b.p. 60—80 °C), b = ethyl acetate

and 2 160 (CN); δ_H 6.8—7.0 (3 H, m, ArH), 4.1 (2 H, q, *J* 8 Hz, OC*H*Me), 3.82 (3 H, s, OMe), 3.8 (2 H, s, $ArCH_2$), 1.41 (3 H, t, *J* 8 Hz, OCH_2CH_3), and 1.5—1.9 (11 H*, m, C_5H_{10} + NH; reduced to 10 H after deuteriation); *m/z* 288 (M^+, 1%), 261 (21), 165 (100), 137 (76), and 107 (3).

1-(3-*Ethoxy*-4-*methoxybenzylamino*)*cyclohexanecarbonitrile* (**13**).—From 3-ethoxy-4-methoxybenzylamine, the isomeric amino nitrile (**13**) was obtained by an identical procedure to that described above (37.2 g, 86%), m.p. 83 °C (Found: C, 70.85; H, 8.35; N, 9.75. $C_{17}H_{24}N_2O_2$ requires C, 70.8; H, 8.3; N, 9.7%); $\nu_{max.}$ 3 350 (NH) and 2 160 (CN); δ_H 6.84—7.0 (3 H, m, ArH), 4.1 (2 H, q, *J* 8 Hz, OCH_2Me), 3.82 (3 H, s, OMe), 3.8 (2 H, s, $ArCH_2$), 1.41 (3 H, t, *J* 8 Hz, OCH_2CH_3), and 1.5—2.0 (11 H, m, C_5H_{10} + NH; reduced to 10 H after deuteriation); *m/z* 288 (M^+, 1%), 261 (11), 165 (100), 137 (14), and 107 (5).

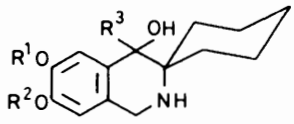
1,2-*Dihydroisoquinolin*-4(3H)-*ones*.—The finely powdered benzylaminocyclohexanecarbonitrile (**13**) (3 g) was added carefully to concentrated sulphuric acid (98%, w/w; 30 ml) at 0 °C with continuous stirring. When dissolution was complete, the temperature was raised to room temperature or 50 °C and

Table 6. Spectroscopic data for 1,2-dihydroisoquinolin-4(3*H*)-ones (**25**)—(**31**)

	$\lambda_{max.}$/nm (log ε) (EtOH)	(0.01M-KOH in EtOH)	$\nu_{max.}$ NH	CO	*m/z*	δ_H
(**25**)[8]			3 380	1 660	275 (M^+, 52%), 247 (18), 203 (13), 178 (8), 151 (100)	7.28 (1 H, s, 5-H), 6.56 (1 H, s, 8-H), 4.03 (2 H, s, $ArCH_2$), 3.92 (6 H, s, 2 × OCH_3), 2.01 (1 H, s, NH), 1.8—1.2 (10 H, m, C_5H_{10}).
(**26**)	314 (3.89) 278 (3.97) 232 (4.15)	351 (4.37) 298 (3.61) 255 (3.95)	3 380 (+OH)	1 665	261 (M^+, 76%), 233 (17), 218 (9), 190 (21), 165 (15), 164 (39), 137 (100), 135 (25)	(Me_2SO) 7.35 (7.08*, 1 H, s 5-H), 6.6 (6.0,* 1 H, s, 8-H), 3.84 (2 H, s, $ArCH_2$), 3.8 (3 H, s, OCH_3), 3.0—1.0 (12 H, m, C_5H_{10} + NH + OH)
(**27**)			3 400	1 660	289 (M^+, 41%), 261 (8), 218 (11), 192 (36), 166 (11), 165 (100), 164 (14) 137 (10)	7.48 (1 H, s, 5-H), 6.55 (1 H, s, 8-H), 4.13 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.0 (2 H, s, $ArCH_2$), 3.84 (3 H, s, OCH_3), 1.97 (1 H, s, NH), 1.8—1.5 (10 H, m, C_5H_{10}) 1.45 (3 H, t, *J* 7 Hz, OCH_2CH_3)
(**28**)			3 350	1 645	289 (M^+, 49%), 261 (11), 218 (20), 192 (40), 166 (10), 165 (100), 164 (10), 137 (58)	7.5 (1 H, s, 5-H), 6.54 (1 H, s, 8-H), 4.12 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.0 (2 H, s, $ArCH_2$), 3.89 (3 H, s, OCH_3), 1.93 (1 H, s, NH), 1.84—1.50 (10 H, m, C_5H_{10}), 1.49 (3 H, t, *J* 7 Hz, OCH_2CH_3)
(**29**)	319 (3.75) 276 (4.06) 232 (4.25)	367 (3.61) 290 (3.90) 255 (4.39)	3 370 (+OH)	1 650	261 (M^+, 75%), 233 (17), 218 (8), 190 (20), 164 (37), 137 (100), 136 (21)	(Me_2SO) 9.2 (1 H, s, OH), 7.24 (6.78*, 1 H, s, 5-H), 6.76 (6.45*, 1 H, s, 8-H), 3.87 (2 H, s, $ArCH_2$), 3.8 (3 H, s, OCH_3), 1.56 (11 H, m, C_5H_{10} + NH)
(**30**)	313 (3.93) 279 (4.04) 232 (4.19)	348 (4.36) 295 (3.61) 252 (3.99)	3 360 (+OH)	1 650	275 (M^+, 65%), 247 (18), 246 (8), 218 (13), 178 (37), 151 (100), 123 (56), 122 (11)	(Me_2SO) 7.25 (7.08*, 1 H, s, 5-H), 6.65 (6.0*, 1 H, s, 8-H), 4.09 (2 H, q, *J* 7 Hz, OCH_2CH_3), 3.8 (2 H, s, $ArCH_2$), 1.6 (12 H, m, C_5H_{10} + NH + OH), 1.27 (3 H, t, *J* 7 Hz, OCH_2CH_3)
(**31**)	314 (3.89) 278 (4.06) 232 (4.21)	350 (4.30) 285 (3.72) 260 (3.87)	3 375 (+OH)	1 665	261 (M^+, 52%), 233 (5), 218 (17), 208 (12), 202 (60), 190 (23), 176 (24), 165 (9), 164 (9), 152 (34), 149 (64), 137 (100)	(Me_2SO) 7.60 (7.35*, 1 H, d, *J* 8 Hz, 5-H), 6.7 (6.15*, 1 H, d, *J* 8 Hz, 6-H), 3.9 (2 H, s, $ArCH_2$), 3.7 (3 H, s, OCH_3), 1.8—1.2 (12 H, m, C_5H_{10} + NH + OH)

* After addition of 30% (w/v) NaOD in D_2O.

Table 7. Analytical data for the 4-benzyl or 4-ethyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**32**)—(**38**)



	Compd. (Formula)					Found (%) (Required)		
	R^1	R^2	R^3	Yield (%)	M.p. (°C)			
(**32**)	Me	Me	Et	72	120	70.6	8.9	4.5
($C_{19}H_{29}NO_3$)						(70.8)	(8.9)	(4.6)
(**33**)	Me	Me	CH_2Ph	67	171	75.1	8.0	3.85
($C_{23}H_{29}NO_3$)						(75.2)	(7.9)	(3.8)
(**34**)	Me	H	CH_2Ph	59	184—185	74.9	7.8	3.95
($C_{22}H_{27}NO_3$)						(74.8)	(7.65)	(3.95)
(**35**)	Me	Et	CH_2Ph	63	148	75.65	8.2	3.75
($C_{24}H_{31}NO_3$)						(75.6)	(8.1)	(3.7)
(**36**)	Et	Me	CH_2Ph	60	183	75.9	8.25	3.6
($C_{24}H_{31}NO_3$)						(75.6)	(8.1)	(3.7)
(**37**)	H	Me	CH_2Ph	62	150	74.9	7.75	3.95
($C_{22}H_{27}NO_3$)						(74.8)	(7.65)	(3.95)
(**38**)	Et	H	CH_2Ph	60	172	75.3	8.15	3.75
($C_{23}H_{29}NO_3$)						(75.2)	(7.9)	(3.8)

Table 8. Spectroscopic data for the 4-benzyl- or 4-ethyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**32**)—(**38**)

Compd.	$\nu_{max.}$/cm^{-1}	*m/z*	δ_H
(**32**)	3 350	305 (M^+, 2%), 287 (76), 272 (15), 258 (83), 244 (38), 242 (10), 208 (13), 206 (11), 205 (11), 191 (8), 179 (56), 151 (14), 98 (100)	7.06 (1 H, s, 5-H), 6.46 (1 H, s, 8-H), 3.86 (6 H, s, 2 × OCH_3), 3.8 (2 H, s, $ArCH_2NH$), 1.85 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.0—1.0 (12 H, m, C_5H_{10} + NH + OH), 0.85 (3 H, t, *J* 7 Hz, CH_2CH_3)
(**33**)	3 400	367 (M^+, 4%), 349 (22), 276 (3), 258 (43), 151 (6), 136 (4), 98 (100), 91 (12)	7.2—6.7 (6 H, m, CH_2Ph), 6.4 (1 H, s, 8-H), 6.0 (1 H, s, 5-H), 3.9 (2 H, d, $ArCH_2N$), 3.76 (3 H, s, 7-OCH_3), 3.3 (3 H, s, 6-OCH_3), 3.1 (2 H, s, CH_2Ph), 2.0—1.0 (12 H, m, C_5H_{10} + NH + OH)
(**34**)	3 400	353 (M^+, 3%), 335 (21), 334 (14), 278 (13), 244 (34), 165 (69), 137 (8), 98 (100), 91 (11)	(Me_2SO) 8.35 (1 H, br s, $ArOH$), 7.2—6.5 (5 H, m, CH_2Ph), 6.3 (1 H, s, 8-H), 5.95 (1 H, s, 5-H), 4.3 (1 H, s, OH), 3.7 (2 H, s, Ar-CH_2 NH), 3.15 (3 H, s, 6-OCH_3), 3.15—2.8 (2 H, q, J_{AB} 13 Hz, CH_2Ph), 2.3—1.0 (11 H, m, C_5H_{10} + NH)
(**35**)	3 445	381 (M^+, 2%), 363 (36), 362 (24), 320 (11), 306 (19), 272 (100), 244 (10), 193 (68), 165 (15), 98 (84), 91 (14)	7.4—6.7 (5 H, m, CH_2Ph), 6.45 (1 H, s, 8-H), 6.0 (1 H, s, 5-H), 4.0 (2 H, q, *J* 7 Hz, OCH_2CH_3), 3.85 (2 H, d, $ArCH_2NH$), 3.3 (3 H, s, 6-OCH_3), 3.05 (2 H, s, CH_2Ph), 2.0—1.4 (12 H, m, C_5H_{10} + NH + OH), 1.3 (3 H, t, *J* 7 Hz, OCH_2CH_3
(**36**)	3 400	381 (M^+, 2%), 363 (40), 362 (25), 320 (14), 306 (17), 272 (100), 244 (10), 193 (72), 165 (17), 137 (8), 98 (87), 91 (12)	7.2—6.5 (5 H, m, CH_2Ph), 6.4 (1 H, s, 8-H), 6.05 (1 H, s, 5-H), 3.85 (2 H, d, $ArCH_2NH$), 3.75 (3 H, s, 7-OCH_3), 3.45 (2 H, m, 6-OCH_2CH_3), 3.05 (2 H, s, CH_2Ph), 2.0—1.2 (12 H, m, C_5H_{10} + NH + OH), 1.1 (3 H, t, *J* 7 Hz, OCH_2CH_3)
(**37**)	3 400	353 (M^+, 3%), 335 (28), 334 (20), 278 (17), 244 (86), 165 (90), 137 (21), 98 (100), 91 (17)	(Me_2SO) 8.0 (1 H, s, $ArOH$), 7.2—6.6 (5 H, m, CH_2Ph), 6.45 (1 H, s, 8-H), 6.15 (1 H, s, 5-H), 4.3 (1 H, s, OH), 3.7 (5 H, s, 7-OCH_3 + $ArCH_2NH$), 3.2—2.8 (2 H, q, J_{AB} 13 Hz, CH_2Ph), 2.1—1.0 (11 H, m, C_5H_{10} + NH)
(**38**)	3 420	367 (M^+, 2%), 349 (20), 348 (19), 258 (41), 230 (13), 179 (76), 151 (7), 123 (7), 98 (100), 91 (13)	(Me_2SO) 8.25 (1 H, s, $ArOH$), 7.0—6.6 (5 H, m, CH_2Ph), 6.28 (1 H, s, 8-H), 5.94 (1 H, s, 5-H), 4.25 (1 H, s, OH), 3.65 (2 H, s, $ArCH_2NH$), 3.3 (2 H, m, 6-OCH_2CH_3), 3.15—2.8 (2 H, q, J_{AB} 13 Hz, CH_2Ph), 2.0—1.2 (11 H, m, C_5H_{10} + NH), 1.08 (3 H, t, *J* 7 Hz, OCH_2CH_3)

stirring continued for a further 4 h. In the case of cyclisations at −10 °C, this temperature was maintained throughout the procedure. The solution was then poured onto crushed ice, stirred for 45 min, and basified with 5M-aqueous sodium hydroxide. After extraction with chloroform (5 × 100 ml), the combined extracts were washed, dried, and evaporated to give the crude dialkoxyisoquinolinone.

The extracted aqueous solution was re-acidified with concentrated hydrochloric acid, basified with aqueous potassium hydrogen carbonate, and extracted with chloroform (8 × 100 ml). The combined extracts were dried and evaporated to yield the crude phenolic isoquinolinone.

After t.l.c. analysis, the crude dialkoxyisoquinolinone was recrystallised from an appropriate solvent (Table 5). The amino nitile (**12**) gave a mixture of phenolic products (**26**) and (**31**) which was separated by preparative t.l.c. using light petroleum

(b.p. 60—80 °C)–ethyl acetate (1:1) as solvent on a silica gel 6 OPF stationary phase, followed by removal of the two absorption zones (R_F 0.75 and 0.43) and their extraction with chloroform. The amino nitrile (**13**) when cyclised at room temperature, gave a mixture of phenolic products (**29**) and (**30**) which were separated by fractional crystallisation from light petroleum (b.p. 60—80 °C)–ethyl acetate (1:1).

4-*Benzyl*- and 4-*Ethyl*-4-*hydroxy*-1,2,3,4-*tetrahydroisoquinolines*.—A solution of the 1,2-dihydroisoquinolin-4(3*H*)-one (0.5 g) in dry ether (50 ml) was added dropwise to a cold solution of benzyl- or ethyl-magnesium chloride (0.1 mol) in dry ether (100 ml) with continuous stirring. The reaction mixture was stirred for a further 2 h poured onto crushed ice, and acidified with dilute hydrochloric acid. The aqueous phase was washed twice with ether, basified with ammonia solution, and extracted with ether (3 × 100 ml). The combined extracts were dried, evaporated, and the residue recrystallised from light petroleum (b.p. 60—80 °C) to give the corresponding 4-benzyl or 4-ethyl 4-hydroxy-1,2,3,4-tetrahydroisoquinoline.

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