B. The rate constants for the individual reactions A, B, and C (Table I) were calculated from the overall rate constant and the composition data. To this end the product composition was determined under kinetics conditions. Four ampules from each set of rate measurements were kept at 130 °C for a time interval corresponding to 80–100% reaction. The content of the ampules (5 mL) was transferred into a 10-mL flask, acidified with 0.2 M HCl, and evaporated to dryness on a rotary evaporator at 40 °C. The solid residue was treated with 5 M NaOH (2 mL) and the organic bases extracted with pentane (3 mL). The pentane extract was analyzed by gas chromatography which was carried out with a Carlo Erba Fractovap Model GI instrument, fitted with a 20% Carbowax 20M on a firebrick (pretreated with sodium hydroxide) column operating in the range 70–180 °C. In the case of compound III a portion of the content (2–3 μL) of the ampules was directly injected into the gas chromatograph. The peaks were identified by comparison with authentic specimens of the compounds. The areas were measured and the molar ratios among the various components were determined by internal calibration based on the analysis of "synthetic" mixtures. Correction factors used for the quantitative evaluation of peak areas were obtained by subjecting standard mixtures of the three reaction products (prepared by accurately mixing weighed amounts of the three products) to the operations involved in the actual isolation procedure. For the cyclic ammonium salts I and II, the percentage found for each tertiary amine in the reaction mixture was the actual percentage of the corresponding reaction; for the open-chain ammonium salt III, the tertiary amine $CH_3CH_2CH_2CH_2N(CH_3)_2$ was produced by both reactions B and C. The contribution of reaction B was evaluated by the VPC determination of the content of $CH_3CH_2CH_2CH_2OCH_3$.

Registry No.—I, 872-44-6; II, 3333-08-2; III, 61134-94-9; sodium methoxide, 124-41-4; methanol, 67-56-1; 4-dimethylamino-1-butene, 55831-89-5; *N*-methylpyrrolidine, 120-94-5; 4-dimethylamino-1-butylmethyl ether, 33962-95-7; 5-dimethylamino-1-pentene, 1001-91-8; *N*-methylpiperidine, 626-67-5; 5-dimethylamino-1-pentylmethyl ether, 58390-18-4; butyl methyl ether, 628-28-4; butyldimethylamine, 927-62-8; dibutylmethylamine, 3405-45-6.

References and Notes

(1) G. Wittig and T. F. Burger, *Justus Liebigs Ann. Chem.*, **632**, 85 (1960).
(2) A. C. Cope and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 4656 (1960).
(3) J. Angel, *C. R. Acad. Sci., Ser. C*, **257**, 920 (1963).
(4) J. Angel, R. Michelot, and B. Tchoubar, *C. R. Acad. Sci., Ser. C*, **271**, 557 (1970), and references cited therein.
(5) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).
(6) W. H. Saunders and A. F. Cockerill, "Mechanisms of Elimination Reactions", Wiley, New York, N.Y., 1973, pp 38–39.
(7) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **97**, 4960 (1975), and preceding papers in the series.
(8) G. Illuminati, *Ric. Sci.*, **45**, 679 (1975).
(9) J. von Braun, W. Teuffert, and K. Weissbach, *Justus Liebigs Ann. Chem.*, **472**, 121 (1929).
(10) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927).
(11) C. K. Ingold and C. S. Patel, *J. Chem. Soc.*, 68 (1933).
(12) E. L. Eliel, R. O. Hutchins, R. Mebane, and R. L. Willer, *J. Org. Chem.*, **41**, 1052 (1976).
(13) M. Havel, J. Krupička, M. Svoboda, J. Závada, and J. Sicher, *Collect. Czech. Chem. Commun.*, **33**, 1429 (1968).
(14) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Org. Chem.*, **93**, 1637 (1971).
(15) K. Jewers and J. McKenna, *J. Chem. Soc.*, 2209 (1958).
(16) B. Tchoubar and M. Verrier, *Bull. Soc. Chim. Fr.*, 2151 (1960).
(17) H. Noguchi and A. Rembaum, *Macromolecules*, **5**, 253 (1972).
(18) W. D. Emmons, K. S. McCallum, and J. P. Freeman, *J. Org. Chem.*, **19**, 1472 (1954).
(19) M. Ferles and Z. Polívka, *Collect. Czech. Chem. Commun.*, **33**, 2121 (1968).
(20) R. N. Icke and B. B. Wisegarver, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 723.
(21) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

Synthesis and Structure of Alloxazine 5,10-Dioxides

Katherine L. Perlman*

School of Pharmacy, University of Wisconsin—Madison, Madison, Wisconsin 53706

Wolfgang E. Pfeiderer and Margarete Gottlieb

Fachbereich Chemie der Universität Konstanz, D-7750 Konstanz, West Germany

Received December 22, 1976

Various alloxazine 5,10-dioxides (**7–9**) have been synthesized by direct H_2O_2/trifluoroacetic acid oxidation and their structures proven to consist preferentially in the 1H tautomeric lactam configuration. The three methyl blocked tautomeric forms **12–14** of 3-methylalloxazine 5,10-dioxide (**8**) could be obtained by diazomethane methylation of **8**. Comparisons of the UV spectra are used for the structural assignments.

The first alloxazine *N*-oxide was prepared by Petering,[1,2] who oxidized 8-chloroalloxazine with 30% H_2O_2 in 88% formic acid at 65–95 °C and believed that the 5,10-dioxide was synthesized. In trying to repeat this procedure Berezovskii et al.[3–5] claimed to have obtained only the 10-oxides when oxidizing alloxazine and its methyl derivatives with H_2O_2 in formic acid, with peracetic acid, and with monopersulfuric acid. However, Gladys and Knappe[6] were unable to confirm this.

There is some agreement that the conditions used by Petering will lead to mono-*N*-oxides, specifically the *N*-10-oxide if the N-1 is unsubstituted and the *N*-5-oxide if there is an alkyl substituent in the 1-position. This sensitivity toward steric (peri) hindrance parallels the findings with lumazine *N*-oxides by Pfeiderer and Hutzenlaub.[7] In related studies, alloxazine 5-oxides were prepared by the "indirect" cyclization methods[8–14] which permitted unambiguous placement of the *N*-oxide grouping in the 5-position. Alloxazine 5,10-dioxides have not yet been synthesized via this route.

Since close relationships can be expected between the published structures of lumazine 5,8-dioxides and its alloxazine analogues, we decided to study the structure of alloxazine 5,10-dioxides. These compounds can exist mainly in two energetically favored tautomeric forms, where A would be con-

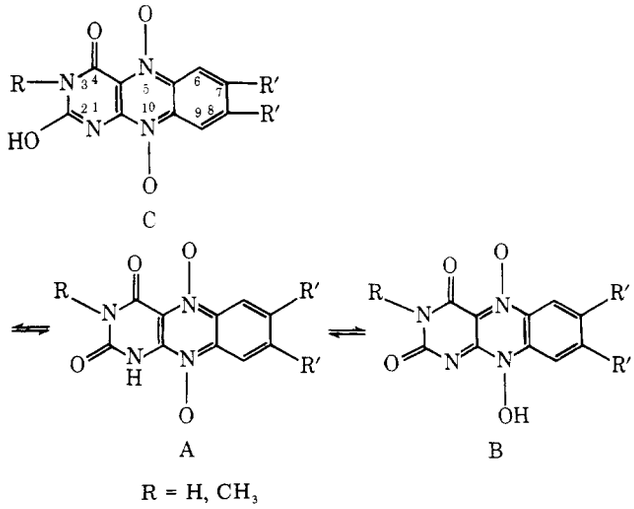


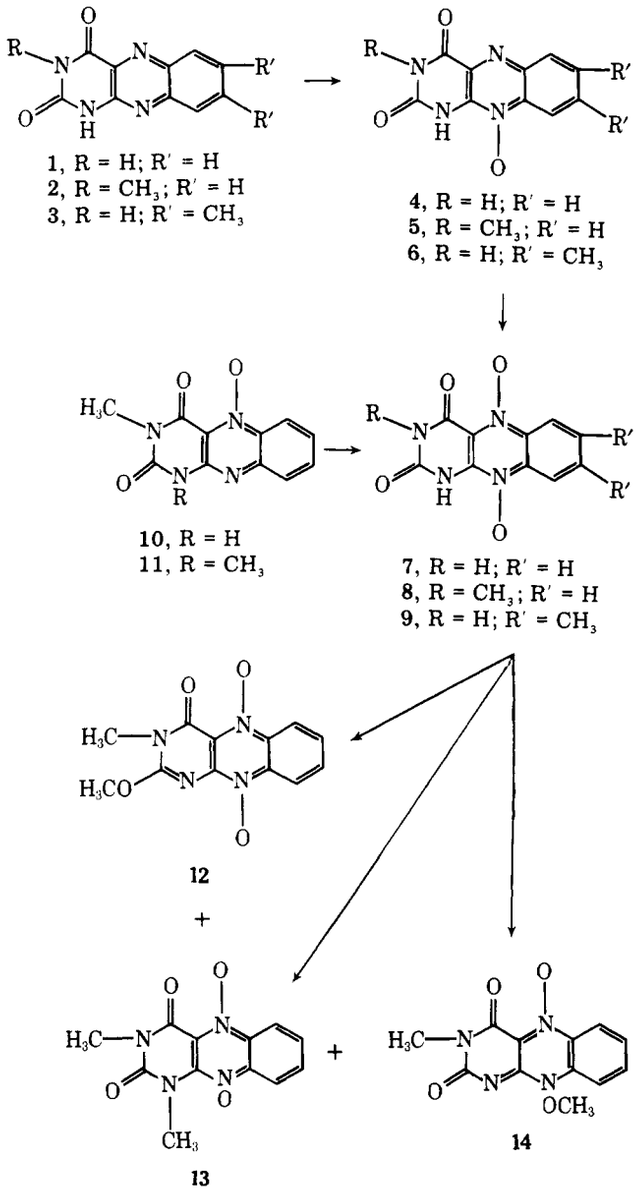
Table I. 90-MHz NMR Spectra of Alloxazine *N*-Oxides in $CDCl_3$[a]

	Aromatic protons	*O*-CH_3 (3)	*N*-CH_3
1,3-Dimethylalloxazine 5-oxide (11)	8.29 m (1), 7.86 m (2), 7.64 m (1)		3.79 s (3)
			3.50 s (3)
1,3-Dimethylalloxazine 5,10-dioxide (13)	8.55 m (2), 7.84 m (2)		4.00 s (3)
			3.44 s (3)
3,2-*O*-Dimethylalloxazine 5,10-dioxide (12)	8.69 m (2), 7.82 m (2)	4.35 s	3.57 s (3)
3-Methyl-10-methoxyalloxazine 5-oxide (14)	8.49 m (1), 7.89 m (2), 7.60 m (1)	4.31 s	3.45 s (3)

[a] δ values in parts per million, Me_4Si internal standard; s = singlet, m = multiplet, number of protons in parentheses.

sidered as a true di-*N*-oxide and B as a vynologous cyclic hydroxamic acid. The lactim form, C, is another disfavored tautomer of less importance. It was necessary to prepare in addition to the alloxazine di-*N*-oxides their methyl blocked tautomers for spectral comparison in order to differentiate between these forms.

When alloxazine (1), its 3-methyl (2), and 7,8-dimethyl derivative (lumichrome) (3) were oxidized at room temperature with a large excess of H_2O_2 in trifluoroacetic acid for several days, the corresponding 5,10-dioxides **7–9** were formed via the *N*-10-monooxides **4–6.** We then prepared 1,3-dimethylalloxazine 5-oxide (11) using the procedure of Goldner



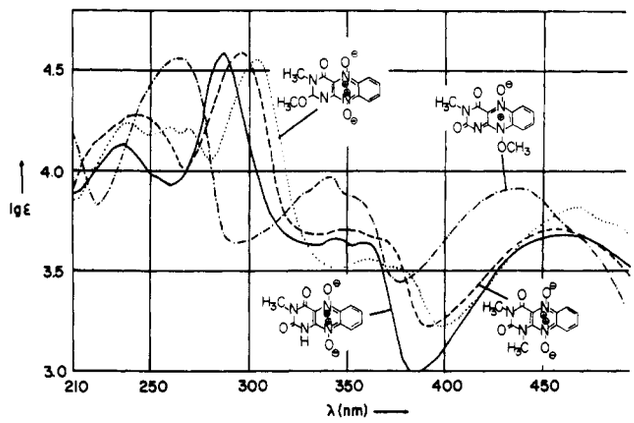


Figure 1. UV spectra of 3-methyl- (8) —, 1,3-dimethyl- (13) - - -, 2,3-*O*-dimethylalloxazine 5,10-dioxide (12) · · ·, and 3-methyl-10-methoxyalloxazine 5-oxide (14) - · - · - in methanol.

et al.[9] and when this was treated with the H_2O_2 (in trifluoroacetic acid) only unchanged starting material was recovered.

An alternative pathway to **13** appeared to be through the methylation of 3-methylalloxazine 5,10-dioxide (8), which was obtained by H_2O_2 oxidation of 3-methylalloxazine (2) and its 5-oxide (10), respectively, in trifluoroacetic acid: Treatment of 8 in methanol with ethereal diazomethane gave a complex mixture of at least six compounds which were separated by thick layer chromatography on silica gel with $CHCl_3$/acetone (9:1). The well separated bands were eluted and the substances isolated and crystallized. The fastest moving component was 1,3-dimethylalloxazine 4-oxide (11), which must have been formed by deoxygenation at N-10 and subsequent methylation. The other three compounds which were purified appeared to be isomeric dimethyl derivatives on the basis of C, H, and N elementary analysis. Two also showed the presence of methoxy group by Zeisel determination under conditions where the main product of the reaction was almost inert. We therefore assigned the 1,3-dimethylalloxazine 5,10-dioxide structure (13) to the main reaction product. The structural assignment of the two other methoxy derivatives has been based on NMR studies where one shows in analogy to **13** a symmetrical splitting of the aromatic protons is two multiplets of 2 H each. The other isomer is characterized by a more complicated pattern illustrating a unsymmetrical neighborhood of the benzene ring. This information supports the structure **12** for the former isomer and **14** for the latter isomer (Table I).

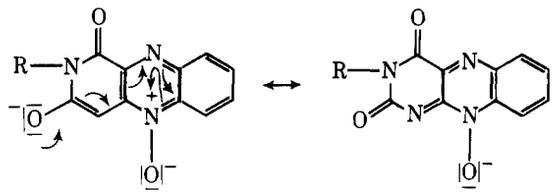
A comparison of the UV spectra of 3-methylalloxazine 5,10-dioxide (8) with the 3-methyl blocked tautomers **12–14** in methanol (Figure 1) clearly demonstrates that the predominant tautomeric form of alloxazine 5,10-dioxides is represented by the 1*H*,3*H*-2,4-dioxotetrahydro structure (**7–9**) and not a N-10 or C-2–OH tautomer.

Table II. Physical Data of Alloxazine *N*-Oxides

	pK_a value in H_2O	UV absorption spectra[a] ϵ_{max}, nm	Log ϵ	pH	Molecular form[b]
3-Methylalloxazine (2)	8.31 ± 0.08	212, 42, [252], 331, 377, 219, 258, [280], 330, 420	4.53, 4.54, [4.47], 3.93, 3.87, 4.49, 4.66, 3.72, 3.89	6.0 11.0	0 –
3-Methylalloxazine 5-oxide (10)	7.95 ± 0.1	[238], 263, 296, 305, 338, 402, [243], 266, [305], [313], 342, 455	[4.17], 4.49, 3.73, 3.73, 3.77, 3.60, [4.07], 4.59, [3.77], [3.73], 3.68, 3.58	2.2 10.0	0 –
1,3-Dimethylalloxazine 5-oxide (11)		266, [305], 323, 337, 402	4.62, [3.81], 3.88, 3.91, 3.68	MeOH	0
3-Methylalloxazine 10-oxide (5)	6.00 ± 0.1	226, 262, [330], 345, 395, 228, 270, 285, [338], 352, 447	4.11, 4.77, [3.89], 4.06, 3.79, 4.14, 4.56, 4.49, [3.75], 3.86, 3.87	4.0 9.0	0 –
Alloxazine 5,10-dioxide (7)	5.30 ± 0.05 11.42 ± 0.1	228, 253, 283, [344], 367, 440, 222, 234, 257, 294, [350], 363, 495, 235, 286, [352], 367, 503	4.22, 4.01, 4.70, [3.77], 3.76, 3.78, 4.07, 4.08, 4.17, 4.59, [3.79], 3.81, 3.78, 3.98, 4.71, [3.84], 3.94, 3.85	3.0 8.0 14.0	0 – 2–
7,8-Dimethylalloxazine 5,10-dioxide (9)	5.60 ± 0.1 11.54 ± 0.1	232, 287, [359], 371, 440, 232, 258, 301, [362], 375, 492, 236, 255, 292, [360], 374, 500	4.21, 4.69, [3.81], 3.89, 3.71, 4.08, 4.11, 4.65, [3.75], 3.82, 3.72, 4.02, 3.92, 4.85, [3.83], 3.93, 3.82	3.0 8.0 11.0	0 – 2–
3-Methylalloxazine 5,10-dioxide (8)	5.02 ± 0.1	230, 254, 282, 343, 358, 442, 223, 235, 257, 286, [351], 365, 503, 233, [253], 288, 344, 358, 462	4.21, 4.00, 4.72, 3.79, 3.83, 3.81, 4.02, 4.03, 4.09, 4.58, [3.78], 3.85, 3.79, 4.13, [3.97], 4.58, 3.66, 3.64, 3.69	2.0 8.0 MeOH	0 – 0
1,3-Dimethylalloxazine 5,10-dioxide (13)		239, 296, 351, [362], 460	4.28, 4.59, 3.71, [3.67], 3.71	MeOH	0
3,2-*O*-Dimethylalloxazine 5,10-dioxide (12)		237, 260, 269, 304, 358, [373], 468	4.24, 4.22, 4.20, 4.56, 3.56, [3.52], 3.82	MeOH	0
3-Methyl-10-methoxyalloxazine 5-oxide (14)		265, [325], 340, [355], 440	4.57, [3.88], 3.97, [3.87], 3.81	MeOH	0

[a] Values in brackets denotes a shoulder. [b] 0 = neutral form, – = monoanion, 2– = dianion.

A determination of the pK_a values of the different alloxazine *N*-oxides showed (see Table II) that all compounds with the *N*-10-oxide function are stronger acids than the *N*-5-oxides. (This is in good agreement with observations with the lumazine series.[7]) These observations can be explained by the



hypothesis that the anion of the *N*-10-oxide can be stabilized through a mesomeric effect, while in the case of the 5-oxides only an inductive influence is possible.

The UV spectra indicate that the introduction of a *N*-oxide function in position 5 or 10 is associated with a bathochromic shift of the longwave absorption band of 30–40 nm and the monoanion formation, by deprotonation at N-1, causes in all mentioned compounds another red shift of about 50 nm independent of their oxidation state.

Experimental Section

NMR spectra were determined in deuteriochloroform with a Bruker HFX-90 spectrometer and the UV spectra with a Cary recording spectrometer, Model 1115/15 (Applied Physics Corp.). The pK_a values are based on the spectrophotometric method.[15] Chromatographic studies were carried out using precoated cellulose and silica gel plates (Schleicher and Schüll). Merck silica gel PF_{254} thick plates (2 mm) were used for the preparative separations. All melting points are uncorrected.

Alloxazine 5,10-Dioxide (7). Alloxazine (1) (1 g) was dissolved by warming in 60 mL of trifluoroacetic acid. H_2O_2 (30%, 4 mL) was added dropwise (with stirring) at room temperature and stirring was continued for 24 h. An additional 4 mL of 30% H_2O_2 was then added and the mixture stirred for another 24 h. The deep yellow solution was then poured onto ice and the resulting orange precipitate filtered by suction and washed with water and ethanol. After drying at 100 °C 0.6 g (52% yield) of yellow crystalline powder with mp 300 °C was obtained. Recrystallization from dimethyl sulfoxide/water solution gave a yellow powder which dissolves in 0.1 N NaOH to give a deep red color and shows a positive dark blue color with 1% $FeCl_3$ solution in water/methanol mixture.

Anal. Calcd for $C_{10}H_6N_4O_4$: C, 48.79; H, 2.46; N, 22.76. Found: C, 48.60; H, 2.54; N, 22.42. Mol wt 246.18 (mass spectrum *m/e* 246).

3-Methylalloxazine 5,10-Dioxide (8). A mixture of 3-methylalloxazine (2) and its 5-oxide (10) (2 g) prepared according to the Goldner et al. procedure[9] was dissolved in 30 mL of trifluoroacetic acid and treated with three 3-mL portions of 30% hydrogen peroxide as described above to give 1.8 g of yellow crystalline powder of mp 320–325 °C dec. The chromatographically pure material can further be purified by recrystallization from Me_2SO/water or glacial acetic acid.

Anal. Calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.68; H, 3.07; N, 21.06. Mol wt 260.2 (mass spectrum *m/e* 260).

7,8-Dimethylalloxazine 5,10-Dioxide (9). 7,8-Dimethylalloxazine (1 g) in 35 mL of trifluoroacetic acid was treated in four portions with a total of 12 mL of 30% peroxide in the same way as described for **8.** Recrystallization of the crude reaction product from glacial acetic acid gave 0.8 g (71%) of yellow crystalline powder of mp 330 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.56; H, 3.78; N, 20.50. Found: C, 52.37; H, 3.68; N, 20.43. Mol wt 274.2 (mass spectrum *m/e* 274).

Methylation of 3-Methylalloxazine 5,10-Dioxide (8). To a suspension of 0.3 g of finely ground 8 in 20 mL of absolute methanol was added with stirring an ethereal solution of diazomethane (prepared from 5 g of *N*-nitroso-*N*-methylurea). The yellow solution changed gradually to an orange-red precipitate after stirring for 1 day at room temperature. The reaction mixture was evaporated to dryness, the residue dissolved in a small amount of chloroform, and applied to five preparative silica gel plates (40 × 20 × 0.2 cm) for separation. The plates were developed twice, first with a chloroform/acetone mixture 9:1 and the second time with a 9:2 mixture. There was good separation into four main bands of yellow and orange fluorescence which consisted of increasing R_f values of **14, 12, 13,** and **11.** The bands were cut out and eluted with acetone and evaporated to dryness to give chromatographically pure amorphous solids.

1,3-Dimethylalloxazine 5-Oxide (11). Crude product of the above separation (30 mg) was recrystallized from 5 mL of water/ethanol (1:1) yielding 12 mg of yellow needles with mp 216 °C (lit. mp 237 °C)[9,14] (authentic sample mp 218 °C, no depression).

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.79; H, 3.88; N, 21.39. Mol wt 258.2.

2,3-Dimethylalloxazine 5,10-Dioxide (12). Orange colored eluate (40 mg) was purified by recrystallization from 10 mL of ethanol to give 20 mg of orange crystals with mp 236–238 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43; OCH_3, 11.3. Found: C, 52.85; H, 3.67; N, 20.20; OCH_3, 9.8.

1,3-Dimethylalloxazine 5,10-Dioxide (13). Crude reaction product (0.1 g) was recrystallized from a mixture of 5 mL of water and 2 mL of ethanol to give 0.076 g of shiny crystals, mp 194 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43. Found: C, 52.81; H, 3.67; N, 20.10. Mol wt 274.2.

3-Methyl-10-methoxyalloxazine 5-Oxide (14). Crude material (40 mg) was recrystallized from 10 mL of ethanol to give 20 mg of orange crystals with mp 196–198 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43; OCH_3, 11.3. Found: C, 52.39; H, 3.71; N, 20.22; OCH_3, 11.7.

Biological Activity of Alloxazine Di-*N*-oxide. Assays were performed under the supervision of the Drug Research and Development Section, Division of Cancer Treatment, National Cancer Institute, U.S. Public Health Services by the procedures described in Geran et al.[16] A compound is considered to show significant in vivo activity against the Walker 256 tumor system if it causes reduction of tumor weight in the treated rats to 42% or less of the tumor weight in the control animals. In this test system the alloxazine di-*N*-oxide at 60 mg/kg showed an 80% reduction in tumor weight. In other tests using mouse leukemia L-1210 no life prolongation was noted. The alloxazine di-*N*-oxide inhibited the growth of *Lactobacillus casei* (ATCC 7469) growing in folic acid limited medium at 20 mcg/mL, and this inhibition was not reversed by citrovorum factor, thymidine, or riboflavin.

Registry No.—**1**, 490-59-5; **2**, 2891-59-0; **3**, 1086-80-2; **5**, 22525-79-7; **7**, 50628-74-5; **8**, 54011-43-7; **9**, 39132-80-4; **10**, 4897-17-0; **11**, 2962-89-2; **12**, 62015-56-9; **13**, 32706-14-2; **14**, 62015-57-0.

References and Notes

(1) H. G. Petering, U.S. Patent 2 973 359; *Chem. Abstr.*, **55**, 11772d (1961).
(2) H. G. Petering and G. J. van Giessen, *J. Pharm. Sci.*, **52**, 1192 (1961).
(3) W. M. Berezovskii and Zh. I. Aksel'Rod, *Dokl. Akad. Nauk SSSR*, **168**, 577 (1966); p 506 in English edition.
(4) W. M. Berezovskii and Zh. I. Aksel'Rod, *Dokl. Akad. Nauk SSSR*, **171**, 1101 (1966); p 1169 in English edition.
(5) W. M. Berezovskii, Zh. I. Aksel'Rod, N. D. Grigor'eva, V. Z. Mel'nikov, and N. I. Kirillova, *Dokl. Akad. Nauk SSSR*, **198**, 829 (1971).
(6) M. Gladys and W. Knappe, *Z. Naturforsch. B*, **29**, 549 (1974).
(7) W. Pfleiderer and W. Hutzenlaub, *Chem. Ber.*, **106**, 3149 (1973).
(8) E. C. Taylor, "Topics in Heterocyclic Chemistry", R. N. Castle, Ed., Wiley-Interscience, New York, N.Y., 1969, pp 25–27.
(9) H. Goldner, G. Dietz, and E. Carstens, *Justus Liebigs Ann. Chem.*, **694**, 142 (1966).
(10) H. G. Kazmirowski, H. Goldner, and E. Carstens, *J. Prakt. Chem.*, **32**, 43 (1966).
(11) F. Yoneda and M. Ichiba, *Chem. Pharm. Bull.*, **20**, 1832 (1972).
(12) F. Yoneda and Y. Sakuma, *Chem. Pharm. Bull.*, **21**, 448 (1973).
(13) F. Yoneda, Y. Sakuma, and S. Matsumoto, *Heterocycles*, **3**, 113 (1975).
(14) F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *J. Am. Chem. Soc.*, **98**, 830 (1976).
(15) A. Albert and E. P. Serjeant, "The Determination of Ionization Constants", Chapman and Hall, London, 1971, p 44.
(16) R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3**, 1 (1972).

(17) We thank Mrs. M. Bischler and Mr. E. Krienitz, Department of Chemistry, University of Konstanz, for the determination of the physical data, and Professor D. Perlman, School of Pharmacy, for assistance with the bioassay determinations.

Structural Studies of Organosulfur Compounds.[1] 3. Stereochemistry and Conformational Distortions in *trans*-Hexahydro-1,4-benzoxathiane *S*-Oxides

Donna M. Frieze, Philip F. Hughes, Robert L. Merrill, and Slayton A. Evans, Jr.*

William Rand Kenan, Jr., Laboratories of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514

Received October 25, 1976

trans-Hexahydro-1,4-benzoxanthiane and the 4-oxides have been prepared and the stereochemistry of the sulfinyl derivatives determined. Acid-catalyzed equilibration of the sulfoxides indicate that the axial sulfoxide is more stable than the equatorial by 0.85 ± 0.07 kcal/mol. Application of the *R*-value method indicates that the axial sulfoxide is severely flattened when compared to the equatorial diastereomer.

In a recent report[1] we had established the preferred conformation of the sulfinyl oxygen atom in the 1,4-oxathiane system **1** in the absence of other substituents[2] as predominantly *axial* by low temperature ^{13}C NMR techniques. This result was found to be in keeping with a number of previous reports describing sulfinyl oxygen conformations with other heteroatoms within the six-membered ring or as substituents,[3] but yet contrary to a number of other studies describing the conformational characteristics of sulfoxides.[4] We reasoned that the calculated conformational free energy difference, $\Delta\Delta G^\circ \simeq 0.4$ kcal/mol, for the sulfinyl oxygen atom in thiane 1-oxide (**2**) and 1,4-oxathiane 4-oxide (eq $\rightleftharpoons$ ax; $\Delta G^\circ = -0.17$ kcal/mol for thiane 1-oxide[3b] and $\Delta G^\circ = -0.68$ kcal/mol for 1,4-oxathiane 4-oxide[1]) results, in part, from the presence of an attractive intramolecular electrostatic interaction in 1,4-oxathiane 4-oxide which is absent in the pentamethylene sulfoxide, **2**. This may be viewed as a 1,4-attractive interaction between the negatively charged oxygen of the sulfoxide and the positive carbon atoms (and perhaps hydrogens) at C2 and C6.[5] Intramolecular dipole–dipole interactions appear to be dominant features in a number of heterosubstituted sulfoxides. In fact, a recent report describing the results of empirical force field (molecular mechanics[6]) calculations on six-membered ring sulfoxides[7] suggests that the conformations of the sulfinyl oxygen atom are controlled largely by dipolar considerations which exist between a ring heteroatom and the sulfinyl oxygen atom.

An attractive or repulsive interaction, which might result in a decrease or increase in the distance between the axial sulfinyl oxygen and the C2, C6 carbons and hydrogens, would be expected to induce either mild puckering or flattening of the central ring of **1** when compared to a system without an axial sulfinyl oxygen.[8] This distortion could be identified from precise determinations of vicinal coupling constants which could ultimately be translated into torsional angles.[9,10]

In this report, we have examined the conformational distortions caused by the sulfinyl and sulfonyl oxygens in the 4-oxides of *trans*-hexahydro-1,4-benzoxathiane (**6**). We view