# Investigation of the Bischler Indole Synthesis from 3,5-Dimethoxyaniline

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## Abstract

Cyclization of the amino ketones (3a,b) derived from 3,5-dimethoxyaniline, and phenacyl bromide and 4-bromophenacyl bromide respectively, afforded 2-arylindoles (8a,b) in preference to 3-arylindoles (7). The 3-(4'-bromophenyl)indole (7b) was also isolated in the presence of polyphosphoric acid, but not when amine hydrochloride catalysis was employed. The structure of 2-(4'-bromophenyl)-4,6-dimethoxyindole (8b) was confirmed by X-ray diffraction studies.

In connection with a program of ligand synthesis some 4,6-dimethoxyindoles were required. Consequently the behaviour of 3,5-dimethoxyaniline (1) under conditions of the Bischler reaction was investigated.



#### Scheme 1

Reaction of 3,5-dimethoxyaniline (1) with phenacyl bromide (2a) and 4-bromophenacyl bromide (2b) respectively afforded the aryl amino ketones (3a,b) in good yield (Scheme 1). Compounds (3a,b) were characterized fully by analytical and spectroscopic data.

The Bischler cyclization of amino ketones such as (3a,b) to indoles is usually performed at relatively high temperatures under conditions which allow equilibration of intermediates such as (4)–(6) to occur (Scheme 2). The rate of equilibration (4)  $\rightleftharpoons$  (6) is usually faster than the rate of cyclization and as a consequence 2-arylindoles are formed in preference to 3-arylindoles.<sup>1,2</sup> Thus, it could be predicted that the amino

<sup>&</sup>lt;sup>1</sup> Sundberg, R. J., 'The Chemistry of Indoles' p. 164, and references cited therein (Academic Press: New York 1970).

<sup>&</sup>lt;sup>2</sup> Brown, R. K., in 'Indoles Part One' (Ed. W. J. Houlihan) p. 317, and references cited therein (Wiley-Interscience: New York 1972).

ketones (3a,b) would yield 2-arylindoles (8) in preference to the 3-substituted isomers (7). However, the presence of the two methoxy groups should result in a very significant increase in the rate of cyclization relative to that of equilibration and should enhance the possibility of the formation of the 3-arylindoles (7). No such highly activated substrates have been tested in the Bischler reaction with  $\alpha$ -halo ketones which could lead to different products.



The amino ketone (3a) was heated in silicone oil at  $120-140^{\circ}$  with added 3,5dimethoxyaniline (1) and its hydrobromide salt, and afforded only one observable product, as an oil which could not be crystallized. The same product was obtained after heating the amino ketone (3a) in polyphosphoric acid. By analogy with previous work, the 2-arylindole structure (8a) could be assigned, but the spectroscopic data could be consistent with either structure (7) or (8).



Reaction of the amino ketone (3b) in silicone oil, as described above, afforded a single product, m.p.  $135-136^{\circ}$ , while the polyphosphoric acid conditions yielded two isomeric products, of m.p.  $135-136^{\circ}$  and  $180-181^{\circ}$  respectively in the ratio of 4 : 3. Again, by analogy, the lower-melting isomer could be assigned the 2-arylindole

structure (8b) and the higher-melting isomer that of (7b). However, again the spectroscopic data provided only circumstantial evidence in favour of these assignments. For instance, the <sup>1</sup>H n.m.r. spectra of the lower- and higher-melting isomers each contained three doublets for the indole hydrogens at  $\delta$  6.25, 6.42, 6.85 and 6.37, 6.55, 7.04 respectively. These can be compared with <sup>1</sup>H n.m.r. data for indoles in general<sup>3</sup> and 4,6-dimethoxyindole in particular, and for which the following assignments have been reported:<sup>4</sup>  $\delta$  6.13 (H 5), 6.30 (H 3), 6.48 (H 7), 7.01 (H 2). Assuming some effect of a 2- or 3-(4'-bromophenyl) substituent on chemical shift values, it is possible to assign H 5, H 3, H 7 or H 5, H 7, H 2 in that order to either group of values shown for the two isomers. The value of  $\delta$  7.04 as compared with 6.85 provides a marginal preference for an assignment of H 2, which would indicate structure (7b) for the higher-melting isomer, but such an assignment is far from secure.

Chemical replacement of selected indole hydrogens by electrophilic substitutions would not be of help because substitution could occur at C3, C2 or C7.

The lower-melting isomer absorbs at longer wavelength (335 nm) than the highermelting compound (300 nm) and this would support the assignments of structure (8b) and (7b) respectively.

Use of the Fischer indole synthesis would provide an unambiguous preparation of the compound (8b) by reaction of 3,5-dimethoxyphenylhydrazine with 4-bromoacetophenone. In our hands, all attempts to prepare the hydrazine led to self-coupling of the amine with the intermediate diazonium salt to form an azo dye.<sup>†</sup>

In view of the uncertainty of the above assignments based on spectroscopic properties, the X-ray crystal structure of the lower-melting isomer was determined, as described below, and this confirmed the validity of the assignment of structure (8b) to it. On this basis the proposed assignment of structure (7b) is confirmed and the assignment of structure (8a) is placed on a firmer but still circumstantial basis.

These results show that, even with the presence of electron-donating methoxy substituents in the amino ketones (3), the formation of 2-arylindoles is preferred in the Bischler reaction.

## **Crystal Structure Analysis**

The molecular structure of 2-(4'-bromophenyl)-4,6-dimethoxyindole (8b) is illustrated in Fig. 1 together with the numbering scheme used; bond lengths are given in Table 1 and both these and the bond angles<sup>‡</sup> are within the ranges normally observed. Details of least-squares planes and selected torsion angles are given in Tables 2 and 3 and show that the plane of the bromophenyl substituent is inclined at an angle of  $29 \cdot 8^{\circ}$  to the plane of the indole skeleton. O(4) and O(6) are 0.04(1) and 0.01(1) Å below the plane of the indole skeleton respectively. The structure analysis has confirmed the formation of 2-(4'-bromophenyl)-4,6-dimethoxyindole.

<sup>†</sup> Since the completion of our investigation, suitable conditions have been reported for the formation of 3,5-dimethoxyphenylhydrazine fluoroborate.<sup>5</sup>

<sup>‡</sup> A table of bond angles and a list of observed and calculated structure factors can be obtained on application to the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, East Melbourne, Vic. 3002.

<sup>3</sup> Hiremath, S. P., and Hosmane, R. S., Adv. Heterocycl. Chem., 1973, 15, 277.

<sup>4</sup> Brown, V. H., Skinner, W. A., and De Graw, J. I., J. Heterocycl. Chem., 1969, 6, 539.

<sup>5</sup> Ibaceta-Lizana, J. S., Iyer, R., Jackson, A. H., and Shannon, P. V. R., J. Chem. Soc., Perkin Trans. 2, 1978, 734.



Table 1. Interatomic distances (Å) with estimated standard deviations in parentheses

Atoms	Dist.	Atoms	Dist.	Atoms	Dist.	Atoms	Dist.
C(1')-C(2')	1.42(2)	C(4')-Br	1.92(1)	N-C(2)	1.40(2)	C(4)-O(4)	1.36(2)
C(2')-C(3')	1.37(2)	C(1')-C(2)	$1 \cdot 49(2)$	C(3a)-C(4)	$1 \cdot 40(2)$	O(4)-C(8)	$1 \cdot 43(2)$
C(3')-C(4')	$1 \cdot 36(2)$	C(2) - C(3)	$1 \cdot 35(2)$	C(4) - C(5)	$1 \cdot 37(2)$	C(6)–O(6)	$1 \cdot 43(2)$
C(4')-C(5')	$1 \cdot 39(2)$	C(3)-C(3a)	$1 \cdot 43(2)$	C(5)–C(6)	$1 \cdot 41(2)$	O(6)-C(9)	$1 \cdot 45(2)$
C(5')-C(6')	$1 \cdot 41(1)$	C(3a)–C(7a)	$1 \cdot 41(2)$	C(6)-C(7)	$1 \cdot 37(2)$		
C(1')-C(6')	1.39(2)	C(7a)-N	$1 \cdot 37(2)$	C(7)–C(7a)	$1 \cdot 43(2)$		

Table 2. Equations of mean planes and deviations of individual atoms

Plane	Defining	Orthogonal		Deviati	ons (Å)		Coord, of centre
	atoms	coordinates <sup>A</sup>	Atom	$\Delta d$	Atom	$\Delta d$	of gravity
I	C(4) C(5) C(6) C(7)	$\begin{array}{ccc} X & -0.6747 \\ Y & 0.6672 \\ Z & -0.3156 \end{array}$	C(3a) C(7a) C(3) N C(2)	$ \begin{array}{c} -0.04(1) \\ 0.01(1) \\ -0.04(1) \\ 0.02(1) \\ 0.01(1) \end{array} $	C(8) O(4) C(9) O(6)	$ \begin{array}{r} 0.17 \\ -0.04(1) \\ -0.13(1) \\ -0.01(1) \end{array} $	2 · 1075 - 2 · 4436 2 · 3839
<b>II</b>	C(1') C(2') C(3') C(4') C(5') C(6')	$\begin{array}{ccc} X & -0.2185 \\ Y & 0.8716 \\ Z & -0.4389 \end{array}$	C(2) C(3)	0.02(1) -0.50(1)	N	0.64(1)	1 · 7709 0 · 2116 8 · 5966

The angle between normals to the planes is  $29 \cdot 8^{\circ}$ 

<sup>A</sup> Of the plane equation X + Y + Z = 0.

	Table 3.	Torsion angles	(degrees) :	for a cha	in of	'atoms 1–:	2-3-4
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1	2	3	4	Angle	Remarks
C(9)	O(6)	C(6)	C(7)	5(2)	the sign of the angle is
C(9)	O(6)	C(6)	C(5)	-176(1)	positive if when looking
C(8)	O(4)	C(4)	C(3a)	172(1)	from 2 to 3 one could
C(8)	O(4)	C(4)	C(5)	-11(2)	superimpose 1 on 4 by
C(2')	C(1')	C(2)	C(3)	-34(2)	a clockwise motion
C(2')	C(1')	C(2)	N	150(1)	

### Collection and Reduction of X-ray Data

A single crystal, suitable for X-ray structural analysis, was mounted on a silica fibre with an epoxy cement. The space group was determined as  $P2_{1/n} (C_{2h}^5, \text{ No. 14})^6$  from systematic absences 0k0 for k odd, h0l for h+l odd. (The alternative setting  $P2_{1/n}$  was chosen to make  $\beta$  near 90°.) Reflection intensity data were measured with a Philips PW 1100 computer-controlled four-circle diffractometer by the  $\theta$ -2 $\theta$  scan technique. The procedures for data collection and reduction have been described in detail elsewhere.<sup>7</sup>

Crystal data.— $C_{16}H_{14}BrNO_2$ , M 332·2, a 14·583(7), b 8·554(4), c 11·569(5) Å,  $\beta$  93·3(4)°, U 1440·76 Å<sup>3</sup>,  $\rho_{obs}$  1·53(2) g cm<sup>-3</sup> (flotation),  $\rho_{calc}$  1·53 g cm<sup>-3</sup> for Z = 4. Crystal dimensions (solvent eroded, ovoid in shape) 0·11 by 0·19 by 0·19 mm,  $\mu$  (Mo K $\alpha$ ) 30·2 cm<sup>-1</sup>.

Data collection.—Mo K $\alpha$  radiation,  $\lambda 0.7107$  Å, graphite crystal monochromated,  $2\theta_m 12.3^\circ$ ,  $\theta$  scan rate  $0.05^\circ$  s<sup>-1</sup>;  $\theta$  range 3–30°; scan width  $(1.00+0.30\tan\theta)^\circ$ ; three standard reflections monitored every 2 h showed no significant variations in angle or intensity. Total number of reflections measured, 4192; number of unique data with  $I/\sigma(I) \ge 4.0$ , 790. No absorption or extinction corrections were applied.

#### Structure Solution and Refinement

The bromine atom was located by the Patterson method and all remaining atoms, with the exception of hydrogen, were located in successive difference Fourier syntheses. Full-matrix least-squares refinement with anisotropic thermal parameters for bromine and isotropic thermal parameters for all other atoms converged at  $R \ 0.066$ ,  $R_w \ 0.048$ ;  $\dagger$  individual reflection weights of  $[\sigma(F)]^{-2}$  were used. Although a difference Fourier revealed some hydrogen atom positions the coordinates of all hydrogen atoms bonded to carbon and nitrogen were calculated with C-H or N-H = 1.08 Å. During refinement the hydrogen atoms were allowed to ride on the atom to which they are bonded; two isotropic thermal parameters were used, one for a benzene type hydrogen, the other for primary CH<sub>3</sub> type hydrogen atoms.

In the final cycle of refinement no parameter shift exceeded 1.0% of the e.s.d. in that parameter, with the exception of  $U_{11}$  of the benzene type hydrogen atoms; this was 3%. The final difference Fourier synthesis was featureless with residual electron density in the range -0.4 to  $0.4 \text{ e/Å}^3$ . Analysis of the weighting scheme showed that the function minimized by the least-squares procedure,  $\Sigma w \Delta^2$ , was essentially independent of both  $F_0$  and  $\sin(\theta/\lambda)$ . Scattering factors for all atoms, with the exception of Br°, were taken from ref.<sup>6</sup> (Vol. 4), Br° from ref.<sup>8</sup>, and were corrected for anomalous dispersion effects ( $\Delta f', \Delta f''$ ).

The final atomic positional and thermal parameters, with estimated standard deviations, are given in Tables 4 and 5. Tables of the final observed and calculated structure factor amplitudes are available.<sup>‡</sup> All calculations were performed on the Monash University Burroughs B6700 computer with the aid of the following programs: PW1100 Data Processing Program,<sup>9</sup> sHELX-76,<sup>10</sup> ORTEP,<sup>11</sup> ORTEF<sup>12</sup> and MEANPL.<sup>13</sup>

## Experimental

Melting points and boiling points were uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Ultraviolet spectra were measured with a Unicam

 $\dagger R = \Sigma \Delta / \Sigma |F_{o}|, R_{w} = [\Sigma w \Delta^{2} / \Sigma w |F_{o}|^{2}]^{1/2}, \text{ where } \Delta = ||F_{o}| - |F_{c}||.$ 

‡ See footnote on page 345.

<sup>6</sup> 'International Tables for X-Ray Crystallography' Vol. 1 (Kynoch Press: Birmingham 1974).

<sup>7</sup> Gatehouse, B. M., and Miskin, B. K., Acta Crystallogr., Sect. B, 1974, 30, 1311.

<sup>8</sup> Cromer, D. T., and Mann, J. B., Acta Crystallogr., Sect. A, 1968, 24, 31.

<sup>9</sup> Hornstra, J., and Stubbe, B., Philips Research Laboratories, Eindhoven, The Netherlands, 1972.
 <sup>10</sup> Sheldrick, G., SHELX-76, Program for Crystal Structure Determination, 1976, Cambridge University, U.K.

<sup>11</sup> Johnson, C. K., ORTEP, 1965, Oak Ridge National Laboratory Report ORNL-3794.

<sup>12</sup> Busing, W. R., Martin, K. O., and Levy, H. A., ORFFE, 1964, Oak Ridge National Laboratory Report ORNL-TM-306.

<sup>13</sup> Blow, D. M., MEANPL, Acta Crystallogr., Sect. A, 1960, 13, 168.

SP800 spectrophotometer and refer to solutions in 95% ethanol. Infrared spectra were recorded by a Perkin-Elmer 257 grating infrared spectrometer and refer to thin films of liquids and paraffin mulls of solids. <sup>1</sup>H n.m.r. spectra were measured at 60 MHz with a Varian A56/60 spectrometer and refer to solutions in deuterochloroform with tetramethylsilane as internal reference, unless otherwise stated. Spectra are reported in the following order: chemical shift ( $\delta$ ), multiplicity, coupling constant, assignment. Signals due to the protons of NH and OH groups were identified by exchange with D<sub>2</sub>O. Low-resolution mass spectra were measured at 70 eV with a Hitachi Perkin-Elmer RMU-6E spectrometer. The principal ion peaks (*m/e*) are reported together with their intensities (usually >20%) relative to the base peak.

	$U_{33}l^{-}c^{+}+2U$	$\frac{12^{nka}b^{*}+2U_{13}na}{2}$	$d^{+}c^{+}+2U_{23}\kappa lb^{+}$	<i>c</i> +)]
Atom	10 <sup>4</sup> x	10 <sup>4</sup> <i>y</i>	10 <sup>4</sup> z	$10^{3} U_{11}/U_{ m isc}$
Br	1208(1)	1950(2)	9957(1)	110(1) <sup>A</sup>
O(4)	49(6)	-4768(11)	2945(7)	62(2)
O(6)	2206(6)	- 2606(10)	439(7)	60(3)
Ν	1808(7)	-715(12)	4386(8)	50(3)
C(2)	1206(9)	-1251(14)	5196(11)	46(4)
C(3)	716(8)	-2466(14)	4752(10)	46(4)
C(3a)	984(8)	-2737(16)	3599(10)	46(4)
C(4)	709(9)	-3732(16)	2686(11)	54(4)
C(5)	1121(9)	-3658(14)	1656(11)	48(4)
C(6)	1823(9)	-2551(14)	1544(10)	49(4)
C(7)	2129(8)	-1482(14)	2355(10)	48(4)
C(7a)	1664(8)	-1605(15)	3406(10)	42(4)
C(8)	- 358(9)	-5695(14)	2019(11)	69(5)
C(9)	2977(8)	-1588(14)	267(9)	57(4)
C(1')	1235(9)	-483(15)	6352(10)	43(4)
C(2')	409(9)	-414(14)	6945(10)	45(4)
C(3′)	409(9)	284(14)	8013(11)	49(4)
C(4′)	1191(10)	954(15)	8468(10)	55(4)
C(5')	2028(9)	945(14)	7949(11)	57(4)
C(6')	2014(10)	199(15)	6858(11)	58(4)

Table 4. Final non-hydrogen atomic cell coordinates and thermal parameters Thermal parameters are of the form  $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+$ 

<sup>A</sup> Bromine atom refined anisotropically:  $U_{22}$  88(1),  $U_{33}$  51(1),  $U_{23}$  -20(1),  $U_{13}$  26(1),  $U_{12}$  -4(2).

Table 5. Hydrogen atomic cell coordinat
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Hydrogen thermal parameters were 127(20) for benzene type atom-H, and 81(17) for methyl type C-H (see text)

Atom	10 <sup>3</sup> x	10 <sup>3</sup> y	10 <sup>3</sup> z	Atom	$10^{3}x$	10 <sup>3</sup> y	10 <sup>3</sup> z
H(1)	230	23	451	H(91)	320	- 174	- 60
H(3)	21	- 312	519	H(92)	353	-187	89
H(5)	91	- 443	95	H(93)	277	- 39	39
H(7)	266	64	222	H(2')	-22	-91	656
H(81)	-87	- 646	235	H(3')	-21	30	848
H(82)	71	- 639	164	H(5')	264	147	835
H(83)	- 68	- 494	137	H(6')	264	16	640

2-[(3,5-Dimethoxyphenyl)amino]-1-phenylethanone (3,5-Dimethoxy-N-phenacylaniline) (3a)

A mixture of 3,5-dimethoxyaniline ( $6 \cdot 2$  g,  $0 \cdot 04$  mol), phenacyl bromide ( $8 \cdot 3$  g,  $0 \cdot 04$  mol) and sodium hydrogen carbonate ( $4 \cdot 2$  g,  $0 \cdot 05$  mol) in absolute ethanol (150 ml) was heated under reflux

for 4 h with stirring. After cooling, the resulting precipitate was filtered off, washed thoroughly with water, then recrystallized from methanol to afford the *product* (3a) (7·7 g, 73%) as needles, m.p. 116–117° (Found: C, 71·0; H, 6·5; N, 5·3.  $C_{16}H_{17}NO_3$  requires C, 70·8; H, 6·3; N, 5·2%).  $\nu_{max}$  3400m, 1690s, 1610s, 1590s, 1320m, 1250m, 1200s, 1070s, 960m, 800m, 760s, 690s cm<sup>-1</sup>. <sup>1</sup>H n.m.r. spectrum:  $\delta 3 \cdot 78$ ,  $3 \cdot 81$ , each s, OCH<sub>3</sub>; 4·60, s, CH<sub>2</sub>; 5·92–5·97, m, aryl protons; 7·42–8·12, m, phenyl protons. Mass spectrum: *m/e* 271 (M, 33%), 165 (100), 138 (20), 123 (20), 122 (31).

#### 1-(4-Bromophenyl)-2-[(3,5-dimethoxyphenyl)amino]ethanone (3b)

3,5-Dimethoxyaniline (8 · 0 g, 0 · 05 mol), 4-bromophenacyl bromide (15 · 0 g, 0 · 05 mol) and sodium hydrogen carbonate (5 · 0 g, 0 · 06 mol) in absolute ethanol (150 ml) similarly afforded the *amino ketone* (3b) (13 · 5 g, 75%) as prisms, m.p. 134–135° (from methanol) (Found: C, 54 · 9; H, 4 · 7; N, 3 · 9. C<sub>16</sub>H<sub>16</sub>BrNO<sub>3</sub> requires C, 54 · 9; H, 4 · 6; N, 4 · 0%).  $v_{max}$  3400w, 1675s, 1610s, 1580s, 1310s, 1250m, 1200s, 1150s, 1090m, 810m, 680m cm<sup>-1</sup>. <sup>1</sup>H n.m.r. spectrum:  $\delta$  3 · 78, s, OCH<sub>3</sub>; 4 · 52, s, CH<sub>2</sub>; 5 · 90–5 · 95, m, aryl protons; 7 · 60–7 · 95, m, aryl protons. Mass spectrum: *m/e* 351 (M, <sup>81</sup>Br, 35%), 349 (M, <sup>79</sup>Br, 33), 185 (50), 183 (50), 166 (100), 157 (28), 155 (28), 124 (21).

#### Cyclization of Amino Ketone (3a)

(i) The amino ketone (3a) (1.2 g, 0.004 mol), 3,5-dimethoxyaniline (1.36 g, 0.008 mol) and its hydrobromide (0.06 g, 0.3 mmol) were intimately mixed in silicone oil (10 ml) and the mixture heated at 120–140° for 1 h. After cooling, the reaction mixture was washed thoroughly with n-hexane, and the residue was dissolved in chloroform and the chloroform solution washed with 10% hydrochloric acid, dried and concentrated to afford 4,6-dimethoxy-2-phenylindole (8a) as an oil (0.85 g, 75%) which could not be crystallized.  $\lambda_{max}$  250 nm ( $\varepsilon$  16800), 325 (17200).  $\nu_{max}$  3400m, 1620m, 1500m, 1360m, 1330m, 1270s, 1200s, 1140s, 1120s, 1040s, 800s, 750s cm<sup>-1</sup>. <sup>1</sup>H n.m.r. spectrum:  $\delta$  3.85, 3.97, each s, OCH<sub>3</sub>; 6.29, 6.55, 6.94, each d, J 2 Hz, indole protons; 7.30–7.80, m, phenyl protons and NH. Mass spectrum: m/e 253 (M, 100%), 238 (49), 195 (74), 167 (21), 166 (20), 139 (39).

(ii) Phosphoric acid (2 ml) was added to phosphorus pentoxide (2 g) and the mixture was stirred at 100° while the amino ketone (3a) (0.5 g) was added in small portions. The resulting mixture was stirred at 110° for a further 45 min. On cooling, it was diluted with water (50 ml) and extracted with chloroform. The extract was washed with 5% sodium hydrogen carbonate, dried and concentrated to give a red oil (0.45 g) which was purified by chromatography on silica gel and elution with light petroleum/chloroform (2 : 1) to give 4,6-dimethoxy-2-phenylindole (8a) (0.2 g, 46%), with identical spectroscopic properties as the previously prepared sample.

#### Cyclization of Amino Ketone (3b)

(i) The amino ketone (3b)  $(1 \cdot 0 \text{ g}, 0 \cdot 002 \text{ mol})$  was heated with 3,5-dimethoxyaniline  $(0 \cdot 75 \text{ g}, 0 \cdot 004 \text{ mol})$  and its hydrobromide  $(0 \cdot 04 \text{ g})$  in silicone oil (5 ml) as described above. The reaction mixture afforded 2-(4'-bromophenyl)-4,6-dimethoxyindole (8b)  $(0 \cdot 65 \text{ g}, 70\%)$  as needles, m.p. 135–136° (from light petroleum/chloroform) (Found: C, 57 · 7; H, 4 · 3; N, 4 · 1. C<sub>16</sub>H<sub>14</sub>BrNO<sub>2</sub> requires C, 57 · 8; H, 4 · 2; N, 4 · 2%).  $\lambda_{max}$  254 nm ( $\epsilon$  16900), 335 (20600).  $\nu_{max}$  3405w, 1620m, 1590m, 1365m, 1270s, 1215s, 1200s, 1150m, 1130m, 1040m, 810m, 790s cm<sup>-1</sup>. <sup>1</sup>H n.m.r. spectrum:  $\delta$  3 · 80, 3 · 91, each s, OCH<sub>3</sub>; 6 · 25, 6 · 42, 6 · 85, each d, J 2 Hz, indole protons; 7 · 25–7 · 46, m, bromophenyl protons; 8 · 18, s(b), NH. Mass spectrum: m/e 333 (M, <sup>81</sup>Br, 90%), 331 (M, <sup>79</sup>Br, 90), 318 (27), 316 (26), 275 (100), 273 (100), 252 (36), 237 (28), 209 (28), 195 (27), 167 (34).

(ii) The amino ketone  $(1 \cdot 0 \text{ g})$  was treated with polyphosphoric acid (from phosphoric acid (5 ml) and phosphorus pentoxide (5 g)) as described above. The crude product was purified by chromatography on silica gel. Elution with light petroleum/chloroform (85 : 15) afforded 3-(4'-bromophenyl)-4,6-dimethoxyindole (7b) (0 \cdot 3 g, 32%) as needles, m.p. 180–181° (from light petroleum/chloroform) (Found: C, 57 · 6; H, 4 · 4; N, 4 · 2. C<sub>16</sub>H<sub>14</sub>BrNO<sub>2</sub> requires C, 57 · 8; H, 4 · 2; N, 4 · 2%).  $\lambda_{max}$  248 nm ( $\epsilon$  19800), 275 (15600), 300sh (12500).  $\nu_{max}$  3340w, 1610m, 1580m, 1535m, 1370s, 1320m, 1210m, 1200s, 1150s, 1125m, 1045m, 1000m, 960m, 830m cm<sup>-1</sup>. <sup>1</sup>H n.m.r. spectrum:  $\delta$  3 · 82, 3 · 89, each s, OCH<sub>3</sub>; 6 · 37, 6 · 55, 7 · 04, each d, J 1 · 5 Hz; 7 · 32–7 · 65, m, bromophenyl protons; 8 · 10, s(b), NH. Mass spectrum: m/e 333 (M, <sup>81</sup>Br, 100%), 331 (M, <sup>79</sup>Br, 100), 275 (50), 273 (48), 252 (22), 222 (45), 195 (36), 187 (23), 167 (23), 135 (27).

Elution with light petroleum/chloroform (75:25) gave 2-(4'-bromophenyl)-4,6-dimethoxyindole (8b) (0.4 g, 42 %), which showed identical spectroscopic properties to those described for the sample obtained from method (i).

## 2,6,3',5'-Tetramethoxyazobenzen-4-amine Hydrochloride

A solution of 3,5-dimethoxyaniline (4.0 g) in concentrated hydrochloric acid (3 ml) and water (10 ml) was cooled to 0° and treated carefully with a cold solution of sodium nitrite (2.0 g) in water (10 ml) at 0°. The resulting red precipitate was recrystallized from aqueous methanol to give the *product* (2.6 g, 56%) as bright red flakes, m.p. 215° (Found: C, 53.7; H, 5.6; N, 11.6.  $C_{16}H_{20}ClN_3O_4$  requires C, 54.2; H, 5.7; N, 11.9%).  $\lambda_{max}$  455 nm ( $\varepsilon$  24900).  $\nu_{max}$  3200w, 3050m, 1620s, 1600s, 1540s, 1460s, 1380s, 1230m, 1150m, 1050m, 950m, 820s cm<sup>-1</sup>. <sup>1</sup>H n.m.r. spectrum [(CD<sub>3</sub>)<sub>2</sub>SO]:  $\delta$  3.35, s(b), NH; 3.84, 4.02, each s, OCH<sub>3</sub>; 6.30–6.50 and 6.85–7.00, each m, aryl protons. Mass spectrum: *m/e* 317 (M–HCl, 59%), 258 (24), 180 (78), 166 (21), 137 (100), 122 (71).

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