Thermolysis of *o*-Alkylnitrosobenzenes. Unusually Ready [1,5] Hydrogen Shift involving a Nitroso-group

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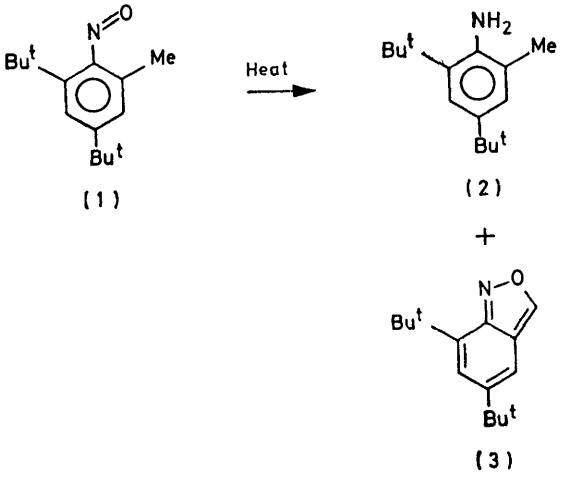
Thermolysis of 2,4-di-t-butyl-6-methylnitrosobenzene (1) in benzene afforded the corresponding aniline (2) and 5,7-di-t-butyl-2,1-benzisoxazole (3) in the ratio of 1 : 2; in methanol 2-t-butyl-4-methoxy-6-methylaniline (4) and 1-hydroxyimino-2,4-di-t-butyl-6-methoxy-6-methylcyclohexa-2,4-diene (5) were formed in addition to (2) and (3). In the presence of dimethyl acetylenedicarboxylate, (1) gave (3) and *N*-(1,2-dimethoxycarbonylethylidene)-2,4-di-t-butyl-6-methylaniline *N*-oxide (7) in benzene. These facts together with the evidence of deuterium incorporation in product (3) and the recovery of (1) in the reaction in CH_3OD, allows us to postulate a reaction mechanism, the first step of which is formation of an *o*-quinone methide imine type intermediate *via* a [1,5] hydrogen migration from the benzylic position to the nitroso-oxygen. Thermolysis of 2,4-di-t-butyl-6-ethyl (or isopropyl)-, 2,4,6-trimethyl-, and 2-methylnitrosobenzenes were also found to proceed *via* a similar reaction mechanism.

PREVIOUSLY, in connection with the reaction of sterically hindered nitrosobenzenes with free radicals, we reported that 2,4-di-t-butyl-6-methylnitrosobenzene (1) underwent thermal disproportionation to give 2,4-di-t-butyl-6-methylaniline (2) and 5,7-di-t-butyl-2,1-benzisoxazole (3).[1] The mechanism of this unusual mutual oxidation–



(1) (2) + (3)

reduction reaction, however, has remained unexplored. We recently became interested in the reaction mechanism and the extension of this type of reaction to other *o*-alkylnitrosobenzenes, and undertook some investigations along these lines.

RESULTS AND DISCUSSION

Thermolysis of 2,4-*Di-t-butyl*-6-*methylnitrosobenzene* (1). —(*a*) *Reaction products.* Thermolysis of (1) in refluxing benzene for 35 h afforded the aniline (2) and the benzisoxazole (3). Reaction of (1) in methanol under reflux for 7.3 h resulted in (2), (3), 2-t-butyl-4-methoxy-6-methylaniline (4), and 1-hydroxyimino-2,4-di-t-butyl-6-methylcyclohexa-2,4-diene (5).

The yields of the products and the reaction conditions are shown in the Table.

The structures of (4) and (5) were established by the spectral data. An alternative isomeric structure (6) possible for (5) can be ruled out by the n.m.r. spectrum of (5) which did not show olefinic methyl protons.

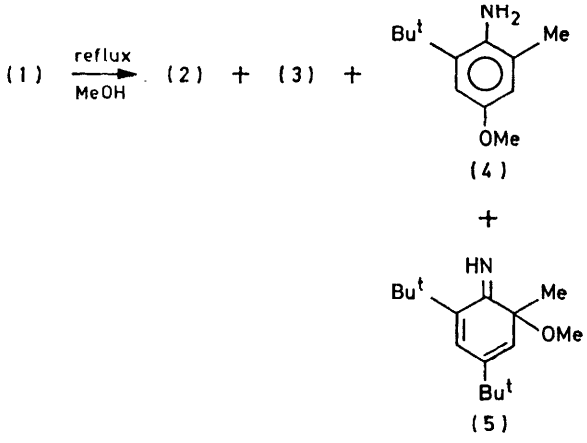
When heated in refluxing benzene for 4.5 h in the presence of dimethyl acetylenedicarboxylate, the nitrosobenzene (1) afforded (3) (48%) and *N*-(1,2-dimethoxycarbonylethylidene)-2,4-di-t-butyl-6-methylaniline *N*-oxide (7) (46%).

Yields (%) of the reaction products of (1)

Solvent	Reaction time (h)	(1)	Yields (%) (2)	(3)	(4)	(5)
Benzene	7 [a]		23	60		
	35 [b]		25	50		
Methanol	7.3	3	8	48	18	16

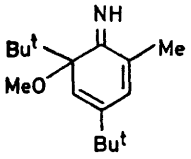
[a] Ref. 1. [b] Present work.

(*b*) *Reaction mechanism.* The results of the reaction in methan[^{2}H]ol provided important information for the mechanism. The benzisoxazole (3) obtained and the nitrosobenzene (1) recovered from the reaction in methan[^{2}H]ol were found to contain deuterium at the 3-position of the isoxazole ring (8%) and at the 6-methyl

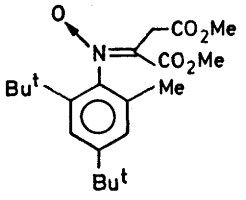


(30%), respectively. This indicates the occurrence of reversible [1,5] sigmatropic shift between the methyl hydrogen and the nitroso-oxygen as shown in Scheme 1 [(1) $\rightleftharpoons$ (8)].

The deuterium exchange takes place in the hydroxy-hydrogen of (8), thus introducing deuterium on the 3-position of the benzisoxazole (3) and the methyl group of the nitrosobenzene (1). There seem to be two other possibilities for incorporation of deuterium; one is that it occurs after the formation of (3) and the other is that it



(6)



(7)

takes place in (1) without the intermediacy of (8) because of the electron-withdrawing ability of the N=O group. The possibilities, however, were eliminated by the fact that compound (3) underwent no deuterium incorporation, and *p*-nitrosotoluene was recovered with no deuterium at the methyl, under comparable conditions.

Cyclization of (8) leads to an intermediate (9) which undergoes a mutual oxidation–reduction reaction with the nitrosobenzene (1) to give the hydroxylamine (10) and (3).

Although trapping of the *o*-quinone methide imine type intermediate (8) by *N*-phenylmaleimide was unsuccessful, probably because of steric hindrance and rapid cyclization into (9), the aforementioned deuterium incorportion, the formation of (3), and the involvement of hydroxylamine (10) as an intermediate (see below) clearly suggest the existence of (8) as an intermediate in the thermolysis.

The hydroxylamine (10) thus formed is almost quantitatively trapped as the nitrone (7) in the presence of dimethyl acetylenedicarboxylate (Scheme 2).

Winterfeldt *et al.* reported that the reaction of *N*-phenylhydroxylamine with the ester gave rise to 1 : 1 adduct similar to (11) but that it was unstable under the reaction conditions to dimerization.[2] The isolation of (7) in the present case is presumably due to steric inhibition of the dimerization.

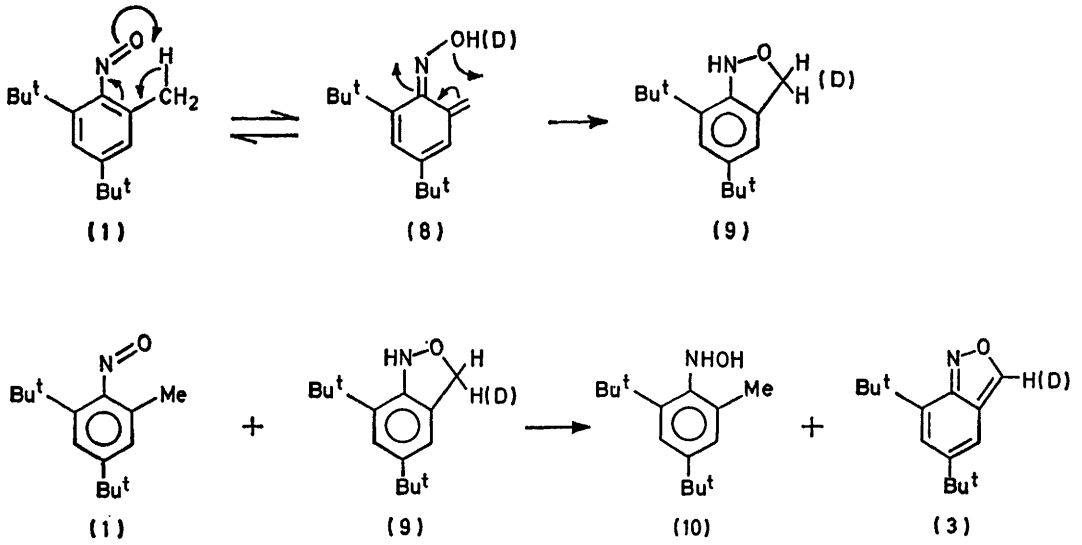
In the absence of the dimethyl ester, (10) is reduced by (9) into the aniline (2). The reducing ability of the hydroxylamine derivative (9) obviously comes from the aromatic stability of its oxidation product (3).

The yield of the aniline (2) in the reaction in methanol decreases compared with that in benzene and new products (4) and (5) are formed. This result can be interpreted in terms of attack of methanol on the aromatic ring of the hydroxylamine.[3]

Formation of (4) is most likely explained by elimination of 2-methylpropene from the initial product (12); the loss of 2-methylpropene of this kind is often observed in the reactions of t-butylbenzenes.[4]

Thus the mechanism and stoicheiometry of thermal disproportionation of the nitrosobenzene (1) can be summarized as shown in Scheme 3.

This scheme requires the stoicheiometry, Y(3) = 2Y-(2) in benzene and Y(3) = 2Y(2) + Y(4) + Y(5) in methanol (Y stands for a yield), and indeed, as shown in Table, the observed values satisfy this requirement.

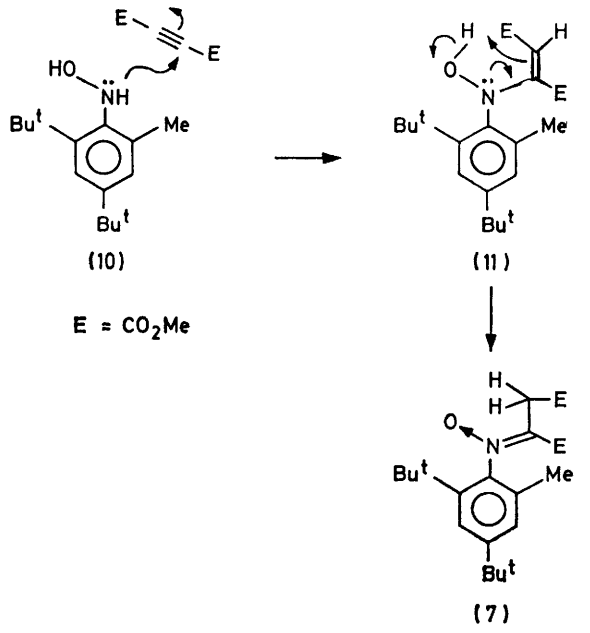


SCHEME 1

Thermolysis of Other o-Alkylnitrosobenzenes.—The [1,5] sigmatropy described above is expected to occur in other *o*-alkylnitrosobenzenes. Reaction of 2,4-di-t-butyl-6-ethylaniline (13) with *m*-chloroperbenzoic acid (MCPBA) at −40 °C afforded 2,4-di-t-butyl-6-ethylnitrosobenzene (14) (39%) after chromatographic purification at −78 °C. On standing overnight at 5 °C, however, the nitrosobenzene (14) decomposed to give 5,7-di-t-butyl-3-methyl-2,1-benzisoxazole (15) and the aniline (13).

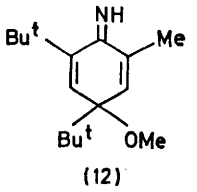
The reaction of 2,4-di-t-butyl-6-isopropylaniline with MCPBA followed by chromatography at −78 °C resulted in isolation of the corresponding nitrosobenzene (16%).

Although the n.m.r. spectrum indicated that the nitrosobenzene was stable at −30 °C it decomposed gradually above 0 °C. From the reaction mixture there was obtained a small amount (3%) of what was believed to be



SCHEME 2

the dihydroisoxazole (16). The isolation of (16) is in keeping with Scheme 3 and provides supporting evidence for the intermediacy of a dihydrobenzisoxazole of type (9) in these disproportionation reactions.



The above facts indicate that the reactivity to thermal disproportionation of 2,4-di-t-butyl-6-alkylnitrosobenzenes varies systematically with a change in the 6-alkyl group; increasingly bulkier groups accelerate the

$$(1) \rightleftharpoons (8) \longrightarrow (9)$$
$$(1) + (9) \longrightarrow (10) + (3)$$
$$(9) + (10) \longrightarrow (3) + (2) + H_2O$$

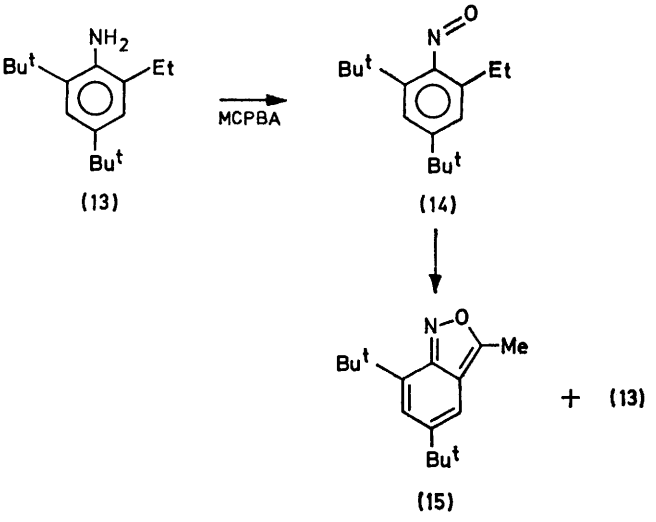
in total

$$3\,(1) \longrightarrow 2\,(3) + (2) + H_2O$$

SCHEME 3

reaction. This trend can be rationalized in terms of the stability of the initially formed *o*-quinone methide imine (17) which would be enhanced by an increasing number of methyl groups. We consider this as another piece of supporting evidence for the mechanism described in Schemes 2 and 3.

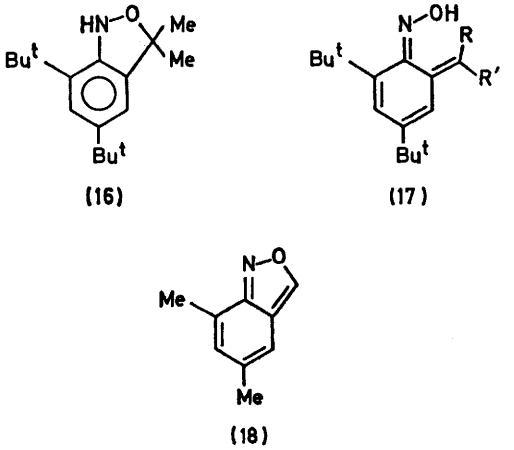
Thermolysis of 2,4,6-trimethylnitrosobenzene at 80 °C for 45 min afforded 2,2′,4,4′,6,6′-hexamethylazoxybenzene (18%) and the benzisoxazole (18) (10%), while the reaction of *o*-methylnitrosobenzene gave only 2,2′-dimethylazoxybenzene as an identifiable product. The formation of the azoxybenzenes in the reactions of these *o*-methyl substituted nitrosobenzenes can be explained in terms of the reaction of the nitrosobenzenes with the corresponding hydroxylamines formed by the reduction



of the nitrosobenzenes as shown in Scheme 3. Thus, the hydroxylamines formed from less hindered 2-methyl- and 2,4,6-trimethyl-nitrosobenzenes react with the nitrosobenzenes to give the azoxybenzenes rather than with an intermediate of type (9) to afford the corresponding anilines.

These results suggest that the thermal [1,5] hydrogen shift between *o*-methyl hydrogen and a nitroso-group is general for *o*-alkylnitrosobenzenes.

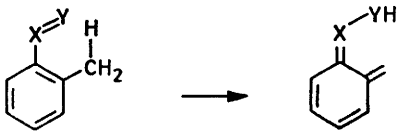
This type of [1,5] sigmatropic hydrogen shift to yield



an *o*-quinonoid compound as represented in Scheme 4 is rare although a large number of [1,5] hydrogen shifts are known.[5] The loss of aromaticity is obviously responsible for the paucity of results and the only example is that of mesityl- and 2′-isopropylphenyl-allenes,[6] which

have been reported to rearrange thermally at 150—190 °C.

The ease with which the nitrosobenzenes undergo [1,5] sigmatropic shifts is presumably due to the low π-bond strength of the N=O group (201 kJ mol^{-1} or 48.1 kcal mol^{-1}) in comparison with that of the C=C group (248 kJ mol^{-1} or 59.4 kcal mol^{-1}).[7] In this connection, it should be



SCHEME 4

noted that 2,4-di-t-butyl-6-methylnitrobenzene is so thermally stable as to be recovered without any decomposition and deuterium incorporation after prolonged heating in methanol.

EXPERIMENTAL

Melting points are uncorrected. The i.r. and u.v. spectra were recorded with Hitachi EPI-G2 and EPS-3 spectrophotometers respectively. The n.m.r. spectra were measured with a Hitachi R-20B (60 MHz) spectrometer using tetramethylsilane as an internal standard. The mass spectra were recorded with a Hitachi RMU-6L mass spectrometer (70 eV).

Thermolysis of 2,4-*Di-t-butyl*-6-*methylnitrosobenzene* (1) *in Benzene*.—The nitrosobenzene (1)[8] (679 mg, 2.9 mmol) was refluxed in benzene (20 ml) for 35 h under a nitrogen atmosphere. After removal of the solvent the residue (867 mg) was chromatographed on silica gel with hexane–dichloromethane (2 : 1). The first fraction afforded the benzisoxazole (3) as pale yellow crystals (70 mg). The second fraction gave pale yellow crystals (397 mg), which were rechromatographed on silica gel with hexane–dichloromethane (3 : 1) to give two fractions A and B. Fraction A gave 264 mg of (3) as white crystals, which had i.r., n.m.r., and u.v. spectra identical with those of an authentic sample.[1] Thus the total amount of (3) was 334 mg (50%). Fraction B afforded 55 mg of the aniline (2), which was identified by comparison with an authentic sample.[9] The third fraction afforded 106 mg of (2), thus the total amount of (2) was 161 mg (25%).

Thermolysis of (1) *in Methanol*.—The nitrosobenzene (1) (245 mg, 1.05 mmol) was refluxed in methanol (5 ml) under an argon atmosphere for 7.3 h. The removal of solvent afforded tarry material (240 mg), which was subjected to preparative t.l.c. [silica gel, hexane–dichloromethane (3 : 2)] to give four fractions, which were eluted with dichloromethane. The first fraction was composed of recovered (1) (8 mg, 3%) and (3) (2 mg). The second fraction afforded (3) (115 mg), thus bringing the total amount of (3) to 117 mg (48%). The third fraction afforded (2) (18 mg, 8%). The fourth fraction gave pale yellow, partly crystalline material (81 mg), which on repeated preparative t.l.c. (silica gel, dichloromethane) gave (4) (37 mg, 18%); $\nu_{max.}$ (neat) 3 505 and 3 415 cm^{-1} (NH_2); δ (CCl_4) 1.41 (9 H, s), 2.12 (3 H, s), 3.36 (2 H, bs), 3.66 (3 H, s), and 6.50 (2 H, AB q, J = 2.7 Hz, $\Delta\delta$ = 0.18); *m/e* 193 (M^+, 35%), 178 (100), 163 (15), 91 (15), 77 (17), and 57 (9). The fifth fraction afforded (5) (42 mg, 16%) as pale yellow crystals, m.p. 97—99 °C (ethanol) (Found: C, 77.20; H, 10.88; N, 5.43. $C_{16}H_{27}NO$ requires C, 77.06; H, 10.91; N, 5.61%); $\nu_{max.}$ (KBr) 3 249 cm^{-1}; δ (CCl_4) 1.16 (9 H, s), 1.26 (3 H, s), 1.38 (9 H, s), 3.05 (3 H, s), 5.74 (1 H, d, J 2.2 Hz), and 6.49 (1 H, d, J 2.2 Hz) (the signal of NH proton was obscure); *m/e* 249 (M^+, 30%), 234 (100), 204 (60), 192 (36), 178 (38), 162 (14), 91 (14), (12), and 57 (48).

Thermolysis of (1) *in the Presence of Dimethyl Acetylenedicarboxylate in Benzene*.—A mixture of (1) (392 mg, 1.68 mmol) and dimethyl acetylenedicarboxylate (364 mg, 2.56 mmol) was refluxed in benzene (8 ml) for 4.5 h. The solvent was removed under reduced pressure and the residue was subjected to preparative t.l.c. [silica gel, hexane–dichloromethane (3 : 2)]. From the first fraction was isolated 12 mg of recovered (1). The second fraction gave (3) (186 mg, 48%). The third fraction afforded 290 mg (46%) of the nitrone (7), m.p. 98.5—99.5 °C (white crystals from ethanol) (Found: C, 66.9; H, 8.6; N, 3.9. $C_{21}H_{31}NO_5$ requires C, 66.82; H, 8.28; N, 3.71%); $\nu_{max.}$ (KBr) 1 753 and 1 720 cm^{-1}; δ (CCl_4) 1.30 (9 H, s), 1.34 (9 H, s), 2.10 (3 H, s), 3.58 (3 H, s), 3.71 (3 H, s), 3.75 (2 H, s), and 7.15 (2 H, AB q, J 2.2 Hz, $\Delta\delta$ = 0.28); δ (CD_3OD) 1.32 (9 H, s), 1.34 (9 H, s), 2.15 (3 H, s), 3.59 (3 H, s), 3.70 (3 H, s), 3.89 (2 H, s), and 7.30 (2 H, AB q, J 2.0 Hz, $\Delta\delta$ = 0.28) (the signal of the CH_2 protons (δ 3.89) disappeared upon addition of a small amount of sodium); $\lambda_{max.}$ (hexane) 281 nm (ε 15 300); *m/e* 377 (M^+, 17%), 360 (38), 318 (64), 286 (52), 163 (38), 91 (14), 77 (8), and 57 (100).

Thermolysis of (1) *in Methan*[^{2}H]*ol*. (*a*) In a sealed tube, (1) (209 mg, 0.90 mmol) was heated in methan[^{2}H]ol (3 ml) at 76 °C for 2.5 h. Removal of the solvent afforded 195 mg of brown tarry material, which was subjected to preparative t.l.c. [silica gel, hexane–dichloromethane (7 : 3)]. The first fraction afforded 98 mg (47%) of (3), whose n.m.r. and mass spectra indicated the incorporation of deuterium of 8.1 and 7.6%, respectively, at the C-3 position. The second and third fractions gave 13 mg (7%) of (2) and 24 mg of (4), respectively. The fourth fraction was a mixture of (4) (11 mg) and (5) (11 mg, 4%) according to the signal intensity on the n.m.r. spectrum. Thus the total amount of (4) was 35 mg (17%).

(*b*) In a sealed tube, (1) (228 mg, 0.98 mmol) was heated in methan[^{2}H]ol (2.8 ml) at 65 °C for 15 min. After removal of the solvent the residue was subjected to preparative t.l.c. [silica gel, hexane–dichloromethane (3 : 2)] at 0 °C. The first fraction afforded 74 mg (32%) of recovered (1), whose mass spectrum indicated the incorporation of deuterium of 30% in the methyl group. The second fraction gave 80 mg (35%) of (3).

Reaction of 2,4-*Di-t-butyl*-6-*ethylaniline* (13) *with* m-*Chloroperbenzoic Acid* (*MCPBA*).—A dichloromethane solution (80 ml) of (13) (1.52 g, 6.52 mmol) and MCPBA (85%, 2.22 g, 13.2 mmol) were mixed and stirred for 1 h at −40 °C. The green reaction mixture was shaken with cold aqueous sodium hydrogencarbonate, washed with cold water, and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure with minimum heating gave a green tarry residue, which was chromatographed on silica gel (Wakogel C-200) with pentane as eluant at −78 °C. The first eluted green fraction afforded 624 mg (39%) of (14) as a green tar, the colour of which was discharged on standing overnight at 5 °C. The resulting colourless tar was allowed to stand for a month at 5 °C to give white crystals, which were purified by dry column chromatography (silica gel, dichloromethane) to give white crystals (451 mg). This was found to be a mixture of

the aniline (13) (84 mg, 14%) and the benzisoxazole (15) (367 mg, 59%) according to the n.m.r. spectrum. Purification by means of preparative t.l.c. (silica gel, carbon tetrachloride, two developements) followed by recrystallization from methanol (three times) afforded (15) as white crystals, m.p. 101.5—102.5 °C (Found: C, 78.55; H, 9.25; N, 5.55. $C_{16}H_{23}NO$ requires C, 78.32; H, 9.45; N, 5.71%); $\nu_{max.}$ (KBr) 1 635, 1 567, and 1 520 cm^{-1}; δ (CCl_4) 1.32 (9 H, s), 1.49 (9 H, s), 2.73 (3 H, s), and 7.00 (2 H, AB q, *J* 1.2 Hz, $\Delta\delta = 0.05$); *m/e* 245 (M^+, 12%), 230 (100), 132 (30), and 57 (51).

Reaction of 2,4-*Di-t-butyl*-6-*isopropylaniline with MCPBA*.—(*a*) A dichloromethane solution (80 ml) of the aniline (434 mg, 1.76 mmol) and MCPBA (82% purity, 642 mg, 3.72 mmol) were stirred for 40 min at −78 °C. After additional stirring for 30 min at room temperature, the reaction mixture was treated in a similar manner to that in the reaction of (13) with MCPBA. The green tarry residue thus obtained was chromatographed on silica gel with pentane as eluant at −78 °C to give 73 mg (16%) of 2,4-di-t-butyl-6-isopropylnitrosobenzene as green crystals; δ ($CDCl_3$, −30 °C) 1.10 (6 H, d, *J* 6.6 Hz), 1.48 (9 H, s), 1.62 (9 H, s), 1.70—2.30 (1 H, m), and 7.41 (2 H, AB q, *J* 2.2 Hz, $\Delta\delta = 0.29$). The n.m.r. spectrum suggested that the decomposition of the nitrosobenzene began around 0 °C and went to completion at 34 °C.

(*b*) A dichloromethane solution (100 ml) of the aniline (500 mg, 2.02 mmol) and MCPBA (82% purity, 909 mg, 4.33 mmol) were stirred for 2 h at −78 °C. After additional stirring for 1 h at room temperature, the green reaction mixture was similarly treated as above. In this case there was obtained a yellow tarry residue, which was chromatographed on silica gel with pentane and then dichloromethane–hexane (1 : 1) to give an orange tar (216 mg) as the third fraction. This was rechromatographed on silica gel with hexane–dichloromethane (3 : 2) to afford 17 mg of pale yellow crystals which were tentatively assigned as (16); δ (CCl_4) 1.07 (6 H, s), 1.31 (9 H, s), 1.40 (9 H, s), 6.62 (1 H, d, *J* 1.7 Hz), and 7.18 (1 H, d, *J* 1.7 Hz); *m/e* 261 (M^+, 20), 260 (23), 246 (30), 232 (25), 230 (28), 204 (25), 190 (30), and 57 (100).

Thermolysis of 2,4,6-*Trimethylnitrosobenzene*.—(*a*) In a sealed tube, the nitrosobenzene (165 mg, 1.11 mmol) was heated in xylene (5 ml) at 200—210 °C for 45 min. Removal of the solvent afforded 168 mg of dark brown tar, which was subjected to preparative t.l.c. (silica gel, hexane–dichloromethane (4 : 1), two developments). The first fraction afforded 45 mg (15%) of 2,2′,4,4′,6,6′-hexamethylazoxybenzene, which was identified by comparison with an authentic sample (i.r. and n.m.r.).[10] The second fraction afforded 38 mg (23%) of (18) as an oil; δ (CCl_4) 1.25 (3 H, s), 1.49 (3 H, s), 6.84 (2 H, AB q, *J* 1.3 Hz, $\Delta\delta = 0.23$), and 8.82 (1 H, s); *m/e* 147 (M^+, 51%), 134 (45), 119 (77), 118 (100), 105 (53), 104 (56), 91 (91), and 77 (66).

(*b*) The nitrosobenzene (185 mg, 1.24 mmol) was refluxed in benzene (5 ml) for 45 min. After similar treatment to (*a*) there were obtained 62 mg (18%) of the azoxybenzene, 19 mg (10%) of (18), and 35 mg (19%) of the recovered nitrosobenzene.

Thermolysis of o-*Methylnitrosobenzene*.—In a sealed tube, the nitrosobenzene (169 mg, 1.40 mmol) was heated in xylene (5 ml) at 200—210 °C for 45 min. Purification with preparative t.l.c. [silica gel, hexane–dichloromethane (4 : 1)] afforded 91 mg (29%) of 2,2′-dimethylazoxybenzene as yellow crystals, which was identified by comparison with an authentic sample (i.r. and n.m.r.).[11]

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