A Reinvestigation of Some Purported 1,2,4-Oxadiazetidines

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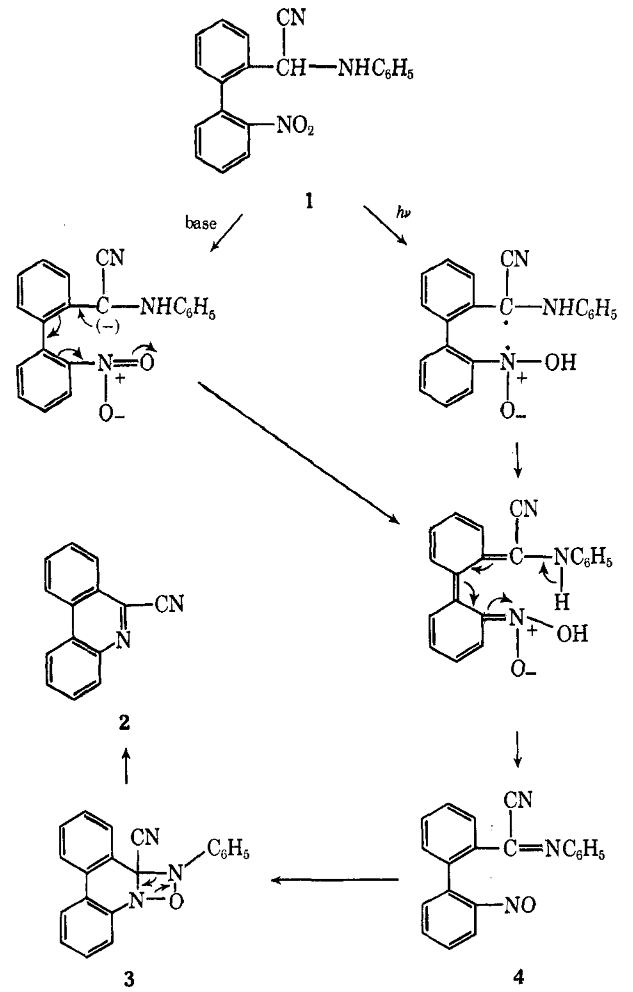
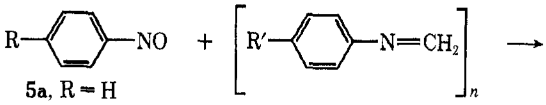
The reaction of methyleneanilines (hexahydro-1,3,5-triazines) (6) with aryl nitroso compounds, previously claimed to proceed *via* intermediate 1,2,4-oxadiazetidines, has been reinvestigated. It has been found that oxadiazetidines are *not* involved in the above reaction which (under the previously described conditions) yields formanilides (10) and azoxybenzene and, under modified conditions, yields α-arylamino-*N*-arylnitrones (9). Mechanisms for these reactions are discussed.

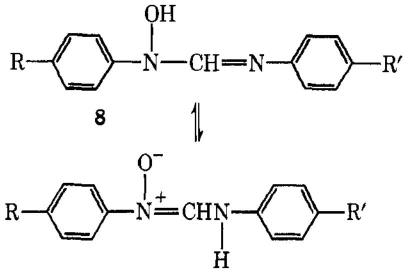
Intramolecular cyclization of 2-(2′-nitro-2-biphenylyl)-*N*-phenylglycinonitrile (**1**) to 6-cyanophenanthridine (**2**) occurs under either photolytic or basic reaction conditions.[1] The mechanism proposed for this unusual conversion involved spontaneous cyclization of an intermediate nitrosoimine **4** to a 1,2,4-oxadiazetidine (**3**), followed by collapse to **2** and nitrosobenzene (which was shown to be formed in the reaction). An apparent intermolecular precedent for the cyclization of **4** to **3** is the reported[2] formation of oxadiazetidines **7** from the reaction of aryl nitroso compounds (**5**) with "methyleneanilines" (**6**).[3] However, the products of these reactions were later claimed to be *N*-hydroxy-*N*,*N*′-diarylformamidines (**8**), α-arylamino-*N*-arylnitrones (**9**),[8] with the oxadiazetidines **7** suggested as probable reaction intermediates.[4]



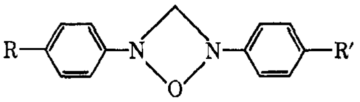


5a, R = H
b, R = Cl
c, R = CH₃

6a, R′ = H
b, R′ = Cl
c, R′ = CH₃
d, R′ = OCH₃
e, R′ = Br



9a, R = R′ = H
b, R = H; R′ = Cl
c, R = H; R′ = Br
d, R = H; R′ = CH₃
e, R = H; R′ = OCH₃
f, R = Cl; R′ = H
g, R = CH₃; R′ = H



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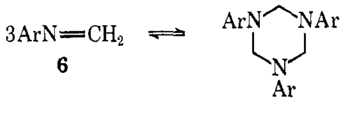
[1] E. C. Taylor, B. Furth, and M. Pfau, *J. Amer. Chem. Soc.*, **87**, 1400 (1965).

[2] C. K. Ingold, *J. Chem. Soc.*, **125**, 87 (1924).

[3] "Methyleneanilines" were earlier believed to be either monomeric (**6**) or dimeric,[2,4,5] but more recent studies have shown that they exist primarily in the trimeric hexahydro-1,3,5-triazine form (**6a**).[6,7] Evidence for partial dissociation of the trimer to the monomeric imine has been advanced;[6] we have found no peaks at *m/e* higher than those corresponding to monomer in the mass spectra of **6**, indicating dissociation of the trimer to the monomer under thermal and/or electron impact conditions.



6 **6a**

[4] M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924).

[5] C. K. Ingold and H. A. Piggott, *ibid.*, **121**, 2793 (1922); **123**, 2745 (1923).

[6] W. V. Farrar, *Rec. Chem. Progr.*, **29**, 85 (1968).

[7] E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience, New York, N. Y., 1959, pp 473–544.

[8] These compounds appear to be the tautomeric nitrones **9** rather than *N*-hydroxyformamidines **8**.[9] We have observed M − 16 peaks of moderate intensity in the mass spectra of all of the derivatives of **9** prepared. No M − 17 peaks were observed with the above compounds with the single exception of a very weak M − 17 peak for **9a** itself. Nitrones have been shown to exhibit significant M − 16 peaks,[10,11] while aryl hydroxylamines exhibit both significant M − 16 and M − 17 peaks.[12]

[9] H. G. Aurich, *Chem. Ber.*, **101**, 1761 (1968).

[10] T. H. Kinstle and J. G. Stam, *Chem. Commun.*, 185 (1968).

[11] B. Soegaard Larsen, G. Schroll, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968).

[12] R. T. Coutts and G. Mukherjee, *Org. Mass Spectrom.*, **3**, 63 (1970).

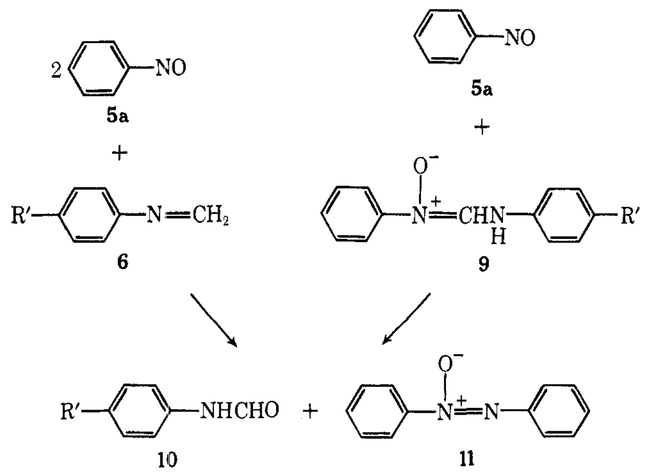
Some sort of symmetrical intermediate (*e.g.*, **7**?) was indeed implied by the earlier work because, *e.g.*, **9d** was claimed to be the product of the reaction of **5a** and **6c**, as well as the product of **5c** and **6a**.[4] However, no reason was advanced for unilateral ring opening of the suggested symmetrical intermediate **7** to give only one of the two possible isomeric nitrones **9**.

The intermediacy of oxadiazetidines such as **7** in these condensation reactions was challenged[13] on the basis of conflicting analytical results for degradation products of **9**. No further experimental work has appeared, however; the existence of **7** as a reaction intermediate has recently received further support in reviews on cycloaddition reactions[14] and imines.[15]

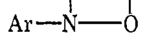
This ambiguous situation, coupled with refutations[16] of earlier claims of other four-membered systems,[17] led us to a reinvestigation of this phase of "oxadiazetidine chemistry."

Contrary to the original work,[4] we found that *different* nitrones **9** were formed from the reaction of permuted pairs of aryl nitroso compounds (**5**) and "methyleneanilines" (**6**). Thus, reaction of **5a** with **6b** gave **9b**, and reaction of **5b** with **6a** gave **9f**. The nonidentity of the products of these reactions was established beyond question by comparison of ir, uv, nmr, tlc, and mass spectral data. Furthermore, many of the nitrones **9** were synthesized independently from aryl hydroxylamines and imidate esters, according to the method of Farrow and Ingold.[4] Our results are thus incompatible with a symmetrical intermediate such as **7**. We note, however, that this refutation of an intermolecular precedent for the intermediate **3** does not necessitate rejection of the previously proposed mechanism[1] for the formation of 6-cyanophenanthridine (**2**) from the biphenyl **1**, since steric proximity of the ortho,ortho′ substituents in biphenyls leads to many unique cyclization reactions which have no intermolecular precedent.[18]

We have found that the reaction of equimolar amounts of an aryl nitroso compound (**5**) and a "methyleneaniline" (**6**), or reaction of an excess of **6** with **5**, is required for the formation of the nitrones **9**. Use of the previously prescribed ratio of reactants (a 2:1 molar excess of **5**)[2,4] led to the formation of formanilides (**10**) and azoxybenzene (**11**). That these products arose by condensation of the initially formed nitrone **9** with excess **5** was demonstrated by the independent observation that preformed **9** reacted with an equimolar amount of **5** to give both **10** and **11**.[19]



We suggest that the reaction of aryl nitroso compounds (**5**) with "methyleneanilines" (**6**) proceeds by nucleophilic attack by the nitrogen lone pair of **5** on the monomeric imine form of **6**[3] to give **9** directly. However, the reaction of **5** with the nitrones **9** to give formanilides (**10**) and azoxybenzene (**11**) may well involve a discrete 1,2,3-oxadiazetidine intermediate (**13**).



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Experimental Section[21]

Preparation of Intermediates.—"Methyleneanilines" (**6**) were prepared from the appropriate aniline and aqueous formaldehyde as previously described.[2] Aryl hydroxylamines were prepared by standard methods.[22] Nitrosobenzene (**5a**) (Aldrich Chemical Co.) was purified by sublimation before use. Other aryl nitroso compounds were prepared by dehydrogenation of aryl hydroxylamines with diethyl azodicarboxylate.[23] Formimidates were prepared from the corresponding anilines and ethyl orthoformate as described.[24] The nitrones **9** were prepared by a modification of the published procedure.[2]

α-Anilino-*N*-*p*-chlorophenylnitrone (**9f**).—A solution of 2.10 g (0.02 mol) of *p*-chloronitrosobenzene and 1.41 g (0.01 mol) of "methyleneaniline" (**6a**) in 150 ml of chloroform was allowed to stand in the dark at room temperature for 2 days. Evaporation of the solvent gave a solid which was recrystallized from benzene to give 0.70 g (28%) of almost colorless crystals, mp 148.5–149.5°.

Anal. Calcd for $C_{13}H_{11}N_2OCl$: C, 63.27; H, 4.50; N, 11.36; Cl, 14.38. Found: C, 63.41; H, 4.43; N, 11.08; Cl, 14.45.

α-*p*-Anisidino-*N*-phenylnitrone (**9e**).—In a similar manner, 2.02 g (0.015 mol) of nitrosobenzene and 1.61 g (0.015 mol) of "methyleneanisidine" (**6d**) gave 1.96 g (40%) of almost colorless crystals, mp 149–150°.

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[13] G. N. Burkhardt, A. Lapworth, and E. B. Robinson, *J. Chem. Soc.*, **127**, 2234 (1925).

[14] L. L. Muller and J. Hamer, "1,2-Cycloaddition Reactions," Interscience, New York, N. Y., 1967, pp 301–304.

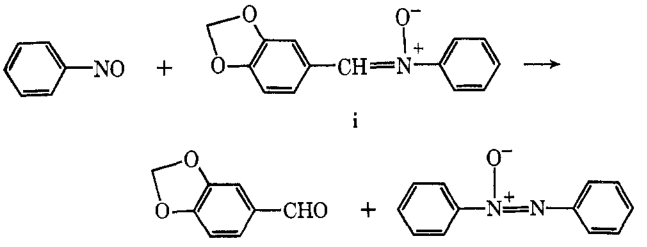
[15] R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

[16] (a) G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, **127**, 1742 (1925); (b) G. N. Burkhardt, A. Lapworth, and J. Walkden, *ibid.*, **127**, 2458 (1925); (c) N. F. Hepfinger and C. E. Griffin, *Tetrahedron Lett.*, 1361 (1963); (d) C. E. Griffin, N. F. Hepfinger, and B. L. Shapiro, *Tetrahedron*, **21**, 2735 (1965); (e) J. Hamer and A. Macaluso, *Tetrahedron Lett.*, 381 (1963); (f) E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.*, **5**, 372 (1966); (g) reference 14, pp 257–261.

[17] (a) C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, **125**, 1456 (1924); (b) C. K. Ingold and S. D. Weaver, *ibid.*, **127**, 378 (1925).

[18] R. E. Buntrock and E. C. Taylor, *Chem. Rev.*, **68**, 209 (1968).

[19] A precedent for this condensation of nitrosobenzene with the nitrone **9** to give a formanilide and azoxybenzene is found in the reported reaction of nitrosobenzene with the nitrone i to give piperonal and azoxybenzene.[20]



[20] L. Alessandri, *Gazz. Chim. Ital.*, **54**, 426 (1924).

[21] All melting points are uncorrected. Mass spectra were determined on an AEI MS-9 instrument.

[22] (a) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1895 (1954); (b) G. E. Utzinger, *Justus Liebigs Ann. Chem.*, **556**, 50 (1944); (c) A. A. Staklis, Ph.D. Thesis, University of Nebraska, Lincoln, 1965; *Diss. Abstr.*, **26**, 1354 (1965).

[23] E. C. Taylor and F. Yoneda, *Chem. Commun.*, 199 (1967).

[24] R. M. Roberts and D. J. Vogt in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 464.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.26; H, 5.74; N, 11.59.

All other nitrones were prepared similarly; the results are summarized in Table I.

TABLE I

PREPARATION OF NITRONES (**9**)

Reactants	Product	Mp, °C	Lit. mp, °C	Yield, %
5a + **6a**[d]	**9a**	119–122	126–127[a]	29
5a + **6b**[d]	**9b**	158–158.5	162[b]	32
5a + **6c**[d]	**9c**	166–168	171[b]	35
5a + **6d**[d]	**9d**	148.5–149	150[b]	54
5c + **6a**[e]	**9g**	148.5–150	151–152[c]	39

[a] Beilstein's "Handbuch der Organischen Chemie," 4th ed, Vol. 15, Springer Verlag, Berlin, 1932, p 8. [b] Reference 2. [c] Reference 4. [d] 2:1 molar excess of **6**. [e] Equimolar amounts of reactants employed.

In addition, these nitrones were prepared independently by condensation of aryl hydroxylamines with imidate esters as previously described.[4]

***p*-Bromoformanilide (10, R′ = Br). Method A.**—A solution of 4.28 g (0.04 mol) of nitrosobenzene and 3.66 g (0.02 mol) of "methylene-*p*-bromoaniline" (**6e**) in 150 ml of chloroform was allowed to stand in the dark at room temperature. After 1 day, tlc examination of the reaction mixture revealed the presence of the nitrone **9c**. After 4 days, the reaction mixture was evaporated to dryness and the residue recrystallized from benzene to give 2.05 g (52%) of tan crystals of **10** (R = Br), identical with an authentic sample prepared independently.[25] The presence of azoxybenzene in the reaction mixture was confirmed by vpc.

Method B.—A mixture of 1.46 g (0.005 mol) of the nitrone **9c**, 0.54 g (0.005 mol) of nitrosobenzene, and 50 ml of chloroform was allowed to stand at room temperature in the dark for 5 days. Evaporation of the reaction mixture and recrystallization of the residue from benzene gave 0.28 g (28%) of tan crystals of *p*-bromoformanilide, identical with the material prepared by method A above. Again, azoxybenzene was present in the crude reaction mixture, as determined by vpc.

Other substituted formanilides (**10**) were prepared analogously; the results are summarized in Table II.

TABLE II

PREPARATION OF PARA-SUBSTITUTED FORMANILIDES (**10**)

Reactants	Product	Yield, %
2 **5a** + **6a**	**10**, R = H	*a*
2 **5a** + **6b**	**10**, R = Cl	49
5a + **9b**	**10**, R = Cl	38
2 **5a** + **6c**	**10**, R = CH_3	*a*
5a + **9d**	**10**, R = CH_3	*a*
5a + **9e**	**10**, R = OCH_3	*a*

[a] Product identified by vpc but not isolated.

Registry No.—**9e**, 27396-35-6; **9f**, 27396-36-7.

[25] L. F. Fieser and J. F. Jones in "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 590.

Study of the Michael and Mannich Reactions with Benzothiazole-2-thiol[1a]

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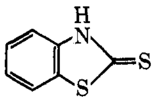
The reaction of the anion of benzothiazole-2-thiol (MBT) with activated olefins in the presence of sodium hydride with Michael reaction acceptors produced 3-substituted benzothiazoline-2-thiones. Similarly, the Mannich reaction of MBT anion with formaldehyde and primary or secondary amines produced the N- (or 3-) substituted benzothiazoline-2-thiones. Possible mechanisms and supporting nmr, ir, and uv data are discussed. The N substitution of MBT anion is discussed within the framework of the oxibase scale which can predict the condition for formation of N products or S products from this ambident anion.

The object of the present investigation was to study the Michael and Mannich reactions of the ambident anion of benzothiazoline-2-thione (I), the so-called 2-mercaptobenzothiazole or MBT of the rubber industry, with various activated vinyl compounds as well as with formaldehyde and various amines. Harman,[1b,2] studying the reaction of organic mercaptans such as I with acrylonitrile, formulated the MBT addition product as an S-substituted benzothiazole-2-thiol derivative. We have now found that the correct structure is the N derivative. Likewise we have shown that the Michael reaction products with activated carbon–carbon double bonds such as methyl vinyl ketone, phenyl vinyl ketone, 2-vinylpyridine, 4-vinylpyridine, divinyl sulfone (which produces a diadduct), and 2-nitro-1-butene, are all N-substituted benzothiazoline-2-thione derivatives.



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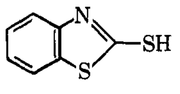

IA

The fact that benzothiazoline-2-thione (I) also enters into a variety of Mannich reactions with formaldehyde and various aliphatic and aromatic amines or phenols to give N-substituted 3-alkylbenzothiazoline-2-thiones is not well known. This paper constitutes a correction for a number of such products incorrectly postulated as S-substituted compounds[3–9] reported in the older literature. The structural assignments of the few N-substituted products were made by Morton and Stubbs[10] based on the absorption at 320–325 mμ indicative of the (–N–(S=)C–S dithio carbamate) structure. These results were confirmed later by Koch[11] and Moore

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[1] (a) Presented in part before the Organic Chemistry Division of the American Chemical Society, Atlantic City, N. J., Sept 17, 1965; (b) M. W. Harman, *Ind. Eng. Chem.*, **29**, 205 (1937).

[2] M. W. Harman, U. S. Patents 1,951,052 (1934); 2,010,000 (1935); and 2,049,229 (1935).

[3] M. H. Zimmerman, U. S. Patent 1,960,197 (1934).

[4] W. J. S. Naunton, W. Baird, and H. M. Bunbury, *J. Soc. Chem. Ind. London Trans.*, **53**, 127 (1934); *Rubber Chem. Technol.*, **7**, 417 (1934).

[5] D. F. Twiss and F. A. Jones, *J. Soc. Chem. Ind. London Trans.*, **54**, 13 (1935).

[6] J. L. Kurlychek, U. S. Patent 2,358,402 (1944).

[7] M. Bogemann and E. Zauker, German Patent 575,114 (1933).

[8] C. Cokman, U. S. Patent 1,901,582 (Sept 13 1933).

[9] R. Robinson, H. Bunbury, J. Davies, and W. J. S. Naunton, British Patent 377,253 (1944).

[10] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1321 (1939).

[11] H. P. Koch, *ibid.*, 401 (1949).