Aliphatic Azoxy Compounds. II. Synthesis of New Azoxy Compounds by Photolytic Isomerizations[1a,b]

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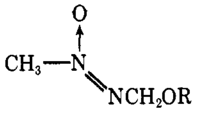
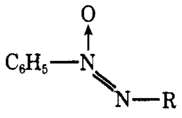
Abstract: Photolysis of the known unsymmetrical azoxy compounds **2** resulted in oxygen migration as well as cis–trans isomerization yielding the new isomers **3**, **4**, and **5**. The geometry of substitution on the azoxy group was seen to have a marked influence on the nmr, uv, and ir, but not mass spectra of the compounds. The position of the N–O bond influenced all the spectral properties. The uv and nmr data were used along with published data to deduce trans geometries for the azoxy groups of the α,β-unsaturated azoxy antibiotics elaiomycin (**11a**) and LL-BH872α (**12**). Some preliminary observations concerning the mechanisms of the isomerizations are also presented.

Without exception, naturally occurring aliphatic azoxy compounds have exhibited potent physiological properties.[2] Cycasin (**1a**), which exhibits neurotoxicity and occurs naturally, together with its aglycone **1b**, a mutagen, and its acetate **1c** are a trio among the most potent chemical carcinogens known.[2a,d] In view of the broad physiological activity of this general class of compounds, and the resulting economic importance of certain members,[2d] we have begun a general study of their chemistry. In this paper we wish to report some of our initial results on the photolytic isomerizations of two known phenyl alkylazoxy compounds, **2a**[3] and **b**,[4] work which has been principally directed toward the development of this method as a synthetic tool for the preparation of new azoxy compounds.

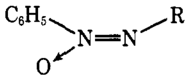


1a, R = 1-β-D-glucosyl
b, R = H
c, R = CH_3CO

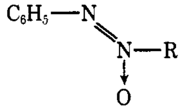


2a, R = CH_3
b, R = C_2H_5

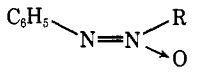
At the outset it was anticipated, from the work of Jaffe[5] and Greene,[6] that photolysis of **2** under appropriate conditions should result in the formation of **3**, **4**, and **5** with the hopeful exclusion of the "photo-Wallach" rearrangement[7] products, **6**. Jaffe[5] had shown that the photolytic cis–trans isomerization of symmetrically substituted azoxybenzenes was very rapid compared to the "photo-Wallach" rearrangement. Further, in keeping with the mechanism proposed for that rearrangement,[7] only one isomer of our series, **4**, would have the structure appropriate for the required intramolecular migration of the oxygen atom to the benzene ring.[7] Greene and Hecht[6] had demonstrated that azoxybutanes underwent a valence reorganization of the azoxy function upon photolysis with the formation of oxadiaziridines (**7**). Heterocycles **7** had surprising thermal stability ($t_{1/2}$ = 3–8 hr at 20°), but did thermally revert to the starting azoxybutane. Judging from the known decreased thermal stability of *N*-aryloxaziridines compared to *N*-alkyloxaziridines,[8] we felt there was little chance, at convenient temperatures, of isolating an oxadiaziridine in our series. But the *in situ* thermal decomposition of such an intermediate could proceed with the resulting formation of **4** and/or **5** as well as the re-formation of **2** and/or **3**. Thus, it was felt that photolytic isomerization of the available compounds **2** was the best approach for the synthesis of the heretofore unavailable isomers **3**, **4**, and **5**.



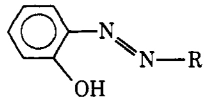
3a, R = CH_3
b, R = C_2H_5



4a, b



5a, b



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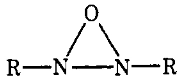

7a, R = *tert*-C_4H_9
b, R = *n*-C_4H_9

Photolysis Results. The photolyses of **2a** and **2b** were qualitatively similar. The results with **2a**, described below, are illustrative. Irradiation of a methanol solution of **2a** at 2537 Å (quartz) produced a mixture containing **3a**, **4a**, and **5a** in addition to the starting material. Periodic nmr analysis of the reaction mixture indicated a relatively rapid trans → cis isomerization of **2a** to **3a** accompanied by a slower oxygen migration reaction which produced **4a** and **5a**. After about 4 hr of irradiation the trans/cis ratio of **2a**/**3a** was constant at 0.72 and that of **4a**/**5a** was constant at 1.41. The amount of oxygen migration products was still increasing at t = 16 hr, but continued photolysis past 16 hr resulted in a considerably darkened reaction

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[1] (a) Partial support for this work by the National Institutes of Health, Grant No. NB07119, is acknowledged with thanks. (b) Paper I: J. Swigert and K. G. Taylor, *J. Amer. Chem. Soc.*, **93**, 7337 (1971). (c) Taken, in part, from the M.S. Thesis of T. Riehl, University of Louisville, 1970.

[2] Some leading references are: (a) G. L. Laqueur and M. Spatz, *Cancer Res.*, **28**, 2262 (1968); (b) W. J. McGahren and M. P. Kunstmann, *J. Amer. Chem. Soc.*, **92**, 1587 (1970); (c) C. L. Stevens, B. T. Gillis, and T. H. Haskell, *ibid.*, **81**, 1435 (1959); (d) M. Whiting, M. Spatz, and H. Matsumoto, *Econ. Bot.*, 20, 98 (1966).

[3] J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).

[4] T. E. Stevens, *ibid.*, **29**, 311 (1964).

[5] D. Webb and H. H. Jaffe, *Tetrahedron Lett.*, 1875 (1964).

[6] (a) S. S. Hecht and F. D. Greene, *J. Amer. Chem. Soc.*, **89**, 6761 (1967); (b) F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970).

[7] G. G. Spence, E. C. Taylor, and O. Buchardt (*Chem. Rev.*, 70, 231 (1970)) give a thorough review of this and other photochemical reactions of azoxy compounds, nitrones, and amine oxides.

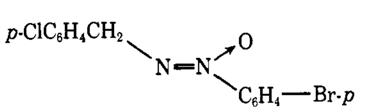
[8] J. S. Splitter and M. Calvin, *J. Org. Chem.*, **30**, 3427 (1965).

mixture. Thus, a reaction time of about 4 hr per 75 mg of **2a** was used for preparative runs. The four isomers could be separated by column silica gel chromatography and were eluted in the order **2a**, **4a**, **5a**, **3a**. The isolated yields of analytically pure compounds are shown in Table I.

Table I. Yields of Photolysis Products

Compd	Yield, %	Compd	Yield, %
2a	14.2	**2b**	13.9
3a	20.5	**3b**	20.4
4a	9.6	**4b**	9.3
5a	3.2	**5b**	3.9

Product Geometry. Some confusion has existed in the literature as to the relative stability of cis and trans azoxy compound isomers. Brough, Lythgoe, and Waterhouse[9] interpreted the facile basic conversion of azoxy compound **8** (mp 104°) into an "isomer" of mp 186° as a trans to cis isomerization. Several authors[2b,3,10] have used this publication as a basis for assigning geometry to azoxy compounds with the implication by some[2b,10] that the cis isomer was the more thermodynamically stable. In contrast, Jaffe[11] showed that cis azoxybenzenes, prepared by peracid oxidation of cis azo compounds, were thermally unstable relative to the trans isomers. Woodward and Wintner[12] further clarified the situation by demonstrating that Lythgoe's[9] 186° melting "cis isomer" of **8** was actually a product of oxidative dimerization possessing a structure of type **9**. Thus, azoxy compounds represent no unusual exception to the general rules governing the stability of geometric isomers about a double bond, and the cis isomers **3** and **5** could be identified by thermal isomerization to the corresponding trans isomers.



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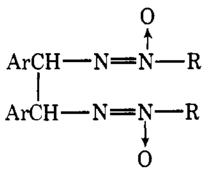

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Refluxing **3b** in benzene for 5 hr caused no change in its nmr spectrum, but at the temperature of refluxing toluene, compound **2b** began to appear and after 5 hr **3b** was converted completely to **2b**. Also, refluxing a mixture of **2a**, **3a**, **4a**, and **5a** in benzene caused the isomerization of **5a** to **4a** but not **3a** to **2a** as observed by nmr. From these preliminary experiments it would appear that the thermal conversion of **5** → **4** is more facile than the conversion of **3** → **2**, a result in keeping with the general observation that *N*-arylimines undergo cis–trans isomerization faster than *N*-alkylimines.[13] It was also noted that the cis isomers were isomerized to the corresponding trans isomers under the vpc conditions used (see Experimental Section).

Spectra. Spectral identification of geometric isomers of azoxy compounds is sparingly dealt with in the literature. Along with Jaffe's[11] work on cis and trans azoxybenzenes, two recent publications[14,15] dealing with the nmr and ir features of cyclic, hence cis, azoxyalkanes comprise the total. Determination of the position of the N–O bond has been accomplished by a combination of chemical means[2c] and (for conjugated azoxy compounds) ultraviolet spectroscopy,[2b,c,16] and most recently, by nmr chemical-shift measurements.[3,16] As will be seen below, for reliable assignment of the N–O bond position by spectral means, a knowledge of the azoxy group geometry is desirable.

Nmr. The data of Table II demonstrate that (excluding from discussion the more remote meta and para phenyl protons) the protons of the cis isomers **3** and **5** resonate at higher field than those of the corresponding trans isomers. The most dramatic shifts are seen in the ortho protons of the phenyl substituents. The upfield shifts are approximately the same, 0.92–1.05 ppm, whether the phenyl escapes a cis relationship to the N–O bond or the N nonbonding electrons upon isomerization. This shift, in part, is probably due to shielding by the alkyl groups; however, such effects would be expected to be relatively small and on the order of 0.1 ppm.[17] An explanation for the rather high magnitude of the shift might be found by ascribing an anisotropy to the azoxy function similar to that found for the nitro group.[18] Thus, because the phenyl rings of the cis isomers may be forced from coplanarity[19] with the azoxy function, the ortho protons may be, on the average, situated above the plane, and in the shielding "cone," of the azoxy function.

Table II. Nmr Chemical Shifts (δ) of Azoxy Compounds[a]

Compd	Ortho phenyl	Meta, para phenyl	CH_2	CH_3
2a	8.17	7.40		3.45[b]
3a	7.12	7.37		3.27
4a	7.87	7.35		4.19[c]
5a	6.95	7.30		3.85
2b[d]	8.17	7.40	3.63[e]	1.33
3b	7.22	7.47	3.46	1.27
4b[d]	7.95	7.37	4.32	1.59
5b	6.97	7.37	4.13	1.47

[a] Solvent: $CDCl_3$ unless noted otherwise. [b] Reported 3.40 in CCl_4.[3] [c] Reported 4.15 in CCl_4.[3] [d] Solvent: CCl_4. [e] Reported: 3.78 in CCl_4.[4]

The upfield changes in chemical shift of the alkyl groups attending trans–cis isomerization are, again, in the same range (0.17–0.34 ppm) whether the alkyl group escapes a cis relationship with the N–O bond (**2** → **3**) or the N nonbonding electrons (**4** → **5**). Sp^2 nonbond-

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(9) J. N. Brough, B. Lythgoe, and P. Waterhouse, *J. Chem. Soc.*, 4069 (1954).

(10) B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962).

(11) D. L. Webb and H. H. Jaffe, *J. Amer. Chem. Soc.*, **86**, 2419 (1964).

(12) (a) C. E. Wintner, Ph.D. Thesis, Harvard University, 1963; (b) R. B. Woodward and C. E. Wintner, *Tetrahedron Lett.*, 2693 (1969).

(13) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966).

(14) F. D. Greene and S. S. Hecht, *Tetrahedron Lett.*, 575 (1969).

(15) V. T. Bandurco and J. P. Snyder, *ibid.*, 4643 (1969).

(16) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 95 (1967).

(17) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 78–79, 225, and references therein.

(18) Reference 17, p 94.

(19) Even the phenyl rings of *trans-p*-azoxyanisol are skewed in the solid state: W. R. Krigbaum, Y. Chatini, and P. G. Barber, *Acta Crystallogr, Sect. B*, **26**, 97 (1970).

ing N electrons are known to deshield neighboring cis protons[13,20] but the influence of N–O bonds is, as yet, unpredictable. For example, Freeman[3] has observed an effect opposite to that noted above in that the methyl signal for nitrosomethane dimer undergoes a downfield shift on going from the trans to the cis isomer. It should also be noted that shifts of this magnitude and direction can be brought about by placing a methyl or ethyl group cis to a tilted phenyl ring.[21] Whatever the causes, however, the data of Table II and previously published data[14,15] indicate that one can expect considerable chemical-shift differences between analogous protons of geometric isomers of azoxy compounds.

Uv. The uv spectra of the azoxy compounds are listed in Table III. Again, the spectra show a dependence on the geometry of the azoxy group with the cis isomers invariably exhibiting their most intense absorptions at wavelengths shorter than the corresponding trans isomers. The most dramatic effects are seen in the cis–trans isomers with the longest conjugation, **4** and **5**. This behavior strongly parallels that observed for *cis*- and *trans*-azoxybenzenes,[11] azobenzenes,[22] and *N*-alkyl-*N*-nitrosoanilines.[23] Such behavior can be, in large part, attributed to twisting about the *N*-phenyl bond rendering the conjugated system nonplanar.[22,23]

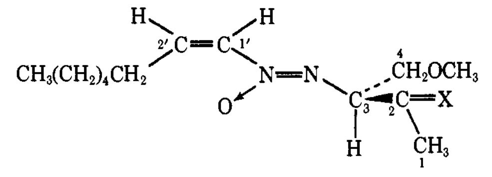
Table III. Ultraviolet Absorption Spectra of Azoxy Compounds[a]

Compd	λ_{max}, nm (ϵ)
2a[b]	245 (9300)
3a	235 (7400)
4a[c]	288 (10,500); 228 (6600); 223 (7000)
5a	295 (1600); 233 (10,700)
2b	246 (9000)
3b	236 (8300)
4b	288 (11000); 228 sh (6800); 223 (7300)
5b	296 (2200); 233 (12,600)

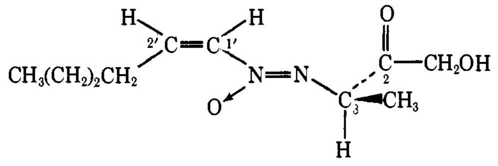
[a] In 95% ethanol. [b] Reported λ_{max} 245 (ϵ 10,300).[3] [c] Reported λ_{max} 290.[3]

The Antibiotics Elaiomycin[2b] and LL-BH872α.[2b] In a recent paper[2b] reporting circular dichroism studies on elaiomycin (**11a**), oxidized elaiomycin (**11b**), and LL-BH872α (**12**), the authors assigned a cis azoxy geometry to **11a** and **b** and a trans azoxy geometry to **12**. These assignments were based on (1) the belief that **11a** and **12** have the same absolute configuration at the asymmetric carbon bound to the azoxy function, and (2) the observation that the CD curves of **11a** and **b** showed Cotton effects of the same sign but opposite in sign to that of **12**. The selection of cis azoxy geometry for **11a** and **b** was based on the observation that those compounds were more "stable" than **12** and hence, according to ref 9, should be cis.

In reality, **11** and **12** have opposite absolute configurations, a fact which readily explains[24] the observed CD results. Also, other reported spectroscopic evidence indicates that the geometries of **11** and **12** are the same. Thus, the nmr signal of the proton on C-1′ is seen at δ 6.83[25] in **11a**,[2c] 6.77 in **11b**, and again at 6.83 in **12**,[25] results which, in the light of Table II, indicate identical geometries for all three compounds. More convincing evidence is found in the ultraviolet spectra of **11** and **12** (**11a**,[2c] λ_{max} 237.5 (ϵ 11,000); **11b**,[2b] 238 (ϵ 9000); **12**,[2b] 238 (ϵ 9000), a result which, in the light of Table III, is incompatible with the proposed [2b] different azoxy geometries for **11** and **12**.



11a, X = H, OH
b, X = O



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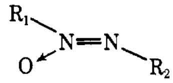
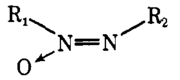
An analysis of available ultraviolet data indicates a trans geometry for **11** and **12**. We have prepared the trans unsymmetrical azoxyalkanes **13a** and **b** as well as their cis counterparts **14a** and **b**.[1b,26] The trans compounds **13** exhibit an ultraviolet maximum in the range observed (217–223 nm) for numerous azoxyalkanes.[27] The maxima of the cis compounds **14** are red-shifted by 13–14 nm and appear at slightly longer wavelength than the cyclic azoxyalkane **15**.[14] McGahren and Kunstman[25] have reported the preparation of a dihydro derivative of LL-BH872α, presumably **16**, which exhibited an ultraviolet λ_{max} at 223 (ϵ 4600) in the range of the *trans*-azoxyalkanes **13**, and outside the range of the cis compounds **14**. Since **3a** and **14a** were seen to be geometrically stable under conditions simulating the preparation of **16** (5% Rh/Al$_2$O$_3$), it follows that the azoxy geometry of the antibiotics **11** and **12** is trans.



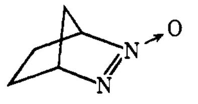
(λ_{max} 218–219)

13a, $R_1 = R_2 = i\text{-}C_3H_7$
b, $R_1 = C_6H_{11}; R_2 = CH_3$



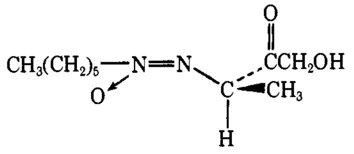
(λ_{max} 232)

14a and **b**



(λ_{max} 228)

15



16 (λ_{max} 223)

Mass Spectra. Some details of the mass spectra of aromatic azoxy compounds have been reported.[28,29]

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(20) Reference 17, pp 81–82.

(21) S. Sternhell and J. R. Wilmshurst, *Aust. J. Chem.*, **18**, 1759 (1965).

(22) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, Chapter 15.

(23) J. T. D'Agostino and H. H. Jaffe, *J. Amer. Chem. Soc.*, **92**, 5160 (1970).

(24) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, Chapter 11.

(25) W. J. McGahren and M. P. Kunstman, *J. Amer. Chem. Soc.*, **91**, 2808 (1969).

(26) K. G. Taylor and R. Isaac, to be published.

(27) B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952).

Table IV. Principal 70-eV Mass Spectral Fragments of the Phenyl Methylazoxy Compounds

Fragment (*m/e*)	Elemental composition[a]	Rel abundance			
		2a[a]	**3a**[b]	**4a**[a]	**5a**[a,c]
$M\cdot^{+}$ (136)	$C_7H_8N_2O$	55 (27)[d]	7	58	57
$M\cdot^{+} - 15$ (121)	$C_6H_5N_2O$			30	21
$M\cdot^{+} - 17$ (119)	$C_7H_7N_2$	19 (12)	3		
$M\cdot^{+} - 28$ (108)	C_6H_6NO	100 (70)	23		
$M\cdot^{+} - 29$ (107)	C_6H_5NO	37 (22)	8		
$M\cdot^{+} - 45$ (91)	C_6H_5N	2 (20)	15	30	39
$M\cdot^{+} - 58$ (78)	C_6H_6	54 (56)	65	8	17
$M\cdot^{+} - 59$ (77)	C_6H_5	98 (100)	100	35	100
$M\cdot^{+} - 71$ (65)	C_5H_5	16 (24)	33	100	79
$M\cdot^{+} - 72$ (64)	C_5H_4	3 (5)	8	29	25
$M\cdot^{+} - 85$ (51)	C_4H_3	44 (75)	92	20	34

[a] Based on high-resolution spectra obtained on an AEIMS-9 double focusing instrument located at Battelle Memorial Institute, Columbus, Ohio. [b] Medium-resolution spectrum obtained on a Hitachi RMU-6. [c] Due to technical difficulties this spectrum contained a high background. Hence the relative abundances are qualitative. [d] Intensities in parentheses are those from a spectrum obtained on a Hitachi RMU-6.

Table V. Principal 70-eV Mass Spectral Fragments of the Phenyl Ethylazoxy Compounds[a]

Fragment (*m/e*)	Elemental composition[b]	Rel abundance			
		2b	**3b**	**4b**	**5b**
$M\cdot^{+}$ (150)	$C_8H_{10}N_2O$	15	7	24	25
$M\cdot^{+} - 17$ (133)	$C_8H_9N_2$	23	26		
$M\cdot^{+} - 29$ (121)	$C_6H_5N_2O$			17	26
$M\cdot^{+} - 42$ (108)	C_6H_6NO	3	10	3	
$M\cdot^{+} - 43$ (107)	C_6H_5NO	49	48		
$M\cdot^{+} - 59$ (91)	C_6H_5N	4	6	14	15
$M\cdot^{+} - 72$ (78)	C_6H_6	35	44	8	6
$M\cdot^{+} - 73$ (77)	C_6H_5	100	100	62	62
$M\cdot^{+} - 85$ (65)	C_5H_5	4	9	100	100
$M\cdot^{+} - 86$ (64)	C_5H_4	2	2	16	16
$M\cdot^{+} - 99$ (51)	C_4H_3	46	51	23	20

[a] Medium-resolution spectra obtained on a Hitachi RMU-6. [b] Probable composition based on analogy with high-resolution results.

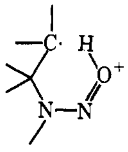
For aliphatic azoxy compounds only scattered data exist. Mass spectra were obtained on azoxy compounds **2–5** and the data are summarized in Tables IV and V above. In the case of **2a**, two principal fragmentation pathways exist (Scheme I). The proposal of pathway a is supported by the presence of the appropriate metastables (*) for all of the fragmentations shown. Pathway b is supported by the presence of a metastable in the fragmentation pattern of the ethyl compound **2b** at *m/e* 117.9, appropriate for the loss of OH from the parent ion. Likewise, a metastable at 45.0 for the loss of HCN from *m/e* 91 is not seen in the spectrum of **2a** itself, but is seen in the spectra of **4b** and **5a**. Thus, cleavage of the N–N bond(s) either before or after OH loss dominates the fragmentation of azoxy compounds **2** and **3**. It is interesting to note that in pathway a the ions *m/e* 108 and 78 carry a hydrogen atom presumably present by way of H shift from the alkyl group. In this regard, Billets, Jaffe, and Kaplan[30] have noted that the molecular ions of dialkyl-*N*-nitrosamines are rearranged and proposed structure **17**.

Scheme I

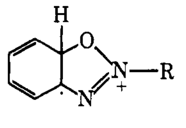
$$\begin{tikzcd}
\begin{array}{c}\mathbf{2a}[C_7H_8N_2O]\cdot^{+}\\ m/e\ 136\end{array} \arrow[r, "a", "*"'] \arrow[d, "117.9*"', "b\text{-}OH\cdot"] & \begin{array}{c}[C_6H_6NO]^{+}\\ m/e\ 108\end{array} \arrow[d, "*"', "-NO\cdot"] & + & \begin{array}{c}[C_6H_5NO]\cdot^{+}\\ m/e\ 107\end{array} \arrow[d, "*"', "-NO\cdot"] \\
\begin{array}{c}[C_7H_7N_2]^{+}\\ m/e\ 119\end{array} \arrow[d, "-CH_2N\cdot"] & \begin{array}{c}[C_6H_6]\cdot^{+}\\ m/e\ 78\end{array} & & \begin{array}{c}[C_6H_5]^{+}\\ m/e\ 77\end{array} \arrow[d, "*"', "-C_2H_2"] \\
\begin{array}{c}[C_6H_5N]\cdot^{+}\\ m/e\ 91\end{array} \arrow[r, "45.0*", "-HCN,\ CN\cdot"'] & \begin{array}{c}[C_5H_{4-5}]\cdot^{+}\\ m/e\ 64\text{–}65\end{array} & & \begin{array}{c}[C_4H_3]^{+}\\ m/e\ 51\end{array}
\end{tikzcd}$$

The spectrum of **4a** is decidedly different from that of **2a**. With this isomer an $M\cdot^{+} - CH_3$ fragment appears accompanied by the appropriate metastable at *m/e* 107.6. In the spectrum of **4b**, an analogous $M\cdot^{+} - C_2H_5$ fragment appears accompanied by a metastable at *m/e* 97.6. Further sequential loss of the stable NO and CN radicals or HCN molecule (metastable at 45.0) from the $M\cdot^{+}$ – alkyl fragments of **4** and **5** could account for the relatively high abundances of the C_6H_5N and C_5H_{4-5} fragments in the spectra of these azoxy isomers.

To account for the direct loss of CO and N_2 from the molecular ion of azoxybenzenes, previous workers[28] postulated a rearranged molecular ion formulated as **18**. While a $C_6H_4O\cdot^{+}$ ion of 3% abundance was noted in the spectrum of **4a**, direct loss of CO and N_2 was not observed for the azoxy compounds **2a–5a**; hence, intermediate **18** would appear to have secondary importance at best in the present applicable cases.



17



18

Mechanistic Observations. During the course of this study it was observed (1) that oxygen had no effect upon the photolysis, (2) that photolysis of **4** and **5** did not yield oxygen migration, and (3) that photolysis through Pyrex gave facile trans ⇄ cis isomerization to the practical exclusion of oxygen migration.

Tanikaga[31] has reported that both the cis–trans isomerization and the photo-Wallach rearrangement of azoxybenzene result directly from an excited singlet state, a fact with which observation 1 is consistent. To explain observation 2, were the oxygen migration and the photo-Wallach rearrangement of **4a** and **4b** to proceed through the same singlet intermediate, the latter reaction, requiring a less strained transition state, might proceed preferentially. Regarding the third observation, Jaffe and Orchin[23] have surmised that an n → π* transition of azoxybenzene is submerged under a high-intensity π → π* band which absorbs at 323 nm. Both **2a** and **3a** (and to a lesser extent **2b** and **3b**) show substantial "tailing" on the long-wavelength side of their absorption maxima and have appreciable (ϵ 300–500) absorption at 290–300 nm. It is possible that an n → π* band is responsible for the "tailing" and that this transition is responsible for the observed trans–cis isomerizations. In the related cis–trans isomerizations

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(28) J. H. Bowie, G. E. Lewis, and R. G. Cooks, *Chem. Commun.*, 284 (1967).

(29) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 524–525.

(30) S. Billets, H. H. Jaffe, and F. Kaplan, *J. Amer. Chem. Soc.*, **92**, 6964 (1970).

(31) R. Tanikaga, *Bull. Chem. Soc. Jap.*, **41**, 2151 (1968).

of aliphatic azo compounds, $^1n,\pi^*$ excitation followed by efficient intersystem crossing to the $^3\pi,\pi^*$ state is the proposed mechanism.[32]

Experimental Section

General. All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained with a Varian Associates A-60A spectrometer using tetramethylsilane as the internal standard. Infrared spectra were determined using a Perkin-Elmer Model 521 grating spectrophotometer. A Cary Model 14 spectrophotometer was utilized for determining ultraviolet spectra. Mass spectral data were obtained with a Hitachi Perkin-Elmer RMU-6 single focusing mass spectrometer and Battelle Memorial Institute's A.E.I. MS-9 double focusing mass spectrometer. Midwest Microlab, Inc. (Indianapolis, Ind.) performed all elemental analyses.

Vpc analyses were performed on an F&M Model 700 gas chromatograph equipped with a thermal conductivity detector. All vpc analyses were carried out using a 9 ft × $^1/_4$ in. aluminum column packed with 20% Carbowax 20M coated on 60–80 mesh Chromosorb W (acid washed and Me_2Cl_2Si-treated). At 200° and a He flow of 60 ml/min, the azoxy compounds exhibited retention times of 8.5 (**2b**), 12.0 (**4b**), 8.0 (**2a**), and 13.0 (**4a**) min, respectively. Due to their thermolabile nature, **3a**, **5a**, **3b**, and **5b** were converted under the vpc conditions (injection port temperatures of 210–250°) to their respective trans isomers; hence, these compounds displayed retention times identical with those listed for the appropriate trans isomers.

Photochemical reactions were conducted in a Rayonet Photochemical Reactor Model RPR 100 equipped with 3500- (16 tubes), 3000- (16 tubes), or 2537-Å (15 tubes) light sources. All photochemical reactions were carried out in either a 2.5 × 27 cm water-jacketed all-quartz vessel or a 2.5 × 25 cm water-jacketed all-Pyrex vessel. Temperature of irradiated solutions were maintained at 18–30°. Methanol was distilled before use in photoreactions, and pentane was purified by successive treatments with concentrated sulfuric acid and water, followed by distillation from sodium hydroxide pellets. Prior to all photochemical reactions, the reaction vessel and its contents were purged with nitrogen gas. During the reactions, the nitrogen purge was discontinued, and the vessel was equipped with only a drying tube unless otherwise noted.

Photolysis of *trans*-*N*-Phenyl-*N'*-ethyldiimide *N*-Oxide (2b) at 2537 Å. The azoxy compound **2b**[4] (1.40 g) was photolyzed in methanol at 2537 Å using the quartz reaction vessel. The photolyzed sample was prepared in a piecemeal fashion in quantities ranging from 50 to 390 mg. In general, the reactions conditions employed consisted of 1 ml of solvent per 10 mg of compound, and the solutions were irradiated for 1 hr per 15–18 mg of sample.

The photolysis mixture was slurried in 10% CH_2Cl_2 in hexane and placed on a 2.5 × 65 cm column containing 105 g of silica gel. Elution of the column progressed from increasing concentrations of CH_2Cl_2 in hexane to increasing concentrations of ethyl acetate in CH_2Cl_2. The column initially developed as successive yellow, red-brown, and yellow bands. The first two bands were removed from the column with 20% CH_2Cl_2, and after elution with 30% CH_2Cl_2, the second yellow band was eluted with 40 and 50% CH_2Cl_2 in hexane. Vpc analysis of the material (195 mg) comprising the second yellow band showed it to be +99% pure **2b** (13.9% recovery).

A second 50% CH_2Cl_2 in hexane fraction was taken prior to the elution of a brown band. Analysis of this fraction (45 mg) by vpc revealed a 25/75 mixture of **2b** and **4b**.

The brown band was then removed from the column with 60% CH_2Cl_2 in hexane, providing 130 mg (9.3% yield) of +99% vpc pure **4b**.

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65; O, 10.65. Found: C, 64.21; H, 6.85; N, 18.48; O, 10.67.

Continued washing of the column with 70 and 80% CH_2Cl_2 in hexane, CH_2Cl_2, and 1% ethyl acetate in CH_2Cl_2 removed trace quantities of unknown materials and in addition, moved two brown bands down the column. The less intense, front-running brown band was contained within a second 1% as well as a 3% ethyl acetate–CH_2Cl_2 fraction. Vpc analyses of these two eluents showed them to be pure **4b**, resulting from thermal isomerization of the corresponding cis isomer **5b** on the hot injection port block. The two fractions were combined (70 mg) and placed in a microsublimator. "Distillation" under mild conditions, 40–43° (0.01–0.02 mm), afforded 54 mg (3.86% yield) of pure **5b** as a yellow viscous liquid. After storage at −20° for 2–3 days, the compound crystallized and remained a solid at room temperature.

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.70; H, 6.73; N, 18.80.

The second, more intense brown band was removed with 6% ethyl acetate in CH_2Cl_2. Vpc analysis of this fraction (430 mg) showed it to consist of 99% **2b** and 1% **4b**, resulting from thermal isomerization of the corresponding cis isomers **3b** and **5b**. Pure **3b** was obtained by chromatography of the fraction on a 2 × 38 cm column packed with 45 g of silica gel. Washing of the column with a large volume of CH_2Cl_2 (*ca.* 600 ml) removed 85 mg of material consisting of 95% **3b** and 5% **5b**. Further elution with 2 and 4% ethyl acetate in CH_2Cl_2 afforded 300 mg of **3b** which was further purified by "distillation" in a microsublimator at 42–44° (0.01–0.02 mm). In this manner, 285 mg (20.4% yield) of pure **3b** was obtained as a yellow liquid.

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.19; H, 6.98; N, 18.74.

Photolysis of *trans*-*N*-Phenyl-*N'*-methyldiimide *N*-Oxide (2a) at 2537 Å. Two samples (500 mg each) of **2a**[3] in methanol (50 ml) were separately photolyzed at 2537 Å in the quartz vessel for 25 hr. A third sample (200 mg) was photolyzed in a similar manner except for a reaction time of 11 hr. The three samples were combined (1200 mg) and then analyzed by nmr which provided the following relative concentrations: 31% **2a**, 39% **3a**, 19% **4a**, and 11% **5a**.

The four isomers were isolated by chromatography on a 2.5 × 65 cm column packed with 105 g of silica gel. The column initially developed, upon elution with 10% CH_2Cl_2 in hexane, as successive yellow, orange, and yellow bands. These three bands were removed with 20, 30, and 40% CH_2Cl_2, respectively. Washing of the column with 50% CH_2Cl_2 in hexane afforded 35 mg of material consisting of 85% **2a** as determined by vpc analysis. A second 50% CH_2Cl_2, as well as a 60% CH_2Cl_2 eluate removed a total of 170 mg (14.2% recovery) of +98% pure **2a**. A second 60% CH_2Cl_2 fraction contained 11% **2a** and 89% **4a**. Continued washing of the column with 70 and 80% CH_2Cl_2–hexane provided a total of 115 mg (9.6% yield) of pure **4a**.

Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.79; H, 5.94; N, 20.37.

Trace quantities of unknown materials were then removed with 90% CH_2Cl_2–hexane and CH_2Cl_2. Further elution with 1% ethyl acetate in CH_2Cl_2 provided 20 mg of 95% pure **5a** as determined by vpc analysis. The subsequent column fraction (3% ethyl acetate) contained 65 mg of nearly pure **5a**. Distillation of this fraction at 41–44° (0.01–0.02 mm) afforded 38 mg (3.2% yield) of pure **5a** as a yellow oil. The compound crystallized after storage at −20° for several days and remained a solid at room temperature.

Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 62.00; H, 6.01; N, 20.86.

The column was then rinsed with 6% ethyl acetate–CH_2Cl_2 affording 70 mg of material containing 92% **3a** and 8% **5a**.

The succeeding two column eluents (12 and 25% ethyl acetate) contained a substantial quantity of material which was sublimed at 42–44° (0.01–0.02 mm) providing 246 mg (20.5% yield) of **3a** as a yellow solid, mp 50–52°. Although the compound was quite pure, a colorless sample, mp 51.5–53.5°, could be obtained by small scale chromatography similar to that described for **3b**. The color of the compound is not necessarily a rigid criterion of purity as a light yellow sample gave a satisfactory elemental analysis.

Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 62.00; H, 5.76; N, 20.53.

Effect of Nitrogen and Oxygen Atmospheres on the Photolysis of 2b. A solution of 50 mg of **2b** in 5 ml of *n*-pentane was placed in the quartz vessel, and the system was purged with nitrogen for 5–10 min. The nitrogen purge was then discontinued, and the solution was irradiated, with stirring, at 2537 Å for 2 hr. Vpc analysis of the reaction mixture revealed a **2b**/**4b** ratio of 87/13.

A solution of 50 mg of **2b** in 5 ml of pentane was placed in the quartz vessel, and the system was purged with oxygen for 10 min. The oxygen purge was discontinued, and the solution was photolyzed for 2 hr at 2537 Å. Vpc analysis revealed an 86/14 ratio of **2b**/**4b**.

Photolysis of 2a at 3000 Å in Quartz and Pyrex Reaction Vessels. A solution of 50 mg of **2a** in 50 ml of methanol was photolyzed in the quartz vessel at 3000 Å for 2.25 hr. The resulting brown solution was concentrated *in vacuo* with mild heating (~40°),

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[32] I. I. Abram, G. S. Milne, B. S. Solomon, and C. Steel, *J. Amer. Chem. Soc.*, **91**, 1220 (1969).

affording a brown concentrate which was found by nmr analysis to consist of 43–44% **2a**, 46–47% **3a**, 5–6% **4a**, and 4–5% **5a**.

An identical photolysis in the all-Pyrex vessel provided a colorless solution which contained 70% **2a** and 30% **3a** as determined by nmr analysis. Vpc analysis of the product revealed 1–2% **4a**, indicating that the reaction afforded a 1–2% total yield of oxygen migration.

Optimum conditions for the reaction at 3000 Å in Pyrex appeared to be 3.33–3.50 hr of irradiation per 50 mg of **2a** in 50 ml of methanol. At this point, an apparent equilibrium mixture of **2a** (56%) and **3a** (44%) was generated. Under these conditions, a total of 2–3% **4a** plus **5a** was evident by vpc analysis.

Photolysis of 2a at 2537 and 3000 Å in an Oxygen Atmosphere. A solution of 40 mg of **2a** in 50 ml of methanol (in Pyrex) was purged for 10 min with oxygen and then irradiated at 3000 Å for 2 hr under an oxygen atmosphere. Nmr analysis of the reaction mixture indicated that 70% **2a** and 30% **3a** were present.

A similar reaction of **2a** using 2537-Å irradiation and the quartz reaction vessel resulted in the formation of isomers **3a**, **4a**, and **5a** in proportions essentially the same as when the reaction was carried out under nitrogen atmosphere.

Photolysis of 4a at 2537 Å. A vpc pure sample of **4a** (34 mg) was dissolved in 50 ml of methanol and the solution was photolyzed at 2537 Å for 1.7 hr in the quartz vessel. The resulting brown solution was concentrated under reduced pressure, affording a dark brown concentrate containing a significant quantity of $CDCl_3$-insoluble material. An nmr analysis of the concentrate showed 57% **4a** and 43% **5a**. There was no evidence in the spectrum of either **2a** or **3a**.

Photolysis of 4a at 3000 Å. The reaction mixture from the photolysis of **4a** at 2537 Å was dissolved in methanol (50 ml) and irradiated at 3000 Å in quartz for 1.25 hr. Nmr analysis of the concentrated reaction product revealed 41% **4a** and 59% **5a**. Neither nmr nor vpc analyses showed the presence of **2a** or **3a**.

Photolysis of 4b at 2537 Å. Approximately 15 μl of vpc-pure **4b** was dissolved in 5 ml of *n*-pentane, and the solution was photolyzed at 2537 Å in the quartz vessel for 1 hr. The pentane was then removed under a slow nitrogen flow. Analysis of the concentrate by nmr showed 79% **4b** and 21% **5b**.

Further photolysis of the above mixture in methanol (5 ml) for 2.5 hr provided a reaction product relatively enriched in **5b** but containing a substantial amount of $CDCl_3$-insoluble material.

Thermal Isomerization of 3a. A solution of 54 mg of **3a** in 25 ml of dry, distilled benzene was immersed in an oil bath preheated to 84°. The solution was then stirred at reflux under nitrogen for 3 hr. An nmr spectrum of the concentrate obtained by removal of the benzene under reduced pressure showed signals due only to **3a**. The sample from the benzene reflux was then dissolved in 12 ml of dry, distilled toluene, immersed in a preheated oil bath (118–121°), and refluxed under a nitrogen atmosphere for 0.75 hr. Nmr analysis of the product showed it to consist of 81% **3a** and 19% **2a**. Refluxing of the product in toluene was then repeated three times which provided the following data: 1.75 hr of total reflux, 52% **3a** and 48% **2a**; 2.75 hr, 38% **3a** and 62% **2a**; 3.50 hr, 22% **3a** and 78% **2a**.

Thermal Isomerization of 3b. A solution of 35 μl of pure **3b** in 4 ml of benzene was stirred at reflux for a total of 5 hr. No cis to trans isomerization could be detected by nmr analysis of the product.

The compound was subsequently refluxed in 4 ml of toluene for 2.5 hr. Analysis of the product revealed 35% **3b** and 65% **2b**. A further 2.5 hr of thermal treatment of the reaction product in toluene resulted in a complete cis to trans conversion.

Relative Thermal Stability of 3a and 5a. A photolysis mixture containing by nmr integration the relative proportions of 28% **2a**, 39% **3a**, 22% **4a**, and 10% **5a** was dissolved in toluene, immersed in a preheated (115°) oil bath, and refluxed for 1.5 hr. Nmr analysis of the concentrate showed the following relative proportions: 35% **2a**, 35% **3a**, and 30% **4a**. No *cis*-**5a** was detected by nmr.

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Organic Photochemistry. XVII. The Solution-Phase Photodimerization of Dimethylthymine[1,2]

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Abstract: Dimethylthymine photodimerizes in solution to give four cis-fused cyclobutane-type dimers. Dimerization of a 0.1 *M* aqueous solution is efficient and apparently singlet derived (intersystem crossing in this solvent seems to be negligible). Thermal osmometry data give evidence for appreciable ground-state aggregation, and dimerization from these aggregates through excimer intermediates is proposed. Dimerization in nonaqueous solvents is less efficient and arises from both the singlet and triplet states (reaction from the singlet state may involve efficient dimerization of trace amounts of aggregates). The product distribution, percentage of triplet involvement, and efficiency of DMT intersystem crossing (ϕ_{ic}) all vary with solvent polarity, and an explanation of the latter two phenomena, involving level inversion, is presented. A wavelength dependence of ϕ_{ic} may also be due to the population of upper excited states. The extensive base stacking of DMT in water makes this system a reasonable model for the thymine units in DNA.

The photodimerization of thymine has been a subject of intense interest to the area of photobiology for a number of years, primarily because this reaction is known to be involved in the photoinactivation of deoxyribonucleic acid (DNA) *in vivo* and *in vitro*.[4] Our attention was drawn to this area several years ago, since the considerable effort which had been

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(1) Part XVI: O. Rodriquez and H. Morrison, *Chem. Commun.*, 679 (1971).

(2) Abstracted from the doctoral dissertation of Robert Kleopfer, Purdue University, January, 1971. Presented, in part, at the 155th National Meeting of the American Chemical Society, April 1–5, 1968, San Francisco, Calif. For preliminary communications, see (a) H. Morrison, A. Feeley, and R. Kleopfer, *Chem. Commun.*, 358 (1968); (b) H. Morrison and R. Kleopfer, *J. Amer. Chem. Soc.*, **90**, 5037 (1968).

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(4) For a recent review, see: J. G. Burr, *Advan. Photochem.*, **6**, 193 (1968).