In respect of the reaction mechanism of I with strong acid, the 18-methyl group migrated to 17-carbon with the preceding retropinacolic elimination of 17-hydroxyl group to give the carbonium ion (X) which may then be dehydrogenated into the protonated states (XI) of trienone (VI) through disproportionation. The dienones, III and IV, which are the conjugate bases of X, may also be oxidized to VI by the acid. The isomerization of VI may subsequently occur in the acid medium to the conjugated trienone (V) responsible for the absorption maximum at 480 nm.

Details of the chemical species responsible for the light absorption at 596 nm are now under investigation.

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Syntheses of Isoalloxazines. A New Synthesis of Riboflavin

The customary synthetic routes to isoalloxazines involve the condensation of (a) *o*-phenylenediamines with alloxan, alloxantin, dialuric acid, halobarbituric acid or violuric acid, (b) 2-arylazoanilines with barbituric acid, (c) anilines with violuric acid, (d) *o*-benzoquinones with 5,6-diaminopyrimidines, (e) dimeric biacetyl and diaminouracils, or diacetyl and preformed lumazines, and (f) quinoxalines with guanidine. Recently, these procedures were well documented in the literature.[1] In continuation of our studies[2–14] on the syntheses of purine, pteridines and related systems, we are now reporting two new synthetic approaches to isoalloxazines.

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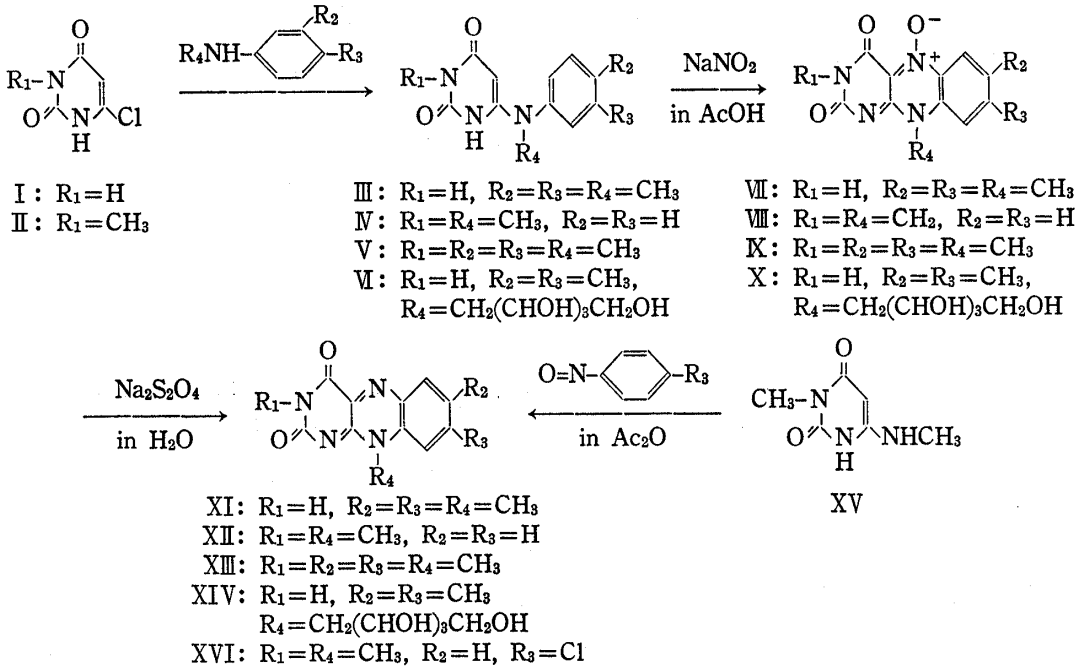
Method A

Fusion of 6-chlorouracil (I) with N-methyl-3,4-xylidine at 180° for 10 min gave 6-(N-methyl-3,4-xylidino)uracil (III),[15] mp 205°, in quantitative yield. Similarly, fusion of 6-chloro-3-methyluracil (II) with N-methylaniline and N-methyl-3,4-xylidine gave 3-methyl-6-(N-methylanilino)uracil (IV), mp 201°, and 3-methyl-6-(N-methyl-3,4-xylidino)uracil hydrochloride (V), mp>300°, in 90 and 95% yield respectively. Nitrosation of III, IV, and V with excess sodium nitrite in acetic acid led to the exclusive formation of lumiflavin-5-oxide (VII), mp>300°, 3,10-dimethylisoalloxazine-5-oxide (VIII), mp 301°, and 3-methyl-lumiflavin-5-oxide (IX), mp 259°, in 75, 72, and 70% yield respectively. Compounds VII, VIII, IX, and X (*vide infra*) are the first representatives of the isoalloxazine-N-oxide system. Deoxygenation of these N-oxides using sodium dithionite in water yielded lumiflavin[16] (XI), mp 325°, 3,10-dimethylisoalloxazine[17] (XII), mp 325°, and 3-methyllumiflavin[16] (XIII), mp 298—301°, in quantitative yields.



I: R_1=H
II: R_1=CH_3

III: R_1=H, R_2=R_3=R_4=CH_3
IV: R_1=R_4=CH_3, R_2=R_3=H
V: R_1=R_2=R_3=R_4=CH_3
VI: R_1=H, R_2=R_3=CH_3, R_4=$CH_2(CHOH)_3CH_2OH$

VII: R_1=H, R_2=R_3=R_4=CH_3
VIII: R_1=R_4=CH_2, R_2=R_3=H
IX: R_1=R_2=R_3=R_4=CH_3
X: R_1=H, R_2=R_3=CH_3, R_4=$CH_2(CHOH)_3CH_2OH$

XI: R_1=H, R_2=R_3=R_4=CH_3
XII: R_1=R_4=CH_3, R_2=R_3=H
XIII: R_1=R_2=R_3=R_4=CH_3
XIV: R_1=H, R_2=R_3=CH_3, R_4=$CH_2(CHOH)_3CH_2OH$
XVI: R_1=R_4=CH_3, R_2=H, R_3=Cl

XV

Chart 1

This new isoalloxazine synthesis has been extended to the preparation of riboflavin. Heating I with N-D-ribityl-3,4-xylidine at 160° for 5 min gave 90% of sirupy 6-(N-D-ribityl-3,4-xylidino)uracil (VI). Nitrosation of VI in acetic acid with excess aqueous sodium nitrite solution for 2 hr, removal of the solvent by partial evaporation *in vacuo*, and dilution with water caused riboflavin-5-oxide (X), mp>300° to separate in 85% yield and in a good state of purity. Treatment of X with sodium dithionite in water yielded riboflavin[18] (XIV), mp 280° (decomp.), in quantitative yield.

Method B

Refluxing 1 equiv of 3-methyl-6-methylaminouracil (XV) with 2 equiv of nitrosobenzene and *p*-chloronitrosobenzene in acetic anhydride for 15 min, followed by dilution with water, gave 3,10-dimethylisoalloxazine (XII) and 8-chloro-3,10-dimethylisoalloxazine (XVI), mp

15) Satisfactory microanalytical and spectral data were obtained for all the products.
16) R. Kuhn and H. Rudy, *Chem. Ber.*, **67**, 1298 (1934).
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>330°, in 47 and 76% yield respectively. The former compound was in all respects identical with the product prepared by Method A.

This procedure is a successful application of the known alloxazine synthesis[19] from 6-amino-1,3-dimethyluracil and nitrosobenzenes. However, it should be noted that the reaction of 6-alkylamino-1,3-dimethyluracils with nitrosobenzenes under the same conditions yields interestingly the corresponding 7-aryltheophyllines.[20]

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Syntheses of 1-Pyrazylpyridinium Salts, and Pyrido[1',2':1,2]imidazo-[4,5-*b*]pyrazines, a New Type of Heterocyclic Compounds

In the course of our studies on pyrazine derivatives, we have synthesized a series of pyrazine derivatives (IIa—c, IIId—f) bearing pyridinium groups by reaction of pyrazine N-oxides (Ia—f) with tosyl chloride in the presence of pyridine.[1] The structure of these compounds was determined by their nuclear magnetic resonance (NMR) coupling constants

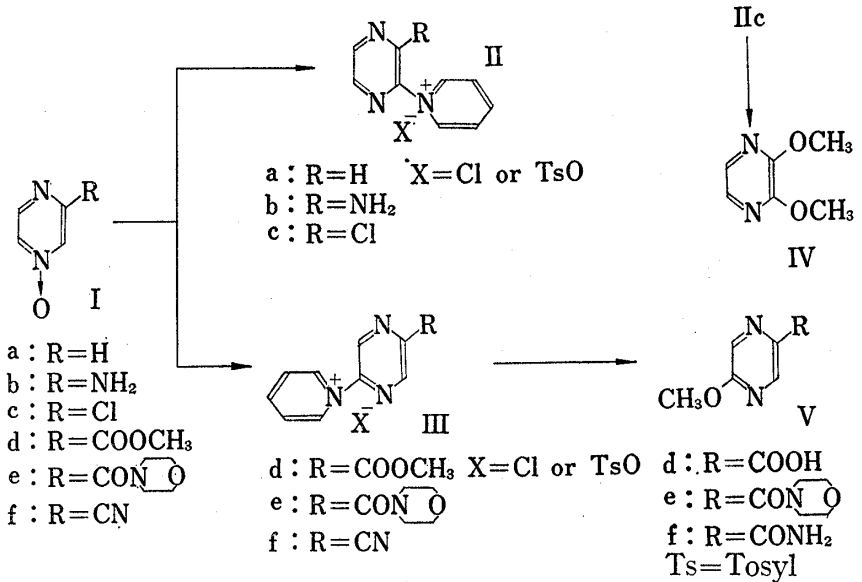

Chart 1

1) For the reaction in pyridine and quinoline N-oxides, see M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 23, 28 (1964).