N HCl was added until complete solution resulted. Sodium bicarbonate was added to neutralize the hydrochloride salt. The mixture was extracted with two 50-ml. portions of ether and the combined ether layers were dried over $CaCl_2$. The ether was evaporated and the residue was washed with benzene to provide 0.85 g., 96% yield of product, m.p. and m.m.p. (with product from A) 138–139°.

N-(3,5-Dimethyl-4-hydroxybenzyl)-N-(2-hydroxy-1-naphthylmethyl)methylamine. A.—2,3-Dihydro-2-methyl-1H-naphth-[1,2-*e*][1,3]oxazine (I, 2.00 g., 0.01 mole) and 2,6-dimethylphenol (1.23 g., 0.01 mole) were dissolved in 50 ml. of methanol and the solution was left stoppered at room temperature. After several weeks large prisms had grown in clusters. After 8 months they were separated and washed with cold methanol: 1.49 g., m.p. 162.5–163°. The filtrate yielded an additional 0.95 g., m.p. 154–155° undepressed by mixture with first crop, total yield 76%.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.20. Found: C, 78.34; H, 7.04.

B.—The reactants were dissolved in 40 ml. of ethanol in 0.0075 *M* quantities and refluxed gently (80°) for 6 days in a closed system. Evaporation at room temperature gave a thick syrupy residue. This was taken up in ethanol, and water was added nearly to the emulsion point. The crystals which deposited upon stirring were collected and the process was repeated with the filtrate except that methanol was used instead of ethanol. As the methanol was allowed to evaporate, the solid formed slowly in large crystals which were collected and washed with methanol. No more product was obtained from the 1.46 g. of oil remaining. Total product isolated was 0.93 g., 39% yield, m.p. 158–159.5°. Mixture melting point with product from A was undepressed.

N-(2-Hydroxy-5-methylbenzyl)-N-(3,5-dimethyl-2-hydroxybenzyl)methylamine and 2,6-Bis[N-(3,5-dimethyl-2-hydroxybenzyl)-N-methylaminomethyl]-*p*-cresol (Table I, 28).—3,4-Dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine (VII, 1.77 g., 0.01 mole) and *p*-cresol (1.08 g., 0.01 mole) were dissolved in 15 ml. of methanol and left stoppered for 5 days at 25°. Evaporation of the solvent left an oil, which was taken up in 5 ml. of methanol. Addition of a few drops of water led to crystal formation in 4 hr. After 2 weeks from the start of the reaction, the solid was collected and washed with cold methanol to obtain 1.70 g. of material which melted at 85–115°. Fractional recrystallization from methanol separated 0.44 g. which melted at 103–113° and 1.26 g. with m.p. 120–124°. Additional material, 0.79 g., m.p. 122–124°, was obtained from the mother liquor. The fraction melting between 120 and 124° was recrystallized by solution in propanol-2 and addition of water. It showed a correct analysis for N-(2-hydroxy-5-methylbenzy)-N-(3,5-dimethyl-2-hydroxybenzyl)methylamine, 2.05 g., 72% yield, m.p. 124–124.5°.

The 0.44-g. fraction melting between 103 and 113° was recrystallized twice from benzene–methanol: m.p. 121–121.5°. The analysis corresponded to that calculated for the diaminoalkylation product, 2,6-bis[N-(3,5-dimethyl-2-hydroxybenzyl)-N-methylaminomethyl]-*p*-cresol, yield 19% based on the oxazine.

Anal. Calcd. for $C_{29}H_{38}N_2O_3$: C, 75.29; H, 8.28; neut. equiv., 231. Found: C, 75.35; H, 8.42; neut. equiv., 234.

3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI).—Methylamine in 25% aqueous solution (54 ml., 0.40 mole) was added slowly with stirring to a cooled mixture of 37% aqueous formaldehyde (60 ml., 0.80 mole) and 150 ml. of purified 1,4-dioxane. *o*-Cresol (43.2 g., 0.40 mole) in 50 ml. of dioxane was added, and the mixture refluxed for 3 hr. at *ca.* 90°. The solvent was removed under vacuum at 30°, and 35 ml. of 6 *N* NaOH was added to the residue. It was extracted with saturated aqueous Na_2SO_4 *vs.* ether. Removal of the ether in a vacuum rotator left 65.18 g. of liquid product with a characteristic odor. A sample frozen over solid CO_2 melted at 35–38°, m.p. 37.5–38.5° after recrystallization from ethanol. Distillation (b.p. 80–90° at 0.3 mm.) gave 41% recovery.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.59; neut. equiv., 163. Found: C, 73.17; H, 7.99; N, 8.50; neut. equiv., 163.

3,4-Dihydro-3,6-dimethyl-2H-1,3-benzoxazine.—An 80% yield of liquid oxazine was obtained from *p*-cresol and methylamine by reaction under conditions similar to those above, followed by ether–10% KOH extraction. Stirring the liquid with cold propanol-2 induced crystallization. The crystals (m.p. 45–46°) were used to seed the supercooled liquid form. The compound readily sublimed to needles, m.p. 49–49.5°.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; neut. equiv., 163. Found: C, 73.60; H, 7.98; neut. equiv., 163.

The aqueous layer from the KOH extraction was neutralized with $NaHCO_3$. The solid which separated was washed on a filter with several small portions of methanol and then with 1 l. of hot water. The remaining solid (8.48 g., 7% yield, m.p. 156–157.5°) recrystallized from ethanol as prisms, m.p. 159°. It gave an undepressed mixture melting point with an authentic sample of N,N-bis(2-hydroxy-5-methylbenzyl)methylamine (Table I, 22).

Oxaziridines. I. The Irradiation Products of Several Nitrones[1]

JANET S. SPLITTER AND MELVIN CALVIN

Department of Chemistry, University of California, Berkeley, California

Received April 30, 1965

The properties and reactions of some oxaziridines resulting from the irradiation of the corresponding nitrones are described. The mechanism of the thermal reactions of the oxaziridines as inferred from substituent effects is discussed.

The investigation of the properties and reactions of 2-alkyl-3-aryl- and 2,3-diaryloxaziridines[2] has continued since the publication of the preliminary communication.[3] The N,α-diarylnitrones and corresponding oxaziridines chosen for study include a wide range of substituent effects. In this paper is given a description of the oxaziridines resulting from the irradiation of these nitrones and of end products resulting from further thermal reaction of the unstable 2,3-diaryloxaziridines. In the following papers of this series the photochemical reaction of the nitrones, the kinetics of the oxaziridine thermal reactions, as well as reactions of the oxaziridines with acids, iodine, and light, will be discussed.

The sensitivity of nitrones to light has been known for many years.[4] In 1910, Alessandri[4a] first reported the isolation of benzanilide and hydrolysis products from the irradiation of N,α-diphenylnitrone. During the study of the irradiation products of *o*-nitrostilbenes,[5] several nitrones were prepared and found to be photosensitive in solution. Following the report by

(1) For a short review, see O. Chapman, *Advan. Photochem.*, **1**, 410 (1963).
(2) A review, E. Schmitz, *Advan. Heterocyclic Chem.*, **2**, 83 (1963).
(3) J. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 65 (1958).
(4) (a) L. Alessandri, *Atti accad. nazl. Lincei, Mem. Classe-sci. fis. mat. nat. Sez.*, **19**, **2**, 122 (1910); *Chem. Zentr.*, **2**, 1043 (1910); *Chem. Abstr.*, **5**, 276 (1911); (b) O. Brady and A. McHugh, *J. Chem. Soc.*, **125**, 547 (1924); (c) L. Chardonnens and P. Heinrich, *Helv. Chim. Acta*, **32**, 656 (1949); (d) J. Landquist, *J. Chem. Soc.*, 2830 (1953).
(5) J. Splitter and M. Calvin, *J. Org. Chem.*, **20**, 1086 (1955).

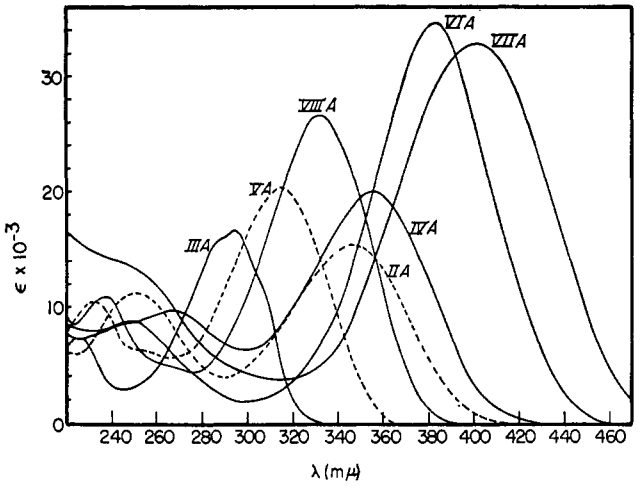


Figure 1.—Absorption spectra of the substituted nitrones in absolute ethanol. The spectrum of nitrone IA (not given) is similar to that of nitrone IIA.

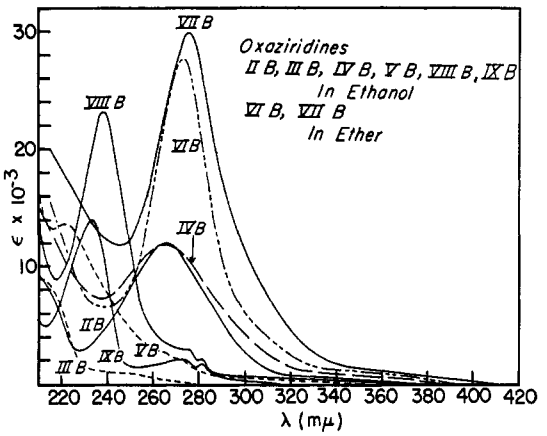
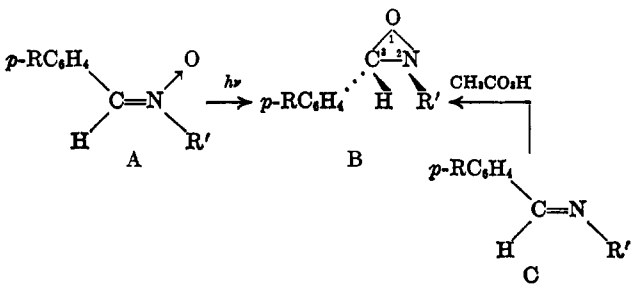


Figure 2.—Absorption spectra of the substituted oxaziridines. The spectrum of oxaziridine IB (not given) is similar to that of oxaziridine IIB.

Emmons[6a] of the synthesis of oxaziridines by the peracetic acid oxidation of certain imines, the possibility arose that oxaziridines might be early irradiation products of nitrones. At this time, others also considered the same possibility.[7]

In the prior communication,[3] three oxaziridines, IB, IIB, and IIIB, synthesized by the peracetic acid method were shown to be identical with the irradiation product of the corresponding nitrone (A). Although



I, R = NO_2; R′ = C_2H_5
II, R = NO_2; R′ = t-C_4H_9
III, R = H; R′ = t-C_4H_9
IV, R = NO_2; R′ = C_6H_5
V, R = H; R′ = C_6H_5
VI, R = $(CH_3)_2N$; R′ = C_6H_5
VII, R = $(CH_3)_2N$; R′ = m-$NO_2C_6H_4$
VIII, R = CH_3O; R′ = C_6H_5
IX, R = CH_3O; R′ = C_2H_5

the oxaziridines IVB, VB, VIB, and VIIB could not be synthesized by oxidation of the corresponding imine,[8] the properties and reactions of the first products of irradiation of the corresponding nitrones were consistent with the oxaziridine as an intermediate. Since that time, there have been other reports describing the isolation of oxaziridines formed by the irradiation of the corresponding nitrones.[9]

Absorption Spectra

The absorption spectra of the nitrones[10] used in this study are given in Figure 1, and the spectra of the corresponding oxaziridines in Figure 2. The 2,3-diaryloxaziridines were sufficiently stable in most solvents to obtain absorption spectra immediately after minimum irradiation of the corresponding nitrones.[11] The spectra of oxaziridines VIB and VIIB could not be obtained readily in ethanol because of extensive rearrangement. The spectral data reported by Kamlet and Kaplan[7a] in methanol after irradiation of three N,α-diarylnitrones (IVA, VA,[12] and VIIIA) were not of oxaziridines alone, but of mixtures of oxaziridines with rearranged products.[13]

For comparison, spectroscopic data on some of the oxaziridines[14] and corresponding oxiranes are given in Table I. The oxirane ring has been shown to be electron withdrawing with respect to aryl substituents.[15] In explanation, the second-order resonance structure **1** was considered to make an enhanced contribution to the excited state hybrid of *p*-methoxystyrene oxide.[15] The equivalent structures in the oxaziridine series are **2** and **3**.[16] In addition, structures **4**–**7** make important contributions, particularly to the excited state, as discussed below.

(6) (a) W. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956); **79**, 5739 (1957). Others[6b,c] also reported this reaction. (b) L. Horner and E. Jurgens, *Chem. Ber.*, **90**, 2184 (1957); (c) H. Krimm, *ibid.*, **91**, 1057 (1958).

(7) (a) M. Kamlet and L. Kaplan, *J. Org. Chem.*, **22**, 576 (1957); (b) F. Kröhnke, *Ann.*, **604**, 203 (1957).

(8) Because the peracetic acid oxidation method could be used only on acid-stable imines, giving stable oxaziridines, the method was useful for only a limited number of oxaziridines.

(9) (a) R. Bonnett, J. M. Clark, and A. Todd, *J. Chem. Soc.*, 2102 (1959); (b) L. H. Sternbach, B. A. Keochlin, and E. Reeder, *J. Org. Chem.*, **27**, 4671 (1962).

(10) Nitrone spectra have been discussed: (a) O. Wheeler and P. Gore, *J. Am. Chem. Soc.*, **78**, 3363 (1956); (b) see ref. 7a; (c) P. Brocklehurst, *Tetrahedron*, **18**, 299 (1962); (d) T. Kubota, M. Yamakawa, and Y. Mori, *Bull. Chem. Soc. Japan*, **36**, 1552 (1963); (e) T. Kubota and M. Yamakawa, *ibid.*, **36**, 1564 (1963). Ref. 10d reports a blue shift in nitrones. However, nitrones VIA and VIIA, which were not in their series, show a marked red shift in ethanol. This indicates increased electron density at the oxygen atom in the excited state with strongly electron-donating α-aryl groups.

(11) Oxaziridine VIIB was particularly susceptible to irradiation (Pyrex filter) giving rise to a product with λ_{max} of 316 mμ in benzene. The other oxaziridines were affected minimally under these conditions. In quartz, oxaziridine VIB in benzene was irradiated by direct sunlight to give a product with λ_{max} 313 mμ similar to the spectrum of 4-dimethylaminobenzanilide. Under the same conditions, IVB and VB were relatively unaffected. More details will be given in a later publication.

(12) Recently, the spectra of 2,3-diphenyloxaziridine (VB) in cyclohexane and in ethanol, taken immediately after irradiation of the nitrone, have been reported: K. Shinzawa and I. Tanaka, *J. Phys. Chem.*, **68**, 1205 (1964).

(13) This was due to the long irradiation time used, during which the thermal reaction was proceeding.

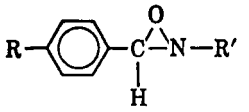
(14) Oxaziridines IIB and IIIB also were prepared by the method of Emmons.[6a]

(15) (a) L. A. Strait, D. Jambotkar, R. Ketcham, and M. Hrenoff, 9th International Conference on Spectroscopy, Lyons, France, 1961, Trans., Vol. 1–3, G. A. M. S., Paris, 1962, p. 125; (b) L. A. Strait, R. Ketcham, D. Jambotkar, and V. P. Shah, *J. Am. Chem. Soc.*, **86**, 4628 (1964).

(16) For similarity of spectra of oxiranes with corresponding aziridines, see N. H. Cromwell, F. H. Schumacher, and J. L. Adelfang, *ibid.*, **83**, 974 (1961); N. H. Cromwell, R. E. Bambury, and J. L. Adelfang, *ibid.*, **82**, 4241 (1960).

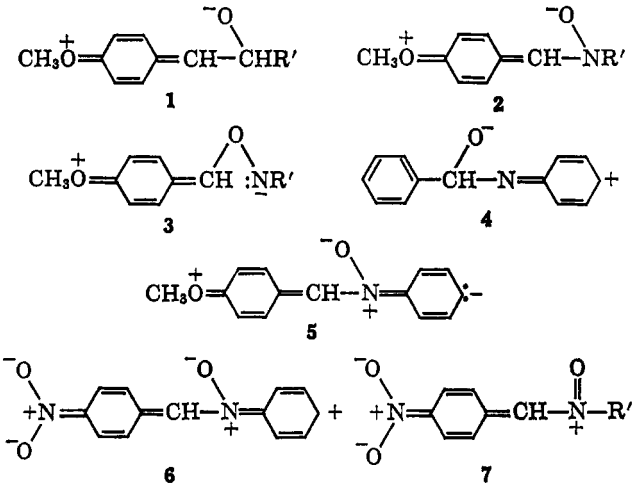
TABLE I

SPECTROSCOPIC DATA ON SOME SUBSTITUTED OXAZIRIDINES, OXIRANES,[a] AND AN AMINE IN ETHANOL



Compd.	R	R′	Substituent (K) band λ_{max}, mμ (ε)	Benzenoid (B) band[b] λ_{max}, mμ (ε)
IXB	CH_3O	C_2H_5	233 (14,000)	275 (2000), 282 (1700)
Oxirane	CH_3O	H	230 (12,400)[c]	275 (1700), 285 (1500)[c]
IIIB	H	t-C_4H_9	210 (9000)	249 (930)[d]
Oxirane	H	CH_3	217 (8000)[e]	247 (526)[e]
IIB	NO_2	t-C_4H_9	265 (12,000)[f]	
Oxirane	NO_2	H	274 (10,900)[g]	
VIIIB	CH_3O	C_6H_5	238 (23,200)	276 (3100), 282 (2100)
Oxirane	CH_3O	C_6H_5	238 (24,200)[h]	278 (1720), 285 (1400)[h]
VB	H	C_6H_5	222 (13,600)	265 (2800), 272 (2200)
Oxirane	H	C_6H_5	228 (23,500)[h]	267 (902)[h]
IVB	NO_2	C_6H_5	266 (11,800)	
Oxirane	NO_2	C_6H_5	274 (13,500)[h]	
Amine	H	C_6H_5	250 (12,600)[i]	294 (2100)[i]

[a] N is replaced by CH. [b] Where no data are given, this band is presumed to be submerged under the K band. [c] Ref. 15b, in hexane. [d] Ref. 6a. [e] T. Campbell, S. Linden, S. Godshalk, and W. G. Young, *J. Am. Chem. Soc.*, **69**, 880 (1947). [f] For comparison, nitrobenzene in EtOH has λ_{max} 260 mμ (ε 9500), 340 sh (160): A. Burawoy and E. Spinner, *J. Chem. Soc.*, 2557 (1955); P. Grammaticakis, *Bull. soc. chim. France*, 158 (1950). [g] Ref. 15b. [h] Ref. 15a. [i] E. A. Smirnov, *Sb. Statei Obsch. Khim., Akad. Nauk SSSR*, **2**, 1394 (1953).



In the 2-alkyloxaziridines, comparison of the K band of the 3-anisyloxaziridine (IXB) with the corresponding oxirane indicates the oxaziridine ring to be more electron withdrawing than the oxirane ring. This can be explained by structure **3** as well as **2** making a greater contribution to the excited state than to the ground state of IXB. However, in the 3-phenyloxaziridine (IIIB) the opposite appears to be true. Similar behavior has been observed in the corresponding imine and ethylene series.[17]

A bathochromic shift occurs in going from 2-alkyl- (IIIB) to 2-phenyloxaziridine (VB) just as occurs in the corresponding oxiranes. Also, the lack of greatly enhanced intensity in the 250-mμ region in VB compared with that in the corresponding N-phenylamine indicates little resonance interaction of the phenyl group with the unshared electrons on the ring nitrogen. Presumably, this interaction is inhibited by the steric requirements of the oxaziridine ring. In addition, there is more absorption in the 210–230-mμ region by the 2-phenyloxaziridines than by the 2-alkyloxaziridines (for example, IVB and IIB in Figure 2). This relationship is found also in the corresponding oxiranes,[15] indicating a contribution by the Ph–N–O electronic system,[18] **4**, similar to the Ph–C–O electronic system in oxiranes.

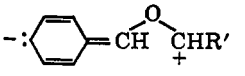
Long wave length absorption of low extinction is observed in the 2,3-diaryloxaziridines beyond that due to the K and B bands (Figure 2), and which has not been reported for the corresponding oxiranes. This absorption is comparable with that of the corresponding nitrones,[19] indicating some π-electron interaction between the two aryl groups across the oxaziridine ring. Structures **5**, **6**, and **7** are possible owing to participation of the nonbonding electrons on the nitrogen atom in the π-electron system. These cannot occur in the diaryloxiranes. Although **5** and **6** are written with double charge separations, they are also structures one would write for contributors to the hybrid of N,α-diarylnitrones to show conjugation throughout the molecule, Structure **7**, as well as the nitrophenyl chromophore. may make some contribution to oxaziridines IIB and IVB. Because of the stereochemistry of the oxaziridine molecule, the coplanar configuration necessary for these structures is difficult to attain. Thus their contributions to both ground and excited states might be expected to be small.[20]

The red shift (in ethanol) of the K band of the oxaziridine spectra is in accord with an increase of electron density on the ring oxygen atom in the excited state. Solvent effects on the long wave length band were somewhat difficult to assess because of the broadness of the band. However, the solvent effects on λ_{max} appeared to be similar to those of the corresponding nitrones. The extinction of this band increased with solvent polarity[21] and with strongly electron-donating or withdrawing groups in the 3 position. In general, as the extinction of this band increased, the extinction of the K band decreased. These effects indicate an increasing contribution to the excited state of forms **5** and **6** with increasing solvent polarity and substituent polarity.

Results

In Table II are given the yields of products from the irradiation of seven nitrones in various solvents and the half-times of the thermal decompositions of the unstable oxaziridines, IVB, VB, VIB, and VIIB. The N-alkyl-α-arylnitrones, IA, IIA, and IIIA, gave fairly stable oxaziridines, IB, IIB, and IIIB, but the N,α-diarylnitrones gave the unstable oxaziridines, the

(17) (a) A. Burawoy and J. Critchley, *Tetrahedron*, **5**, 340 (1959). (b) In the oxirane



appears to be of importance when R′ is *p*-$CH_3OC_6H_4$, C_6H_5, or alkyl.

(18) This observation bears particularly on the thermal rearrangements described later.

(19) There is the possibility that this absorption is due to some imine formed during the irradiation of the nitrone. However, repeated reirradiation of nitrone VIIA in acetone did not show a buildup of imine VIIC.

(20) For a steric effect in *cis*-stilbenes, see M. Calvin and H. Alter, *J. Chem. Phys.*, **19**, 765 (1951); H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 424.

(21) There was no increase in ethanol, presumably owing to hydrogen-bonding effects.

TABLE II

OXAZIRIDINES AND/OR THERMAL DECOMPOSITION PRODUCTS FROM THE IRRADIATION OF NITRONES AT 25°

Nitrone A	Solvent	Oxaziridine B, % active O_2[a]	Stability, $t_{1/2}$[b]	% yield Benzamide D	Formanilide E	Nitrone A	Hydrolysis products F[c]
I	C_2H_5OH	63[d]					
II	C_2H_5OH	91[e]					
III	C_2H_5OH	90[f]					
IV	C_2H_5OH	72[g]	1 hr.	31	19	...	39
	CH_3COCH_3		27 hr.	78	...	...	12
	C_6H_6		48 hr.	72	...	...	23
V	C_2H_5OH	75[g]	2 hr.	11	69	Trace	19
	CH_3COCH_3		63 hr.	85	7	Trace	8
	C_6H_6		66 hr.	74	...	Trace	10
	i-C_8H_{18}		180 hr.	72	...	Trace	10
VI	C_2H_5OH		2 sec.	...	86	4	5
	CH_3COCH_3		5 hr.	47	21	20	Trace
	C_6H_6		10 hr.[h]	38[h]	43[h]	14[h]	Trace
VII	C_2H_5OH		5 sec.	...	5	94[i]	...
	CH_3COCH_3		1.6 hr.	...	...	69	25[i]
	C_6H_6		1.5 hr.[h]	12	...	84	Trace

[a] Active oxygen contents were determined on ethanol solutions of nitrones immediately after irradiation. Under these conditions, thermal decomposition of oxaziridines VIB and VIIB occurred before the determination could be made. [b] Calcd. from the observed first-order rate constant. [c] Precautions were taken to remove water from the solvents, and all glassware was dried at 100°. [d] In acetonitrile, isolated yield was 35%. [e] Isolated yield was 40%. [f] 97% nitrone re-formed by heating the oxaziridine solution. [g] Not isolated because these oxaziridines were unstable at room temperature; reaction was allowed to continue to completion at 25°. [h] The yields of products varied considerably, depending on the reaction vessel surface. The yields and rate given are for a more concentrated solution (10^{-4} M) with low surface-to-volume ratio. In dilute solutions yields were more variable, depending on the acidity of the surface. An example is the thermal decomposition of a 10^{-5} M solution in an aged Pyrex cell, which had not been in contact with acid or basic solution: $t_{1/2}$ = 1.5 hr.; D, 12% yield; E, 78% yield; A, 10% yield. [i] The nitrone re-formed initially had λ_{max} 389 mμ (ε 28,500) which rapidly changed to nitrone VIIA, λ_{max} 400 mμ (ε 32,800). [j] This hydrolysis is probably due to SN2 reaction with water since addition of water to acetone increased rate and amount of nitrone formation and decreased amount of hydrolysis. [k] This value also subject to variation, similar to VIB in benzene.

stability varying according to substituent and solvent. Oxaziridines IVB and VB in ethanol gave a high percentage of active oxygen content, measured by release of iodine from potassium iodide. These oxaziridines were very active oxidizing agents for potassium iodide, reacting instantaneously. In contrast, the 2-alkyl-3-aryloxaziridines IB, IIB, and IIIB required heat for the oxidation to be complete.[6a] Oxaziridines VIB and VIIB were highly reactive in ethanol, rearranging before active oxygen determinations could be made.

The unstable oxaziridines reacted further in the dark to products that varied in amounts with different solvents. For example, in Figure 3 are shown the spectra of nitrone VIA, oxaziridine VIB, and all the products resulting from oxaziridine VIB. Rearrangement to amides predominated in the thermal decomposition of oxaziridines IVB, VB, and VIB. Rearrangement involving aryl migration was favored by the protic solvent, ethanol, and by the electron-releasing substituent in oxaziridine VIB. There were considerable amounts of hydrolysis products in the reactions of oxaziridines IVB and VB. Imine formation occurred to a minor extent. Oxaziridine VIIB isomerized to the nitrone in high yields in all the solvents used. Oxaziridine VIB also isomerized to the nitrone but to a small extent.

The oxaziridine thermal reactions were very fast in ethanol compared with the reactions in the aprotic solvents. In all of the solvents, oxaziridine IVB reacted at a greater rate than oxaziridine VB, but much greater than either of these were the rates of reaction of oxaziridines VIB and VIIB. The dilute benzene solutions of the unstable oxaziridines were very sensitive to traces of acid on the vessel wall. Packing the reaction vessel with glass wool either before or after irradiation of the nitrone did not affect the course of the thermal reaction. Catalysis of the aryl migration in the thermal reaction of oxaziridine VIB occurred to a great extent, resulting in large variations in the half-time of the reaction. With oxaziridines IVB and VIIB, there was lesser but appreciable catalysis of the over-all reactions. Only slightly affected were the thermal decomposition of oxaziridine VB and the formation of benzanilide VID from oxaziridine VIB. The strongly catalytic effect of acid has been noted[22] in the solvolysis of *p*-methoxyneophyl toluenesulfonate in benzene solution, compared with aprotic but basic solvents.

Discussion

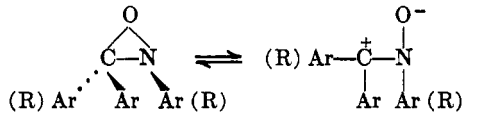
In the three-membered oxaziridine ring, relief of ring strain provides driving force for bond cleavage as

(22) S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Am. Chem. Soc.*, **83**, 618 (1961).

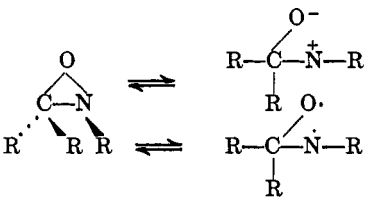
in other three-membered ring systems such as diaziridines,[2] aziridines,[23] oxiranes,[24] and cyclopropanes.[25] The stability of the oxaziridine ring and the nature of the cleavage depend on the kind of substituents present[6] and the solvent used.[3] Previously characterized oxaziridines, which have been sufficiently stable to be isolated, have had alkyl groups on either or both the carbon and nitrogen atoms of the ring.[6,9,26] With aryl groups on both these atoms, the stability is decreased markedly so that they are observed only in solution.[3,7a,12,27] Similar substituent effects on stability have been noted for diaziridines,[2] oxiranes,[15b,24] cyclopropanes,[28] and peroxides.[29]

In a heterolytic bond fission of the oxaziridine ring, the oxygen atom can support a developing negative charge, and either the carbon or nitrogen atoms a developing positive charge. In general, the ionic C–O bond cleavage, leading to nitrone formation or hydrolysis occurs when there is an alkyl group on the nitrogen atom and an aryl group on the carbon atom,[6a,b,9b] or an aryl group on the nitrogen atom and two aryl groups on the carbon atom.[27] This is the result of the

C–O bond cleavage



N–O bond cleavage



Ar = aryl, R = alkyl, H

greater stabilization of the developing carbonium ion relative to the developing nitrogen cation.[6a] When there is one aryl group on each of the carbon and nitrogen atoms, ionic C–O bond fission occurs only with a strongly electron-releasing substituent on the C-phenyl and a strongly electron-withdrawing substituent on the N-phenyl.[3]

The N–O bond cleavage, which can be heterolytic or homolytic depending on conditions and substituents,[6a] is the preferred one when there are alkyl groups on both the carbon and nitrogen atoms,[6a,c] alkyl or acyl groups on the carbon atom and aryl on the nitrogen atom,[6c,7b] or one aryl group on each of the carbon and nitrogen atoms (with the exception noted above).[3,4c] Under acid conditions, these oxaziridines undergo hydrolytic reactions resulting from heterolytic N–O bond fission.[6a] The liquid phase thermal reactions of the alkyl-substituted oxaziridines giving rise to amides and complex reactions are thought to be chain reactions involving homolytic cleavage of the N–O bond.[6a] In the vapor phase, these alkyloxaziridines undergo rearrangement to amides by a mechanism probably involving biradical formation.[6a] The 2-aryloxaziridines rearrange to amides at much lower temperatures,[3,6c] but, up to the present time, there has been little mechanistic investigation carried out. Emmons[6a] also has found that oxaziridine IIIB undergoes one electron-transfer reaction with ferrous ion, involving homolytic fission of the N–O bond in contrast to the C–O bond cleavage that this oxaziridine normally undergoes in polar solvents.

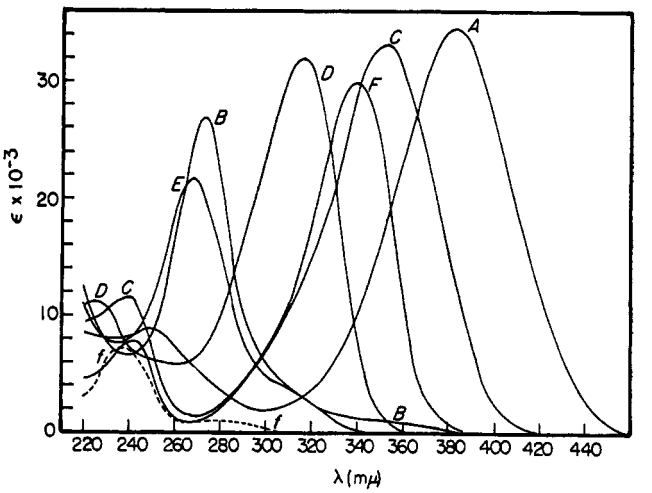


Figure 3.—Absorption spectra in absolute ethanol except where noted: (A) α-(*p*-dimethylaminophenyl)-N-phenylnitrone; (B) 3-(*p*-dimethylaminophenyl)-2-phenyloxaziridine (in ether); (C) N-(*p*-dimethylaminobenzylidene)aniline; (D) 4-dimethylaminobenzanilide; (E) N-(*p*-dimethylaminophenyl)formanilide; (F) *p*-dimethylaminobenzaldehyde; and (f) N-phenylhydroxylamine.

The availability of the relatively unstable 2,3-diaryloxaziridines by photochemical synthesis has permitted their thermal decompositions to be studied. The kinds of products formed in the various solvents varied with the substituents present on the oxaziridine ring (Table II) and were indicative of the type of mechanism involved. Oxaziridines IVB, VB, and VIB represent oxaziridines with substituent effects ranging from strongly electron-releasing (VIB) to strongly electron-withdrawing (IVB) in the 3-aryl system. In all three oxaziridines, N–O bond cleavage predominated, giving rise to rearrangement to amides and hydrolytic reactions. The developing nitrogen cation from a heterolytic cleavage as well as a nitrogen radical from a homolytic cleavage has resonance stabilization by the N-phenyl group that is not available in the N-alkyloxaziridines. Added driving force for the 1,2 shift of the group or hydrogen on the carbon atom to the nitrogen atom[30] in the rearrangement to amides is gained from the negative charge generated on the oxygen atom in an ionic cleavage, or from the oxygen radical in a homolytic cleavage, in forming the double

(23) R. C. Elderfield, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 61–77.

(24) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(25) R. Breslow in "Molecular Rearrangements," part 1, P. de Mayo, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p. 233.

(26) Oxaziridines with hydrogen only on the carbon or nitrogen atom were not very stable[6a]: E. Schmitz, *Z. Chem.*, **3**, 190 (1963).

(27) A 2,3,3-triaryloxaziridine was presumed to be a very short-lived intermediate in the formation of nitrone: A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963). Reference 7b also presumes an oxaziridine to be an intermediate.

(28) (a) W. Doering and W. Roth, *Angew. Chem. Intern. Ed. Engl.*, **2**, 115 (1963); (b) R. J. Ouellette and D. L. Shaw, *J. Am. Chem. Soc.*, **86**, 1651 (1964).

(29) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, footnote, p. 473.

(30) 1,2 shifts to electron-deficient nitrogen, similar to 1,2 shifts to electron-deficient carbon occur in Beckmann, Schmidt, Curtius, and similar type rearrangements: J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 159–166; P. A. S. Smith, ref. 25, p. 457.

bond of the carbonyl group of the amide. The *p*-nitro substituent in oxaziridine IVB should facilitate ionic cleavage similar to its effect in the ionization of substituted benzoic acids (ρ 1.00),[31] phenylacetic acids (ρ 0.5),[31] and peresters (ρ 1.34).[32] The rate of thermal decomposition of oxaziridine IVB was greater than that of oxaziridine VB in the solvents used. The *p*-dimethylamino substituent should also facilitate ionic cleavage by increasing neighboring-group participation of the aryl group in the ionization.[33] The rate of the thermal decomposition of oxaziridine VIB was much greater than that of oxaziridine VB, particularly in the protic solvent, ethanol. Participation by an aryl group is strongest with electron-releasing substituents in highly ionizing solvents.[33] In ethanol, aryl migration occurred to a great extent, with the highest yield of the corresponding formanilide obtained from oxaziridine VIB (86%) and the lowest from oxaziridine IVB (19%). This migratory aptitude is similar to that commonly found in ionic rearrangement reactions[34] where the transition states or intermediates have been stabilized by neighboring aryl participation.[33] Phenyl participation usually is weak in the solvent ethanol, requiring more strongly ionizing solvents such as formic acid.[35] However, in oxaziridines there is driving force for ionization from relief of ring strain and migration is facilitated by the developing negative charge on the oxygen atom. In the aprotic solvents, ionizing conditions were not sufficient to effect rearrangement of the aryl group in oxaziridines IVB and VB and hydride migration resulted. There was also less hydrolysis in the aprotic solvents.

With the strongly electron-releasing substituent in oxaziridine VIB, aryl migration was expected as the major reaction in all the solvents, since *p*-anisyl migration was found to result in the solvolysis of *p*-methoxyneophyl toluenesulfonate in many kinds of solvents.[22] However, considerable benzanilide VID was formed in the aprotic solvents.

The rate of formation of the benzanilide VID was not very sensitive to solvent polarity, whereas the formanilide VIE and nitrone VIA rates were quite sensitive. This formation of benzanilide VID could be the result of a competing hydride migration of the "no mechanism" reaction type.[36] The hydride migration would be of more importance in the aprotic solvents since these solvents do not have the ionizing conditions favorable for the delocalization of charge that occurs in aryl participation. Collins, *et al.*,[37] have shown that both hydride and aryl migration can occur simultaneously, and that the ratio varies depending on solvent acidity. The migrating *p*-dimethylaminophenyl group as a nucleophile competes with the nucleophilic solvent, acetone, and was less effective in that solvent.

In the oxaziridine rearrangement as in epoxide–carbonyl rearrangements,[38] stereochemistry of the oxaziridine molecule requires a rotation about the C–N single bond in order for the migrating group to enter from the backside of the leaving oxygen as the N–O bond cleaves. Thus, in order for the neighboring aryl participation to occur, there must be considerable stretching of the N–O bond in the transition state. Under less ionizing conditions, there would be expected either less cleavage in the transition state leading to simultaneous bond breaking and bond formation or a "tight ion pair." A strictly concerted mechanism would have a high energy barrier because of bond deformations required.[39] The "tight ion pair" mechanism relatively free of directional requirements is of the "no mechanism" reaction type[36] and may very well account for the hydride migration in oxaziridines VB and VIB in the aprotic solvents. The rates of formation of both benzanilide VD and VID were least sensitive to solvent polarity which is also in accord with the "no mechanism" reaction type.[36] The other extreme of the "no mechanism" category is a homolytic-type cleavage,[36] which would be facilitated by electron-releasing substituents in the 3-aryl system in nonpolar solvents. The homolyses of the O–O bond in peroxides[40] and of the N–N bond in hydrazines[41] and tetrazanes[42] occur readily with a substituent effect of negative ρ value. In a homolytic-type cleavage of the N–O bond, the *p*-dimethylaminophenyl group would not be expected to migrate readily,[43] thus allowing hydrogen migration which is known to occur in the pyrolysis of cyclopropanes[39] and alkyloxaziridines.[6a] The action of light on oxaziridines VIB and VIIB in aprotic solvents[11] is indicative of a possible homolytic-type cleavage of the N–O bond in these compounds.

Oxaziridine VIIB gave nitrone VIIA as the major product of thermal decomposition in all the solvents used. Oxaziridine VIB, with the same strongly electron-releasing group on the carbon atom of the ring as in oxaziridine VIIB, gave only small amounts of nitrone VIA. Thus, the *m*-nitrophenyl group on the nitrogen atom has a pronounced inductive effect, which is in accord with an ionic cleavage of the C–O bond. It has destabilized the developing nitrogen cation relative to the developing carbonium ion. This ionic cleavage occurred readily in the aprotic solvents, but was extremely rapid in ethanol.

The thermal instability of the 2,3-diaryloxaziridines appears to be due mainly to the polar effects of the aryl substituents contributing to ionic bond cleavage of the oxaziridine ring. This is in contrast to the probable homolytic bond cleavage in the thermal decomposition of alkyloxaziridines.[6a] Further information on the mechanism of the thermal decomposition will be obtained from more detailed kinetic and thermodynamic data.

(31) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 189–190; (b) A. Fischer, D. R. Mann, and J. Vaughan, *J. Chem. Soc.*, 1093 (1961).

(32) P. D. Bartlett and J. L. Kice, *J. Am. Chem. Soc.*, **75**, 5591 (1953).

(33) S. Winstein, M. Brown, K. C. Schreiber, and A. M. Schlesinger, *ibid.*, **74**, 1140 (1952).

(34) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 590–597.

(35) S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *J. Am. Chem., Soc.*, **75**, 147 (1953).

(36) S. J. Rhoads, ref. 25, p. 655.

(37) C. J. Collins, W. T. Rainey, W. B. Smith, and I. A. Kaye, *J. Am. Chem. Soc.*, **81**, 460 (1959).

(38) R. N. McDonald and P. A. Schwab, *ibid.*, **85**, 4004 (1963).

(39) S. W. Benson, *J. Chem. Phys.*, **34**, 521 (1961).

(40) (a) C. G. Swain, W. Stockmayer, and J. Clarke, *J. Am. Chem. Soc.*, **72**, 5426 (1950); (b) A. Blomquist and A. J. Buselli, *ibid.*, **73**, 3883 (1951).

(41) H. Wieland, *Chem. Ber.*, **48**, 1078, 1091 (1915); **55**, 1804 (1922).

(42) W. Wilmarth and N. Schwartz, *J. Am. Chem. Soc.*, **77**, 4543, 4551 (1955).

(43) The *p*-methoxyphenyl group has a low migratory aptitude compared to *p*-nitrophenyl in homolytic rearrangements: D. Y. Curtin and J. C. Kauer, *J. Org. Chem.*, **25**, 880 (1960); C. Rüchardt, *Chem. Ber.*, **94**, 2609 (1961).

Experimental Section

All spectrophotometric and kinetic measurements were carried out at 25° using a Cary recording spectrophotometer, Model 14.

Materials.—Baker and Adamson reagent grade silicic acid was used. Reagent grade benzene and spectrograde isooctane (2,2,4-trimethylpentane) were distilled over lithium aluminum hydride. Reagent grade acetone was distilled successively from anhydrous potassium carbonate and activated Linde 4A Molecular Sieves. Absolute ethanol was used without further purification. In the kinetic experiments, the solvents were used immediately after distillation. The glassware was rinsed with acetone and distilled water and dried at 100°. Glassware that had been in cleaning solution or in contact with aqueous sulfuric acid was not used.

α-(*p*-Dimethylaminophenyl)-N-(*m*-nitrophenyl)nitrone (VIIA).—Numerous experiments were carried out using 0.1 g. of *m*-nitrophenylhydroxylamine[44] and 0.12 g. (20% molar excess) of 4-dimethylaminobenzaldehyde. The product from each experiment was chromatographed on heavy MgO with benzene as eluent. The eluted orange band was treated with 3 vol. of petroleum ether (b.p. 30–60°) and the dark red crystals were filtered. With no solvent, and when heated at 100° for 45 min., nitrone was obtained, m.p. 165–168° dec., yield 0.047 g. (25%). A lower and a higher temperature for 45 min. and a longer time (4 hr. at 100°) gave smaller yields. The best yield was obtained after dissolving the starting materials in 7.5 ml. of 95% ethanol, using 0.1 g. of 4-dimethylaminobenzaldehyde instead of 0.12 g., pouring the solution into an evaporating dish, and allowing the residue to stand for 3 days after the solvent had evaporated. The yield of nitrone was 0.096 g. (52%), m.p. 165–168° dec.

For analysis, 0.4 g. of crude material, melting about 160°, was dissolved in 80 ml. of benzene and the nitrone was precipitated by addition of 80 ml. of petroleum ether. This procedure was repeated twice, yielding a product melting at 170–172° dec.: $\lambda_{max}^{C_6H_6}$ 390 mμ (ε 27,300), λ_{max}^{ether} 386 mμ (ε 27,300), λ_{max}^{EtOH} 402 mμ (ε 32,800), $\lambda_{max}^{acetone}$ 390 mμ (ε 28,500), $\lambda_{max}^{CH_3CN}$ 388 mμ, λ_{max}^{DMSO} 400 mμ.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.37; H, 5.52; N, 14.92.

This nitrone forms a 1:1 complex with *m*-nitrophenylhydroxylamine, m.p. 129–130°.

N-(*p*-Dimethylaminophenyl)formanilide (VIE).—A solution of 150 mg. of α-(*p*-dimethylaminophenyl)-N-phenylnitrone (VIA)[5] in 450 ml. of absolute ethanol was irradiated in seven portions, each one for 4 min., in a water-cooled glass container 1 cm. thick, equidistant between two DxB photospots[45] 20 in. apart. After removal of the solvent, the remaining oil solidified, m.p. 65–68°, yield 145 mg. (97%). This was dissolved in 10 ml. of 95% ethanol and precipitated by the addition of 30 ml. of water, m.p. 72–74°, yield 109 mg. After redissolving in 5 ml. of 95% ethanol and decolorizing with charcoal, the filtrate was treated with 10 ml. of water and the solid was filtered, m.p. 74–75°, yield 66 mg., λ_{max}^{EtOH} 268 mμ (ε 21,800).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66; mol. wt., 240. Found: C, 75.06; H, 6.58; N, 11.60; mol. wt., 232 (cryoscopic method in diphenyl).

Additional product was obtained from the filtrate, as well as a small amount of *p*-dimethylaminobenzaldehyde. The infrared spectrum of this formanilide was similar to that of diphenylformamide (VE).[46]

4-Dimethylaminodiphenylamine.—A solution of 30 mg. of N-(*p*-dimethylaminophenyl)formanilide (VIE), 3.5 ml. of 95% ethanol, 2 drops of water, and 1 pellet of 85% potassium hydroxide (0.12 g.) was heated at boiling for 15 min The solution then was diluted with 10 ml. of water. The resulting precipitate was filtered: m.p. 126–127°, unchanged on admixture with authentic material[47]; yield 23.5 mg. (89%); λ_{max}^{EtOH} 290 mμ. The formanilide also could be hydrolyzed with alcoholic sulfuric acid.

The formanilide obtained from irradiation of 46 mg. of nitrone VIA was hydrolyzed as described above and then heated with 5 ml. of 88% formic acid for 15 min. The residue from evaporation of the solution was dissolved in a small amount of absolute ethanol, treated with charcoal (no heat), and filtered. Water was added to the filtrate until it became cloudy. The resulting precipitate was filtered, m.p. 70–73°, yield 15 mg. A mixture melting point with the formanilide obtained from irradiation of nitrone showed no depression; absorption spectra were identical.

4-Dimethylaminobenzanilide (VID).—A solution of 400 mg. of nitrone VIA in 900 ml. of anhydrous ether was irradiated in 12 portions for 6 min. each in the apparatus described above. After standing for 5 days at room temperature (reirradiated on the second and third days) and evaporation of the ether, 20 mg. of feathery crystals was collected: m.p. 177–180°, unchanged on admixture with authentic material[48]; λ_{max}^{EtOH} 316 mμ (ε 32,000). Suspension of the remainder of the solid in a small amount of ethanol yielded 134 mg., m.p. 177–179°. All the filtrate and some dark-colored material were diluted in ethanol and determined spectrophotometrically for additional benzanilide VID, 41 mg., total yield 195 mg. (49%); there was also 43 mg. of benzaldehyde VIF (17%) and 78 mg. of formanilide VIE (19.5%). A similar experiment in acetone yielded 40% benzanilide VID, 25% formanilide VIE, 4% nitrone VIA, and 4% hydrolysis products. In both experiments, the nitrone formed in the reactions was reirradiated.

For a similar experiment in benzene, a different procedure was used. A solution of 16 mg. of nitrone VIA in 75 ml. of benzene, freshly distilled over $LiAlH_4$, in a 250-ml. glass-stoppered flask, was irradiated for 3 min. by bright sunlight. The nitrone formed in the dark thermal reaction was reirradiated on the second and third days. After 5 days at room temperature, the benzene was evaporated and the residue was treated twice with 5 ml. of isooctane or light petroleum ether with a slight amount of heat. When cool, the isooctane portions were decanted and evaporated, leaving an oil. The oil was dissolved in ethanol and determined spectrophotometrically; it contained 7.8 mg. of formanilide VIE (49%) and 1.5 mg. of benzanilide VID. The residue from the isooctane washings was also dissolved in ethanol and determined spectrophotometrically: 5.6 mg. of VID, total yield (44%); on evaporation of the ethanol, the melting point and mixture melting point were unchanged from an authentic sample.

N,N-Diphenylformamide (VE).—The N,α-diphenylnitrone (VA)[10a] used was washed with 15% NH_4OH and dried. A solution of 50 mg. of nitrone VA in 460 ml. of absolute ethanol was irradiated in seven portions, as described above, for 20 min. each. After standing for 2 days, and after evaporation of the ethanol, the residue was treated with 50 ml. of petroleum ether. This was decanted from the insoluble part and chromatographed on a column (3.5 × 1.8 cm.) of silicic acid–SuperCel (2:1), with benzene as eluent.

The first fraction contained the material from the yellow band along with some N,N-diphenylformamide. The λ_{max}^{EtOH} of the yellow material was approximately 415 mμ. This changed to 540 mμ in ethanolic sulfuric acid and reverted to 415 mμ when neutralized. Fractions 2–4 yielded 22 mg. of VE, m.p. 57–60°. The column was immediately washed with ethanol, the solvent was evaporated, and petroleum ether was added to the residue. This was decanted from the insoluble material and evaporated, giving 4.5 mg. of VE, m.p. 53–59°, total yield 53%. A second petroleum ether extraction of the original residue yielded 1.5 mg. of benzanilide, m.p. 148–153°; further extraction with benzene yielded 1.2 mg., m.p. 100–140°; total yield 5.4%. The crude VE was recrystallized from ethanol–water, m.p. 67–68°, unchanged on admixture with an authentic sample.[49] Hydrolysis of VE resulted when a solution of 3 mg. in 1 ml. of EtOH and 2 drops of water with 1 pellet of KOH was heated for 20 min. After dilution with water, the diphenylamine was filtered and further purified from ethanol–water, m.p. 50–51°; admixture with an authentic sample showed no depression.

A portion of the original solution before isolation of the products showed about 12% unchanged nitrone VA by spectrophotometric determination. When this portion was heated with 1 drop of concentrated H_2SO_4 for 1 hr. just below the boiling point, the amount of diphenylamine found spectrophotometrically indicated a 65–68% yield of VE in the original solution. Hydrolysis products accounted for the remainder.

Benzanilide (VD).—A solution of 7 mg. of nitrone VA in 70 ml. of isooctane was irradiated for 20 min. between two DxB lamps, as described above. After standing for 1 month, the solution was chromatographed on a column, 1.8 × 2.5 cm., of silicic acid–SuperCel (2:1). With benzene as eluent, three fractions containing benzanilide were obtained. After evaporation of the benzene, there was obtained 4.4 mg., m.p. 156–159°

(44) K. Brand and A. Modersohn, *J. prakt. Chem.*, **120**, 160 (1929).
(45) General Electric Co.; previously RSP2.
(46) F. Pristera, *Anal. Chem.*, **25**, 844 (1953).
(47) O. Fischer and L. Wacker, *Chem. Ber.*, **21**, 2609 (1888).
(48) G. Lockermann and W. Neumann, *ibid.*, **80**, 310 (1947).
(49) A. Henninger, *ibid.*, **8**, 1196 (1875).

(identified by undepressed mixture melting point and absorption spectrum). An additional 0.6 mg. of benzanilide was present in ethanol washings of the evaporating dishes as determined spectrophotometrically, total yield 5 mg. (72%).

When a small amount of the concentrated solution before chromatography was heated with 1 drop of concentrated H_2SO_4 and 4 ml. of ethanol, there was essentially no spectroscopic evidence of the presence of diphenylamine.

A similar experiment in benzene gave a 74% yield of benzanilide, both isolated and determined spectrophotometrically.

A similar experiment in acetone was carried out. After standing 9 days, the solution was evaporated and the residue was extracted with light petroleum ether. A 75% yield of benzanilide was obtained. There was spectroscopic evidence for a 5% yield of formamide VE.

N-(*p*-Nitrophenyl)formanilide (IVE).—A solution of 1.3 g. of 4-nitrodiphenylamine[50] in 70 ml. of 90% formic acid was heated 4 hr. at 60° and then al'owed to stand 6 days at room temperature. The absorption spectrum indicated a 78% yield of the desired formamide. When the solution was concentrated, crystals of the amine precipitated, yield 0.86 g., m.p. 130–132°. The filtrate was evaporated to dryness and the residue was taken up in benzene and chromatographed on a column (11 × 1.8 cm.) of 8 g. of silicic acid and 4 g. of SuperCel. The orange band of the amine was eluted with benzene; after evaporation of the solvent, there was obtained 0.10 g.; total recovered amine was 0.96 g. (74%). Six fractions were taken at the top of the orange band and above, which yielded oils when the benzene was evaporated. After several days, the oils solidified when seeded. Fractions 3–5 were combined, weight 0.160 g. This product was further purified by solution in 13 ml. of absolute ethanol and the addition of 17 ml. of water. The precipitate, which soon formed, was filtered and dried *in vacuo* at 25°: yield 0.122 g.; m.p. 75–76°; λ_{max}^{EtOH} 312 mμ (ε 11,300), 228 mμ (ε 13,900), λ_{min}^{EtOH} 265 mμ (ε 3600). After the addition of 50 ml. of water to the filtrate, 0.028 g. of additional product, m.p. 75–76°, was obtained; the total yield was 0.150 g. (10%).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46, H, 4.16; N, 11.57. Found: C, 64.42; H, 4.11; N, 11.43.

The first crystallization of this compound was effected by dissolving the oil in petroleum ether and chilling the solution on Dry Ice until a precipitate formed. After the petroleum ether was decanted, the solid was air dried. The melting point was 50–56° after 1 day, but 2 months later was 74–75°. This compound forms resinous material in diethyl ether.

A solution of 20 mg. of the formanilide IVE in 13 ml. of 95% ethanol and 2 drops of concentrated H_2SO_4 was allowed to stand 1 week. Then 27 ml. of water was added and the precipitate was filtered. The yield of amine was 13 mg., m.p. 126–127°; the mixture melting point with 4-nitrodiphenylamine showed no depression.

Irradiation of α-(*p*-Nitrophenyl)-N-phenylnitrone (IVA) in Ethanol.—A solution of 20 mg. of nitrone IVA in 350 ml. of absolute ethanol was irradiated in 70-ml. portions, 2 min. each, as described above. After the solution stood for 2 months, it was evaporated. The residue was treated with two 250-ml. portions of petroleum ether. The extract was chromatographed on a column of 6 g. of silicic acid and 3 g. of SuperCel, with benzene as eluent. The absorption spectrum of the eluted first yellow band was similar to that of the corresponding first fraction of the irradiated nitrone VA solution in ethanol. The second yellow band was of 4-nitrodiphenylamine, m.p. 121–124° after elution and evaporation of the benzene. The yield of the amine was 1.4 mg. with 0.73 mg. more determined spectrophotometrically from less pure solid; total yield was 12%. Ether was used to elute the N-(*p*-nitrophenyl)formanilide from the column. Determined spectrophotometrically, the yield of this was 4.3%.

The petroleum ether insoluble residue was dissolved in benzene and chromatographed on a very short silicic acid–SuperCel column with benzene as eluent. After evaporation of the solvent, 4.9 mg. of *p*-nitrobenzanilide was obtained, m.p. 211–213°, no depression of a mixture melting point with an authentic sample.[51] From spectrophotometric determination of other fractions, an additional 1.95 mg. of *p*-nitrobenzanilide was obtained. The total yield was 34%.

Other experiments showed that, if the irradiated solution was worked up after 1 week of standing, approximately the same yield of *p*-nitrobenzanilide was obtained. In addition, there was a 16–18% yield of N-(*p*-nitrophenyl)formanilide, but no 4-nitrodiphenylamine. Hydrolysis of the formanilide IVE with sulfuric acid in ethanol at 75° for 1 hr. gave 4-nitrodiphenylamine. By subtracting the absorption spectrum of the known amounts of formanilide IVE and benzanilide IVD from the absorption spectrum of the solution before evaporation of the ethanol, the remaining absorption approximated that of *p*-nitrobenzaldehyde. The corresponding amount of N-phenylhydroxylamine that should be present accounted for the difference. *p*-Nitrobenzaldehyde could not be isolated after the irradiated solution was evaporated. There was dark-colored material at the top of the column after elution with benzene.

If the ethanolic solution of nitrone IVA was allowed to stand 24 hr. before irradiation, or if all glassware contacting the solution was not previously rinsed with dilute ammonium hydroxide and distilled water, the yields of both N-(*p*-nitrophenyl)formanilide and *p*-nitrobenzanilide were decreased and that of *p*-nitrobenzaldehyde increased.

***p*-Nitrobenzanilide (IVD).**—A solution of 40 mg. of nitrone IVA in 350 ml. of reagent grade acetone was irradiated as above in five portions for 3 min. each. After standing 1 week, the acetone was evaporated, leaving crystals in a small amount of water. The filtered solid (29 mg.) was purified by dissolving in benzene and chromatographing on a 1 cm. long column of silicic acid–SuperCel with benzene as eluent: yield 27.5 mg.; m.p. 213–214°, unchanged on admixture with an authentic sample of IVD; λ_{max}^{EtOH} 242 mμ (ε 16,500), 292 mμ (ε 9200). Another 2.5 mg. was obtained by spectrophotometric determination from ethanol washings of the evaporating dish and filter funnel. Total yield was 30 mg. (75%). The ultraviolet absorption spectrum of the cloudy aqueous filtrate indicated the presence of *p*-nitrobenzaldehyde. Evaporation of this filtrate yielded 5 mg. of resinous material. A similar experiment in benzene gave a 72% yield of *p*-nitrobenzanilide.

2-Ethyl-3-(*p*-nitrophenyl)oxaziridine (IB).—A solution of 10 mg. of N-ethyl-α-(*p*-nitrophenyl)nitrone (IA)[52] in 70 ml. of acetonitrile was irradiated, as above, between two DxB photospots for 1 hr. Upon evaporation of the solvent a light yellow oil remained. The infrared and ultraviolet absorption spectra were identical with those of the oxaziridine obtained by peracetic acid oxidation of the corresponding imine.[6a] The yield of oxaziridine was 35%, with the remainder polymerized. The oil gradually polymerized upon standing and the solid polymer was insoluble in most solvents.

Irradiation of nitrone IA in benzene gave mostly polymer. When nitrone IA was irradiated in absolute ethanol there was considerable hydrolysis to *p*-nitrobenzaldehyde was well as polymerization.

A solution of 7 mg. of nitrone IA in 62 ml. of absolute ethanol was irradiated as above for 20 min. and then immediately analyzed for active oxygen content.[53] This was found to be 63%.

2-(*t*-Butyl)-3-(*p*-nitrophenyl)oxaziridine (IIB).—A solution of 30 mg. of N-(*t*-butyl)-α-(*p*-nitrophenyl)nitrone(IIA)[6a] in 204 ml. of absolute ethanol was irradiated between two DxB photospots in three portions, each for 25 min. After evaporation of the solvent, 50 ml. of light petroleum ether was added to the residue and the insoluble material was filtered. The filtrate was evaporated, leaving 12 mg. (40%) of oxaziridine IIB, m.p. 56–59°. It was further purified by redissolving the material in petroleum ether, filtering, and evaporating the filtrate: m.p. 58–60°, unchanged by admixture with IIB synthesized by peracetic acid oxidation of the imine[6a]; 95% active oxygen content.[53]

A solution of 10 mg. of nitrone IIA in 62 ml. of absolute ethanol was irradiated as above for 20 min. and then immediately analyzed for active oxygen content.[53] The value obtained was 90%.

2-(*t*-Butyl)-3-phenyloxaziridine (IIIB).—N(*t*-Butyl)-α-phenylnitrone (IIIA) was prepared by isomerizing the corresponding oxaziridine.[6a] A solution of 10 mg. of nitrone IIIA in 50 ml. of acetonitrile was irradiated for 2 hr. in a quartz flask with 2-cm. solution thickness, 14 in. above a Hanovia mercury-arc lamp, Type 16200, with SH medium-pressure arc bulb. The absorption spectrum of the irradiated solution showed no nitrone. The solution was then heated under reflux for 3 days,[6a] and the volume

(50) I. Goldberg, *Chem. Ber.*, **40**, 4541 (1907).

(51) O. L. Brady and R. P. Mehta, *J. Chem. Soc.*, 2297 (1924).

(52) G. Watt and C. Knowles, *J. Org. Chem.*, **8**, 540 (1943).

(53) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 100.

was adjusted to 50 ml.; the spectrum then showed 97% of the original nitrone. A reirradiation under the same conditions led again to complete disappearance of the nitrone spectrum.

A solution of 10 mg. of nitrone IIIA in 35 ml. of absolute ethanol was irradiated as above for 2 hr. under slight vacuum. Analysis for active oxygen content[53] showed 90%.

Modified Active Oxygen Determinations.—The method[53] used by Emmons[6a] gave good results for oxaziridines IB, IIB, and IIIB. However, this method could not be used for oxaziridines IVB and VB without modification because the iodine was liberated from the potassium iodide almost instantaneously and then reacted very rapidly, presumably with the imine formed in the reaction. Dilution with water immediately after the addition of the potassium iodide quenched this reaction to a great extent. The active oxygen content obtained by this modified method is probably low due to incomplete liberation of iodine or reaction of the liberated iodine at the time of dilution. Because oxaziridines IVB and VB were not stable in ethanol solutions, the maximum active oxygen content was obtained immediately after irradiation of the corresponding nitrones. Oxaziridines VIB and VIIB were so unstable in ethanol solution that the active oxygen content could not be measured.

A solution of 8 mg. of nitrone VA in 69 ml. of absolute ethanol was irradiated for 17 min. between two DxB photospots as described above. Water (2 ml.) was added to one-half of the solution as it was being chilled for 1 min. in an ice bath. Saturated KI (1 ml.) solution was added, immediately followed by 100 ml. of water. After 6 ml. of acetic acid and 4 ml. of starch indicator solution were added, the liberated iodine was titrated with 0.025 *N* sodium thiosulfate solution. Immediately after the irradiation, the active oxygen content was 75% based on the nitrone used. After varying post-irradiation times (solution kept at 23°), the following active oxygen contents were found: 0.5 hr., 64%; 1 hr., 53%; 2 hr., 39%; 4 hr., 18%; and 6 hr., 7%. For the last two determinations the end point was difficult to determine because of yellow reaction products.

A solution of 4 mg. of nitrone IVA in 30 ml. of absolute ethanol was irradiated in a 600-ml. beaker by direct sunlight until it was colorless (about 6 min.). After the addition of 5 ml. of water, the procedure followed was the same as above. A 69–72% active oxygen content was found based on the nitrone used. A solution which stood 20 hr. after irradiation had no active oxygen.

Absorption Spectra.—The λ_{max}, mμ (ϵ), of nitrones and oxaziridines (immediately after irradiation of the nitrones at 5°) in various solvents are as follows. Nitrone IVA: acetone, 367 (20,000); C_6H_6, 367 (19,8000); isooctane, 360 (23,800); DMSO, 375 (19,300); CH_3CN, 365 (20,400). Nitrone VA: C_6H_6, 322 (20,200); DMSO, 323 (19,200); CH_3CN, 317 (18,500). Nitrone VIA: EtOH, 383 (34,600); acetone, 374 (31,000); C_6H_6, 374 (30,900); isooctane, 367 (30,300); DMSO, 381 (30,700); diethyl ether, 370 (30,500); CH_3CN, 374 (31,000). Nitrone VIIIA: isooctane, 334 (22,600); CH_3CN, 329 (24,500). Oxaziridine IVB: isooctane, 262 (15,300), 350 sh (800); CH_3CN, 268 (14,000), 355 sh (1000); EtOH, 266 (11,800), 345 sh (800). Oxaziridine VB: isooctane, 220.5 (15,500), 315 sh (500); CH_3CN, 219 (13,600), 310 sh (650); EtOH, 222 (13,600), 310 sh (400). Oxaziridine VIB: isooctane, 271 (30,000), 345 sh (1000); diethyl ether, 273 (27,700), 350 sh (1000); CH_3CN, 275 (26,000), 350 sh (1300). Oxaziridine VIIB: diethyl ether, 276 (30,000), 360 sh (1000). Oxaziridine VIIIB: isooctane, 237 (23,500), 315 sh (550); CH_3CN, 237.5 (23,300), 315 sh (700); EtOH, 238 (23,200), 315 sh (450). The long wave length bands in the oxaziridine spectra were broad and, thus, the λ_{max} are approximate. Spectra of the more reactive oxaziridines were obtained by combining spectra taken over short wave length ranges. The spectrum of oxaziridine VIIB in ether was obtained by 55-sec. irradiation at 5° between two DxB photospots, 16 in. apart; nitrone, O.D. 0.74. Correction was made for unchanged nitrone, O.D. 0.045. Irradiation by sunlight in a quartz cell caused an increase in absorption in the 315-mμ region, while irradiation with a Corning filter no. 3850 caused an increase in the 210–250-mμ region.

Spectrophotometric Determinations.—Various procedures were used to determine spectrophotometrically the yields of products from the thermal reactions of the oxaziridines. Small amounts (4 ml.) of nitrone solutions (10^{-4} to 10^{-5} *M*) were irradiated by DxB photospots (Pyrex filter) until there was complete disappearance of the nitrone (Table III). When there was no further change in the ultraviolet absorption spectrum (after standing in the dark at 25°), further irradiation was done to detect isomerization to the nitrone. The yields of the benzanilides, formanilides, and aldehydes were determined through their specific optical absorptions.[54] Yields of formanilides were determined also by hydrolysis with ethanolic sulfuric acid to the corresponding amines.[54a,55] Spectrophotometric analysis was carried out on acetone and benzene solutions before and after evaporation of the solvent, and redissolving the residue in an equal volume of ethanol.

A reaction which was detected only in small amounts (5% or less) was the formation of imines in the thermal reactions of the oxaziridines. The imines were detected by their absorption spectra and their behavior to dilute sulfuric acid (1 drop of 0.1 *N* H_2SO_4 or 10% H_2SO_4). Benzene solutions were diluted with an equal volume of ethanol before the addition of acid.

In the thermal reaction of oxaziridine IVB in ethanol, and to a lesser extent, of oxaziridine VB, there also was found in small amounts a compound with λ_{max} of 415 mμ, which, with sulfuric acid, was converted to a form with λ_{max} of 535 mμ. This behavior resembles that of 4-phenylaminoazobenzene,[56] which may have been formed by a series of oxidation–reduction reactions and condensation from phenylhydroxylamine.[57] Also in the thermal reaction of oxaziridine IVB, there was a small amount of a compound with absorption at shorter wave lengths than imine IVC and which reacted with dilute sulfuric acid. The greatest amount of this compound occurred in the reaction in acetone.

The nitrone that was formed in the thermal reaction of oxaziridine VIIB in acetone was reirradiated until there was a minimal amount of nitrone that could be reirradiated. The resulting absorption spectrum was similar to that of aldehyde VIIF.

TABLE III

EXPERIMENTAL CONDITIONS USED IN DETERMINING THE SPECTRA AND RATES OF DISAPPEARANCE OF OXAZIRIDINES

Nitrone	Solvent[a]	Irrad. time,[b] sec.	Analyzing λ,[c] mμ
IVA	A, B, I,[d] N	90	330 for IVD
	E	140	380 for IVB cation[e]
VA	A,[f] B, I, N	240	280 for VD
	E	300	245, 222 for VE, VB
VIA	A, B, I, N	15	280, 380 for VIB, VIA
	E[g]	5	See text
VIIA	A, B	75	390, 280 for VIIA, VIIB
	E[h]	2.5[h]	400 for *cis,trans*-VIIA
	E[i]	4[i]	412 for VIIA[i]
VIIIA	I, N	80	No data
	E	120	No data

[a] A, acetone; B, benzene; I, isooctane; N, acetonitrile; E, absolute ethanol. Optical density of nitrones at λ_{max} was 1.5–2.0, except where noted. [b] Two DxB photospots were 16 in. apart with the cell held in a small Pyrex beaker of cold water midway between. Solution depth exposed to $h\nu$ was 1 cm. Irradiation times are approximate and about the same for summer sunlight. [c] Temperature 25°; not applicable below 330 mμ for acetone; no data for acetonitrile. [d] Optical density 1.0; analyzing wave length, 240, 320 for IVD, 280 for IVB. [e] Each sample of 3.5 ml. was analyzed at the analyzing wave length for base line. Then 1 drop of 5% H_2SO_4 was added with shaking and immediately analyzed at the same wave length. [f] Each sample of 3.5 ml. was analyzed at 360 mμ for base line. Then 1 drop of 0.1 *N* H_2SO_4 was added with shaking and immediately analyzed at the same wave length for VB cation. [g] Optical density, 1.0. [h] Optical density, 0.27; the photospots were 3 in. apart. [i] Optical density, 0.57; the photospots were 3 in. apart, cell in beaker of cold water; rate of isomerization of *cis* to *trans* nitrone, starting time 1 min. after start of irradiation, $t_{1/2}$ = 32 min.

(54) (a) VE: W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951). (b) IVF: W. Kumler and P. Sah, *J. Pharm. Sci.*, 375 (1952). (c) VF: R. Morton and A. Stubbs, *J. Chem. Soc.*, 1347 (1940). (d) VIF: W. Kumler, *J. Am. Chem. Soc.*, **68**, 1184 (1946).

(55) VI spectrum: A. Mangini and A. Tundo, *Boll. sci. fac. chim. ind. Bologna*, 67 (1958); "Organic Electronic Spectral Data," Vol. IV, Interscience Publishers, Inc., 1963, p. 522.

(56) G. Badger, R. Buttery, and G. Lewis, *J. Chem. Soc.*, 1888 (1954).

(57) E. Bamberger, *Chem. Ber.*, **27**, 1548 (1894); **34**, 61 (1901).

On evaporation of the actone, the aldehyde was converted to the 2,4-dinitrophenylhydrazone, which was identical in spectrum with that of aldehyde VIIF. Imine VIIC was unchanged on similar reirradiation.

In Table III is a summary of the experimental conditions used in following the rates of disappearance of the unstable oxaziridines in the dark. The rate data were found to fit first-order kinetics at several concentrations. The rate of disappearance of the oxaziridine was approximately the same as the rate of formation of products. When treated with acid, the 2,3-diaryloxaziridines show absorption in the 400-mμ region.[58] This absorption rapidly disappears but is useful in following the rates of disappearance of oxaziridine VB in acetone and IVB in ethanol.

The following procedure was used to estimate the $t_{1/2}$ of reaction for oxaziridine VIB in ethanol. Five portions of nitrone VIA in ethanol were irradiated as described in Table III, immediately analyzed at 268 mμ for VIE and at 382 mμ for VIA, and then combined. After standing for 10 min. to allow for completion of reaction, 5 drops of 0.1 N H_2SO_4 were added. Five other portions were irradiated, but immediately after irradiation (at approximately 7 sec.) a drop of 0.1 N H_2SO_4 was added to each portion with shaking. These portions were combined, and after standing about 1 hr., spectra of both combined solutions were compared at 268 mμ for VIE and 340 mμ for VIF. The difference was consistent with about 89% completion of reaction at the time (7 sec.) of addition of the acid. By extrapolation, the $t_{1/2}$ was estimated to be about 2 sec. This also was in agreement with the $t_{1/2}$ estimated by irradiating portions of nitrone VIA, optical density 0.6, for 2 sec. (photospots 3 in. apart) and analyzing at 385 mμ for VIA and 280 mμ for VIB.

The rates of disappearance of the unstable oxaziridines in ethanol and acetone were little affected by traces of acid[59] on the cell wall. However, in benzene there was a catalytic effect. With the same cell treatment, the values of $t_{1/2}$ were found to be IVB, 14 hr.; VB, 60 hr.; VIB, 15 min., 80% yield of VIE; VIIB, 31 min. The values of $t_{1/2}$ reported in Table II were determined in glassware that had not been in contact with sulfuric acid. The rates of disappearance of oxaziridines VIB and VIIB were greatly decreased when benzene saturated with water was used.

Acknowledgment.—The authors are indebted to Dr. E. M. Voigt for helptul discussions of this work. The preparation of this paper was sponsored in part by the U. S. Atomic Energy Commission.

(58) This reaction will be reported in detail in the next communication.

(59) Glassware used had been in contact with cleaning solution or dilute sulfuric acid, but had been repeatedly rinsed with dilute NH_4OH, or NaOH and distilled water.

Cycloserine. III. A Schiff Base and Its Reactions[1]

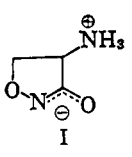
CHARLES H. STAMMER AND JAMES D. MCKINNEY

Department of Chemistry, University of Georgia, Athens, Georgia

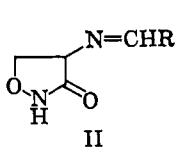
Received May 17, 1965

The first Schiff base of D-cycloserine has been prepared and its chemical reactions have been examined. The first conversion of D-cycloserine into its racemate *via* the Schiff base is reported. Hydrolysis, borohydride reduction, acetylation, and methanolysis of the Schiff base are described. Evidence indicating the probability that the Schiff base is intermediate in the conversion of cycloserine into its dimer derivative is presented. Possible biochemical implications are discussed.

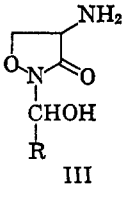
Numerous investigators have established that cycloserine (I) inhibits pyridoxal-dependent transaminase, decarboxylase, and racemase enzyme systems.[2] Speculation about the mechanism of this inhibition has led to sugggestions[3] that cycloserine reacts with pyridoxal forming a Schiff base (II) or possibly a carbinolamine of type III. Michalsky and co-workers found that when DL-cycloserine was allowed to react with pyridoxal



I

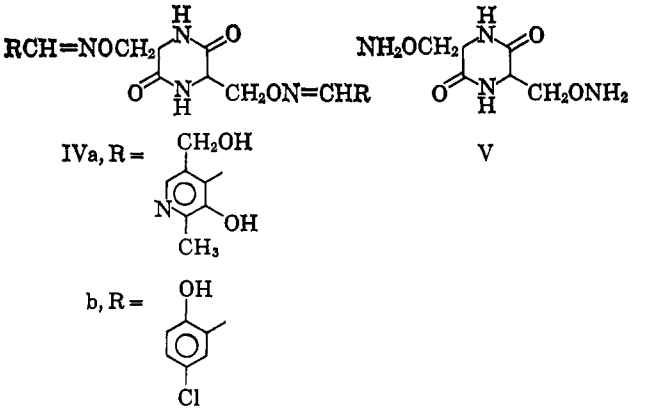


II



III

and various aromatic aldehydes, the 2,5-diketopiperazine derivatives (IV) were the only products formed. These workers reasoned that either II or III might be intermediates in the formation of IV or that cycloserine might first dimerize forming the 3,6-bis(aminoxymethyl)-2,5-diketopiperazine (V) which was rapidly derivatized giving IV.



If we make the biochemically naive assumption that the abstraction of pyridoxal from an enzyme system by cycloserine occurs through its conversion to IVa, the chemical pathway of this conversion becomes of considerable biochemical importance. The essence of the problem is to determine which of the intermediates II, III, or V is most likely.

As outlined in preliminary reports,[4] we have approached this problem by synthesizing an authentic Schiff base of cycloserine and examining its chemical properties. A more detailed discussion of its preparation, reactions, and probable implication in the formation of IV is the subject of this paper.

(1) We gratefully acknowledge the financial assistance of National Institutes of Health, Grant No. AI 05539-02.

(2) J. L. Strominger, *Physiol. Rev.*, **40**, 87 (1960); F. Cedrangolo, *I. U. B. Symp. Ser.*, **30**, 343 (1962); O. T. Dann and C. E. Carter, *Biochem. Pharmacol.*, **13**, 677 (1964); M. R. Alioto, *Biochim. Appl.*, **9**, 238 (1962); *Chem. Abstr.*, **58**, 13015 (1963); G. D. Pretra, F. DeLorenzo, and G. Illiano, *Biochim. Appl.*, **10**, 123 (1963); *Chem. Abstr.*, **60**, 6105 (1964).

(3) (a) J. Michalsky, J. Opichal, and J. Ctvrtnk, *Monatsh.*, **93**, 618 (1962); (b) N. K. Kotschetkow, *Oesterr. Chemiker-Ztg.*, **62**, 276 (1961).

(4) (a) C. H. Stammer, *Experientia*, **20**, 417 (1964); (b) C. H. Stammer and J. D. McKinney, *Tetrahedron Letters*, **No. 38**, 2607 (1964).