Cyclisation of Benzylaminoacetonitriles. Part 2.[1] Evidence for Two Mechanisms of Cyclisation

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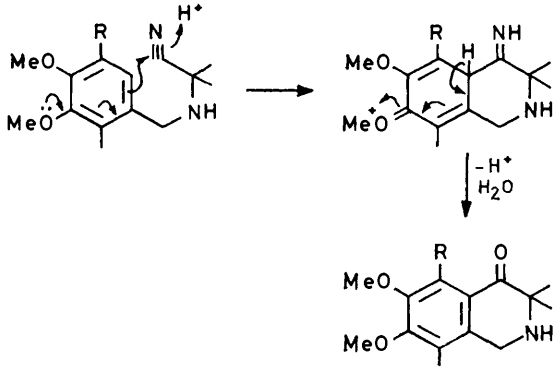
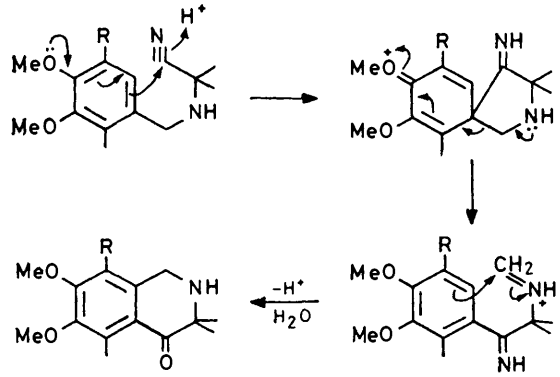
Treatment of 3,4-dimethoxybenzylaminoacetonitriles with concentrated sulphuric acid gives 2,3-dihydroisoquinolin-4(1*H*)-ones. Cyclisation of 1-(3,4,5-trimethoxybenzylamino)cyclohexanecarbonitrile (2) at room temperature gave 3,4-dihydro-5,6,7-trimethoxyisoquinoline-3-spirocyclohexan-4(1*H*)-one (8) (22%) and 1-(3,4,5-trimethoxybenzylamino)cyclohexanecarboxamide (9) (7%). At 50 °C, cyclisation gave 3,4-dihydro-7-hydroxy-6,8-dimethoxyisoquinoline-3-spirocyclohexan-4(1*H*)-one (10) as the major product. A dual mechanism for cyclisation is postulated, one mode involving electrophilic attack *para* to the C-3 methoxy-substituent, the second attack *para* to the C-4 methoxy-substituent, giving a spiro-intermediate which undergoes rearrangement to an iminium ion, the fate of which is dependent on the proximity of differing nucleophiles. The latter mechanism is consistent with the formation of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-(4-methoxyphenacyl)isoquinoline by treatment of 2-[*N*-(3,4-dimethoxyphenethyl)-4-methoxybenzylamino]acetonitrile (6) with sulphuric acid.

We have described [1] the synthesis of 2,3-dihydro-6,7-dimethoxyisoquinolin-4(1*H*)-ones from veratrylaminoacetonitriles, and have postulated a mechanism involving



Scheme 1

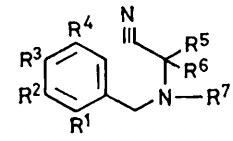
orthodox cyclisation *via* electrophilic attack *para* to the C-3 methoxy-substituent (Scheme 1). Subsequent work, described here, has indicated that cyclisation may



Scheme 2

proceed preferentially by attack *para* to the C-4 methoxy-group (Scheme 2).

The cyclisation of 3,4-dimethoxybenzylaminoacetonitriles [*e.g.* (1)], which lack alternative nucleophilic sites for attack by the iminium ion, would yield the same isoquinoline by orthodox cyclisation or *via* the spiro-intermediate (Schemes 1 and 2, R = H). The 3,4,5-trimethoxybenzylaminonitrile (2) would be expected to yield a 5,6,7-trimethoxyisoquinolinone according to Scheme 1 (R = OMe), but the 6,7,8-trimethoxyisoquinolinone by Scheme 2 (R = OMe). Cyclisation of the amino-nitrile (2) with concentrated sulphuric acid at room temperature gave, after dilution and basification with 5N-sodium hydroxide, an oil which on fractional crystallisation from petroleum gave the amide (9) in 7% yield and the 5,6,7-trimethoxyisoquinolone (8) in 22% yield (Scheme 3). The orientation of the methoxy-groups in 8 was unambiguously established by the chemical shift of the signal due to the aromatic proton, which appears as a singlet at δ 6.38. We envisage the amide (9) being formed by either hydration of the nitrile or hydrolytic attack on the spiro-intermediate (Scheme 3).



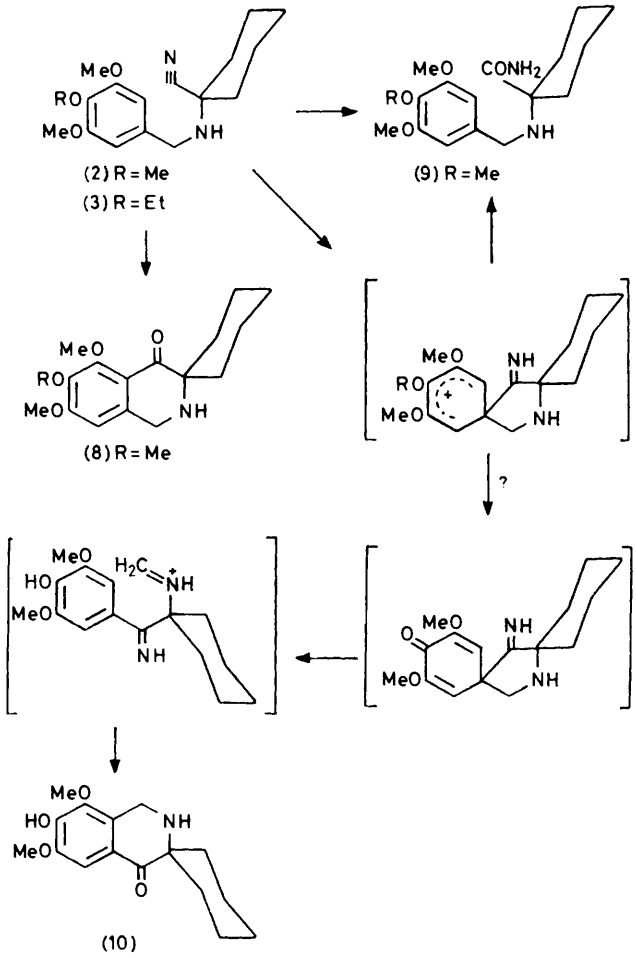
	R^1	R^2	R^3	R^4	R^5 R^6	R^7
(1) *	H	MeO	MeO	H	C_5H_{10}	H
(2)	H	MeO	MeO	MeO	C_5H_{10}	H
(3)	H	MeO	EtO	MeO	C_5H_{10}	H
(4)	H	MeO	H	H	C_5H_{10}	H
(5)	H	MeO	H	H	H H	H
(6)	H	H	MeO	H	H H	DMPE
(7)	MeO	MeO	H	H	C_5H_{10}	H

* Previously reported.[1] DMPE = 3,4-dimethoxyphenethyl.

These products were isolated in the same manner when cyclisation was carried out at 50 °C. The major product was obtained by addition of concentrated hydrochloric acid to the aqueous alkaline solution, which gave a

[1] Part 1, D. N. Harcourt and R. D. Waigh, *J. Chem. Soc.* (*C*), 1971, 967.

copious white precipitate from which was regenerated a phenolic isoquinolinone with sodium hydrogen carbonate solution. Recrystallisation from petroleum gave 2,3-dihydro-7-hydroxy-6,8-dimethoxyisoquinoline-3-spiro-cyclohexan-4(1*H*)-one (10) (Scheme 3) in 20% yield.



SCHEME 3

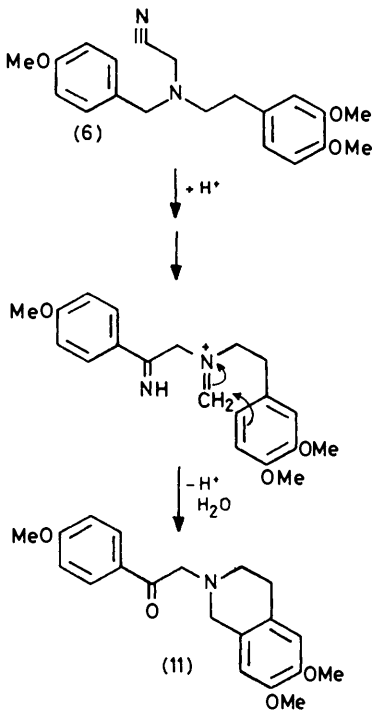
Here, orientation of the aromatic substituent groups was less readily established. Location of the aromatic proton at C-5 was unambiguous on the basis of n.m.r. data, the signal appearing at δ 7.34 owing to deshielding by the C-4 carbonyl function. Double irradiation experiments confirmed a C-6 methoxy-substituent, long-range coupling and the nuclear Overhauser effect being observed between the methoxy-group and the C-5 proton.

Orientation of the remaining methoxy-group could not be established by these techniques. Similarly, attempts to remove the phenolic hydroxy-group by the method of Lonsky and his co-workers [2] were also unsuccessful (dehydroxylation at C-8 would yield a product previously characterised,[1] and at C-7 the product should show *meta*-coupling with the C-5 proton in the n.m.r. spectrum).

Finally identification was accomplished by cyclisation of 1-(4-ethoxy-3,5-dimethoxybenzylamino)cyclohexane-carbonitrile (3), which gave the same phenolic isoquinolone (10).

Whilst the ' central ' methyl group is relatively easily removed by sulphuric acid, as for example in the preparation of syringic aldehyde, it is possible that demethylation occurs in the transition state to give a dienone which might then undergo rearrangement to the phenol (10). There is evidence from other amino-nitrile cyclisations [3] that the latter process may contribute, but in this case we are unable to exclude the possibility that demethylation occurs at a penultimate stage after rearrangement has been completed.

Further evidence for Scheme 2 being the favoured mechanism is seen in the cyclisation of 2-[*N*-(3,4-dimethoxyphenethyl)-4-methoxybenzylamino]acetonitrile (6), which gave 1,2,3,4-tetrahydro-6,7-dimethoxy-2-(4-methoxyphenacyl)isoquinoline (11) (Scheme 4), in 33% yield. This latter reaction clearly demonstrates the ability of the iminium ion to cyclise by interaction with an alternative and more reactive nucleophile when one is present. The structure was unequivocally confirmed by spectroscopy and by an unambiguous synthesis from 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline and 4-methoxyphenacyl bromide.



SCHEME 4

Benzylamino-nitriles with methoxy-substituents in the 2- and 3- or the 3-position [(4), (5), and (7)] and with C-4 unsubstituted were extensively sulphonated during

[2] W. Lonsky, H. Traitler, and K. Kratyl, *J.C.S. Perkin I*, 1975, 169.
[3] R. D. Waigh, unpublished work.

the attempted cyclisation. The 2,3-dimethoxy compound (7) gave 2,3-dihydro-5,6-dimethoxyisoquinoline-3-spirocyclohexan-4(1*H*)-one in 5% yield, the main product being an uncharacterised sulphonic acid. The orientation of the methoxy-groups in this isoquinolinone was assigned on n.m.r. evidence. The calculated chemical shifts of the two aromatic protons (δ 6.90 and δ 7.05) are in agreement with the experimental values, whereas the chemical shifts of the aromatic protons in the 7,8-dimethoxy-isomer are calculated as δ 6.84 and 7.45. Cyclisation must therefore proceed *via* the spiro-intermediate, the activating group being the C-2 methoxy-group.

The cyclisation of benzylaminonitriles with only a *meta*-methoxy-substituent necessarily follows Scheme 1, 3-methoxybenzylaminoacetonitrile (5) giving the known 2,3-dihydro-7-methoxyisoquinolin-4(1*H*)-one in 27% yield. The spirocyclohexane analogue (4) however, did not cyclise, the only product isolated being an uncharacterised sulphonic acid. Elemental and spectroscopic analysis showed this to be a 1-(3-methoxybenzylamino)cyclohexanecarboxamide sulphonic acid, but the orientation of the acid group could not be determined owing to the complexity of the aromatic n.m.r. signal.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus and are corrected. I.r. spectra were obtained with a Unicam SP 200 instrument. N.m.r. spectra were determined for solutions in deuteriochloroform with JEOL P5100 and Varian HA-100 instruments. Mass spectral data were obtained with an A.E.I. MS 12 instrument in the School of Chemistry, University of Bath.

The benzylaminoacetonitriles (1)—(7) were obtained as reported.[1]

Cyclisation of Benzylaminoacetonitriles. General Method.—The benzylaminoacetonitrile (5 g) was added carefully to concentrated sulphuric acid (25 ml) in an ice-bath, with stirring continuously until dissolution was complete. The solution was kept at room temperature overnight (' cold ' cyclisation) or heated to 50 °C for 4 h (' hot ' cyclisation), diluted by pouring on to crushed ice, and set aside for 30 min. The diluted mixture was basified with aqueous sodium hydroxide (20% w/v), ice being added from time to time to prevent an excessive rise in temperature. The product was either filtered off or extracted with chloroform, washed, dried, and recrystallised from petroleum (b.p. 60—80 °C).

Cyclisation of 1-(3,4,5-*trimethoxybenzylamino*)*cyclohexanecarbonitrile* (2). *' Cold ' cyclisation.* The chloroform extract gave on evaporation an oil (1.6 g) which after refluxing with petroleum (b.p. 40—60 °C) gave 1-(3,4,5-*trimethoxybenzylamino*)*cyclohexanecarboxamide* (9) (375 mg, 7%), m.p. 154°, as small white prisms, $\nu_{max.}$ 3 200 and 3 450 (NH_2 amide), 3 320 (NH amine), and 1 660 cm^{-1} (CO); δ 7.17br (1 H, s, exch. NH amide), 6.56 (2 H, s, ArH), 6.14br (1 H, s, exch. NH amide), 3.84—3.88 (9 H, 2 s, 3 MeO), 3.56 (2 H, s, $ArCH_2$), 1.6 (11 H, m, C_5H_{10} and exch. NH); *m/e* 322 (M^+, <1%), 278 (90), 196 (50), and 181 (100) (Found: C, 63.7; H, 8.1; N, 8.5. $C_{17}H_{26}N_2O_4$ requires C, 63.4; H, 8.1; N, 8.7%). Concentration of the petroleum solution yielded 2,3-*dihydro*-5,6,7-*trimethoxyisoquinoline*-3-*spirocyclohexan*-4(1H)-*one* (8) (1.1 g, 22%), m.p. 128°; $\nu_{max.}$ 3 290 (NH) and 1 650 cm^{-1} (CO); δ 6.38 (1 H, s, ArH), 4.00 (2 H, s, $ArCH_2$), 3.90 (6 H, s, 2MeO), 3.84 (3 H, s, MeO), 1.85 (1 H, s, exch. NH), and 1.60 (10 H, m, C_5H_{10}); *m/e* 305 (M^+, 31%), 303 (10), 288 (5), 277 (3), 234 (3), 208 (100), 193 (20), 181 (72), and 165 (20%) (Found: C, 66.5; H, 7.2; N, 4.6. $C_{17}H_{23}NO_4$ requires C, 66.8; H, 7.5; N, 4.6%).

The extracted aqueous solution was reacidified with concentrated hydrochloric acid, basified with potassium hydrogen carbonate, and extracted with chloroform. Drying ($MgSO_4$) and removal of the chloroform gave a small amount of unidentified intractable gum.

TABLE 1

Spectroscopic data for benzylaminoacetonitriles

Compd.	$\nu_{max.}$/cm^{-1} NH	$\nu_{max.}$/cm^{-1} C≡N	δ_H
(2)	3 300	2 200	6.70 (2 H, s, ArH), 3.85 (11 H, d, 3 MeO and $ArCH_2$), 1.0—2.2 (11 H *, m, C_5H_{10} and NH)
(3)	3 300	2 220	6.60 (2 H, s, ArH), 4.05 (2 H, q, *J* 7 Hz, CH_3CH_2O), 3.85 (8 H, s, 2 MeO and $ArCH_2$), 1.7 (11 H *, m, C_5H_{10} and NH), 1.35 (3 H, t, *J* 7 Hz, CH_3CH_2)
(4)	3 300	2 240	6.6—7.4 (4 H, m, ArH), 3.85 (2 H, s, $ArCH_2$), 3.75 (3 H, s, MeO), 1.2—2.2 (11 H *, m, C_5H_{10} and NH)
(5)	3 370	2 200	6.6—7.4 (4 H, m, ArH), 3.50 (2 H, s, $ArCH_2$), 3.40 (2 H, s, NCH_2CN), 1.80 (1 H *, s, NH)
(6)		2 230	7.20 (2 H, d, *J* 9 Hz, MeO C_6H_4), 6.85 (2 H, d, *J* 9 Hz, MeO C_6H_4), 6.71 [3 H, m, $(MeO)_2C_6H_3$], 3.70 (6 H, s, 2 MeO), 3.6 (3 H, s, MeO), 3.62 (2 H, s, $ArCH_2N$), 3.43 (2 H, s, NCH_2CN), 2.80 (4 H, s, N-$[CH_2]_2$Ar)
(7)	3 350	2 250	6.9 (3 H, m, ArH), 3.82 (6 H, s, 2 MeO), 3.42 (2 H, s, $ArCH_2$), 2.50 (1 H *, s, NH), 1.85 (10 H, m, C_5H_{10})

* Integral reduced by 1 H after deuteriation.

' Hot ' cyclisation. The dried chloroform extract, on evaporation and fractional crystallisation from petroleum (b.p. 40—60 °C) gave the amide (9) (320 mg, 6%), m.p. 154°, mixed m.p. 154°, and the isoquinolone (8) (360 mg, 6%), m.p. 128°, mixed m.p. 128°.

TABLE 2

Benzylaminoacetonitriles

Compd.	Yield (%)	M.p.(°C)	Found(%) C	Found(%) H	Found(%) N	Required(%) C	Required(%) H	Required(%) N
(2)	79	70	67.2	7.9	9.1	67.1	7.9	9.2
(3)	89	74	68.3	8.3	8.8	67.9	8.2	8.8
(4)	84	oil	74.0	8.3	11.4	73.8	8.2	11.5
(5)	61	129 (decomp.) *	56.5	6.2	13.3	56.5	6.2	13.2
(6)	63	62	71.4	7.2	8.2	70.6	7.1	8.2
(7)	42	50	70.0	7.8	10.3	70.0	8.1	10.2

* Base HCl.

Reacidification of the extracted aqueous solution with an excess of concentrated hydrochloric acid gave a copious white precipitate (1.4 g) which was collected and suspended in water (100 ml). An excess of potassium hydrogen carbonate was added, the mixture was extracted three times with chloroform (40 ml), and the combined extracts were washed once with water (10 ml), dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from petroleum (b.p. 60—80 °C) gave 2,3-*dihydro*-7-*hydroxy*-6,8-

dimethoxyisoquinoline-3-spirocyclohexan-4(1H)-one (10) (1.0 g, 20%), m.p. 149°; $\nu_{max.}$ 3 450 (OH), 3 350 (NH), and 1 660 cm^{-1} (CO); δ 7.34 (1 H, s, ArH), 4.06 (4 H, s with shoulder, $ArCH_2$, exch. NH and OH), 3.90 (3 H, s, MeO), 3.88 (3 H, s, MeO), and 1.6 (10 H, m, C_5H_{10}); *m/e* 291 (M^+, 40%), 290 (5), 263 (4), 248 (4), 232 (40), 220 (20), 194 (16), 167 (100), and 145.5 (10) (Found: C, 66.2; H, 7.3; N, 4.7. $C_{16}H_{21}NO_4$ requires C, 66.0; H, 7.2; N, 4.8%).

Cyclisation of 1-(4-*ethoxy*-3,5-*dimethoxybenzylamino*)*cyclohexanecarbonitrile* (3). *'Hot' cyclisation.* After basification the mixture was washed with chloroform and the organic layer discarded. Reacidification with concentrated hydrochloric acid gave a white precipitate which was collected and worked up as described in the preparation of the isoquinolone (10). Crystallisation from petroleum (b.p. 60—80 °C) gave white crystals (1.5 g, 30%), m.p. 149°, which i.r. and n.m.r. spectra showed to be identical with the isoquinolinone (10) (mixed m.p. 149°).

Cyclisation of 2-(3-*methoxybenzylamino*)*acetonitrile* (5). *'Hot' cyclisation.* The chloroform extract gave 2,3-dihydro-7-methoxyisoquinolin-4(1*H*)-one as a white solid (1.07 g, 27%). The hydrochloride was prepared by addition of an excess of ethereal hydrogen chloride to an ether–propan-2-ol solution and after crystallisation from ether–methanol (1 : 1) had m.p. 216—218° (decomp.) (capillary tube, heated at 10° min^{-1} after insertion at 200°) lit.,[4] 214—215° and 224—225°); $\nu_{max.}$ (hydrochloride) 1 675 cm^{-1} (CO).

Cyclisation of 2-[N-(3,4-*dimethoxyphenethyl*)-4-*methoxybenzylamino*]*acetonitrile* (6). *'Hot' cyclisation.* The dried chloroform extract, on removal of the solvent and recrystallisation from petroleum (b.p. 60—80 °C), gave 1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-(4-*methoxyphenacyl*)*isoquinoline* (11) (1.7 g, 33%), m.p. 121°, as pale yellow needles; $\nu_{max.}$ 1 675 cm^{-1} (CO); δ 8.04 (2 H, d, *J* 8 Hz) and 6.88 (2 H, d, *J* 8 Hz, $MeOC_6H_4$), 6.56 (1 H, s, ArH), 6.47 (1 H, s, ArH), 3.88 (2 H, s, $COCH_2N$), 3.79—3.82 (9 H, 3s, 3MeO), 3.70 (2 H, s, $ArCH_2N$), and 2.74 (4 H, s, $ArCH_2 \cdot CH_2 \cdot N$); *m/e* 341 ($M^+$, 6%), 206 (100), 192 (60), 135 (26), and 107 (12) (Found: C, 70.5; H, 6.7; N, 4.1. $C_{20}H_{23}NO_4$ requires C, 70.4; H, 6.7; N, 4.1%).

Cyclisation of 1-(2,3-*dimethoxybenzylamino*)*cyclohexanecarbonitrile* (7). *'Hot' cyclisation.* The dried chloroform extract on removal of solvent and recrystallisation from petroleum (b.p. 80—100 °C) gave 2,3-*dihydro*-5,6-*dimethoxy*-3-*spirocyclohexylisoquinoline*-3-*spirocyclohexan*-4(1H)-*one* (12) (0.25 g, 5%), m.p. 106°; $\nu_{max.}$ 3 250 (NH) and 1 660 cm^{-1} (CO); δ 7.05 (1 H, d, *J* 8 Hz, ArH), 6.80 (1 H, d, *J* 8 Hz, ArH), 3.9 (2 H, s, $ArCH_2N$), 3.80 (6 H, s, 2MeO), 1.95 (1 H, s, exch. NH), and 1.70 (10 H, m, C_5H_{10}); *m/e* 275 (M^+, 30%), 247 (14), 232 (3), 178 (48), 151 (100), and 150 (8) (Found: C, 70.0; H, 7.7; N, 5.2. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7; N, 5.1%).

Attempted cyclisation of 1-(3-*methoxybenzylamino*)*cyclohexanecarbonitrile* (4). *'Hot' cyclisation.* The aminonitrile (4) (5 g), after dissolution in concentrated sulphuric acid, dilution, basification, and extraction with chloroform gave only a trace of intractable gum. The extracted aqueous solution was acidified to pH 7 (pH meter) and after two days white crystals (4 g) appeared. These were collected, recrystallised from distilled water and dried; m.p. 305° (micro-hot-stage; uncorrected); $\nu_{max.}$ 1 090 and 1 160 (SO_2 str.), 1 660 (CO amide), and 3 150 and 3 400 cm^{-1} (NH_2 amide); δ 9.10 (2 H, s, $CONH_2$), 7.0—7.80 (5 H, m, ArH_3, NH, and SO_3H), 4.30 (2 H, s, $ArCH_2$), 3.80 (3 H, s, MeO), and 1.4—2.2 (10 H, m, C_5H_{10}) (Found: C, 52.35; H, 6.45; N, 7.9; S, 9.1. $C_{15}H_{22}N_2O_5S$ requires C, 52.5; H, 6.45; N, 8.2; S, 9.35%).

Synthesis of 1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-2-(4-*methoxyphenacyl*)*isoquinoline* (11).—2-Bromo-4′-methoxyacetophenone (5.95 g, 0.026 mol) dissolved in absolute ethanol (50 ml) was added dropwise to a refluxing mixture of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (5 g, 0.026 mol) and anhydrous sodium carbonate (5 g) in absolute ethanol (50 ml). After 8 h the mixture was filtered and cooled giving pale yellow crystals. Recrystallisation from absolute ethanol gave the product (4 g, 45%) as pale yellow needles, m.p. 121° (mixed m.p. 121°).

[7/1304 *Received*, 20*th July*, 1977]

[4] G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, 1968, **33**, 491.