The pK_a values for these monocarboxylic acids were calculated using the computer program of Leung.[21,23,24]

The water used was distilled water which was passed slowly through a Barnstead Mixed Bed Demineralizer Cartridge (#8902) and redistilled. The ethanol was twice distilled 95% ethanol.

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[23] C. Leung, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1967.

[24] R. R. Reitz, Ph.D. Thesis, Kansas State University, Manhattan, Kans., 1971.

Registry No.—4-Azulylacetic acid, 26157-13-1; azulene-1,2-dicarboxylic acid, 34906-10-0.

Acknowledgment.—We wish to thank the National Science Foundation (GP-10691) for research support and Kansas State University for computer time.

Intermolecular Aromatic Substitution by Aryl Nitrenes

R. A. ABRAMOVITCH,* S. R. CHALLAND, AND E. F. V. SCRIVEN

Department of Chemistry, University of Alabama, University, Alabama 35486

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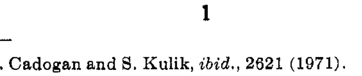
Thermally generated aryl nitrenes have been shown to undergo intermolecular aromatic substitutions provided that the nitrene is made sufficiently electrophilic by the introduction of an electron-withdrawing substituent in the aromatic nucleus and the aromatic substrate is sufficiently nucleophilic. The nitrenes were generated both by the thermolysis of aryl azides and from monomeric nitrosobenzenes and triethyl phosphite. The rate of first-order decomposition of *p*-cyanophenyl azide was found to be independent of the presence of *N*,*N*-dimethylaniline or of its concentration. The formation of a number of by-products is discussed.

The intermediacy of nitrenes in the thermolysis and photolysis of aryl azides is well documented.[1-3] Evidence for the involvement of nitrenes in deoxygenation reactions of nitro and nitroso compounds[4] is good in some cases but more tenuous in others, and depends largely upon analogy of the products of these reactions with those of the corresponding azide reactions. In particular, aryl nitrenes (or their rearrangement products) generated by thermolysis or photolysis of aryl azides or by deoxygenation of nitroso compounds have been trapped by nucleophiles, such as aniline,[5] diethylamine,[6] and carbon monoxide.[7]

Singlet aryl nitrenes generated thermally drop readily to the triplet ground state, so that these species can exhibit reactions typical of both singlet (intramolecular substitution[1] and rearrangement[2]) and triplet states (C–H insertion and hydrogen abstraction[8]). Intramolecular electrophilic aromatic substitution has been extensively studied; the thermal[1] and photolytic[2,9] conversion of *o*-azidobiphenyls to carbazoles involves free nitrenes except in those cases where there is a phenylazo, nitro, acetyl, or benzoyl group ortho to the azido function. Kinetic studies have indicated that there is a concerted loss of nitrogen and cyclization in these cases.[10] Cadogan and Todd[11] have cyclized a number of substituted *o*-nitrobiphenyls to carbazoles with phosphorus reagents. Nitrenes appeared to be involved, but the possibility of a concerted loss of phosphate could not be ruled out, though easy cyclization onto both electron-rich and electron-poor rings make this last rather unlikely. Products of intramolecular aromatic substitution have also been observed from the thermolysis of *o*-azidodiphenyl sulfides,[12] and the deoxygenation of *o*-nitro-*N*-acetyldiphenylamines.[13]

In contrast to the ready intramolecular aromatic substitutions by aryl nitrenes, the corresponding intermolecular reactions are relatively unknown. The decomposition of phenyl azide in aromatic solvents did not yield any diphenylamines. In benzene, only azobenzene and aniline were formed[14] even when 1000-fold excess of benzene was present.[15] On the other hand, intermolecular attack of an aromatic nucleus by ethoxycarbonyl-,[16] cyano-,[17] and sulfonylnitrenes[18] is well known. The absence of intermolecular aromatic substitution by aryl nitrenes could be attributed to rapid decay of the thermally generated singlet nitrene to the triplet[8] before substitution could take place, but could also be due to the possibility that, unlike the above nitrenes, phenylnitrene was insufficiently electrophilic to substitute into benzene. If the latter is true, then it should be possible to increase the electrophilic character of the aryl nitrene by the introduction of electron-withdrawing substituents into the aromatic ring, which would have the effect of decreasing the contribution of **1b** to the structure of the singlet



a b

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TABLE I

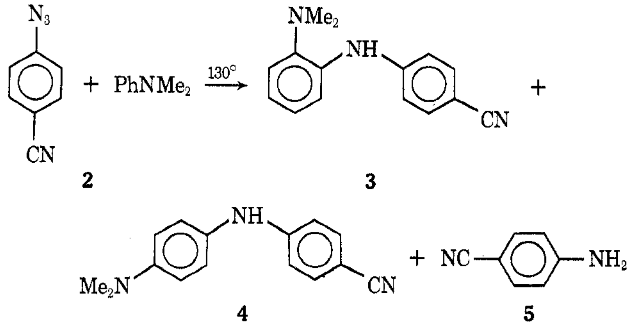
THERMOLYSIS OF ARYL AZIDES IN AROMATIC SOLVENTS

Azide	Registry no.	Solvent	Products, % Ortho substitution	Para substitution	Azo	Amine	Other
p-CN		Benzene			25.2	4.9	
p-CN		Anisole			2.4	18.1	
p-CN		*p*-Dimethoxybenzene			3.4	41.0	
p-CN		1,3,5-Trimethoxybenzene	19.2		2.0	13.6	
p-CN		*N*,*N*-Dimethylaniline	25.1	3.4		20.3	
p-CN		Mesitylene	13.2			16.4	23.0[a]
p-NO_2	1516-60-5	*N*,*N*-Dimethylaniline	13.5	Trace	1.0	18.3	23.7[b]
p-NO_2		1,3,5-Trimethoxybenzene	18.9			16.8	3.4[c]
p-CF_3	5586-13-0	*N*,*N*-Dimethylaniline	13.4			Trace	9.0[b]
o-CN	31656-77-6	1,3,5-Trimethoxybenzene	38.6			4.0	
m-CN	31656-78-7	1,3,5-Trimethoxybenzene	8.4			7.3	

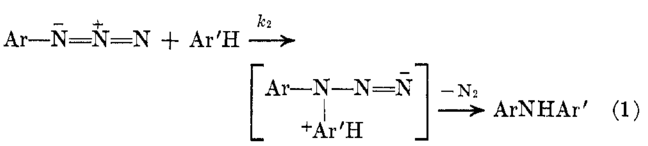
[a] 3,3'5,5'-Tetramethylbibenzyl. [b] 4,4'-Methylenebis(*N*,*N*-dimethylaniline). [c] 2,4,6-Trimethoxy-4'-nitrobiphenyl.

nitrene **1**. This, indeed, has now been found to be the case.

Thermolysis of *p*-cyano-, *p*-nitro-, or *p*-trifluoromethylphenyl azide in benzene at 140° gave no products of intermolecular aromatic substitution, the only compounds isolated being the azo compound and the primary amine, both probably arising from the triplet aryl nitrene. Similarly, no diphenylamines were obtained by the triethyl phosphite deoxygenation of the corresponding nitrosobenzenes in benzene. Thermolysis of *p*-cyanophenyl azide (**2**) in the more nucleophilic anisole and *p*-dimethoxybenzene also failed to reveal any aromatic substitution products. On the other hand, when **2** was decomposed in *N*,*N*-dimethylaniline, mesitylene, or *sym*-trimethoxybenzene the desired diphenylamines were obtained. Thus, **2** and *N*,*N*-dimethylaniline yielded a mixture of 4-cyano-2'-(**3**) (25.1%) and 4-cyano-4'-(*N*,*N*-dimethylamino)diphenylamine (**4**) (3.4%), together with the hydrogen-abstraction product **5** (20.3%). The orientation of the diphenylamines was assigned on the basis of their infrared and nmr spectra and confirmed by unambiguous synthesis from *N*,*N*-dimethyl-*o*- and -*p*-phenylenediamine and the appropriate aryl halide. The decomposition of *p*-nitrophenyl and *p*-trifluoromethylphenyl azide in dimethylaniline and *sym*-trimethoxybenzene also gave the products of intermolecular aromatic substitution. The results are summarized in Table I.



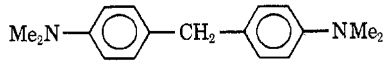
The possibility had to be considered that, since aromatic substitution was only observed between highly nucleophilic substrate and an aryl azide bearing an electron-attracting group, a change of mechanism—from the stepwise nitrene intermediate mechanism (eq 2) to a concerted nucleophilic attack (say by the tertiary amine nitrogen) on the azide followed by nitrogen elimination (eq 1)—had occurred to account for the formation of the substitution products. This was discounted readily by studying the kinetics of the decomposition of *p*-cyanophenyl azide in chlorobenzene solution at 132° in the presence of varying amounts of *N*,*N*-dimethylaniline (from none to a fivefold excess over azide concentration) which showed that the rate of the first-order decomposition of the azide was unaffected by the presence of the amine, thus confirming the partial mechanism given in eq 2.



$$\mathrm{Ar{-}\bar{N}{=}\overset{+}{N}{=}N + Ar'H \xrightarrow{k_2} \left[\begin{array}{c}\mathrm{Ar{-}N{-}N{=}\bar{N}} \\ \mathrm{{}^{+}Ar'H}\end{array}\right] \xrightarrow{-N_2} ArNHAr'} \quad (1)$$

$$\mathrm{Ar{-}\bar{N}{-}\overset{+}{N}{\equiv}N \xrightarrow[-N_2]{k_1} Ar\ddot{N}: \xrightarrow[Ar'H]{fast} ArNHAr'} \quad (2)$$

From the decomposition of **2** in mesitylene (as in all other cases as well) the hydrogen-abstraction product **5** was isolated. In addition 3,3',5,5'-tetramethylbibenzyl was obtained in 23% yield. This undoubtedly arises by hydrogen abstraction by the triplet aryl nitrene to give a benzyl radical which dimerizes. In both the decompositions of *p*-nitrophenyl azide and *p*-trifluoromethylphenyl azide in *N*,*N*-dimethylaniline, 4,4'-methylenebis(*N*,*N*-dimethylaniline) (**6**) was obtained. The same product has been obtained from the decomposition of benzenesulfonyl azide in dimethylaniline,[19] and it has been suggested that it arises from formaldehyde (formed during aqueous work-up) and the aniline.[20]



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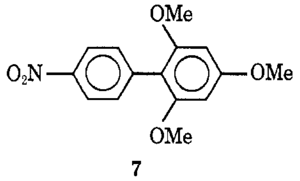

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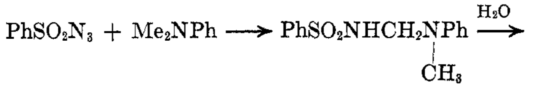
TABLE II

DEOXYGENATION OF NITROSOBENZENES IN AROMATIC SOLVENTS

Registry no.	Nitroso-benzene	Solvent	Products, % Ortho substitution	Para substitution	Azoxy	Amine	Other
31125-07-2	p-CN	N,N-Dimethylaniline	17.5	7.6	16.8	6.9	2.4[a]
		Anisole			26.6	7.6	
		Mesitylene			40.0	2.6	
		1,3,5-Trimethoxybenzene	2.5		40.0	4.2	
4485-08-9	p-NO_2	N,N-Dimethylaniline	19.7	6.1	2.8	5.7	
		Mesitylene			51.0	13.4	
34913-26-3	p-CF_3	N,N-Dimethylaniline	6.2	4.3	16.0		1.5[b]
		Mesitylene			30.6		

[a] 4,4′-Dicyanoazobenzene. [b] 4,4′-Ditrifluoromethylazobenzene.



$$PhSO_2N_3 + Me_2NPh \longrightarrow PhSO_2NHCH_2\underset{CH_3}{N}Ph \xrightarrow{H_2O}$$

$$PhSO_2NH_2 + HCHO + PhNHMe$$

$$2PhNMe_2 + HCHO \longrightarrow 6$$

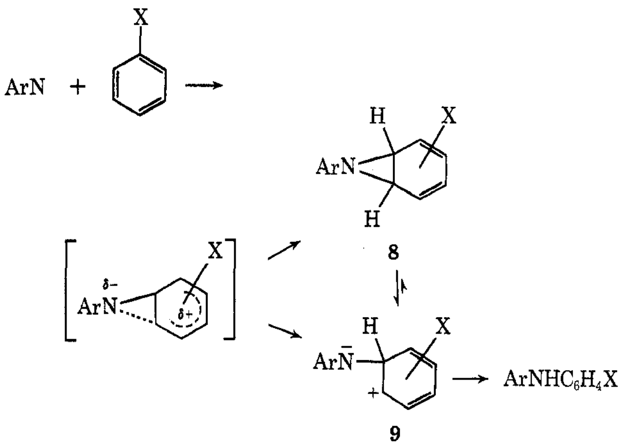
In the present case no aqueous work-up was used so that either formaldehyde was formed by the accidental intrusion of atmospheric moisture or a formaldehyde precursor, *e.g.*, PhN(Me)CH$_2$·, was the active condensing agent.

The decomposition of p-nitrophenyl azide in 1,3,5-trimethoxybenzene gave, in addition to substitution and hydrogen-abstraction products, a small amount (3.4%) of 2,4,6-trimethoxy-4′-nitrobiphenyl (**7**). It seems likely that **7** arises from the homolytic cleavage of $p\text{-}NO_2C_6H_4N_3 \rightarrow p\text{-}NO_2C_6H_4\cdot + N_3\cdot$, followed by arylation of the *sym*-trimethoxybenzene by the p-nitrophenyl radical. There is some precedent for the homolysis of C–N$_3$ bonds. Thus, thermolysis of ferrocenyl azide in benzene gave ferrocene and phenylferrocene together with nitrene products.[21] Similarly, cleavage of the C–N bond in tertiary alkyl azides has been reported on photolysis[22] and thermolysis.[23]

Similar results have been obtained by generation of the aryl nitrene from the corresponding nitrosobenzene and triethyl phosphite in nucleophilic aromatic solvents (Table II). In dimethylaniline and 1,3,5-trimethoxybenzene the nitrosobenzene appears to be mainly monomeric, but in mesitylene the solutions are a light yellow, indicating that the nitroso dimer is present. This would account for the fact that, unlike the thermolysis of **2** in mesitylene, deoxygenation of p-cyanonitrosobenzene (and of the other nitroso compounds) in that solvent does not give any diphenylamine derivative, the major product being the azoxy compound. The latter probably arises from the deoxygenation of the nitroso dimer in these cases, though in those examples where the monomeric nitroso compound exists in solution it can arise by a trapping of the aryl nitrene by the nitrosobenzene.[24] Some azo compound is also formed in some of the reactions in which substitution is observed, while the primary amine hydrogen abstraction product is obtained in most cases, except with p-trifluoromethylnitrosobenzene. As expected, the nitroso function in p-nitronitrosobenzene is deoxygenated much more readily than is the nitro group.

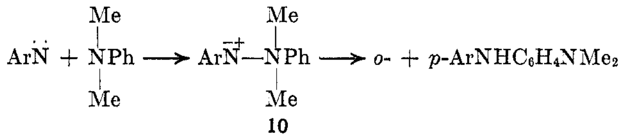
The main question remaining to be answered is that of the mechanism of formation of the substitution products. Two pathways appear possible for the intermolecular attack of an aromatic nucleus by an aryl nitrene.

Reaction *via* the benzaziridine intermediate **8** would



be analogous to the behavior of sulfonyl-,[13] ethoxycarbonyl-,[16] and cyanonitrene,[17] and would readily account for the preferred ortho/para orientation observed. On the other hand, no N-arylazepines, which could arise by an electrocyclic ring opening of **8**, were observed in this work, but this could be due to thermodynamic control obtaining and favoring ring opening to **9** with irreversible formation of the diarylamine. It is not possible to decide between the alternative pathways on the basis of the present results.

A comment may be appropriate concerning the predominant (if not exclusive) ortho substitution in the reactions of the aryl nitrenes (generated from the azides) and dimethylaniline. This could either be due to the reaction proceeding by one of the above routes, with attack at C$_2$ (or upon the C$_1$–C$_2$ or C$_2$–C$_3$ double bond) being favored over attack at C$_4$ (or at the C$_3$–C$_4$ double bond), as is the case, say with phenylsulfonylnitrene and anisole,[25] or the nitrene once formed could attack the tertiary nitrogen atom to form an ylide **10**



$$Ar\ddot{N} + \overset{Me}{\underset{Me}{N}}Ph \longrightarrow Ar\bar{N}\text{—}\overset{+}{\overset{Me}{\underset{Me}{N}}}Ph \longrightarrow o\text{-} + p\text{-}ArNHC_6H_4NMe_2$$

10

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which could then rearrange thermally to give mainly the ortho-substituted aminodiphenylamine.

Such an attack by a nitrene at an aniline nitrogen atom has been observed with carbethoxynitrene[26] and cyanonitrene,[27] and at a pyridine nitrogen atom by a sulfonylnitrene.[28] The isomer ratio observed with aryl nitrene generated by deoxygenation of the nitrosobenzene at low temperatures is appreciably different, with much more para isomer being formed (Table II). This could be accommodated in an addition–ring-opening pathway in which the azepine (formed under kinetic control) leading (under thermodynamic control) to the *p*-phenylenediamine was less stable at higher temperatures than that leading to the ortho isomer, and went to by-product more readily. On the other hand, the ratio of products observed could just be a reflection of the effect of temperature upon the relative rates of the two substitution processes.

A comparison of the percentage of substitution of 1,3,5-trimethoxybenzene as a function of the position of the nitrile group in the three cyanophenylnitrenes indicated (Table I) that, as expected, the most electrophilic species, *o*-CNC_6H_4N, gives most substitution, while the meta isomer gives the least.

After our work on the aryl azide decomposition was completed, Huisgen and von Fraunberg[29] reported intramolecular aromatic substitutions by 2-pyridyl- and 4,6-dimethyl-2-pyrimidylnitrene into activated substrates. Their results fit well with the concept of the electrophilicity requirement for aryl nitrenes to undergo such reaction.

Experimental Section

General.—Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 spectrophotometer. Nmr spectra were measured on a Varian HA-100 spectrometer, and mass spectra were determined at 70 eV on a CEC 21-104 mass spectrometer. For column chromatography, Alcoa chromatographic alumina F-20 was used, and Merck silica gel PF_{254} was used for thin layer chromatography. Light petroleum ether refers to the fraction of bp 30–60°.

Starting Materials.—Azides were synthesized from the corresponding amine by diazotization, followed by treatment of the diazonium salt with sodium azide. Thus prepared were *p*-azidobenzonitrile, mp 70° (lit.[30] mp 70°), *m*-azidobenzonitrile, mp 57–58° (lit.[31] mp 57°), *o*-azidobenzonitrile, mp 55° (lit.[32] mp 58°), *p*-nitrophenylazide, mp 71–72° (lit.[33] mp 74°), and *p*-trifluoromethylphenyl azide, bp 66° (15 mm), n_D 1.4850 (lit.[34] n_D 1.4870). *p*-Nitrosobenzonitrile, mp 136–137°, was prepared by Caro's acid oxidation of *p*-aminobenzonitrile according to the method of Ashley and Berg.[35] Similarly prepared were *p*-nitrosonitrobenzene, mp 119–120° (lit.[36] mp 118–119°), and ***p*-trifluoromethylnitrosobenzene**, mp 51–53° (sublimed *in vacuo*).

Anal. Calcd for $C_7H_4F_3NO$: C, 48.00; H, 3.28. Found: C, 47.85; H, 2.34.

4-Cyano-2′-*N*,*N*-dimethylaminodiphenylamine.—*N*,*N*-Dimethyl-*o*-phenylenediamine (0.61 g), *p*-bromobenzonitrile (1.82 g), potassium carbonate (1.38 g), and powdered copper (100 mg) were intimately mixed and heated at 140° for 36 hr. The cooled residue was extracted with chloroform and purified by chromatography on alumina and elution with benzene. The product (0.20 g, 19%), mp 123°, was recrystallized from light petroleum ether–chloroform: ir (KBr) 3355 (NH), 2200 ($C{\equiv}N$), 760 cm^{-1}; nmr ($CDCl_3$) δ 7.48 (d, J = 8 Hz, 2 H), 7.11 (d, J = 8 Hz, 2 H), 7.44–6.96 (m, 4 H), 6.78 (b s, 1 H, exchanges with D_2O), 2.47 (s, 6 H); mass spectrum m/e (rel intensity) 237 (100), 222 (47), 206 (24), 205 (64), 133 (17), 121 (18), 119 (25), 94 (15), 92 (20), 91 (17), 77 (22), 69 (17), 65 (23).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.34. Found: C, 75.82; H, 6.52.

The following diphenylamines were prepared similarly.

4-Cyano-4′-*N*,*N*-dimethylaminodiphenylamine (6%) had mp 164–165° (from light petroleum ether–chloroform); ir (KBr) 3313 (NH), 2216 ($C{\equiv}N$), 818, 803 cm^{-1}; nmr ($CDCl_3$) δ 7.40 (d, J = 9 Hz, 2 H), 7.10 (d, J = 9 Hz, 2 H), 6.76 (d, J = 9 Hz, 4 H), 5.93 (b s, 1 H, exchanges with D_2O), 3.98 (s, 6 H); mass spectrum m/e (rel intensity) 237 (100), 236 (23), 222 (43), 221 (18), 192 (17), 118 (39), 65 (16).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.34. Found: C, 75.93; H, 6.64.

2-(*N*,*N*-Dimethylamino)-4′-trifluoromethyldiphenylamine (7%) had mp 48–49° (from hexane); ir (KBr) 3350 (NH), 1325 (CF), 840, 765 cm^{-1}; nmr ($CDCl_3$) δ 7.43 (d, J = 9 Hz, 2 H), 7.08 (d, J = 9 Hz, 2 H), 7.35–6.85 (m, 4 H), 6.65 (b s, 1 H, exchanges with D_2O), 2.61 (s, 6 H); mass spectrum m/e (rel intensity) 280 (100), 265 (28), 248 (40), 196 (20), 180 (22), 133 (14), 119 (19), 92 (13), 91 (14), 77 (20). 65 (17), 44 (22), 42 (18).

Anal. Calcd for $C_{15}H_{15}F_3N_2$: C, 64.28; H, 5.36. Found: C, 63.95; H, 5.51.

4-(*N*,*N*-Dimethylamino)-4′-trifluoromethyldiphenylamine (5%) had mp 112–114° (from light petroleum ether); ir (KBr) 3400 (NH), 1324 (CF), 830 cm^{-1}; mass spectrum m/e (rel intensity) 280 (62), 279 (12), 265 (20), 235 (4), 140 (5), 125 (5), 87 (12), 85 (73), 83 (100), 47 (37).

Anal. Calcd for $C_{15}H_{15}F_3N_2$: C, 64.28; H, 5.36. Found: C, 64.54; H, 5.48.

4,4′-Bis(trifluoromethyl)azobenzene.—4,4′-Bis(trifluoromethyl)azoxybenzene (1.0 g) (from the performic acid oxidation of *p*-$CF_3C_6H_4NH_2$) and triethyl phosphite (0.5 g) were heated at 160–170° for 18 hr, after which the mixture was cooled and chromatographed on silica gel (10 × 4 cm). Elution with benzene–light petroleum ether (3:1, v/v) gave **4,4′-bis(trifluoromethyl)-azobenzene** (0.79 g, 83%): mp 101–102° (light petroleum ether); ir (KBr) 1609, 1320, 1170–1100, 1061, 852 cm^{-1}; mass spectrum m/e (rel intensity)) 318 (19), 299 (8), 173 (20), 145 (100).

Anal. Calcd for $C_{14}H_8F_6N$: C, 52.84; H, 2.52. Found: C, 52.84; H, 2.57.

Thermolysis of *p*-Azidobenzonitrile in *N*,*N*-Dimethylaniline.—*p*-Azidobenzonitrile (0.5 g) was heated in *N*,*N*-dimethylaniline (10 ml) at 130° for 48 hr under nitrogen. The reaction mixture was chromatographed on alumina (30 × 3 cm). Elution with light petroleum ether gave *N*,*N*-dimethylaniline. Elution with benzene gave *p*-azidobenzonitrile (80 mg, 15%), mp 67° (from water) (lit.[29] mp 70°). Elution with ether–benzene (1:3, v/v) gave 4-cyano-2′-(*N*,*N*-dimethylamino)diphenylamine (180 mg, 25.1%), mp 123° (from light petroleum ether), ir (KBr) 3355 (NH), 2200 ($C{\equiv}N$), 760 cm^{-1}, identical with an authentic sample. Elution with ether–benzene (3:1, v/v) gave 4-cyano-4′-(*N*,*N*-dimethylamino)diphenylamine (24 mg, 3.4%), mp 163–164° (from EtOH), ir (KBr) 3325 (NH), 2200 ($C{\equiv}N$), 810, 800 cm^{-1}, identical with an authentic sample. Elution with ether gave *p*-aminobenzonitrile (144 mg, 20.3%), mp 86–87° (from water) (lit.[37] mp 86°).

Thermolysis of *p*-Azidobenzonitrile in *sym*-Trimethoxybenzene.—*p*-Azidobenzonitrile (0.5 g) was heated in *sym*-trimethoxybenzene (3 g) at 130° for 50 hr under nitrogen. The reaction mixture was chromatographed on alumina (30 × 3 cm). Light petroleum ether–benzene (1:3, v/v) gave *sym*-trimethoxybenzene. Elution with benzene gave *p*-azidobenzonitrile (43 mg, 8.5%), mp 67–70° (from water). Elution with ether–benzene (1:3, v/v) gave 4,4′-dicyanoazobenzene (7 mg, 2.3%), mp 272° (from EtOH) (lit.[38] mp 270°). Elution with ether–benzene

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(3:1, v/v) gave **4-cyano-2′,4′,6′-trimethoxydiphenylamine** (176 mg, 19.2%): mp 159° (from EtOH); ir (KBr) 3325 (NH), 2205 ($C\equiv N$), 840 cm^{-1}; nmr ($CDCl_3$) δ 7.38 (d, J = 8 Hz. 2 H), 6.57 (d, J = 8 Hz, 2 H), 6.22 (s, 2 H), 3.84 (s, 3 H), 3.79 (s, 6 H); mass spectrum *m/e* (rel intensity) 284 (100), 269 (54), 241 (32), 226 (15), 142 (20), 69 (12).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.65; H, 5.87.

Further elution with ether gave *p*-aminobenzonitrile (56 mg, 13.6%), mp 86°.

Similar reaction conditions were used in the thermolyses of *p*-$N_3C_6H_4CN$ in *p*-dimethoxybenzene and in mesitylene (see below).

Thermolysis of *p*-Azidobenzonitrile in *p*-Dimethoxybenzene.—Chromatography of the reaction mixture gave 4,4′-dicyanoazobenzene (5.4%), mp 265° (from EtOH), and *p*-aminobenzonitrile (41%), mp 84°.

Thermolysis of *p*-Azidobenzonitrile in Mesitylene.—Chromatography of the reaction mixture over alumina gave 3,3′5,5′-tetramethylbibenzyl (23%), mp 70° (from EtOH) (lit.[39] mp 72°), and **4-cyano-2′,4′,6′-trimethyldiphenylamine** (13.2%): bp 175–180° (0.5 mm); ir (film) 3360 (NH), 2215 ($C\equiv N$), 830 cm^{-1}; nmr (CCl_4) δ 7.34 (d, J = 8 Hz, 2 H), 6.80 (b s, 2 H), 6.46 (d, J = 8 Hz, 2 H), 4.19 (b s, 1 H, exchanges with D_2O), 2.24 (s, 6 H), 2.09 (s, 3 H); mass spectrum *m/e* (rel intensity) 236 (1.1), 152 (3.3), 148 (2.9), 133 (4.1), 119 (26), 118 (100), 113 (12), 91 (63), 90 (13), 81 (21), 65 (17), 63 (17), 55 (17), 43 (50).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.26; H, 6.79. Found: C, 81.15; H, 6.96.

Further elution gave *p*-aminobenzonitrile (25.2%), mp 86°.

Thermolysis of *p*-Azidobenzonitrile in Benzene.—*p*-Azidobenzonitrile (0.5 g) was heated in a bomb in benzene (10 ml) at 140° for 45 hr. Only 4,4′-dicyanoazobenzene (75 mg, 25.2%), mp 268–270°, and *p*-aminobenzonitrile (20 mg, 4.9%), mp 85–87°, were detected.

Deoxygenation of *p*-Nitrosobenzonitrile in *N*,*N*-Dimethylaniline.—Triethyl phosphite (435 mg) in *N*,*N*-dimethylaniline (5 ml) was added dropwise at 0° to a stirred solution of *p*-nitrosobenzonitrile (346 mg) in *N*,*N*-dimethylaniline (15 ml). After 30 min the mixture was diluted with light petroleum ether and chromatographed on alumina (20 × 5 cm). Elution with light petroleum ether gave *N*,*N*-dimethylaniline. Benzene–light petroleum ether (3:1, v/v) eluted 4-cyano-2′-(*N*,*N*-dimethylamino)diphenylamine (104 mg, 17.5%), mp 121° (from light petroleum ether). Elution with benzene gave 4,4′-dicyanoazobenzene (7 mg, 2.4%), mp 271–274°. Further elution with benzene gave 4,4′-dicyanoazoxybenzene (53 mg, 16.8%), mp 226–228° (from $CHCl_3$) (lit.[35] mp 228°), and 4-cyano-4′-(*N*,*N*-dimethylaminodiphenylamine (46 mg, 7.6%), mp 159–162°. Elution with ether–benzene (1:4, v/v) gave *p*-aminobenzonitrile (21 mg, 6.9%).

Similar reaction conditions were used in the deoxygenation of *p*-nitrosonitrobenzene and *p*-nitrosotrifluoromethylbenzene in dimethylaniline (see below).

Thermolysis of *p*-Azidonitrobenzene in *N*,*N*-Dimethylaniline.—The following were isolated by chromatography of the reaction mixture: *p*-azidonitrobenzene (2.5%), mp 71–73°; 4,4′-bis(*N*,*N*-dimethylamino)diphenylmethane (23.7%), mp 90° (from light petroleum ether, bp 60–110°) (lit.[40] mp 90°); 4,4′-dinitroazobenzene (1.0%), mp 223–225° (from light petroleum ether, bp 60–110°) (lit.[35] mp 222–223°); **2-(*N*,*N*-dimethylamino)-4′-nitrodiphenylamine** (13.5%): mp 121° (from $CHCl_3$); ir (KBr) 3315 (NH), 752 cm^{-1}; nmr (CDCl)$_3$ δ 8.04 (d, J = 9 Hz, 2 H), 7.30 (m, 1 H), 6.97 (m, 6 H), 2.59 (s, 6 H); mass spectrum *m/e* (rel intensity) 257 (100), 242 (20), 196 (23), 195 (29), 181 (17), 180 (23), 179 (20), 133 (15), 77 (16).

Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.37; H, 5.84. Found: C, 65.47; H, 5.86.

Elution with ether–benzene (3:1, v/v) gave *p*-nitroaniline (18.3%), mp 145–147°.

Thermolysis of *p*-Azidonitrobenzene in *sym*-Trimethoxybenzene.—*p*-Azidonitrobenzene (1.0 g) in *sym*-trimethoxybenzene (6.0 g) was heated at 130° for 50 hr under nitrogen. The reaction mixture was chromatographed on alumina. Elution with benzene gave *sym*-trimethoxybenzene. Elution with ether–benzene (1:3, v/v) gave **4-nitro-2′,4′,6′-trimethoxybiphenyl** (60 mg, 3.4%): mp 170° (from EtOH); ir (KBr) 1590, 1490, 1320, 850 cm^{-1}; nmr ($CDCl_3$) δ 8.27 (d, J = 9 Hz, 2 H), 7.56 (d, J = 9 Hz, 2 H), 6.29 (s, 2 H), 3.93 (s, 3 H), 3.80 (s, 6 H); mass spectrum *m/e* (rel intensity) 288 (15), 287 (100), 227 (13), 212 (8), 113 (7).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19. Found: C, 62.37; H, 5.38.

Elution with ether–benzene (3:1, v/v) gave **4-nitro-2,′4′,6′-trimethoxydiphenylamine** (350 mg, 18.9%): mp 145° (from light petroleum ether); ir 3380 (NH), 1580, 1490, 1375, 835 cm^{-1}; nmr ($CDCl_3$) δ 7.97 (d, J = 9 Hz, 2 H), 6.47 (d, J = 9 Hz, 2 H), 6.18 (s, 2 H), 5.87 (b s, 1 H, exchanges with D_2O), 3.81 (s, 3 H), 3.75 (s, 6 H); mass spectrum *m/e* (rel intensity) 305 (19), 304 (100), 288 (32), 261 (18), 243 (22).

Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.26. Found: C, 59.28; H, 5.36.

Elution with ether gave *p*-nitroaniline (50 mg, 16.8%).

Deoxygenation of *p*-Nitrosonitrobenzene in *N*,*N*-Dimethylaniline.—Chromatography of the reaction mixture gave 4,4′-dinitroazoxybenzene (2.8%), mp 190–191° (lit.[41] mp 193°); 2-(*N*,*N*-dimethylamino)-4′-nitrodiphenylamine (19.7%), mp 119° (from $CHCl_3$) undepressed on admixture with an authentic sample; 4-(*N*,*N*-dimethylamino)-4′-nitrodiphenylamine (6.1%), mp 148–150° (from $CHCl_3$) (lit.[42] 152°); and *p*-nitroaniline (5.7%).

Deoxygenation of *p*-Nitrosotrifluoromethylbenzene in *N*,*N*-Dimethylaniline.—The reaction mixture was chromatographed over silica gel (25 × 5 cm). Elution with light petroleum ether gave *N*,*N*-dimethylaniline and three other compounds as an unresolved mixture. The *N*,*N*-dimethylaniline was evaporated under reduced pressure and the residue was subjected to preparative tlc. Elution with benzene–light petroleum ether (1:3, v/v) gave 4,4′-bis(trifluoromethyl)azobenzene (1.5%), mp 101–102° (light petroleum ether), identical with an authentic sample; and **4,4′-bis(trifluoromethyl)azoxybenzene** (16.0%): mp 106–108° (from light petroleum); ir (KBr) 1611, 1320, 1160–1100, 849 cm^{-1}; mass spectrum *m/e* (rel intensity) 334 (25), 318 (13), 299 (5), 173 (19), 145 (100).

Anal. Calcd for $C_{14}H_8F_6N_2O$: C, 50.30; H, 2.40. Found: C, 50.62; H, 2.55.

Further elution gave 2-(*N*,*N*-dimethylamino)-4′-trifluoromethyldiphenylamine (6.2%), mp 46–48°, ir (NaCl) 3358, 1328, 760 cm^{-1}, identical with an authentic sample.

Thermolysis of *o*-Azidobenzonitrile in *sym*-Trimethoxybenzene.—*o*-Azidobenzonitrile (0.5 g) in *sym*-trimethoxybenzene (3 g) was heated at 130° for 60 hr under nitrogen. The reaction mixture was chromatographed on alumina (3 × 35 cm). Elution with benzene gave *sym*-trimethoxybenzene. Elution with ether–benzene (1:3, v/v) gave **2-cyano-2′,4′,6′-trimethoxydiphenylamine** (380 mg, 38.6%): mp 125–126° (from light petroleum ether); ir (KBr) 3330 (NH), 2215 ($C\equiv N$), 1290, 1230, 1210, 1160, 1130, 810, 770, 760 cm^{-1}; nmr ($CDCl_3$), δ 7.74–7.40 (m, 2 H), 6.92 (t, J = 8 Hz, 1 H), 6.62 (d, J = 8 Hz, 1 H), 6.06 (b s, 1 H, exchanges with D_2O), 3.93 (s, 3 H), 3.86 (s, 6 H); mass spectrum *m/e* (rel intensity) 284 (100), 268 (36), 241 (46), 226 (12), 198 (12), 155 (15), 142 (21), 141 (16), 129 (19), 102 (24), 76 (14), 75 (13), 69 (37), 66 (12), 59 (15), 55 (18), 39 (32).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.67; H, 5.80.

Elution with ether gave *o*-aminobenzonitrile (10 mg, 4.0%), mp 49–50° (lit.[43] mp 51°).

Thermolysis of *m*-Azidobenzonitrile in *sym*-Trimethoxybenzene.—The reaction was carried out as for the ortho isomer to give **3-cyano-2′,4′,6′-trimethoxydiphenylamine** (8.4%): mp 78–80° (from EtOH); ir (KBr) 3360 (NH), 2230 ($C\equiv N$), 1330, 1300, 1230, 1210, 1160, 1130, 790 cm^{-1}; nmr ($CDCl_3$) δ 7.24–6.70 (m, 4 H), 6.19 (s, 2 H), 5.38 (b s, 1 H, exchanges with D_2O), 3.80 (s, 3 H), 3.76 (s, 6 H); mass spectrum *m/e* (rel intensity) 284 (29), 269 (22), 147 (13), 142 (14), 129 (64), 125 (16), 118 (40), 112 (23), 102 (20), 97 (21), 91 (20), 83 (34), 71 (63), 69

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(55), 57 (100), 55 (71), 43 (79). *m*-Aminobenzonitrile (7.3%), mp 52-54°, mmp 52-54° (lit.[44] mp 53-54°), was also obtained.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.39; H, 5.68.

Kinetics of the Thermal Decomposition of *p*-Azidobenzonitrile in the Presence of *N*,*N*-Dimethylaniline.—*p*-Azidobenzonitrile was thermolyzed in chlorobenzene solution at 132° in the presence of varying amounts of *N*,*N*-dimethylaniline. During the thermolyses, portions were removed at regular intervals with a syringe, diluted fourfold with chlorobenzene, and assayed by measuring the area of the asymmetric azide stretching band in the infrared (2160 and 2110 cm^{-1}). Concentrations of azide were obtained from a previously prepared calibration curve,[45] and rate constants for the disappearance of azide were obtained from the slopes of plots of log [azide] *vs.* time. The results are summarized below.

[*p*-Cyanophenyl azide], *M*	[*N*,*N*-dimethylaniline], *M*	Rate constant (× 10^5), sec^{-1}
0.02		1.47
0.02	0.02	1.47
0.02	0.06	1.70
0.02	0.10	1.48

Registry No.—**2**, 18523-41-6; **3**, 29547-82-8; **4**, 29547-83-9; **7**, 34915-93-0; 2-(*N*,*N*-dimethylamino)-4′-trifluoromethyldiphenylamine, 29547-88-4; 4-(*N*,*N*-dimethylamino)-4′-trifluoromethyldiphenylamine, 34913-28-5; 4,4′-bis(trifluoromethyl)azobenzene, 34913-29-6; 4-cyano-2′,4′,6′-trimethoxydiphenylamine, 29547-84-0; 4-cyano-2′,4′,6′-trimethyldiphenylamine, 29547-85-1; 2-(*N*,*N*-dimethylamino)-4′-nitrodiphenylamine, 29547-86-2; 4-nitro-2′,4′,6′-trimethoxydiphenylamine, 29547-87-3; 4,4′-bis(trifluoromethyl)azoxybenzene, 34913-34-3; 2-cyano-2′,4′,6′-trimethoxydiphenylamine, 34913-35-4; 3-cyano-2′,4′,6′-trimethoxydiphenylamine, 34913-36-5.

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(45) The variation of the area of this band with concentration deviated from linearity above 0.05 *M*, suggesting possible association of the azide in solution.

Organic Disulfides and Related Substances. 34. Synthesis and Reactions of Some Substituted Cyclic Disulfides and Corresponding *S*-Oxides[1]

LAMAR FIELD* AND YONG H. KHIM

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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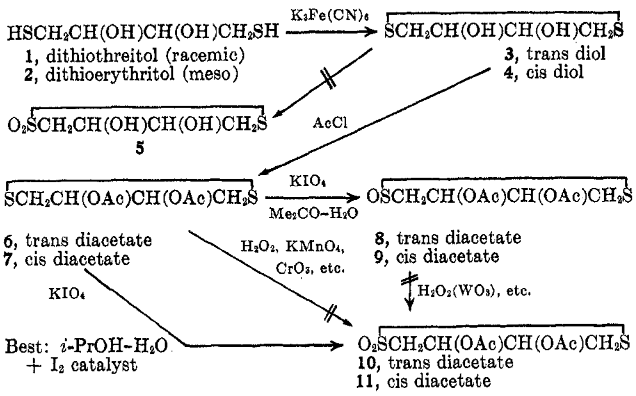
Functionally substituted 1,2-dithianes, 1,2-dithiolanes, and *S*-oxides were sought for study of their properties and reactions and for testing as antiradiation drugs. Oxidation of *trans*- and *cis*-1,2-dithiane-4,5-diol diacetate (**6** and **7**) gave the 1-monoxides **8** and **9**. Oxidation of **6** and **7** to the trans and cis 1,1-dioxides **10** and **11** failed with numerous agents but finally was accomplished using potassium metaperiodate in aqueous 2-propanol with iodine as an effective catalyst as the best means. A thiolate ion cleaved the 1,1-dioxide **10**, giving a disulfide sulfinate (**14**), but amines did not cleave 1,2-dithiane 1,1-dioxide (**12**). Procedures are compared for the synthesis of 1,2-dithiolane-4-carboxylic acid (**16**), and syntheses of some other dithiolanes are discussed.

This paper reports some syntheses and reactions of substituted five- and six-membered cyclic disulfides and of the corresponding *S*-oxides. There were two motivations for the work. One was to permit testing of representative compounds as antiradiation drugs, since *trans*-1,2-dithiane-4,5-diol (**3**) has been said to be active in this respect;[2] such activity would be of considerable interest because most antiradiation drugs contain nitrogen functions that may have much to do with their toxicity. A second motivation was to begin an extension to substituted systems of earlier studies of unsubstituted cyclic disulfides and their *S*-oxides.[3]

In Scheme I, conversion of dithiothreitol (**1**) to *trans*-1,2-dithiane-4,5-diol (**3**) and of dithioerythritol (**2**) to the cis isomer **4** proceeded by standard methods (70–75% yield); recrystallization provided a convenient purification. Although 1,2-dithiane can be oxidized to the 1,1-dioxide by hydrogen peroxide or potassium metaperiodate (KIO_4) in 66–68% yield,[3a] the dihydroxydithiane **3** gave only intractable oil with no indication of the dioxide **5** (ir); cleavage of **3** to sulfonic acids evidently predominated, since the products were strongly acidic, probably complicated by cleavage at the glycol moiety.

SCHEME I



It seemed likely that adverse reactions of the glycol moiety could be prevented by prior acetylation. Both of the diols **3** and **4** have been acetylated by means of acetic anhydride and pyridine but, since the diacetates **6** and **7** were desired for nmr studies, few other details were given.[4] Acetyl chloride gave the trans diacetate **6** and cis diacetate **7** in yields of 74–82% (Scheme I).

Oxidation of the diacetates **6** and **7** to the 1-monoxides **8** and **9** occurred, but oxidation to the 1,1-dioxides

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(1) (a) Paper 33: L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA17-69-C-9128. (c) We are indebted to Professor H. E. Smith of Vanderbilt University for helpful discussion.

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