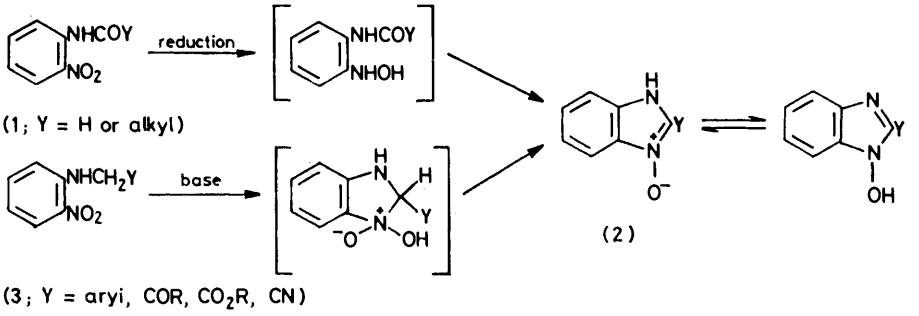
o-Nitroaniline Derivatives. Part 7.[1] The Synthesis of 2-Alkoxybenzimidazole *N*-Oxides (2-Alkoxy-*N*-hydroxybenzimidazoles) from *o*-Nitroanilines †

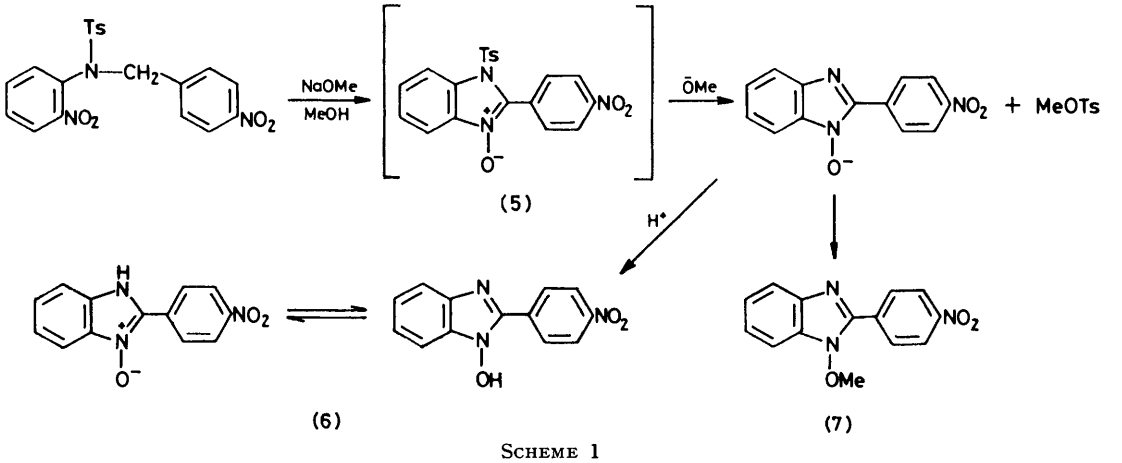
By **John Machin** and **David M. Smith,*** Department of Chemistry, University of St. Andrews, Purdie Building, St. Andrews, Fife KY16 9ST

N-Phenacyl-*N*-*p*-tolylsulphonyl-*o*-nitroanilines (8) are cyclised to 2-alkoxybenzimidazole *N*-oxides (⇌ 2-alkoxy-*N*-hydroxybenzimidazoles) (13)—(16) by sodium alkoxides in the appropriate alcohol. *N*-Phenacyl-*o*-nitroanilines themselves undergo cleavage, or at best give low yields of 2-benzoylbenzimidazole *N*-oxides, by reaction with alkoxides under similar conditions. *N*-Acetonyl-*N*-*p*-tolylsulphonyl-*o*-nitroanilines (9) are also cyclised to 2-alkoxybenzimidazole *N*-oxides by sodium alkoxides. When the ketonic functions of (8) and (9) are replaced by ester or cyano groups, however, cleavage occurs in alcoholic base in preference to cyclisation. *N*-Phenacyl- (8f) and *N*-acetonyl-*N*-*p*-tolylsulphonyl-6-methyl-2-nitroaniline (9f) are anomalous in that they are cyclised by alkoxides to 1-hydroxy-4-methylbenzimidazolone (21).

BENZIMIDAZOLE *N*-oxides or *N*-hydroxybenzimidazoles cannot normally be prepared by direct *N*-oxidation of benzimidazoles, and they are thus usually obtained by cyclisation of an appropriately substituted *o*-nitroaniline.[2] The two most familiar types of cyclisation involve reduction of an *o*-nitroanilide, *e.g.* (1) ⟶ (2),[3] and intramolecular base-catalysed condensation between the nitro-group and a reactive methylene group adjacent to the amino-nitrogen, *e.g.* (3) ⟶ (2).[4-9]



nitrobenzyl-*o*-nitroaniline (3; Y = $C_6H_4NO_2$-*p*) and its *N*-*p*-tolylsulphonyl derivative (4). In both reactions, the main product is the sodium salt of 2-*p*-nitrophenylbenzimidazole *N*-oxide (*N*-hydroxy-2-*p*-nitrophenylbenzimidazole) (6); but in the case of the tosylated compound (4) the reaction is considerably faster, and an appreciable proportion of the product undergoes *in situ* methylation, giving the *N*-methoxy derivative (7), the most likely mechanism being that shown in Scheme 1.



SCHEME 1

In previous papers[8,9] we have compared the cyclisations, in methanolic sodium methoxide, of *N*-*p*-tolylsulphonyl derivatives of other compounds of type (3), namely those in which Y = COAr, COMe, CO_2Et, and CN, and to bases other than sodium methoxide. The starting sulphonamides, *viz.* (8)—(12), are easily

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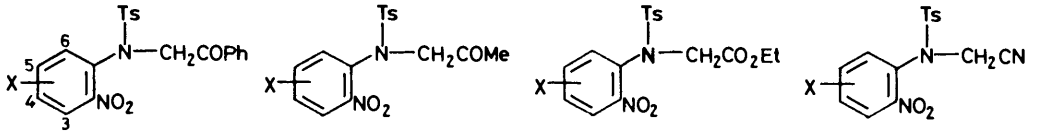
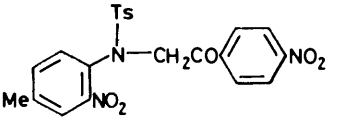
obtained from the appropriate α-halogeno-ketone, -ester, or -nitrile and the sodium salt of the *N*-*p*-tolylsulphonyl-*o*-nitroaniline in dimethylformamide.

N-Phenacyl-*N*-*p*-tolylsulphonyl-*o*-nitroaniline (8a) reacts with sodium ethoxide in ethanol giving 2-ethoxybenzimidazole *N*-oxide (⇌ 2-ethoxy-1-hydroxybenzimidazole) (13a) in high yield, and the 5- and 6-substituted benzimidazole oxides (13b—e) are similarly obtained in good yield by cyclisation of the sulphonamides (8b—e). The structures of these products follow from their elemental analyses, n.m.r. and mass spectra, and, in the case of the 5-methyl derivative (13b), from deoxygenation to 2-ethoxy-5-methylbenzimidazole (17), which may be synthesised independently from 3,4-diaminotoluene and tetraethoxymethane (Scheme 2).[10]



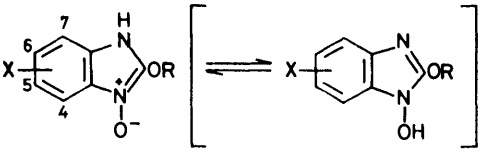
(8) (9) (10) (11)

a; X = H b; X = 4 - Me c; X = 4 - Cl d; X = 4 - OMe e; X = 5 - Me f; X = 6 - Me



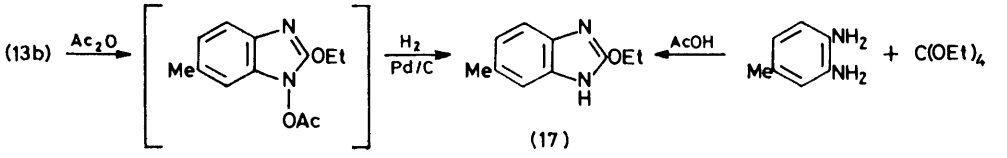
(12)

Hitherto, 2-alkoxybenzimidazole *N*-oxides have been relatively little studied, presumably because of their comparative inaccessibility. Obviously they cannot be prepared from compounds such as (1; Y = OR), since



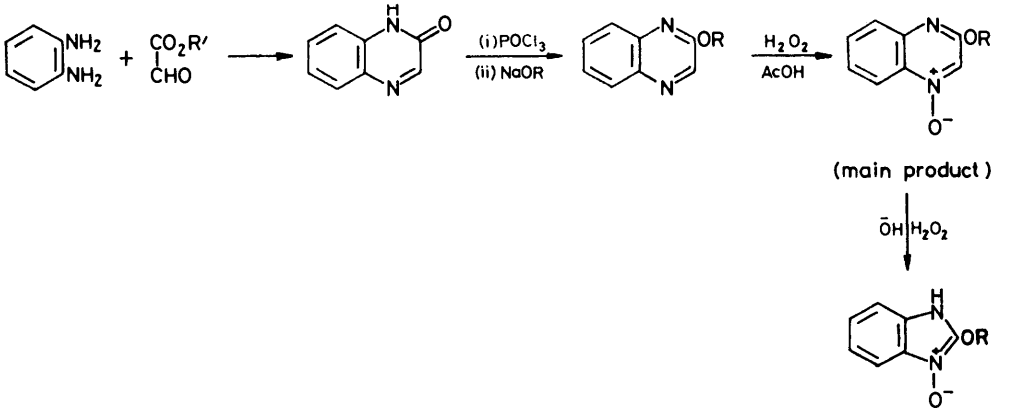
(13) R = Et
(14) R = Me
(15) R = Pr^n
(16) R = Pr^i

a; X = H
b; X = 5 - Me
c; X = 5 - Cl
d; X = 5 - OMe
e; X = 6 - Me



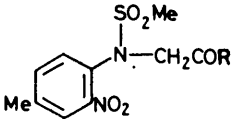
(17)

SCHEME 2

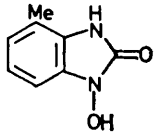


SCHEME 3

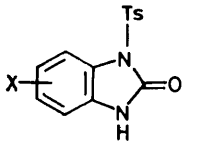
reductive cyclisation of these would be expected to yield *N*-hydroxybenzimidazolones, and equally they cannot be obtained from compounds of the type (3; Y = OR), since cyclisations of the type (3) ⟶ (2) require that Y be an electron-acceptor. They have previously been obtained [11] only by the alkaline hydrogen peroxide oxidation of 3-alkoxyquinoxaline 1-oxides (18), which are themselves the end-product of a multi-step synthesis (Scheme 3).[12] Our synthesis thus possesses two advantages over the previous route: simplicity, and applicability to the preparation of derivatives [*e.g.* (13b—e)] unsymmetrically substituted in the carbocyclic ring.



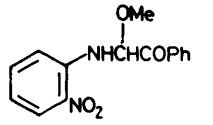
(19) R = Ph
(20) R = OEt



(21)



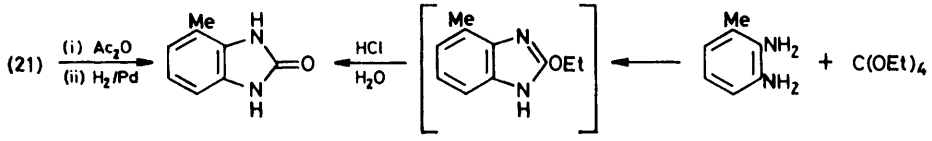
(22)
a; X = H
b; X = Me



(23)

both of these are cyclised, by sodium methoxide or ethoxide, to 1-hydroxy-4-methylbenzimidazolone (21) (Scheme 4).

Attempts to enlarge the scope of these cyclisations, by further variation of the base used, have met with only limited success. In the reaction of (8b) and (9b) with

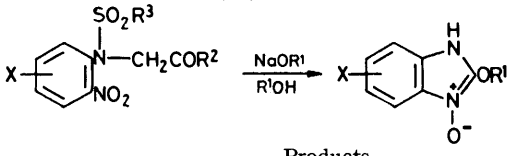


SCHEME 4

The general usefulness of the reaction is illustrated by the results in Table 1. The use of sodium methoxide (in methanol) in place of sodium ethoxide (in ethanol) gives the corresponding 2-methoxybenzimidazole *N*-oxides (14), albeit in lower yield; and in two representative cases examined, the use of sodium n-propoxide gives the 2-propoxybenzimidazole *N*-oxides (15b) and (15c). The phenacyl group in the starting material may be replaced by acetonyl, as in compounds (9a—d), and the *p*-tolylsulphonyl group by methylsulphonyl, as in compound (19). The two instances where zero yield is obtained, in a reaction with methoxide, possibly represent a problem of isolation rather than one of non-formation, although it must be admitted that, even with a modified work-up, only traces of the required product (14a) have been detected.

TABLE 1

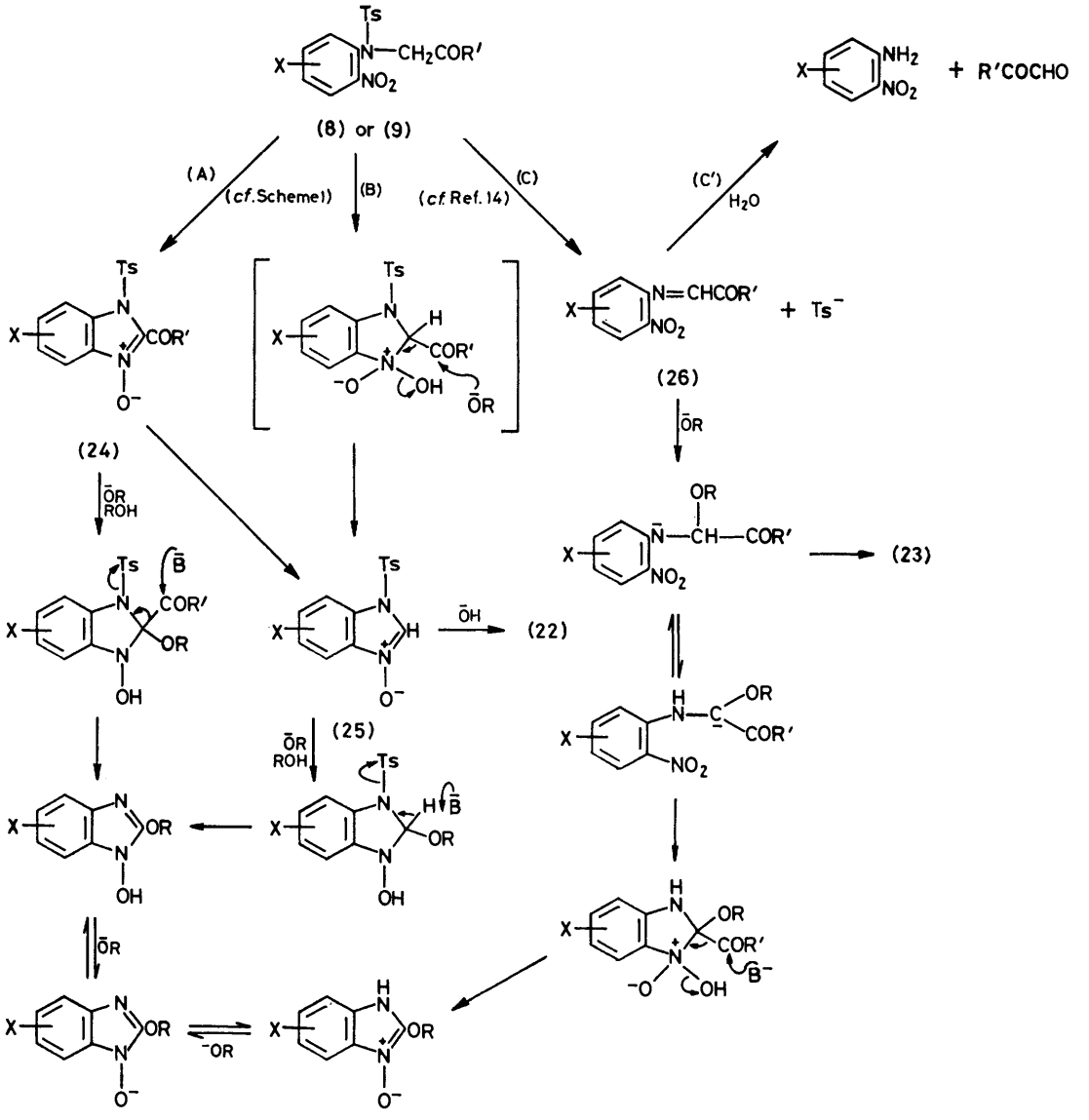
Product yields (%) in the cyclisations



Starting compound	Products (14)	(13)	(15)	(16)
(8a)	0	80		
(8b)	47	62	65	24
(8c)	28	68	54	
(8d)	34	68		
(8e)	45	41		
(9a)	0	40		
(9b)	47	82	38	28
(9d)	15	53		
(19)		31		

Sodium isopropoxide in isopropanol, cyclisation (to 16b) is accompanied by cleavage (to 4-methyl-2-nitroaniline). When sodium (or potassium) t-butoxide is used, cleavage is the only observed reaction, and the primary amine is obtained in high yield. Potassium hydroxide has proved unreliable as a cyclising agent for (8b): in ethanol, the expected benzimidazole *N*-oxide (13b) is indeed obtained, but in methanol the reaction takes a different course and gives a product which is considered to be the *N*-tosylbenzimidazolone (22b) (m.p. and spectroscopic evidence). Sodium carbonate is similarly unreliable as a cyclising agent: for example, in ethanol it effects the cyclisation (8b) ⟶ (13b) but leaves (8a) unaffected; in methanol (8a) is converted into either (22a) or (23) according to the reaction conditions. These apparent inconsistencies clearly require further investigation before a satisfactory explanation can be reached.

Three possible mechanisms for the cyclisations are shown in Scheme 5. Pathway (A) involves base-catalysed intramolecular condensation, followed by nucleophilic addition at C-2 and elimination of the acyl group (as a carboxylic acid or ester) and toluene-*p*-sulphinate. In pathway (B) the initial aldol-type adduct of the condensation process undergoes elimination of the acyl group rather than dehydration, and the resulting benzimidazole oxide (25) then undergoes nucleophilic addition and elimination of toluene-*p*-sulphinate. Pathway (C) involves initial elimination of sulphinate, and several of the remaining steps have analogy, to a



SCHEME 5

certain extent, in the cyclisations of *o*-nitroanils by cyanide ion.[1,13]

Of these three possible pathways, (C) is considered the least likely. There is little doubt as to the feasibility of the initial elimination step,[14] since the Schiff's base (26) is the most likely intermediate in the cleavage reactions of (8) which are brought about by isopropoxide or t-butoxide [pathway (C')], and since (26; X = H, R' = Ph) is almost certainly the intermediate in the conversion of (8a) into (23) by methanolic sodium carbonate. However, we have never obtained any direct evidence for the cyclisation of an *o*-nitroanil (or an alcohol adduct thereof) to a benzimidazole *N*-oxide by an alkoxide alone, or by an alkoxide in presence of toluene-*p*-sulphinate ion.

On the evidence available, there is little to choose between pathways (A) and (B), and indeed it is possible that both may be involved in the cyclisations of (8) and (9). The intermediates in these pathways, (24) and (25), respectively, are 1-tosylbenzimidazole 3-oxides, a type of benzimidazole derivative hitherto unknown but presumed to be highly reactive towards nucleophiles. Comparison with previous work (our own [9] and that of others [5-7]) suggests that (24) is the more likely to be formed from the starting materials; on the other hand, (25) is the most obvious precursor * of the *N*-tosylbenzimidazolone (22) produced in some of the cyclisations involving hydroxide or carbonate as the base. Of course, it is conceivable that (25) is formed from (24) and not directly from (8) or (9), since it has recently been shown [16] that deacylation of a 2-acylbenzimidazolium compound is a particularly facile process [*e.g.* (27) ⟶ (28)].

One mechanism for the cyclisation of (8) and (9) which

* *Cf.* the formation of *N*-alkylbenzimidazolones by heating 1-alkylbenzimidazole 3-oxides in a (wet ?) polar solvent.[15]

may be disregarded is that involving substitutive detosylation as the first step. The detosylated analogues of (8), *e.g.* (29a) and (29b), are not cyclised by alkoxides to 2-alkoxybenzimidazole *N*-oxides; instead they undergo cleavage to give the primary amines in moderate to good yield. The mechanism of this cleavage is far from clear: the only other products obtained (in small yields) are the alkyl benzoate and [in the case of (29b), as already reported [5]] the 2-benzoylbenzimidazole *N*-oxide.

It remains only to consider the anomalous cyclisation of the sulphonamides (8f) and (9f) by sodium alkoxides. These two sulphonamides differ from the other members of series (8) and (9) by having a second substituent *ortho-* to the sulphonamido-group, and steric interaction of the adjacent methyl and sulphonamido-groups provides the most straightforward explanation of the anomaly.

The steric effect of the 6-methyl substituent in (8f) and (9f) is to impose a severe restriction on rotation about the aryl–amido nitrogen bond, and this restricted rotation is reflected [17] in the magnetic non-equivalence of the methylene protons in these compounds. Whereas the methylene resonances in (8b) and (9b) coalesce to singlets at −10 and −9 °C, respectively, those in (8f) and (9f) remain as sharply defined AB quartets at least up to 140 °C. Thus it is assumed that the conformation of (8f) and (9f) in which the methyl and tosyl groups are ' eclipsed ' is one of high energy.

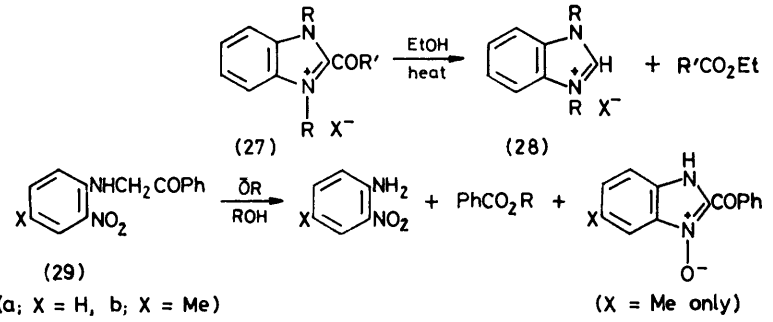
It follows that the intermediates (24; X = 7-Me) and (25; X = 7-Me) should be highly strained molecules, by virtue of the *peri*-interaction of the methyl and tosyl groups, and that such intermediates should be exceptionally reactive towards nucleophilic attack at C-2, since the steric strain is thereby reduced. As to their preferred reaction with hydroxide rather than alkoxide ions, we believe that these intermediates, which may be generated from the initial aldol-type adduct by a step involving loss of a hydroxide ion, are so reactive that they are able to recapture this hydroxide ion before the latter can escape into the solution and equilibrate with the alkoxide. This capture of the hydroxide ion leads to 2-hydroxy-7-methylbenzimidazole 3-oxide (*cf.* Scheme 5; R = H), and this readily tautomerises to 1-hydroxy-4-methylbenzimidazolone (21).

In all of the cyclisations described above, the methylene group in the starting sulphonamide has been ' activated ' by a ketonic carbonyl group. The corresponding sulphonamides (10), in which the activation is provided by an ester function, are not cyclised by alkoxides, but undergo cleavage (presumably elimination followed by hydrolysis) to give the primary amine. The same is true of the methylsulphonyl analogue (20). The sulphonamido-nitriles (11) similarly fail to cyclise, but they undergo a different type of cleavage to give the tosyl derivative of the primary amine [equation (1)].

$$ArN(Ts)CH_2CN \xrightarrow{\bar{O}R'} Ar\bar{N}Ts \xrightarrow{H^+} ArNHTs \quad (1)$$

In the absence of identifiable co-products, it is not yet possible to decide whether this last reaction is a simple nucleophilic substitution at the methylene carbon, or a process involving cyanocarbene.

The sulphonamido-ketone (12) undergoes cleavage of both the above kinds in preference to cyclisation. This provides one last illustration of the fine balance between competing reaction pathways which we have encountered throughout this work.



EXPERIMENTAL

I.r. spectra were recorded as Nujol mulls. N.m.r. spectra were recorded with tetramethylsilane as internal reference for solutions in deuteriochloroform unless otherwise indicated (TFA = trifluoroacetic acid, DMSO = dimethyl sulphoxide.) ' Petroleum ' refers to the fraction of b.p. 40—60°.

N-p-Tolylsulphonyl-*o*-nitroaniline, m.p. 111—112° (lit.,[18] 112—114°), was obtained (yield 75%) from *o*-nitroaniline, toluene-*p*-sulphonyl chloride, and pyridine, according to the published procedure.[18] The *N-p*-tolylsulphonyl derivatives of the following amines were similarly prepared: 4-methyl-2-nitroaniline, yield 66%, m.p. 102—103° (lit.,[19] 101°); 4-chloro-2-nitroaniline, yield 79%, m.p. 109—110° (lit.,[20] 107.5—109°); 4-methoxy-2-nitroaniline, yield 73%, m.p. 106—107° (lit.,[21] 104°); 5-methyl-2-nitroaniline, yield 50%, m.p. 132—134° (lit.,[22] 136—137°); and 6-methyl-2-nitroaniline, yield 88%, m.p. 124—126° (lit.,[23] 121.5—123.5°). *N*-Methylsulphonyl-*o*-nitroaniline, prepared by an analogous method [18] (yield 75%), had m.p. 99—101° (lit.,[18] 101—102°).

N-*Phenacyl*-N-p-*tolylsulphonyl*-o-*nitroaniline* (8a) *and its Derivatives* (8b—f).—*N-p*-Tolylsulphonyl-*o*-nitroaniline (11.68 g) or the appropriate derivative thereof (0.04 mol) was dissolved in a solution of sodium ethoxide (from sodium, 0.92 g) in ethanol (60 ml). The ethanol was removed *in vacuo*, the residue was redissolved in dimethylformamide (50 ml), and phenacyl bromide (8.0 g, 0.04 mol) was added. The mixture was stirred at room temperature for 48 h,

then poured on to crushed ice and the resultant precipitate filtered off and recrystallised from acetic acid–ethanol or ethanol.

N-*Phenacyl*-N-p-*tolylsulphonyl*-o-*nitroaniline* (8a) was obtained in 83% yield, m.p. 141° (Found: C, 61.6; H, 4.4; N, 6.9. $C_{21}H_{18}N_2O_5S$ requires C, 61.5; H, 4.4; N, 6.8%). The 4-*methyl analogue* (8b) (yield 75%) had m.p. 170—171° (Found: C, 62.3; H, 4.8; N, 6.6. $C_{22}H_{20}N_2O_5S$ requires C, 62.3; H, 4.75; N, 6.6%). The 4-*chloro-derivative* (8c) (yield 73%) had m.p. 180—182° (Found: C, 56.6; H, 3.7; N, 6.2. $C_{21}H_{17}ClN_2O_5S$ requires C, 56.7; H, 3.85; N, 6.3%); the 4-*methoxy-derivative* (8d) (yield 80%) had m.p. 160—161° (Found: C, 59.9; H, 4.7; N, 6.4. $C_{22}H_{20}N_2O_6S$ requires C, 60.0; H, 4.6; N, 6.4%); the 5-*methyl derivative* (8e) (yield 95%) had m.p. 157—159° (Found: C, 62.2; H, 4.8; N, 6.7%. $C_{22}H_{20}N_2O_5S$ requires C, 62.3; H, 4.75; N, 6.6%); and the 6-*methyl derivative* (8f) (yield 88%) had m.p. 167—169° (Found: C, 62.3; H, 4.7; N, 6.6%).

The infrared spectra of all these sulphonamido-ketones showed $\nu_{max.}$ 1 690—1 700 cm^{-1} (C=O). The n.m.r. spectra of (8a)—(8e) each contained a singlet (2 H) at δ 5.3—5.4. The methylene resonance of (8f) was an AB quartet (*J* 19 Hz) with δ_A 5.14 and δ_B 5.93 (TFA).

N-*Acetonyl*-N-p-*tolylsulphonyl*-o-*nitroaniline* (9a) *and its Derivatives* (9b, d, and f).—These were prepared as above, with chloroacetone (3.7 g; 0.04 mol) in place of phenacyl bromide. The *parent compound* (9a), obtained in 50% yield, had m.p. 104—105° (from CCl_4) (Found: C, 55.1; H, 4.6; N, 8.0. $C_{16}H_{16}N_2O_5S$ requires C, 55.2; H, 4.7; N, 8.2%). The 4-*methyl derivative* (9b) (yield 90%) had m.p. 132° (from ethanol) (Found: C, 56.0; H, 5.0; N, 7.7. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7%). The 4-*methoxy-derivative* (9d) (yield 77%) had m.p. 91—93° (from ethanol) (Found: C, 54.0; H, 4.9; N, 7.4. $C_{17}H_{18}N_2O_6S$ requires C, 54.0; H, 4.8; N, 7.4%). The 6-*methyl derivative* (9f) (yield 52%) had m.p. 94—96° (from ethanol) (Found: C, 56.5; H, 5.1; N, 7.5. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7%).

For this series, $\nu_{max.}$ (C=O) = 1 725—1 730 cm^{-1}; δ 4.6—4.7 (CH_2CO) [singlets except for (9f) which shows an AB quartet, *J* 19 Hz, with δ_A 4.13 and δ_B 5.11].

Ethyl (N-*o*-*Nitrophenyl*-N-p-*tolylsulphonylamino*)*acetate* (10a) *and its Derivatives* (10b and d).—These were prepared in a similar manner, using ethyl bromoacetate in place of phenacyl bromide; they were recrystallised from ethanol. The *parent compound* (10a) (yield 73%) had m.p. 74—75° (Found: C, 54.0; H, 4.7; N, 7.3. $C_{17}H_{18}N_2O_6S$ requires C, 54.0; H, 4.8; N, 7.4%). The 4-*methyl derivative* (10b) (yield 51%) had m.p. 59—60° (Found: C, 55.2; H, 5.0; N, 7.1. $C_{18}H_{20}N_2O_6S$ requires C, 55.1; H, 5.1; N, 7.1%). The 4-*methoxy-derivative* (10d) (yield 57%) had m.p. 82—84° (Found: C, 52.7; H, 5.0; N, 6.7. $C_{18}H_{20}N_2O_7S$ requires C, 52.9; H, 4.9; N, 6.9%).

For this series, $\nu_{max.}$ (C=O) = 1 735—1 750 cm^{-1}; δ 4.4—4.6 (CH_2CO_2Et).

N-*Cyanomethyl*-N-p-*tolylsulphonyl*-o-*nitroaniline* (11a) *and its Derivatives* (11c *and* f).—These were prepared similarly, using chloroacetonitrile in place of phenacyl bromide, and were recrystallised from ethanol. The *parent compound* (11a) (yield 50%) had m.p. 96—98° (Found: C, 54.4; H, 3.9; N, 12.7. $C_{15}H_{13}N_3O_4S$ requires C, 54.4; H, 4.0; N, 12.7%). The 4-*chloro-derivative* (11c) (yield 60%) had m.p. 116—118° (Found: C, 49.0; H, 3.3; N, 11.4. $C_{15}H_{12}ClN_3O_4S$ requires C, 49.25; H, 3.3; N, 11.5%). The 6-*methyl derivative* (11f) (yield 87%) had m.p. 115—116° (Found: C, 55.5; H, 4.4; N, 12.1. $C_{16}H_{15}N_3O_4S$ requires C, 55.65; H, 4.4; N, 12.2%). For (11a) and (11c), δ 4.72 (br s, CH_2CN); for (11f), this signal is an AB quartet (*J* 18 Hz) with δ_A 4.39 and δ_B 4.98.

N-p-*Nitrophenacyl*-N-p-*tolylsulphonyl*-4-*methyl*-2-*nitroaniline* (12) was also prepared by this general method, using *p*-nitrophenacyl bromide;[24] yield 85%, m.p. 192—194° (from methanol) (Found: C, 56.3; H, 4.1: N, 8.9. $C_{22}H_{19}N_2O_7S$ requires C, 56.3; H, 4.1; N, 8.95%). N-*Methylsulphonyl*-N-*phenacyl*-4-*methyl*-2-*nitroaniline* (19), m.p. 89—91° (from ethanol) (Found: C, 55.2; H, 4.5; N, 8.1. $C_{16}H_{16}N_2O_5S$ requires C, 55.2; H, 4.6; N, 8.0%), and *ethyl* [N-(4-*methyl*-2-*nitrophenyl*)-N-*methylsulphonylamino*]*acetate* (20), m.p. 68—70° (from ethanol) (Found: C, 45.6; H, 5.1; N, 9.1. $C_{12}H_{16}N_2O_6S$ requires C, 45.6; H, 5.1; N, 8.9%), were each prepared (yields 72% and 51%, respectively) analogously to their *N*-*p*-tolylsulphonyl analogues.

Preparation of 2-Alkoxybenzimidazole N-Oxides.—(i) *General procedure.* A solution of the sodium alkoxide (from sodium, 0.46 g) in the appropriate alcohol (20 ml) was added to a solution or suspension of the sulphonamido-ketone (8, 9, or 19) (0.01 mol) in the same alcohol (40 ml), and the mixture was heated under reflux for 2 h. The alcohol was then evaporated *in vacuo*, and the residue was extracted into ether–water (1 : 1; 200 ml). Careful neutralisation of the aqueous layer (5M-H_2SO_4) gave the 2-alkoxybenzimidazole *N*-oxide, which was filtered off and recrystallised. Yields of compounds so obtained are collected in Table 1, and their characteristics are shown in Table 2.

TABLE 2

2-Alkoxybenzimidazole *N*-oxides (13)—(16)

Compound	Substituents	M.p. (°) *	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(13a)	2-OEt	162—164 †							
(13b)	2-OEt, 5-Me	181—183	$C_{10}H_{12}N_2O_2$	62.3	6.3	14.5	62.5	6.3	14.6
(13c)	2-OEt, 5-Cl	201—202	$C_9H_9ClN_2O_2$	50.65	4.3	13.2	50.8	4.3	13.2
(13d)	2-OEt, 5-OMe	147—148	$C_{10}H_{12}N_2O_3$	57.5	5.65	13.5	57.7	5.8	13.45
(13e)	2-OEt, 6-Me	163—164	$C_{10}H_{12}N_2O_2$	62.4	6.4	14.5	62.5	6.3	14.6
(14b)	2-OMe, 5-Me	166—168	$C_9H_{10}N_2O_2$	60.5	5.45	15.7	60.7	5.7	15.7
(14c)	2-OMe, 5-Cl	191—192	$C_8H_7ClN_2O_2$	48.6	3.9	13.7	48.4	3.6	14.1
(14d)	2,5-$(OMe)_2$	144	$C_9H_{10}N_2O_3$	55.6	5.2	14.3	55.7	5.2	14.4
(14e)	2-OMe, 6-Me	164—165	$C_9H_{10}N_2O_2$	60.4	5.8	15.4	60.7	5.7	15.7
(15b)	2-OPr^n, 5-Me	158—160	$C_{11}H_{14}N_2O_2$	63.8	6.7	13.6	64.1	6.8	13.6
(15c)	2-OPr^n, 5-Cl	183	$C_{10}H_{11}ClN_2O_2$	53.2	5.1	12.7	53.0	4.9	12.4
(16b)	2-OPr^i, 5-Me	151—152	$C_{11}H_{14}N_2O_2$	63.8	6.75	13.55	64.1	6.8	13.6

* (13a) was recrystallised from ethanol–water, (14b) from methanol, and the remainder from ethanol. † Lit.,[11] 166°.

(ii) *The reaction* (8b) ⟶ (16b). Reaction of the sulphonamido-ketone (8b) with sodium isopropoxide in isopropanol according to the above procedure give 2-isopropoxy-5-methylbenzimidazole *N*-oxide (16b) in 24% yield. Evaporation of the ether extract and chromatography of the residue (silica gel; $CHCl_3$ eluant) gave 4-methyl-2-nitroaniline, m.p. and mixed m.p. 111—112°, in 14% yield.

The corresponding reaction of (9b) with sodium isopropoxide gave (16b) in 28% yield, and 4-methyl-2-nitroaniline in 20% yield.

(iii) *Attempt to isolate 2-methoxybenzimidazole* N-*oxide* (14a). The sulphonamido-ketone (8a) (1.025 g) and sodium methoxide (from sodium, 0.12 g) were allowed to react as in (i). The residue obtained by evaporation of the methanol was washed with ether, and was then re-dissolved in methanol. Hydrogen chloride was bubbled into the solution until the deep red colour faded, the methanol was evaporated *in vacuo*, and the residue was recrystallised from acetic acid, giving a solid (0.25 g) with m.p. *ca.* 250° and the correct mass spectrum for 2-methoxybenzimidazole *N*-oxide (14a) (Found: *m/e* 164.057 611 and 133.040 322. $C_8H_8N_2O_2$ requires *M*, 164.058 573; *M* — OMe, 133.040 185). Elemental analysis, however, showed this material to be mainly inorganic.

N.m.r. Spectra of 2-Alkoxybenzimidazole N-*Oxides*.—In TFA the aromatic resonances all lie within the range δ 7.0—7.8, and are either singlets [(13a), (13b), (14b), (15b), or unresolved multiplets. The protons of the 2-alkoxy-substituents resonate at δ 4.6—4.7 (OMe), 4.85—4.95 (2 H) and 1.7—1.75 (3 H; OEt), 4.75—4.9 (2 H), 2.0—2.1 (2 H), and 1.15—1.25 (3 H; OPr^n). Absorptions in [$^2H_6$]DMSO are δ 6.7—7.3 (m, ArH), 4.1 (OMe), and 5.18 (1 H) and 1.42 (6 H) (OPr^i). Other absorptions are δ(TFA) 2.58 (5-Me), 2.50 (6-Me), and 4.03 (5-OMe); δ([$^2H_6$]DMSO) 2.38 (5-Me).

2-*Ethoxy-5-methylbenzimidazole* (17).—(a) *From its* N-*oxide* (13b). The *N*-oxide (0.75 g) was dissolved in a mixture of acetic anhydride (2 ml) and acetic acid (5 ml). The solution was stirred for 1 h, and was then diluted with ethanol (20 ml) and hydrogenated over 10% palladium–charcoal (0.1 g). Removal of the catalyst and evaporation gave 2-ethoxy-5-methylbenzimidazole (0.15 g, 22%), m.p. 162—164° (from benzene–petroleum) (lit.,[25] 163°) (Found: C, 67.9; H, 6.8; N, 15.75. Calc. for $C_{10}H_{12}N_2O$: C, 68.2; H, 6.9; N, 15.9%), δ 1.43 (3 H, t) and 4.53 (2 H, q) (*J* 7.5 Hz, OEt), 2.40 (3 H, 5-Me), 6.89 (1 H, dd,H-6), 7.15 (1 H, d, H-4), and 7.24 (1 H, d, H-7) ($J_{6,7}$ 7.5 Hz, $J_{4,6}$ 1.5 Hz).

(b) *From* 3,4-*diaminotoluene*. Tetraethoxymethane (2.0 g) was added to a solution of 3,4-diaminotoluene (1.0 g) in acetic acid (5 ml). The mixture was stirred for 24 h at room temperature, and the solvent was then evaporated *in vacuo*, giving 2-ethoxy-5-methylbenzimidazole (0.96 g, 67%), identical in all respects with the specimen prepared by method (a).

1-*Hydroxy*-4-*methylbenzimidazolone* (21).—Sodium ethoxide (from sodium, 0.23 g) in ethanol (25 ml) was added to a suspension of 6-methyl-2-nitro-*N*-phenacyl-*N*-*p*-tolylsulphonylaniline (8f) (2.12 g; 0.005 mol) in ethanol (15 ml). The mixture was heated under reflux for 2 h, the ethanol was evaporated *in vacuo*, and the residue was partitioned between ether and water. Neutralisation (5M-H_2SO_4) of the aqueous layer gave 1-*hydroxy*-4-*methylbenzimidazolone* (21) (0.30 g, 33%), m.p. 254—257° (from ethanol) (Found: C, 58.8; H, 5.0; N, 17.0. $C_8H_8N_2O_2$ requires C, 58.5; H, 4.9; N, 17.1%), $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ(TFA) 2.48 (3 H, s, Me) and 7.25 (3 H, s, ArH).

The corresponding reaction of (8f) with sodium methoxide, and the reactions of the *N*-acetonyl analogue (9f) with ethoxide and methoxide, gave (21) in yields of 22%, 25%, and 17%, respectively.

4-*Methylbenzimidazolone*.—(a) *From* (21). 1-Hydroxy-4-methylbenzimidazolone was subjected to the acetylation–hydrogenolysis procedure described above for the preparation of (17) from (13b). 4-Methylbenzimidazolone, m.p. 299—302° (from acetic acid; lit.,[26] 297—300°), was obtained in 25% yield.

(b) *From* 6-*methyl*-2-*nitroaniline*.—6-Methyl-2-nitroaniline (2.0 g) was hydrogenated in ethanol solution over palladium–charcoal (10%; 0.2 g). The crude 2,3-diaminotoluene so obtained was dissolved in acetic acid (5 ml); tetraethoxymethane (2.0 g) was added and the mixture was stirred for 24 h at room temperature. Ethanol (70 ml) was added, and the solution was then concentrated *in vacuo*. The crude product (presumably 2-ethoxy-4-methylbenzimidazole) was hydrolysed in concentrated hydrochloric acid (8 ml) by heating at 100 °C for 3 h; addition of the acid solution to crushed ice gave 4-methylbenzimidazolone (0.38 g, 17%), identical with the sample prepared in (a).

Further Reactions of the Sulphonamido-ketones (8a) *and* (8b) *with Bases*.—(a) (8a) *and* (8b) *with potassium t-butoxide*. These reactions, carried out according to the 'general procedure' for preparation of 2-alkoxybenzimidazole *N*-oxides, gave no acidic product, but only *o*-nitroaniline (75%) and 4-methyl-2-nitroaniline (82%). (*b*) (8b) *with potassium hydroxide*. Compound (8b) (6.80 g), potassium hydroxide (2.56 g), and ethanol (50 ml) were heated together under reflux for 2 h. Work-up gave 2-ethoxy-5-methylbenzimidazole *N*-oxide (13b) (1.65 g, 53%). The corresponding reaction in methanol however gave only methyl benzoate (3%; correct i.r. and n.m.r. spectra) and 5-methyl-1-*p*-tolylsulphonylbenzimidazolone (22b) (6%), m.p. 258—261° (from acetic acid) (lit.,[20] 263—265°). (c) (8a) *and* (8b) *with sodium carbonate*. Solid sodium carbonate (3.1 g) was added to a suspension of compound (8a) (2.05 g) in methanol (20 ml). The mixture was heated under reflux for 2 h and worked up. The non-acidic fraction yielded methylbenzoate (0.03 g, *ca.* 5%) and 1-*p*-tolylsulphonylbenzimidazolone (22a) (0.07 g, 5%), m.p. 207—210° (from acetic acid) (lit.,[20] 211—215°); no acidic product was found. The corresponding reaction in ethanol was unsuccessful, starting material being recovered, but the reaction of (8b) with sodium carbonate in ethanol gave 2-ethoxy-5-methylbenzimidazole *N*-oxide (13b) (33%).

Compounds (22a) and (22b) had $\nu_{max.}$ *ca.* 1 700 cm^{-1} (C=O) and mass spectra with prominent peaks corresponding to $M^{+\cdot}$, $(M - CO)^{+\cdot}$, $(M - Ts)^+$, and Ts^+.

N-(o-*Nitrophenyl*)-α-*methoxyphenacylamine* (23).—A slurry of sodium carbonate (1.56 g) in methanol (20 ml) was added to *N*-phenacyl-*N*-*p*-tolylsulphonyl-*o*-nitroaniline (8a) (1.02 g), and the mixture heated under reflux for 2 h, then filtered. The filtrate was evaporated *in vacuo*, and the residue washed with water and recrystallised from methanol, giving the *amine* (23) (0.50 g, 70%), m.p. 110—112° (Found: C, 63.0; H, 4.9; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 63.0; H, 4.9; N, 9.8%); $\nu_{max.}$ 3 330 (N–H), 1 680 (C=O), 1 520, and 1 340 cm^{-1} (NO_2); δ 3.08 (3 H, s, OMe), 6.13 (1 H, d, *J* 6 Hz, *CH*NH), 6.6—6.9 (1 H), 7.2—7.7 (5 H), and 8.1—8.3 (3 H), (ArH), and 9.23 (1 H, br d, *J* 6 Hz, NH).

N-*Phenacyl*-o-*nitroaniline* (29a).—*N*-Phenacyl-*N*-*p*-tolyl-

sulphonyl-*o*-nitroaniline (8a) (8.0 g) was heated for 1.5 h at 100° with a mixture of concentrated sulphuric acid (12 ml) and acetic acid (8 ml). The mixture was then poured on to crushed ice, and the product was filtered off and recrystallised from ethanol. The *amine* (29a) (4.25 g, 85%) had m.p. 147—149° (Found: C, 65.5; H, 4.7; N, 11.0. $C_{14}H_{12}N_2O_3$ requires C, 65.6; H, 4.7; N, 10.9%); $\nu_{max.}$ 3 330 (NH), 1 680 (C=O), 1 555, and 1 360 cm^{-1} (NO_2); δ 4.77 (2 H, d, *J* 4 Hz, CH_2NH), 6.6—6.9 (2 H), 7.2—7.6 (4 H), and 7.8—8.3 (3 H) (Ar-H), and 8.80 (1 H, br, NH). *N-Phenacyl-4-methyl-2-nitroaniline* (29b), similarly prepared from (8b) in 79% yield, had m.p. 162—164° (lit.,[27] 163—165°), and was identical with a sample prepared by nitration of *N*-phenacyl-*p*-toluidine.[27]

TABLE 3

Reaction of sulphonamides and sodium alkoxides

Substrate	Base	Products
(10a)	NaOMe	*o*-nitroaniline (53%)
(10b)	NaOMe,	4-methyl-2-nitroaniline (61%)
	NaOEt,	4-methyl-2-nitroaniline (59%)
	$NaOBu^t$	4-methyl-2-nitroaniline (67%)
(10d)	NaOMe,	4-methoxy-2-nitroaniline (50%)
	NaOEt	4-methoxy-2-nitroaniline (52%)
(11a)	NaOEt	*N-p*-tolylsulphonyl-*o*-nitroaniline (25%)
(11c)	NaOEt	*N-p*-tolylsulphonyl-4-chloro-2-nitroaniline (15%)
(11f)	NaOEt	*N-p*-tolylsulphonyl-6-methyl-2-nitroaniline (12%)
(12)	NaOMe, NaOEt	Complex mixture containing 4-methyl-2-nitroaniline, its *N-p*-tolylsulphonyl derivative, and methyl or ethyl benzoate
(20)	NaOEt	4-methyl-2-nitroaniline (35%)

Reactions of (29a) *and* (29b) *with Sodium Alkoxides*.—The amine (29a) (2.56 g) in methanol (15 ml) was heated under reflux with a solution of sodium methoxide (from sodium, 0.46 g), in methanol (40 ml) for 2 h. The methanol was evaporated off and the residue extracted into ether–water (100 ml, 1 : 1). The ether-soluble products were separated by chromatography (silica gel; $CHCl_3$) and identified as methyl benzoate (0.25 g, 18%) and *o*-nitroaniline (0.70 g, 51%). The corresponding reaction with sodium ethoxide gave ethyl benzoate (10%) and *o*-nitroaniline (53%). Under similar conditions the amine (29b) reacted with sodium methoxide and ethoxide to give the appropriate alkyl benzoate (yields 14 and 11%, respectively), 4-methyl-2-nitroaniline (42 and 45%, respectively), and (by acidification of the aqueous layer) 2-benzoyl-5-methylbenzimidazole *N*-oxide (2 and 3%, respectively), m.p. 129—130° (lit.,[5] 132°), identical with an authentic sample.

Reactions of the Sulphonamides (10), (11), (12), *and* (20) *with Sodium Alkoxides*.—The results of these reactions, carried out according to the ' General procedure ', are shown in Table 3.

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