A New Modification of the Pomeranz–Fritsch Isoquinoline Synthesis

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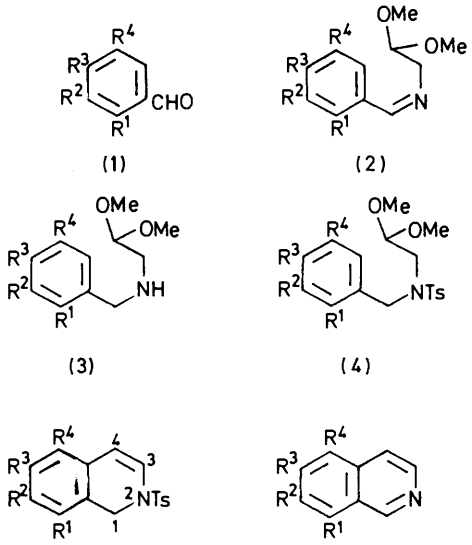
Schiff's bases formed from a variety of alkoxybenzaldehydes and aminoacetaldehyde dimethyl acetal have been hydrogenated to the corresponding benzylamines and converted into *N*-tosylates. The latter are readily cyclised in dilute mineral acid to isoquinolines in a one-pot reaction; intermediates in this reaction are *N*-tosyl-1,2-dihydroisoquinolines which can be isolated. *N*-Benzyl-*N*-tosylaminoacetaldehyde dimethyl acetal on treatment with dilute acid under the same conditions as for the cyclisation reactions gave *N*-benzyl-*N*-tosylaminoacetaldehyde, and then *N*-tosylbenzylamine; other substituted benzylamino-acetal derivatives behaved similarly when the benzyl group lacked sufficiently activating substituents for cyclisation of the acetal.

MOST of the many well-known syntheses of isoquinolines give a 1,2,3,4-tetrahydroisoquinoline as the initial product, and only one general synthesis, the Pomeranz–Fritsch [1] reaction gives isoquinolines directly, *e.g.* (2) ⟶ (6). In the original procedure strong mineral acid was usually used for the cyclisation but several modifications have been introduced subsequently including the use of different cyclisation agents.[2] The disadvantages of the cyclisation of benzylideneamino-acetals (2) to isoquinolines are well documented,[1] and these were partially overcome by the Schlittler–Müller modification.[3] More recently Bobbitt has introduced a useful modification [4] in which the benzylideneamino-acetal is reduced to a benzylamino-acetal before cyclisation; however, the product is a mixture of isoquinoline, tetrahydroisoquinoline, and other components which is normally reduced *in situ* to give the tetrahydroisoquinoline.[4] Conversion of the tetrahydroisoquinoline into the corresponding isoquinoline is, however, often difficult to achieve, or is inefficient, and none of the modifications of the Pomeranz–Fritsch method offers any great advantage either in the scope or in the overall yield of isoquinoline; however, the Bobbitt procedure [4] provides an excellent route to certain otherwise inaccessible oxygenated tetrahydroisoquinolines.

During our recent synthetic studies related to the alkaloid cularine [5] we investigated a new route to isoquinolines in which the intermediate *N*-(2-benzyloxy-3-methoxybenzyl)-*N*-tosylaminoacetaldehyde dimethyl acetal (4a) was cyclised under very mild acidic conditions to 8-benzyloxy-7-methoxy-*N*-tosyl-1,2-dihydroisoquinoline (5a). Elimination of toluene-*p*-sulphinic acid under alkaline conditions then gave 8-benzyloxy-7-methoxyisoquinoline (6a), in good yield. It was hoped that these conditions might be applied as a general synthesis of isoquinolines, and consequently veratraldehyde (1b) was condensed with aminoacetaldehyde dimethyl acetal, and the resulting Schiff's base (2b) was catalytically hydrogenated over Adams catalyst to the benzylamino-acetal (3b). Treatment of the latter with toluene-*p*-sulphonyl chloride in pyridine at 20° yielded *N*-3,4-dimethoxybenzyl-*N*-tosylaminoacetaldehyde dimethyl acetal (4b) in very good yield. This was heated under reflux in dioxan containing dilute hydrochloric acid and the course of the reaction monitored by t.l.c.; the initial product, of higher R_F than the acetal (4b), slowly disappeared with



(1) (2) (3) (4) (5) (6)

a $R^1 = OCH_2Ph$, $R^2 = OMe$, $R^3 = R^4 = H$
b $R^1 = R^4 = H$, $R^2 = R^3 = OMe$
c $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
d $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
e $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
f $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
g $R^1 = R^3 = H$, $R^2 = R^4 = OMe$
h $R^1 = R^4 = H$, $R^2,R^3 = OCH_2O$
i $R^1 = R^2 = R^3 = OMe$, $R^4 = H$
j $R^1 = H$, $R^2 = R^3 = R^4 = OMe$
k $R^1 = OH$, $R^2 = OMe$, $R^3 = R^4 = H$
l $R^1 = R^2 = R^4 = H$, $R^3 = Me$
m $R^1 = Me$, $R^2 = R^3 = R^4 = H$
n $R^1 = R^3 = Me$, $R^2 = R^4 = H$
o $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
p $R^1 = R^2 = R^3 = R^4 = H$

the concurrent formation of a second stable product of lower R_F than the acetal. When the reaction was complete, work-up yielded 6,7-dimethoxyisoquinoline (6b) in 80% overall yield from veratraldehyde; the cyclisation from the acetal (4b) to the isoquinoline proceeded in 85% yield in *ca.* 4·5 h. By working up the reaction after only 15 min, it was possible to isolate the intermediate 6,7-dimethoxy-*N*-tosyl-1,2-dihydroisoquinoline (5b) which

[1] W. J. Gensler, *Org. Reactions*, 1951, **6**, 191.
[2] M. J. Bevis, E. T. Forbes, N. N. Naik, and B. C. Uff, *Tetrahedron*, 1971, 1253.
[3] E. Schlittler and J. Müller, *Helv. Chim. Acta*, 1948, **31**, 914.
[4] J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.
[5] A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149; G. A. Charnock, A. H. Jackson, J. A. Martin, and G. W. Stewart, *J.C.S. Perkin I*, 1974, 1911.

was identified from its n.m.r. spectrum. As with other 1,2-dihydroisoquinolines,[6] compound (5b) was unstable, decomposing to a complex mixture (t.l.c.); however, when it was subjected to the original cyclisation conditions it gave 6,7-dimethoxyisoquinoline (6b) in good yield. The reaction did not proceed under purely thermal conditions and so was evidently an acid-catalysed detosylation. In a subsequent example toluene-*p*-sulphinic acid was isolated, and its presence was recognised (by t.l.c.) in most of the reactions producing isoquinolines. A possible mechanism for the reactions is shown in Scheme 1.

To test the generality of this synthetic process a series of *N*-tosyl-*N*-benzylaminoacetaldehyde dimethyl acetals was prepared (Table 1) and subjected to the same reaction conditions as those used for the cyclisation of (4b). Isoquinolines were produced directly in most cases (see Table 2) in yields of 60—98%. *N*-Tosyl-1,2-dihydroisoquinolines (5) (Table 3) were detected as intermediates in each case although their stability and ease of detosylation varied with the substituents present. The two 1,2-dihydroisoquinolines, (5a) and (5e), could not be detosylated in acid and it was necessary to use potassium t-butoxide in t-butyl alcohol to obtain the isoquinolines.

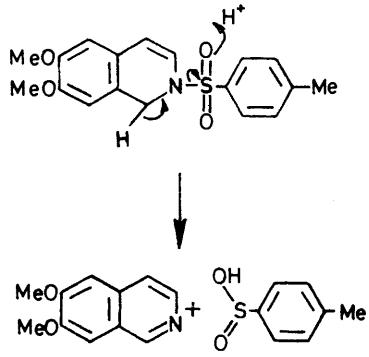
[6] S. F. Dyke, *Adv. Heterocyclic Chem.*, 1972, **14**, 279.

TABLE 1

N-Benzyl-*N*-tosylaminoacetaldehyde dimethyl acetals (4) from amines (3)

			Analyses					
			Required (%)			Found (%)		
(4)	M.p. (°)	Yield (%)	C	H	N	C	H	N
a	*	94	64·4	6·4	2·9	64·4	6·5	2·7
b	46—47	92	58·7	6·7	3·4	58·4	6·8	3·5
c	*	90	60·2	6·7	3·7	60·4	6·9	3·5
d	*	90	60·2	6·7	3·7	60·1	6·7	3·6
e	38—40	88	58·7	6·7	3·4	58·8	6·4	3·7
f	*	96	58·7	6·7	3·4	58·9	6·7	3·2
g	43—44	95	58·7	6·7	3·4	58·4	6·6	3·6
h	69—70	91	58·0	5·9	3·6	58·1	5·9	3·8
i	63—64	81	57·4	6·7	3·2	57·1	6·5	3·4
j	60—61	89	57·4	6·7	3·2	57·4	6·8	3·5
k	*	91	57·7	6·4	3·5	57·5	6·5	3·4
l	*	87	62·8	6·9	3·9	62·5	6·9	4·0
m	72—73	85	62·8	6·9	3·9	62·9	6·9	4·0
n	45—46	85	63·6	7·2	3·7	63·8	7·2	3·0
o	63—64	84	56·4	5·7	3·7	56·4	5·8	3·5
p	50—52	85	61·1	6·6	4·0	61·7	6·6	4·1

* Oil.



SCHEME 1

In general the rate of the initial cyclisation (4) ⟶ (5) seems to be governed by the reactivity of the benzene ring towards electrophilic attack, the slowest reactions being those in which there was no methoxy-substituent *para* to the position of ring closure. The second stage of the reaction [*i.e.* (5) ⟶ (6)] showed greater rate variations, ranging from no reaction at all (5a and e) to 1·5 h for complete detosylation of 5,7-dimethoxy-*N*-

TABLE 2

Isoquinolines (6) from *N*-benzyl-*N*-tosylaminoacetaldehyde dimethyl acetals (4)

	Analyses								
	Required (%)			Found (%)					
(6)	C	H	N	C	H	N	M.p. (°) [lit. m.p. (°)]	Picrate m.p. (°) [lit. m.p. (°)]	Yield (%) [lit. yield (%)]
a	55·9	3·7	11·2 [a]	55·7	3·6	11·2	*b*	172—175	74 [0] [c]
b	69·8	5·9	7·4	69·9	5·7	7·6	90—91 [89—91]	215—220	90 [70] [c]
c	49·5	3·1	14·4 [a]	49·4	2·9	14·4	49—49·5 [49] [f]	194—196 [194—195] [f]	70 [73] [c]
e	48·9	3·4	13·3 [a]	48·8	3·4	13·1	*b*	197—198 [204] [c]	88 [60—82] [c]
f	69·8	5·9	7·4	69·5	5·9	7·8	57—58 [58] [g]	210—212 [210] [g]	75
g	69·8	5·9	7·4	69·7	5·7	7·5	75—76	227	91
h	69·4	4·1	8·1	69·7	4·0	7·8	119—120 [124] [c]	204—206	85 [24] [h]
i					*i*		*b*	179—180	87
j	48·2	3·6	12·5 [a]	48·3	3·6	12·7	*b*	180—181 [179] [j]	98 [65] [j]
k					*k*		159—163 [183—184] [c]	220—225	60 [50—63] [c]

[a] For the picrate. [b] Oil. [c] Ref. 2. [d] N. Polgar, *Monatsh.*, 1929, **51**, 190. [e] F. D. Popp and W. L. McEwan, *J. Amer. Chem. Soc.*, 1957, **79**, 3773. [f] P. Fritsch, *Annalen*, 1895, **1**, 286. [g] Ref. 10. [h] P. Fritsch, G.P. 86,561 (' Friedlanders Fortschritte der Teefarbenfabrikation,' Springer, Berlin, 1894—1897, vol. 4, p. 1867). [i] Found: M^+, 219·0886. Required: *M*, 219·0895. [j] M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.*, 1970, **35**, 1867. [k] Found: M^+, 175·0631. Calc.: *M*, 175·0633.

TABLE 3

Dihydroisoquinoline intermediates (5)

	Analyses							
	Required (%)			Found (%)				
(5)	C	H	N	C	H	N	M.p. (°)	Yield (%)
a	68·4	5·5	3·3	68·3	5·4	3·1	99·5—100·5	
b							107—108	90
c	64·7	5·4	4·4	64·5	5·4	4·3	*a*	
e	62·6	5·5	4·0	62·5	5·6	3·7	101—102	75
f	62·6	5·5	4·0	62·9	5·7	3·9	144—145	75
h							*b*	70
i							*a*	80
j							*a*	84

[a] Unstable. [b] Oil.

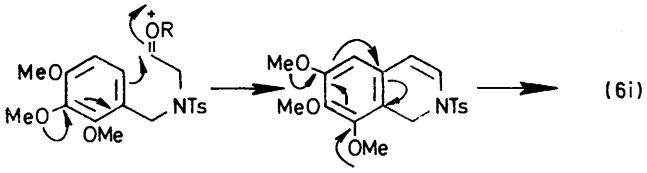
tosyl-1,2-dihydroisoquinoline (5g). In general a slow reaction occurs when an 8-methoxy-substituent is present, the reaction is slightly faster with a 6-substituent, while without either a 6- or an 8-substituent the reaction proceeds even more rapidly (see Table 4). This suggests

TABLE 4

Approximate times for complete conversions (4) ⟶ (5) and (5) ⟶ (6) under the reaction condition described in text

	Time (h)		
(4)	⟶	(5)	⟶ (6)
a	6	No reaction	
b	0·5	4·5	
c	1	4	
e	0·75	7·5	
f	6	No reaction	
g	Fast	1·5	
h	Fast	4	
i	1	11	
j	0·25	4	

that there is an electron donating effect to the 1 position which inhibits the loss of the 1-proton in the final step [(5) ⟶ (6)]. These electronic effects are summarised in Scheme 2.

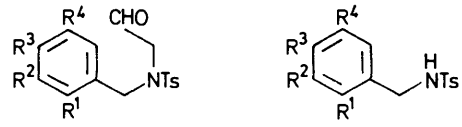


(6i)

SCHEME 2

More quantitative information could be obtained about the two-stage reaction sequence by following the changes in the n.m.r. signals associated uniquely with each of the species (4)—(6). Reactions were carried out in a mixture of dioxan and 6M-hydrochloric acid in a sealed n.m.r. tube at 30°. The pseudo-first-order rate constants for the transformations (4j) ⟶ (5j) and (4g) ⟶ (5g) were $2{\cdot}6 \times 10^{-5}$ and $3{\cdot}0 \times 10^{-5}$ s^{-1} respectively, thus showing by their similarity that the methoxy-groups *ortho* and *para* to the position of cyclisation were the determining factors, and that the *meta* methoxy-group in (4j) had little effect. However, the rate constants for the detosylations (5j) ⟶ (6j) and (5g) ⟶ (6g) were $0{\cdot}9 \times 10^{-5}$ and 9×10^{-5} s^{-1} respectively, and the ten-fold slower rate for (5j) is attributed to the additional 6-methoxy-group *para* to the 1-methylene group, as suggested previously on the basis of semi-quantitative observations (Table 4). It was shown, within the limits of accuracy of the spectra, that as expected, both reactions (4j) ⟶ (5j) and (5j) ⟶ (6j) were first order in starting material.

During these investigations it became clear that for some tosylates an alternative occurred and t.l.c. analyses showed products and intermediates of markedly different chromatographic properties from those described above. For example the initial product obtained by treatment of *N*-benzyl-*N*-tosylaminoacetaldehyde dimethyl acetal (4p) (under the same conditions as described above) was first hydrolysed to *N*-benzyl-*N*-tosylaminoacetaldehyde (7p), which was isolated as an oil, and characterised by its i.r. and n.m.r. spectra. Prolonged treatment of (7p) gave *N*-tosylbenzylamine (8p) as the final stable product.

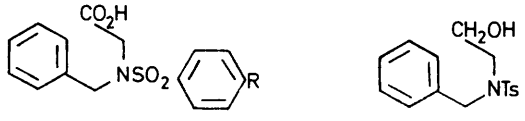


(7) (8)

d $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
l $R^1 = R^2 = R^4 = H$, $R^3 = Me$
m $R^1 = Me$, $R^2 = R^3 = R^4 = H$
n $R^1 = R^3 = Me$, $R^2 = R^4 = H$
o $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
p $R^1 = R^2 = R^3 = R^4 = H$

This reaction was general for tosylates lacking sufficiently activating substituents in the benzyl group to bring about cyclisation. The rate of hydrolysis to the aldehyde in those cases was generally slightly slower than the rate of the successful cyclisations to the dihydroisoquinolines, although in no instances were the products of both reaction pathways observed simultaneously. The acetal (4p) was stable to acid hydrolysis at 20° at higher acid concentrations than employed in the cyclisation, although hydrolysis occurred easily at higher temperatures. Consequently the reaction of the acetals in general may involve at least partial hydrolysis to the aldehyde. This is accompanied either by cyclisation, if the aromatic ring is sufficiently activated, or by complete hydrolysis to the aldehyde, and subsequently to the *N*-tosylbenzylamine, if it is unreactive.

The decomposition of the *N*-benzyl-*N*-tosylaminoacetal to give *N*-tosylbenzylamines, was unexpected. Precedents exist [7] for the specific loss of *N*-benzyl groups from sulphonamides, the products being those formed from the most stable carbonium ions. In particular *N*-benzyl-*N*-phenylsulphonylglycine (9; R = H) under *strong* acid conditions gave *N*-phenylsulphonylglycine; [7] this reaction was repeated under our milder acid conditions both with *N*-phenylsulphonyl- and *N*-tosyl-*N*-benzylglycines but no reaction occurred in either case. Reduction of (7p) gave *N*-benzyl-*N*-tosyl-2-aminoethanol (10) which likewise did not decompose under acidic conditions.

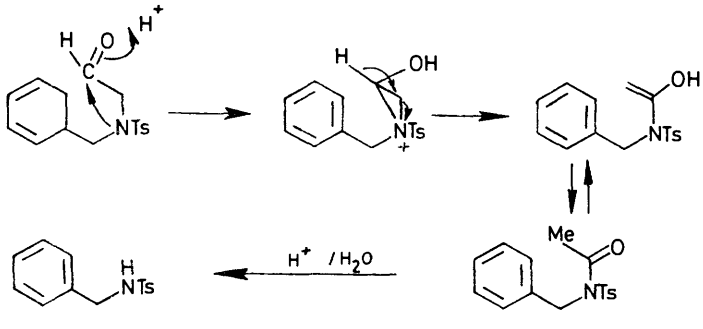


(9) (10)

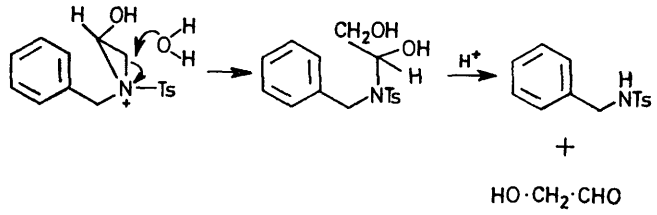
It would therefore seem that little protonation occurs under our acidic conditions, and that the aldehyde function is an essential feature in the fragmentation reaction. A kinetic comparison of this reaction for the 4-methyl- and 4-methoxy-benzylaminoacetaldehydes (7d) and (7l) was made by following the disappearance of the aldehyde

[7] W. Cocker, *J. Chem. Soc.*, 1937, 1693.

protons in the n.m.r. spectrum of the reaction mixture. This showed no difference in rate, ruling out the possibility of anchimeric assistance *via* a 5-membered spiro-intermediate, as postulated recently in the isoquinoline field.[8]



SCHEME 3



SCHEME 4

Several mechanisms can be written for this reaction, *e.g.* Schemes 3 and 4. If Scheme 3 applied, acetic acid should be formed as a stable product but no trace was found when the reaction was carried out in a sealed n.m.r. tube (addition of an equivalent amount of acetic acid resulted in an easily discriminated signal). Hence it seems likely that hydroxyacetaldehyde is formed, possibly by the route shown in Scheme 4, but rapidly decomposes; attempts to isolate this aldehyde by g.l.c. or t.l.c. were unsuccessful, as were attempts to form derivatives *in situ*, and an authentic sample was shown to decompose rapidly under the conditions of the reaction.

The reaction sequence described above is as general as existing methods of synthesising isoquinolines, and it usually gives better yields, often without the need for isolation of any intermediates. However, if the aromatic ring is not sufficiently reactive, hydrolysis of the acetal occurs; it is possible that cyclisation of these less reactive acetals (4) might occur under more anhydrous conditions.

The successful isoquinoline cyclisations can very easily be carried out as ' one-pot ' preparations which offer both convenience and high yields for large-scale synthetic work. For example, veratraldehyde (1b) reacted with aminoacetaldehyde dimethyl acetal and the resulting Schiff's base (2b) was catalytically hydrogenated *in situ* without removal of benzene. Removal of solvent followed by addition of pyridine and tosyl chloride yielded the tosylate; the latter, after removal of pyridine and excess of tosyl chloride, was cyclised to 6,7-dimethoxyisoquinoline (6b) and the pure product was obtained in 64% overall yield from veratraldehyde. The usefulness of this isoquinoline synthesis in the benzylisoquinoline alkaloid field is likely to be considerable and is exemplified in the following paper.

* Data marked with an asterisk are listed in Supplementary Publication No. SUP 21103 (7 pp.). For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

EXPERIMENTAL

M.p.s were determined on a hot stage and are corrected. I.r. and u.v. spectra (in spectroscopic ethanol) were determined with Unicam SP200 and SP800 instruments respectively. N.m.r. spectra were determined in deuteriochloroform with Perkin-Elmer R14 (100 MHz) and R10 (60 MHz) instruments. Mass spectra were measured with a Varian CH5-D double-focusing mass spectrometer, using a Varian 620i data system and Statos 21 fast printer. Light petroleum refers to the fraction of boiling range 40—60°.

Condensations of Substituted Benzaldehydes (1) *with Aminoacetaldehyde Dimethyl Acetals.*—The substituted benzaldehyde (0·04 mol) was dissolved in dry benzene (150 ml) and aminoacetaldehyde dimethyl acetal (0·042 mol) was added. The solution was boiled under reflux in a Dean–Stark apparatus until no further water was evolved (usually 3–4 h); removal of solvent under vacuum then gave the required Schiff's base (2). Purification for analysis was carried out by distillation at low pressure. Yields were virtually quantitative and the benzylideneamino-acetals (2) were normally used without further purification. All the compounds were characterised by spectroscopic methods, especially n.m.r.

Substituted Benzylamino-acetals (3).—The benzylideneamino-acetal (0·02 mol) was dissolved in absolute alcohol (150 ml) and platinum dioxide (100 mg) was added. The solution was hydrogenated at 1 atm and 20° until the theoretical amount of hydrogen was taken up. Filtration through Celite and removal of solvent under vacuum yielded the required benzylamino-acetals (3). These were usually used without further purification and the yields were nearly quantitative. All the compounds were characterised by their n.m.r. spectra.

Substituted N-*Benzyl*-N-*tosylaminoacetaldehyde Dimethyl Acetals* (4).—The substituted benzylamino-acetal (3) (0·02 mol) was dissolved in dry pyridine (15 ml) and tosyl chloride (freshly recrystallised, 0·022 mol) in dry pyridine (15 ml) was added. The solution was stirred at 20° for 3 days, during which time plates of pyridine hydrochloride usually separated. The mixture was poured into water (100 ml) and extracted with ether (3 × 50 ml). The ether was then washed with *dilute* (<1M) hydrochloric acid (2 × 50 ml), water (2 × 50 ml), and dried ($MgSO_4$). Filtration and removal of solvent yielded the required *tosylates* (4), usually as oils most of which crystallised. Recrystallisation from ethanol–water or light petroleum was followed by characterisation by n.m.r. spectra * and elemental analysis (see Table 1).

Cyclisation of N-*Benzyl*-N-*tosylamino-acetals* (4) *to the Corresponding Isoquinolines* (6).—The *N*-tosyl-*N*-benzylamino-acetals (4) (2 g) were dissolved in dioxan (48·4 ml) under dry nitrogen in the dark and 6M-hydrochloric acid (3·7 ml) was added. The solution was heated under reflux until t.l.c. (after neutralisation of sample) showed that no further reaction occurred. At first a spot of higher R_F

[8] D. N. Harcourt, N. Taylor, and R. D. Waigh, *J.C.S. Chem. Comm.*, 1972, 643.

than the starting tosylate appeared and this then disappeared, and was replaced by a spot of lower R_F than the tosylate. The solution was poured into water (100 ml), extracted with ether (3 × 50 ml), and the aqueous layer was made alkaline with dilute ammonium hydroxide solution and re-extracted with ether (3 × 50 ml). The combined second extracts were washed with water (2 × 50 ml) and dried ($MgSO_4$). After removal of solvent the required isoquinolines (6) were obtained and characterised by elemental analysis (Table 2) and n.m.r.* and u.v.* spectra. The tosyl group was eliminated in the reaction as toluene-*p*-sulphinic acid and in one reaction this was isolated as a solid, m.p. 82—84° (lit.,[9] 85°).

Cyclisation of N-*Benzyl*-N-*tosylamino-acetals* (4) *to* N-*Tosyl*-1,2-*dihydroisoquinolines* (5).—The *N*-benzyl-*N*-tosylamino-acetal (4) (2 g) in dioxan (48·4 ml) under nitrogen, in the dark, was treated with 6M-hydrochloric acid (3·7 ml). The solution was boiled under reflux until t.l.c. showed reaction was complete and there was one spot at higher R_F than the starting material. The mixture was poured into water (100 ml) and extracted with ether (3 × 50 ml). The ether extracts were washed with water (2 × 50 ml), dried ($MgSO_4$), and solvent was removed to yield the *N*-tosyl-1,2-dihydroisoquinoline (5) as an oil or as a solid, recrystallised where possible from ethanol–water and characterised where possible by m.p. and elemental analysis (Table 3), and u.v.* and n.m.r.* spectra.

5,8-*Dimethoxyisoquinolines* (6f).—*N*-2,5-Dimethoxybenzyl-*N*-tosylaminoacetaldehyde dimethyl acetal (2 g) in dry, peroxide-free dioxan (48·5 ml) was treated under nitrogen in the dark with 6M-hydrochloric acid (3·9 ml) and the solution was boiled under reflux. After 6 h, t.l.c. (light petroleum–ether 4 : 1) showed only one spot of higher R_F than the starting material. No further change occurred after heating overnight. The solution was poured into water (100 ml) and extracted with ether (3 × 50 ml). The ether extracts were washed with water (2 × 50 ml), dried ($MgSO_4$), filtered, and the solvent was removed to yield 5,8-*dimethoxy*-N-*tosyl*-1,2-*dihydroisoquinoline* (5f) (1·4 g, 81%) as a yellow solid which gave needles (from ethanol), m.p. 130—133°.

Potassium t-butoxide in t-butyl alcohol [3·5 ml of a solution of potassium (6·7 g) in t-butyl alcohol (145 ml)] was added to the foregoing 1,2-dihydroisoquinoline (0·35 g). The solution was boiled for 30 min and then the solvent was removed under vacuum; the residual solid was extracted into ether (20 ml), washed with water (2 × 20 ml), and extracted into 1M-hydrochloric acid (3 × 10 ml). The resulting yellow solution was made alkaline with dilute ammonium hydroxide solution and re-extracted with ether (3 × 10 ml). The ether extracts were washed with water (3 × 10 ml), dried ($MgSO_4$), and the solvent was removed to yield a thick oil. P.l.c. (light petroleum–ether 3 : 7) yielded the required isoquinoline (6f) (0·8 g, 75%) as needles, m.p. 56·5—57° (lit.,[10] 58°) (from light petroleum–ether). The picrate crystallised from ethanol, m.p. 210° [lit.,[10] 210° (decomp.)].

N.m.r. Spectral Study of the Cyclisation of N-*Tosyl*-N-3,5-*dimethoxy- and* N-*Tosyl*-N-2,4,5-*trimethoxy-benzylamino-acetaldehyde Dimethyl Acetals* (4g *and* j).—The tosylate (100 mg) was dissolved in 0·5 ml of a solution of dioxan (13 ml) and 6M-hydrochloric acid (1 ml) in an n.m.r. tube. The reaction was followed initially at the spectrometer probe temperature (30°) and subsequently (after the formation of the dihydroisoquinoline) at 90°. Spectra were run at frequent intervals until formation of the isoquinoline was complete.

Conversion of the Tosylates (4d, l, m, n, o, *and* p) *into* N-*Tosylbenzylamines* (8) via *the Aldehydes* (7).—The foregoing tosylates (2 g) were treated with dilute hydrochloric acid in dioxan as previously. Work-up as for the dihydroisoquinolines after heating under reflux for 1 h gave the *N*-benzyl-*N*-tosylaminoacetaldehydes (7), characterised by n.m.r.* and i.r.* spectra and elemental analysis (Table 5). Prolonged heating (overnight) followed by a similar work-up afforded the *N*-tosylbenzylamines (8) in nearly quantitative yields; n.m.r.* and i.r.* spectra were recorded, and m.p. and elemental analyses are in Table 6.

TABLE 5

Aldehydes (7) formed from ' unreactive ' acetals

		2,4-Dinitrophenylhydrazone	Analysis					
			Required (%)			Found (%)		
(7)	M.p. (°)	m.p. (°)	C	H	N	C	H	N
d	106—107	151—152	61·2	5·7	4·2	61·1	5·9	4·0
l	66	120—123	55·5	4·7	14·1	55·5	4·6	14·1 [a]
m	*b*	147—148	55·5	4·7	14·1	55·6	4·7	13·8 [a]
n	91—92	155—156	56·4	4·9	13·7	56·6	4·9	13·4 [a]
o	*b*	148—149						
p	*b*	177—178						

[a] For the 2,4-dinitrophenylhydrazone. [b] Oil.

TABLE 6

N-Tosylamines (8)

		Analyses					
		Required (%)			Found (%)		
(8)	M.p. (°) [lit. m.p. (°)]	C	H	N	C	H	N
d	115—116	61·9	5·9	4·8	61·8	5·8	4·6
i	91·5—92 [94] [a]	65·4	6·2	5·1	65·6	6·1	5·5
m	118—119 [118—119] [b]	65·4	6·2	5·1	65·2	6·2	5·3
n	77—77·5	66·4	6·6	4·8	66·4	6·7	5·0
o	101—101·5 [107—108] [a]	56·8	4·8	4·8	56·9	4·6	4·9
p	113—114 [113—115] [c]	64·4	5·8	5·4	64·4	5·9	5·1

[a] Ref. 11. [b] W. H. Carothers and G. A. Jones, *J. Amer. Chem. Soc.*, 1925, **43**, 3051. [c] Ref. 12.

N.m.r. Study of the Conversion of N-*Benzyl*-N-*tosylamino-acetaldehydes* (7d *and* l) *into the Corresponding* N-*Tosylbenzylamines* (8d *and* l).—*N*-4-Methylbenzyl-*N*-tosylaminoacetaldehyde (7l) (35 mg) was dissolved in 0·5 ml of a solution of dioxan (10 ml) and 6M-hydrochloric acid (1 ml) in a sealed n.m.r. tube. The reaction was allowed to proceed at 100° and spectra at τ 0—2 were recorded at suitable intervals. The peak area of the aldehyde proton signal was plotted against time using the toluene-*p*-sulphonyl aromatic proton resonances as an internal standard. The same procedure was repeated with the aldehyde (7d). The aldehydes (7d and l) showed virtually indistinguishable rates of reaction.

N-*Benzyl*-N-*phenylsulphonylaminoacetalde Dimethyl Acetal*.—Benzylaminoacetaldehyde dimethyl acetal (3p) (18·9 g) and benzenesulphonyl chloride (19 g) were dissolved in dry pyridine (50 ml) and the solution was stirred at 20°

[9] E. Fromm and F. Erfurt, *Ber.*, 1909, **42**, 3816.
[10] T. R. Govindachari and M. V. Lakshmikantham, *Proc. Indian Acad. Sci.*, 1957, **46***A*, 406.

for 2 days. The mixture was then worked up, as for the previous tosylates, and gave the dimethyl acetal as a brown oil which deposited crystals from light petroleum (26·8 g, 80%), m.p. 80—82°, τ 2·15, 2·52, and 2·79 (10H, 3m, ArH), 5·51 (2H, s, ArCH_2), 5·70 (1H, t, *J* 7 Hz, C*H*OMe), 6·77 (2H, d, *J* 7 Hz, CHCH_2), and 6·81 (6H, s, OMe).

N-*Phenylsulphonylbenzylamine*.—The foregoing acetal (12 g) in the usual dioxan–hydrochloric acid mixture (310 ml) was heated under reflux for 1 h. Work-up *via* ether gave the oily *N*-benzyl-*N*-phenylsulphonylaminoacetaldehyde (10 g, 70%), τ 0·69 (1H, s, CHO) 2·35 and 2·72 (10H, m and s, ArH), and 5·65 (2H, s, CH_2CHO), $\nu_{max.}$ (film) 1733 (CHO) cm^{-1}; 2,4-dinitrophenylhydrazone, m.p. 177—178°, *m/e* (field desorption) 469 (M^+).

When the acetal was heated under reflux overnight in the dioxan–hydrochloric acid mixture work-up gave a quantitative yield of *N*-phenylsulphonylbenzylamine, m.p. 84—85° (lit.,[11] 88°), τ 2·14 (10H, m, ArH), 4·7 (1H, t, *J* 6 Hz, removed with D_2O, NH), and 6·90 (2H, d, *J* 6 Hz, s with D_2O, CH_2), $\nu_{max.}$ (Nujol) 3400 (NH) cm^{-1} (Found: C, 63·1; H, 5·4; N, 5·7. Calc. for $C_{13}H_{13}NO_2S$: C, 63·1; H, 5·3; N, 5·7%).

N-*Benzyl*-N-*tosylglycine* (9; R = Me).—*N*-Benzyl-*N*-tosylaminoacetaldehyde (7p) (1·47 g) in methanol (10 ml) and water (3 ml) was added with stirring to a mixture of silver nitrate (1·7 g) in water (12·5 ml) and sodium hydroxide (0·85 g) in water (12·5 ml). The solution was kept for 1 h, a silver mirror formed after 10 min, and further methanol (10 ml) was added to aid solubility. The mixture was filtered, and the filtrate diluted with water (60 ml), acidified with conc. hydrochloric acid, and extracted with ether (3 × 30 ml). The combined extracts were washed with water, dried ($MgSO_4$), and the solvent was removed to give *N*-benzyl-*N*-tosylglycine (9; R = Me) (0·8 g, 45%) which crystallised from ethanol–water, m.p. 134—135° (lit.,[12] 136—138°), τ 2·23 and 2·63 (4H, 2d, *J* 8 Hz, *m*-Ar*H*), 2·73 (5H, 6s, *Ar*CH_2), 5·57 (2H, s, ArCH_2), 6·20 (2H, s, C$H_2$$CO_2H$), and 7·58 (3H, s, Ar*Me*), $\nu_{max.}$ 1727 (CO_2H) cm^{-1} (Found: C, 60·0; H, 5·4; N, 4·1. Calc. for $C_{16}H_{17}NO_4S$: C, 60·2; H, 5·4; N, 4·4%).

N-*Benzyl*-N-*phenylsulphonylglycine* (9; R = H).—The foregoing experiment was repeated using *N*-benzyl-*N*-phenylsulphonylaminoacetaldehyde (1·47 g), giving the sulphonamide (9; R = H) as a solid (0·85 g, 50%). Recrystallisation from ethanol–water gave needles, m.p. 123—124° (lit.,[7] 124·5—125·5°), τ 0·78 (1H, s, CO_2H), 2·30 (5H, m, Ar*H*), 2·74 (5H, s, *Ar*CH_2), 5·51 (2H, s, ArCH_2), and 6·05 (2H, s, CH_2-CO_2H), $\nu_{max.}$ (Nujol) 1715 (CO_2H) cm^{-1} (Found: C, 59·0; H, 4·8; N, 4·9. Calc. for $C_{15}H_{15}NO_4S$: C, 59·0; H, 4·9; N, 4·6%).

N-*Benzyl*-N-*tosyl*-2-*aminoethanol* (10).—Sodium borohydride (0·4 g) in 20% aqueous methanol (3 ml) and 2M-sodium hydroxide solution (0·4 ml) was added in portions to a solution of *N*-benzyl-*N*-tosylaminoacetaldehyde (2 g) in 20% aqueous methanol (40 ml). The solution was stirred for 3 h at 20°, acidified with 2M-hydrochloric acid, and the solution then poured into water (100 ml). This solution was extracted with ether (3 × 30 ml) and the extract was washed with water (2 × 50 ml), dried ($MgSO_4$), and the solvent removed to give the alcohol (10) (1·4 g, 70%). Recrystallisation from ethanol–water gave crystals, m.p. 101—102° (lit.,[13] 107°), τ 2·28 (2H, d, *J* 8 Hz, Ar*H*), 2·76 (7H, m, Ar*H*), 5·66 (2H, s, ArCH_2), 6·58 (2H, t, *J* 5 Hz, CH_2OH or CH_2CH_2N), 6·80 (2H, t, *J* 5 Hz, CH_2OH or CH_2CH_2N), 7·36 (1H, s, OH), and 7·62 (3H, s, Ar*Me*), $\nu_{max.}$ (Nujol) 3610 (OH) cm^{-1}.

Treatment of the Sulphonamides (9; R = Me), (9; R = H), *and* (10) *with Dilute Hydrochloric Acid*.—Solutions of (9; R = Me), (9; R = H), and (10), (1 g) in dioxan (24 ml) and 6M-hydrochloric acid (1·8 ml) were taken separately and heated under reflux overnight. Each solution was poured into water (50 ml) and extracted with ether (3 × 30 ml). In each experiment only starting material was recovered in yields of 0·9 g (90%), 0·95 g (95%), and 0·9 g (90%) respectively.

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