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Studies on Flavin Derivatives. X-Ray Structure Investigation of 1′,2′,3′,4′-Tetraacetyl-3-ethyl-riboflavin Zinc-chelate Perchlorate

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This work is part of a series of systematic studies of flavin derivatives, currently in progress at this institute. The crystal structure of 1′,2′,3′,4′-tetraacetyl-3-ethyl-riboflavin zinc-chelate perchlorate, $(C_{27}H_{32}N_4O_{10}ClO_4H_2O)_2Zn$, has been determined by X-ray diffraction methods in order to obtain information about isoalloxazine interaction with metals. The studies were carried out on red single crystals selected from material kindly provided by S. Ghisla, P. Hemmerich and J. Lauterwein, University Konstanz, Germany.

X-Ray diffraction data. Preliminary rotation and Weissenberg photographs indicated monoclinic symmetry with systematic absence of reflections with $h+k=2n+1$. Therefore, possible space groups were $C2/m$, $C2$, and Cm. The non-centric space group $C2$ was assumed, which was subsequently confirmed to be correct by the determination of the structure. Powder photographs, taken in a Guinier-Hägg type focusing camera with strictly monochromatized Cu$K\alpha_1$ radiation ($\lambda = 1.54056$ Å) and with KCl ($a = 6.2930$ Å) as an internal standard, were used for the determination and least-squares refinement of the lattice parameters. The following result was obtained: $a = 20.438 \pm 3$ Å, $b = 7.673 \pm 2$ Å, $c = 21.389 \pm 4$ Å, $\beta = 104.40 \pm 2°$. There are two formula units in the unit cell. The calculated and observed density is 1.471 g/cm³ and 1.465 g/cm³, respectively. The intensity data were collected by integrated multiple-film Weissenberg technique using Ni-filtered CuK radiation. The 640 observed independent intensities were corrected for Lorentz and polarisation effects. Correction for absorption was not made, in view of the small size of the specimen and the low absorption coefficient, 21 cm^{-1}.

Determination of the structure. The general positions of the space group $C2$ are fourfold. The zinc atoms must be on twofold special positions, since there are two formula units in the cell. The approximate position of the isoalloxazine ring system was deduced from a three-dimensional Patterson synthesis. The isoalloxazine was treated as a rigid body, and the position was refined by a least-squares program kindly supplied by Sheringer.[1] The remaining non-hydrogen atoms were found from subsequent iterative Fourier calculations. From a three-dimensional difference electron density map it was found that four peaks, arranged tetrahedrally around the chlorine atom position, stood out clearly from the background. Accordingly, these sites were adopted as alternative positions for the oxygen atoms of the perchlorate ion, keeping the chlorine atom position unchanged. A least-squares refinement of the occupancies of the eight oxygen positions revealed that the oxygen sites have occupancies close to 0.5. Owing to the large number of atoms in the unit cell, leading to 152 positional parameters for the non-hydrogen atoms, and the small number of observed reflections, it has not been found possible to make a detailed structure refinement. Therefore, the structure was refined isotropically by least-squares treatment keeping groups of parameters constant in a step-wise manner. When the refinements were terminated a discrepancy index $R = 0.14$ ($R = \sum||kF_o| - |F_c||/\sum|kF_o|$) was cal-

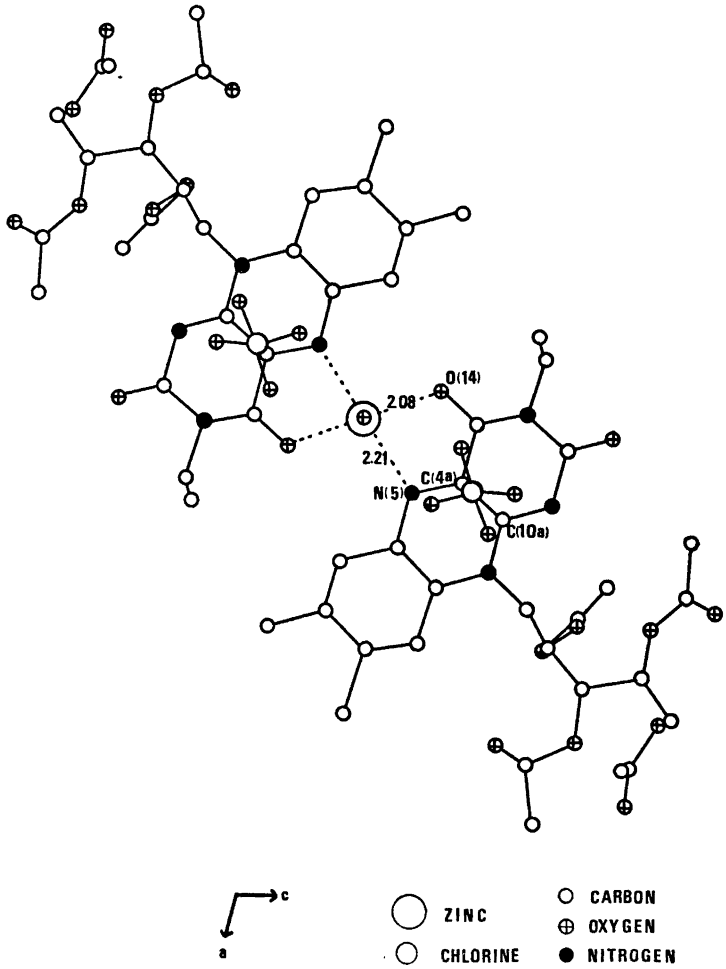

Fig. 1. Projection of 1′,2′,3′,4′-tetraacetyl-3-ethylriboflavin zinc-chelate perchlorate along *b* which is perpendicular to the plane of the paper. The zinc atom is located on a 2-fold axis coincident with the *b* cell edge. Hydrate oxygen atoms lie on the axis 2.02 Å above and below zinc. One of the two possible orientations of the perchlorate group is shown in the figure.

culated. From the single bond C–C distances found in the structure it may be concluded that the standard deviations are approximately 0.05 Å.

Discussion of the structure. Since the zinc atom is located on a twofold axis it is evident that the flavin chelate must be present in its *trans*-form. The octahedral zinc coordination, shown in Fig. 1, indicates a stronger metal interaction with O(14) than with N(5). The isoalloxazine rings form planar sheets separated by perchlorate ions located above and below the C(4a)–C(10a) bonds. This feature is in accordance with the planar sheets of oxidized flavin cations found in iodide compounds former investigated at this institute.[2–4] The largest calculated deviation of any atom from a least-squares plane through the 14 non-hydrogen atoms of the three-membered flavin ring system is 0.14 Å: the atom is C(4*a*).

Within experimental error, the perchlorate oxygen atoms form regular tetrahedra, and the average Cl – O bond distance of 1.47 Å found in the present structure is in agreement with the accepted value of 1.46 Å given by Cruickshank.[5] It is also noted that the two perchlorate positions are related by a rotation of approximately 90° around an axis through the centre of the chlorine atom.

A more detailed examination of intra- and intermolecular bond lengths has to wait until a new data set has been collected from a crystal kept at lower temperature (liquid nitrogen). We believe that this work, which is now in progress will allow a complete refinement of the obtained structure model.

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On a Synthesis of Thieno-annelated Five-membered Heterocyclics

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Recently, a new route to the benzo[b]-thiophene series has been described, consisting of heating cinnamic acids with thionyl chloride and pyridine, which leads to 3-chloro-2-benzo[b]thiophenecarbonyl chlorides.[1-3] The acid chlorides could then in the usual way be transformed to the acids and their derivatives. The disadvantage of this method is that, if the benzene ring contains substituents which activate electrophilic substitution, polychlorination is obtained. Thus, *p*-methoxycinnamic acid yields 3,7-dichloro-6-methoxy - 2 - benzo[b]thiophenecarbonyl chloride in 40 % yield.[3] The reaction is normally slow; six days heating at 100°C was necessary to obtain a 48 % yield with cinnamic acid.[3] Gronowitz and coworkers have for some time been interested in the chemistry and spectroscopic properties of thiophenes annelated to five-membered aromatic heterocyclics. Methods for the synthesis of thieno[2,3-b]thiophene [4] and seleno[2,3-b]thiophene [5] have been described, and the NMR spectra [6,7] and chemical properties [8] of some derivatives studied.

We were therefore interested in investigating the scope of the cinnamic acid ring-closure for the synthesis of thieno-, seleno-, and furothiophenes. A recent paper by Wright [9] on the preparation of 3-chlorothieno[3,2-b]thiophene derivatives from 3-(2-thienyl)acrylic acid has prompted us to publish the results we have hitherto obtained.

Wright found that the reaction mixture obtained from 3-(2-thienyl)acrylic acid, thionyl chloride, and pyridine was rather complex. He isolated 11 – 13 % of 3-chloro - 2 - thieno[3,2-b]thiophenecarbonyl chloride. From the mother liquor, methyl 3,5 - dichloro - 2 - thieno[3,2-b]thiophenecarboxylate and methyl 2-chloro-3-(5-chloro-2-thienyl)acrylate were obtained after reaction with methanol, along with unidentified by-products. When chlorobenzene was used as solvent, 3,5-dichloro-