the crystal of 3-deazaadenosine. The molecules which do interact, to some extent, are those related by the *a*-axis translation. The planar base moieties of these molecules are separated by approximately 3.47 Å with an almost complete overlap of atoms C(6), H1N(6), and H2N(6) of one molecule with atoms C(3), N(1), and C(5), respectively, of the other molecule. The interatomic separations, C(6)-C(3) = 3.51 Å, H1N(6)—N(1) = 3.55 Å and H2N(6)-C(5) = 3.55 Å, when compared with the interplanar separation of 3.47 Å indicate quite clearly an almost perfect overlap of the respective atoms but, as stated above, very little stacking interaction because of the large distances involved.

Acknowledgments. This research was supported by Public Health Service Grant No. CA-15171-02 from the National Cancer Institute. We are also grateful to our colleague Professor L. G. Pedersen for helpful discussions concerning the molecular orbital calculations.

Supplementary Material Available. Tables III (Observed and Calculated Structure Amplitudes for 3-Deazaadenosine), IV (Bond Lengths Involving the Hydrogen Atoms), V (Bond Angles Involving the Hydrogen Atoms), VI (Deviations of Atoms from the Least-Squares Planes), and VII (Distances and Angles Associated with the Hydrogen Bonds) (11 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) University of North Carolina; (b) University of Utah.
(2) (a) A. Bloch in "Drug Design", Vol. IV, E. J. Ariëns, Ed., Academic Press, New York, N.Y., 1973, pp 285–378; (b) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970.
(3) R. M. Stroud, *Acta Crystallogr., Sect. B*, **29**, 690 (1973).
(4) J. Abola and M. Sundaralingam, *Acta Crystallogr., Sect. B*, **29**, 697 (1973).
(5) R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Biochemistry*, **5**, 756 (1966).
(6) J. A. May, Jr., and L. B. Townsend, *J. Chem. Soc., Chem. Commun.*, 64 (1973).
(7) P. C. Zamecnik, *Biochem. J.*, **85**, 257 (1962).
(8) W. L. Busing and H. A. Levy, *Acta Crystallogr.*, **22**, 457 (1967).
(9) P. W. R. Corfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).
(10) M. Meyer, P. Singh, W. E. Hatfield, and D. J. Hodgson, *Acta Crystallogr., Sect. B*, **28**, 1607 (1972).
(11) H. Hauptman and J. Karle, American Crystallographic Association Monograph No. 3, 1953.
(12) P. Main, M. M. Woolfson, and G. Germain, "A Computer Program for the Automatic Solution of Crystal Structures", Department of Physics, University of York, York, England, 1971.
(13) W. L. Busing, K. O. Martin, and H. A. Levy, Oak Ridge National Laboratory Report ORNL-TM-305. Oak Ridge, Tenn.
(14) "International Tables for X-Ray Crystallography", Vol. III, Birmingham, England, Kynoch Press, Table 3.3.1A.
(15) R. F. Stewart, E. R. Davidson, and W. R. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(16) W. H. Zachariasen, *Acta Crystallogr., Sect. A*, **24**, 212 (1968).
(17) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(18) J. Donohue and K. N. Trueblood, *J. Mol. Biol.*, **2**, 363 (1960).
(19) M. Sundaralingam, *Biopolymers*, **7**, 821 (1969).
(20) A. E. V. Haschemeyer and A. Rich, *J. Mol. Biol.*, **27**, 369 (1967).
(21) S. Sprang and M. Sundaralingam, *Acta Crystallogr., Sect. B*, **29**, 1910 (1973).
(22) P. Prusiner and M. Sundaralingam, *Acta Crystallogr., Sect. B*, **29**, 2328 (1973).
(23) T. F. Lai and R. E. Marsh, *Acta Crystallogr., Sect. B*, **28**, 1982 (1972).
(24) E. Ohtsuka, T. Nagura, K. Shimokawa, S. Nishikawa, and M. Ikehara, *Biochem. Biophys. Acta*, **383**, 236 (1975).
(25) M. Sundaralingam, *J. Am. Chem. Soc.*, **93**, 6644 (1971).
(26) (a) M. Sundaralingam *Jerusalem Symp. Quantum Chem. Biochem.*, **5**, 450 (1973); (b) *ibid.*, **5**, 438 (1973).
(27) P. Singh and D. J. Hodgson, *Biochemistry*, **13**, 5445 (1974).
(28) See, however, F. Jordan, *J. Am. Chem. Soc.*, **96**, 5911 (1974), and references cited therein, for a more detailed analysis of the relationship between atomic charges and basicities.
(29) The significance of a difference of 0.02 e in the net atomic charge density can be appreciated by the fact that, in a typical charge density calculation, the positive charge on an $-NH_2$ proton increased by a 0.0014 e when the bond length was decreased by 0.01 Å and by 0.0163 e when the bond length was decreased by 0.19 Å. It is clear, therefore, that charge density changes of the order of 0.02 e could not arise from slight errors in the dimensions of the molecule. Correlations based on similar changes in charge densities have been made by others.[28]
(30) B. Pullman and H. Berthod, *Jerusalem Symp. Quantum Chem. Biochem.*, **5**, 209 (1973).
(31) These regions may be compared with the allowed regions given as $-10 \leq \chi_{CN} \leq 60°$ and $85 \leq \chi_{CN} \leq 140°$ in Table 3 of ref 20 based on normal contact for C(3')-*endo* purine nucleosides (note the change of sign from ϕ_{CN}, used in ref 20, to χ_{CN}[19]). The major difference in the allowed regions quoted above and those calculated for 3-deazaadenosine is the presence in the latter of a small barrier in the range $113 \leq \chi_{CN} \leq 144°$ due to the contact of HC(8) with HC(2').
(32) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids", W. A. Benjamin, New York, N.Y., 1968, p 16.
(33) S. H. Kim and A. Rich, *Proc. Natl. Acad. Sci. U.S.A.*, **60**, 402 (1968).

Syntheses of Isoalloxazines and Isoalloxazine 5-Oxides. A New Synthesis of Riboflavin[1]

Fumio Yoneda,*[2a] Yoshiharu Sakuma,[2a] Misuzu Ichiba,[2b] and Kazuko Shinomura[2b]

Contribution from the Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan, and Pharmaceutical Institute, School of Medicine, Keio University, Shinanomachi, Shinjuku-ku 160, Tokyo, Japan. *Received June 5, 1975*

Abstract: The nitrosative and nitrative cyclizations of 6-(*N*-alkylanilino)uracils gave the corresponding isoalloxazine 5-oxides including riboflavin 5-oxide. The reduction of the 5-oxides with sodium dithionite in water gave the corresponding isoalloxazines. The condensation of 6-alkylaminouracils with nitrosobenzenes in acetic anhydride also gave isoalloxazines. The *m*-chloroperbenzoic acid oxidation of riboflavin in acetic acid gave 7,8-dimethyl-10-acetoxymethylisoalloxazine 5-oxide, which was unstable toward hydrolysis, producing lumichrome.

The traditional synthetic routes to isoalloxazines involve the condensations of (a) *o*-phenylenediamines with alloxan, alloxantin, dialuric acid, or halobarbituric acid; (b) 2-arylazoanilines with barbituric acid; (c) anilines with violuric acid; (d) *o*-benzoquinones with 5,6-diaminopyrimidines; (e) dimeric biacetyl with diaminouracils, or diacetyl with preformed lumazines; and (f) quinoxalines with guanidine. These procedures are well documented in the literature.[11] We now wish to report two new and convenient syntheses of isoalloxazines including riboflavin, which consist of (1) the nitrosative and nitrative cyclizations of 6-(*N*-alkylanilino)uracil precursors followed by deoxygenation of the isoalloxazine 5-oxides thus obtained, and (2) the condensation reaction of 6-alkylaminouracils with nitrosobenzenes.[1] Ad-

Scheme I

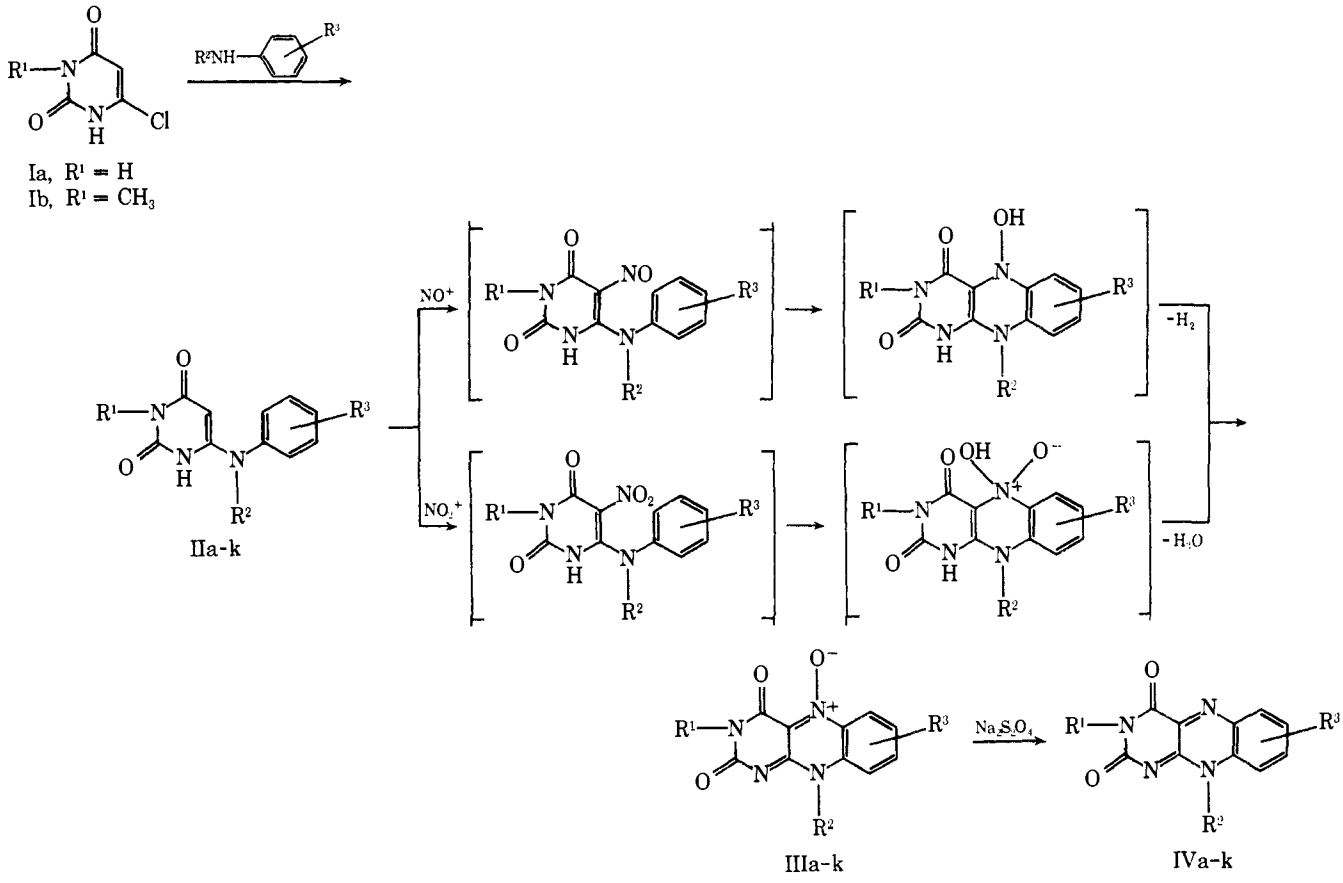
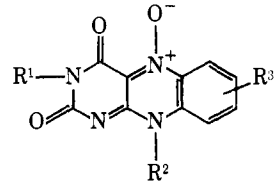


Table I. Isoalloxazine 5-Oxides



Compd no.	R¹	R²	R³	Mp, °C	Yield, %[a] A	Yield, %[a] B	Formula	Analyses
IIIa	H	CH_3	H	>360	82	76	$C_{11}H_8N_4O_3$	C, H, N
IIIb	H	C_2H_5	H	305	83		$C_{12}H_{10}N_4O_3$	C, H, N
IIIc	H	n-C_3H_7	H	336	80		$C_{13}H_{12}N_4O_3$	C, H, N
IIId	H	n-C_4H_9	H	328	90		$C_{14}H_{14}N_4O_3$	C, H, N
IIIe	CH_3	CH_3	H	322	86	77	$C_{12}H_{10}N_4O_3$	C, H, N
IIIf	CH_3	C_2H_5	H	267	89	80	$C_{13}H_{12}N_4O_3$	C, H, N
IIIg	CH_3	n-C_3H_7	H	319	86		$C_{14}H_{14}N_4O_3$	C, H, N
IIIh	CH_3	n-C_4H_9	H	308	91		$C_{15}H_{16}N_4O_3$	C, H, N
IIIi	H	CH_3	7,8-$(CH_3)_2$	>350	80	78	$C_{13}H_{12}N_4O_3$	C, H, N
IIIj	CH_3	CH_3	7,8-$(CH_3)_2$	283	85	80	$C_{14}H_{14}N_4O_3$	C, H, N
IIIk	H	D-Ribityl	7,8-$(CH_3)_2$	225 dec	85	75	$C_{17}H_{20}N_4O_7$	C, H, N

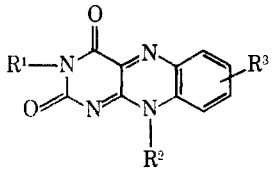
[a] Method A, nitrosative cyclization; method B, nitrative cyclization.

ditionally, we wish to describe the *m*-chloroperbenzoic acid oxidation of riboflavin, which leads eventually to the elimination of the ribityl side chain to give lumichrome.

Isoalloxazine Synthesis via Its 5-Oxide

Fusion of 6-chlorouracil (Ia) with *N*-methylaniline for 10 min gave 6-(*N*-methylanilino)uracil (IIa) in good yield. Similarly, fusion of Ia or 3-methyl-6-chlorouracil (Ib) with several *N*-alkylanilines gave the corresponding 6-(*N*-alkylanilino)uracil derivatives (IIb–j) (see Table IV in the Experimental Section). Nitrosation of II with excess sodium nitrite in acetic acid at room temperature led to the exclusive formation of isoalloxazine 5-oxides (IIIa–j) in good yields (see Table I). It is noted that III is the first representative of the isoalloxazine *N*-oxide system. The structures of III were assigned by elemental analyses, satisfactory spectral data, especially the presence of their strong parent ions, and remarkable M − 16 ions in their mass spectra. Furthermore, several of the derivatives were identified with authentic samples prepared by the direct oxidation of the respective isoalloxazines with *m*-chloroperbenzoic acid (vide infra).

Table II. Isoalloxazines



Compd no.	R^1	R^2	R^3	Mp, °C	Yield, %	Formula	Analyses
IVa[a]	H	CH_3	H	>360	95	$C_{11}H_8N_4O_2$	C, H, N
IVb	H	C_2H_5	H	347	93	$C_{12}H_{10}N_4O_2$	C, H, N
IVc	H	n-C_3H_7	H	349	96	$C_{13}H_{12}N_4O_2$	C, H, N
IVd	H	n-C_4H_9	H	335	98	$C_{14}H_{14}N_4O_2$	C, H, N
IVe[b]	CH_3	CH_3	H	334	93	$C_{12}H_{10}N_4O_2$	C, H, N
IVf	CH_3	C_2H_5	H	299	95	$C_{13}H_{12}N_4O_2$	C, H, N
IVg	CH_3	n-C_3H_7	H	332	95	$C_{14}H_{14}N_4O_2$	C, H, N
IVh	CH_3	n-C_4H_9	H	315	98	$C_{15}H_{16}N_4O_2$	C, H, N
IVi[c]	H	CH_3	7,8-$(CH_3)_2$	330 dec	90	$C_{13}H_{12}N_4O_2$	C, H, N
IVj[d]	CH_3	CH_3	7,8-$(CH_3)_2$	318	92	$C_{14}H_{14}N_4O_2$	C, H, N
IVk[e]	H	D-Ribityl	7,8-$(CH_3)_2$	280 dec	85	$C_{17}H_{20}N_4O_6$	

[a] R. Kuhn and F. Weygand, *Chem. Ber.*, 67, 1409 (1934). [b] R. Kuhn and F. Weygand, *ibid.*, 67, 1459 (1934). [c] P. Hemmerich, S. Fallab, and H. Erlenmeyer, *Helv. Chim. Acta*, 39, 1242 (1956). [d] P. Hemmerich and H. Erlenmeyer, *ibid.*, 40, 180 (1957). [e] Riboflavin.

Table III. Visible and Uv Maxima of Isoalloxazine 5-Oxides (III) and Isoalloxazines (IV)

Compd no.	λ_{max} (EtOH), nm (log ϵ)	λ_{max} (5 N HCl in 50% EtOH), nm (log ϵ)
IIIa	451 (3.69), 355 sh (3.64), 340 (3.74), 265 (4.33), 213 (3.96)	395 sh (3.58), 369 (3.79), 267 (4.27)
IIIb	450 (3.66), 356 sh (3.65), 341 (3.70), 265 (4.26), 212 (3.95)	395 sh (3.66), 368 (3.84), 268 (4.27)
IIIc	452 (4.04), 356 sh (4.04), 340 (4.10), 266 (4.67), 213 (4.34)	395 sh (4.01), 368 (4.19), 268 (4.34)
IIId	452 (3.85), 354 sh (3.85), 341 (3.91), 266 (4.49), 212 (4.14)	396 sh (3.77), 368 (3.98), 268 (4.44)
IIIe	452 (3.85), 355 sh (3.88), 342 (3.96), 271 (4.49), 213 (4.02)	397 sh (3.80), 367 (4.04), 271 (4.51)
IIIf	451 (3.75), 356 sh (3.78), 342 (3.85), 271 (4.58), 213 (4.07)	398 sh (3.64), 366 (3.89), 270 (4.36)
IIIg	453 (3.82), 356 sh (3.86), 343 (3.92), 271 (4.48), 212 (4.10)	395 sh (3.76), 367 (3.99), 270 (4.60)
IIIh	453 (3.87), 358 sh (3.92), 343 (3.98), 271 (4.55), 213 (4.26)	397 sh (3.81), 367 (4.06), 270 (4.52)
IIIj	461 (3.93), 362 sh (3.92), 348 (3.93), 275 (4.61), 217 (4.34)	388 (4.12), 273 (4.68)
IIIk[a]	461 (3.72), 370 (3.71), 272 (4.37), 217 (4.23)	393 (3.88), 272 (4.27)
IVa	436 (3.93), 333 (3.77), 267 (4.46), 217 (4.37)	369 (4.11), 259 (4.38), 213 (4.33)
IVb	436 (3.98), 333 (3.81), 267 (4.50), 219 (4.43)	369 (4.10), 259 (4.37), 213 (4.34)
IVc	437 (3.84), 334 (3.67), 267 (4.36), 219 (4.26)	369 (3.96), 259 (4.24), 215 (4.18)
IVd	439 (3.92), 338 (3.82), 267 (4.47), 219 (4.31)	369 (4.07), 262 (4.37), 214 (4.26)
IVe	438 (3.92), 334 (3.82), 268 (4.51), 218 (4.40)	368 (4.10), 259 (4.40), 214 (4.30)
IVf	438 (4.01), 335 (3.90), 269 (4.58), 219 (4.44)	368 (4.16), 259 (4.44), 215 (4.34)
IVg	440 (4.01), 335 (3.91), 269 (4.59), 219 (4.44)	368 (4.13), 259 (4.41), 215 (4.32)
IVh	438 (3.95), 336 (3.86), 270 (4.55), 218 (4.43)	368 (4.13), 260 (4.42), 216 (4.31)
IVj	447 (4.02), 349 (3.90), 271 (4.53), 223 (4.45)	393 (4.23), 265 (4.47), 221 (4.35)
IVk[a]	447 (4.03), 373 (3.96), 268 (4.46), 224 (4.41)	396 (4.29), 267 (4.47), 222 (4.31)
IVl	434 (4.23), 338 (4.09), 269 (4.71), 224 (4.67)	389 (4.46), 259 (4.57), 222 (4.57)

[a] These spectra were taken in water and 5 N hydrochloric acid, because these compounds were not soluble in ethanol.

The deoxygenation of III with sodium dithionite in water yielded the corresponding isoalloxazines (IVa-j) in almost quantitative yields (Table II). This new isoalloxazine synthesis has been extended to the preparation of riboflavin. Thus, the heating of Ia with N-D-ribityl-3,4-xylidine in dimethylformamide for a few minutes afforded 6-(N-D-ribityl-3,4-xylidino)uracil (IIk). In this reaction, heating for a long time should be avoided, because the ribityl side chain is eliminated to give 6-(3,4-xylidino)uracil. The nitrosation of IIk with excess sodium nitrite in acetic acid at slightly higher than room temperature led to the formation of riboflavin 5-oxide (IIIk). The treatment of IIIk with sodium dithionite in water yielded riboflavin (IVk).

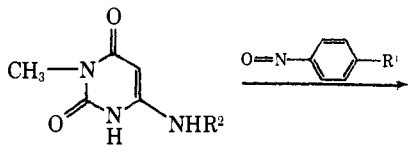
Compound IIIk appeared to be stable in its solid state but sensitive in ethanolic solution toward light. The irradiation of IIIk in ethanol or acetonitrile under aerobic conditions caused deoxygenation at first and then elimination of the ribityl side chain to give lumichrome.[3]

The isoalloxazine 5-oxides described above were also obtained by the nitrative cyclization of II.[1b] Thus, heating of II in acetic acid with potassium nitrate in the presence of sulfuric acid gave the corresponding isoalloxazine 5-oxides (III) in slightly lower yields than by the nitrosative cyclization (Table I).

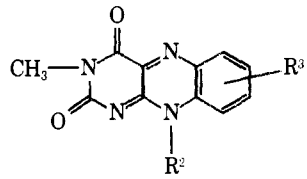
Although the identity of the products prepared by nitrosation and nitration of II has been observed as stated above, the reaction pathways would be different. A reasonable intermediate in the former process is the hydroxylamine which is formed by the cyclization of a 5-nitroso derivative. Dehydrogenation with excess nitrous acid gives III on the analogy of the formation of alloxazine 5-oxides in the nitrosation of 6-anilinouracils.[4] The latter process involves apparently the key intermediates 6-(N-alkylanilino)-5-nitrouracils which undergo dehydrative cyclization in the presence of the acid catalyst to give III (see Scheme I).

Absorption maxima for the isoalloxazine 5-oxides synthesized in this study are presented and compared by those of the corresponding isoalloxazines in Table III. It is apparent from these data that III show maxima similar to the flavins; one band in the 450-nm region, and one in the 340-nm region, and two in the uv region are seen in ethanolic solution. In general, the longest wavelength bands of III show red

Scheme II



Va, $R^2 = CH_3$
Vb, $R^2 = C_2H_5$



IVe, $R^2 = CH_3$; $R^3 = H$
IVf, $R^2 = C_2H_5$; $R^3 = H$
IVl, $R^2 = CH_3$; $R^3 = 8\text{-}Cl$

shifts of 13–15 nm compared with those of IV. On the protonation of III, the longest wavelength maxima are shifted to shorter wavelength, while the next bands are shifted to longer wavelength; these blue and red shifts are quite similar to the behavior of the typical flavins.[5]

Isoalloxazine Synthesis by the Condensation of 6-Alkylaminouracils with Nitrosobenzenes

The refluxing of 3-methyl-6-methylaminouracil (Va) or 6-ethylamino-3-methyluracil (Vb) with excess nitrosobenzene in acetic anhydride for 20 min, followed by dilution with water, caused the separation of IVe or IVf, identical in all respects with the products prepared by the former method. Similarly, the condensation of Va with *p*-chloronitrosobenzene under the same conditions gave 8-chloro-3,10-dimethylisoalloxazine (IVl).

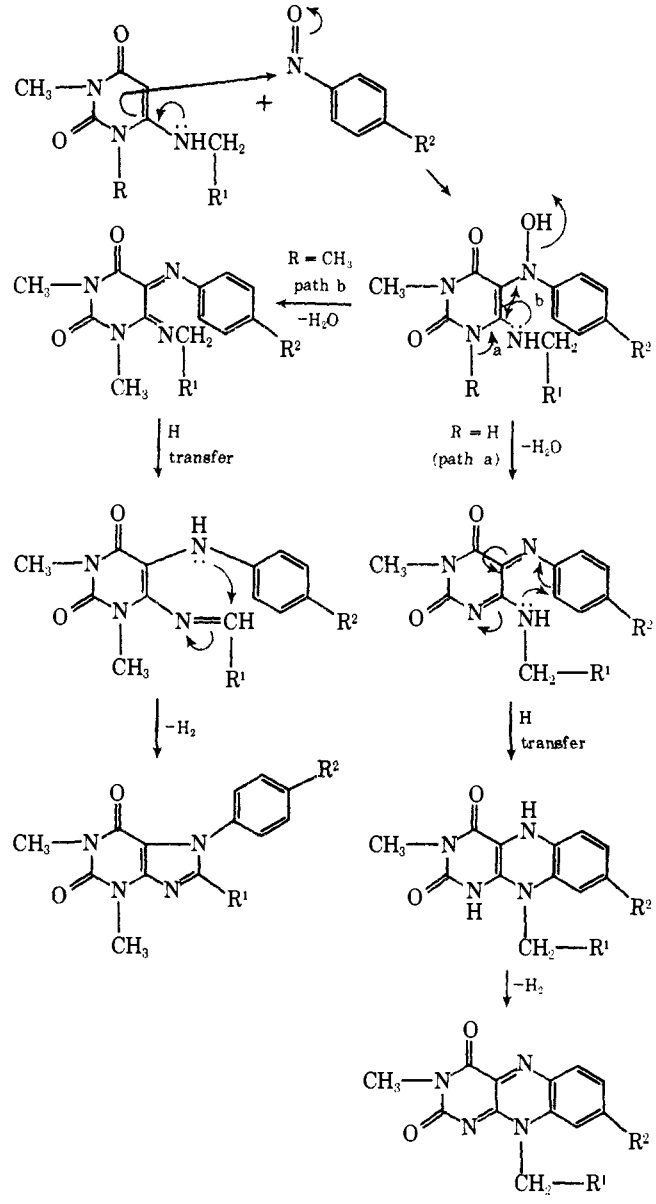
This process is a successful application of the known alloxazine synthesis from 6-amino-1,3-dimethyluracil and nitrosobenzene.[6] However, it is interesting to note that the reaction of 6-alkylamino-1,3-dimethyluracils with nitrosobenzenes under the same conditions does not afford 1,3-dimethyl-10-alkylleucoflavins but the corresponding 7-aryltheophyllines.[7]

We suggest that this new isoalloxazine synthesis involves the intermediacy of a 5-hydroxylamine derivative, whose dehydration to the diimine by path a is presumably facilitated by the presence of acidic hydrogen at the 3 position of the uracil. Cyclization and hydrogen transfer would then give the 1,5-dihydroisoalloxazine, which is dehydrogenated with excess nitrosobenzene to lead the isoalloxazine. However, it appears that the use of a 6-alkylamino-1,3-dimethyluracil in this condensation prevents the final dehydrogenation step and therefore has a preference for the pathway to the aromatization leading to the 7-aryltheophylline, as had been already discussed[7] (Scheme III).

Oxidation of Riboflavin with *m*-Chloroperbenzoic Acid in Acetic Acid

In connection with the new syntheses of isoalloxazine 5-oxides, we have carried out the *m*-chloroperbenzoic acid oxidation of riboflavin in acetic acid. The heating of riboflavin with excess *m*-chloroperbenzoic acid in acetic acid for several hours, followed by concentration of the reaction solution and dilution with ether, caused the separation of fluorescing yellow prisms in moderate yield.[8] This product had the following spectral characteristics: uv and visible maxima (EtOH) 465 sh (3.62), 446 (3.72), 429 sh (3.65), 354 (3.59), 270 (4.10), and 224 (4.15); NMR (CF_3COOH, Me_4Si) 8.09 (s, 1, C-6 H), 8.06 (s, 1, C-9 H), 6.68 (s, 2, C-1′ H), 2.79 (s, 3, C-8 methyl H), 2.65 (s, 3, C-7 methyl H), 2.29 (s, 3, $COCH_3$); ir (Nujol) ester absorptions at 1740 and 1228 cm^{-1}. These data appeared to be consistent with 7,8-dimethyl-10-acetoxymethylisoalloxazine 5-oxide (VI), whose structure was ascertained by elemental analysis. Compound VI was relatively stable toward light but sensitive in alkaline medium. The treatment of VI with both potassium hydroxide in aqueous alcohol and sodium dithionite in water led to the formation of lumichrome (VII). Catalytic reduction over palladium on charcoal in ethanol also gave VII. These procedures offer a nonphotochemical method for the elimination of the ribityl side chain of riboflavin.

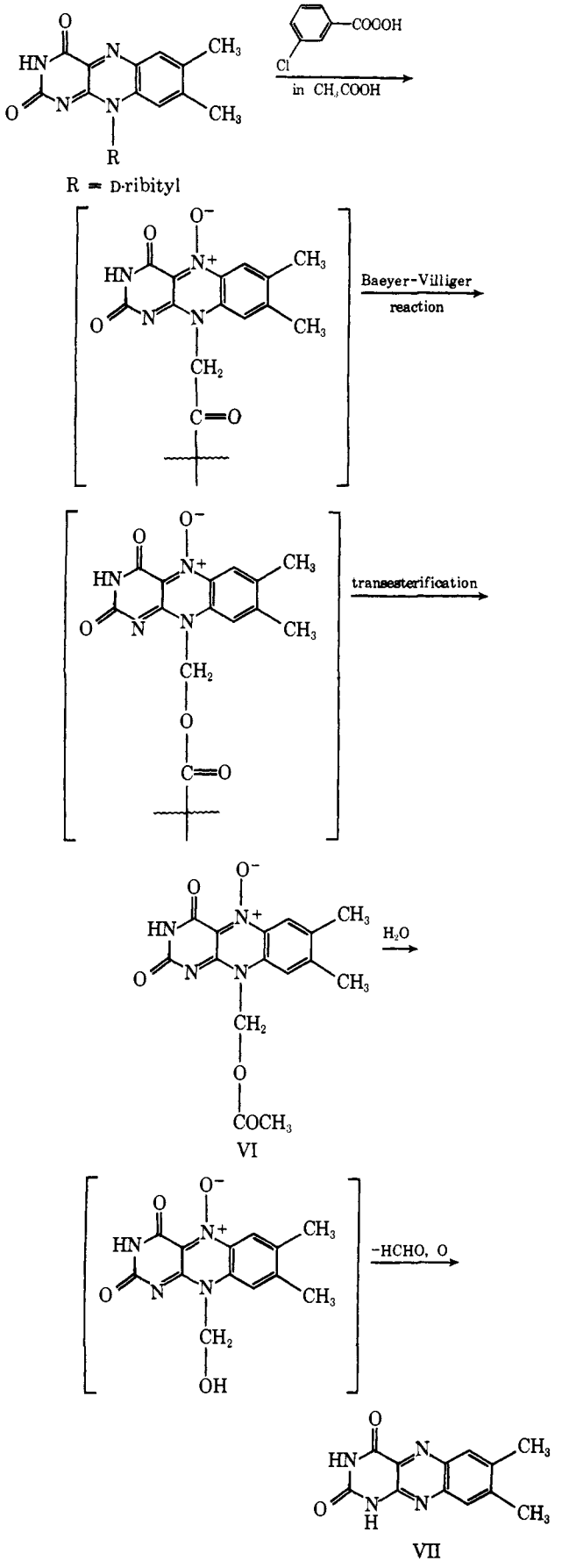
Scheme III



Cerman and Hais[9] reported an analogous photochemical oxidation of riboflavin whose product is 7,8-dimethyl-10-acetoxymethylisoalloxazine. The mechanism of our peracid oxidation of riboflavin probably includes a Baeyer–Villiger reaction, which is outlined in Scheme IV.

On the other hand, the isoalloxazines possessing simple alkyl groups at the 10 position gave the corresponding 5-oxides by peracid oxidation. For example, Gladys and Knappe[10] reported that the oxidation of 3,10-dimethylisoalloxazine with trifluoroperacetic acid gave the 5-oxide, which was identical in all respects with an authentic sample

Scheme IV



prepared by the nitrosative cyclization described above. Independently, we have also obtained isoalloxazine 5-oxides by the *m*-chloroperbenzoic acid oxidation of the respective isoalloxazines. The refluxing of IVa and IVb in acetic acid with excess *m*-chloroperbenzoic acid gave their 5-oxides (IIIa and IIIb) in moderate yields.

Experimental Section

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. NMR spectra were determined on a JNM 3H-60 spectrometer, using tetramethylsilane as the internal standard. The chemical shifts were expressed in δ values. Ultraviolet and visible spectra were obtained with a Japan Spectroscopic Co., Ltd., spectrophotometer, Model UVIDEC-1, 1-cm quartz cells being employed. Identity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a Japan Spectroscopic Co., Ltd., spectrophotometer, Model IR-1 A.

6-(*N*-Alkylanilino)uracils (IIa–j). General Procedure. A mixture of chlorouracil (0.01 mol) and *N*-alkylaniline (0.03 mol) was heated at 170–180° for 10 min with stirring. After cooling, the reaction mixture was crushed in ether, collected by filtration, and washed with water. The crushed mass was recrystallized from ethanol to give colorless crystals.

When *N*-methyl-3,4-xylidine is used as a starting material, the reaction should be carried out at 140–150° for about 5 min, because the long heating causes the elimination of the *N*-methyl group.

6-(*N*-D-Ribityl-3,4-xylidino)uracil (IIk). A mixture of chlorouracil (Ia) (1.47 g, 0.01 mol) and *N*-D-ribityl-3,4-xylidine (2.55 g, 0.01 mol) in dimethylformamide (0.8 ml) was heated at 155° (oil bath) for 7 min under vigorous stirring. After cooling, the reaction mixture was diluted with ethanol (10 ml) and allowed to stand for a few days to cause the separation of colorless crystals, which were collected by filtration and recrystallized from aqueous ethanol to give 2.5 g of colorless needles.

Isoalloxazine 5-Oxides (IIIa–j). General Procedure. 6-(*N*-Alkylanilino)uracil (0.01 mol) was dissolved in acetic acid (20 ml), and to the solution sodium nitrite (3.5 g, 0.05 mol) was added all at once. The mixture was stirred at room temperature for 2–3 hr, diluted with water (50 ml), and allowed to stand for another 2–3 hr. The crystals thus separated were collected by filtration, washed with water several times, and dried. Recrystallization from aqueous acetic acid gave orange needles.

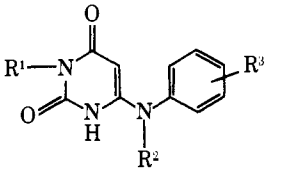
Riboflavin 5-Oxide (IIIk). A mixture of 6-(*N*-D-ribityl-3,4-xylidino)uracil (3.7 g, 0.01 mol) and sodium nitrite (3.5 g, 0.05 mol) in acetic acid (20 ml) was stirred at 40° for 30 min and then allowed to stand for 2 hr at room temperature. The inorganic substances which precipitated were filtered off; the filtrate was diluted with ether (50 ml) and allowed to stand overnight. The precipitates were collected by filtration and recrystallized from water to give 3.3 g of orange powder.

Isoalloxazines (IVa–k). General Procedure. To a solution of sodium dithionite (5.2 g, 0.03 mol) in water (10 ml) was added the *N*-oxide (0.01 mol), and the mixture was stirred for 2–3 hr at room temperature. To the reaction mixture, 30% hydrogen peroxide (2 ml) was added, and the mixture was allowed to stand overnight. The crystals thus separated were collected by filtration, washed with water, and recrystallized from acetic acid or ethanol to give yellow or orange needles.

Isoalloxazine Synthesis by the Nitrative Cyclization of II. General Procedure. A mixture of 6-(*N*-alkylanilino)uracil (0.01 mol) and potassium nitrate (2 g, 0.02 mol) in acetic acid (10 ml) was warmed at 90°. To this solution was added dropwise sulfuric acid (0.5 g, 0.005 mol) with stirring, and the mixture was heated at 90° for 30 min. Concentration of the reaction mixture to a small volume and dilution with water (50 ml) precipitated orange crystals, which were collected by filtration. The filtrate was extracted with ether, and the ether extracts were evaporated to dryness to give more crystals. The combined crystals were recrystallized from dioxane or ethanol to give orange prisms or needles.

Isoalloxazine Synthesis by the Condensation of 6-Alkylaminouracils and Nitrosobenzenes. General Procedure. A mixture of 6-alkylaminouracil (0.01 mol) and nitrosobenzene (0.03 mol) in acetic anhydride (20 ml) was refluxed for 20 min, during which time the reaction mixture changed color from green to brown. After cooling, the reaction mixture was diluted with water (100 ml) and allowed to stand overnight at room temperature. The crys-

Table IV. 6-(*N*-Alkylanilino)uracils



Compd no.	R^1	R^2	R^3	Mp,[a] °C	Yield, %	Formula	Analyses
IIa	H	CH_3	H	304	95	$C_{11}H_{11}N_3O_2$	C, H, N
IIb	H	C_2H_5	H	299	94	$C_{12}H_{13}N_3O_2$	C, H, N
IIc	H	*n*-C_3H_7	H	242	88	$C_{13}H_{15}N_3O_2$	C, H, N
IId	H	*n*-C_4H_9	H	229	85	$C_{14}H_{17}N_3O_2$	C, H, N
IIe	CH_3	CH_3	H	210	96	$C_{12}H_{13}N_3O_2$	C, H, N
IIf	CH_3	C_2H_5	H	218	92	$C_{13}H_{15}N_3O_2$	C, H, N
IIg	CH_3	*n*-C_3H_7	H	166	93	$C_{14}H_{17}N_3O_2$	C, H, N
IIh	CH_3	*n*-C_4H_9	H	138	88	$C_{15}H_{19}N_3O_2$	C, H, N
IIi	H	CH_3	7,8-$(CH_3)_2$	281	88	$C_{13}H_{15}N_3O_2$	C, H, N
IIj	CH_3	CH_3	7,8-$(CH_3)_2$	232	93	$C_{14}H_{17}N_3O_2$	C, H, N
IIk	H	D-Ribityl	7,8-$(CH_3)_2$	185	80	$C_{17}H_{23}N_3O_6$	C, H, N

[a] All the products were recrystallized from ethanol.

tals thus separated were collected by filtration, washed with water, dried, and recrystallized from ethanol.

By this method, IVe, IVf, and 8-chloro-3,10-dimethylisoalloxazine (IVl) were prepared. IVl did not melt below 330°. Anal. ($C_{12}H_9N_4O_2Cl$) C, H, N.

10-Acetoxymethyl-7,8-dimethylisoalloxazine 5-Oxide (VI). A suspension of riboflavin (0.5 g, 0.0013 mol) and *m*-chloroperbenzoic acid (3 g, 0.017 mol) in acetic acid (100 ml) was heated at 90° for 5 hr, whereby the reaction mixture became clear. After cooling, the reaction solution was concentrated to one-third volume and diluted with ether (100 ml) and allowed to stand overnight at room temperature to cause the separation of orange crystals, which were collected by filtration and washed with ether. Recrystallization from a mixture of acetic acid and ether gave 0.23 g (52%) of orange prisms, mp 270°. Anal. ($C_{15}H_{14}N_4O_5$) C, H, N.

Decomposition of VI to Lumichrome (VII). Stirring of **VI** (0.2 g, 0.0006 mol) in aqueous solution (5 ml) including sodium dithionite (0.4 g) for 1 hr at room temperature. The precipitates were collected by filtration, washed with water, and dried. Recrystallization from ethanol gave 0.09 g (61%) of pale yellow needles.

References and Notes

(1) A part of this paper has been reported in a preliminary form: (a) F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *Chem. Pharm. Bull.*, **20**, 1832 (1972); (b) F. Yoneda and Y. Sakuma, *ibid.*, **21**, 448 (1973).
(2) (a) Kumamoto University; (b) Keio University.
(3) Photochemical studies on these 5-oxides will be published in a separate paper.
(4) H. Goldner, G. Dietz, and E. Carstens, *Justus Liebigs Ann. Chem.*, **694**, 142 (1966).
(5) For example, O. Gawron, A. Rampal, and P. Johnson, *J. Am. Chem. Soc.*, **94**, 5396 (1972).
(6) E. C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Am. Chem. Soc.*, **89**, 3369 (1967).
(7) E. C. Taylor and F. Yoneda, *J. Org. Chem.*, **37**, 4464 (1972).
(8) The oxidation of riboflavin with 35% hydrogen peroxide in acetic acid was not effective, with the starting material being recovered.
(9) J. Cerman and I. M. Hais, *J. Am. Chem. Soc.*, **94**, 1741 (1972).
(10) M. Gladys and W.-R. Knappe, *Z. Naturforsch., Teil B*, **29**, 549 (1974).
(11) J. P. Lambooy, *Heterocycl. Compd.*, **9**, 118 (1967).

On the Superexchange Mechanism in Polymeric, Pyrazine-Bridged Copper(II) Complexes

H. Wayne Richardson and William E. Hatfield*

Contribution from the Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514.

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Abstract: Magnetic susceptibilities (1.9-250 K) and electron paramagnetic resonance and electronic spectra have been obtained on a variety of systems related to $[Cu(pyr)(NO_3)_2]_n$ (pyr = pyrazine) in order to determine the mode of superexchange; a novel π mechanism has been formulated on the basis of the results. All the systems can be described by the isotropic Heisenberg model for antiferromagnetically coupled linear chains of $S = \frac{1}{2}$ ions.

There has been considerable interest in polymeric transition metal complexes in which the metal ions are bridged by heterocyclic aromatic diamines, especially pyrazine (pyr).[1-7] Magnetic susceptibility measurements made at low temperatures on powdered[3] and single-crystal[4] samples of the pyrazine-bridged linear polymer[8] $[Cu(pyr)(NO_3)_2]_n$ revealed antiferromagnetic chainlike behavior which could be described by the Heisenberg linear-chain model[9] and not the Ising model.[10]

In addition to the pyrazine bridges in $[Cu(pyr)(NO_3)_2]_n$, there are also rather weakly bound nitrate bridges between the copper(II) ions of the chains. Since it is known[11,12] that nitrate bridges between copper(II) ions support antiferromagnetic superexchange interactions in $Cu(NO_3)_2 \cdot 2.5H_2O$,[13] it was deemed necessary to investigate the nature of the superexchange interactions in related polymeric chain complexes of copper(II) nitrate in order to determine the exchange pathway. Spectroscopic and magnetic investi-