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π...π-INTERACTIONS OF FLAVINS: SYNTHESIS AND MOLECULAR STRUCTURE OF A FLAVINOCYCLOPHANE

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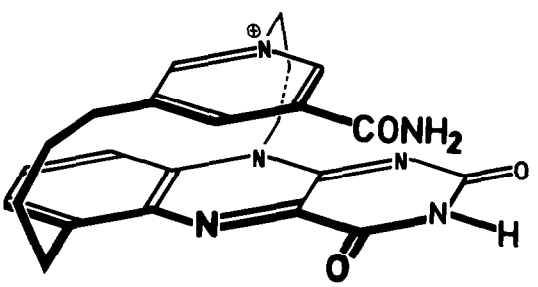
Summary: [4]Metacyclo[3](6,10)isoalloxazinophane (2) has been synthesized. The molecular structure of 2 is discussed based on X-ray structure analysis.

In connection with recent discussions on mechanistic aspects of flavin enzymes [1] we became interested in model compounds which allow to study interactions of flavins with other π-systems as a function of distance and orientation. A model of special biochemical significance is compound 1 where a flavin moiety is linked face-to-face to a nicotinamide unit in the specific geometry shown. As preparatory steps in the approach to 1 we report here the synthesis of the analogous [4]metacyclo[3](6,10)isoalloxazinophane (2) and discuss, on the basis of X-ray structure data, the conformational arrangement in 2 to which that of 1 is expected to be similar.



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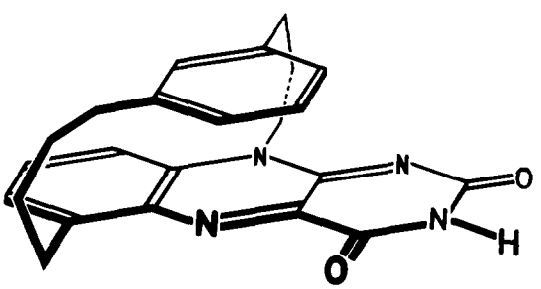
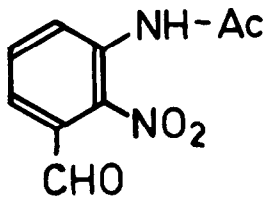


2

The strategy for the synthesis of 2 had to deviate from conventional routes to cyclophanes where, in general, two preformed units are cyclized to corresponding dithiacyclophanes from which the cyclophanes proper may be obtained by a variety of methods of sulfur extrusion from the cyclophane bridges. In the case of 2, due to the sensitivity of the isoalloxazine system, it was necessary to build up the methylene bridges first and to complete the synthesis of the isoalloxazine unit at the end of the synthetic route.

As key step in the synthesis of 2 the Wittig reaction of 3 and 4 was envisaged. From 3-acetylamino-2-nitrobenzoic acid [2] via the corresponding benzoyl chloride ($SOCl_2$, DMF; 73 %; mp 147.5°C) [3] by LiAl[(t-BuO)$_3$H] reduction [4] 3-acetylamino-2-nitrobenzaldehyde (3; 50 %; mp 144°C) [3] was obtained. The monophosphonium salt 4 was prepared from 1,3-bis(3-bromopropyl)-benzene [5] with PPh_3 in methylcyclohexane (160 h, 110 - 115°C; 89 %; mp 187 - 188°C) [3]. Reaction of 3 and 4 (t-BuOK, THF, -78°C) led to a mixture of Z,E-isomers 5/6 (7:3, total yield 69 %) [3] which were separated by chromatography (silica, toluene/diethylether).



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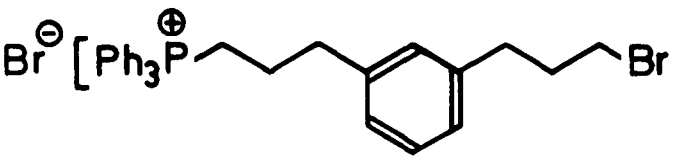

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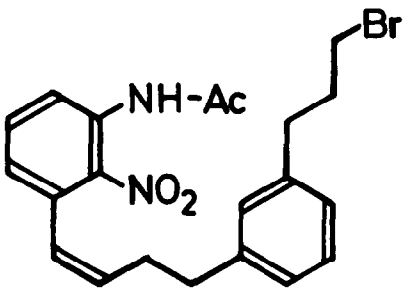

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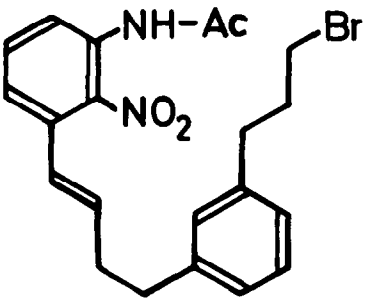
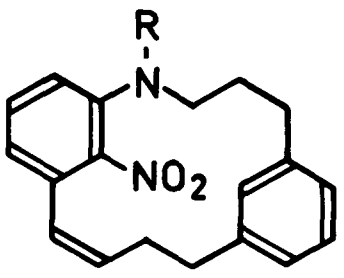
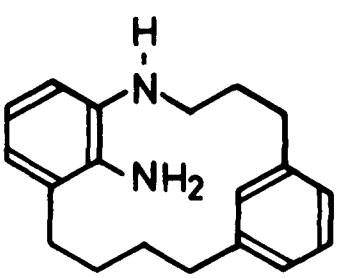


6

Cyclization of 5 (phase-transfer catalysis, toluene, NaOH/H_2O, $[Bu_4N]Cl$) [6] resulted in the formation of 7 (85 %; mp 161°C) [3], whereas starting from 6 under the same reaction conditions only the dimer was obtained (23 %; dec. > 330°C) [3]. Hydrolysis (KOH, ethanol/water) converted 7 into 8 (79 %; red crystals, mp. 119°C). Hydrogenation (4 equivs. H_2, Pd/C, AcOH, 20°C) led to 1-aza-20-amino[4.4]metacyclophane (9) which, as a N-monosubstituted o-pheny-



7: R = Ac; 8: R = H



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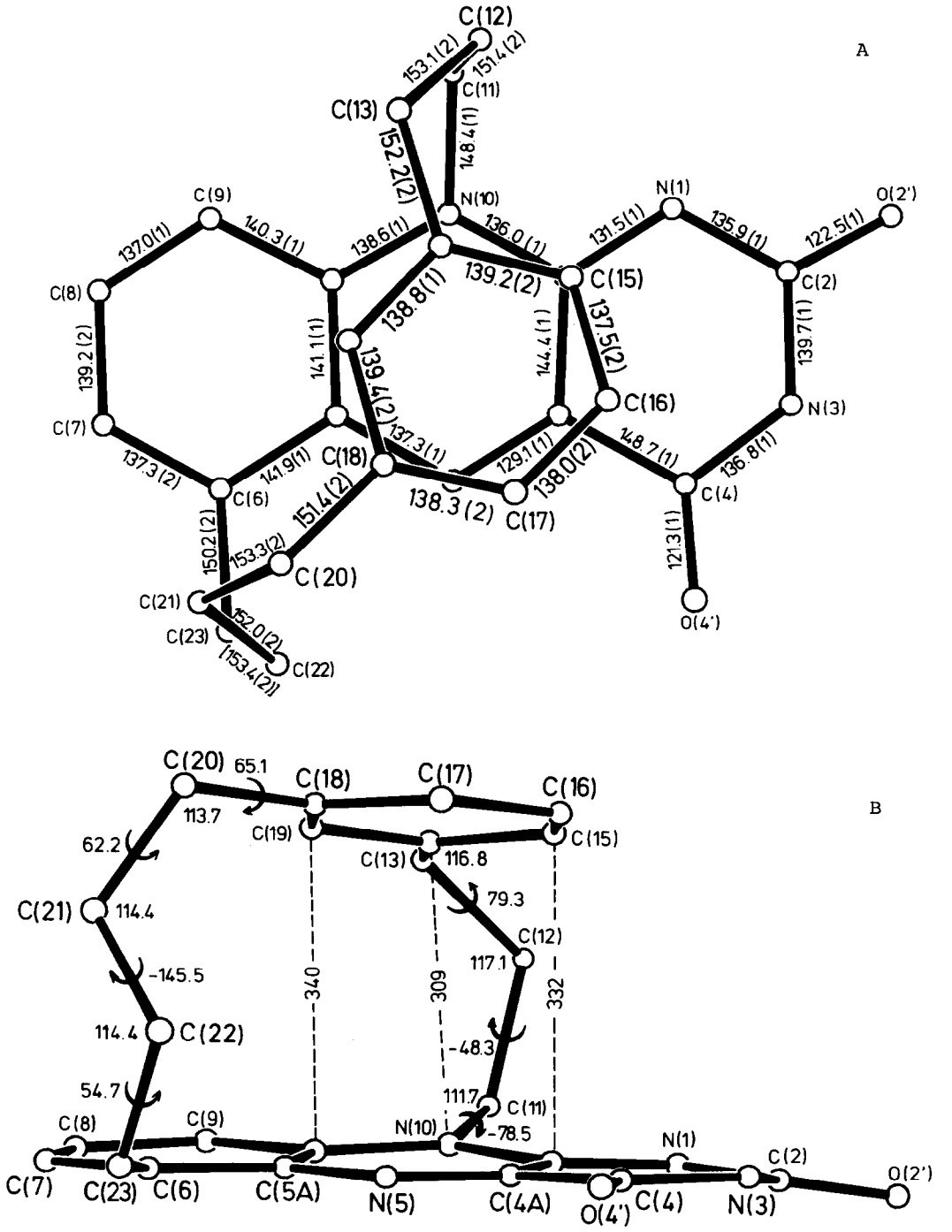

Fig. 1. Molecular structure of 2 in a top-view (A) and a side-view (B).

lenediamine, underwent the condensation with alloxane tetrahydrate (AcOH, $B(OH)_3$, 12 h, 60°C) according to the flavin synthesis of Kuhn and Weygand [7]; 2 was obtained in 71 % yield (related to 8).

The flavinophane 2 forms deep-yellow crystals (m. p. 293 - 296°C, dec.) which in solution show strong yellow-green fluorescence. UV/VIS ($CHCl_3$): λ_{max} = 447 nm (lg ε = 3.892), 365 (3.892), 271 (4.402); MS: m/z = 386 (100 %, M^+), 255 (18), 242 (24), 229 (22), 228 (18). The ^{1}H-NMR spectrum (360 MHz, $CDCl_3$), assignable for the majority of protons in first-order approximation, is in agreement with the geometrical structure as shown in formula 2. Especially the upfield-shift to δ = 5.67 for H-19 of the meta-bridged aromatic ring (for numbering cf. fig. 1) supports strongly a nearly parallel arrangement of this ring above the central section of the flavin unit which puts H-19 into the shielding region of the lateral aromatic ring of the neighbouring flavin.

More details about the conformational situation in 2 were derived from X-ray structure analysis. 2 forms monoclinic prisms; $P2_1/c$; a = 1239.5(1), b = 898.5(1), c = 1804.8(2) pm, β = 105.74(2)°; D_x = 1.32 gcm^{-3}, Z = 4. The structure was solved by direct method (MULTAN); full-matrix least-squares refinement led to R = 0.041. Fig. 1A shows the molecular structure of 2 in a top-view along the projection upon the isoalloxazine unit; in fig. 1B a side-view of 2 with transanular distances and torsional angles of the methylene bridges is shown. The structure reveals that there is considerable overlap between the two π-systems linked together in 2. An interesting feature of the crystal lattice of 2 is the dimerisation of two 2-molecules across a center of symmetry by two hydrogen bonds [N(3)-H···O(2')=C(2)].

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1) Cf. G. E. Schulz, R. H. Schirmer and E. F. Pai, J. Mol. Biol. 160, 287 (1982); E. F. Pai and G. E. Schulz, ibid. (in press).

2) A. Kaiser, Ber. Dtsch. Chem. Ges. 18, 2942 (1885).

3) Elemental analyses and spectroscopic data are in accordance with the structures suggested.

4) H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc. 80, 5377 (1958).

5) F. Effenberger and W. Kurtz, Chem. Ber. 106, 511 (1973).

6) In analogy to R. Brehme, Synthesis 1976, 113; G. Isele, J. A. Martinez and G. Schill, ibid. 1981, 455.

7) R. Kuhn and F. Weygand, Ber. Dtsch. Chem. Ges. 68, 1282 (1935).

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