The Dimethyl Sulfoxide Oxidation of 2,3-Bis(bromomethyl)quinoxaline[1,2]

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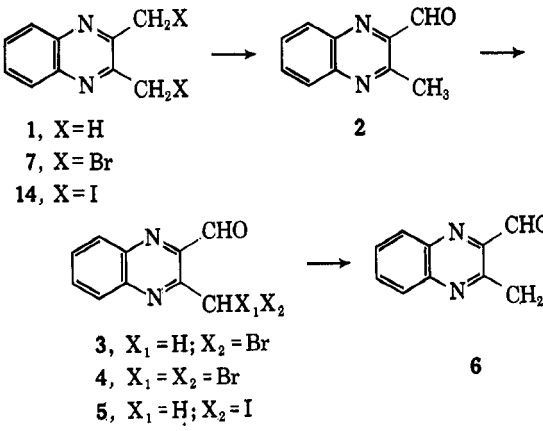
The reaction of 2,3-bis(bromomethyl)quinoxaline (**7**) with dimethyl sulfoxide produced in varying amounts 3-methyl- (**2**), 3-bromomethyl- (**3**), and 3-dibromomethyl-2-quinoxalinecarboxaldehyde (**4**), in addition to 2,3-bis(dibromomethyl)quinoxaline (**11**), and 2,3-quinoxalinedicarboxaldehyde (**12**) isolated as the intramolecular hemihydrate **13**. A similar oxidation of 2,3-bis(iodomethyl)quinoxaline (**14**) led to **2** and 3-iodomethyl-2-quinoxalinecarboxaldehyde (**5**). The Hunsberger and Tien general mechanism of dimethyl sulfoxide oxidation can account for the formation of all these products, whose structures and mode of formation were independently verified by the chemical interconversion of **1**, **3–5**, **7**, and **12–14**. In the presence of the nonalkaline, hydrogen bromide scavenger, 1,2-epoxy-3-phenoxypropane, dimethyl sulfoxide oxidation of **7** and **14** led to compounds tentatively identified as *dl*-1,2-dibromo- (**15**) and *dl*-1,2-diiodo-1,2-bis(3-methyl-2-quinoxalyl)ethane (**16**). Both **15** and **16** were dehalogenated to *trans*-1,2-bis(3-methyl-2-quinoxalyl)ethylene (**17**) whose structure was determined by ozonolysis to **2** and by synthesis from 2,3-dimethylquinoxaline (**1**) and **2**. Bromination of **17** led to *meso*-1,2-dibromo-1,2-bis(3-methyl-2-quinoxalyl)ethane (**18**). Dimethyl sulfoxide oxidation of **15**, **16**, and **18** led to the same product, bis(3-methyl-2-quinoxalyl)glyoxal (**19**). A number of 6-chloro-, 6-methyl-, 6,7-dichloro-, and 6,7-dimethyl derivatives of **4**, **7**, **8**, **11**, **12**, and **14** are reported.

In an unsuccessful attempt to apply the Wittig olefin procedure to the synthesis (*via* intramolecular cyclization[3] of the triphenylphosphonium salt **6**)[5] of a four-membered ring fused to a quinoxaline frame, precursor 3-bromomethyl-2-quinoxalinecarboxaldehyde (**3**) was required. Compound **3** was prepared from 2,3-dimethylquinoxaline (**1**) in a two-step synthesis: limited selenium dioxide oxidation of **1** gave 3-methyl-2-quinoxalinecarboxaldehyde (**2**) in 16% yield[9]; bromination of **2** in acetic acid led to **3** in 30% yield, in addition to 35% 3-dibromomethyl-2-quinoxalinecarboxaldehyde (**4**) and recovery of 30% unreacted **2**. Since the over-all yield of **3** from **1** was only 5%, the oxidation of 2,3-bis(bromomethyl)quinoxaline (**7**) with dimethyl sulfoxide (DMSO) was examined as an alternative route to **3**. The unexpected results of this oxidation are the subject of this paper.

When **7** was treated with DMSO at 30° for 24 hr., four products were isolated: 3-methyl- (**2**, 31%), 3-bromomethyl- (**3**, 1%), and 3-dibromomethyl-2-quinoxalinecarboxaldehyde (**4**, 2%), in addition to 4% of 2,3-bis(dibromomethyl)quinoxaline (**11**). When



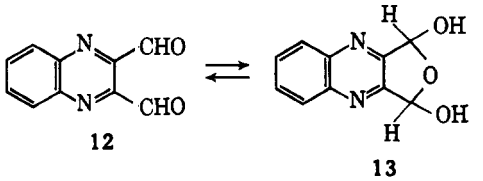
1, X=H
7, X=Br
14, X=I

2

3, X_1=H; X_2=Br
4, X_1=X_2=Br
5, X_1=H; X_2=I

6

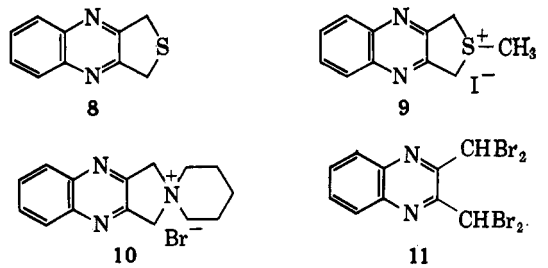
the reaction was quenched at the first appearance of carbonyl,[6] a 10–15% yield of the desired **3** could be isolated, in addition to smaller amounts of **2**, **4**, and **11** (Table II). At 60° for 6 hr., or 90° for 45 min., oxidation of **7** was complete to 2,3-quinoxalinedicarboxaldehyde (**12**), isolated in 60% yield as the intramolecular hemihydrate **13**; a 30% yield of **4** was also obtained.



12 **13**

The formation of the five products (**2–4**, **11**, and **13**) isolated from the DMSO oxidation can be nicely accommodated in the general ionic mechanism suggested by Hunsberger and Tien[7] in their study of the stoichiometry of the reaction between DMSO and ethyl α-bromoacetate.

Carbonyl formation in **2**, **3**, **4**, and **12** must involve oxidation (major reaction 1) by DMSO of active halide sites.[8] In side reaction 2, DMSO oxidation of the



8 **9**

10 **11**

(1) This research was supported by the Directorate of Chemical Sciences Air Force Office of Scientific Research, under Grant AF-AFOSR-62-18.

(2) Taken in part from the Ph.D. Thesis of A. J. Fritsch, S.J., 1964.

(3) Other unsuccessful intramolecular cyclization techniques which were tried include (i) reduction of **7**[4a] with zinc in ethanol which led only to a separable mixture of *cis*[4b] and *dl-trans* forms of 2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline[4b,c]; (ii) reductive desulfurization of 1,3-dihydrothieno-[3,4-*b*]quinoxaline (**8**) which gave only **1**; (iii) under conditions of the Stevens reaction, rearrangements of the sulfonium salt **9** and the spiro quaternary salt **10**; and (iv) reaction of 2,3-bis(dibromomethyl)quinoxaline (**11**) under Finkelstein conditions,[4d] and with potassium *t*-butoxide.[4e]

(4) (a) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **79**, 1701 (1957); (b) R. C. DeSelms and H. S. Mosher, *ibid.*, **82**, 3762 (1960); (c) C. S. Gibson, *J. Chem. Soc.*, 342 (1927); (d) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **78**, 500 (1956); (e) F. R. Jensen and W. E. Coleman, *Tetrahedron Letters*, **No. 20**, 7 (1959).

(5) T. I. Bieber and E. H. Eisman, *J. Org. Chem.*, **27**, 678 (1962); C. E. Griffin and G. Witschard, *ibid.*, **27**, 3334 (1962); C. E. Griffin and J. A. Peters, *ibid.*, **28**, 1715 (1963).

(6) As evidenced by visible reaction with 2,4-dinitrophenylhydrazine (2,4-DNP).

(7) (a) I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1959); (b) I. M. Hunsberger, AD-26411, U. S. Department of Commerce, Office of Technical Services, 1959.

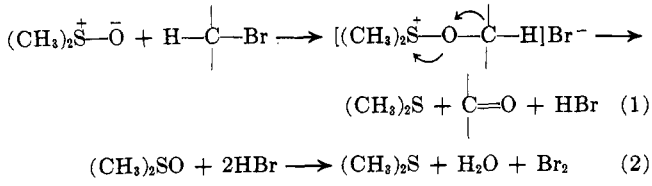
(8) N. Kornblum, J. W. Bowers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

TABLE I

QUINOXALINE DERIVATIVES

Compd.	Formula	—Calcd., %— C	H	—Found, %— C	H	M.p., °C.	Method of purification[a]
3-Dibromomethyl-2-quinoxalinecarboxaldehyde (**4**)							
6-, 7-CH_3[b] (**4a**)	$C_{11}H_8Br_2N_2O$	38.40	2.34	38.33	2.41	140–150[b]	T.l.c.
6,7-$(CH_3)_2$ (**4b**)	$C_{12}H_{10}Br_2N_2O$	40.25	2.82	40.43	3.08	135.5–137.5	T.l.c.
6-, 7-Cl[b] (**4c**)	$C_{10}H_6Br_2ClN_2O$	33.00	1.38	33.21	1.57	152–163[b]	T.l.c.
6,7-Cl_2 (**4d**)	$C_{10}H_4Br_2Cl_2N_2O$	30.11	1.01	30.13	1.16	162–164	T.l.c.
2,3-Bis(bromomethyl)quinoxaline (**7**)							
6-CH_3	$C_{11}H_{10}Br_2N_2$	40.03	3.05	40.27	3.31	126–127.5	E
6,7-$(CH_3)_2$	$C_{12}H_{12}Br_2N_2$	41.89	3.52	42.04	3.73	158.5–159.5	E
6-Cl	$C_{10}H_7Br_2ClN_2$	34.27	2.01	34.41	2.09	150.5–152	E
6,7-Cl_2	$C_{10}H_6Br_2Cl_2N_2$	31.20	1.57	31.26	1.69	171–172.5	A
1,3-Dihydrothieno[3,4-*b*]quinoxaline (**8**)							
6-CH_3	$C_{11}H_{10}N_2S$	65.31	4.98	65.16	5.18	129.5–130.5	E
2,3-Bis(dibromomethyl)quinoxaline (**11**)							
6-CH_3	$C_{11}H_8Br_4N_2$	27.08	1.65	26.90	1.81	200–200.5	A
6,7-$(CH_3)_2$	$C_{12}H_{10}Br_4N_2$	28.72	2.01	28.75	2.12	201–202	A
6-Cl	$C_{10}H_6Br_4ClN_2$	23.63	0.99	23.46	1.23	218–219.5	A
6,7-Cl_2	$C_{10}H_4Br_4Cl_2N_2$	22.13	0.74	21.98	0.80	198.5–200.5	A
2,3-Quinoxalinedicarboxaldehyde (**12**)							
6-Cl	$C_{10}H_5ClN_2O_2$	54.44	2.28	54.60	2.40	147.5–148	S
6,7-Cl_2	$C_{10}H_4Cl_2N_2O_2$	47.09	1.58	46.89	1.46	162–164	S
2,3-Bis(iodomethyl)quinoxaline (**14**)							
6-CH_3	$C_{11}H_{10}I_2N_2$	31.16	2.38	31.33	2.45	149.5–151.5	A
6,7-$(CH_3)_2$	$C_{12}H_{12}I_2N_2$	32.90	2.76	32.92	2.85	176–178	A
6C-l	$C_{10}H_7ClI_2N_2$	27.02	1.59	27.03	1.69	161.5–162.5	A
6-,7Cl_2	$C_{10}H_6Cl_2I_2N_2$	25.08	1.26	25.17	1.53	198–200	A

[a] E, recrystallized from ethanol; A, recrystallized from acetone; t.l.c., thin layer chromatography; S, sublimed. [b] Mixtures of 6- and 7-methyl derivatives were not separated.



$$(CH_3)_2SO + 2HBr \longrightarrow (CH_3)_2S + H_2O + Br_2 \quad (2)$$

primary HBr product produces molecular bromine and water. Side reaction 2 proceeds quite rapidly above 80° and more slowly at lower temperatures.[7b] Thus bromination of the bromomethyl groups in **3** and **7** would lead to the dibromomethyl derivatives **4** and **11**, respectively. The water formed would also suffice to react with **12** to form **13**.

Identity of products of the DMSO oxidation of **7** and the possible interconversions previously discussed were verified in the following independent series of reactions. Compound **2** was prepared by reaction of **1** in DMSO containing 1 mole equiv. of bromine, by oxidation of **1** with stoichiometric amounts of selenium dioxide[9] and by heating **11** in DMSO at 60–90° for 1 hr.[10] Compound **2** was converted to **3** and **4**, respectively, with 1 and 2 mole equiv. of bromine in acetic acid. Compound **3** on standing in DMSO and HBr for 24 hr. was reduced to **2**; if this reaction was permitted to stand for 2 or more weeks, the only isolable product was **4**. In addition to the methods already noted, **4** was prepared by oxidative bromination of **1** with DMSO and excess bromine and by bromination of **3** with 1 mole equiv. of bromine in acetic acid. The dibromomethyl groups in **4** and **11** were unreactive to acids and bases and sodium iodide in acetone, nor could the HBr salts be formed in ethereal solution, as was the case with **2** and **3**. Compound **4** formed a 2,4-dinitrophenylhydrazone. The ultraviolet spectrum of **4** indicated a fully conjugated quinoxaline, while the n.m.r. showed a multiplet and singlet with intensity ratios of 5:1. The dibromomethyl methine proton absorption in **4** is awash in the aromatic multiplet region. This methine absorption could be delineated in the 6-chloro (**4c**) and 6,7-dichloro (**4d**) derivatives of **4** (Table I).

3-Iodomethyl-2-quinoxalinecarboxaldehyde (**5**) was obtained in 1% yield by reaction of **14** with DMSO, and in higher yield by treatment of **3** with sodium iodide in acetone. Hydrate **13** was also prepared by irradiation of **14** with sunlight in the presence of oxygen and moisture.[11]

The DMSO oxidation of **14** was faster than **7** under similar conditions but much less productive of products. A limited examination of this reaction indicated that DMSO oxidation of **14** at 30° led to a maximum yield of the major product **2** (28%). Higher temperatures combined with shorter reaction times led to a maximum yield of 25% of **2**. In one instance, a 1% yield of **5** was also obtained.

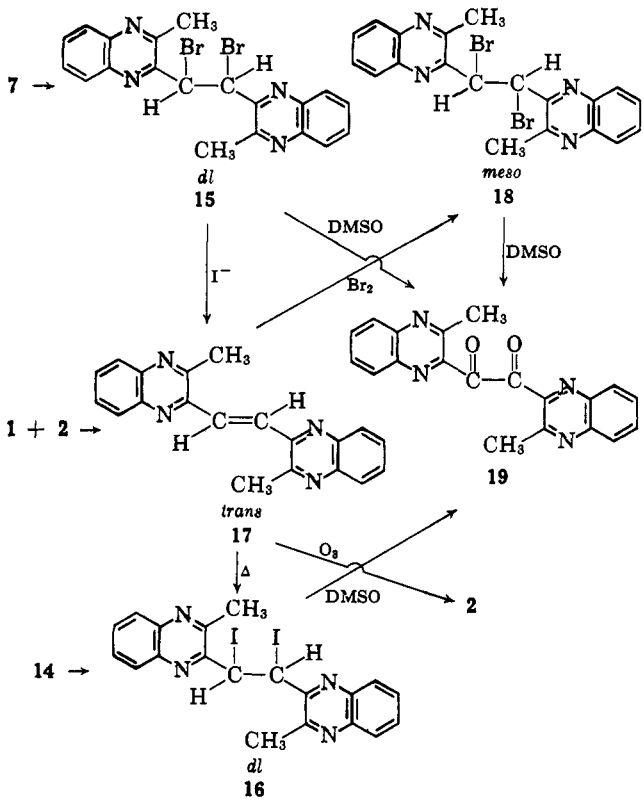
Finally, the iodinated quinoxalines **5** and **14** were found to be quite sensitive to light, liberating molecular iodine in benzene and carbon disulfide solutions. Thus carbon disulfide or benzene solutions of **14** exposed to sunlight led to **5**. If the solution was permitted to stand for 2 weeks, an 80% yield of **13** was obtained. When the benzene and carbon disulfide solvents were carefully dried and irradiation was

(9) J. Francis, J. K. Lindquist, A. A. Levi, J. A. Silk, and J. M. Thorpe, *Biochem. J.*, **63**, 455 (1956).

(10) Compound **2** easily forms an HBr salt which can be brominated to a mixture of **3** and **4** and reduced with formalin and base to 2-hydroxymethyl-3-methylquinoxaline. This latter compound has been used to prepare the highly antibacterial 1,4-dioxide.[9]

(11) Only one of the two possible geometric isomers was isolated. An n.m.r. study of the equilibration of these *cis* and *trans* isomers in aqueous DMSO solution, and of **12** and **13** will be reported separately.

CHART I



effected under nitrogen, **14** was reduced to **1** in 55% yield.

In Hunsberger and Tien's work on the oxidation of ethyl α-bromoacetate with DMSO,[7] a nonalkaline HBr scavenger, 1,2-epoxy-3-phenoxypropane, was added to repress side reaction 2. On heating **7** in DMSO with this scavenger, **15** precipitated in 11% yield as a yellow, insoluble product of empirical formula $(C_{10}H_8BrN_2)_n$. Similarly compound **14**, under identical conditions, led to a less stable, bright orange powder (**16**) of formula $(C_{10}H_8IN_2)_n$ in 20% yield.[12] Owing to its insolubility, n.m.r. spectra and molecular weight data were unattainable. Sublimation of **16** at 150° (2 mm.) or heating it in refluxing acetone–ethanol for 16 hr. converted it to the more soluble, dehalogenated derivative **17**, $C_{20}H_{16}N_4$. When **15** was treated with sodium iodide in refluxing acetone for 5 days, **17** was also obtained. Although **17** was also too insoluble for molecular weight determinations, its spectral data provided sufficient clues to its structure. Its n.m.r. spectrum in deuteriochloroform at 50° showed a singlet at δ 2.98 (CH_3), an aromatic multiplet at 7.56–8.32, and a singlet at 8.44 (CH), with an intensity ratio of 3:4:1. The ultraviolet absorption spectrum of **17** was most informative since it displayed a strong bathochromic shift [278 mμ (ϵ 24,200) and 382 mμ (ϵ 24,800)] relative to **2** and enhanced extinctions at the longer wave lengths. These absorption maxima shifts were reminiscent of the striking wave length increase observed by Bohlmann[13] with increased conjugation among the quinoxalines and their 2-styryl and 2,3-distyryl derivatives. *trans*-1,2-Bis(methyl-2-quinoxalyl)ethylene (**17**) fits all the observed analytical and spectral data.[14] Confirmation of structure **17** was obtained by (i) independent synthesis [condensation of **1** with an equimolar amount of 3-methyl-2-quinoxalinecarboxaldehyde (**2**) in refluxing acetic anhydride led to **17** in 56% yield] and (ii) degradation [ozonolysis of **17** led to **2** in 95% yield]. Bromination of **17** led to the *meso* dibromide **18** whose infrared spectrum differed from **15**. However, **15**, **16**, and **18** showed typical quinoxaline ultraviolet maxima at 237–244 and 322–325 mμ. Further, oxidation of **15**, **16**, and **18** led to the same bis(3-methyl-2-quinoxalyl)glyoxal (**19**), suggesting that **15** is the *dl* dibromide, as **16** must then be the *dl* diiodide (see Chart I).

A number of 6- and 6,7-substituted quinoxaline derivatives of **4**, **7**, **8**, **11**, **12**, and **14** were prepared by methods used to synthesize the parent quinoxalines, and these are summarized in Table I.

Experimental[15]

2,3-Dimethylquinoxaline (**1**) had m.p. 106.5–107°, lit.[17] m.p. 106°; $\lambda_{max}^{95\%\ EtOH}$ 237 mμ (ϵ 27,800) and 315 mμ (ϵ 7700); δ 2.65 (CH_3 singlet, six protons) and 7.46–8.02 (aromatic multiplet, four protons). The monohydrochloride salt of **1** was obtained as white needles (sublimation), m.p. 187–188° (sealed tube).

Anal. Calcd. for $C_{10}H_{10}N_2 \cdot HCl$: C, 61.70; H, 5.70; Cl, 18.21. Found: C, 61.83; H, 5.88; Cl, 18.23.

The monohydrate hydrogen sulfate salt of **1** was obtained as pale green plates, m.p. 151–152° (from acetone–chloroform), lit.[18] m.p. 151–152° dec.

Anal. Calcd. for $C_{10}H_{10}N_2 \cdot H_2SO_4 \cdot H_2O$: C, 43.79; H, 5.19; N, 10.20; S, 11.69. Found: C, 43.57; H, 5.24; N, 10.02; S, 11.89.

3-Methyl-2-quinoxalinecarboxaldehyde (**2**) was prepared in 16% yield by the selenium dioxide oxidation of **1**[9] as pale yellow leaflets (*from b.p. 90–100° petroleum ether*): m.p. 143.5–144°, lit.[9] m.p. 140°; λ_{max}^{KBr} 5.84 μ (C=O); $\lambda_{max}^{95\%\ EtOH}$ 237 mμ (ϵ 31,600) and 316 mμ (ϵ 6800); δ 3.01 (CH_3 singlet, three protons), 7.67–8.25 (aromatic multiplet, four protons), and 10.15 (CH singlet, one proton).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68. Found: C, 69.61; H, 4.64.

The hydrobromide of **2** was obtained as yellow plates (sublimation), m.p. 190–191°.

Anal. Calcd. for $C_{10}H_8N_2O \cdot HBr$: C, 47.45; H, 3.59; Br, 31.57. Found: C, 47.17; H, 3.70; Br, 31.29.

3-Bromomethyl-2-quinoxalinecarboxaldehyde (**3**).—A solution of 1.72 g. (0.01 mole) of **2** and 1.60 g. (0.01 mole) of bromine in 20 ml. of glacial acetic acid was heated at 60° for 30 min. Upon cooling and dilution to 100 ml. with water, the solution was extracted with three 30-ml. portions of petroleum ether (b.p. 30–60°). The combined extracts were evaporated to dryness, and

(12) Compound **16** was also obtained in lower yields by reaction of **14** with DMSO in such solvents as benzene, carbon tetrachloride, and chloroform but without scavenger. No such solvent effect was observed in the DMSO oxidation of **7** without scavenger.

(13) F. Bohlmann, *Ber.*, **84**, 860 (1951).

(14) Our preference for *trans* stereochemistry is based on the strong out-of-plane =CH deformation absorption at 10.26 μ observed in **17** [L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 45], and the ultraviolet absorption spectrum which suggests an extensively conjugated and, consequently, planar structure. Models indicate the *cis* isomer to be sterically crowded and nonplanar.

(15) Melting points are corrected. Boiling points are uncorrected. The infrared spectra were run on Perkin-Elmer Model 21 and 337 spectrophotometers; ultraviolet spectra were determined on a Cary 15 spectrophotometer and are reported in mμ followed by extinction in parentheses; the n.m.r. spectra were determined on a Varian A-60 spectrometer[16] and run in deuteriochloroform, unless otherwise noted, with tetramethylsilane as an internal reference.

(16) We acknowledge with pleasure the assistance of a National Science Foundation Grant GP-1482 to the Department of Chemistry toward the purchase of this instrument.

(17) S. Gabriel and A. Sonn, *Ber.*, **40**, 4850 (1907).

(18) R. W. Bost and E. E. Towell, *J. Am. Chem. Soc.*, **70**, 903 (1948).

the residue was purified by t.l.c.[19] The plate was developed with chloroform–benzene to yield bands at *ca.* 4 cm. (30% of unreacted **2**), 11 cm. (**3**, 30%), and 15 cm. (3-dibromomethyl-2-quinoxalinecarboxaldehyde **4**, 35%). The 11-cm. band was eluted with methylene chloride; the solution was evaporated to dryness and then recrystallized from chloroform to yield **3** as white plates: m.p. 158–159°; λ_{max}^{KBr} 5.82 μ (C=O); $\lambda_{max}^{95\% EtOH}$ 241 mμ (ϵ 29,600) and 321 mμ (ϵ 6500); δ 5.14 (CH_2 singlet, two protons), 7.06–8.40 (aromatic multiplet, four protons), and 10.26 (CH singlet, one proton).

Anal. Calcd. for $C_{10}H_7BrN_2O$: C, 47.83; H, 2.81. Found: C, 47.70; H, 2.75.

3-Dibromomethyl-2-quinoxalinecarboxaldehyde (4).—Bromine (3.2 g.) was added dropwise (30 min.) to a solution of 1.72 g. of **2** in 10 ml. of acetic acid, and the whole was heated at 60° for 1 additional hr. The reaction mixture was cooled, diluted with water, and neutralized, and the aqueous solution was extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate and evaporated to dryness to give crude **4** in almost quantitative yields (3.25 g.). Recrystallization from 50:50 petroleum ether–chloroform led to **4**, m.p. 171.5–172°, as grayish white plates: λ_{max}^{KBr} 5.82 μ (C=O); $\lambda_{max}^{95\% EtOH}$ 244 mμ (ϵ 31,000) and 325 mμ (ϵ 6800); δ 7.80–8.48 (aromatic multiplet and a masked CH, five protons) and 10.30 (CHO singlet, one proton).

Anal. Calcd. for $C_{10}H_6Br_2N_2O$: C, 36.39; H, 1.83. Found: C, 36.20; H, 2.05.

The 2,4-dinitrophenylhydrazone of **4** was obtained as yellow needles, m.p. 246–247°, from 50:50 ethanol–ethyl acetate.

Anal. Calcd. for $C_{16}H_{10}Br_2N_6O_4$: C, 37.67; H, 1.98. Found: C, 37.87; H, 2.14.

N.m.r. spectra of the 6- and 7-methyl (chloro) and 6,7-dimethyl (dichloro) derivatives of **4** reported in Table I are as follows: **4a**, δ 2.63 (CH_3 singlet, three protons), 7.72–8.36 (aromatic multiplet and a masked CH, four protons), and 10.32 (CHO singlet, one proton); **4b**, δ 2.58 (CH_3 singlet, six protons), 8.00–8.24 (aromatic multiplet and a masked CH, three protons), and 10.32 (CHO singlet, one proton); **4c**, δ 8.10 ($CHBr_2$ singlet, one proton), 8.16–8.44 (aromatic multiplet, three protons), and 10.34 (CHO singlet, one proton); **4d**, δ 8.00 ($CHBr_2$ singlet, one proton), 8.40 (aromatic singlet, two protons), and 10.24 (CHO singlet, one proton).

Preparation and Wittig Reaction on the Triphenylphosphonium Bromide Salt 6.—A solution of 0.063 g. of triphenylphosphine in 10 ml. of anhydrous DMSO was added dropwise (30 min.) under nitrogen to 0.060 g. of **3** dissolved in 10 ml. of DMSO. If this reaction was run in carbon tetrachloride, the salt **6** precipitated. Compound **6** was unstable and decomposed in the presence of air or moisture; the Wittig reaction was run directly on the solution of **6** in DMSO. The sodium methylsulfinyl carbanion solution was prepared by heating a solution of 0.264 g. (0.011 mole) of sodium hydride in 10 ml. of anhydrous DMSO.[20] To this was added the yellow-green solution of **6** in DMSO. The dark brown solution was diluted with water and extracted with petroleum ether to yield 0.066 g. of triphenylphosphine oxide. No other organic products could be identified.

2,3-Bis(bromomethyl)quinoxaline (7), m.p. 150–151°, lit.[21a] m.p. 150°, was obtained as tan crystals from the condensation of recrystallized *o*-phenylenediamine (Eastman) with 1,4-dibromo-2,3-butanedione[21b]: $\lambda_{max}^{95\% EtOH}$ 248 mμ (ϵ 37,300) and 337 mμ (ϵ 6800); δ 4.92 (CH_2 singlet, four protons) and 7.65–8.17 (aromatic multiplet, four protons).

Reduction of 7 with Zinc.—Activated zinc dust (0.5 g.), 1.0 g. of **7**, and 50 ml. of 75% ethanol were refluxed for 3 hr. The metal was removed by filtration, and the filtrate was concentrated to one-third its original volume. Extraction of the filtrate with three 5-ml. portion of ether, followed by evaporation of the combined extracts to dryness, gave a brown tar which was dissolved in petroleum ether and chromatographed on a 2.5 × 15 cm., neutral alumina column with petroleum ether as the eluent. Ultimately, 16% of a crude mixture of *cis*- and *trans*-2,3-dimethyl 1,2,3,4-tetrahydroquinoxaline was isolated. Repeated recrystallization from petroleum ether ultimately led to separation of the *cis* compound, m.p. 112–113°, lit.[4b] m.p. 114–115°, from the *dl-trans* derivative, m.p. 106–107°, lit.[4b] m.p. 104–105. Both the *cis* and *trans* compounds gave the appropriate color with 1% ferric chloride solution.

2,3-Bis(iodomethyl)quinoxaline (14) was recrystallized from acetone as long yellow needles: m.p. 145–145.5°, lit.[21a] m.p. 152–153°; $\lambda_{max}^{95\% EtOH}$ 252 mμ (ϵ 26,500) and 334 mμ (ϵ 6700); δ 4.82 (CH_2 singlet, four protons) and 7.58–8.06 (aromatic multiplet, four protons).

Anal. Calcd. for $C_{10}H_8I_2N_2$: C, 29.29; H, 1.97. Found: C, 29.18; H, 1.88.

1,3-Dihydrothieno[3,4-*b*]quinoxaline (8).—The general procedure of Cava and Deane[22] was used. Anhydrous sodium sulfide (0.01 mole) was prepared by dissolving 0.23 g. of sodium in absolute ethanol and then saturating the solution with *in situ* prepared hydrogen sulfide. The sodium hydrosulfide thus formed was neutralized (ice bath) with an equimolar quantity of sodium ethoxide in ethanol. To the sodium sulfide solution was then added 3.2 g. of **2** dissolved in 100 ml. of absolute ethanol. The white precipitate which formed immediately was filtered, and the filtrate was diluted to 300 ml. and extracted with three 50-ml. portions of petroleum ether. Evaporation to dryness left long pink needles of **8**, m.p. 112–113.5° (49%). Repeated recrystallizations from petroleum ether ultimately gave **8** as white needles, m.p. 116–116.5°. Compound **8** was mildly unstable in air and decomposed on oxidation with dilute peracetic acid: $\lambda_{max}^{95\% EtOH}$ 239 mμ (ϵ 24,000) and 231 mμ (ϵ 6100); δ 4.35 (CH_2 singlet, four protons) and 7.58–8.12 (symmetrical aromatic multiplet, four protons).

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.83; H, 4.25; N, 14.90; S, 17.02. Found: C, 64.06; H, 4.48; N, 14.83; S, 17.27.

Reduction of 8 With Raney Nickel.—The sulfide **8** (0.50 g.) was refluxed for 7.5 hr. in 42 ml. of absolute ethanol containing 5 g. of freshly prepared Raney nickel. Upon cooling, the insoluble material was filtered, and the filtrate, after dilution to 150 ml. with water, was extracted successively with three 50-ml. portions of petroleum ether and two 50-ml. portions of methylene chloride. The combined extracts were evaporated to dryness and purified by column chromatography over Woelm neutral alumina (activity grade I), for a yield 85% of **1** and recovery of 15% of unreacted **8**.

1,3-Dihydrothieno[3,4-*b*]quinoxaline Methyl Iodide (9).—Sulfide **8** (0.38 g., 2.0 mmoles) was stirred overnight under nitrogen in 20 ml. of anhydrous carbon tetrachloride containing 1.0 ml. (2.18 g., 15.3 mmoles) of methyl iodide. Solvent and excess methyl iodide were then removed by evaporation to leave a solid material which was triturated with boiling petroleum ether to remove unreacted **8** (20%). The violet-black residue, which melted at 200–240° with decomposition, defied purification by fractional crystallization and chromatographic techniques and decomposed both on sublimation and refluxing in higher boiling organic solvents. This residue (0.5 g.) was treated directly with 0.275 g. of freshly prepared phenyl lithium in 200 ml. of carbon tetrachloride and the whole was refluxed for 16 hr. Evaporation to dryness left a black residue from which no products could be separated or identified.

Quinoxaline [2,3-*c*]pyrroline-1′-spiro-1″-piperidinium Bromide (10).—Piperidine was added over a 6-hr. period to an ethanolic solution of **7**. The crude **10** was recrystallized twice from absolute ethanol to give **10** as white plates, m.p. 268–269° dec., lit.[23] m.p. 265–266° dec., in 66% yield. Under Stevens conditions,[24] the ultraviolet absorption spectrum of a solution of **10** showed no change after 5 hr. reflux in sodium hydroxide. The use of stronger bases (sodium hydride, potassium *t*-butoxide, and phenyl lithium) led only to unworkable tars. The ultraviolet absorption spectrum of **10** showed $\lambda_{max}^{95\% EtOH}$ 241 mμ (ϵ 33,500) and 322 mμ (ϵ 9400).

2,3-Bis(dibromomethyl)quinoxaline (11) was obtained quantitatively by the bromination of **1** in acetic acid as white needles (from acetone): m.p. 241–241.5°, lit.[25] m.p. 233°; $\lambda_{max}^{95\% EtOH}$ 252 mμ (ϵ 45,000) and 330 mμ (ϵ 8000); δ 7.72 (CH singlet, two protons) and 7.76–8.23 (aromatic multiplet, four protons).[26]

(19) Silica gel G (Brinkmann) with 13% calcium sulfate binder was used. The plates were prepared in the following manner: 60 g. of silica gel G [grain size: 60 μ (max., 5–10 μ)] were shaken for 90 sec. with 120 ml. of distilled water. This was spread on glass plates (8 × 40 in.) at 1-mm. thickness with a standard applicator. The plates were allowed to dry at 150° for 45 min.

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(23) J. K. Landquist and J. A. Silk, *J. Chem. Soc.*, 2052 (1956).

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(25) G. M. Bennett and G. H. Willis, *ibid.*, 1960 (1928).

(26) In DMSO-d_6.

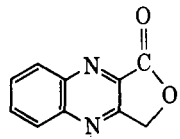
Anal. Calcd. for $C_{10}H_6Br_4N_2$: C, 25.35; H, 1.58; Br, 67.46; N, 5.91. Found: C, 25.45; H, 1.39; Br, 67.44; N, 5.90.

Finkelstein Reaction on 11.—Using the procedure of Cava and Napier,[4d] 10.0 g. of **4** and 13.5 g. of sodium iodide were refluxed for 68 hr. in 500 ml. of absolute ethanol containing 0.5 ml. of water. The yellow insoluble material (12.0 g.) was filtered and dissolved in warm benzene (protected from light). On cooling, a compound, tentatively identified as 2,3-bis(bromoiodomethyl)-quinoxaline, deposited in 12% yield. This light- and heat-sensitive material was recrystallized from benzene as yellow needles: m.p. 207–208°; $\lambda_{max}^{95\%\ EtOH}$ 242 mμ (ε 36,800), 294 mμ (ε 9300), and 320 mμ (shoulder).

Anal. Calcd. for $C_{10}H_6Br_2I_2N_2$: C, 21.08; H, 1.53. Found: C, 21.15; H, 1.07.

Work-up of the benzene mother liquors led only to unreacted **11**.

Reaction of 11 with Potassium *t*-Butoxide.—Compound **11** (11.25 g.) was added over a 10-min. period to a freshly prepared solution of potassium *t*-butoxide made by dissolving 7.0 g. of potassium in 150 ml. of anhydrous *t*-butyl alcohol. After stirring for 1 hr., the reaction mixture was poured onto ice and neutralized with acetic acid. Filtration gave 10.7 g. (95%) of unreacted **11**. Liquid–liquid extraction of the red filtrate with petroleum ether (b.p. 60–75°) gave, after evaporation of the extracts to dryness, 1% of a compound tentatively identified as the phthalide **20**.[27] Sublimation of this material at 150° led



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to a pale yellow solid which, after recrystallization from carbon tetrachloride, melted at 153°: λ_{max}^{KBr} 5.62 μ (C=O); $\lambda_{max}^{95\%\ EtOH}$ 245 and 326 mμ; δ 5.62 (CH_2 singlet, two protons) and 7.70–8.68 (aromatic multiplet, four protons).

Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.51; H, 3.25. Found: C, 64.82; H, 3.51.

General Reactions of 7 with DMSO.—DMSO was dried over calcium hydride for 24 hr. and distilled in *vacuo*. Compound **7** was recrystallized from acetone, dried *in vacuo*, and placed in a 100-ml. round-bottom flask equipped with a calcium chloride drying tube. As the reaction proceeded with stirring, the point of carbonyl formation was determined by periodically removing a drop of the reaction mixture and placing it in dilute ethanolic 2,4-DNP solution.[6] Aqueous solutions of other aldehyde reagents caused **7** to precipitate. 2,4-Dinitrophenylhydrazone formation was accompanied by a visible color change, yellow to varying shades of red. Upon completion of the reaction, the solution was extracted with petroleum ether (b.p. 30–60°), and the extracts were chilled below 10° to freeze out dissolved DMSO. The filtered petroleum ether solution was evaporated to dryness and the residue was separated by t.l.c. Results are summarized in Table II.

Preparation of Specific Products of the DMSO–2 Reaction. 3-Methyl-2-quinoxalinecarboxaldehyde (**2**).—Compound **7** (3.2 g., 0.01 mole) was dissolved in 12 ml. of DMSO and the solution was stirred for 24 hr. at 30°. The reaction mixture was then diluted with water to 80 ml., and the whole was extracted for 8 hr. with petroleum ether (b.p. 60–75°) using a liquid–liquid extractor. DMSO removal from extracts (by freezing), followed by evaporation of the extracts to dryness and recrystallization of the residue from petroleum ether (b.p. 90–100°), gave 0.53 g. (31%) of **2**, m.p. 140–141°.

3-Bromomethyl-2-quinoxalinecarboxaldehyde (**3**).—Compound **7** (3.2 g., 0.01 mole) was dissolved in 20 ml. of DMSO and stirred for 5.5 hr. at 30°. The reaction mixture was then diluted with water to 100 ml., and the whole was extracted with three 50-ml. portions of petroleum ether (b.p. 30–60°). After DMSO removal, evaporation of the extracts to dryness, followed by t.l.c. purification, ultimately led to 0.38 g. (15%) of **3**, m.p. 158–159°.

(27) This could have been formed by alkaline hydrolysis of **11** to the dialdehyde **12**, followed by an intramolecular Cannizzaro reaction to the acid alcohol, and lactonization to **20**.

TABLE II

REACTION OF 2,3-BIS(BROMOMETHYL)QUINOXALINE (**7**) IN DMSO

Compd. **7**, g.	DMSO, ml.	Temp., °C.	Time, hr.	Products (% yield)
1.0	15	30	5.5	**2** (5–6)
				3 (10–15)
				4 (2–6)
1.0	12	30	24	**2** (31)
				3 (1)
				4 (2)
				11 (4)
1.0	12	60	1	**2** (trace)
				3 (10–12)
				4 (2–9)
1.0	15	60	6	**4** (29)
				11 (2)
				13 (60)
1.0	15	90	0.75[a]	**4** (30)
				11 (trace)
				13 (60)

[a] If heating was prolonged to 1.5 hr., only difficultly separable tars were obtained.

3-Dibromomethyl-2-quinoxalinecarboxaldehyde (**4**).—Compound **7** (2.0 g., 0.00625 mole) was dissolved in 20 ml. of DMSO and stirred for 45 min. at 90°. Upon cooling and dilution to 100 ml. with water, the reaction mixture was extracted with three 50-ml. portions of petroleum ether (b.p. 30–60°). After DMSO removal, evaporation of the combined extracts to dryness left 0.63 g. (30%) of crude **4**. Recrystallization of this material from 50:50 petroleum ether–chloroform gave pure **4**, m.p. 171.5–172°.

1,3-Dihydro-1,3-dihydroxyfuro[3,4-*b*]quinoxaline (**13**).—The aqueous DMSO solution remaining after the extraction of **4** in the previous preparation was allowed to stand for 24 hr., whereupon a brown solid precipitated. The material was collected by filtration, washed with water, and air dried to give 1.2 g. (60%) of crude **13**. Recrystallization from water gave pure **13** as fine white needles which lost water on heating to melt at 176.5–177° dec. (*cf.* melting point of **12**): λ_{max}^{KBr} 3.19 μ (OH), no carbonyl absorption; $\lambda_{max}^{95\%\ EtOH}$ 238 mμ (ε 30,400) and 322 mμ (ε 8100). The n.m.r. spectrum had a CH doublet centered at δ 6.48 (two protons, J = 8 c.p.s.), an OH doublet centered at 7.36 (two protons, J = 8 c.p.s.), and an aromatic multiplet at 7.80–8.42 (four protons).[26]

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; mol. wt., 204. Found: C, 58.74; H, 4.06; mol. wt., 208.

2,3-Quinoxalinedicarboxaldehyde (**12**).—The dialdehyde **12** was prepared by subliming **13** at 110–120° (2 mm.). The pale green crystals which formed were resublimed to yield **12** as white flakes: m.p. 177–178° dec.; λ_{max}^{Nujol} 5.84 μ (C=O); $\lambda_{max}^{abs\ EtOH}$ 238 mμ (ε 28,000) and 332 mμ (ε 9100); δ 8.02–8.54 (aromatic multiplet, four protons) and 10.50 (CH singlet, two protons).[26]

Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.51; H, 3.25; mol. wt., 186. Found: C, 64.62; H, 3.22; mol. wt., 178.

Reaction of 14 with DMSO.—Compound **14** (1.0 g.) was dissolved in 20 ml. of DMSO and stirred at 60° for 1 hr. The reaction mixture was then diluted with water to 100 ml., and the whole was extracted with three 50-ml. portions of petroleum ether. After DMSO removal by freezing, the extracts were evaporated to dryness and the residue was separated by t.l.c. The bands were eluted with methylene chloride to lead to a 5% yield of **2** and 1% of 3-iodomethyl-2-quinoxalinecarboxaldehyde (**5**) as white flakes, m.p. 138.5–139.5° sub. The infrared spectrum of **5** showed λ_{max}^{KBr} 5.83 μ (C=O); the ultraviolet spectrum showed $\lambda_{max}^{95\%\ EtOH}$ 243 mμ (ε 31,900) and 324 mμ (ε 7500); n.m.r. spectrum gave δ 5.20 (CH_2 singlet, two protons), 7.14–8.26 (aromatic multiplet, four protons), and 10.30 (CH singlet, one proton).

Anal. Calcd. for $C_{10}H_7IN_2O$: C, 40.29; H, 2.37. Found: C, 40.43; H, 2.31.

Running the DMSO–**14** reaction at 30° for 24 hr. or at 100° for 1 hr. raised the yields of **2** to 25–28%; however, no **5** could be isolated under these conditions. Compound **5** would also be obtained by reaction of **3** with sodium iodide in acetone.

Oxidation of 7 and 14 with DMSO in the Presence of 1,2-Epoxy-3-phenoxypropane.—Compound **7** (1.0 g.) and 2.0 ml. of

1,2-epoxy-3-phenoxypropane (Aldrich) were dissolved in 10 ml. of DMSO, and the stirred solution was heated at 90° for 1 hr. (or at 30° for 48 hr.). On cooling, the bright yellow, insoluble material was filtered on a sintered-glass funnel and washed successively with water, acetone, and petroleum ether. Crude *dl*-1,2-dibromo-1,2-bis(3-methyl-2-quinoxalyl)ethane (**15**, 11%) was recrystallized from dimethylformamide as yellow needles which darkened between 250 and 270° and did not melt below 350°: $\lambda_{max}^{95\% EtOH}$ 242 and 325 mμ.[28]

Anal. Calcd. for $C_{20}H_{16}Br_2N_4$: C, 50.87; H, 3.41; N, 11.87. Found: C, 50.67; H, 3.37; N, 11.70.

Addition of water to the original filtrate precipitated 0.35 g. (35%) of crude unreacted **7**.

Similarly **14** (2.0 g.), 2.0 ml. of 1,2-epoxy-3-phenoxypropane, and 15 ml. of DMSO were warmed to solution and then stirred for 12 hr. at room temperature. The resulting orange precipitate was filtered and washed successively with water, acetone, and petroleum ether. This crude material was insoluble in dimethylformamide. Ultimately, trituration with petroleum ether left *dl*-1,2-diiodo-1,2-bis(3-methyl-2-quinoxalyl)ethane (**16**, 15%) as a bright orange powder: m.p. 194–195° dec, $\lambda_{max}^{95\% EtOH}$ 237 and 322 mμ.[28]

Anal. Calcd. for $C_{20}H_{16}I_2N_4$: C, 42.43; H, 2.85. Found: C, 42.42; H, 2.61.

trans-**1,2-Bis(3-methyl-2-quinoxalyl)ethylene** (**17**). **A. By Dehalogenation.**—Compound **17** was obtained by the following various routes: (i) reaction of **15** with sodium iodide in refluxing acetone for 5 days gave a 10% yield of **17**; (ii) sublimation of **16** at 150° (2 mm.); and (iii) refluxing **16** in acetone. Procedure iii was as follows: 0.100 g. of **16** was dissolved over a 16-hr. period in 250 ml. of refluxing acetone. The solution was then reduced in volume to 25 ml. by evaporation and refrigerated. A brown fluorescent solid (55 mg.) precipitated. This crude material was filtered, dissolved in 30 ml. of methylene chloride, and deposited on an Woelm acid alumina column (activity grade II). Elution with methylene chloride led to the first and major fraction which was collected; the eluate volume was reduced to 10 ml., and the product was further purified by t.l.c. using 90:10 chloroform–acetic acid as the developer. The bright yellow fluorescent material obtained in this manner was collected and recrystallized from acetone–methylene chloride to yield 15 mg. of **17**, as yellow flakes: m.p. 259.5–260.5°; $\lambda_{max}^{95\% EtOH}$ 235 mμ (ε 16,900), 278 (24,200), and 382 (24,800); δ 2.98 (CH_3 singlet, six protons), 8.44 (CH singlet, two protons), and 7.56–8.32 (aromatic multiplet, eight protons).

Anal. Calcd. for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16. Found: C, 76.90; H, 5.05.

B. Condensation of 2,3-Dimethylquinoxaline (**1**) **with 3-Methyl-2-quinoxalinecarboxaldehyde** (**2**).—Equimolar quantities of **1** (0.158 g.) and **2** (0.172 g.) in 10 ml. of acetic anhydride were refluxed for 8 hr. On cooling, the precipitated **17** (56%) was collected by filtration, washed with water, and recrystallized from methylene chloride to yield **17** as yellow needles.

Ozonolysis of 17.—Ozone–oxygen (0.75 mmole of O_3) was bubbled through a solution of **17** (0.078 g., 0.25 mmole) in 100 ml. of methylene chloride at −78°. The now colorless solution was reduced with 40 ml. of a 5% acetic acid solution containing 2.0 g. of sodium iodide. The methylene chloride solution was then washed with 20 ml. of 10% sodium thiosulfate solution, dried over anhydrous sodium sulfate, and, after filtration, evaporated to dryness. The tan residue (0.082 g., 95%) was recrystallized from petroleum ether (b.p. 90–100°) to give pure **2**, m.p. 140–141°.

meso-**1,2-Dibromo-1,2-bis(3-methyl-2-quinoxalyl)ethane** (**18**). —Compound **17** (0.050 g.) was dissolved in 100 ml. of hot carbon tetrachloride, and to this solution was added (15 min.) 0.026 g. of bromine dissolved in 7 ml. of carbon tetrachloride. The solution was stirred and warmed for an additional 30 min.; evaporation to dryness quantitatively left crude **18**. Recrystallization of this material from petroleum ether (b.p. 90–100°) gave pure **18** as a yellow powder: m.p. 172–173° dec.; $\lambda_{max}^{95\% EtOH}$ 244 and 325 mμ.[28]

Anal. Calcd. for $C_{20}H_{16}Br_2N_4$: C, 50.87; H, 3.41. Found: C, 50.82; H, 3.49.

Bis(3-methyl-2-quinoxalyl)glyoxal (**19**).—The *dl* dibromide **15** (0.100 g.), suspended in 5 ml. of DMSO, was heated in an oil bath at 110° until all the solid had dissolved (30 min.). The brown solution was then refrigerated overnight. The resulting dark brown precipitate was filtered to yield 0.048–0.062 g. (67–86%) of crude product, which was successively washed with 10% NaOH solution, water, acetone, and ether, and then recrystallized from DMSO to give **19** as a brown powder. This material was contaminated with a noncombustible ash. Finally, sublimation at 220° (0.5 mm.) gave **19** as a yellow powder: m.p. 285–290° dec.; λ_{max}^{KBr} 5.87 μ (C=O); $\lambda_{max}^{95\% EtOH}$ 237, 281, and 324 mμ.[28]

Anal. Calcd. for $C_{20}H_{14}N_4O_2$: C, 70.16; H, 4.12. Found: C, 70.05; H, 4.35.

Compound **18** (0.025 g.) dissolved in 1 ml. of DMSO and heated at 120–125° for 1 hr. led to the same **19** [superimposable infrared spectra, similar melting point behavior (283–287° dec.) and ultraviolet absorption maximum] in 53–57% yield. Similarly DMSO oxidation of **16** led to **19** in 5% yield.

Irradiation of 2,3-Bis(iodomethyl)quinoxaline (**14**).—Compound **14** (1.0 g.) was dissolved under nitrogen in 50 ml. of anhydrous thiophene-free benzene contained in a 150-ml. soft-glass bottle. This solution was irradiated for 8 hr. in summer sunlight The solution was evaporated to a volume of 10 ml. and deposited on a 2.5 × 15 cm. column packed with Woelm neutral alumina (activity grade I). Elution with petroleum ether gave 0.21 g. (55%) of **1** in the first fraction. No other material could be isolated.

Exposed to air and sunlight, **14** dissolved in 50 ml. of carbon disulfide gave, after 8 hr., 22% of 3-iodomethyl-2-quinoxalinecarboxaldehyde (**5**). In benzene solvent, the reaction produced **5** in less than half the time. If these solutions were permitted to stand 2 weeks, an 80% yield of **13** was obtained.

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(28) Insolubility prevented calculation of extinction and determination of n.m.r. spectra.

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