25b, 116749-39-4; **26a**, 116749-56-5; **26b**, 116749-40-7; **27a**, 116749-57-6; **27b**, 116749-41-8; **28a**, 116749-58-7; **28b**, 116749-42-9; **29a**, 116749-59-8; **29b**, 116749-43-0; **30**, 116749-60-1; **31**, 116749-61-2; isobutyraldehyde, 78-84-2; *trans*-cinnamaldehyde, 14371-10-9; 6-bis[2-amino-3-cyano-5-(4-phenyl-1,3-butadienyl)pyrazyl] sulfide, 116784-48-6; benzaldehyde, 100-52-7; *p*-anisaldehyde, 123-11-5; 2-thiophenecarboxaldehyde, 98-03-3; guanidine hydrochloride, 50-01-1; molybdenum cofactor, 73508-07-3.

An Anomalous Dipyrrole Product from Attempted Synthesis of a Tetraarylporphyrin

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Heating of *o*-acetoxybenzaldehyde with pyrrole in hot acetic acid under Adler/Rothemund conditions yields a bright red (γ_{max} 515 nm) dipyrrolic compound and only minor quantities of the expected tetraarylporphyrin. Using NMR, mass spectrometry, and X-ray crystallography, we show the red material to be the dibenzofuranylpyrromethene **3**. A mechanism for the formation of this material is presented.

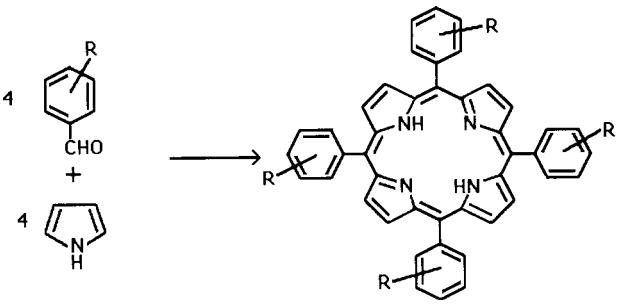
Introduction

Recently there has been considerable interest in the mechanism of the ubiquitous formation of tetraarylporphyrins from pyrrole and aryl aldehydes (Scheme I). These porphyrins have been used extensively in physicochemical studies of biomimetic transformations, as well as being models in a host of biologically related problems.

Badger et al.[3] were the first to exploit the so-called Rothemund reaction[4] and to consider the mechanism and the problem of chlorin formation during the cyclization.[5] In 1970 Dolphin[6] showed that a porphyrinogen was the first isolable true intermediate in the condensation reaction; the mechanism of the subsequent oxidation of porphyrinogen to porphyrin and chlorin (dihydroporphyrin) was discussed, using sterically hindered systems (octamethyltetraphenylporphyrin[6] and octaethyltetraphenylporphyrin[7]). More recently, Gonsalves and Pereira[8] and Lindsey et al.[9] have used the facile formation of porphyrinogens as a means to obtain higher yields of porphyrin in a two-stage process.

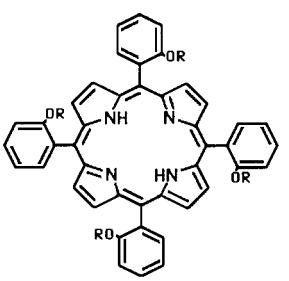
Badger's early work[3] on the Rothemund reaction resulted in isolation of the zinc(II) complex of a pyrromethene when the cyclization was carried out in the presence of zinc(II) acetate and pyridine in a sealed tube; this compound was not a true intermediate in the synthesis because it could not be efficiently converted, under the normal reaction conditions, into porphyrin. A similar zinc(II) pyrromethene was isolated in about 40% yield and fully characterized by Hill and Williamson[10] during the attempted synthesis of tetrakis(2,6-dichlorophenyl)-

Scheme I. Synthesis of Tetraarylporphyrins from Pyrrole and Aryl Aldehydes

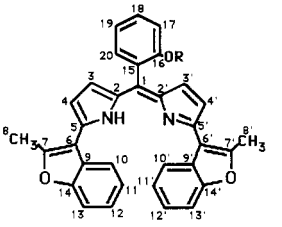


porphyrin from pyrrole and 2,6-dichlorobenzaldehyde in refluxing collidine in the presence of zinc(II) acetate. More recently still, Marchon et al.[11] obtained low yields of zinc(II) pyrromethenes from attempted syntheses of tetramesitylporphyrin under similar conditions.

We have found that the presence of zinc(II) is not always essential for isolation of pure pyrromethenes from Rothemund-type cyclizations. When *o*-hydroxybenzaldehyde or *o*-methoxybenzaldehyde was heated with pyrrole in acetic acid, the expected porphyrins (**1** and **2**, respectively) were isolated. However, when *o*-acetoxybenzaldehyde was



1 R = H
2 R = Me



3 R = COCH$_3$
4 R = H

used with pyrrole, only a minor amount of material bearing a Soret absorption band in its optical spectrum was isolated. Instead, a bright red crystalline product was ob-

(1) University of Aveiro.
(2) University of California.
(3) Badger, G. M.; Jones, R. A.; Laslett, R. L. *Aust. J. Chem.* **1964**, *17*, 1028–1035.
(4) Rothemund, P. *J. Am. Chem. Soc.* **1936**, *58*, 625–627; **1939**, *61*, 2912–2915.
(5) Barnett, G. H.; Hudson, M. F.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1401–1403.
(6) Dolphin, D. *J. Heterocycl. Chem.* **1970**, *7*, 275–283.
(7) Evans, B.; Smith, K. M.; Fuhrhop, J.-H. *Tetrahedron Lett.* **1977**, 443–446.
(8) Gonsalves, A. M. d'A. R.; Pereira, M. M. *J. Heterocycl. Chem.* **1985**, *22*, 931–933.
(9) Lindsey, J. L.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
(10) Hill, C. L.; Williamson, M. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1228–1229.
(11) Marchon, J.-C.; Ramasseul, R.; Ulrich, J. *J. Heterocycl. Chem.* **1987**, *24*, 1037–1039.

0022-3263/88/1953-5847$01.50/0

tained in approximately 15% yield. This product could be separated chromatographically into a major (nonpolar) fraction (10.6%) and a minor (polar) compound (4.2%). Treatment of the latter compound with acetic anhydride in pyridine afforded the former product in quantitative yield, indicating that the minor product had suffered deacetylation during the reaction sequence.

The optical spectrum of the bright red major (least polar) product showed no Soret band, but a strong absorption at 515 nm characteristic of a pyrromethene. The proton NMR spectrum and decoupling experiments of the material suggested that the structure had two equivalent pyrrole rings and three benzene rings, two of which are identical. Also present in the spectrum were two singlets at 2.02 and 2.65 ppm, the former half as large as the latter. Integration with regard to the downfield region suggested that these were two different types of methyl protons. Low-resolution mass spectroscopy gave a molecular ion at m/z 538. FAB mass spectroscopy confirmed this finding. An MS/MS experiment showed that the only fragments expelled from the molecular ion were 43 ($COCH_3$) and 59 ($OCOCH_3$) mass units, showing the compound to be unusually stable towards fragmentation and that there is only one labile acyl group. High-resolution mass spectroscopy provided a molecular weight of 538.1898. On the basis of this information, the only possible molecular formula for this compound is $C_{35}H_{26}N_2O_4$; the calculated molecular weight is 538.1889.

From the molecular formula and proton NMR data, we were led to conclude that the compound has the structure as shown in **3**. Carbon-13 NMR spectroscopy of **3** showed the presence of only one carbonyl carbon. This apparent discrepancy was solved by performing a heteronuclear COSY experiment, which not only disclosed the identity of many of the carbon atoms but also showed a coincidental overlap of two ^{13}C chemical shifts. The methyl protons of the acetyl group were irradiated, and a nuclear Overhauser enhancement was observed on the pyrrole ring and on both benzene systems. This experiment provided information that led to the assignments of all protons and most carbon atoms comprising the structure.

Not surprisingly, when **3** was treated with methanol-/H_2SO_4, the acyl group was lost and **4** was formed. Compound **4** was shown to be identical with the more polar fraction in the original reaction (vide supra). ^1H NMR spectra of **4** showed the loss of the methyl group at 2.02 ppm, and ^{13}C NMR confirmed the loss of both the carbonyl and methyl carbon atoms. Moreover, low-resolution mass specroscopy gave a molecular ion of m/z 496 corresponding to absence of the acetyl group. A mass of 496.1790 was measured by high-resolution mass spectroscopy, which agrees well with the calculated value of 496.1784.

All our data pointed toward the proposed structures **3** and **4** for the pyrromethenes, but because of the unusual and apparently unique presence of the benzofuran ring system, we resorted to X-ray crystallography as a means of confirming the proposed structure.

X-ray Crystal Structure

In order to unequivocally assign the structure of **3**, we carried out an X-ray crystal structure determination. There are two molecules in the asymmetric unit which are of opposite hand. Figure 1 shows one enantiomer. The bond distances and angles within the two molecules are normal. As can be seen from the figure, there are three planar sections of the molecule, but it is not readily apparent that they are not mutually coplanar. Rather, the dipyrrole portion subtends dihedral angles of 28.5° and 35.3° with the other two fused ring systems. In the second molecule, coresponding angles of 23.8° and 34.4° are found. Although the structure is unusual in that left- and right-handed molecules pack around psuedocenters of symmetry in a noncentrosymmetric structure, all the evidence points to this as the correct solution of the structure. Packing diagrams reveal that there is no center of symmetry relating the pairs of molecules. In addition, a comparison of the geometric details of the two molecules shows significant difference in their dihedral angles. Further, systematic absences, as well as the statistical values of the normalized data, support the assignment of the noncentrosymmetric space group $P2_12_12_1$. A drawing of the second molecule and a packing diagram, as well as tables of atomic positional parameters and bond distances and angles, are included as supplementary material.

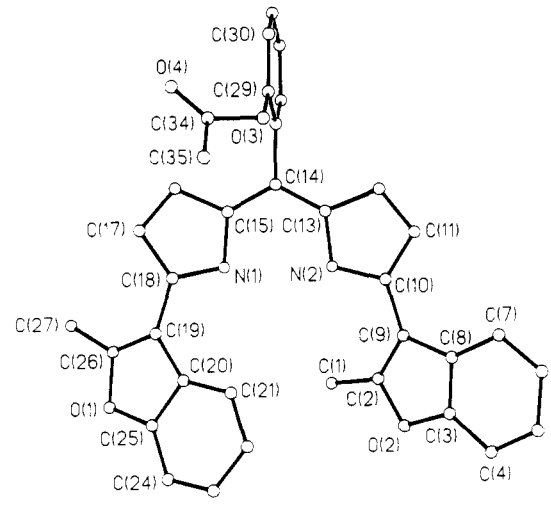


Figure 1. X-ray structure of dibenzofuranylpyrromethene **3**, including crystallographic nomenclature.

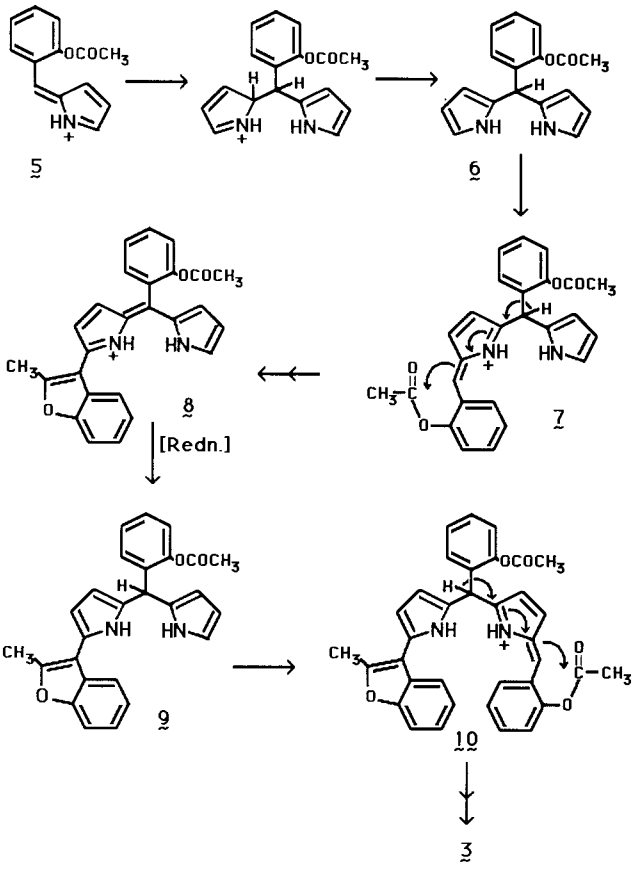
Mechanism for Formation of 3

A possible mechanism for formation of **3** from pyrrole and *o*-acetoxybenzaldehyde is shown in Scheme II. Condensation of pyrrole with the aryl aldehyde would yield the adduct **5**, which would then react with a second mole of pyrrole to give the pyrromethane **6** after loss of a proton. Further reaction with a second mole of the aryl aldehyde would then give the compound **7**, as would be expected in any tetraarylporphyrin synthesis. However, at this stage the *o*-acetate reacts with the methine carbon in **7** to give, irreversibly, the benzofuran **8**. From this point on, as a result of intervention of the *o*-acetate function, the pathway to porphyrin is blocked. Reaction with a third mole of aryl aldehyde is impossible at this point because of the nonnucleophilic nature of the protonated pyrromethene **8**, so this must be reduced, in situ, to give the pyrromethane **9**. Doubtless there are a multitude of hydrogen transfers taking place in the reaction mixture,[6,7] so this step provides no mechanistic problem. Compound **9** then reacts with a third mole of aryl aldehyde to give **10**, which, as previously, cyclizes to the *o*-acetate group to afford the dibenzofuranyl product **3**.

Experimental Section

General. Melting points are uncorrected and were measured on a Thomas/Bristoline hot stage. Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer using solutions in chloroform. Mass spectra were obtained on a VG Analytical ZAB-HS instrument in the FAB or EI (70 eV, mass reference perfluorokerosene) mode. Proton NMR spectra (^1H NMR) were obtained in $CDCl_3$ at 360 MHz (Nicolet NT-360), with chemical shifts reported in parts per million relative to

Scheme II. Proposed Mechanism for the Synthesis of Dibenzofuranylpyrromethene 3 from Pyrrole and *o*-Acetoxybenzaldehyde



chloroform (7.258 ppm); carbon-13 NMR spectra (^{13}C NMR) were measured on the same instrument in the same solvent. Elemental analyses were performed at the Microchemical Analysis Laboratory, U.C. Berkeley. Reactions were monitored by using thin-layer chromatography (TLC) on commercially available Eastman-Kodak 13181 (100 μm thick) silica gel sheets. Gravity column chromatography employed Merck silica gel.

X-ray Crystal Structure Determination. Crystals of **3**, $C_{35}H_{26}N_2O_4$, were obtained as plates from dichloromethane/petroleum ether. The crystal selected for data collection measured 0.06 × 0.14 × 0.63 mm. Crystal data: orthorhombic, space group $P2_12_12_1$, a = 10.624 (2) Å, b = 21.809 (3) Å, c = 23.511 (4) Å, Z = 8, Mo Kα radiation, T = 130 K, Syntex $P2_1$ diffractometer, 2315 unique observed reflections, 347 parameters, R = 0.081. The structure was solved by direct methods and refined by using the SHELXTL crystallographic software. In view of the small number of observed reflections, all atoms were refined with isotropic thermal parameters. Hydrogen atoms bonded to carbon atoms were included at calculated positions by using a riding model, with C–H of 0.96 Å. The largest feature on a final difference map was 0.40 e Å^{-3}. The hydrogen atom shared between the two pyrrole nitrogen atoms was not located, probably because it is disordered between two positions. There are no short intermolecular contacts.

Dibenzofuranylpyrromethene 3. Pyrrole (1.0 mL) and *o*-acetoxybenzaldehyde (3.8 g) [prepared from salicylaldehyde (2.5 mL) and acetic anhydride (2.5 mL) in pyridine (5 mL) at 60 °C during 30 min, followed by evaporation and structure confirmation using ^1H NMR] were heated under reflux in glacial acetic acid (75 mL) during 30 min. The mixture was cooled and reduced in volume to about one-third by evaporation on a rotary evaporator. Dichloromethane and aqueous sodium hydroxide were then added, and the organic phase was washed, dried (Na_2SO_4), and then evaporated to dryness. The residue was passed through a column of silica gel (elution with 10% methanol in dichloromethane), and two blue fractions were collected. These were individually chromatographed on silica gel thick-layer plates (20 × 20 cm plates, 1 mm thick, elution with 10% methanol in dichloromethane), and after removal from the silica gel and crystallization from dichloromethane/hexane, compound **3** (least polar) (410 mg) and compound **4** (most polar) (150 mg) were obtained as red crystalline solids. Treatment of **4** (150 mg) with acetic anhydride in pyridine, overnight at room temperature, gave **3** (160 mg). The total yield of **3** was 15%: mp 129–131 °C; ^1H NMR δ 2.02 (3 H, s, 22-H), 2.65 [6 H, s, (8,8′)-H], 6.66 [2 H, d, $J_{3,4} = J_{3',4'}$ = 4.0 Hz, (3,3′)-H], 6.71 [2 H, d, $J_{4,3} = J_{4',3'}$ = 4.0 Hz, (4,4′)-H], 6.92 [2 H, t, $J_{10,11,12} = J_{10',11',12'}$ = 7.6 Hz, (11,11′)-H], 7.22 [2 H, t, $J_{11,12,13} = J_{11',12',13'}$ = 7.6 Hz, (12,12′)-H], 7.29 (1 H, d, $J_{17,18}$ = 7.6 Hz, 17-H), 7.37 (1 H, t, $J_{18,19,20} = J_{18',19',20'}$ = 7.6 Hz, 19-H), 7.46 [2 H, d, $J_{13,12} = J_{13',12'}$ = 7.6 Hz, (13,13′)-H], 7.53–7.55 [2 H, m, (18,20)-H], 7.84 [2 H, d, $J_{10,11} = J_{10',11'}$ = 7.6 Hz, (10,10′)-H]; ^{13}C NMR δ 14.31 (8-C), 20.86 (22-C), 110.73 (13-C), 111.19, 117.58 (4-C), 120.54 (10-C), 123.07 (11-C, 17-C), 123.98 (12-C), 125.23 (19-C), 127.02, 128.66 (3-C), 129.65, 130.03, 132.40, 132.99, 141.33, 147.85, 148.98, 154.06, 154.59, 169.28 (21-C); MS, m/z (relative intensity), 538 (100), 495 (19), 479 (12); UV/vis λ_{max} 515 nm (ϵ 35 000); calcd for $C_{35}H_{26}N_2O_4$ 538.1889, found 538.1898. Anal. Calcd for $C_{35}H_{26}N_2O_4$: C, 78.05; H, 4.87; N, 5.20. Found: C, 78.01; H, 4.92; N, 5.19. When the above reaction was repeated in the presence of zinc(II) acetate, only approximately 1% of methene material was obtained, the major product being the corresponding tetrakis(*o*-hydroxyphenyl)porphyrin (10%) after demetalation and deacetylation with methanol/sulfuric acid.[12]

Dibenzofuranylpyrromethene 4. Pyrromethene **3** (200 mg) was dissolved in 5% sulfuric acid in methanol (5 mL) and left overnight at room temperature. Dichloromethane (40 mL) and aqueous sodium hydroxide were added. The mixture was washed with aqueous sodium carbonate, then dried (Na_2SO_4), and evaporated to dryness. Crystallization from dichloromethane/hexane gave pyrromethene **4** (175 mg; 95%), identical in all respects with the material (most polar) reported above: mp 167–170 °C; ^1H NMR δ 2.66 (6 H, s, (8,8′)-H), 6.75 [2 H, d, $J_{3,4} = J_{3',4'}$ = 4.3 Hz, (3,3′)-H], 6.78 [2 H, d, $J_{4,3} = J_{4',3'}$ = 4.3 Hz, (4,4′)-H], 6.93 (2 H, t, $J_{10,11,12} = J_{10',11',12'}$ = 7.6 Hz, (11,11′)-H], 7.04–7.10 (2 H, m), 7.23 [2 H, t, $J_{11,12,13} = J_{11',12',13'}$ = 7.6 Hz, (12,12′)-H), 7.39–7.42 (2 H, m), 7.46 (2 H, d, $J_{13,12} = J_{13',12'}$ = 7.6 Hz, (13,13′)-H], 7.83 [2 H, d, $J_{10,11} = J_{10',11'}$ = 7.6 Hz, (10,10′)-H]; ^{13}C NMR δ 14.31, 110.79, 111.07, 116.07, 118.16, 120.03, 120.46, 123.15, 123.32, 124.06, 126.92, 128.78, 130.49, 131.84, 141.01, 148.58, 153.69, 154.07, 154.85; MS, m/z (relative intensity), 496 (100), 479 (10); UV/vis λ_{max} 518 nm (ϵ 33 000), (in $CHCl_3$ + CF_3CO_2H) 608 nm (ϵ 96 000); calcd for $C_{33}H_{24}N_2O_3$ 496.1784, found 496.1790. Anal. Calcd for $C_{33}H_{24}N_2O_3$: C, 79.82; H, 4.87; N, 5.64. Found: C, 79.82; H, 5.05; N, 5.57.

Acknowledgment. We thank the National Institutes of Health (HL 22252, K. M. Smith) and Instituto Nacional de Investigaçao Cientifica (Portugal, J.A.S.C.) for support of this research.

Registry No. **3**, 117096-13-6; **4**, 117096-14-7; pyrrole, 109-97-7; *o*-acetoxybenzaldehyde, 5663-67-2.

Supplementary Material Available: Tables of crystal data and data collection parameters, atomic coordinates, isotropic thermal parameters, bond lengths and bond angles, a view of molecule 2 in the structure, and a packing diagram of compound **3** (9 pages). Ordering information is given on any current masthead page.

(12) Momenteau, M.; Mispelter, J.; Loock, B.; Bisagni, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 189–196.