was not soluble). The ether washings were combined with the Freon and evaporated under reduced pressure to give a pale yellow thick oil (165 mg) which solidified on standing. It was recrystallized from benzene to give 2,6-dimethyl-β-phenethylsulfonamide, identical with an authentic sample.

The dark brown semisolid in the thermolysis tube was treated with hot ethyl acetate, filtered to remove black insoluble solid, and evaporated under reduced pressure to give a dark brwon resin (150 mg): IR (neat) 3240 (m), 1315 (s), 1145 (s), 1130 (s) cm^{-1}. This mixture was chromatographed on neutral alumina (6 g) and eluted with methylene chloride and ethyl acetate to give 2,6-dimethyl-β-phenethylsulfonamide (65.6 mg). Elution with 5% methanol in ethyl acetate gave a fraction (58.9 mg) which was recrystallized from benzene to give 5,8-dimethyl-3,4-dihydro-2,1-benzothiazine 2,2-dioxide (**23**): mp 180.5–182.0 °C (from benzene); IR (Nujol) 3190 (s), 1320 (s), 1145 (s), 1130 (s), 745 cm^{-1} (s); NMR ($CDCl_3$) δ 6.77, 6.64 (d, 2 H), 3.50 (t, 2 H, CH_2SO_2, J = 7 Hz), 2.97 (t, 2 H, $ArCH_2CH_2$, J = 7 Hz), 3.37 (s, 1 H, NH, D_2O exchangeable), 2.19 (s, 3 H), 2.08 (s, 3 H, CH_3); mass spectrum (70 eV), m/e (relative intensity) 211 ($M^{+\cdot}$, 12), 197 (s), 147 (33), 146 (79), 144 (17), 132 (41), 131 (52), 130 (52), 129 (33), 121 (16), 120 (100), 119 (18), 118 (19), 117 (31), 115 (24), 105 (14), 91 (32), 77 (25). Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.87; H, 6.16. Found: C, 56.92; H, 6.22.

At 136 °C. Only starting azide was recovered after heating for 64 h.

Flash Vacuum Pyrolysis of 2,6-Dimethyl-β-phenethylsulfonyl Azide at 400 °C. 2,6-Dimethyl-β-phenethylsulfonyl azide (325 mg, 1.4 mmol) was placed in the reservoir of the pyrolysis apparatus and pyrolyzed at a column temperature of 400 °C, with the preheater temperature at 75 °C, the inlet at 130 °C, and the exit at 250 °C. The initial pressure was 0.001 mmHg before pyrolysis. During the pyrolysis the pressure was 0.04–0.05 mmHg. No carrier gas was used. The cold finger was cooled with liquid nitrogen. The pyrolysis took 5 h. During the pyrolysis some decomposition of the azide occurred in the inlet reservoir itself as shown by the change in color of the azide. After the pyrolysis, a dark brown mass (51 mg) remained in the inlet reservoir which was not investigated further. A pale yellow solid was condensed near the exit in the receiver (57 mg) and near the inlet in the pyrolysis tube (37 mg). Both of these fractions were combined and recrystallized from benzene to give 5,8-dimethyl-3,4-dihydro-2,1-benzothiazine 2,2-dioxide (**23**): mp 181–182 °C (sublimes at 70 °C at 0.05 mm). A dark brown semisolid condensed on the cold finger was dissolved in methanol, treated with activated charcoal, and filtered. The solvent was removed to give a yellow semisolid (35 mg) which showed no infrared absorptions for $-SO_2N<$ group at 1300–1340 and 1140–1180 cm^{-1} but showed absorptions at 3400 (w, br), 1000 (m, v br), 1095 (s), and 1030 (m) cm^{-1}.

***trans*-β-Styrenesulfonyl Azide.** This was prepared (69.9% yield) as usual from the chloride (Aldrich): mp 31.5–33 °C (from light petroleum, bp 30–60 °C); IR (KBr) 2140 (s), 1360 (vs), 1185 (vs), 1145 cm^{-1} (vse; NMR ($CDCl_3$) δ 7.7–7.4 (m, 6 H, ArH and ArCH), 6.83 (d, 1 H, J = 15.4 Hz, $CHSO_2$). Anal. Calcd for $C_8H_7N_3O_2S$: C, 45.92; H, 3.37. Found: C, 45.93; H, 3.37.

Thermolysis of *trans*-β-Styrenesulfonyl Azide. In Freon 113. The azide (483.6 mg, 2.3 mmol) in dry Freon 113 (50 mL) was heated at 157 °C for 36 h. Chromatography on silica gel gave unchanged azide (187.3 mg, 38.7%), mp 32–33.5 °C, and *trans*-β-styrenesulfonamide (63.7 mg, 24.9%), mp 142–142.5 °C, identical with an authentic sample.[19]

The results of the thermolysis in benzene and in cyclohexane are summarized in Table III.

FVP at 650 °C. The products from the pyrolysis of azide (1.39 g) were separated by column chromatography on silica gel to give the following. Unchanged azide (74.8 mg, 5.4%): mp 32–33.5 °C. Phenylacetylene (39.8 mg, 6.2%): bp 50–55 °C (20 mm); IR (film) 3320 (s), 2210 cm^{-1} (w); NMR (CCl_4) δ 7.6–7.2 (m, 5 H, ArH), 3.13 (s, 1 H, ≡CH); identical with a commercial sample (Aldrich Chem. Co.). A mixture of indole and phenylacetonitrile resolved into its components by preparative liquid chromatography on silica gel using CH_2Cl_2 as eluent. Indole (163.4 mg, 22.2%): mp 52–54 °C; identical with an authentic sample (IR, NMR). Phenylacetonitrile (490.1 mg, 66.6%): bp 76–78 °C (2 mm); IR (film) 2250 cm^{-1} (vs); NMR (CCl_4) δ 7.22 (s, 5 H, ArH), 3.68 (s, 2 H, CH_2); identical with an authentic sample.

Acknowledgment. We thank the National Science Foundation (CHE 78-04805 and CHE-8313525) for support of this work.

Registry No. **1a**, 40173-94-2; **1b**, 79927-86-9; **2a**, 96129-58-7; **2b**, 96129-75-8; **3** (R = Cl), 88106-97-2; **3** (R = Me), 88106-96-1; **4** (R = Cl), 88106-83-6; **4** (R = Me), 88106-82-5; **5** (R = Cl), 96129-59-8; **5** (R = Me), 96129-76-9; **6a**, 96129-60-1; **7a**, 96129-61-2; **12**, 96129-78-1; **13**, 96129-74-7; **14**, 96129-69-0; **15**, 96129-71-4; **16**, 96129-72-5; **19**, 96129-62-3; **21**, 96129-63-4; **22**, 96129-79-2; **23**, 96129-77-0; **31**, 80639-78-7; **32**, 64984-09-4; **33a**, 13719-47-6; **33b**, 13719-46-5; *trans*-PhCH=CHN_3, 18756-03-1; 2-chlorophenethyl azide, 96129-64-5; 2-chloro-β-phenethylsulfonamide, 96129-65-6; 5-chloro-3,4-dihydro-2,1-benzothiazine-2,2-dioxide, 96129-62-3; methyl (2,5-dichlorophenyl)acetate, 96129-66-7; (2,5-dichlorophenyl)acetonitrile, 3218-50-6; 2,5-dichloro-β-phenethyl alcohol, 1875-87-2; sodium 2,5-dichloro-β-phenethylsulfonate, 96129-67-8; 2,5-dichloro-β-phenethyl bromide, 40173-98-6; 2,5-dichloro-β-phenethylsulfonyl chloride, 96129-68-9; 2,5-dichloro-β-phenethylsulfonamide, 96129-70-3; 2-bromoethanesulfonyl chloride, 54429-56-0; 2,5-dichloroaniline, 95-82-9; 3,4-dichloroaniline, 95-76-1; 4,7-dichloroindole, 96129-73-6.

Novel Porphyrins from Copper(II)-Mediated Cyclizations of 1′,8′-Dimethyl-a,c-biladiene Salts: Mechanism of the Cyclization Reaction

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Copper(II)-mediated cyclizations of the 1′,8′-dimethyl-a,c-biladiene **8** under various conditions afford the expected porphyrin **7**, along with γ-methyl- (**9**), γ-(dialkylamino)- (**10** and **11**), 6-formyl- (**12**), and γ-formylporphyrins (**13**). Carbon-13-enriched a,c-biladienes (**14** and **15**) were used to establish the origins of the γ carbons, γ substituents, and γ-formyl groups; possible mechanistic pathways for the formation of porphyrins by copper(II)-mediated cyclizations of 1′,8′-dimethyl-a,c-biladiene salts are proposed.

The cyclization of a,c-biladiene salts to give porphyrins can be accomplished under a variety of conditions. 8′-Bromo-1′-methyl- (**1**) and 1′-methyl-8′-unsubstituted-a,c-biladiene dihydrobromides (**2**) yield metal-free porphyrins

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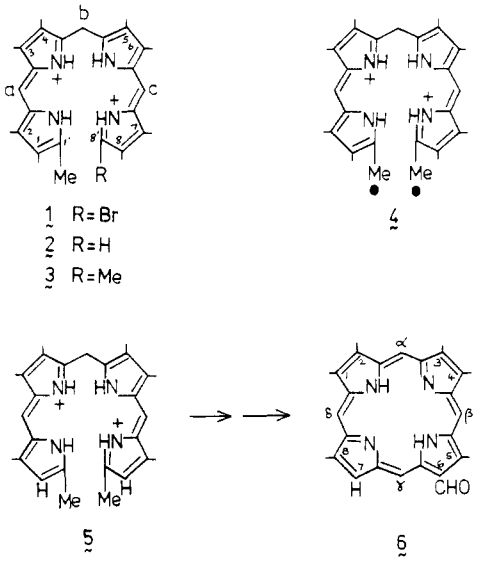


when they are refluxed in *o*-dichlorobenzene,[1] the latter in the presence of iodine and bromine.[2] Grigg et al.[3] postulated a free radical mechanism wherein the terminal methyl group is oxidized and incorporated as the bridging carbon in the newly formed porphyrin. In contrast, the cyclization of 1′,8′-dimethyl-a,c-biladiene salts **3** is accomplished in the presence of an oxidizing agent (copper salt) by refluxing in dimethylformamide (DMF). This reaction, discovered by Johnson and Kay,[4] may follow two paths: (a) either one of the methyl groups is lost in an oxidized form and the other is incorporated as the γ carbon or (b) both methyls are lost and the new γ carbon is incorporated from the DMF solvent. Johnson and co-workers[3] suggested that incorporation of one of the terminal methyls is more likely. In a recent paper[5] we showed, by utilizing a ^{13}C-labeled a,c-biladiene (**4**), that the bridging carbon is indeed derived from one of the terminal methyl groups and not from the solvent. In 1971, Kulish et al.[6] reported that cyclization of a 1,8-diunsubstituted-1′,8′-dimethyl-a,c-biladiene salt **5** in the presence of copper salts and lead dioxide gives 6-formylporphyrins **6**. These interesting results can be extended to reveal important facts pertaining to the mechanistic route in the oxidative cyclization of a,c-biladienes to give porphyrins. Once again, the formyl group can be derived either from the DMF solvent (which is frequently used as masked one-carbon unit, e.g., in the Vilsmeier reaction) or from the 1′- or 8′-terminal methyl group which is modified by some oxidation reaction, followed by migration to an unsubstituted peripheral position.

In this paper we describe a series of experiments that enable us to propose a general mechanism for the oxidative cyclization of 1′,8′-dimethyl-a,c-biladiene in the presence of copper salts.

We recently described a total synthesis of deoxophylloerythroetioporphyrin;[7] the key intermediate in this synthesis was pyrroetioporphyrin XV (**7**). In the course of the work a variety of copper salts were used in an attempt to improve the yield of **7** from the corresponding a,c-biladiene salt **8**. Depending upon the particular copper salt used, no less than five porphyrins along with the desired product **7** were isolated and characterized. These findings are shown in Figure 1 and are summarized in Table I. In the first entry of the table, use of copper acetate in DMF gave the 6-unsubstituted porphyrin **7**, as well as the γ-methyl- (**9**) and γ-(dimethylamino)porphyrins (**10**). Use of a different solvent, *N*,*N*-diethylformamide, afforded the γ-(diethylamino) analogue (**11**). Copper acetate together with lead dioxide, as expected,[6] gave the unsubstituted porphyrin **7** and the 6-formylporphyrin **12**. Similarly, copper ammonium chloride gave **7** and the 6-formylporphyrin **12**, together with the γ-formylporphyrin **13**. Other data in Table I represent the remainder of experiments performed in the course of the study. In order to propose a firm mechanism for the cyclization, several additional experiments were required in order to ascertain the fate or origin of the various carbon atoms involved in the reaction.

The key points to be settled in any mechanistic interpretation of the cyclization involve determination of the origins and fates of the various carbon atoms around the cyclization site. These objectives could be accomplished by use of two ^{13}C-labeled a,c-biladienes, **14** and **15**. The first (**14**) would be ^{13}C enriched in both the 1′- and 8′-

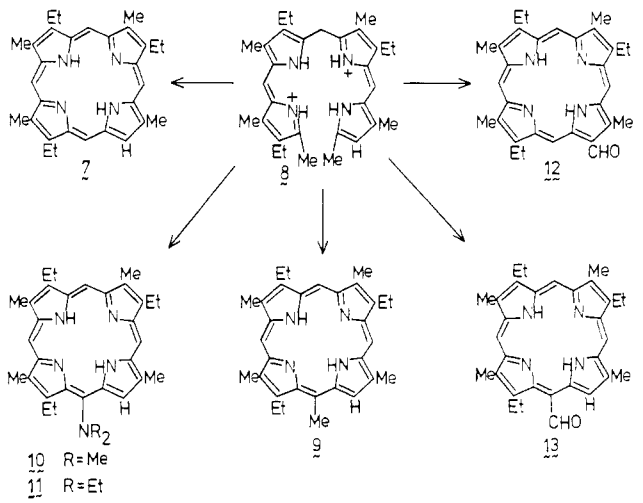


Figure 1. Products obtained from copper(II)-mediated cyclizations of the a,c-biladiene dihydrobromide **8**.

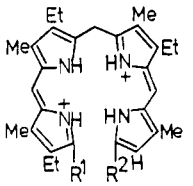
Table I. Experimental Details and Yields of Porphyrins from a,c-Biladiene Cyclizations[a]

		porphyrin yield, %		
salt	solvent	6-H **7**	6-CHO **10**	γ-R
$Cu(OAc)_2$[b]	DMF	4.4		8.1 (R = NMe_2, **10**) 9.3 (R = Me, **9**)
$Cu(OAc)_2$[b]	DEF[c]	11.0	2.3	1.2 (R = NEt_2, **11**)
$CuCl_2/PbO_2$	DMF	1.3	9.1	
$Cu(NH_4)_2Cl_4$	DMF	10.2	2.0	3.7 (R = CHO, **13**)
$CuCl_2$	DMF	0.2		
$Cu(OAc)_2/PbO_2$	DMF	10.6		
$Cu(OAc)_2$	NMF[d]	19.0		
$Cu(OAc)_2$	F[e]	6.0		
$Cu(OAc)_2$	acetamide	7.6	1.0	1.0 (R = Me, **9**)
$Cu(NO_3)_2$	DMF	12.0		
$CuBr_2$	DMF	13.4		
$CuSO_4$	DMF	23.4		

[a] 10 equiv of salts used, unless otherwise stated. [b] 8 equiv of salt used. [c] DEF = *N*,*N*-diethylformamide. [d] NMF = *N*-methylformamide. [e] F = formamide.

(1) Bamfield, P.; Harris, R. L. N.; Johnson, A. W.; Kay, I. T.; Shelton, K. W. *J. Chem. Soc. C* **1966**, 1436–1433.
(2) Mironov, A. F.; Rumyansteva, V. P.; Fleiderman, L. I.; Evstigneeva, R. P. *Zh. Obsch. Khim.* **1975**, *45*, 1150–1153.
(3) Grigg, R.; Johnson, A. W.; Kenyon, R.; Math, V. B.; Richardson, K. *J. Chem. Soc. C* **1969**, 176–182.
(4) Johnson, A. W.; Kay, I. T. *J. Chem. Soc.* **1960**, 2148–2423.
(5) Smith, K. M.; Kehres, L. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2329–2335.
(6) Kulish, M. A.; Mironov, A. F.; Roxynov, B. V.; Evstigneeva, R. P. *Zh. Obsch. Khim.* **1971**, *41*, 2743–2747.
(7) Smith, K. M.; Langry, K. C.; Minnetian, O. M. *J. Org. Chem.* **1984**, *49*, 4602–4609.

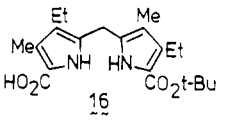
methyls, while the second (**15**) would contain only one label, at the 8′-position.



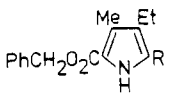
14 $R^1 = R^2 = {}^{\bullet}Me$

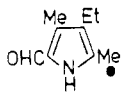
15 $R^1 = {}^{\bullet}Me$; $R^2 = Me$

The appropriate a,c-biladienes were synthesized by introduction of the enriched carbons at the monopyrrole stage, and then condensed with the pyrromethane **16** to



16





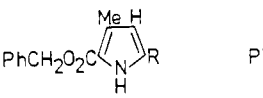
17 R = Me
18 R = CO_2H
19 R = I
20 R = H
21 R = $^{\bullet}CHO$
22 R = $^{\bullet}Me$

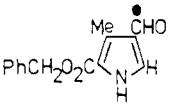
23

• = ^{13}C label

give the tripyrrene and eventually the unsymmetrical a,c-biladiene salt **8**.

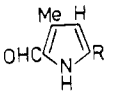
The ^{13}C-labeled formylpyrrole for ring D was prepared in the following manner. Benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (**17**) was trichlorinated with sulfuryl chloride and then hydrolyzed to give the corresponding pyrrolecarboxylic acid **18** in 87% yield. Iodinative decarboxylation afforded a 98% yield of the iodopyrrole **19**, and subsequent selective hydrogenation (Adams' catalyst) gave the 5-unsubstituted pyrrole **20** in 92% yield. Treatment of **20** with 95% ^{13}C-enriched DMF and phosphoryl chloride (Vilsmeier complex), followed by alkaline hydrolysis of the intermediate iminium ion, gave the labeled formylpyrrole **21** in 94% yield. The proton NMR spectrum showed a ^{13}C coupling constant of 175 Hz at 9.77 ppm for the aldehydic proton., Reduction with borane–tetrahydrofuran gave smoothly a 93% yield of the methylpyrrole **22**. Hydrogenolysis of the benzyl ester protecting group, followed by treatment with trifluoroacetic acid/triethyl orthoformate gave the desired ring-D pyrrole **23** in 50% yield. The ring-C pyrrole was prepared by formylation of the 4,5-unsubstituted pyrrole **24** using ^{13}C-enriched DMF/$POCl_3$ and gave a 5:2 mixture of 5-formyl- and 4-formylpyrroles, **25** and **26**, respectively. This mixture, which predominated in the required compound **25**, would have been marginally acceptable, but all attempts to reduce the 5-formyl group to 5-methyl using borane–tetrahydrofuran failed. A similar problem had been encountered in earlier work.[5] A new approach was therefore investigated; this involved protection of the aldehyde with ethanedithiol to give the thioketal **27**, and this was accomplished in 95% yield. Reduction of **27** with Raney nickel (W-2) at 30 psi of hydrogen for 1.5 h gave a 69% yield of the reduced product **28**. Further reduction of the benzyl ester with palladized charcoal and subsequent



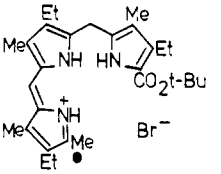


24 R = H
25 R = $^{\bullet}CHO$
27 R = $^{\bullet}CHSCH_2CH_2S$
28 R = $^{\bullet}Me$

25



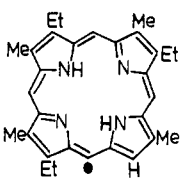
29
a R = $^{\bullet}Me$
b R = Me



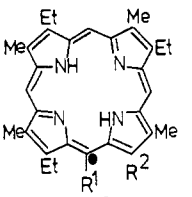
30

• = ^{13}C label

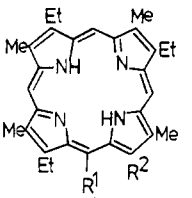
treatment of the resulting carboxylic acid with trifluoroacetic acid/triethyl orthoformate gave the desired ring-C pyrrole **29a**. Pyrromethane **16** was treated with labeled formylpyrrole **23** and gave the tripyrrene salt **30** in a yield of 80%. Further condensation with unlabled pyrrole **29b** afforded the 8′-labeled a,c-biladiene dihydrobromide **15**



31
35 (50% label)



32 $R^1 = {}^{\bullet}Me$; $R^2 = H$
34 $R^1 = Me$; $R^2 = {}^{\bullet}H$
36 $R^1 = H$ $R^2 = {}^{\bullet}CHO$
37 $R^1 = H$; $R^2 = CHO$
38 $R^1 = {}^{\bullet}CHO$; $R^2 = H$
40 $R^1 = CHO$; $R^2 = {}^{\bullet}H$



33 $R^1 = {}^{\bullet}Me$; $R^2 = H$
39 $R^1 = {}^{\bullet}CHO$; $R^2 = H$

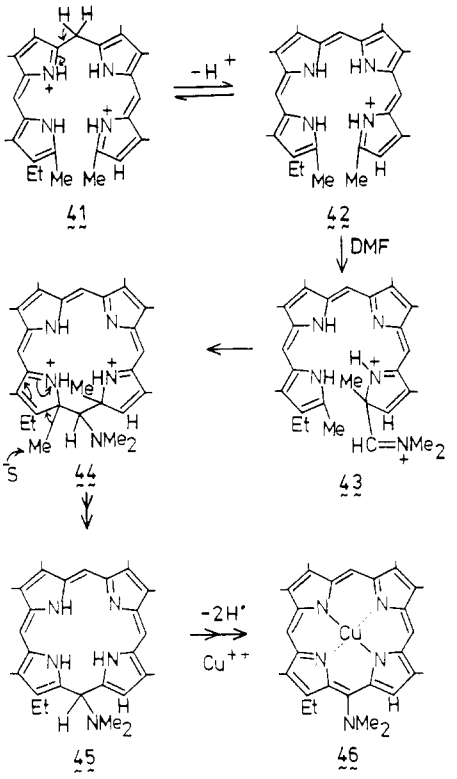
• = ^{13}C label

in 73% yield. Similarly, use of the labeled pyrrole **29a** gave a 75% yield of the 1′,8′-dilabeled a,c,-biladiene salt **14**.

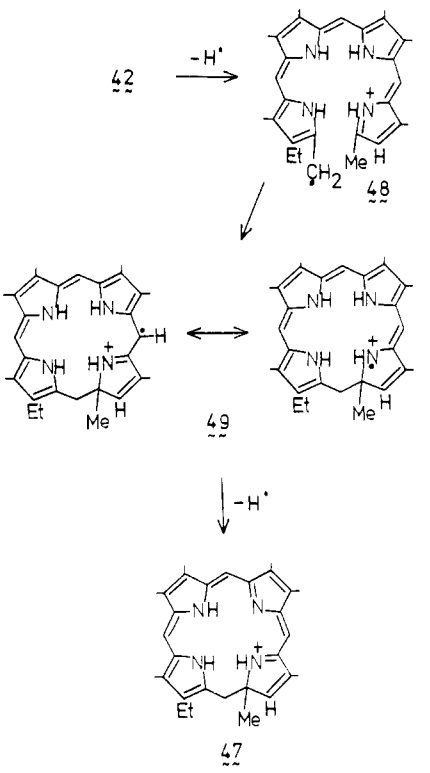
The first study of the cyclization using ^{13}C-enriched a,c-biladiene salts utilized copper(II) acetate and gave three porphyrins as products, **7**, **9**, and **10**. When either the singly (**15**) or doubly labeled (**14**) a,c-biladiene was used, the γ-(dimethylamino)porphyrin did not contain any enrichment at the γ carbon. However, use of the dilabeled a,c,-biladiene **14** gave porphyrins **31** and **32** in which both the γ and γ-methyl carbons were labeled. When the a,c-biladiene **15** was used, a mixture of three labeled porphyrins **33**, **34**, and **35** was produced. These results confirm that the solvent plays a definite role and can be incorporated as the γ carbon and also that either of the terminal methyl groups can migrate to the γ position, indicating a symmetrical intermediate (Scheme I).

The second study was accomplished with copper(II) chloride and lead dioxide and gave two porphyrins, **7** and **12**. Use of the 1′,8′-dilabeled a,c-biladiene **14** afforded porphyrins **31** and **36**, where both the γ and formyl carbons were enriched. However, when the 8′-labeled a,c,-biladiene salt **15** was used, porphyrins **35** and **37** were recovered, wherein the formyl group was not enriched. This confirms that both the γ and formyl carbons are derived from the

Scheme I



Scheme II



terminal methyl groups and that only the 1′-methyl group, which is in close proximity to the unsubstituted position, can migrate as a modified methyl group.

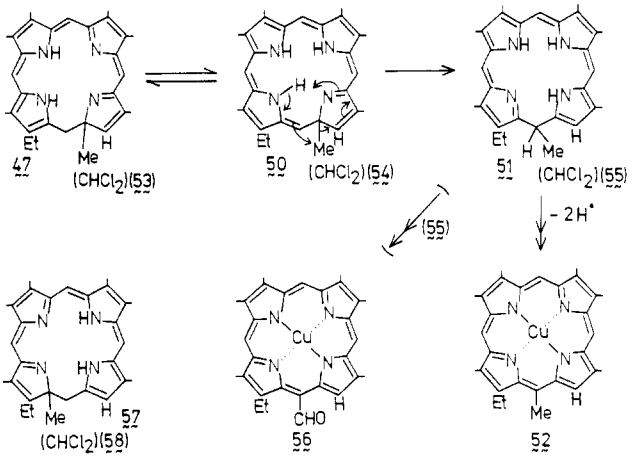
The use of copper(II) ammonium chloride gave the 6- and γ-formyl porphyrins **12** and **13**, respectively. Cyclization of the a,c-biladiene salt **14** gave **31** and the dilabeled porphyrins **36** and **38**, whereas use of a,c-biladiene salt **15** gave the singly labeled porphyrins **35**, **37**, **39**, and **40**. These results are again consistent with the symmetrical intermediate where the γ carbon can be derived from either methyl but the 6-formyl must be derived from the 1′-methyl.

Mechanism of the Cyclization Process. Scheme I shows the mechanism proposed for the formation of the γ-(dimethylamino)porphyrin **10**. As suggested by Grigg at al.,[3] we anticipate that the first step is formation of the a,b,c-bilatriene **42** from the a,c-biladiene **41**. The DMF solvent is then attacked by **42** to give **43**, which undergoes attack from the other terminal position to give the adduct **44**. Two separate nucleophilic attacks by solvent upon the 1′- and 8′-methyl groups give **45**, which is then oxidized by the copper(II) reagent to give **46** after insertion of copper. Subsequent removal of copper with TFA and sulfuric acid then affords the γ-(dimethylamino)porphyrin.

In all of the mechanisms proposed herein (Schemes I–IV) several of the steps are speculative since the intermediates have not been isolated. In particular, the step at which the chelating copper is inserted is unknown and so, for simplicity it is only inserted in the last step. Since a,c-biladienes are known to form metal chelates (of variable stability), it is likely that the copper is inserted very early in the mechanistic sequence.

We suggest that the other porphyrins (**9**, **12**, and **13**) are produced by way of the cyclized intermediate **47**, as shown in Scheme II. The a,b,c-bilatriene is oxidized, as suggested by Grigg et al.,[3] to give **48**, which cyclizes to give **49**, and is then further oxidized to produce **47**. Movement of electrons (Scheme III, structure **50**) then gives the γ-substituted derivative **51**, which loses two hydrogens to give

Scheme III



52 after insertion of copper. If at some point in the sequence, the quaternary methyl group is oxidized, for example, to the dichloromethyl compound **53** with copper(II) chloride as the oxidant, a similar series of compounds (**54** and **55**) results in formation of the γ-formyl derivative **56**. If the cyclization occurs by using the other terminal methyl group as the bridging carbon, then the cyclic analogues **57** and **58** result, and these account for the labeling results. Finally, as shown in Scheme IV, the 6-formylporphyrin **12** is formed from the derivative **53** by migration of the dichloromethyl group (to give **59**), which loses two hydrogens under the oxidizing conditions, and then is hydrolyzed to give the 6-formylporphyrin **60** after insertion of copper. In the mechanism outlined in Scheme IV it can be seen that only the terminal methyl on the 6-unsubstituted ring can migrate to give the observed product, and this is fully in accord with the labeling results. Thus, the isomer **61**, in which the oxidized quaternary carbon is on the fully substituted D ring, does not have the option to migrate its substituent; it is therefore simply extruded (Scheme

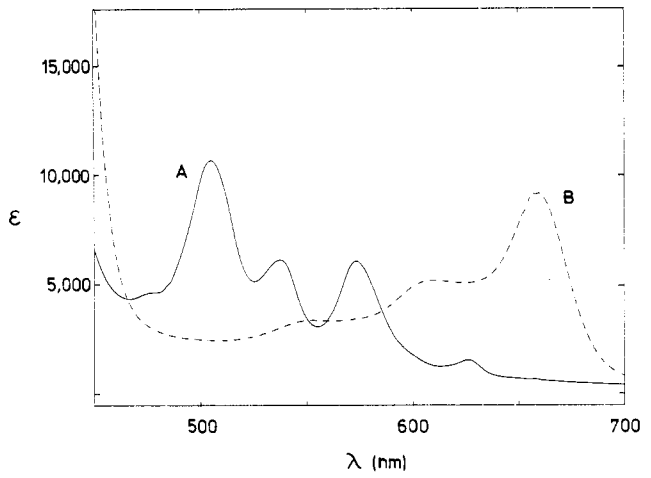
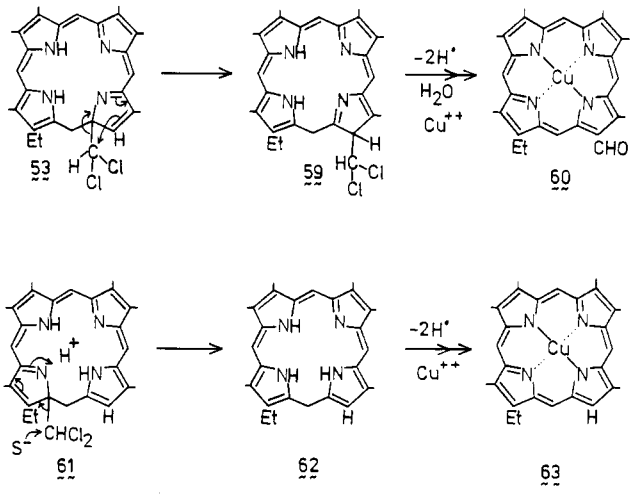


Figure 2. Electronic absorption spectra of the γ-(dimethylamino)porphyrin **10**: (A) free base in dichloromethane; (B) the dication in dichloromethane containing 1% trifluoroacetic acid.

Scheme IV

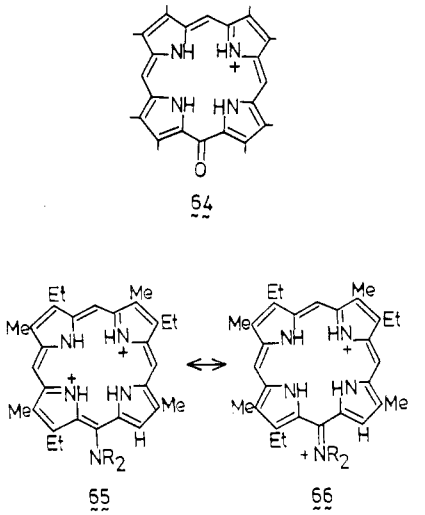


IV) to give the copper complex **63** of pyrroetioporphyrin XV.

Optical Spectra of Products. The electronic absorption spectra, in neutral solution, for the (dialkylamino)porphyrins **10** (Figure 2) and **11** and the γ-methylporphyrin **9** were of the "phyllo" type;[8] however, addition of acid to solutions of the (dialkylamino)porphyrins gave unusual optical spectra (Figure 2B),[9] resembling those of oxophlorin free bases and monocations (e.g., **64**).[10] Thus, it appears that the dication of the (dialkylamino)-porphyrin **65** has significant resonance contributions from species such as **66** in which the conjugated pathway is interrupted. These conclusions have been confirmed in NMR studies.[11] The 6-formyl- and γ-formylporphyrins **12** and **13** both displayed "rhodo"-type spectra, and the 6-unsubstituted porphyrin possessed the expected "etio" spectrum.

Experimental Section

Melting points were measured on a hot-stage apparatus and are uncorrected. Neutral alumina (Merck) or silica gel 60 (70–230 mesh) (Merck) was used for column chromatography, and preparative TLC was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1 mm thick). Analytical TLC was performed with Merck silica gel 60 F 254 precoated sheets (0.2 mm). Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer (solutions in dichloromethane), proton NMR spectra were measured at 360 MHz with a Nicolet NT-360 spectrometer (solutions in $CDCl_3$), and low-resolution mass spectra were measured (direct insertion probe, 70 eV, 50 μA, source temperature ca. 200 °C) with a Finnigan 3200 mass spectrometer. High-resolution mass spectra were measured at the Department of Pharmaceutical Chemistry, UC, San Francisco. Elemental analyses were performed at the Berkeley Microchemical Analysis Laboratory, Department of Chemistry, UC, Berkeley.



Benzyl 4-Ethyl-5-iodo-3-methylpyrrole-2-carboxylate (19). 2-(Benzyloxycarbonyl)-4-ethyl-3-methylpyrrole-5-carboxylic acid (**18**)[12] (23.5 g) in methanol (400 mL) containing sodium bicarbonate (20.0 g) and water (100 mL) was warmed to 60 °C with stirring. To this mixture iodine (22.8 g) and potassium iodide (30.0 g) in methanol (160 mL) and water (80 mL) were added dropwise over a period of 1 h. The reaction mixture was stirred further for 24 h when sodium thiosulfate (15 g) in water (100 mL) was added with stirring. The solution was cooled to 0 °C, and the crystals were filtered, washed with water, and air-dried. Recrystallization from methanol/water gave the title compound in 98% yield (29.6 g): mp 112.5–113 °C; ^{1}H NMR δ 1.02 (t, 3 H, CH_2CH_3), 2.32 (s, 3 H, ring Me), 2.36 (q, 2 H, CH_2CH_3), 5.33 (s, 2 H, CH_2Ph), 7.40 (s, 5 H, Ph), 9.22 (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{16}NO_2$: C, 48.80; H, 4.37; N, 3.79. Found: C, 49.02; H, 4.38; N, 3.79.

Benzyl 4-Ethyl-3-methylpyrrole-2-carboxylate (20). The foregoing iodopyrrole (16 g) in methanol (260 mL) containing sodium acetate trihydrate (15 g) and Adams' catalyst (PtO_2) (300 mg) was hydrogenated at room temperature and pressure until the uptake of hydrogen has ceased (about 8 h). After filtration of the catalyst through Celite and evaporation of the solvent, dichloromethane (100 mL) was added, the solution was washed with water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was filtered through a short column of silica gel (elution with dichloromethane). Evaporation of the solvent gave a white crystalline solid (9.70 g, 92%): mp 31–32 °C; ^{1}H NMR δ 1.18 (t, 3 H, CH_2CH_3), 2.30 (s, 3 H, ring Me), 2.39 (q, 2 H, CH_2CH_3), 5.30 (s, 2 H, CH_2Ph), 6.58 (d, 1 H, 5-H), 7.38 (s, 5 H, Ph), 8.90 (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.76; H, 7.12; N, 5.67.

Benzyl 4-Ethyl-5-formyl-3-methylpyrrole-2-carboxylate (21, Unlabeled). The foregoing pyrrole (1.67 g) dissolved in dichloromethane (25 mL) was added to the Vilsmeier complex prepared from phosphoryl chloride (1.28 mL) and DMF (1.06 mL). The solution was refluxed for 45 min, and then aqueous sodium

(8) Smith, K. M. In "Porphyrins and Metalloporphyrins"; Elsevier: Amsterdam, 1975; p 23.
(9) Spectrophotometric titration with trifluoroacetic acid in dichloromethane gave isobestic points at 471, 547, 567, and 582 nm.
(10) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. C* **1968**, 302–310.
(11) Smith, K. M.; Bobe, F. W.; Minnetian, O. M.; Abraham, R. J. *Tetrahedron* **1984**, *40*, 3263–3272. Abraham, R. J.; Smith, K. M.; Bobe, F. W.; Minnetian, O. M. *Org. Magn. Reson.*, in press.
(12) Jackson, A. H.; Kenner, G. W.; Warburton, D. *J. Chem. Soc.* **1965**, 1328–1337.

acetate (50 mL) was cautiously added followed by aqueous sodium bicarbonate until the solution reached pH 8. The mixture was stirred at 30 °C for 3 h until TLC monitoring showed complete hydrolysis of the imine salt. The solution was extracted with dichloromethane (3 × 25 mL), washed with water (3 × 50 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the title compound in 94% yield (1.75 g) as white crystals: mp 84.9–85.8 °C; ^1H NMR δ 1.12 (t, 3 H, CH_2CH_3), 2.30 (s, 3 H, ring Me), 2.70 (q, 2 H, CH_2CH_3), 5.32 (s, 2 H, CH_2Ph), 7.37 (s, 5 H, Ph), 9.77 (s, 1 H, CHO), 10.17 (br s, 1 H, NH). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.87; H, 6.32; N, 5.16. Found: C, 70.54; H, 6.52; N, 5.09.

The reaction was repeated with 90% ^{13}C-enriched DMF (on the same scale) to give a 95% yield of the labeled formylpyrrole **21**. This material was identical with the unlabeled compound described above except that the proton NMR spectrum showed a ^{13}C–^1H coupling of 175 Hz at 9.77 ppm.

Benzyl 4-Ethyl-3,5-dimethylpyrrole-2-carboxylate (22, Unlabeled). Benzyl 4-ethyl-5-formyl-3-methylpyrrole-2-carboxylate (458 mg) in tetrahydrofuran (3 mL) was cooled to 0 °C. A solution of borane–tetrahydrofuran complex (20 mL, 1 M in THF) was slowly added to the stirred suspension under a stream of nitrogen. After 84 h, methanol (15 mL) was cautiously added followed by dichloromethane (50 mL). The organic phase was washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to dryness to give a pale yellow solid. The residue was purified (silica gel, elution with 20% ethyl acetate/*n*-hexane) to give a white crystalline solid (405 mg, 93%): mp 103–104 °C (lit.[13] mp 103 °C); ^1H NMR δ 1.02 (t, 3 H, CH_2CH_3), 2.18, 2.29 (each s, 3 H, ring Me), 2.33 (q, 2 H, CH_2CH_3), 5.27 (s, 2 H, CH_2Ph), 7.37 (s, 5 H, Ph), 8.83 (br s, 1 H, NH). When the reaction was repeated with 90% ^{13}C-enriched formylpyrrole (on a 1.60-g scale) the reduced product was recovered in 85% yield. This material was identical with the unlabeled compound described above except that the proton NMR spectrum showed a ^{13}C–^1H coupling for the 5-methyl of 126 Hz at 2.18 ppm.

4-Ethyl-2-formyl-3,5-dimethylpyrrole (23). The foregoing labeled pyrrole (**22**) (1.9 g) in tetrahydrofuran (150 mL) and triethylamine (0.1 mL) was hydrogenated at room temperature and atmospheric pressure over 10% palladized charcoal (0.2 g) until the uptake of hydrogen had ceased (about 3 h). The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness to give a white solid, which was recrystallized from dichloromethane/*n*-hexane to give the pyrrolecarboxylic acid as white prisms (1.25 g, 96%): mp 132–133 °C; ^1H NMR δ 0.98 (t, 3 H, CH_2CH_3), 2.09 (d, 3 H, ring Me, J = 129 Hz), 2.20 (s, 3 H, ring Me), 2.25 (q, 2 H, CH_2CH_3), 9.21 (br s, 1 H, NH). This material (1.06 g) was immediately dissolved in dichloromethane (25 mL) and added dropwise to the Vilsmeier complex prepared from phosphoryl chloride (1.28 mL) and DMF (1.06 mL). The solution was refluxed for 4 h, and then aqueous sodium acetate (50 mL) was cautiously added followed by aqueous sodium bicarbonate until the solution reached pH 8. The mixture was stirred at 30 °C for 4 h, and TLC monitoring showed complete hydrolysis of the Vilsmeier imine salt. The mixture was extracted with dichloromethane (3 × 25 mL), and the organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4), and evaporated to dryness to give a white solid in 28% yield (272 mg) after recrystallization from methanol/water: mp 104–105 °C (lit.[14] mp 105–106 °C); ^1H NMR δ 0.93 (t, 3 H, CH_2CH_3), 2.17 (d, 3 H, ring Me, J = 126 Hz), 2.17 (s, 3 H, ring Me), 2.26 (q, 2 H, CH_2CH_3), 9.38 (s, 1 H, CHO), 10.96 (br s, 1 H, NH).

Benzyl 5-Formyl-3-methylpyrrole-2-carboxylate (25) and Benzyl 4-Formyl-3-methylpyrrole-2-carboxylate (26). Benzyl 3-methylpyrrole-2-carboxylate (**24**)[15] (1.48 g) was formylated as above with 90% ^{13}C-enriched DMF to give two formylpyrroles. The faster moving compound (**25**) was recovered in 72% yield (1.2 g) and the slower moving compound (**26**) was obtained in 28% yield (0.45 g).

Compound **25**: mp 82.5–83 °C; ^1H NMR δ 2.33 (s, 3 H, ring Me), 5.32 (s, 2 H, CH_2Ph), 6.68 (d, 1 H, 4-H), 7.33 (s, 5 H, Ph), 9.58 (d, 1 H, CHO, J = 175 Hz). Anal. Calcd for $C_{14}H_{13}NO_3$ (unlabeled sample): C, 69.13; H, 5.39; N, 5.76. Found: C, 69.13; H, 5.45;, N, 5.72.

Compound **26**: mp 110.5–111 °C; ^1H NMR δ 2.60 (s, 3 H, ring Me), 5.32 (s, 2 H, CH_2Ph), 7.38 (s, 5 H, Ph), 7.42 (d, 1 H, 5-H), 9.90 (d, 1 H, CHO, J = 175 Hz), 9.96 (br s, 1 H, NH). Anal. Calcd for $C_{14}H_{13}NO_2$ (unlabeled sample): C, 69.13; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.46; N, 5.74.

Dithioacetal 27 from Benzyl 5-Formyl-3-methylpyrrole-2-carboxylate. Benzyl 5-formyl-3-methylpyrrole-2-carboxylate (**25**) (1.50 g) in glacial acetic acid (20 mL) containing ethanedithiol (6 mL) was refluxed for 3 h under nitrogen. After cooling, the mixture was diluted with dichloromethane, and the organic layer was washed with water and saturated sodium bicarbonate and then dried (Na_2SO_4). Evaporation of the solvent gave a yellowish residue, which was chromatographed (silica gel, elution with 30% ethyl acetate/*n*-hexane) to give white needles of the desired compound (1.96 g, 99%): mp 94–95 °C; ^1H NMR δ 2.30 (s, 3 H, ring Me), 3.34 (m, 4 H, SCH_2CH_2S), 5.33 (s, 2 H, CH_2Ph), 5.62 (d, 1 H, acetal H, J = 120 Hz), 6.10 (s, 1 H, 4-H), 7.40 (s, 5 H, Ph), 9.10 (br s, 1 H, NH). Anal. Calcd for $C_{16}H_{17}NO_2S_2$ (unlabeled sample): C, 60.16; H, 5.36; N, 4.38. Found: C, 60.21; H, 5.40; N, 4.41.

Benzyl 3,5-Dimethylpyrrole-2-carboxylate (28, Unlabeled). The foregoing pyrrole (0.87 g) in tetrahydrofuran (30 mL) was hydrogenated in the presence of Raney nickel (W-2) (17.5 g, 20 equiv) at 30 psi for 1.5 h. The mixture was filtered through a 3-cm pad of Celite to remove the catalyst, and the filtrate was diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL) followed by a water wash, drying (Na_2SO_4), and removal of the solvent under reduced pressure. The residue was chromatographed (silica gel, elution with 30% ethyl acetate/*n*-hexane) to give the title compound (0.40 g, 64%): mp 101.5–102.3 °C (lit.[16] mp 102–104 °C); ^1H NMR δ 2.19, 2.23 (each s, 3 H, ring Me), 5.30 (s, 2 H, CH_2Ph), 5.72 (d, 1 H, 4-H), 7.33 (s, 5 H, Ph), 9.57 (br s, 1 H, NH). When the reaction was repeated on the labeled pyrrole (on a 1.96-g scale) the product (**28**) was obtained in 69% yield (0.97 g). This material was identical in all respects with the unlabeled compound described above except that the proton NMR spectrum showed a ^{13}C–^1H coupling constant of 128 Hz for the 5-methyl at 2.19 ppm.

2-Formyl-3,5-dimethylpyrrole (29a). Benzyl 3,5-dimethylpyrrole-2-carboxylate (**28**) (0.97 g) was hydrogenated as previously described above with palladized charcoal to give the pyrrolecarboxylic acid in 79% yield (0.47 g), mp 135–136 °C (lit.[17] mp 136 °C). This acid (0.47 g) was added portionwise at room temperature with stirring to trifluoroacetic acid (15 mL) over 5 min. The mixture was then cooled to 0 °C, and triethyl orthoformate (5.0 mL) was added in one portion. After 5 min the solution was warmed to room temperature, diluted with water (80 mL), and extracted with dichloromethane (3 × 25 mL). The organic solvent was washed with water (3 × 50 mL), dried (Na_2SO_4), and removed under reduced pressure to give a pale brown solid. The residue was purified by chromatography (silica gel, elution with dichloromethane) to give the title compound (0.08 g, 21%): mp 89–90 °C (lit.[18] mp 90 °C); ^1H NMR δ 2.33 (s, 3 H, ring Me), 2.33 (d, 3 H, ring Me, J = 129 Hz), 5.84 (s, 1 H, 4-H), 9.47 (s, 1 H, CHO), 11.14 (br s, 1 H, NH).

***tert*-Butyl 1,3,6-Triethyl-2,4,5,6′-tetramethyltripyrrene-b-1′-carboxylate Hydrobromide (30).** 5′-(*tert*-Butoxycarbonyl)-3,4′-diethyl-3′,4-dimethylpyrromethane-5-carboxylic acid (**16**)[19] (574 mg) and labeled 4-ethyl-2-formyl-3,5-dimethylpyrrole (**23**) (230 mg) in dichloromethane (60 mL) were stirred with a solution of *p*-toluenesulfonic acid hydrate (574 mg) in methanol (6 mL) for 40 min. The solution was washed with water, aqueous sodium bicarbonate, and water again and then dried (Na_2SO_4)

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(14) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Academische Verlag: Leipzig, 1934; Vol. I, p 157.
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(17) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Academische Verlag: Leipzig, 1934; Vol. I, p 239.
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(19) Howarth, T. T.; Jackson, A. H.; Kenner, G. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 502–511.

and evaporated to dryness. Dry dichloromethane (20 L) was added, and then dry HBr gas was passed through the solution for 9 s (color, orange to red). Diethyl ether (70 mL) was added dropwise while the mixture was stirred at 0 °C, and the product was filtered off to give 600 mg (80%): mp 244–245 °C dec (lit.[7] mp 244–245 °C dec); ^{1}H NMR δ 0.94, 1.07, 1.08 (each t, 3 H, CH_2CH_3), 2.05, 2.24, 2.28 (each s, 3 H, ring Me), 2.70 (d, 3 H, ring Me, J = 129 Hz), 2.41, 2.46, 2.71 (each q, 2 H, CH_2CH_3), 4.33 (s, 2 H, CH_2), 7.07 (s, 1 H, CH=), 10.25, 12.97, 12.98 (each br s, 1 H, NH); visible spectrum λ_{max} 494 nm (ε 87 700).

3,5,8-Triethyl-1′,2,4,6,7,8′-hexamethyl-a,c-biladiene Dihydrobromides 14 and 15. The foregoing labeled tripyrrene **30** (202 mg) was stirred in trifluoroacetic acid (4.5 mL) for 5 min before the addition of labeled 2-formyl-3,5-dimethylpyrrole **29a** (50 mg) and then 30% HBr in acetic acid (2.5 mL). After the mixture was stirred for 1 h, ether (80 mL) was added dropwise with continued stirring. The a,c-biladiene salt was filtered off and washed with ether to give greenish brown microprisms (191 mg, 75%): mp 258–269 °C dec (lit.[7] mp 258–269 °C); ^{1}H NMR δ 0.67, 1.09, 1.16 (each t, 3 H, CH_2CH_3), 1.94, 2.26, 2.31, 2.40, 2.67 (each s, 3 H, ring Me), 2.46, 2.47, 2.64 (each q, 2 H, CH_2CH_3), 2.70 (d, 6 H, ring Me, J = 130 Hz), 5.10 (s, 2 H, CH_2), 6.25 (s, 1 H, 1-H), 7.13 (s, 2 H, CH=), 12.96, 12.99, 13.03, 13.20 (each br s, 1 H, NH); visible spectrum, λ_{max} 446 nm (ε 104 300), 522 (122 000). Repeating the reaction with the unlabeled formylpyrrole **29b** afforded the singly labeled a,c-biladiene salt **15** in 73% yield (187 mg). All physical properties were identical with those of the above compound except for the proton NMR spectrum, which contained only one labeled methyl group at 2.70 ppm with a ^{13}C–^{1}H coupling constant of 130 Hz.

2,4,7-Triethyl-1,3,5,8-tetramethylporphyrin (7), 2,4,7-Triethyl-1,3,5,8,γ-pentamethylporphyrin (9), and 2,4,7-Triethyl-1,3,5,8-tetramethyl-γ-(dimethylamino)porphyrin (10). 3,5,8-Triethyl-1′,2,4,6,7,8′-hexamethyl-a,c-biladiene dihydrobromide (**8**)[7] (200 mg) in dry DMF (50 mL) containing anhydrous copper(II) acetate (1.26 g) was stirred under nitrogen at 160 °C for 5 min. After cooling, the solution was poured into water (100 mL) and extracted with dichloromethane (2 × 50 mL). The organic phase was dried (Na_2SO_4) and evaporated to dryness under vacuum to give a residue, which was chromatographed (alumina Brockmann Grade III, elution with dichloromethane). The red fractions were evaporated to dryness, and the residue was taken up in trifluoroacetic acid (8.5 mL) and concentrated sulfuric acid (1.5 mL) and set aside for 45 min. The mixture was then diluted with water (50 mL), extracted with dichloromethane (3 × 50 mL), and then dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on preparative plates (silica gel, elution with dichloromethane), and the three major bands were extracted from the silica gel. Each band was recrystallized from dichloromethane/*n*-hexane. The least most mobile band afforded compound **10** in 9.4% yield (15.2 mg): mp 74–75 °C (hygroscopic); ^{1}H NMR δ −3.43, −3.31 (each br s, 1 H, NH), 1.69, 1.84, 1.86 (each t, 3 H, CH_2CH_3), 3.56, 3.62, 3.65, 3.72 (each s, 3 H, ring Me), 3.89 (s, 6 H, NMe), 3.99, 4.11, 4.21 (each q, 2 H, CH_2CH_3), 10.04 (s, 1 H, meso H), 10.06 (s, 2 H, meso H); visible spectrum, λ_{max} 402 nm (ε 120 000), 504 (11 720), 538 (5100), 572 (5200), 626 (1400); MS, *m/e* (relatively intensity) 494 (14), 493 (100), 479 (10), 464 (32), 449 (10), 435 (7), 433 (4), 419 (5); MS, calcd for $C_{32}H_{39}N_5$ 493.321; found 493.321. When the reaction was repeated with a,c-biladiene **14** the isolated product contained no ^{13}C enrichment at the γ carbon by ^{13}C NMR analysis.

The middle band afforded compound **9** in 3% yield (2.3 mg): mp 256–257 °C (lit.[20] mp 258 °C); ^{1}H NMR δ −3.20 (br s, 2 H, NH), 1.78, 1.84, 1.87 (each t, 3 H, CH_2CH_3), 3.57, 3.61, 3.63, 3.72 (each s, 3 H, ring Me), 4.00, 4.10 (each q, 2 H, CH_2CH_3), 4.66 s, 3 H, γ-Me), 9.33 (s, 1 H, 6-H), 9.86, 10.03, 10.04 (each s, 1 H, meso H); visible spectrum, λ_{max} 400 nm (ε 137 000), 504 (12 200), 538 (4400), 574 (5200), 626 (600); MS, *m/e* (relative intensity) 466 (42), 464 (100), 450 (24), 435 (5), 421 (3), 406 (2). Anal. Calcd for $C_{31}H_{36}N_4$: C, 80.13; H, 7.81; N, 12.06. Found: C, 79.97; H, 7.80; N, 12.08.

When the reaction was repeated with the doubly labeled a,c-biladiene **14** (44 mg), the recovered product (3.3 mg, 7.4%) contained two ^{13}C labels **32**. The proton NMR spectrum showed a doublet of doublets at 4.66 ppm with J = 6.2 and 127.6 Hz. When the reaction was repeated with the singly labeled a,c-biladiene **15** (97 mg), the product (5.1 mg, 7.1%) contained one ^{13}C label shown in compounds **33** and **34**. The proton NMR spectrum showed two doublets at 4.66 ppm with J = 6.2 and 127.6 Hz.

The faster moving band afforded **7**: mp 269–270 °C (lit.[7] mp 269–270 °C); ^{1}H NMR δ −3.80 (br s, 2 H, NH), 1.86 (t, 6 H, 2 × CH_2CH_3), 1.88 (t, 3 H, CH_2CH_3), 3.62, 3.64, 3.66, 3.75, (each s, 3 H, ring Me), 4.10 (q, 6 H, 3 × CH_2CH_3), 9.08 (s, 1 H, 6-H), 10.03, 10.09, 10.13 (each s, 1 H, meso H). When the reaction was repeated with the doubly labeled a,c,-biladiene **14** (60 mg), the product **31** was obtained in 12.1% yield (3.5 mg) and contained a label at the γ carbon. The proton NMR spectrum showed a doublet at 10.03 ppm with J = 156 Hz. When the reaction was repeated with the singly labeled a,c-biladiene **15** (97 mg), the product was obtained in 11% yield (7.4 mg) containing a partial label at the γ carbon of **35**. The proton NMR spectrum showed a 50% labeled γ carbon at 10.03 ppm with J = 156 Hz.

3,6,8-Triethyl-2-formyl-1,4,5,7-tetramethylporphyrin (12). 3,5,8-Triethyl-1′,2,4,6,7,8′-hexamethyl-a,c-biladiene dihydrobromide (500 mg) was cyclized as described above in the presence of anhydrous copper(II) chloride (2.10 g) and lead dioxide (2.3 g) to give porphyrins **7** and **12** in 1.3% and 9.2% yield, respectively. Porphyrin **7** was identical in all respects with that from the previously described synthesis. The slower moving band was recrystallized from dichloromethane/cyclohexane to give 35 mg of the formylporphyrin as deep purple needles: mp 317 °C dec: ^{1}H NMR δ −3.63 (br s, 2 H, NH), 1.83, 1.86, 1.88 (each t, 3 H, CH_2CH_3), 3.52, 3.64, 3.65, 3.94 (each s, 3 H, ring Me), 3.97, 4.11, 4.15 (each q, 2 H, CH_2CH_3), 9.94, 9.95, 10.11, 10.96 (s , 1 H, meso H), 11.48 (s, 1 H, CHO); visible spectrum, λ_{max} 410 nm (ε 199 000), 516 (10 200), 556 (20 400), 578 (13 270), 642 (1800); MS, *m/e* (relative intensity) 481 (1.3), 480 (6), 479 (8), 478 (100), 463 (34), 450 (20), 435 (28), 419 (10), 405 (10), 391 (7), 375 (4), 369 (22), 355 (12). Anal. Calcd for $C_{31}H_{34}N_4O$: C, 76.35; H, 7.24; N, 11.49. Found: C, 76.65; H, 7.24; N, 11.49.

When the reaction was repeated with the doubly labeled a,c-biladiene **14** (60 mg), the product **36** was recoverd in 96% yield (4.0 mg). The proton NMR spectrum showed two ^{13}C labels at the γ carbon (10.96 ppm, d, 1 H, J = 160 Hz) and the formyl carbon (11.48 ppm, d, 1 H, J = 170 Hz). When the reaction was repeated with the singly labeled a,c-biladiene **15** (100 mg), the product **37** was isolated in 9.2% yield (7.0 mg). The proton NMR spectrum showed only one ^{13}C label at the γ carbon (10.96 ppm, d, 1 H, J = 160 Hz).

3,6,8-Triethyl-γ-formyl-1,4,5,7-tetramethylporphyrin (13). 3,5,8-Triethyl-1′,2,4,6,7,8′-hexamethyl-a,c-biladiene dihydrobromide (**8**) (458 mg) was cyclized in DMF as described above in the presence of copper(II) ammonium chloride (1.78 g) to give the three porphyrins **7**, **12**, and **13** in 10.2%, 2%, and 3.7% yield, respectively. Compounds **7** and **12** were identical with those described above. The γ-formylporphyrin was recrystallized in dichloromethane/cyclohexane to give deep purple needles (13 mg): mp 258–259 °C; ^{1}H NMR δ −2.88 (br s, 2 H, NH), 1.78, 1.81, 1.84 (each t, 3 H, CH_2CH_3), 3.57 (s, 9 H, 3 × ring Me), 3.69 (s, 3 H, ring Me), 3.93 (q, 2 H, CH_2CH_3), 4.00 (q, 4 H, 2 × CH_2CH_3), 9.68 (s, 1 H, 6-H), 9.99 (s, 1 H, meso H), 10.07 (s, 2 H, 2 × meso H), 12.57 (s, 1 H, γ-CHO); visible spectrum, λ_{max} 406 nm (ε 133 000), 512 (3210), 560 (4470), 646 (2550), 658 (770); MS, *m/e* (relative intensity) 479 (13), 478 (55), 464 (13), 450 (76), 449 (20), 435 (29), 434 (100), 420 (14), 405 (11); MS, calcd for $C_{31}H_{34}N_4O$ 478.273, found 478.267. When the reaction was repeated with the doubly labeled a,c-biladiene **14** (66 mg), the product **38** was obtained in 6.9% yield (3.5 mg). The porphyrin was labeled at both the γ and formyl carbons (12.57 ppm, d of d, 1 H, J = 23 and 177.1 Hz). When the reaction was repeated with the singly labeled a,c-biladiene **15** (80 mg), the products **39** and **40** were produced in 7.2% yield (4.4 mg). The two porphyrins were each singly labeled, one at the γ carbon and the other at the formyl carbon. The proton NMR spectrum showed two doublets at 12.57 ppm with J = 23 and 177.1 Hz.

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Registry No. **7**, 96246-88-7; **8**, 92284-77-0; **9**, 94098-79-0; **10**, 94098-80-3; **11**, 96258-26-3; **12**, 96246-95-6; **13**, 96246-98-9; **14**, 96246-86-5; **15**, 96246-87-6; **16**, 31862-33-6; **18**, 967-38-4; **19**, 83089-91-2; **20**, 51089-83-9; **21** (unlabeled), 965-20-8; **21** (labeled), 96246-74-1; **22** (unlabeled), 1925-61-7; **22** (labeled), 96246-75-2; **23**, 96246-77-4; **24**, 3284-46-6; **25**, 96246-78-5; **26**, 96246-79-6; **27** (unlabeled), 96246-81-0; **27** (labeled), 96246-80-9; **28** (unlabeled), 40236-19-9; **28** (labeled), 96246-82-1; **29a**, 96246-84-3; **29b**, 2199-58-8; **30**, 96246-85-4; **31**, 96246-94-5; **32**, 96246-91-2; **33**, 96246-92-3; **34**, 96246-93-4; **36**, 96246-96-7; **37**, 96246-97-8; **38**, 96246-99-0; **39**, 96247-00-6; **40**, 96247-01-7; $HS(CH_2)_2SH$, 540-63-6; $Cu(OAc)_2$, 142-71-2; $CuCl_2$, 7447-39-4; $CuNH_4Cl_2$, 10534-87-9; $Cu(NO_3)_2$, 3251-23-8; $CuBr_2$, 7789-45-9; $CuSO_4$, 7758-98-7; 4-ethyl-2,5-dimethyl-2-pyrrolecarboxylic-*5-methyl*-^{13}C acid, 96246-76-3; 3,5-dimethyl-2-pyrrolecarboxylic-*5-methyl*-^{13}C acid, 96246-83-2.

Some Regio- and Stereochemical Aspects of the Diels–Alder Reaction of Nitrosocarbonyl Compounds with N-Substituted 1,2-Dihydropyridines

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The intramolecular cycloaddition reaction of N-substituted 1,2-dihydropyridines **1** with (nitrosocarbonyl)benzene, phenyl nitrosoformate, and benzyl nitrosoformate afforded 2,3,5-oxadiazabicyclo[2.2.2]oct-7-enes **2**, **5**, and **7** and/or 2,3,6-oxadiazabicyclo[2.2.2]oct-7-enes **3**, **6**, and **8**. The regiochemistry of the cycloaddition reaction is dependent upon the electronic effects of substituents present in the dienophile and dienamide. The regiochemistry of the cycloaddition products was determined with ^{13}C NMR spectral data together with an X-ray analysis of **4b**, a product arising from a [3,3]-sigmatropic rearrangement reaction of **2b**.

Various *C*-nitroso compounds are versatile reagents for the preparation of 3,6-dihydro-1,2-oxazines, which have been utilized for the preparation of 1,4-amino alcohol derivatives.[1] Although Kirby[2] has employed nitrosocarbonyl compounds as dienophiles in Diels–Alder reactions, the reaction with heterocyclic dienamines and dienamides has not been reported. N-Substituted 1,2-dihydropyridines (**1**) are useful synthons for use in heterodiene condensation reactions and they have played a significant role in the synthesis of various alkaloids[3] and bicycloheterocycles of pharmacological interest.[4-7] In some earlier studies we reported the reactions of 1,2-dihydropyridines **1** with azides,[4] nitrosobenzene,[5] oxyamination reagents,[6] and phenylsulfonyl cyanide *N*-oxide.[7] We now report the Diels–Alder reaction of 1,2-dihydropyridines **1** with nitrosocarbonyl compounds of varied dienophilicity, the electronic effect of substituents upon regiochemistry, the stereochemistry of the cycloadducts formed, and the structures of rearrangement products.

Chemistry

The reaction of *N*-acetyl-2-*n*-butyl-1,2-dihydropyridine (**1a**) with *N*-benzoylhydroxylamine in the presence of tetraethylammonium periodate at −78 °C in methylene chloride afforded **2a** as the major product (70% yield) and **4a** as a minor product (about 5% yield, Scheme I). The formation of both **2a** and **4a** initially suggested the addition of (nitrosocarbonyl)benzene to the C_3–C_6 diene system as well as the C_3–C_4 olefinic bond of **1a** had occurred. It was subsequently observed that **2a** undergoes a slow conversion into **4a** at room temperature, indicating that **4a** may not be a primary reaction product. Similar reactions of **1b,c** with (nitrosocarbonyl)benzene yielded **2b,c** in 84% and 55% yield, respectively. The regioisomer **2b** also undergoes a slow conversion to **4b** at 25 °C. In contrast **2c** is stable at 25 °C, but heating a solution of **2c** in Me_2SO at 60 °C afforded **4c** in quantitative yield. On the other hand, a similar reaction of the 1,5-bis(methoxycarbonyl)-1,2-dihydropyridine (**1d**) gave both regioisomers **2d** and **3** in a 93% combined yield in a ratio of 4:1. Regioisomer **3** is stable at 25 °C but **2d** slowly converted to **4d** at room temperature.

Reaction of **1a,b** with phenyl nitrosoformate yielded **5a,b** in 24% and 25.5% yield,[8] respectively, whereas reaction with **1c** gave both regioisomers **5c** and **6** in 47% overall yield in a ratio of 4:3, respectively. The related reactions of **1a–c** with benzyl nitrosoformate afforded regioisomers **7a–c** and **8a–c**. The regioisomer **8a** could not be isolated since it was converted to **9** (36.5% yield from **1a**) during silica gel chromatography, presumably due to reaction with water. When a solution of **9** in methanol was heated at reflux, **10** was obtained in near-quantitative yield. Silica gel column purification of **8b** gave rise to **11** and **12** in 13.6% and 6.8% yield, respectively, from **1b**. The ^1H NMR spectrum of the reaction mixture containing **7b** and **8b** exhibited absorptions at δ 6.29 and 6.12 which can be attributed to the H_1 proton of **8b**.

Discussion

The assignment of the regio- and stereochemistry of products **2–12** was based on their ^1H and ^{13}C NMR spectral

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(8) The low yield of products in this series of compounds is attributed to a low formation of the phenyl nitrosoformate. The crude reaction mixture exhibited the smell of phenol and a substantial quantity of unreacted N-substituted 1,2-dihydropyridines was recovered.

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