Synthesis of 3,3'-Dimethyl-1,1'-azobenzimidazolium Salts

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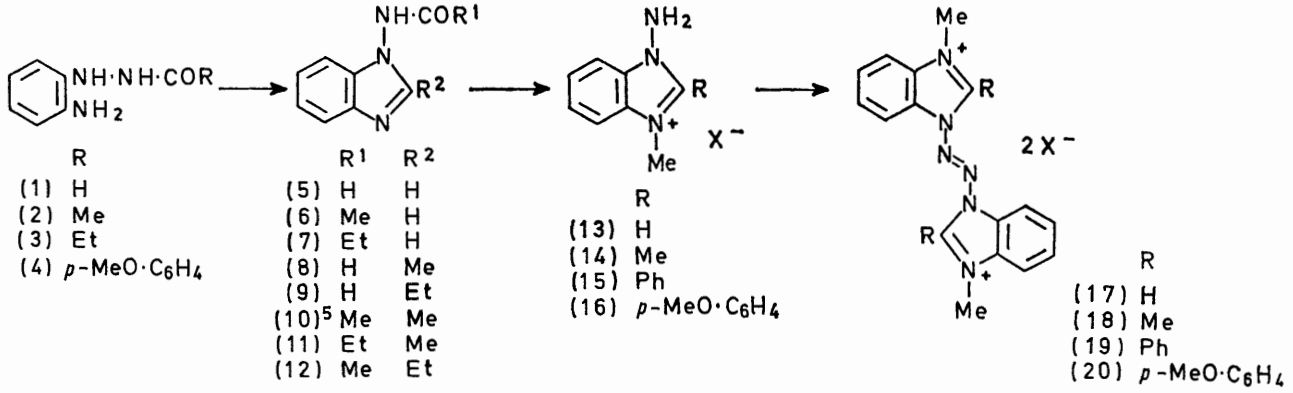
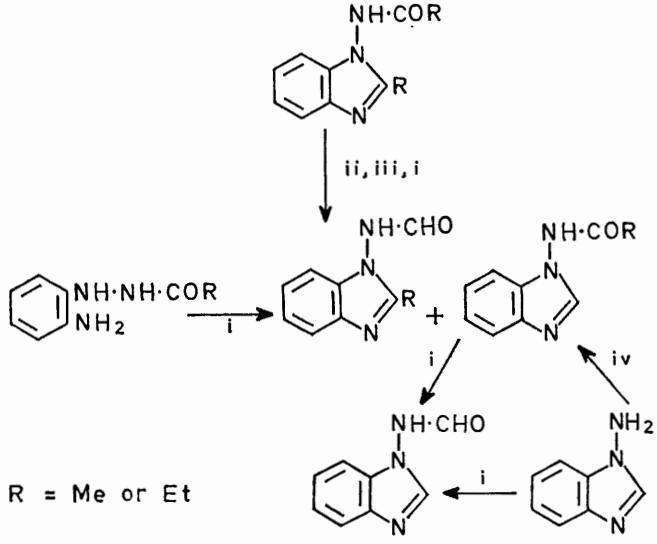
The synthesis of 1-aminobenzimidazoles and some rearrangements that were encountered are discussed. The oxidation of derived methyl quaternary salts to the title compounds, which have interesting neuromuscular blocking properties, is described.

THE neuromuscular blocking properties of some di-quaternary heterocyclic tetrazenes have been previously reported [1-3] and in the continued search for active drugs the synthesis of the title compounds (17)—(20) was undertaken. The necessary precursors were 1-amino-benzimidazoles, which have been previously prepared from *o*-acylhydrazinoanilines by Abramovitch and Schofield [4] and by Sheng and Day,[5] cyclisation being effected by *m*-nitrobenzenesulphonic acid and boiling aliphatic carboxylic acids, respectively.



Like Sheng and Day [5] we found the most convenient route to 1-amino-2-alkylbenzimidazoles to be *via* cyclisation, in boiling aliphatic acids, of *o*-acylhydrazino-anilines; some of our observations were, however, at variance with those of Sheng and Day. We found that cyclisation of *o*-formylhydrazinoaniline (1) in boiling acetic or propionic acid resulted exclusively in the formation of the acyl aminobenzimidazoles (6) and (7), respectively. Similarly when *o*-acetylhydrazinoaniline (2) was boiled under reflux in propionic acid, the only product isolated was the 2-methyl-1-propionylamino-benzimidazole (11). However, when *o*-acetylhydrazino-aniline (2) or the corresponding propionyl compound (3) was boiled under reflux in formic acid, mixed products were obtained in which either the alkyl radical of the original acylhydrazino-group or the carbon-bound proton of the cyclising formic acid had become attached to C-2 of the resulting aminobenzimidazole. Prolonged boiling in formic acid resulted in the replacement of the acetyl or propionyl group in the initially formed 1-acylamino-benzimidazole. Structural assignments for the mixed products followed from their unambiguous synthesis as illustrated and from a comparison of their n.m.r. spectra with those of authentic model compounds (Table 1).

The formation of compounds (6) and (7) exclusively when *o*-formylhydrazinoaniline (1) was boiled with acetic or propionic acid supports the suggestion [4] that cyclisation proceeds *via* migration of the formyl group in (1) and the intermediacy of *o*-formylaminophenyl-hydrazine (21). Similarly the formation of the 2-methyl compound (11) from *o*-acetylhydrazinoaniline (2) in boiling propionic acid presumably occurs *via* the



Reagents: i, HCO_2H; ii, HCl; iii, OH^-; iv, $MeCO_2H$ or $EtCO_2H$.

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[3] D. C. Bishop, E. E. Glover, and K. T. Rowbottom, *J.C.S. Perkin I*, 1972, 2927.
[4] R. A. Abramovitch and K. Schofield, *J. Chem. Soc.*, 1955, 2326.
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TABLE 1

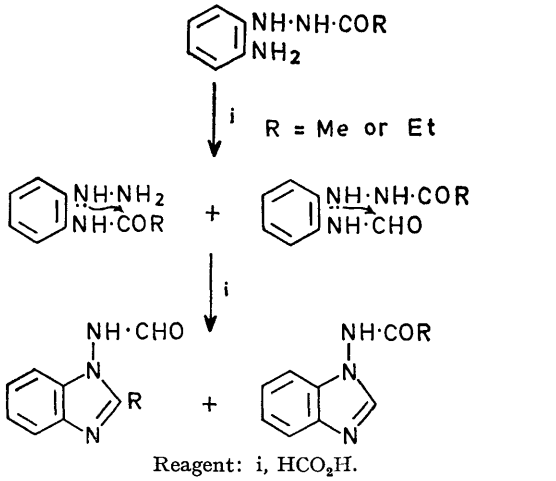
^{1}H N.m.r. spectra of 1-acylaminobenzimidazoles in trifluoroacetic acid (δ values; $Me_3Si{\cdot}[CH_2]_3{\cdot}SO_3Na$ standard)

Compd.	4-, 5-, 6-, 7-H *	2-H	2-Alkyl	*N*-Acyl
(5)	7·8	9·22(s)		8·78(s)
(6)	7·73	9·17(s)		2·43(s)
(7)	7·72	9·17(s)		2·7(q), 1·3(t)
(8)	7·7		2·88(s)	8·8(s)
(9)	7·7		3·2(q), 1·52(t)	8·8(s)
(10)	7·68		2·88(s)	2·49(s)
(11)	7·68		2·88(s)	2·8(q),[a] 1·4(t)
(12)	7·63		3·18(q), 1·5(t)	2·46(s)

* Centre of poorly resolved multiplet.

[a] Overlaps the 2-Me signal.

migration of the acetyl group in (2) and the intermediacy of *o*-acetylaminophenylhydrazine (22).



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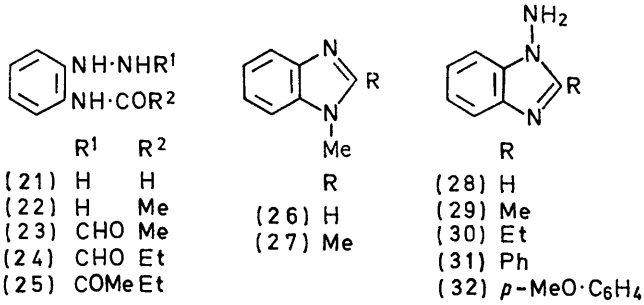

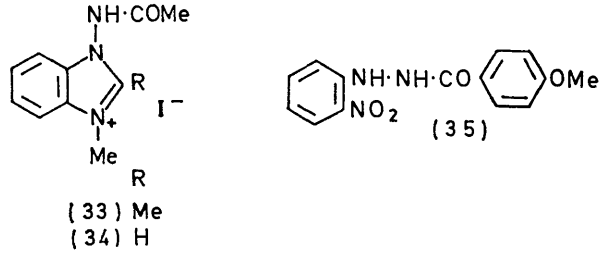

The formation of mixed products when acetyl- or propionylhydrazinoaniline [(2) or (3)] is boiled with formic acid presumably results from a reduced rate of acyl group migration and competitive formylation of the remaining free *o*-amino-group as illustrated. This suggestion is supported by the observation that 1-(*o*-acetylaminophenyl)-2-formylhydrazine (23) in boiling formic acid gave 1-formylamino-2-methylbenzimidazole (8) exclusively; likewise the mixed acetyl propionyl compound (25), in boiling acetic acid, gave 1-acetylamino-2-ethylbenzimidazole (12) exclusively.

The compounds recorded by Sheng and Day [5] as 1-formylamino-2-methyl- and 1-formylamino-2-ethylbenzimidazole have m.p.s identical with the respective samples of 1-acetylamino- (6) and 1-propionylaminobenzimidazole (7) prepared by us. Further, the routes to the compounds used by Sheng and Day were the ones found by us to give products in which migration of the formyl group, in the original *o*-formylhydrazinoaniline (1), occurs prior to cyclisation, resulting exclusively in the formation of compounds (6) and (7), respectively. It is, therefore, unnecessary to postulate [5] the unlikely opening of the imidazole ring in the acid-catalysed hydrolysis of the so-called 2-alkyl-1-formylaminobenzimidazoles. We found that hydrolysis of authentic 1-formylamino-2-methyl- (8) and 2-ethyl-1-formylaminobenzimidazole (9) in 2M-hydrochloric acid gave the corresponding 2-alkyl-1-aminobenzimidazoles (29) and (30), respectively.

Quaternisation of 1-acetylamino-2-methylbenzimidazole (10) with methyl iodide was readily effected and hydrolysis yielded the corresponding *N*-amino-salt (14). Quaternisation of 1-formylaminobenzimidazole (5) with methyl iodide in methanol gave the corresponding *N*-amino-salt (13) directly. The aryl *N*-amino-salts (15) and (16) were obtained by direct quaternisation of the corresponding 1-amino-2-arylbenzimidazoles, (31) and (32), respectively, prepared by the procedure described by Abramovitch and Schofield [4] for the preparation of the 2-phenyl compound.

Oxidation of the quaternary bromides (13)—(16) with aqueous bromine gave the required tetrazenes (17)—(20), but attempts to prepare picrates of either the parent tetrazene (17) or the methyl-substituted compound (18) resulted in the isolation of the picrates of the corresponding benzimidazoles (26) and (27), respectively; the two aryl-substituted tetrazenes (19) and (20), however, gave the expected quaternary dipicrate salts. The u.v. spectra of the four tetrazenes (17)—(20) showed a characteristic long-wave maximum in the 350 nm region although the u.v. absorption of an aqueous solution of the parent tetrazene (17) became, when set aside overnight, similar to that of 1-methylbenzimidazole. The action of picric acid on the tetrazenes (17) and (18) and the obvious instability of the parent compound (17) in neutral aqueous solution implies a progressive decrease in stability in the presence of nucleophiles in the order (17) < (18) < (19).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. U.v. spectra were determined on a Perkin-Elmer model 137 spectrophotometer and n.m.r. spectra on a Perkin-Elmer model R12A spectrometer.

1-Aminobenzimidazoles were prepared by heating the appropriate *N*-acyl compounds (5)—(12) with 2M-hydrochloric acid on a boiling water bath for 5 h. Each solution was then neutralised with 4M sodium hydroxide and the base was extracted and worked up in the usual way. Hydrolysis of the 2-alkyl-1-formylaminobenzimidazoles (8) and (9) gave the corresponding 2-alkyl-1-aminobenzimidazoles, (29) and (30), respectively, and not 1-aminobenzimidazole (28) as suggested by Sheng and Day.[4]

TABLE 2

1-Acylaminobenzimidazoles *

Precursor	Reagent	Heating time, temp.	Product	Cryst. solvent or purification procedure	Yield (%)	M.p. (°C)	Found (%) C	H	N	Reqd. (%) C	H	N
(1) [4] (3·5 g)	HOAc (17 ml)	24 h, reflux	(6)	EtOH–benzene–petroleum (b.p. 40—60°)	65	212—214 [a]	61·5	5·1	24·05	61·7	5·2	24·0
(28) [3,4] (0·1 g)	Ac_2O (0·08 g)–C_5H_5N (4 ml)	2 h, reflux	(6)	EtOH–benzene–petroleum (b.p. 60—60°)	91	212—214 [a]						
(1) [4] (1·19 g)	$EtCO_2H$ (50 ml)	21 h, reflux	(7)	MeOH–benzene	42	139—141 [b]	63·1	5·9	22·5	63·5	5·9	22·2
(28) [3,4] (0·1 g)	$(EtCO)_2O$ (0·9 g) C_5H_5N (10 ml)	5 h, room temp.	(7)	MeOH–benzene	51	139—141 [b]						
(29 [c]) (0·3 g)	HCO_2H (15 ml; 90%)	5 h, reflux	(8)	Evaporation onto a cold finger at 194° and 0·7 mmHg	49	224—225	61·6	5·2	23·9	61·7	5·2	24·0
(23) (0·1 g)	HCO_2H (5 ml; 90%)	2 h, reflux	(8)	MeOH–benzene	66	224—225						
(24) (0·2 g)	HCO_2H (10 ml; 90%)	2·5 h, reflux	(9) [d]	Evaporation onto a cold finger at 154° and 1·0 mmHg	84	Oil	60·35	6·0	21·4	60·6	6·1	21·2
			(9) picrate	$MeNO_2$–Et_2O		169—170	45·8	3·8	20·2	45·9	3·4	20·1
(2) [4] (0·815 g)	$EtCO_2H$ (30 ml)	4 h, reflux	(11)	H_2O	78	163—165	65·5	6·4	21·25	65·0	6·45	20·7
(25) (0·2 g)	HOAc (10 ml)	2·5 h, reflux	(12) [g]	H_2O	92	208	64·6	6·5	20·8	65·0	6·45	20·7

* The precursors and reagents were heated at the temperatures and for the times indicated; the reaction mixture was then evaporated under reduced pressure; the residue was treated with ethanol–benzene and re-evaporated. The residue was then triturated before recrystallisation from the solvent given.

[a] This m.p. was reported by Sheng and Day,[5] presumably in error, for compound (8). [b] This m.p. (138—139°) was reported by Sheng and Day,[5] presumably in error, for compound (9). [c] Prepared by the hydrolysis of (10) in 2M-hydrochloric acid.[5] [d] Hydrolysis in boiling 2M-hydrochloric acid (5 h) followed by basification and extraction with chloroform gave 1-amino-2-ethylbenzimidazole (30), m.p. 124—126° (lit.,[5] 126—127°). [e] For $C_{10}H_{11}N_3O,0{\cdot}5H_2O$. [f] Hydrolysis in boiling 2M-hydrochloric acid (5 h) followed by basification and extraction with chloroform gave 1-amino-2-methylbenzimidazole (29).[5] [g] Hydrolysis and work-up as in *f* gave 1-amino-2-ethylbenzimidazole (30).[5]

1-*Formyl*-2-(o-*acetylaminophenyl*)*hydrazine* (23).—A solution of compound (1) [4] (0·2 g) in pyridine (10 ml) containing acetic anhydride (0·135 g) was boiled under reflux for 0·5 h. Evaporation of the solution under reduced pressure followed by treatment of the residue with ether gave the *diacyl compound* (0·2 g, 78%) which crystallised from methanol–benzene as prisms, m.p. 174—176° (Found: C, 55·7; H, 5·8; N, 21·65. $C_9H_{11}N_3O_2$ requires C, 55·95; H, 5·7; N, 21·75%).

1-*Formyl*-2-(o-*propionylaminophenyl*)*hydrazine* (24).—A solution of compound (1) [4] (0·54 g) in pyridine (20 ml) containing propionic anhydride (0·47 g) was boiled under reflux for 4 h. Evaporation under reduced pressure followed by treatment of the residue with ether gave the *propionyl compound* (0·43 g, 58%) which crystallised from n-propanol–petroleum (b.p. 60—80°) as prisms, m.p. 152° (Found: C, 57·85; H, 6·6; N, 20·4. $C_{10}H_{13}N_3O_2$ requires C, 58·0; H, 6·3; N, 20·3%).

1-*Acetyl*-2-(o-*propionylaminophenyl*)*hydrazine* (25).—A solution of compound (2) [5] (1·26 g) in pyridine (30 ml) containing propionic anhydride (1·0 g) was boiled under reflux for 4 h. Evaporation under reduced pressure followed by treatment of the residue with ether gave the *propionylamino-compound* (1·63 g, 92%), which crystallised from methanol–benzene as prisms, m.p. 184° (Found: C, 59·55; H, 6·8; N, 18·9. $C_{11}H_{15}N_3O_2$ requires C, 59·7; H, 6·8; N, 19·0%).

1-(p-*Methoxybenzoyl*)-2-(o-*nitrophenyl*)*hydrazine* (35).—A solution of *o*-nitrophenylhydrazine (1·0 g) and anisoyl chloride (1·11 g) in pyridine (25 ml) was boiled under reflux for 0·5 h. The pyridine was then evaporated off under reduced pressure and the residue treated with ice-cold 2M-hydrochloric acid. Trituration gave the *nitro-compound* as an orange solid (1·36 g, 72·5%), which crystallised from ethanol as orange plates, m.p. 178—180° (Found: C, 57·8; H, 4·65; N, 14·6. $C_{14}H_{13}N_3O_4$ requires C, 58·5; H, 4·6; N, 14·6%).

1-(o-*Aminophenyl*)-2-(p-*methoxybenzoyl*)*hydrazine* (4).—5% Palladium–charcoal (0·2 g) was added to a warm (60°) solution of the nitro-compound (35) (0·5 g) in absolute ethanol (100 ml) and the mixture was shaken at room temperature under hydrogen at 45 lb in^{-2} pressure. After 45 min the catalyst was filtered off under carbon dioxide. Evaporation gave the *amino-compound* (0·35 g, 78%), m.p. 188—189° (from ethyl acetate) (Found: C, 65·1; H, 5·8; N, 16·4. $C_{14}H_{15}N_3O_2$ requires C, 65·4; H, 5·9; N, 16·3%).

1-*Amino*-2-(4-*methoxyphenyl*)*benzimidazole* (32).—A suspension of the amine (4) (0·4 g) and sodium *m*-nitro-

TABLE 3

Quaternary salts of 1-amino- and 1-acylamino-benzimidazoles *

Precursor	Reagents, solvents	Heating time, temp.	Product, X	Cryst. solvent	Yield (%)	M.p. (°C)	Found (%) C	H	N	Reqd. (%) C	H	N
(5) [4] (2·53 g)	MeI (15 ml), MeOH (20 ml)	24 h, reflux	(13) I	MeOH–Et_2O	74	214 [a]	34·8	4·0	15·3	34·9	3·7	15·3
			(13) Br [b,c]	EtOH		262	42·0	4·2	18·2	42·1	4·4	18·4
(3) [3] (0·2 g)	MeI (10 ml), MeOH (5 ml)	24 h, reflux	(15) I	EtOH–Et_2O	71	209	48·1	4·0	11·6	47·9	4·0	12·0
			(15) Br [b]	EtOH		255	55·4	4·7	13·6	55·3	4·6	13·8
(10) [4] (1·59 g)	MeI (10 ml)	24 h, reflux	(33) I	EtOH–Et_2O	59	241—243	40·2	4·4	12·3	39·9	4·3	12·7
(33) (1·0 g)	24% HBr (20 ml)	1 h, reflux	(14) Br	EtOH–Et_2O	65	217	41·4	5·4	16·1	41·5	5·4	16·2 [d]
(6) (2·6 g)	MeI (15 ml), MeOH (20 ml)	24 h, reflux	(34) I	EtOH–Et_2O	70	195 [a]	38·3	3·8	13·3	37·9	3·8	13·3
(32) (0·16 g)	MeI (1 ml), MeOH (1 ml)	18 h, reflux	(16) I	MeOH–Et_2O	79	205—207 [a]	46·9	4·4	10·85	47·25	4·24	11·0
			(16) Br [b]	MeOH–Et_2O		224—226	51·6	4·7	12·0	51·1	5·2	11·9 [d]

* Solutions of the precursors in the reagents and solvents shown were boiled under reflux for the times indicated, then evaporated under reduced pressure. The residues were recrystallised from the solvents shown.

[a] Decomp. [b] Produced from the iodide by ion-exchange in Amberlite IRA 400 (Br^-). [c] Also produced in 86% yield by boiling the iodide (34) in 24% hydrobromic acid for 2 h followed by evaporation under reduced pressure. [d] For the monohydrate.

TABLE 4

3,3′-Dimethyl-1,1′-azobenzimidazolium salts *

Starting bromide	Volume of sat. aq. bromine (ml)	Product X	Yield (%)	Cryst. solvent	M.p. (°C)	Found (%) C	H	N	Reqd. (%) C	H	N
(13) (0·26 g)	30	(17) [a] Br [b,c]	37	48% HBr–Me_2CO	255	40·9	3·6	17·7	40·9	3·9	17·9 [d]
		(17) ClO_4 [e]		MeCN	305—307	38·3	3·4	16·75	38·4	3·4	16·8 [f]
(14) (0·55 g)	64	(18) [g] Br [h]	49	48% HBr–Me_2CO	239	44·4	4·2	17·3	44·2	4·3	17·2 [f]
		(18) ClO_4 [e]		MeCN	288—290	39·7	3·85	15·6	39·6	4·25	15·4 [i]
(15) (0·3 g)	30 [j]	(19) Br [k]	50	48% HBr–Me_2CO	218	51·1	4·5	12·7	51·1	4·6	12·8 [l]
		(19) $C_6H_2N_3O_7$		$MeNO_2$–Et_2O	237—239	55·3	3·2	18·5	55·3	3·1	18·7
		(19) Cl [m]		Conc. HCl–Me_2CO	131—132	59·5	5·2	15·1	59·0	5·3	14·8 [l]
(16) (0·2 g)	20 [j]	(20) Br	38	MeOH–Et_2O	244	54·0	4·4	12·6	54·2	4·3	12·65
		(20) $C_6N_2N_3O_7$		$MeNO_2$–Et_2O	190—192	52·4	3·6	16·8	52·5	3·4	17·5

* A saturated aqueous solution of the bromide was rapidly treated with the volume of saturated aqueous bromine indicated; the precipitated material was triturated until solid, filtered off, and boiled with acetone. The resulting dibromides were then recrystallised from the solvents indicated.

[a] Treatment of the bromide with alcoholic picric acid gave 1-methylbenzimidazole picrate, m.p. 249° (lit.,[6] 246—247°) (Found: C, 46·6; H, 3·1; N, 19·2. Calc. for $C_8H_8N_2,C_6H_3N_3O_7$: C, 46·55; H, 3·1; N, 19·4%). [b] $\lambda_{max.}$ (M-HCl) 239sh, 255sh, 262, 275, and 343 nm (log ε 4·2, 4·32, 4·38, 3·88, and 4·28). [c] After being set aside overnight, $\lambda_{max.}$ (H_2O) 249sh, 253, 261sh, 267, 274, and 281 nm; showing good agreement with that reported for 1-methylbenzimidazole.[8] [d] For the monohydrate. [e] Prepared by dissolving the bromide in 70% perchloric acid and precipitating the perchlorate with acetone. [f] For the hemihydrate. [g] Treatment of the bromide with alcoholic picric acid gave 1,2-dimethylbenzimidazole picrate, m.p. 242—244° (decomp.) (lit.,[7] 243°) (Found: C, 47·5; H, 3·8; N, 18·7. Calc. for $C_9H_{10}N_2,C_6H_3N_3O_7$: C, 48·0; H, 3·5; N, 18·7%). [h] $\lambda_{max.}$ (H_2O) 235sh, 257sh, 264, 277, and 344 nm (log ε 4·13, 4·3, 4·42, 3·85, and 4·12). [i] For $C_{18}H_{20}Cl_2N_6O_8,1{\cdot}5H_2O$. [j] Reaction carried out at 60°. [k] $\lambda_{max.}$ (H_2O) 239, 269, and 350 nm (log ε 4·43, 4·52, and 4·31). [l] For the trihydrate. [m] Prepared by dissolving the bromide in the minimum volume of concentrated hydrochloric acid and precipitating the chloride with acetone.

benzenesulphonate (0·8 g) in water (25 ml) was treated with concentrated hydrochloric acid until the solution was acidic to Congo Red. It was then boiled under reflux for 1·5 h, cooled, and neutralised with 4M-sodium hydroxide. The yellow precipitate was recrystallised from benzene giving the N-*amino-compound* (0·164 g, 44%) as colourless plates, m.p. 187—188° (Found: C, 70·2; H, 5·7; N, 17·8. $C_{14}H_{13}N_3O$ requires C, 70·3; H, 5·5; N, 17·6%). Evaporation of the filtrate and recrystallisation of the residual solid from petroleum (b.p. 60—80°) gave 3-(*4-methoxyphenyl*)-*1,2,4-benzotriazine* (0·135 g, 37%), m.p. 139° (Found: C, 70·55; H, 4·8; N, 17·8. $C_{14}H_{11}N_3O$ requires C, 70·9; H, 4·7; N, 17·7%).

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