The Cyclisation of Benzylaminonitriles. Part 7.[8] Regiospecific Formation of Methoxy-substituted Isoquinolin-4-ones using Methylthio Activating Groups

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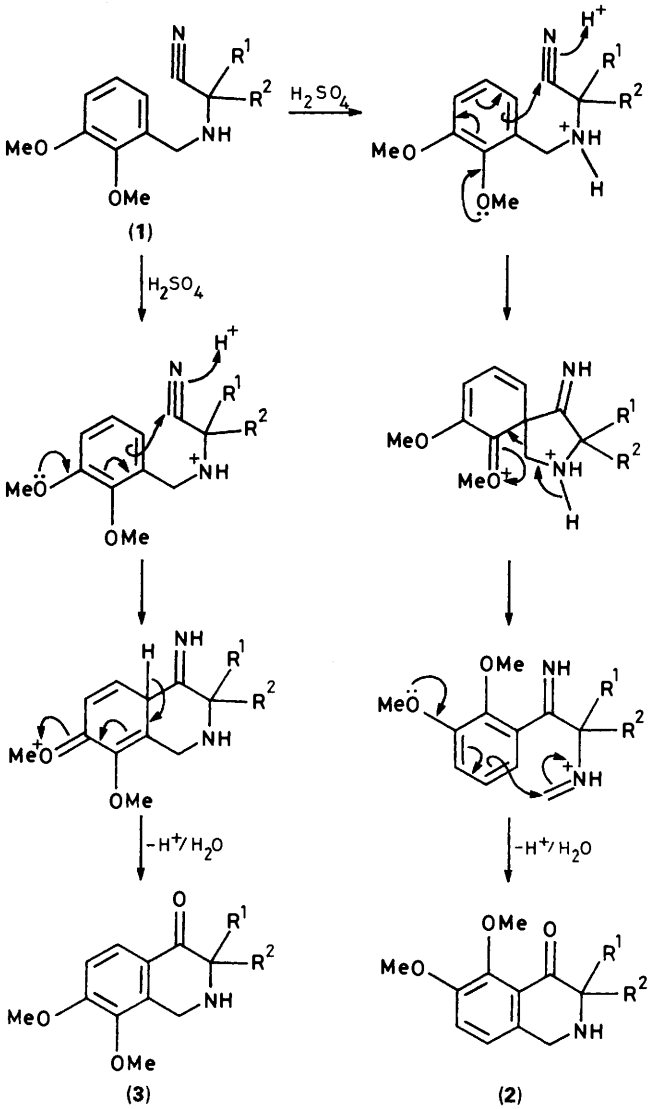
Cyclisation of 3,4-dialkoxybenzylaminoacetonitriles proceeds preferentially through a spiro intermediate. A 2,3-dialkoxy analogue will therefore normally give a 5,6-dialkoxyisoquinolinone after rearrangement and 7,8-dimethoxy substitution is not obtained. It is shown that a suitably placed methylthio group, which can be removed after cyclisation, can change the mode of cyclisation from rearrangement *via* a spiro intermediate to simple *ortho*-attack, giving the desired 7,8-dialkoxy substitution pattern. In principle, this approach to regiocontrol could be of value in many reactions involving electrophilic attack on a benzene ring.

The cyclisation of a 2,3-dimethoxybenzylaminoacetonitrile such as the cyclohexyl derivative (**1a**) has been shown to give the 5,6-dimethoxyisoquinolinone (**2a**) on treatment with sulphuric acid.[2] This can be readily explained, as in Scheme 1, by rearrangement through a spiro intermediate. In our hands this reaction also produced a small amount of 7,8-dimethoxyisoquinolinone (**3a**), presumably by orthodox cyclisation (Scheme 1); this cannot be regarded as a viable synthesis of 7,8-dimethoxyisoquinolinones, however, in view of the strong preference for the spiro route. The aminonitrile cyclisation provides an efficient route to valuable intermediates in the synthesis of benzo[*c*]phenanthridines[3,4] which makes attention to control of the substitution pattern worthwhile.

Methylthio substituents have been shown to activate benzene rings sufficiently for a variety of cyclisations involving electrophilic attack.[5–9] As an extension of the approach we envisaged several combinations of methoxy and methylthio substituents which could give the desired 7,8-dimethoxy substituted isoquinolinone, two of which are described here. To simplify isolation of the products of cyclisation we chose 2-spirocyclohexane and 2,2-dimethyl derivatives throughout, thereby avoiding problems arising through enolisation and oxidation of the isoquinolinone.

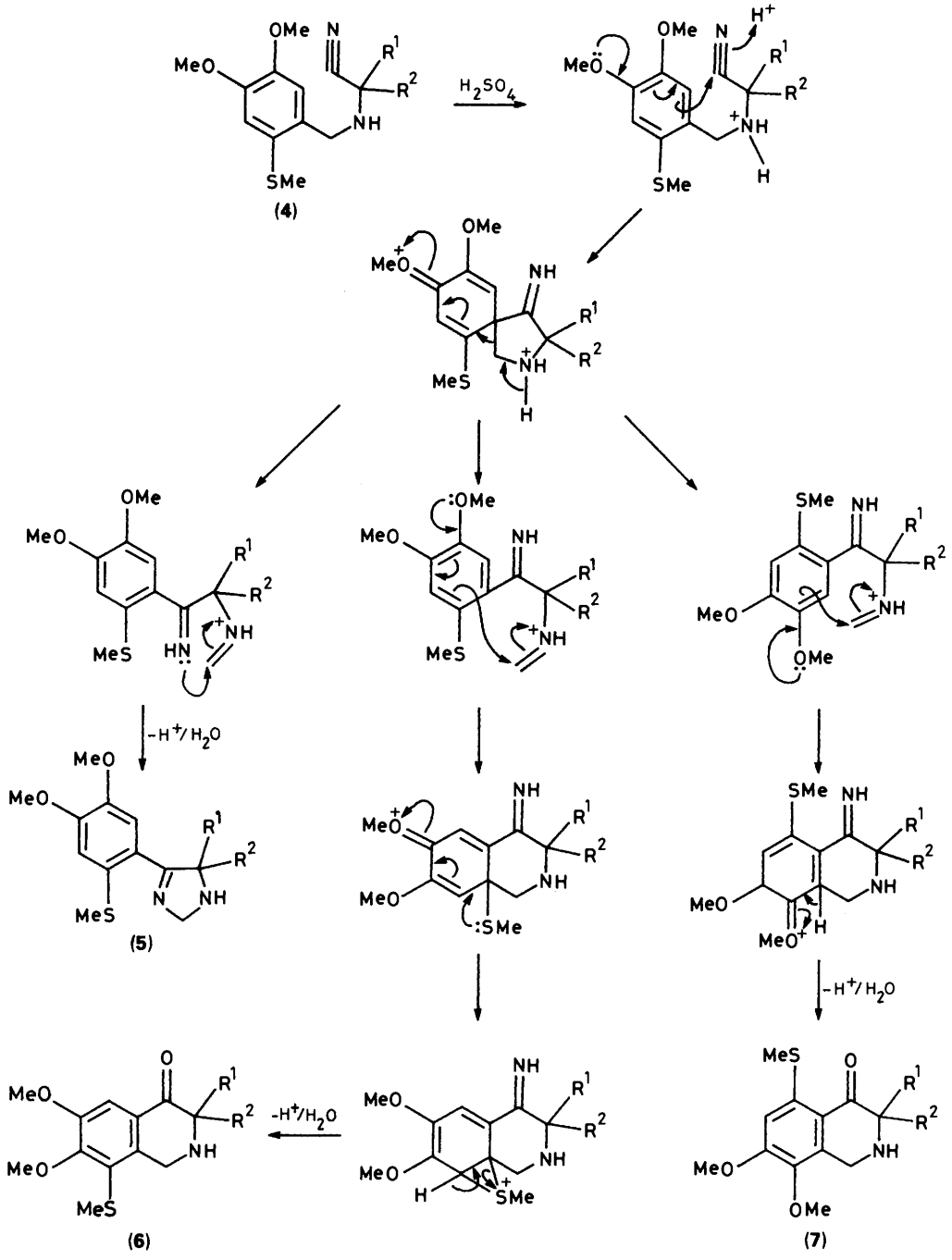


Scheme 1. a; $R^1R^2 = -(CH_2)_5-$. b; $R^1 = R^2 = Me$.

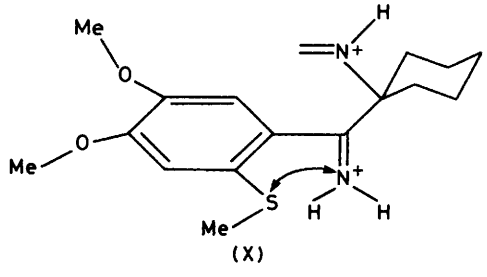
Results and Discussion

With 2-methylthio-4,5-dimethoxy substitution as in (**4a, b**) treatment of the aminonitrile with sulphuric acid gave fairly good yields of the imidazolines (**5a, b**), together with small amounts of the two isoquinolines (**6a, b**) and (**7a, b**) (Scheme 2). The imidazolines (**5a, b**) are characteristic of reactions in which formation of the spiro intermediate is favoured but cyclisation to the *ortho*-position of the benzene ring is inhibited. In previous examples this has been attributable to lack of a suitably placed electron donor, but this is not the case here, since the 5-methoxy group could fulfil this function and does so to a certain extent, accounting for the formation of small amounts of the desired 7,8-dimethoxyisoquinolinones (**7a, b**). That this secondary cyclisation does not occur readily is attributable to adverse steric interactions, as in structure (X). As a minor alternative, attack at the methylthio-substituted carbon followed by a 1,2 shift of MeS^+ can account for formation of the isoquinolinones (**6a, b**). Proof of structure of all the isoquinolinones is described below.

The 2,3-dimethoxy-5-methylthio derivatives (**8a, b**) had two groups activating the 6-position (Scheme 3), with the result that cyclisation proceeded by direct attack and formation of the spiro intermediates was precluded. Although yields were only moderate there were no major by-products and attention to detail is likely to bring substantial improvements; our aim of



Scheme 2. a; $R^1R^2 = -(CH_2)_5-$. b; $R^1 = R^2 = Me$.

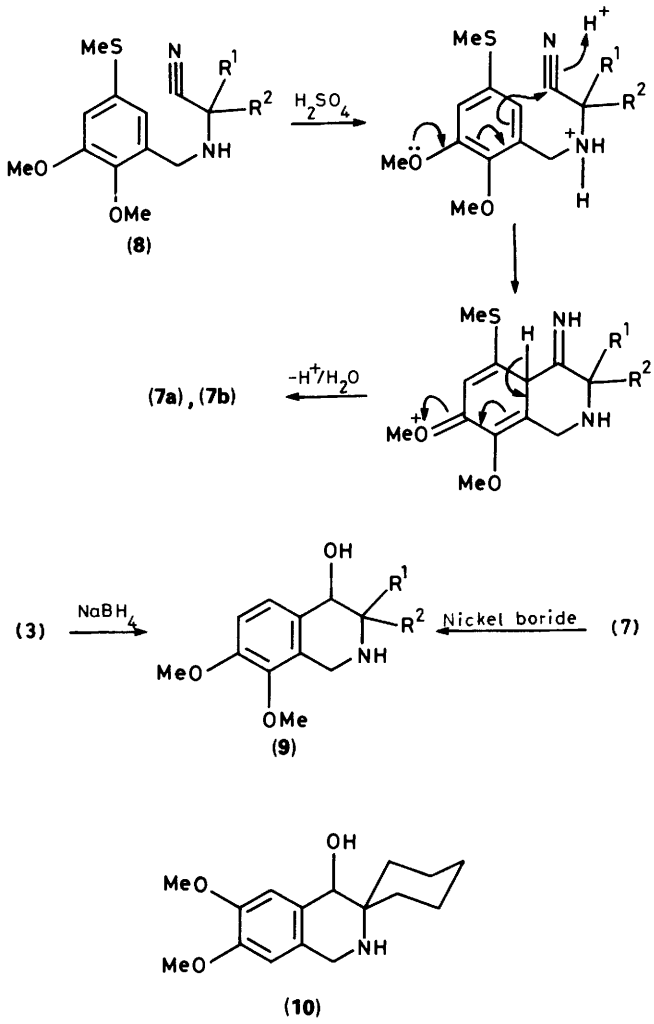


Scheme 3. a; $R^1R^2 = -(CH_2)_5-$. b; $R^1 = R^2 = Me$.

finding a simple route to 3-substituted 7,8-dimethoxy-isoquinolinones has thus been achieved.

Several methods were used to identify the cyclisation products. The isomers (**2**) and (**3**) were readily distinguished by the chemical shift differences between the two aromatic protons. In the 5,6-dimethoxy isomers (**2a, b**) the differences were only 0.25 and 0.24 ppm, whereas in the 7,8-dimethoxy analogues (**3a, b**) the differences were 0.93 and 0.92 ppm, owing to deshielding of the proton in the 5-position by the carbonyl. Reduction of these ketones with sodium borohydride gave four isomeric alcohols, two of which (**9a, b**) (Scheme 4) were shown to be identical with the products of nickel boride desulphurisation of (**7a, b**).

The identity of the 6,7-dimethoxy-8-methylthio analogue (**6a**)



Scheme 4. **a**; $R^1R^2 = -(CH_2)_5-$. **b**; $R^1 = R^2 = Me$.

was partly established by reductive desulphurisation to the alcohol (**10**). The chemical shift (δ 6.82) of the single aromatic proton in (**6a**) was indicative of a position *peri* to the carbonyl, and this was confirmed by examination of nuclear Overhauser effects within the molecule. Irradiation of the *S*-methyl protons in (**6a**) produced an enhancement of the signal from the methylene protons at position 1, and *vice versa*.

The 7,8-dimethoxy-5-methylthio analogues (**7**) produced in the cyclisation of (**4**) were shown to be identical with the products obtained from orthodox cyclisation of (**8**).

It is of primary importance, if this approach to regiocontrol is to be generally useful, that the appropriate synthons are readily available. A valuable method for the introduction of methylthio onto a benzene ring involves bromination and a Grignard reaction with dimethyl disulphide.[10] This approach was adopted for the synthesis of 2,3-dimethoxy-5-methylthiobenzaldehyde, starting from *o*-vanillin. The isomeric 2-methylthio-4,5-dimethoxybenzaldehyde was prepared by the method of Jacob and co-workers.[11]

Experimental

M.p.s were taken on a Reichert hot-stage apparatus and are corrected. IR spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer for potassium bromide discs for solids and liquid films for oils. ^1H NMR spectra were recorded on Bruker WP80 and Varian SC300 instruments with $CDCl_3$ as solvent and $SiMe_4$ as internal standard. Mass spectral data were obtained with an A.E.I. MS30 instrument in the School of Chemistry, University of Manchester. Cyclisation products were separated on grade 1 basic alumina, with ethyl acetate–light petroleum (b.p. 60–80 °C) (2:1) as eluant. R_f Values were obtained using UV_{254} sensitive alumina plates, with ethyl acetate–light petroleum (b.p. 60–80 °C) (2:1) as eluant.

2,3-*Dimethoxy*-5-*methylthiobenzaldehyde*.—To *o*-vanillin (100 g, 0.66 mol) and potassium bromide (156.6 g, 1.32 mol) in 80% acetic acid (1 300 ml), bromine (35.5 ml, 0.74 mol) in glacial acetic acid (65 ml) was added, dropwise. After stirring for 15 min at 110 °C and 24 h at room temperature, water (2 500 ml) was added. The precipitate was filtered off, washed with water, and recrystallised from aqueous ethanol (50% v/v) to yield 5-bromo-2-hydroxy-3-methoxybenzaldehyde (144.3 g, 95%) as a white solid, m.p. 129 °C (lit.,[12] 128–129 °C); ν_{max} 3 200 (OH) and 1 660 (C=O) cm^{-1}; δ_H 10.94 (1 H, s, OH exchangeable), 9.86 (1 H, s, CHO), 7.31 1 H, d, *J* 1.5 Hz, ArH), 7.17 (1 H, d, *J* 1.5 Hz, ArH), and 3.92 (3 H, s, OMe); *m/z* 232 (M^+, 98%), 230 (100), 186 (37), 184 (34), 161 (13), 159 (14), 108 (22), 79 (30), 51 (69), and 29 (38).

5-Bromo-2-hydroxy-3-methoxybenzaldehyde (141 g, 0.62 mol) was dissolved in dimethylformamide (DMF; 1 200 ml), containing sodium hydroxide (24.5 g), and stirred at 70 °C for 30 min. Methyl iodide (115 ml, 1.84 mol) was added, and the mixture set aside for 12 h, then poured into water. After extraction with ether (4 × 50 ml), the solution was washed with 2M aqueous sodium hydroxide (4 × 50 ml) and water (2 × 50 ml), dried, and evaporated, and the product recrystallised from ethanol to yield 5-bromo-2,3-dimethoxybenzaldehyde (114.3 g, 76%) as a white solid, m.p. 82–83 °C (lit.,[13] 85 °C); ν_{max} 1 670 (C=O) cm^{-1}; δ_H 10.34 (1 H, s, CHO), 7.53 (1 H, d, *J* 2.5 Hz, ArH), 7.23 (1 H, d, *J* 2.5 Hz, ArH), 3.98 (3 H, s, OMe), and 3.91 (3 H, s, OMe); *m/z* 246 (M^+, 98%), 244 (M^+, 98%), 231 (30), 229 (38), 200 (30), 198 (22), 188 (48), 186 (27), 107 (33), 94 (92), 44 (100), and 29 (78).

5-Bromo-2,3-dimethoxybenzaldehyde (114.3 g, 0.47 mol) was dissolved in absolute ethanol (82 ml, 1.43 mol). Triethyl orthoformate (85.3 ml, 0.51 mol) was then added, followed by 32% hydrochloric acid (0.2 ml), whereupon the temperature rose quickly. The reaction mixture was heated under reflux on a steam bath for 30 min, then rapidly cooled, and basified with aqueous sodium hydroxide (20% w/v). The combined ethereal extracts were washed with water (50 ml), dried, and evaporated to yield 5-bromo-2,3-dimethoxybenzaldehyde diethyl acetal (133 g, 93%) as an oil, ν_{max} 1 050 (COC) cm^{-1}; δ_H 7.31 (1 H, d, *J* 1 Hz, ArH), 7.00 (1 H, d, *J* 1 Hz, ArH), 5.72 (1 H, s, CH), 3.85 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.66 (4 H, q, *J* 7 Hz, 2 × CH_2O), and 1.23 (6 H, t, *J* 7 Hz, 2 × CH_2CH_3); *m/z* 320 (M^+, 15%), 318 (M^+, 13%), 275 (100), 273 (96), 245 (37), 138 (54), 75 (42), 44 (52), and 29 (57).

5-Bromo-2,3-dimethoxybenzaldehyde diethyl acetal (133 g, 0.42 mol) was added to dry tetrahydrofuran (THF; 1 l) containing magnesium (10.25 g, 0.42 mol), under an atmosphere of nitrogen. Upon formation of the Grignard complex, dimethyl disulphide (37.7 ml, 0.42 mol), in dry THF (250 ml) was added dropwise over 30 min. The solution was heated under reflux for 3½ h and cooled, and aqueous NH_4Cl (20% w/v; 2 l) added cautiously, keeping the temperature below 20 °C, and employing a thiol trap.[10] The mixture was filtered and extracted with ether (3 × 250 ml), and the extracts were dried and evaporated to yield 2,3-dimethoxy-5-methylthiobenzaldehyde diethyl acetal (108.6 g, 91%) as an oil; ν_{max} 1 050 (COC) cm^{-1}; δ_H 7.09 (1 H, d, *J* 1 Hz, ArH), 6.82 (1 H, d, *J* 1 Hz, ArH), 5.72 (1 H, s, CH), 3.85 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.60 (4 H, q, *J* 7 Hz, 2 × CH_2O), 2.48 (3 H, s, OMe), and 1.23 (6 H, t, *J* 7 Hz, 2 × CH_2CH_3); *m/z* 286 (M^+, 47%), 241 (80), 212 (17), 195

Table 1. Spectroscopic data for benzylaminoacetonitriles.

Compound	ν_{max}/cm^{-1} NH	C≡N	*m/z*	δ_H
(1b)	3 300	2 240	234 (M^+, 0.3%), 207 (15), 192 (7.5), 176 (38) 167 (54), 165 (34), 152 (59), 151 (60), 136 (100), 121 (28), 106 (32), 77 (31)	6.97–6.91 (3 H, m, ArH), 3.89 (5 H, s, OMe and CH_2N), 3.87 (2 H, s, OMe), 1.92 (1 H, s, NH[a]), 1.52 (6 H, s, CH_3)
(4a)	3 310	2 200	293 (M^+ −27, 15%), 278 (7), 246 (56), 197 (100), 182 (23), 151 (19), 138 (16), 27 (7)	6.92 (1 H, s, ArH), 4.0 (2 H, s, $ArCH_2N$), 3.88 (6 H, s, OMe), 2.45 (3 H, s, SMe), 1.69 (1 H, s, NH[a]), 1.83–1.54 (10 H, br, C_5H_{10})
(4b)	3 300	2 200	253 (M^+, 74%), 238 (29), 206 (64), 197 (100), 182 (53), 151 (40), 138 (40), 70 (15), 45 (10)	6.93 (1 H, s, ArH), 6.90 (1 H, s, ArH), 3.98 (2 H, s, $ArCH_2N$), 3.89 (6 H, s, OMe) 2.45 (3 H, s, SMe), 1.60 (1 H, s, NH[a]), 1.55 (6 H, s, CH_3)
(8a)	3 300	2 200	320 (M^+, 0.5%), 293 (12), 262 (36) 197 (17), 182 (48), 98 (45), 56 (88) 41 (68), 27 (100)	6.86 (1 H, s, ArH), 6.84 (1 H, s, ArH), 3.86 (8 H, s, 2 × OMe and CH_2N), 2.48 (3 H, s, SMe), 1.77 (1 H, br, NH[a]), 2.12–1.48 (10 H, br, C_5H_{10})
(8b)	3 300	2 200	253 (M^+ −27, 47%), 238 (20), 222 (35) 213 (37), 198 (20), 197 (100), 193 (29) 161 (36), 137 (45), 77 (33), 45 (46), 30 (43)	6.83 (2 H, br, 2 ArH), 3.86 (8 H, s, 2 × OMe and $ArCH_2N$), 2.48 (3 H, s, SMe), 1.84 (1 H, br, N*H*[a]), 1.52 (6 H, s, 2 × CH_3)

[a] 1 H exchangeable.

Table 2. Benzylaminoacetonitriles.

Compound	Yield (%)	M.p., *t*/°C	Found (%) C	H	N	Required (%) C	H	N
(1b)	80	98–101	57.2	7.2	9.8	57.6	7.2	10.3
(4a)	78	81	63.6	7.6	8.8	63.7	7.6	8.7
(4b)	88	77	60.0	7.3	9.8	60.0	7.2	10.0
(8a)	92	119–121[a]	57.3	7.1	7.8	57.2	7.1	7.9
(8b)	88	Oil			*b*			

[a] Of hydrochloride. [b] Found: M^+, 280.1251; $C_{14}H_{20}N_2O_2S$ requires *M*, 280.1246.

(29), 138 (56), 105 (100), 77 (51), 47 (48), and 29 (15) (Found: M^+, 286.1249. $C_{14}H_{22}O_4S$ requires *M*, 286.1248).

2,3-Dimethoxy-5-methylthiobenzaldehyde diethyl acetal (108.5 g, 0.38 mol) was heated under reflux with 2M sulphuric acid (1 l) for 1 h. The mixture was rapidly cooled and extracted with ether (3 × 150 ml). The combined extracts were washed with dilute aqueous sodium hydroxide (50 ml) and water (50 ml), dried, and evaporated to yield a brown oil (49.8 g, 79%). Vacuum distillation afforded the *aldehyde* as a pale yellow oil, b.p. 117 °C at 0.05 mmHg, which rapidly solidified. Recrystallisation from ethanol yielded pale yellow needles, m.p. 60–61 °C (Found: C, 56.3; H, 5.8%. $C_{10}H_{12}O_3S$ requires C, 56.5; H, 5.7%); ν_{max} 1 680 (C=O) cm^{-1}; δ_H 10.38 (1 H, s, CHO), 7.26 (1 H, d, *J* 1.5 Hz, ArH), 7.15 (1 H, d, *J* 1.5 Hz, ArH), 3.96 (3 H, s, OMe), 3.90 (3 H, s, OMe), and 2.50 (3 H, s, SMe); *m/z* 212 (M^+, 100%), 197 (70), 169 (22), 154 (27), 141 (30), 111 (24), and 32 (15).

2-Methylthio-4,5-dimethoxybenzaldehyde.—This compound was prepared according to the method of Jacob and co-workers,[11] in 50% overall yield, m.p. 111 °C (lit.,[11] 112–113 °C).

Preparation of Benzylamines and Benzylaminoacetonitriles.—These compounds were obtained by established methods.[5]

2,3-Dimethoxy-5-methylthiobenzylamine hydrochloride was recrystallised from ethanol (95% yield over 2 steps), m.p. 153 °C (Found: C, 48.0; H, 6.5; N, 5.3%. $C_{10}H_{16}ClNO_2S$ requires C, 48.1; H, 6.5; N, 5.6%); ν_{max} 3 400 (NH) cm^{-1}; δ_H 7.21 (1 H, d, *J* 2.5 Hz, ArH), 6.78 (1 H, d, *J* 2.5 Hz, ArH), 4.24 (2 H, s, $ArCH_2N$), 4.00 (3 H, s, OMe), 3.82 (3 H, s, OMe), 2.49 (3 H, s, Me), and 2.38 (2 H, br, NH_2, exchangeable); *m/z* 214 (M^+, 11%), 213 (88), 198 (15), 182 (21), 166 (14), 151 (15), 36 (93), and 31 (100).

4,5-Dimethoxy-2-methylthiobenzylamine hydrochloride was recrystallised from ethanol (89% yield over 2 steps), m.p. 180 °C (Found: C, 48.3; H, 6.7; N, 5.4%. $C_{10}H_{16}ClNO_2S$ requires C, 48.1; H, 6.5; N, 5.6%); ν_{max} 3 380 (NH) cm^{-1}; δ_H 6.92 (2 H, s, ArH), 3.92 (2 H, s, CH_2N), 3.89 (6 H, s, 2 × OMe), 2.44 (3 H, s, SMe), and 1.64 (2 H, br, NH_2, exchangeable); *m/z* 213 (M^+, 76%), 212 (91), 198 (100), 181 (60), 164 (25), 151 (29), 138 (49), and 30 (36).

Cyclisation of Benzylaminoacetonitriles: General Methods.—The benzylaminoacetonitrile (2 g) in chloroform (8 ml) was added to 94% sulphuric acid (10 ml) at 0 °C during 5 min. The mixture was then stirred for 15 min at room temperature. Work-up was then achieved using method A or B.

Method A. The solution was added dropwise to ice–water and stirred for 5 min after which it was added slowly to an ice-cooled saturated solution of sodium hydrogen carbonate. The free base was extracted with chloroform, and the extracts were washed with water, dried ($MgSO_4$), and evaporated.

Method B. The solution was added dropwise cautiously to ice–dilute aqueous ammonia. The cyclised products were extracted with chloroform, and the extracts were washed with water, dried, and evaporated (water bath < 30 °C).

Spectral and analytical data for the novel isoquinolin-4(3*H*)-one products are presented in Tables 3 and 4.

Cyclisation of 1-(2,3-dimethoxybenzylamino)cyclohexanecarbonitrile (**1a**). Work-up using method A yielded a brown oil (0.5 g). ^1H NMR and TLC of the crude mixture suggested the presence of 1,2-dihydro-5,6-dimethoxyisoquinoline-3-spirocyclohexan-4(3*H*)-one (**2a**) (R_f 0.61) and the corresponding 7,8-dimethoxy compound (**3a**) (R_f 0.73), in a 4:1 ratio. Partial purification of the mixture was achieved by formation of the hydrochloride salt, by addition of ethereal hydrogen chloride. Preparative TLC of the rebasified mixture gave (**2a**) (0.26 g, 13%), and (**3a**) (0.06 g, 3%) as green translucent plates. Spectroscopic properties of (**2a**) were identical with those found previously.[2]

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

Compound	ν_{max}/cm^{-1} NH	C=O	*m/z*	δ_H
(**2b**)	3 300	1 680	235 (M^+, 18%), 207 (10), 176 (27), 167 (41), 151 (36), 136 (100), 91 (46), 77 (17), 58 (10)	7.09 (1 H, d, *J* 8.4 Hz, ArH), 6.85 (1 H, d, *J* 8.4 Hz, ArH), 4.07 (2 H, s, $ArCH_2N$), 3.89 (2 H, s, OMe), 3.87 (3 H, s, OMe), 2.08 (1 H, br, NH[a]), 1.35 (6 H, s, CH_3)
(**3a**)	3 300	1 660	275 (M^+, 23%), 216 (52), 204 (13), 178 (11), 151 (17), 136 (17), 91 (16), 40 (100), 29 (63)	7.82 (1 H, d, *J* 8 Hz, ArH), 6.89 (1 H, d, *J* 8 Hz, ArH) 4.12 (2 H, s, NCH_2N), 3.91 (3 H, s, OMe), 3.83 (3 H, s, OMe), 1.93 (1 H, s, NH[a]), 2.12–1.35 (10 H, br, C_5H_{10})
(**3b**)	3 300	1 680	235 (M^+, 16%), 219 (4), 207 (10), 178 (59), 151 (100), 136 (49), 120 (17), 91 (37), 77 (14), 58 (26), 40 (47), 32 (64)	7.77 (1 H, d, *J* 4.7 Hz, ArH), 6.85 (1 H, d, *J* 4.7 Hz, ArH), 3.87 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.68 (2 H, s, $ArCH_2N$), 1.69 (1 H, br, NH[a]), 1.41 (6 H, s, CH_3)
(**6a**)	3 400	2 680	321 (M^+, 60%), 306 (17), 250 (48), 246 (88), 224 (31), 197 (96), 182 (58), 84 (55), 49 (84), 36 (100)	7.58 (1 H, s, ArH), 4.21 (2 H, s, $ArCH_2N$), 3.96 3.90 (3 H, s, OMe), 2.39 (3 H, s, SMe), 1.88 (1 H, s, NH[a]), 1.67–1.50 (10 H, br, C_5H_{10})
(**6b**)	3 320	1 660	281 (M^+, 49%), 224 (100), 208 (34), 197 (8), 182 (61), 58 (81), 29 (15)	7.59 (1 H, s, ArH), 4.28 (2 H, $ArCH_2N$), 3.97 (3 H, s, OMe), 3.94 (3 H, OMe), 2.39 (3 H, s, SMe), 2.08 (1 H, s, NH[a]), 1.36 (6 H, s, CH_3)
(**7a**)	3 300	1 650	321 (M^+, 60%), 306 (17), 250 (48), 246 (88), 224 (31), 197 (96), 182 (58), 84 (55), 49 (84), 36 (100)	6.68 (1 H, s, ArH), 4.12 (2 H, s, $ArCH_2N$), 3.95 (3 H, s, OMe), 3.80 (3 H, s, OMe), 2.42 (3 H, s, SMe) 2.05 (1 H, s, NH[a]), 1.84–1.68 (10 H, br, C_5H_{10})
(**7b**)	3 280	1 650	321 (M^+, 37%), 224 (100), 209 (41), 196 (45), 182 (50), 58 (97)	6.65 1 H, s, ArH), 4.15 (2 H, s, $ArCH_2N$), 3.92 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.42 (3 H, s, SMe), 2.10 (1 H, s, NH[a]), 1.42 (6 H, s, CH_3)

[a] 1 H exchangeable.

Table 4. 1,2-Dihydroisoquinolin-4(3*H*)-ones.

Compound	M.p., *t*/°C[a]	Found (%) C	H	N	Required (%) C	H	N
(**2a**)	98[b]						
(**2b**)	198[c]	57.6	6.8	5.2	57.4	6.7	5.2
(**3a**)	75	69.4	7.6	5.2	69.6	8.0	5.1
(**3b**)	—			*d*			
(**6a**)	67–68	63.8	7.2	4.3	63.5	7.2	4.3
(**6b**)	Oil						
(**7a**)	102–104	63.8	7.5	4.3	63.5	7.2	4.3
(**7b**)	110–112	60.1	6.8	4.9	59.8	6.8	5.0

[a] From light petroleum (b.p. 60–80 °C). [b] Lit.,[2] 106 °C. [c] Of hydrochloride (from methanol–ether, 1:1). [d] Found: M^+, 235.1179; $C_{13}H_{17}NO_3$ requires *M*, 235.1176.

Cyclisation of 2-(2,3-*dimethoxybenzylamino*)-2-*methylpropionitrile* (**1b**). Work-up using method A yielded a brown oil (0.66 g). ^{1}H NMR and TLC of the product suggested the presence of 1,2-dihydro-5,6-dimethoxy-3,3-dimethylisoquinolin-4(3*H*)-one (**2b**) (R_f 0.39), and 1,2-dihydro-7,8-dimethoxy-3,3-dimethylisoquinolin-4(3*H*)-one (**3b**) (R_f 0.43), in a 4:1 ratio. Formation of the hydrochloride salt followed by preparative TLC gave (**2b**) as yellow–green needles (0.28 g, 14%), and (**3b**) as a pale yellow oil (0.06 g, 3%).

Cyclisation of 1-(4,5-*dimethoxy*-2-*methylthiobenzylamino*)-*cyclohexanecarbonitrile* (**4a**). Work-up using method B yielded a pale oil (1.55 g). TLC showed the presence of one major product plus three minor ones. These were separated by column chromatography. The three minor components were 1,2-dihydro-6,7-dimethoxy-8-methylthioisoquinoline-3-spirocyclohexan-4(3*H*)-one (**6a**) (0.12 g, 6%; R_f 0..87), the starting aminoacetonitrile (**4a**) (0.06 g, 3%; R_f 0.75), and the corresponding 7,8-dimethoxy compound (**7a**) (0.04 g, 2%; R_f 0.58). The major product obtained as a colourless oil was 4-(4,5-dimethoxy-2-methylthiophenyl)-4,5-dihydroimidazole-5-spirocyclohexane (**5a**) (1.34 g, 67%; R_f 0.39) (Found: M^+, 320.1552; $C_{17}H_{24}N_2O_2S$ requires *M*, 320.1545); ν_{max} 3 260 (NH) and 1 590 (C=N) cm^{-1}; *m/z* 320 (M^+ 1.3%), 305 (2), 276 (3), 111 (100), 110 (23), 83 (40), and 82 (10); δ_H 6.97 (1 H, s, ArH), 6.66 (1 H, s, ArH), 4.89 (2 H, s, $ArCH_2N$), 3.92 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.40 (3 H, s, SMe), 1.85 (1 H, br, NH, exchangeable), and 1.84–1.48 (10 H, br, C_5H_{10}).

Cyclisation of 2-(4,5-*dimethoxy*-2-*methylthiobenzylamino*)-2-*methylpropionitrile* (**4b**). Work-up using method B yielded a pale oil (1.8 g). TLC showed one major product plus two minor ones. These were separated by column chromatography. The two minor products were identified as 1,2-dihydro-6,7-dimethoxy-3,3-dimethyl-8-methylthioisoquinolin-4(3*H*)-one (**6b**) (0.08 g, 4%; R_f 0.78), and 1,2-dihydro-7,8-dimethoxy-3,3-dimethyl-5-methylthioisoquinolin-4(3*H*)-one (**7b**) (0.06 g, 3%; R_f 0.59). The major product, obtained as a white solid was 2,5-*dihydro*-4-(4,5-*dimethoxy*-2-*methylthiophenyl*)-5,5-*dimethylimidazole* (**5b**) (1.2 g, 60%; R_f 0.45), m.p. 64–66 °C (Found: C, 60.1; H, 7.5; N, 9.8%. $C_{14}H_{20}N_2O_2S$ requires C, 60.0; H, 7.2; N, 10.0%); ν_{max} 3 260 (NH) and 1 590 (C=N) cm^{-1}; *m/z* 280 (M^+, 0.8%), 265 (1.4), 84 (13), 72 (36), and 71 (100); δ_H 6.96 (1 H, s, ArH), 6.74 (1 H, s, ArH), 4.89 (2 H, s, $ArCH_2N$), 3.93 (3 H, s, OMe), 2.42 (3 H, s, SMe), 2.39 (1 H, s, NH, exchangeable), and 1.36 (6 H, s, CH_3).

Cyclisation of 1-(2,3-*dimethoxy*-5-*methylthiobenzylamino*)-*cyclohexanecarbonitrile* (**8a**). Work-up using method A yielded a brown oil (1.05 g). TLC showed one major and one minor component which were separated by column chromatography. The major product was the dimethoxy compound (**7a**) (0.68 g, 34%; R_f 0.60). The minor component was uncyclised starting material (0.32 g, 16%; R_f 0.79).

Cyclisation of 1-(2,3-*dimethoxy*-5-*methylthiobenzylamino*)-2-

Table 5. 1,2,3,4-Tetrahydroisoquinolin-4-ols.

Compound	Yield (%)	ν_{max}/cm^{-1} (NH)	*m/z*	δ_H
(**9a**)	60[a]/48[b]	3 440	227 (M^+, 16%), 275 (21), 257 (21), 206 (19), 180 (43), 165 (24), 136 (21), 98 (100), 40 (76), 29 (51)	6.95 (2 H, ABq, *J* 7 Hz, 2 ArH), 4.14 (1 H, s, C*H*OH) 3.96 (2 H, d, *J* 3 Hz $ArCH_2N$), 3.85 (3 H, s, OMe) 3.81 (3 H, s, OMe), 2.23 br (2 H, br, NH[c] and OH[c]), 1.60–1.26 (10 H, br, C_5H_{10})
(**9**)	55[a]/41[b]	3 300	237 (M^+, 10%), 220 (5), 204 (3), 101 (31), 165 (11), 58 (100), 42 (53), 39 (20), 27 (23)	6.92 (2 H, ABq, *J* 8 Hz, 2 ArH), 4.19 (1 H, s, C*H*OH) 4.11 (2 H, d, *J* 4.5 Hz, $ArCH_2N$), 3.84 (3 H, s. OMe) 3.80 (3 H, s, OMe), 1.42 (2 H, br, NH[c] and OH[c]), 1.40 (3 H, s, Me), 1.29 (3 H, s, Me)
(**10**)	55[a]	3 340	277 (M^+, 11%), 275 (10), 257 (44), 180 (73), 166 (50), 151 (6.8), 136 (54), 98 (100), 40 (60), 29 (42)	6.82 (1 H, s, ArH), 6.40 (1 H, s, ArH), 4.10 (1 H, s, C*H*OH), 3.86 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.79 (2 H, s. $ArCH_2N$), 2.45 (2 H, br, NH[c] and OH[c]), 1.59–1.19 (10 H, br, C_5H_{10})

[a] From sodium borohydride reduction of 1,2-dihydroisoquinolin-4(3*H*)-ones. [b] From nickel boride desulphurisation of 1,2-dihydroisoquinolin-4(3*H*)-ones. [c] 1 H exchangeable.

methylpropionitrile (**8b**). Work-up using method A yielded a brown oil (0.8 g). TLC showed two products, which were identified by column chromatography as the isoquinolinone (**7b**) (0.6 g, 30%; R_f 0.47) and uncyclised starting material (0.2 g, 10%; R_f 0.84).

Sodium Borohydride Reductions.—Isoquinolin-4(3*H*)-ones (**3a**), (**3b**) and (**6a**) were reduced under standard conditions to give the corresponding 1,2,3,4-tetrahydroisoquinolin-4-ols (**9a**), (**9b**), and (**10**). Spectroscropic and analytical data are presented in Table 5.

Nickel Boride Desulphurisations.—Isoquinolin-4(3*H*)-ones (**7a**) and (**7b**) were reductively desulphurised in accordance with literature methods.[7,8] The respective products (**9a**) and (**9b**) were isolated upon work-up as uncrystallisable glasses. Spectroscopic and analytical data are presented in Table 5.

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