evaporated, and the residue was chromatographed by using 1:1 ether/petroleum ether as the eluant, resulting in 10 mg (77%) of slaframine azide **38** as a colorless oil: $[\alpha] = -29.3°$ ($c = 0.04$, dichloromethane); NMR 1.50–1.65 (m, 3 H), 1.71–1.79 (m, 1 H), 1.82–1.90 (m, 1 H), 2.02–2.07 (m, 2 H), 2.08 (s, 3 H), 2.15–2.19 (m, 1 H), 2.21–2.30 (m, 1 H), 3.15 (td, 1 H, $J = 7.2, 2.0$), 3.23 (dd, 1 H, $J = 2.4, 12.0$), 3.82 (br s, 1 H), 5.22 (ddd, 1 H, $J = 2.0, 4.8, 7.2$); IR 2110, 1740. Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.18; N, 24.98. Found: C, 53.80; H, 7.21; N, 24.79.

1(*S*)-Acetoxy-6(*S*)-amino-(8a*S*)-indolizidine, Slaframine (5). A mixture of 4 mg (0.018 mmol) of azido acetate **38**, 5 mg of 5% palladium-on-carbon, and 1 mL of ethanol was stirred under an atmosphere of hydrogen gas for 10 min. The mixture was filtered through Celite, and the ethanol was evaporated to give approximately 3 mg of slaframine (**5**) which showed $[\alpha] = -32.3°$ ($c = 0.3$, chloroform): NMR 1.54–1.60 (m, 2 H), 1.65–1.82 (m, 2 H), 1.87–1.96 (m, 2 H), 2.02–2.05 (m, 1 H), 2.08 (s, 3 H), 2.14–2.30 (m, 2 H), 2.75 (br s, 2 H), 3.07–3.18 (m, 2 H), 3.28 (br s, 1 H), 5.20 (ddd, 1 H, $J = 2.3, 4.9, 7.4$); IR 3500–3400, 1735.

A solution of slaframine as obtained above in 1 mL of pyridine and 0.5 mL of acetic anhydride was stirred for 0.5 h. The solvents were evaporated, and the product was crystallized from petroleum ether/ethanol to give 4 mg of *N*-acetylslaframine (**39**) as tiny white needles, mp 140–141 °C: $[\alpha] = -14.6°$ ($c = 0.3$, ethanol); NMR 1.40–2.12 (m, 2 H), 2.18 (dd, 1 H, $J = 2.7, 11.5$), 2.25–2.31 (m, 1 H), 3.03 (dt, 2 H, $J = 11.5, 2.1$), 3.08 (td, 1 H, $J = 9.2, 2.1$), 4.19 (dt, 1 H, $J = 8.4, 2.8$), 5.25 (ddd, 1 H, $J = 2.0, 4.8, 7.2$), 6.33 (br d, 1 H, $J = 6.0$); IR 3350, 1735, 1665.

Porphyrins with Exocyclic Rings. 1. Chemistry of 4,5,6,7-Tetrahydro-1*H*-indoles: Synthesis of Acetoxy Derivatives, Dihydroindoles, and Novel Porphyrins with Four Exocyclic Rings[1,2]

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A variety of 4,5,6,7-tetrahydro-1*H*-indoles (THI's) and 4-oxo-4,5,6,7-tetrahydro-1*H*-indoles (4-oxoTHIs) have been synthesized from cyclohexanone and 1,3-cyclohexanedione, respectively. The THI's reacted regioselectively with lead tetraacetate in acetic acid to give the 7-acetoxy derivatives. The isomeric 4-acetoxyTHI's were prepared by first reducing the corresponding 4-oxoTHI's with sodium borohydride and then reacting the resulting hydroxyTHI's with acetic acid–pyridine. Both series of acetoxyTHI's underwent elimination of acetic acid when heated with pyridine–acetic anhydride to give dihydroindoles. The 7-acetoxyTHI's were hydrolyzed with potassium hydroxide in methanol–water and carefully neutralized with hydrochloric acid to give the corresponding hydroxyTHI carboxylic acids. Treatment with potassium ferricyanide in refluxing acetic acid gave good yields of tetrapropanoporphyrins when 3-methyl-, 3-ethyl-, or 3-*n*-propyl substituents were present. The 3-phenylTHI gave variable yields of the corresponding tetraphenylporphyrin. The 3-isopropylTHI gave only trace amounts of porphyrin under these conditions, and the 3-*tert*-butylTHI failed to give any porphyrin product. THI's with 6-methyl or 6,6-dimethyl substituents were prepared in two steps from 5-methyl-1,3-cyclohexanedione or dimedone, respectively. These compounds also reacted smoothly with lead tetraacetate to give the 7-acetoxy derivatives in high yield. Attempts to convert the 6,6-dimethylTHI's into symmetrical porphyrins were unsuccessful, although the 6-methylTHI gave a mixture of porphyrin stereoisomers in low yield. The influence of alkyl substituents and carbocyclic rings on the cyclotetramerization of THI's is discussed.

Introduction

Complex mixtures of metalloporphyrins are present[3] in organic-rich sediments such as oil shales, petroleum, bitumens, and coal. These compounds are believed to be the degradation products from biological pigments such as the chlorophylls. The peripheral substituents of these "molecular fossils" have undergone considerable modification, and the analysis of metalloporphyrins from a given organic sediment can give information about its geochemical history (depositional environment, thermal maturity, etc.). Since sedimentary porphyrins differ structurally from biological tetrapyrroles, the terms "petroporphyrin" and "geoporphyrin" have been coined[4] to describe these compounds. Over the last 10 years, individual petroporphyrins have been isolated and characterized by mass spectrometry and proton NMR spectroscopy.[5] Two major

(1) Preliminary communication: Lash, T. D.; Bladel, K. A.; Johnson, M. C. *Tetrahedron Lett.* **1987**, *28*, 1135.

(2) Results presented, in part, at the Tenth International Congress of Heterocyclic Chemistry, University of Waterloo, Ontario, Canada, Aug 1985 (Abstract: Lash, T. D. *Book of Abstracts*, P5–164); 193rd National American Chemical Society Meeting, Denver, Colorado, April 1987 (Abstract: Bladel, K. A.; Lash, T. D. *Book of Abstracts*, CHED 78); 82nd Annual Meeting of the Illinois State Academy of Science, Loyola University, Chicago, Illinois, Oct. 1989 (Abstract: Shiner, C. M.; Lash, T. D. *Trans. Ill. St. Acad. Sci.* **1989**, *Suppl. to Vol. 82*, 43).

(3) Baker, E. W.; Palmer, S. E. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 486–552.

(4) Eglinton, E.; Calvin, M. *Sci. Am.* **1967**, *216*, 32.

(5) (a) Filby, R. H.; Van Berkel, G. J. In *Metal Complexes in Fossil Fuels. Geochemistry, Characterization, and Processing*. Filby, R. H., Branthaver, J. F., Ed.; American Chemical Society: Washington DC, pp 2–37. (b) Chicarelli, M. I.; Kaur, S.; Maxwell, J. R. *Ibid.* pp 40–67. (c) Ocampo, R.; Callot, H. J.; Albrecht, P. *Ibid.* pp 68–73.

Chart I

1

2

3 M = VO   a. R = Et
             b. R = Me

4 M = Ni; R = H or Et

5 M = VO or Ni; R = H, Me or Et

6
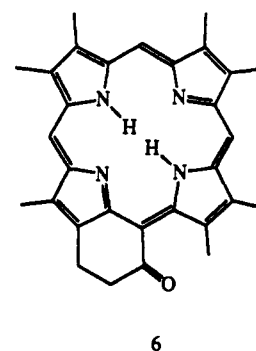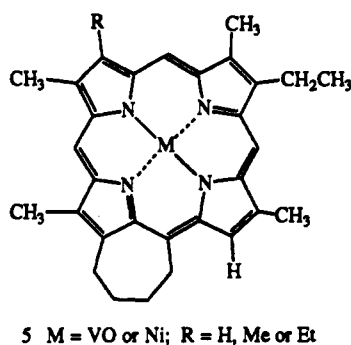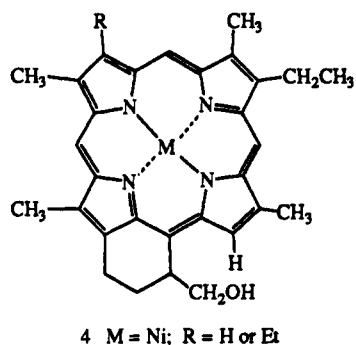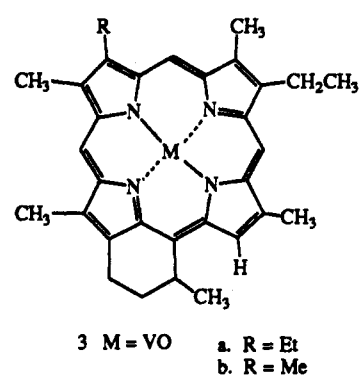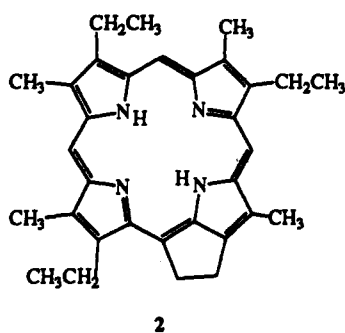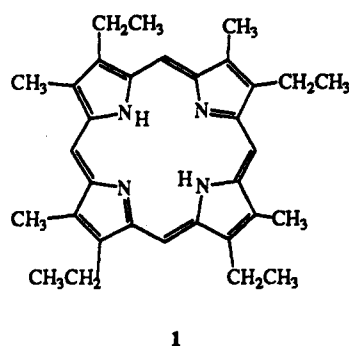
series, the ETIOporphyrins and the DPEP's, are present in oil shales and petroleum.[3] The ETIOporphyrins are structurally related to etioporphyrin-III (1)[6] and represent relatively straightforward targets for total synthesis.[7] The DPEP's are petroporphyrins with five-membered exocyclic rings structurally related to deoxophylloerythroetioporphyrin (DPEP; 2).[8] Minor series of petroporphyrins are also present in organic-rich sediments, and many of these compounds bear exocyclic rings. Porphyrins 3a and 3b have been isolated[9] from Serpiano Oil Shale (Triassic, Switzerland) and two related (hydroxymethyl)propanoporphyrins 4 were recently characterized[9b] from the Messel Oil Shale (Eocene, West Germany). The origins of these six-membered ring structures are presently not known, although they are probably related to the more widespread 15,17-butanoporphyrins 5.[5,10] Many additional examples of geoporphyrins with diverse carbon skeletons have been

Scheme I

7 a. R = Me; n = 2
   b. R = H; n = 3

8

9

10
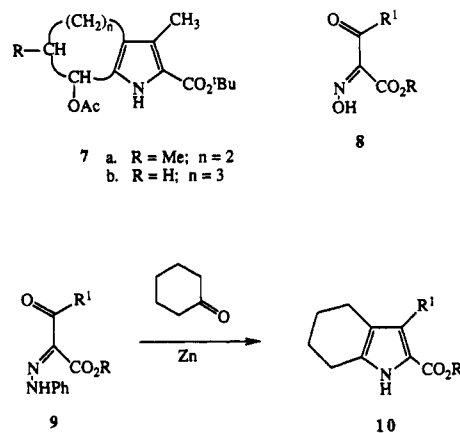
a. R¹ = Me; R = Et
b. R¹ = Et; R = Me
c. R¹ = ⁿPr; R = Et
d. R¹ = Ph; R = Et
e. R¹ = ⁱˢᵒPr; R = Et
f. R¹ = ᵗᵉʳᵗBu; R = Me

recognized in recent years.[5] Synthetic porphyrins[11] are needed as chromatographic, mass spectrometric and spectroscopic standards in the analysis of organic sediments and to provide unambiguous confirmation of petroporphyrin structures. We have targeted the total synthesis of porphyrins with exocyclic rings (e.g., structures 2, 3, and 5) as an aid to ongoing structure determination studies.

(6) Quirke, J. M. E.; Maxwell, J. R. *Tetrahedron* **1980**, *36*, 3453. Fookes, C. J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 706. Chicarelli, M. I.; Wolff, G. A.; Maxwell, J. R. *Ibid.* 723.

(7) Clezy, P. S.; Fookes, C. J. R.; Prashar, J. K. *Aust. J. Chem.* **1989**, *42*, 775. Clewlow, P. J.; Jackson, A. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1925.

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(9) (a) Chicarelli, M. I.; Wolff, G. A.; Murray, M.; Maxwell, J. R. *Tetrahedron* **1984**, *40*, 4033. (b) Prowse, W. G.; Maxwell, J. R. *Geochim. Cosmochim. Acta* **1989**, *53*, 3081. (c) The free bases of methylpropanoporphyrins 3a and 3b were reported to be racemic modifications. In addition, the vanadyl complex of 3a has been shown to be present in the Serpiano Oil Shale as a mixture of diastereomers: Boreham, C. J.; Clezy, P. S.; Robertson, G. B. *Energy Fuels* **1990**, *4*, 661.

(10) Wolff, G. A.; Murray, M.; Maxwell, J. R.; Hunter, B. K.; Sander, J. K. M. *J. Chem. Soc., Chem. Commun.* **1983**, 922. Fookes, C. J. R. *Ibid.* 1474.

(11) (a) Lash, T. D. *Org. Geochem.* **1989**, *14*, 213. (b) Lash, T. D.; Balasubramaniam, R. P.; Catarello, J. J.; Johnson, M. C.; May, D. A., Jr.; Bladel, K. A.; Feeley, J. M.; Hoehner, M. C.; Marron, T. G.; Nguyen, T. H.; Perun, T. J., Jr.; Quizon, D. M.; Shiner, C. M.; Watson, A. *Energy Fuels* **1990**, *4*, 668.

Scheme II

a. R = H; X = OAlkyl
b. R = CH₃; X = OAlkyl
c. R = H; X = NMe₂
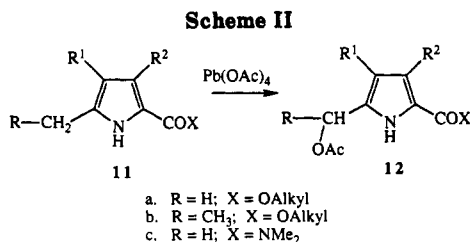
When we initiated our researches, few studies had been carried out on the synthesis of porphyrins with exocyclic rings. Most research in this area had been directed toward the synthesis of deoxophylloerythroetioporphyrin (2).[12] Porphyrins bearing propionic acid side chains were known to undergo cyclization reactions in oleum to give "rhodins" 6,[13] but otherwise porphyrins with six-membered or larger exocyclic ring structures had received little attention. We speculated that petroporphyrins 3 and 5 might be synthesized from acetoxycycloalka[b]pyrroles 7a and 7b, respectively. Structures of this type had not been described previously, and we undertook a detailed study on the six-membered ring systems (i.e., the 7-acetoxy-4,5,6,7-tetrahydro-1H-indoles) to provide the groundwork for future research into the total synthesis of petroporphyrins. In this paper, the synthesis and chemistry of 4,5,6,7-tetrahydro-1H-indoles is examined. The preparation of novel symmetrical porphyrins bearing four six-membered exocyclic rings is also described.

Results and Discussion

Oximes 8[14] and phenylhydrazones 9[15] are known to condense with cyclohexanone in the presence of zinc dust and buffered acetic acid to give the corresponding 4,5,6,7-tetrahydro-1H-indoles (THI's) 10 (Scheme I). We decided to use phenylhydrazones 9 in our studies, and these compounds were prepared in high yield from the reaction of benzenediazonium chloride with the corresponding β-keto esters. Using this approach, THI's bearing 3-methyl (10a), 3-ethyl (10b), and 3-n-propyl (10c) substituents were prepared. The yield for the 3-ethylTHI 10b was somewhat inferior, although limited improvements were achieved at higher reaction temperatures.

We required THI's bearing 7-acetoxy substituents in our studies. It is well-known[16] that 5-methylpyrrole-2-carboxylates 11a react with lead tetraacetate to give the corresponding (acetoxymethyl)pyrroles 12a (Scheme II). However, it has been reported[17] that 5-ethylpyrrole-2-

Scheme III

a. R¹ = Me; R = Et
b. R¹ = Et; R = Me
c. R¹ = ⁿPr; R = Et
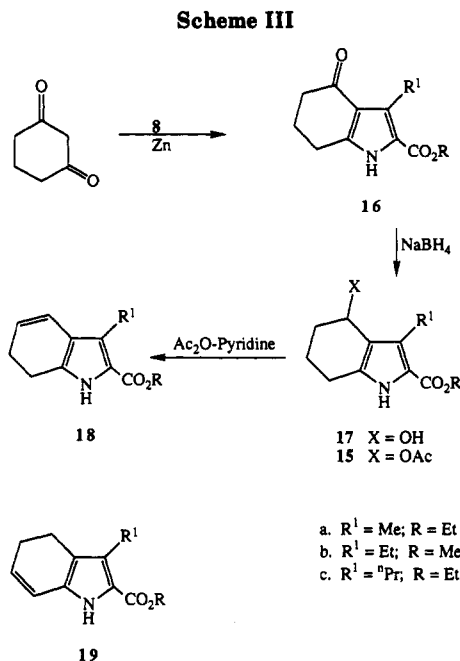
carboxylates 11b fail to give this reaction. Recently, we found[11b] that this reaction is successful for 5-ethylpyrroles 11b (X = OEt) when dichloromethane is used as a solvent. Although this reaction is nearly quantitative, the labile (acetoxyethyl)pyrroles 12b could not be further purified. It is noteworthy that 5-methylpyrrole-2-carboxamides 11c also fail to give the acetoxy derivatives 12c when acetic acid is used as a solvent[18] (dipyrrylmethanes are isolated instead), although the acetoxy compounds could be obtained when dichloromethane was used as the reaction solvent. Hence, while the acetoxy derivatives may further react in acetic acid solution, the reaction appears to be a fairly general one. The tetrahydroindoles 10a–c were found to react smoothly with lead tetraacetate in acetic acid to give the required 7-acetoxyTHI's 13 in high yield. The 3-methyl and 3-ethyl products, 13a and 13b, could be further purified by crystallization, although this often resulted in significant losses of material. Alcohol solvents should be avoided, since solvolysis of the acetoxy function occurs relatively easily. Prolonged exposure to water also resulted in the formation of hydroxyTHI's 14. However, since the reaction with lead tetraacetate was nearly quantitative, these compounds could be used without further purification.

a. R¹ = Me; R = Et
b. R¹ = Et; R = Me
c. R¹ = ⁿPr; R = Et
d. R¹ = Ph; R = Et
e. R¹ = ⁱˢᵒPr; R = Et
f. R¹ = ᵗᵉʳᵗBu; R = Me
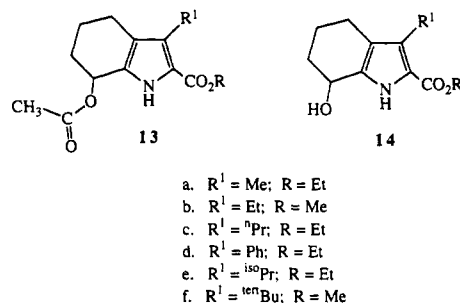
The reaction products 13 were single products by NMR spectroscopy and the 7-acetoxy compounds were to be expected on the basis of mechanistic considerations and literature precedent. However, it was difficult to unambiguously dismiss the 4-acetoxy compounds 15 (Scheme

(12) Fischer, H.; Hofmann, H. J. *Liebigs Ann. Chem.* **1935**, *517*, 274. Sugihara, J. M.; McGee, L. R. *J. Org. Chem.* **1957**, *22*, 795. Baker, E. W.; Corwin, A. H.; Klesper, E.; Wei, P. E. *J. Org. Chem.* **1968**, *33*, 3144. Flaugh, M. E.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 6877. Chaudry, I. A.; Clezy, P. S.; Mirza, A. H. *Aust. J. Chem.* **1980**, *33*, 1095. Evstigneeva, R. P. *Pure Appl. Chem.* **1981**, *53*, 1129. Pomonarev, G. V.; Shul'ga, A. M.; Subock, V. P. *Dokl. Akad. Nauk SSSR* **1981**, *259*, 1121. Pomonarev, G. V. *Khim. Geterotsikl. Soedin.* **1981**, 1693. Smith, K. M.; Langry, K. C.; Minnetian, O. M. *J. Org. Chem.* **1984**, *49*, 4602. Bauder, C.; Ocampo, R.; Callot, H. J. *Synlett* **1990**, *335*; *Tetrahedron Lett.* **1991**, *32*, 2537. Clezy, P. S.; Mirza, A. H.; Prashar, J. K. *Aust. J. Chem.* **1990**, *43*, 857. Clezy, P. S.; Van Phuc, L.; Prashar, J. K. *Ibid.* **1991**, *44*, 1061. Clezy, P. S.; Fookes, C. J. R.; Prashar, J. K.; Salek, A. *Ibid.* **1992**, *45*, 703. See also ref 11.

(13) Fischer, H.; Treibs, A. *Liebigs Ann. Chem.* **1928**, *466*, 188. Fischer, H.; Treibs, A.; Helberger, H. *Ibid.* 243. Clezy, P. S.; Mirza, A. H.; Ravi, B. N.; van Thuc, L. *Aust. J. Chem.* **1984**, *37*, 143. Dixon, D. W.; Callahan, J.; Ghosh, S. B.; Hwang, Y. C.; Shirazi, A.; Tyler, A. W. *Inorg. Chim. Acta* **1986**, *122*, 31. This chemistry was recently adapted for the total synthesis of petroporphyrins 3a and 5a: Clezy, P. S.; Prashar, J. K. *Aust. J. Chem.* **1990**, *43*, 825. Clezy, P. S.; Jenie, U.; Prashar, J. K. *Ibid.* 839.

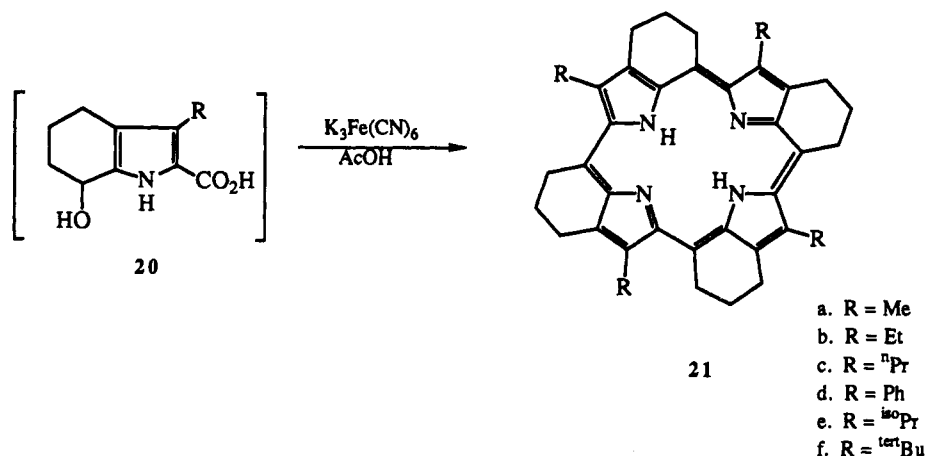(14) Treibs, A.; Dinelli, D. *Liebigs Ann. Chem.* **1935**, *517*, 152.

(15) Shvedov, V. I.; Altukhova, L. P.; Grinev, A. N. *Khim. Geterotsikl. Soedin.* **1972**, 342.

(16) Siedel, W.; Winkler, F. *Liebigs Ann. Chem.* **1943**, *554*, 162.

(17) Cox, M. T.; Jackson, A. H.; Kenner, G. W. *J. Chem. Soc. C* **1971**, 1974.

(18) Jackson, A. H.; Lash, T. D.; Ryder, D. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 287.

Scheme IV

20

21

a. R = Me
b. R = Et
c. R = ^nPr
d. R = Ph
e. R = ^{iso}Pr
f. R = ^{tert}Bu

III) as possible products in this chemistry. Hence, it was desirable to obtain synthetic samples of 15a–c for comparison with the products from the lead tetraacetate reaction. The synthesis of 4-oxo-4,5,6,7-tetrahydro-1H-indoles (4-oxoTHI's; 16) is easily achieved[19,20] by Knorr condensation of oximes 8, obtained by nitrosation of the related β-keto esters, with 1,3-cyclohexanedione (Scheme III). The 3-methyl- (16a), 3-ethyl- (16b) and 3-n-propyl-4-oxoTHI's (16c) were prepared in this manner. Reduction with sodium borohydride afforded the corresponding 4-hydroxyTHI's 17a–c, and further reaction with acetic anhydride in pyridine at room temperature gave the acetoxy derivatives 15a–c. These compounds had different physical (mp) and spectroscopic (NMR; IR) properties from the products of the lead tetraacetate reaction with THI's 10a–c, and the regiospecificity of this chemistry can be affirmed with confidence.

When the 4-hydroxyTHI's 17a–c, or the acetoxy derivatives 15a–c, were heated with acetic anhydride–pyridine, the elimination products 18a–c were obtained in good yield (Scheme III). This provides a convenient route to the 6,7-dihydro-1H-indole system 18. Similarly, the 7-acetoxyTHI's 13a–c underwent elimination reactions under these conditions to give the isomeric 4,5-dihydro-1H-indoles 19a–c. Vinylic pyrroles of this type are of interest in relation to studies on cycloaddition reactions,[21] as well as being potential intermediates for porphyrin synthesis.[22,23]

The utility of THIs in the synthesis of symmetrical porphyrins was investigated. Using the standard conditions for octaethylporphyrin synthesis,[24] the THIs 13a–c were hydrolyzed with potassium hydroxide in methanol–water and carefully neutralized at 0 °C to give the unstable hydroxy carboxylic acids 20a–c (Scheme IV). Treatment with potassium ferricyanide in refluxing acetic acid gave the tetrapropanoporphyrins 21a–c in moderate yield (Scheme IV). Extensive chromatography was required to purify these unusual porphyrins. The Soret absorptions for these pigments appeared at relatively high wavelengths

(approximately 420 nm). Porphyrins 21a–c were unusually basic, and silica gel was sufficiently acidic to convert these compounds to the green dications. The compounds were also somewhat photosensitive in solution, and care was needed when handling these porphyrins or decomposition ensued. These abnormal properties are probably due to steric interactions between the peripheral substituents which distort the porphyrin macrocycle.[25] It should be noted that porphyrin dications have relatively puckered conformations, and protonation would be expected to relieve steric crowding.[25b] The more severely crowded octaalkyltetraphenylporphyrins 22a[25a,c] and 22b[25b,c] have Soret absorptions that are still further shifted into the visible region, and octaethyltetraphenylporphyrin 22b is so basic that the corresponding dication forms in the presence of water. Hence, the spectroscopic properties and enhanced basicities for porphyrins 21a–c are consistent with those previously observed for "crowded" porphyrins.[25]

22

a. R = Me
b. R = Et

23

a. n = 5; b. n = 6
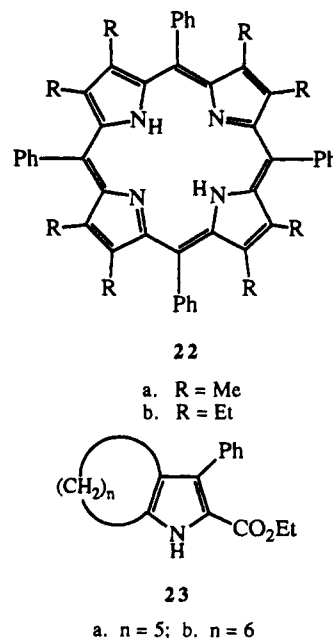
In order the establish the generality of this chemistry, three THI's were prepared with bulky 3-substituents. The 3-phenyl- (10d), 3-isopropyl- (10e), and 3-$tert$-butylTHIs (10f) were prepared from the corresponding phenyl-

(19) Hauptmann, S.; Blume, H.; Hartmann, G.; Haendel, D.; Franke, P. *Z. Chem.* 1966, *6*, 107.

(20) Nenitzescu, C. D.; Scortzeanu, V. *Bull. Soc. Chim. Rom.* 1928, *10*, 134.

(21) E.g.: Gonzalez-Rosende, E.; Jones, R. A.; Sepulveda-Arques, J.; Zaballos-Garcia, E. *Synth. Commun.* 1988, *18*, 1669 and references cited therein.

(22) Burns, D. H.; Smith, K. M. *J. Chem. Res., Synop.* 1990, 178.

(23) Lash, T. D.; Nguyen, T. H. Thirteenth International Congress of Heterocyclic Chemistry, Oregon State University, Corvallis, OR, Aug 1991; Book of Abstracts, GE8-89.

(24) Inhoffen, H. H.; Fuhrhop, J.-H.; Voigt, H.; Brockmann, H., Jr. *Liebigs Ann. Chem.* 1966, *695*, 133.

(25) (a) Dolphin, D. *J. Heterocycl. Chem.* 1970, *7*, 275. (b) Evans, B.; Smith, K. M.; Fuhrhop, J.-H. *Tetrahedron Lett.* 1977, *18*, 443. (c) Barkigia, K. M.; Berber, M. D.; Fajer, J.; Medforth, C. J.; Renner, M. W.; Smith, K. M. *J. Am. Chem. Soc.* 1990, *112*, 8851.

Scheme V

24

25

26 X = OAc
27 X = OH

a. $R^1 = R^2 = Me; R = Et$
b. $R^1 = Et; R = R^2 = Me$
c. $R^1 = Me; R^2 = H; R = Et$
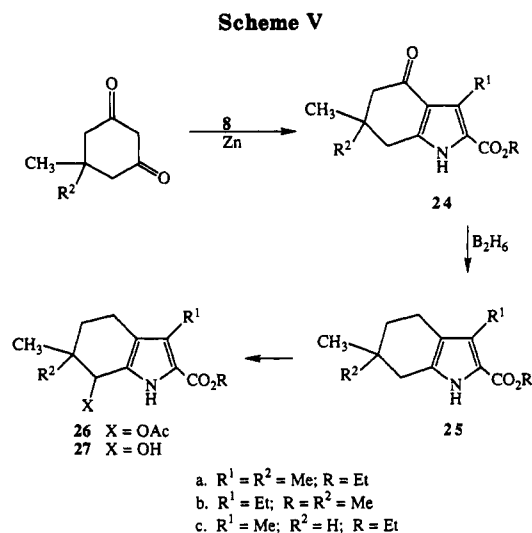
hydrazones 9d–f (Scheme I) using the methodology described above. The phenylhydrazone of ethyl benzoylacetate 9d gave moderate yields of the required 3-phenylTHI when the reaction was carried out in acetic acid at higher temperatures (110–120 °C). The yields were improved somewhat when propionic acid was substituted as the reaction solvent.[26] The phenylhydrazone 9d also condensed with cycloheptanone and cyclooctanone under these reaction conditions to give the cyclohepta- and cyclooocta[b]pyrroles 23a and 23b, respectively, in good yields. The phenylhydrazones 9e and 9f reacted with cyclohexanone to give inferior yields of the 3-isopropyl- (10e) and 3-tert-butylTHI's (10f) under all the conditions investigated, although the best yields were again obtained using propionic acid as a solvent at 150 °C. Since the tert-butylTHI was formed in the lowest yield (8%), it seems probable that these poor results were due to deleterious steric interactions which inhibit pyrrole ring formation. In any case, sufficient quantities of the THI's 10d–f were obtainable by this approach to carry out further studies on porphyrin formation.

Reaction of THI's 10d–f with lead tetraacetate in acetic acid again afforded the corresponding acetoxy derivatives 13d–f in high yield. The acetoxy compounds were hydrolyzed, as previously described, to form the hydroxy carboxylic acids 20d–f (Scheme IV). These unstable intermediates were immediately treated with potassium ferricyanide in refluxing acetic acid. The 3-phenylTHI 20d gave the corresponding tetraphenylporphyrin 21d in highly variable yields (1–20%). The 3-isopropylTHI 20e afforded only trace amounts of porphyrin 21e, and 3-tert-butylTHI 20f failed to give any porphyrin product. Hence, the presence of bulky 3-substituents severely inhibits porphyrin formation in these reactions. Porphyrins 21d and 21e both showed bathochromically shifted Soret absorption bands, and this may be indicative of further distortion to the porphyrin macrocycle.

We were also interested in the influence of alkyl substituents at the 6-position on the tetrahydroindole nucleus on porphyrin formation, in part due to the presence of such a methyl group in the petroporphyrin structures 3a and 3b. Dimedone was found to condense with oximes 8a and 8b under Knorr pyrrole reaction conditions to give the 6,6-dimethyl-4-oxoTHI's 24a and 24b, respectively (Scheme V). Similarly, 5-methyl-1,3-cyclohexanedione

condensed with oxime 8a in the presence of zinc dust and buffered acetic acid to give the 6-methyl-4-oxoTHI 24c. Reduction of 4-oxoTHIs 24a–c with diborane afforded the related THI's 25a–c (Scheme V) in good yield. Further reaction with lead tetraacetate in acetic acid gave the corresponding 7-acetoxy derivatives 26a–c. These acetoxy derivatives were also labile compounds, and prolonged exposure to water led to the formation of the related hydroxy compounds 27. The hydroxy compounds 27a and 27b were isolated as pure crystalline compounds and fully characterized. 7-AcetoxyTHI 26c was obtained as a 50:50 mixture of cis and trans isomers.

Base-catalyzed hydrolysis of 7-acetoxyTHI's 26a–c was carried out as previously described, and the resulting crude hydroxy carboxylic acids were treated with potassium ferricyanide in refluxing acetic acid. The 6,6-dimethyl-THI's 26a and 26b failed to give any trace of porphyrin product under these conditions. However, the 6-methyl-THI 26c afforded a low yield of porphyrin 28c as a mixture of stereoisomers, due to the presence of four chiral centers.[27] The presence of the 6-alkyl substituents clearly had a deleterious effect on porphyrin formation.


28

a. $R^1 = R^2 = Me$
b. $R^1 = Et; R^2 = Me$
c. $R^1 = Me; R^2 = H$
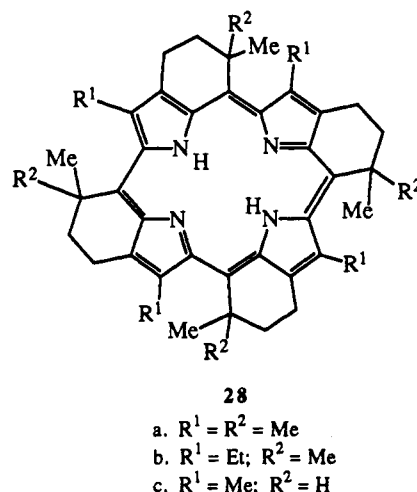
The formation of porphyrins 21a–e probably takes place via the mechanism shown in Scheme VI. The hydroxy carboxylic acids 20 readily undergo decarboxylation; protonation and elimination of water would then afford carbocations 29a (resonance stabilized by the azafulvene contributor 29b). Condensation with a second pyrrole unit would give the dipyrrolic structure 30. Subsequent reaction[28] would lead to tetrapyrrolic structures 31 which could either undergo cyclization to give porphyrinogens (hexahydroporphyrins) 32 or further condense with additional THI units to give polymer. Oxidation of 32 would then lead to the tetrapropanoporphyrins 21. The key step in these reactions is the ring closure of 31 to give porphyrinogen 32. When a bulky 3-substituent is present (i.e., R = Ph, ^{iso}Pr, ^{t}Bu), the periphery of the potential porphyrin macrocycle is very crowded and this presumably inhibits cyclization. It should be noted, however, that oxidation to the porphyrin level is also likely to be inhibited, since the alkyl substituents must lie in the same plane and steric repulsion will be severe, and this may also be a factor in these studies. When 6-alkyl substituents are present, they are liable to sterically interact with the 3-alkyl groups on

(26) Propionic acid was found to be a particularly useful solvent in the preparation of pyrroles fused to 12-, 15-, and 16-membered carbocyclic rings: Lash, T. D.; Marron, T. G.; Hoehner, M. C. Unpublished work.

(27) If rapid NH tautomerization is assumed, there are effectively six stereoisomers for porphyrin 28c: RRRR, SSSS, RRRS, SSSR, RRSS (meso), RSRS (meso).

(28) Oxidation of the pyrrolic intermediates may occur to a certain extent prior to macrocycle formation and multiple mechanistic pathways could be involved.

Scheme VI
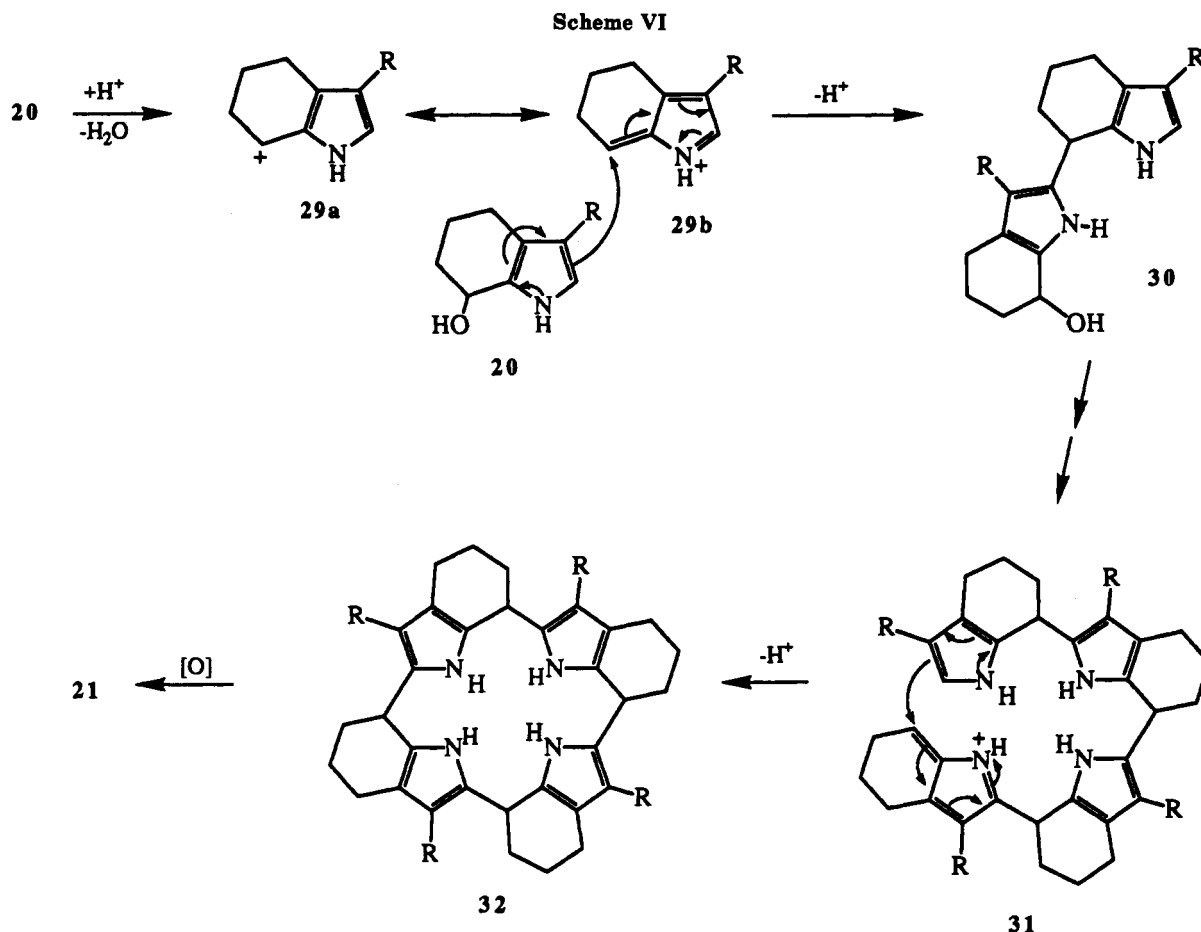
an adjacent THI unit, and this is likely to be the origin of the observed inhibition of porphyrin formation in these examples. We have also attempted to form symmetrical porphyrins of this type with five-, seven-, eight-, 12-, or 16-membered exocyclic rings, but no trace of porphyrin products were found in any of these reactions. It seems likely that the carbocyclic ring conformations do not allow the tetrapyrrolic intermediates to attain the correct geometry to undergo cyclization and further reaction leads to polymer. It may be that porphyrin structures of this type could be formed under milder conditions, such as those recently investigated for the synthesis of meso-tetrasubstituted porphyrins,[29] but this possibility has not been explored.

Conclusions

A general synthesis of 7-acetoxy-4,5,6,7-tetrahydro-1*H*-indoles is described. In refluxing pyridine–acetic anhydride, these compounds eliminate acetic acid to give the related 4,5-dihydro-1*H*-indoles. Using a different approach, 4-acetoxytetrahydro-1*H*-indoles may be prepared in three steps from 1,3-cyclohexanedione. These acetoxy compounds, and the related 4-hydroxytetrahydro-1*H*-indoles, also eliminate acetic acid to give 6,7-dihydro-1*H*-indoles. Hydrolysis of 7-acetoxytetrahydro-1*H*-indoles, followed by cyclotetramerization in refluxing acetic acid containing potassium ferricyanide, often gave unusual symmetrical porphyrins with four exocyclic rings in moderate yields. Bulky 3-substituents inhibited porphyrin

formation, as did the presence of alkyl substituents at the 6-position. The chemistry described in this paper provides the foundations for the total synthesis of petroporphyrins with exocyclic rings.[11,30] Future papers in this series will deal with the synthesis of geochemically significant porphyrins, including petroporphyrins **3** and **5**.

Experimental Section

Ethyl acetoacetate, methyl 3-oxopentanoate, ethyl butyrylacetate, ethyl benzoylacetate, ethyl isobutyrylacetate, methyl 4,4-dimethyl-3-oxopentanoate, cyclohexanone, cycloheptanone, cyclooctanone, 1,3-cyclohexanedione, and dimedone were purchased from Aldrich Chemical Co. and were used without further purification. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 710B spectrometer or a Perkin-Elmer 1600 Series FT-IR spectrometer. UV spectra were obtained on a Beckmann DU-40 spectrophotometer. NMR spectra were recorded on a Hitachi-Perkin-Elmer R24B 60-MHz NMR spectrometer or a Varian Gemini-300 NMR spectrometer. Mass spectral determinations were made at the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262) or at the Washington University Mass Spectrometry Resource, which is supported by a grant from the National Institutes of Health (RR00954). Elemental analyses were obtained from Micro-Analysis, Inc., Wilmington, DE 19808.

Ethyl 2,3-Dioxobutanoate 2-Phenylhydrazone (9a). Freshly distilled aniline (100 g; 98 mL) was added to a mixture of concentrated hydrochloric acid (225 mL) and water (225 mL) in a 2-L Erlenmeyer flask. Sodium nitrite (80 g) in water (350 mL) was added dropwise to the stirred solution while the temperature of the reaction mixture was maintained below 10 °C. After the

(29) Rocha Gonsalves, A. M.; Pereira, M. M. *J. Heterocycl. Chem.* **1985**, *22*, 931. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827. Lindsey, J. S.; Wagner, R. W. *Ibid.* **1989**, *54*, 828. Rocha Gonsalves, A. M.; Varejao, J. M. T. B.; Pereira, M. M. *J. Heterocycl. Chem.* **1991**, *28*, 635.

(30) Lash, T. D.; Perun, T. J., Jr. *Tetrahedron Lett.* **1987**, *28*, 6265. Lash, T. D. *Ibid.* **1988**, *29*, 6877. Lash, T. D.; Johnson, M. C. *Ibid.* **1989**, *30*, 5697. Lash, T. D.; Balasubramaniam, R. P. *Ibid.* **1990**, *31*, 7545.

addition was complete, the resulting diazonium salt solution was neutralized to congo red with saturated sodium acetate solution.

A solution of sodium acetate (130 g) in water (225 mL) was added to a solution of ethyl acetoacetate (130 g; 127 mL) in ethanol (800 mL) in a 4-L Erlenmeyer flask. The mixture was cooled to 10 °C, and the diazonium salt solution was added over a period of several minutes. The resulting mixture was stirred at 0 °C for 30 min and allowed to stand at room temperature for 1 h. The yellow precipitate was filtered off and recrystallized from 95% ethanol to give the title phenylhydrazone as yellow needles (203 g; 87%): mp 60–61 °C (lit.[31,32] mp 59.5 °C;[31a] 75 °C;[31b] 82–83 °C;[31c] 80–84 °C[31d]); ^{1}H NMR (CDCl$_3$) δ 1.38 (3 H, t, J = 8 Hz, CH$_2$CH$_3$), 2.45 (1 H, s), 2.55 (3 H, s, COCH$_3$), 4.30 (2 H, q, J = 8 Hz, OCH$_2$), 6.85–7.70 (5 H, m, Ph).

Methyl 2,3-Dioxopentanoate 2-Phenylhydrazone (9b). Prepared from methyl 3-oxopentanoate (65.1 g) by the procedure detailed above. Recrystallization from ethanol–water gave yellow crystals (115.2 g; 98%): mp 69–70 °C; ^{1}H NMR (CDCl$_3$) 1.16 (3 H, t, CH$_2$CH$_3$), 2.92 (2 H, q, COCH$_2$), 3.87 (3 H, s, OCH$_3$), 7.3 (5 H, m, C$_6$H$_5$). Anal. Calcd for C$_{12}$H$_{14}$N$_2$O$_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.28; H, 6.15; N, 11.57.

Ethyl 2,3-Dioxohexanoate 2-Phenylhydrazone (9c). Prepared from ethyl butyrylacetate (50 g) by the previous procedure. The product formed as an orange oil, which was extracted with ether, washed with water, 5% NaHCO$_3$, and water, dried over magnesium sulfate, and filtered and the solvent removed under reduced pressure to give 9c (80 g; quantitative) as an orange oil: ^{1}H NMR (CDCl$_3$) δ 1.01 (3 H, t, propyl CH$_3$), 1.42 (3 H, t, OCH$_2$CH$_3$), 1.73 (2 H, m, CH$_2$CH$_2$CH$_3$), 2.95 (2 H, m, COCH$_2$), 4.38 (2 H, m, OCH$_2$), 7.14–7.42 (5 H, m, C$_6$H$_5$).

Ethyl 2,3-Dioxo-3-phenylpropanoate 2-Phenylhydrazone (9d). Prepared from ethyl benzoylacetate (107 g) by the procedure described for 9a. Crystallization from 95% ethanol gave the phenylhydrazone (111 g; 69%) as yellow crystals: mp 64–66 °C (lit.[33] mp 65 °C; lit.[34] mp 63–65 °C); ^{1}H NMR (CDCl$_3$) δ 1.32 (3 H, t, CH$_2$CH$_3$), 4.32 (2 H, q, OCH$_2$), 6.8–7.6 (8 H, m), 7.7–8.1 (2 H, m) (2 × C$_6$H$_5$), 12.42 (1 H, NH).

Ethyl 4-Methyl-2,3-dioxopentanoate 2-Phenylhydrazone (9e). Prepared from ethyl isobutyrylacetate (21.52 g) by the procedure detailed above. The product, which separated as an orange oil, was extracted with chloroform and washed with water, 2% HCl, and 5% NaHCO$_3$ solution. The solution was dried over sodium sulfate and evaporated under reduced pressure to give the required phenylhydrazone as an orange oil (37.14 g; quantitative): ^{1}H NMR (CDCl$_3$) δ 1.15 (6 H, d, CH(CH$_3$)$_2$), 1.31 (3 H, t, CH$_2$CH$_3$), 3.65 (1 H, m, CH(CH$_3$)$_2$), 4.28 (2 H, q, OCH$_2$), 6.75–7.55 (5 H, m, C$_6$H$_5$), 12.33, 14.05 (two broad signals integrating for 1 H, NH).

Methyl 4,4-Dimethyl-2,3-dioxopentanoate 2-Phenylhydrazone (9f). Prepared from methyl 4,4-dimethyl-3-oxopentanoate (22.15 g) by the procedure detailed above. Recrystallization from 95% ethanol gave yellow crystals (34.36 g; 94%): mp 86–87.5 °C; ^{1}H NMR (CDCl$_3$) δ 1.38 (9 H, s, –C(CH$_3$)$_3$), 3.81 (3 H, s, OCH$_3$), 6.95–7.48 (5 H, m, C$_6$H$_5$), 11.98 (1 H, s, NH). Anal. Calcd for C$_{14}$H$_{18}$N$_2$O$_3$: C, 64.09; H, 6.93; N, 10.68. Found: C, 64.11; H, 6.71; N, 10.51.

Ethyl 3-Methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10a). A mixture of cyclohexanone (49.0 g), sodium acetate (50 g), and glacial acetic acid (150 mL) was placed in a 2-L Erlenmeyer flask, and the stirred mixture was heated on a water bath to 70 °C. A solution of phenylhydrazone 9a (117.0 g) in acetic acid (150 mL) was added slowly to the foregoing mixture, while small portions of zinc dust were added simultaneously (150 g) and the temperature of the reaction mixture was maintained between 75 and 85 °C. After the addition was complete, the reaction mixture

was stirred on a boiling water bath for 1 h. The mixture was cooled to 70 °C and the solution decanted from the excess zinc into an ice–water slurry (4 L). The residues were washed several times with hot acetic acid and the resulting solutions decanted into the ice–water mixture. A yellow precipitate formed which was filtered, washed well with water, and recrystallized from ethanol–water to give white crystals (43.6 g; 42%): mp 107.5–108.5 °C (lit.[14] mp 110 °C); IR (Nujol mull) ν 3298 (NH str.), 1656 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.34 (3 H, t, J = 7.1 Hz, CH$_2$CH$_3$), 1.78 (4 H, m, CH$_2$CH$_2$CH$_2$CH$_2$), 2.23 (3 H, s, pyrrole-CH$_3$), 2.39 (2 H, t, J = 5.3 Hz, 4-CH$_2$), 2.56 (2 H, t, J = 5.4 Hz, 7-CH$_2$), 4.30 (2 H, q, J = 7.1 Hz, OCH$_2$), 8.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 10.32 (3-CH$_3$), 14.63 (CH$_2$CH$_3$), 21.10, 22.90, 22.97, 23.33, 59.58 (OCH$_2$), 117.17 (C-2), 119.62 (C-4a), 125.84 (C-3), 132.46 (C-7a), 162.16 (C=O).

Methyl 3-Ethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10b). Using the procedure described above, phenylhydrazone 9b (58.5 g) and cyclohexanone (24.5 g) afforded the title pyrrole (4.8 g; 9.3%) as white needles, mp 86.5–87.5 °C from ethanol–water. Marginal improvements in the yield (15%) were obtained when the reaction temperature was raised to 120 °C during the addition of the phenylhydrazone: IR (Nujol mull) ν 3312 (NH str.), 1660 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.12 (3 H, t, J = 7.5 Hz, CH$_2$CH$_3$), 1.77 (4 H, m, CH$_2$CH$_2$CH$_2$CH$_2$), 2.43 (2 H, t, J = 5.4 Hz, 4-CH$_2$), 2.57 (2 H, t, J = 5.4 Hz, 7-CH$_2$), 2.71 (2 H, q, J = 7.5 Hz, CH$_2$CH$_3$), 3.82 (3 H, s, OCH$_3$), 8.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 15.07 (CH$_2$CH$_3$), 18.37 (3-CH$_2$), 21.09, 22.92, 23.35, 50.84 (OCH$_3$), 116.21 (C-2), 118.96 (C-4a), 132.71 (C-3,7a), 162.34 (C=O). Anal. Calcd for C$_{12}$H$_{17}$NO$_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.61; H, 8.38; N, 7.13.

Ethyl 3-Propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10c). Prepared from phenylhydrazone 9c (10.0 g) and cyclohexanone (3.8 g) using the method described for 10a, with the exception that the mixture was maintained at a temperature of 100 °C during the addition of 9c. Recrystallization from ethanol gave the desired tetrahydroindole (2.8 g; 31%) as white crystals: mp 64–67 °C. An analytical sample was obtained by further recrystallization from ethanol: mp 70.5–71.5 °C; IR (Nujol mull) ν 3295 (NH str.), 1667 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.94 (3 H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_3$), 1.34 (3 H, t, J = 7.1 Hz, OCH$_2$CH$_3$), 1.54 (2 H, m, CH$_2$CH$_2$CH$_3$), 1.77 (4 H, m, CH$_2$(CH$_2$)$_2$CH$_2$), 2.42 (2 H, t, J = 5.5 Hz, 4-CH$_2$), 2.57 (2 H, t, J = 5.6 Hz, 7-CH$_2$), 2.66 (2 H, t, J = 7.6 Hz, 3-CH$_2$), 4.29 (2 H, q, J = 7.1 Hz, OCH$_2$), 8.7 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.22, 14.53, 21.25, 22.93, 23.38, 23.92, 27.14, 59.53, 116.91, 119.34, 130.93, 132.25, 161.91. Anal. Calcd for C$_{14}$H$_{21}$NO$_2$: C, 71.44; H, 9.01; N, 5.95. Found: C, 71.02; H, 9.07; N, 5.81.

Ethyl 3-Phenyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10d). A mixture of cyclohexanone (4.9 g), sodium acetate (5.0 g), and propionic acid (30 mL) were placed in a 250-mL Erlenmeyer flask and heated on an oil bath to 145 °C. A solution of phenylhydrazone 9d (14.8 g) in propionic acid (30 mL) was added to the stirred mixture, while small portions of zinc dust (22 g) were added simultaneously and the temperature of the reaction mixture was maintained between 150 and 155 °C. Once the addition was complete, the mixture was stirred at 125 °C for 1 h. The mixture was cooled to 70 °C and poured into ice/water (800 mL). The mixture was allowed to stand overnight and the resulting precipitate filtered and washed well with water to remove traces of propionic acid. Recrystallization from chloroform–hexane gave the 3-phenyltetrahydroindole as white crystals (4.42 g; 33%): mp 194–196 °C. When the reaction was carried out in acetic acid at 110–120 °C, a yield of 21% was achieved. Reaction at the more conventional temperature range of 80–90 °C gave only a 10% yield: IR (Nujol mull) ν 3269 (NH str.), 1655 (C=O str.), 777, 703 (phenyl out-of-plane bending) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3 H, t, J = 7.1 Hz, CH$_2$CH$_3$), 1.73 (2 H, m), 1.82 (2 H, m) (CH$_2$CH$_2$CH$_2$CH$_2$), 2.42 (2 H, t, J = 5.8 Hz, 4-CH$_2$), 2.64 (2 H, t, J = 6.1 Hz, 7-CH$_2$), 4.17 (2 H, q, J = 7.1 Hz, OCH$_2$), 7.2–7.4 (5 H, m, C$_6$H$_5$), 9.0 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.19, 22.13, 22.93, 23.49, 59.81, 116.65, 119.57, 126.55, 127.38, 130.15, 132.40, 134.81, 161.50. Anal. Calcd for C$_{17}$H$_{19}$NO$_2$: C, 75.79; H, 7.12; N, 5.20. Found: C, 75.56; H, 7.31; N, 5.23.

Ethyl 3-Phenylcyclohepta[b]pyrrole-2-carboxylate (23a). Prepared by the procedure described for 10d from cycloheptanone (5.61 g) and 9d (5.61 g). The product was recrystallized from

(31) (a) Zublin, J. Chem. Ber. 1878, 11, 1417. (b) Richter, V.; Munzer, H. Ibid. 1884, 17, 1926. (c) Bamberger, E.; Wheelwright, E. Ibid. 1892, 25, 3201. (d) Kjellin, C. Ibid. 1897, 30, 1965.

(32) The variations in literature mp values for 9a may be due, in part, to the presence of syn and anti isomers. See: Tanner, E. M. Spectrochim. Acta 1959, 20. Drozd, V. N.; Sheichenko, V. I.; Postnov, V. N. Izu. Akad. Nauk SSSR, Ser. Khim. 1965, 1888. Kitaev, Y. P.; Nivorozhkin, L. E.; Titova, Z. S.; Popova, G. V. Ibid. 1968, 729. Malik, W. U.; Garg, H. G.; Arova, V. Ind. J. Chem. 1971, 9, 667.

(33) Bulow, C.; Hailer, E. Chem. Ber. 1902, 35, 923.

(34) Bolhofer, W. A. J. Am. Chem. Soc. 1952, 74, 5459.

chloroform–hexane to yield white crystals (5.28 g; 37%): mp 185–187 °C; IR (Nujol mull) ν 3296 (NH str.), 1652 (C=O str.), 772, 699 (phenyl out-of-plane bending) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.11 (3 H, t, J = 7.1 Hz, CH$_2$CH_3), 1.58 (2 H, m), 1.71 (2 H, m), 1.82 (2 H, m) (CH$_2$(CH_2)$_3$CH$_2$), 2.43 (2 H, m, 4-CH$_2$), 2.74 (2 H, m, 8-CH$_2$), 4.13 (2 H, q, J = 7.1 Hz, OCH$_2$), 7.2–7.4 (5 H, m, C$_6$H$_5$), 8.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.15, 25.57, 27.35, 28.86, 29.38, 32.18, 59.65, 115.06, 124.00, 126.52, 127.29, 130.65, 131.67, 135.07, 136.45, 161.32. Anal. Calcd for C$_{18}$H$_{21}$NO$_2$·^{1}/$_8$H$_2$O: C, 75.69; H, 7.49; N, 4.90. Found: C, 75.74; H, 7.29; N, 4.97.

Ethyl 3-Phenylcyclooocta[b]pyrrole-2-carboxylate (23b). Prepared by the same procedure from **9d** (14.8 g) and cyclooctanone (6.3 g). Recrystallization from chloroform–hexane gave white crystals (6.64 g; 45%): mp 141–143 °C; IR (Nujol mull) ν 3310 (NH str.), 1654 (C=O str.), 754, 700 (phenyl out-of-plane bending) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.09 (3 H, t, J = 7 Hz, CH$_2$CH_3), 1.49 (6 H, m), 1.71 (2 H, m) (CH$_2$(CH_2)$_4$CH$_2$), 2.41 (2 H, t, J = 5.3 Hz, 4-CH$_2$), 2.75 (2 H, t, J = 6.1 Hz, 9-CH$_2$), 4.12 (2 H, q, J = 7 Hz, OCH$_2$), 7.2–7.4 (5 H, m, C$_6$H$_5$), 9.1 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.08, 22.45, 25.53, 25.77, 25.97, 29.63, 30.88, 59.65, 116.28, 121.79, 126.49, 127.31, 130.30, 131.57, 134.77, 135.46, 161.48. Anal. Calcd for C$_{19}$H$_{23}$NO$_2$: C, 76.72; H, 7.81; N, 4.71. Found: C, 76.62; H, 7.59; N, 4.82.

Ethyl 3-Isopropyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10e). The title compound was prepared from phenylhydrazone **9e** (13.10 g) and cyclohexanone (7.35 g) by the procedure described above. The crude products from two separate experiments were combined and recrystallized from 95% ethanol–water to give light tan crystals (3.67 g; 16%): mp 94–96 °C; IR (Nujol mull) ν 3313 (NH str.), 1657 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.26 (6 H, d, J = 7 Hz, CH(CH_3)$_2$), 1.33 (3 H, t, J = 7.1 Hz, CH$_2$CH_3), 1.76 (4 H, m, CH$_2$CH_2CH_2CH$_2$), 2.57 (4 H, m, 2 × pyrrole-CH$_2$), 3.71 (1 H, septet, J = 7 Hz, ^{iso}Pr-CH), 4.28 (2 H, q, J = 7.1 Hz, OCH$_2$), 8.5 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.58, 22.05, 22.65, 22.88, 23.13, 23.21, 23.63, 25.60, 59.55, 115.78, 118.38, 132.33, 136.58, 161.51. Anal. Calcd for C$_{14}$H$_{21}$NO$_2$: C, 71.44; H, 9.01; N, 5.95. Found: C, 71.64; H, 8.93; N, 5.99.

Methyl 3-tert-Butyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10f). Cyclohexanone (7.35 g), anhydrous sodium acetate (70.8 g), and propionic acid (236 mL) were placed in a 1-L Erlenmeyer flask and the mixture heated on an oil bath to 150 °C. Phenylhydrazone **9f** (13.1 g) in propionic acid (236 mL) was added dropwise to the stirred mixture, while small portions of zinc dust (25 g) were added simultaneously and the reaction temperature was maintained between 150 and 160 °C. The mixture was stirred at 130 °C for 1 h, cooled to 70 °C, and poured into ice/water. The precipitate, which was allowed to stand overnight, was filtered and washed well with water to remove trace amounts of propionic acid. The products from two separate experiments were combined and recrystallized from hexane to give light brown crystals (1.88 g; 8%), mp 107–111 °C. Further crystallization from hexane gave an analytical sample as off-white crystals, mp 114–115 °C: IR (Nujol mull) ν 3325 (NH str.), 1686 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.46 (9 H, s, t-Bu), 1.73 (4 H, m, CH$_2$CH_2CH_2CH$_2$), 2.57 (2 H, m, 7-CH$_2$), 2.74 (2 H, m, 4-CH$_2$), 3.79 (3 H, s, OCH$_3$), 8.7 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 22.10, 23.57, 24.22, 25.48, 31.40, 33.99, 50.91, 116.10, 118.16, 131.72, 139.57, 160.68. Anal. Calcd for C$_{14}$H$_{21}$NO$_2$: C, 71.44; H, 9.01; N, 5.95. Found: C, 71.69; H, 8.81; N, 6.11.

Ethyl 3-Methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (16a). Ethyl acetoacetate (130 g) and acetic acid (350 mL) were placed in a 1-L Erlenmeyer flask, and the mixture was cooled in an ice–salt bath to 10 °C. A solution of sodium nitrite (104 g) in water (350 mL) was added dropwise to the stirred mixture, maintaining the reaction temperature below 20 °C throughout. After being stirred for 1 h at room temperature, the mixture was extracted with dichloromethane (3 × 150 mL), washed with water, 10% NaHCO$_3$ solution, and water, dried over MgSO$_4$, and filtered and the solvent evaporated. The required oxime **8a** was obtained as a yellow oil (152.6 g; 96%) and was used without further purification.

Sodium acetate (9.0 g), 1,3-cyclohexanedione (10.0 g), and acetic acid (90 mL) were placed in a 500-mL Erlenmeyer flask and heated on a water bath to 60 °C. A solution of the oxime **8a** (14.2 g) in acetic acid (45 mL) was added dropwise to the stirred mixture, while zinc dust was added simultaneously and the reaction tem-

perature was maintained at 75 °C. The mixture was heated on a boiling water bath for 1 h, cooled to 70 °C, and poured into ice–water. The resulting precipitate was filtered, washed thoroughly with water to remove traces of acetic acid, and recrystallized from 95% ethanol–water to give the desired 4-oxotetrahydroindole (9.35 g; 47%) as white needles: mp 165–166 °C (lit.[19] mp 165–166 °C; lit.[35] mp 165–167 °C; lit.[36] mp 163–164 °C; lit.[37] mp 166–167 °C); IR (Nujol mull) ν 3160 (NH str.), 1688, 1638 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.39 (3 H, t, J = 7.1 Hz, CH$_2$CH_3), 2.13 (2 H, m, 6-CH$_2$), 2.49 (2 H, t, J = 6.2 Hz, 7-CH$_2$), 2.61 (3 H, s, pyrrole-CH$_3$), 2.85 (2 H, t, J = 6.1 Hz, 5-CH$_2$), 4.35 (2 H, q, J = 7.1 Hz, OCH$_2$), 10.2 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 11.62, 14.43, 23.01, 23.43, 38.95, 60.57, 119.67, 120.25, 128.58, 145.93, 162.55, 195.62.

Methyl 3-Ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (16b). Prepared by the procedure detailed above from 1,3-cyclohexanedione (8.5 g) and methyl 3-oxopentanoate. Recrystallization from 95% ethanol–water gave small white needles (7.9 g; 47%): mp 172–173.5 °C; IR (Nujol mull) ν 3179 (NH str.), 1714, 1635 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.17 (3 H, t, J = 7.4 Hz, CH$_2$CH_3), 2.14 (2 H, m, 6-CH$_2$), 2.50 (2 H, t, J = 6.3 Hz, 7-CH$_2$), 2.85 (2 H, t, J = 6.2 Hz, 5-CH$_2$), 3.11 (2 H, q, J = 7.4 Hz, CH_2CH$_3$), 3.89 (3 H, s, OCH$_3$), 9.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 15.14, 18.83, 23.09, 23.40, 39.01, 51.55, 118.68, 119.57, 135.55, 146.02, 162.63, 195.05. Anal. Calcd for C$_{12}$H$_{15}$NO$_3$: C, 65.13; H, 6.85; N, 6.33. Found: C, 65.22; H, 6.87; N, 6.25.

Ethyl 4-Oxo-3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (16c). Prepared, using the previous method, from 1,3-cyclohexanedione (10.0 g) and ethyl butyrylacetate. Recrystallization from 95% ethanol–water gave 16c (8.7 g; 39%) as fluffy white needles: mp 162–164 °C (lit.[19] mp 156 °C); IR (Nujol mull) ν 3158 (NH str.), 1691, 1631 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.95 (3 H, t, J = 7.4 Hz, CH$_2$CH$_2$CH_3), 1.38 (3 H, t, J = 7.1 Hz, OCH$_2$CH_3), 1.59 (2 H, m, CH$_2$CH_2CH$_3$), 2.14 (2 H, m, 6-CH$_2$), 2.48 (2 H, t, J = 6.4 Hz, 7-CH$_2$), 2.83 (2 H, t, J = 6.3 Hz, 5-CH$_2$), 3.07 (2 H, t, J = 7.5 Hz, CH_2CH$_2$CH$_3$), 4.35 (2 H, q, J = 7.1 Hz, OCH$_2$), 9.7 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.06, 14.36, 23.11, 23.39, 23.98, 27.24, 39.03, 60.51, 119.41, 119.88, 133.63, 145.66, 162.32, 194.95. Anal. Calcd for C$_{14}$H$_{19}$NO$_3$: C, 67.43; H, 7.70; N, 5.62. Found: C, 67.39; H, 7.70; N, 5.54.

Ethyl 3,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (24a). Prepared by the procedure detailed above from dimedone (28.0 g) and ethyl acetoacetate. Recrystallization from ethanol–water gave the 4-oxotetrahydroindole (30.8 g; 62%) as white crystals: mp 162–164 °C (lit.[20] mp 171 °C; lit.[35] mp 170–171 °C); IR (Nujol mull) ν 3265 (NH str.), 1673, 1654 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.08 (6 H, s, C(CH$_3$)$_2$), 1.39 (3 H, t, J = 7.1 Hz, CH$_2$CH_3), 2.35 (2 H, s, pyrrole-CH$_2$), 2.61 (3 H, s, pyrrole-CH$_3$), 2.68 (2 H, s, 5-CH$_2$), 4.34 (2 H, q, J = 7.1 Hz, OCH$_2$), 9.5 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 11.52, 14.47, 28.48, 35.21, 36.94, 52.98, 60.51, 119.23, 119.90, 128.36, 144.45, 162.23, 194.84.

Methyl 3-Ethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (24b). Prepared by the procedure given above for 16a from dimedone (28.0 g) and methyl 3-oxopentanoate. Recrystallization from ethanol–water gave 24b (12.0 g; 24%) as white needles: mp 185.5–187.5 °C; ^{1}H NMR (CDCl$_3$) δ 1.11 (6 H, s, C(CH$_3$)$_2$), 1.17 (3 H, t, J = 7.4 Hz, CH$_2$CH_3), 2.36 (2 H, s, 7-CH$_2$), 2.69 (2 H, s, 5-CH$_2$), 3.10 (2 H, q, J = 7.4 Hz, CH_2CH$_3$), 3.88 (3 H, s, OCH$_3$), 9.5 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 15.16, 18.74, 28.47, 35.22, 36.99, 51.46, 53.03, 118.48, 118.89, 135.37, 144.71, 162.37, 194.30. Anal. Calcd for C$_{14}$H$_{19}$NO$_3$: C, 67.43; H, 7.70; N, 5.62. Found: C, 67.68; H, 7.58; N, 5.66.

Ethyl 3,6-Dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (24c). Prepared as above from 5-methyl-1,3-cyclohexanedione (25.2 g) and ethyl acetoacetate. Recrystallization from methanol gave the title compound (15.0 g; 32%) as a white powder: mp 204–205.5 °C; IR (Nujol mull) ν 3265 (NH str.), 1670, 1609 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.14 (3 H, d, J = 6 Hz,

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CHCH$_3$), 1.38 (3 H, t, J = 7.1 Hz, CH$_2$CH$_3$), 2.15–2.3 (1 H, m), 2.3–2.6 (3 H, m), 2.87–3.0 (1 H, m) (ring protons), 2.61 (3 H, s, pyrrole-CH$_3$), 4.35 (2 H, q, J = 7.1 Hz, OCH$_2$), 9.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 11.55, 14.46, 21.17, 31.11, 31.20, 47.34, 60.55, 119.84, 119.95, 128.43, 145.41, 162.46, 195.24. Anal. Calcd for C$_{13}$H$_{17}$NO$_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.42; N, 5.99.

Ethyl 3,6,6-Trimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25a). Diborane gas was generated in a three-necked round-bottomed flask by slow addition of boron trifluoride etherate (90 mL) to a stirred mixture of sodium borohydride (19.0 g) and diglyme (100 mL). The diborane was swept by a slow stream of nitrogen into a second flask containing ethyl 3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (24a; 12.45 g) in anhydrous tetrahydrofuran (100 mL). After the addition of the boron trifluoride was complete, the reaction mixture was allowed to stir for a further 2 h. Methanol was then added to destroy residual diborane. After the solvents were evaporated off under reduced pressure, the residue was taken up in chloroform, washed with water, dried over magnesium sulfate, and evaporated under reduced pressure. Crystallization from ethanol–water gave **25a** (10.3 g; 88%) as fluffy white needles: mp 114.5–116 °C; IR (Nujol mull) ν 3301 (NH str.), 1667 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.99 (6 H, s, C(CH$_3$)$_2$), 1.34 (3 H, t, J = 7.1 Hz, CH$_2$CH$_3$), 1.52 (2 H, t, J = 6.4 Hz, 5-CH$_2$), 2.24 (3 H, s, pyrrole-CH$_3$), 2.33 (2 H, s, 7-CH$_2$), 2.39 (2 H, t, J = 6.4 Hz, 4-CH$_2$), 4.29 (2 H, q, J = 7.1 Hz, OCH$_2$), 8.6 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 10.38, 14.63, 18.45, 28.05, 30.50, 36.30, 36.70, 59.53, 117.47, 118.16, 125.73, 132.11, 161.97. Anal. Calcd for C$_{14}$H$_{21}$NO$_2$: C, 71.44; H, 9.01; N, 5.95. Found: C, 71.04; H, 9.09; N, 6.06.

Methyl 3-Ethyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25b). Prepared from methyl 3-ethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (24b; 12.24 g) by the procedure described above. Recrystallization from ethanol–water gave the tetrahydroindole (9.8 g, 85%) as white needles: mp 151–152 °C; IR (Nujol mull) ν 3310 (NH str.), 1668 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.99 (6 H, s, C(CH$_3$)$_2$), 1.12 (3 H, t, J = 7.5 Hz, CH$_2$CH$_3$), 1.52 (2 H, t, J = 6.4 Hz, 5-CH$_2$), 2.33 (2 H, s, 7-CH$_2$), 2.43 (2 H, t, J = 6.4 Hz, 4-CH$_2$), 2.72 (2 H, q, J = 7.5 Hz, CH$_2$CH$_3$), 3.82 (3 H, s, OCH$_3$), 8.75 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 15.01, 18.39, 18.48, 28.07, 30.42, 36.30, 36.69, 50.82, 116.49, 117.42, 132.50, 130.57, 162.23. Anal. Calcd for C$_{14}$H$_{21}$NO$_2$: C, 71.44; H, 9.01; N, 5.95. Found: C, 71.70; H, 8.81; N, 5.68.

Ethyl 3,6-Dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25c). Prepared by the procedure detailed above from ethyl 3,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (24c; 11.8 g). The product was recrystallized from 95% ethanol to give the title compound (6.50 g; 59%) as an off-white powder: mp 121–122.5 °C; IR (Nujol mull) ν 3302 (NH str.), 1656 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.06 (3 H, d, J = 6.6 Hz, CHCH$_3$), 1.34 (3 H, t, J = 7.1 Hz, CH$_2$CH$_3$), 1.8–1.9 (2 H, m, 5-CH$_2$), 2.1–2.2 (1 H, m), 2.23 (3 H, s, pyrrole-CH$_3$), 2.3–2.4 (1 H, m), 2.43–2.55 (1 H, m), 2.58–2.7 (1 H, m), 4.29 (2 H, q, J = 7.1 Hz, OCH$_2$), 8.6 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 10.33, 14.61, 20.58, 21.55, 29.40, 31.11, 31.62, 59.55, 117.33, 119.35, 125.72, 132.19, 161.96. Anal. Calcd for C$_{13}$H$_{19}$NO$_2$: C, 70.54; H, 8.67; N, 6.33. Found: C, 70.84; H, 8.85; N, 6.36.

Ethyl 7-Acetoxy-3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13a). Lead tetraacetate (4.65 g; 1.05 equiv) was added in one portion to a stirred solution of ethyl 3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (2.07 g) in acetic acid (25 mL)–acetic anhydride (1 mL). The mixture was stirred for 2 h at room temperature, poured into ice–water, and extracted with dichloromethane. The organic solutions were dried over sodium sulfate and evaporated under reduced pressure to give the desired acetoxy compound as a yellow oil (quantitative). Crystallization from dichloromethane–petroleum ether (60–90 °C) gave the 7-acetoxyTHI (2.1 g; 78%) as white crystals: mp 67.5–69.5 °C; IR (Nujol mull) ν 3270 (NH str.), 1732 (acetoxy C=O str.), 1665 (pyrrole C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.34 (3 H, t, CH$_2$CH$_3$), 1.8–2.0 (4 H, m, CH$_2$CH$_2$CH), 2.07 (3 H, s, COCH$_3$), 2.23 (3 H, s, pyrrole-CH$_3$), 2.25–2.4 (1 H, m), 2.5–2.6 (1 H, m) (4-CH$_2$), 4.30 (2 H, m, OCH$_2$), 5.65 (1 H, m, CHOAc), 9.05 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 10.05, 14.55, 19.22, 20.90, 21.30, 29.09, 59.85, 65.31, 119.30, 122.55, 124.62, 128.75, 161.51, 172.47. Anal.

Calcd for C$_{14}$H$_{19}$NO$_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.37; H, 7.36; N, 5.00. Prolonged exposure to moisture gave the corresponding 7-hydroxyTHI (14a): ^{1}H NMR (CDCl$_3$) δ 1.29 (3 H, t, CH$_2$CH$_3$), 1.9 (4 H, m, CH$_2$CH$_2$CH), 2.19 (3 H, s, pyrrole-CH$_3$), 2.3–2.5 (3 H, m, pyrrole-CH$_2$ and OH), 4.28 (2 H, q, OCH$_2$), 4.63 (1 H, m, CHOH), 9.03 (1 H, br, NH).

Methyl 7-Acetoxy-3-ethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13b). Prepared by the previous procedure from methyl 3-ethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10b; 5.0 g). The 7-acetoxyTHI was isolated as a yellow oil (6.4 g; quantitative). A sample was crystallized from petroleum ether to give off-white needles: mp 88–89 °C; IR (Nujol mull) ν 3308 (NH str.), 1730 (acetoxy C=O str.), 1674 (pyrrole C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.07 (3 H, t, CH$_2$CH$_3$), 1.7–2.1 (4 H, m, CH$_2$CH$_2$CH), 2.02 (3 H, s, COCH$_3$), 2.3–2.8 (4 H, m, 2 × pyrrole-CH$_2$), 3.78 (3 H, s, OCH$_3$), 5.57 (1 H, m, CHOAc), 9.05 (1 H, br, NH). Anal. Calcd for C$_{14}$H$_{19}$NO$_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.45; H, 7.49; N, 5.19.

Ethyl 7-Acetoxy-3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13c). Prepared from 10c (1.00 g) by the procedure detailed above. The acetoxy derivative was obtained as a yellow oil (1.23 g; 99%) which could not be induced to crystallize: IR (neat) ν 3300 (NH str.), 1710 (acetoxy C=O str.), 1691 (pyrrole C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.93 (3 H, t, J = 7.4 Hz, propyl CH$_3$), 1.34 (3 H, t, J = 7.1 Hz, ethoxy CH$_3$), 1.53 (2 H, m, CH$_2$CH$_2$CH$_3$), 1.88 (3 H, m), 2.07 (3 H, s, COCH$_3$), 2.0–2.1 (1 H, m), 2.3–2.4 (1 H, m), 2.5–2.8 (3 H, m), 4.29 (2 H, m, OCH$_2$), 5.66 (1 H, m, CHOAc), 9.1 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.17, 14.47, 19.37, 21.09, 21.26, 23.79, 26.93, 29.11, 59.81, 65.43, 119.06, 122.27, 128.75, 129.63, 161.39, 172.44.

Ethyl 7-Acetoxy-3-phenyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13d). Lead tetraacetate (6.95 g) was added to a stirred mixture of ethyl 3-phenyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10d; 4.00 g) in acetic acid (76 mL)–acetic anhydride (4 mL) and the resulting mixture stirred at room temperature for 2 h. The solution was poured into ice–water (800 mL) and the resulting precipitate filtered and washed well with water. Recrystallization from hexane afforded 13d (2.90 g; 60%) as white crystals: mp 120.5–123 °C; IR (Nujol mull) ν 3270 (NH str.), 1726 (acetoxy C=O str.), 1655 (pyrrole C=O str.), 777, 704 (phenyl out-of-plane bending) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.18 (3 H, t, J = 7.1 Hz, CH$_2$CH$_3$), 1.8–2.0 (3 H, m), 2.0–2.1 (1 H, m) (CH$_2$CH$_2$CH), 2.11 (3 H, s, COCH$_3$), 2.3–2.55 (2 H, m, 4-CH$_2$), 4.19 (2 H, m, OCH$_2$), 5.73 (1 H, m, CHOAc), 7.2–7.4 (5 H, m, C$_6$H$_5$), 9.3 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.18, 19.53, 21.31, 21.90, 29.08, 60.09, 65.42, 118.76, 122.52, 126.76, 127.50, 128.86, 129.00, 130.08, 134.24, 160.88, 172.62. Anal. Calcd for C$_{19}$H$_{21}$NO$_4$: C, 69.69; H, 6.48; N, 4.28. Found: C, 69.61; H, 6.52; N, 4.31.

Ethyl 7-Acetoxy-3-isopropyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13e). Prepared from ethyl 3-isopropyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10e; 0.50 g) by the method described previously for 13a. The 7-acetoxyTHI 13e was obtained as a pale brown oil which was not further purified: IR ν 3323 (NH str.), 1703 (acetoxy C=O str.), 1663 (pyrrole C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.25 (6 H, d, CH(CH$_3$)$_2$), 1.32 (3 H, t, CH$_2$CH$_3$), 1.75–2.0 (4 H, m, CH$_2$CH$_2$CH), 2.04 (3 H, s, COCH$_3$), 2.4–2.8 (2 H, m, β-CH$_2$), 3.69 (1 H, m, isopropyl CH), 4.26 (2 H, q, OCH$_2$), 5.63 (1 H, m, CHOAc), 9.0 (1 H, br, NH). Prolonged exposure to water gave the corresponding hydroxyTHI 14e: ^{1}H NMR (CDCl$_3$) δ 1.23 (6 H, d, CH(CH$_3$)$_2$), 1.32 (3 H, t, CH$_2$CH$_3$), 1.7–2.0 (4 H, m, CH$_2$CH$_2$CH), 2.5–2.7 (3 H, m, β-CH$_2$ and OH), 3.66 (1 H, m, isopropyl CH), 4.26 (2 H, q, OCH$_2$), 4.74 (1 H, m, CHOH), 9.2 (1 H, br, NH).

Methyl 7-Acetoxy-3-tert-butyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13f). Prepared from methyl 3-tert-butyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10f; 0.25 g) by the procedure detailed for 13a. The acetoxyTHI 13f was obtained as a pale brown oil (0.264 g; 84%) which was not further purified: ^{1}H NMR (CDCl$_3$) δ 1.44 (9 H, s, tert-butyl), 1.6–2.0 (4 H, m, CH$_2$CH$_2$CH), 2.06 (3 H, s, COCH$_3$), 2.4–3.0 (2 H, m, β-CH$_2$), 3.78 (3 H, s, OCH$_3$), 5.63 (1 H, m, CHOAc), 9.2 (1 H, br, NH).

Ethyl 7-Acetoxy-3,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (26a). Prepared similarly from ethyl 3,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25a; 1.00 g). The acetoxy derivative was isolated as a pale yellow oil (1.24 g; quantitative) which could not be induced to crystallize:

¹H NMR (CDCl₃) δ 0.92 (3 H, s), 1.05 (3 H, s) (C(CH₃)₂), 1.31 (3 H, t, CH₂CH₃), 1.55–1.85 (2 H, m, ring CH₂), 2.03 (3 H, s, COCH₃), 2.21 (3 H, s, pyrrole-CH₃), 2.4 (2 H, m, pyrrole-CH₂), 4.26 (2 H, q, OCH₂), 5.24 (1 H, s, CHOAc), 9.1 (1 H, br, NH).

Methyl 7-Acetoxy-3-ethyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (26b). Prepared similarly from methyl 3-ethyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25b; 1.00 g). Crystallization from petroleum ether (60–90 °C) gave the acetoxyTHI (0.85 g; 80%) as white crystals: mp 94–96 °C; IR (Nujol mull) ν 3311 (NH str.), 1715 (acetoxy C=O str.), 1668 (pyrrole C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 0.92 (3 H, s), 1.05 (3 H, s) (C(CH₃)₂), 1.09 (3 H, t, CH₂CH₃), 1.4–1.9 (2 H, m, ring CH₂), 2.04 (3 H, s, COCH₃), 2.3–2.6 (2 H, m, pyrrole-CH₂CH₂), 2.69 (2 H, q, CH₂CH₃), 3.78 (3 H, s, OCH₃), 5.16 (1 H, s, CHOAc), 8.9 (1 H, br, NH). Anal. Calcd for C₁₆H₂₃NO₄: C, 65.49; H, 7.92; N, 4.77. Found: C, 65.49; H, 8.06; N, 4.68.

Ethyl 7-Acetoxy-3,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (26c). Lead tetraacetate (4.26 g) was added in several portions to a stirred solution of ethyl 3,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25c; 2.00 g) in acetic acid (20 mL)–acetic anhydride (1 mL). The resulting mixture was allowed to stir at room temperature for 2 h. The pale yellow solution was poured into ice–water (500 mL) and extracted with chloroform (3 × 100 mL). The combined organic solutions were washed with 5% sodium carbonate solution and water, dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The oily residue (2.30 g; 91%), which consisted of a mixture of cis and trans isomers, was used without further purification: IR (neat) ν 3449 (NH str.), 1753 (acetoxy C=O str.), 1691 (pyrrole C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 0.99 (3 H, d, J = 6 Hz, CHCH₃), 1.32 (3 H, t, J = 7 Hz, CH₂CH₃), 1.12–2.50 (6 H, m, 3 × ring CH₂), 2.07 (3 H, s, COCH₃), 2.21 (3 H, s, pyrrole-CH₃), 4.28 (2 H, q, J = 7 Hz, OCH₂), 5.38 (d, J = 4 Hz), 5.52 (d, J = 3 Hz) (combined integration of 1 H, cis and trans CHOAc), 9.22 (1 H, br, NH).

Ethyl 7-Hydroxy-3,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (27a). Lead tetraacetate was added in one portion to a stirred solution of ethyl 3,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate 25a (1.00 g) in acetic acid (15 mL) and acetic anhydride (1 mL). After 2 h, water was added dropwise until the mixture turned slightly cloudy, and additional acetic acid was added so that the solution became clear. The mixture was briefly heated on a steam bath allowed to stand at room temperature for 2 h and poured into ice–water (300 mL). The resulting precipitate was filtered off, dissolved in dichloromethane, dried over magnesium sulfate, filtered, evaporated under reduced pressure, and crystallized from dichloromethane–hexane to give the 7-hydroxyTHI 27a (0.65 g; 61%) as white crystals: mp 124–125 °C; IR (Nujol mull) ν 3354 (OH str.), 3307 (NH str.), 1661 (C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 0.95 (3 H, s), 1.02 (3 H, s) (C(CH₃)₂), 1.34 (3 H, t, J = 7.1 Hz, CH₂CH₃), 1.55 (1 H, m), 1.65–1.8 (1 H, m) (5-CH₂), 2.21 (3 H, s, pyrrole-CH₃), 2.3–2.45 (2 H, m, 4-CH₂), 3.1 (1 H, br, OH), 4.29 (2 H, q, J = 7.1 Hz, OCH₂), 4.31 (1 H, s, CHOH), 9.6 (1 H, br, NH); ¹³C NMR (CDCl₃) δ 10.50, 14.51, 18.17, 20.88, 26.00, 34.35, 35.22, 59.95, 118.77, 119.36, 125.36, 133.96, 162.57. Anal. Calcd for C₁₄H₂₁NO₃: C, 66.89; H, 8.44; N, 5.57. Found: C, 67.10; H, 8.34; N, 5.55.

Methyl 3-Ethyl-7-hydroxy-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (27b). Prepared from methyl 3-ethyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (25b; 1.00 g) by the procedure detailed above. Recrystallization from dichloromethane–hexane gave the title 7-hydroxyTHI (0.70 g; 66%) as chunky white crystals: 152.5–154 °C; IR (Nujol mull) ν 3503 (OH str.), 3328 (NH str.), 1646 (C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 0.94 (3 H, s), 1.03 (3 H, s) (C(CH₃)₂), 1.10 (3 H, t, CH₂CH₃), 1.45–1.7 (2 H, m, ring CH₂), 2.3–2.6 (2 H, m, pyrrole-CH₂CH₂), 2.68 (2 H, q, pyrrole-CH₂CH₃), 3.80 (3 H, s, OCH₃), 4.0 (1 H, OH), 4.27 (1 H, m, CHOH), 9.7 (1 H, br, NH). Anal. Calcd for C₁₄H₂₁NO₃: C, 66.89; H, 8.44; N, 5.57. Found: C, 66.54; H, 8.51; N, 5.42.

Ethyl 4-Hydroxy-3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17a). Sodium borohydride (3.00 g) was added in one portion to a stirred mixture of ethyl 3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (16a; 3.00 g) in 95% ethanol (25 mL). After 10 min, 15 mL of water was added and the mixture heated on a boiling water bath for 15 min. After a

further 100 mL of water had been added, the mixture was cooled in ice and the resulting precipitate filtered off. Recrystallization from ethanol–water gave 17a (0.83 g; 82%) as small white crystals: mp 176–178 °C; IR (Nujol mull) ν 3309 (NH str.), 3153 (OH str.), 1675 (C=O str.) cm⁻¹; ¹H NMR (CDCl₃-d₆-DMSO) δ 1.23 (3 H, t, CH₂CH₃), 1.84 (4 H, m, CHCH₂CH₂), 2.31 (3 H, s, pyrrole-CH₃), 2.55 (2 H, m, pyrrole-CH₂), 3.60 (1 H, d, J = 6 Hz, OH), 4.27 (2 H, q, OCH₂), 4.71 (1 H, m, CHOH), 10.05 (1 H, br, NH). Anal. Calcd for C₁₂H₁₇NO₃: C, 64.54; H, 7.69; N, 6.33. Found: C, 64.57; H, 7.83; N, 6.14.

Methyl 3-Ethyl-4-hydroxy-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17b). Prepared by the previous procedure from methyl 3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (16b; 3.00 g). Recrystallization from dichloromethane–petroleum ether (60–90 °C) gave 17b (2.70 g; 90%) as white crystals: mp 133–135 °C; IR (Nujol mull) ν 3378 (OH str.), 3300 (NH str.), 1674 (C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 1.20 (3 H, t, CH₂CH₃), 1.65 (1 H, OH), 1.78 (2 H, m), 1.98 (2 H, m) (CHCH₂CH₂), 2.45–2.65 (2 H, m, pyrrole-CH₂CH₂), 2.78 (2 H, m, pyrrole-CH₂CH₃), 3.84 (3 H, s, OCH₃), 4.82 (1 H, m, CHOH), 8.89 (1 H, br, NH). Anal. Calcd for C₁₂H₁₇NO₃: C, 64.54; H, 7.69; N, 6.33. Found: C, 64.87; H, 7.56; N, 6.23.

Ethyl 4-Hydroxy-3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17c). Prepared from ethyl 3-propyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (16c; 3.0 g) by the procedure detailed above. Recrystallization from chloroform-petroleum ether (60–90 °C) gave 17c (2.4 g; 78%) as white crystals: mp 159–160 °C; IR (Nujol mull) ν 3463 (NH str.), 3181 (OH str.), 1659 (C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 0.97 (3 H, t, J = 7.4 Hz, CH₂CH₂CH₃), 1.35 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.5 (1 H, br, OH), 1.61 (2 H, m, CH₂CH₂CH₃), 1.75–1.85 (2 H, m), 1.9–2.05 (2 H, m), 2.45–2.56 (1 H, m), 2.6–2.7 (1 H, m), 2.77 (2 H, t, J = 7.8 Hz, CH₂CH₂CH₃), 4.30 (2 H, q, J = 7.1 Hz, OCH₂), 4.81 (1 H, m, CHOH), 8.8 (1 H, br, NH); ¹³C NMR (CDCl₃) δ 14.39, 14.47, 17.62, 22.80, 24.71, 27.17, 32.45, 59.82, 62.16, 117.87, 121.50, 131.62, 133.46, 161.72. Anal. Calcd for C₁₄H₂₁NO₃: C, 66.89; H, 8.44; N, 5.57. Found: C, 66.69; H, 8.56; N, 5.45.

Ethyl 4-Acetoxy-3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (15a). Acetic anhydride (1.0 mL) was added to a solution of ethyl 4-hydroxy-3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17a; 0.50 g) in pyridine (5 mL), and the mixture was allowed to stir at room temperature for 24 h. The mixture was partitioned between water (15 mL) and dichloromethane (10 mL), the organic phase was separated, and the aqueous solution was extracted with dichloromethane (2 × 10 mL). The combined organic solutions were dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was crystallized from petroleum ether (60–90 °C) to give the 4-acetoxyTHI 15a (0.47 g; 80%) as an off-white solid: mp 89–90 °C; IR (Nujol mull) ν 3302 (NH str.), 1719 (acetoxy C=O str.), 1670 (pyrrole-C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 1.31 (3 H, t, CH₂CH₃), 1.8–2.0 (4 H, m, CHCH₂CH₂), 2.01 (3 H, s, COCH₃), 2.20 (3 H, s, pyrrole-CH₃), 2.4–2.7 (2 H, m, pyrrole-CH₂), 4.24 (2 H, q, OCH₂), 5.89 (1 H, m, CHOAc), 8.6 (1 H, br, NH). Anal. Calcd for C₁₄H₁₉NO₄: C, 63.37; H, 7.23; N, 5.28. Found: C, 63.05; H, 7.36; N, 5.11.

Methyl 4-Acetoxy-3-ethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (15b). Prepared from methyl 3-ethyl-4-hydroxy-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17b; 0.50 g) by the preceding procedure. Recrystallization from petroleum ether (60–90 °C) gave the product (0.49 g; 82%) as off-white crystals: mp 112–114 °C; IR (Nujol mull) ν 3296 (NH str.), 1703 (acetoxy C=O str.), 1660 (pyrrole C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 1.10 (3 H, t, CH₂CH₃), 1.7–2.1 (4 H, m, CHCH₂CH₂), 2.04 (3 H, s, COCH₃), 2.4–2.9 (4 H, m, 2 × pyrrole-CH₂), 3.80 (3 H, s, OCH₃), 5.92 (1 H, m, CHOAc), 9.3 (1 H, br, NH). Anal. Calcd for C₁₄H₁₉NO₄: C, 63.37; H, 7.23; N, 5.28. Found: C, 63.03; H, 7.25; N, 5.12.

Ethyl 4-Acetoxy-3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (15c). Prepared by the method detailed above from ethyl 4-hydroxy-3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17c; 0.50 g). Recrystallization from dichloromethane–petroleum ether (60–90 °C) gave the 4-acetoxyTHI (0.42 g; 72%) as off-white crystals: mp 100.5–102.5 °C; IR (Nujol mull) ν 3245 (NH str.), 1705 (acetoxy C=O str.), 1683 (pyrrole C=O str.) cm⁻¹; ¹H NMR (CDCl₃) δ 0.93 (3 H, t, CH₂CH₂CH₃), 1.34 (3

H, t, OCH$_2$C*H*$_3$), 1.6 (2 H, m, CH$_2$C*H*$_2$CH$_3$), 1.7–2.1 (4 H, m, CHC*H*$_2$C*H*$_2$), 2.04 (3 H, s, COCH$_3$), 2.52 (4 H, m, 2 × pyrrole-CH$_2$), 4.29 (2 H, q, OCH$_2$), 5.94 (1 H, m, CHOAc), 9.3 (1 H, br, NH). Anal. Calcd for C$_{18}$H$_{23}$NO$_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 66.13; H, 8.03; N, 4.89.

Ethyl 3-Methyl-6,7-dihydro-1H-indole-2-carboxylate (18a). Acetic anhydride (1 mL) was added to a solution of ethyl 3-methyl-4-hydroxy-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17a; 0.50 g) in pyridine (5 mL), and the resulting mixture was stirred under reflux for 1 h. The solution was cooled to room temperature, partitioned between dichloromethane (10 mL) and water (15 mL), the aqueous phase extracted with dichloromethane (2 × 10 mL), and the combined organic solutions dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a light brown solid which was recrystallized from 95% ethanol–water to give 18a (0.34 g; 73%) as small white needles: mp 127–127.5 °C; IR (Nujol mull) ν 3286, 3250 (NH str.), 1666 (C=O str.), 1618 (C=C str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.35 (3 H, t, J = 7.1 Hz, CH$_2$C*H*$_3$), 2.29 (3 H, s, pyrrole-CH$_3$), 2.35–2.46 (2 H, m, 6-CH$_2$), 2.72 (2 H, t, J = 8.6 Hz, 7-CH$_2$), 4.31 (2 H, q, J = 7.1 Hz, OCH$_2$), 5.62 (1 H, dt, =C*H*CH$_2$), 6.38 (1 H, d, J = 9.8 Hz, pyrrole-CH=), 9.1 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 10.06, 14.59, 21.28, 23.58, 59.72, 117.43, 119.51, 120.45, 120.62, 123.45, 132.65, 162.08. Anal. Calcd for C$_{12}$H$_{15}$NO$_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 70.04; H, 7.20; N, 6.79.

Methyl 3-Ethyl-6,7-dihydro-1H-indole-2-carboxylate (18b). Prepared from methyl 3-ethyl-4-hydroxy-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17b; 0.50 g) by the procedure detailed above. Recrystallization from 95% ethanol–water gave the dihydroindole (0.31 g; 68%) as off-white crystals: mp 104–105 °C; IR (Nujol mull) ν 3278 (NH str.), 1664 (C=O str.), 1618 (C=C str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3 H, t, J = 7.4 Hz, CH$_2$C*H*$_3$), 2.38–2.5 (2 H, m, 6-CH$_2$), 2.7–2.83 (4 H, overlapping t and q, 7-CH$_2$ and C*H*$_2$CH$_3$), 3.83 (3 H, s, OCH$_3$), 5.62 (1 H, dt, =C*H*CH$_2$), 6.40 (1 H, d, J = 9.8 Hz, pyrrole-CH=), 8.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 15.77, 18.06, 21.27, 23.51, 50.95, 116.39, 118.74, 120.54, 120.62, 130.48, 132.73, 162.11. Anal. Calcd for C$_{12}$H$_{15}$NO$_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 70.10; H, 7.47; N, 6.77.

Ethyl 3-Propyl-6,7-dihydro-1H-indole-2-carboxylate (18c). Prepared by the foregoing method from ethyl 4-hydroxy-3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (17c; 0.50 g). Recrystallization from 95% ethanol–water afforded the product (0.33 g; 70%) as white crystals: mp 161–162 °C; IR (Nujol mull) ν 3290 (NH str.), 1663 (C=O str.), 1618 (C=C str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.91 (3 H, t, CH$_2$CH$_2$C*H*$_3$), 1.32 (3 H, t, OCH$_2$C*H*$_3$), 1.6 (2 H, m, CH$_2$C*H*$_2$CH$_3$), 2.2–2.9 (6 H, m, ring CH$_2$CH$_2$ and C*H*$_2$CH$_2$CH$_3$), 4.26 (2 H, q, OCH$_2$), 5.4–5.7 (1 H, m, =C*H*CH$_2$), 6.36 (1 H, m, pyrrole-CH=), 8.75 (1 H, br, NH). Anal. Calcd for C$_{14}$H$_{19}$NO$_2$: C, 72.06; H, 8.22; N, 6.00. Found: C, 72.06; H, 8.17; N, 6.01.

Ethyl 3-Methyl-4,5-dihydro-1H-indole-2-carboxylate (19a). Lead tetraacetate (2.25 g) was added to a stirred solution of ethyl 3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10a; 1.00 g) in acetic acid (15 mL)–acetic anhydride (1 mL) and the mixture stirred at room temperature for 3 h. The mixture was diluted with dichloromethane, washed with water, 5% aqueous sodium bicarbonate solution, and water, dried over sodium sulfate, and evaporated under reduced pressure to give a pale yellow oil. The residue was taken up in pyridine (10 mL)–acetic anhydride (2 mL) and heated under reflux for 1 h. The product was worked up using the procedure described for 18a. Recrystallization from ethanol–water gave the 4,5-dihydroindole (0.74 g; 75%) as white needles: mp 113–114 °C; IR (Nujol mull) ν 3280 (NH str.), 1663 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.35 (3 H, t, J = 7.1 Hz, CH$_2$C*H*$_3$), 2.25 (3 H, s, pyrrole-CH$_3$), 2.37 (2 H, m, 5-CH$_2$), 2.57 (2 H, t, J = 8.5 Hz, 4-CH$_2$), 4.31 (2 H, q, J = 7.1 Hz, OCH$_2$), 5.91 (1 H, dt, =C*H*CH$_2$), 6.30 (1 H, d, J = 9.8 Hz, pyrrole-CH=), 9.0 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 10.35, 14.60, 18.85, 24.14, 59.71, 117.68, 117.85, 118.92, 125.46, 128.56, 131.45, 162.06. Anal. Calcd for C$_{12}$H$_{15}$NO$_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 70.13; H, 7.10; N, 6.72.

Methyl 3-Ethyl-4,5-dihydro-1H-indole-2-carboxylate (19b). Prepared from methyl 3-ethyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10b; 1.00 g) by the procedure detailed above. Recrystallization from ethanol–water gave the dihydroindole (0.75 g; 75%) as white hairlike needles: mp 96–97 °C; IR (Nujol mull)

ν 3295 (NH str.), 1672 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.12 (3 H, t, J = 7.5 Hz, CH$_2$C*H*$_3$), 2.39 (2 H, m, 5-CH$_2$), 2.60 (2 H, t, J = 8.5 Hz, 4-CH$_2$), 2.74 (2 H, q, J = 7.5 Hz, pyrrole-C*H*$_2$CH$_3$), 3.83 (3 H, s, OCH$_3$), 5.93 (1 H, dt, =C*H*CH$_2$), 6.28 (1 H, d, J = 9.8 Hz, pyrrole-CH=), 8.6 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 15.16, 18.30, 18.90, 24.18, 50.94, 116.68, 117.79, 118.29, 128.77, 131.50, 132.41, 162.05. Anal. Calcd for C$_{12}$H$_{15}$NO$_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 69.89; H, 7.24; N, 6.70.

Ethyl 3-Propyl-4,5-dihydro-1H-indole-2-carboxylate (19c). Prepared by the previous procedure from ethyl 3-propyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (10c; 1.00 g). Recrystallization from ethanol–water gave 19c (0.69 g; 69%) as a white powder: mp 73–73.5 °C; IR (Nujol mull) ν 3288 (NH str.), 1662 (C=O str.) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.93 (3 H, t, J = 7.4 Hz, CH$_2$CH$_2$C*H*$_3$), 1.35 (3 H, t, J = 7.1 Hz, OCH$_2$C*H*$_3$), 1.55 (2 H, m, CH$_2$C*H*$_2$CH$_3$), 2.37 (2 H, m, 5-CH$_2$), 2.59 (2 H, t, J = 8.5 Hz, 4-CH$_2$), 2.69 (2 H, t, J = 7.5 Hz, C*H*$_2$CH$_2$CH$_3$), 4.30 (2 H, q, J = 7.1 Hz, OCH$_2$), 5.92 (1 H, dt, =C*H*CH$_2$), 6.30 (1 H, d, J = 9.8 Hz, pyrrole-CH=), 8.9 (1 H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.06, 14.52, 19.14, 24.00, 24.25, 27.04, 59.68, 117.37, 117.91, 118.77, 128.57, 130.55, 131.35, 161.85. Anal. Calcd for C$_{14}$H$_{19}$NO$_2$: C, 72.06; H, 8.22; N, 6.00. Found: C, 72.23; H, 8.06; N, 5.91.

2,7,12,17-Tetramethyl-3,5:8,10:13,15:18,20-tetrapropanoporphyrin (21a). A solution of potassium hydroxide (3.00 g) in methanol–water (50:50; 20 mL) was added to a stirred solution of ethyl 7-acetoxy-3-methyl-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (13a; 1.10 g) in methanol, and the resulting mixture was stirred under reflux for 1 h. The mixture was cooled to 0 °C and cautiously neutralized with 6 M hydrochloric acid, maintaining the temperature below 0 °C throughout. The mixture was extracted with chloroform, dried over magnesium sulfate, and evaporated under reduced pressure. The oily residue was dissolved in acetic acid (3.5 mL) containing potassium ferricyanide (85 mg) and heated on a boiling water bath, with constant stirring, for 1 h. The mixture was partitioned between chloroform and water and the organic phase washed with water, 5% aqueous ammonia solution, and water. The solvent was evaporated under reduced pressure and the residue chromatographed twice on Grade 3 alumina, eluting with dichloromethane. The red fractions were evaporated to dryness and crystallized from dichloromethane–methanol to give the title porphyrin (81 mg; 15%) as purple crystals: mp >300 °C; FAB MS m/e 527 ([M + H]$^+$); UV (CH$_2$Cl$_2$) λ$_{max}$ (log$_{10}$ ε) 418 (5.27), 516 (4.12), 549 (3.70), 592 (3.68), 647 (3.49) nm; UV (CH$_2$Cl$_2$–trace TFA): λ$_{max}$ 429, 580, 630; ^{1}H NMR (CDCl$_3$) δ −2.7 (2 H, br, NH), 2.60 (8 H, m, 4 × CH$_2$C*H*$_2$CH$_2$), 3.45 (12 H, s, 4 × porphyrin-CH$_3$), 3.75 (8 H, t, β-CH$_2$), 4.91 (8 H, t, 4 × meso-CH$_2$); NMR (TFA-d–CDCl$_3$) δ 2.67 (8 H, m, 4 × CH$_2$C*H*$_2$CH$_2$), 3.42 (12 H, s, 4 × porphyrin-CH$_3$), 3.79 (8 H, t, J = 5.8 Hz, β-CH$_2$), 5.04 (8 H, t, J = 5.8 Hz, 4 × meso-CH$_2$). Anal. Calcd for C$_{36}$H$_{38}$N$_4$·H$_2$O: C, 79.36; H, 7.41; N, 10.28. Found: C, 79.35; H, 7.26; N, 9.90.

2,7,12,17-Tetraethyl-3,5:8,10:13,15:18,20-tetrapropanoporphyrin (21b): yield 14%; mp >300 °C; FAB MS m/e 583 ([M + H]$^+$); UV (CHCl$_3$) λ$_{max}$ (log$_{10}$ ε) 423 (5.26), 521 (4.11), 557 (3.68), 595 (3.64), 652 (3.47)nm; UV (CH$_2$Cl$_2$–trace TFA): λ$_{max}$ 431, 585, 635; ^{1}H NMR (CDCl$_3$) δ −2.5 (2 H, br, NH), 1.70 (12 H, t, J = 7.4 Hz, 4 × CH$_2$C*H*$_3$), 2.54 (8 H, m, 4 × CH$_2$C*H*$_2$CH$_2$), 3.74 (8 H, t, J = 5.8 Hz, β-C*H*$_2$CH$_2$), 3.91 (8 H, q, J = 7.4 Hz, 4 × C*H*$_2$CH$_3$), 4.93 (8 H, t, J = 5.8 Hz, 4 × meso-CH$_2$). Anal. Calcd for C$_{40}$H$_{46}$N$_4$·^{3}/$_4$H$_2$O: C, 80.56; H, 8.03; N, 9.39. Found: C, 80.51; H, 7.89; N, 8.99.

2,7,12,17-Tetrapropyl-3,5:8,10:13,15:18,20-tetrapropanoporphyrin (21c): yield 12%; mp >300 °C; FAB MS m/e (relative intensity) 771 (8) ([M + Cs]$^+$), 639 (100) ([M + H]$^+$) 638 (52) (M$^+$); HR FAB MS calcd for C$_{44}$H$_{54}$N$_4$ + H 639.4427, found 639.4405; UV (CHCl$_3$) λ$_{max}$ (log$_{10}$ ε) 423 (5.34), 523 (4.16), 558 (3.66), 596 (3.65), 653 (3.45) nm; ^{1}H NMR (CDCl$_3$) δ −2.4 (2 H, br NH), 1.24 (12 H, t, J = 7.2 Hz, 4 × CH$_2$C*H*$_3$), 2.11 (8 H, m, 4 × CH$_2$C*H*$_2$CH$_3$), 2.53 (8 H, m, 4 × CH$_2$C*H*$_2$CH$_2$), 3.73 (8 H, t, J = 5.8 Hz, 4 × β-CH$_2$CH$_2$), 3.84 (8 H, q, J = 7.7 Hz, 4 × C*H*$_2$CH$_2$CH$_3$), 4.90 (8 H, t, J = 5.6 Hz, 4 × meso-CH$_2$). Anal. Calcd for C$_{44}$H$_{54}$N$_4$·^{1}/$_2$H$_2$O: C, 81.56; H, 8.55; N, 8.65. Found: C, 81.46; H, 8.35; N, 8.55.

2,7,12,17-Tetraphenyl-3,5:8,10:13,15:18,20-tetrapropanoporphyrin (21d): yield ca. 1%, although a yield of 20% was obtained in one case; mp >300 °C; HR FAB MS calcd for C$_{56}$H$_{46}$N$_4$ + H 775.3801, found 775.3824; UV (CHCl$_3$) λ$_{max}$ (log$_{10}$ ε) 430 (5.34),

527 (4.18), 561 (3.72), 604 (3.66), 662 (3.56) nm; ^{1}H NMR (CDCl$_3$) δ –2.17 (2 H, br, NH), 2.30 (8 H, 4 × CH$_2$C*H*$_2$CH$_2$), 3.50 (8 H, 4 × β-CH$_2$), 4.30 (8 H, 4 × meso-CH$_2$), 7.5–7.9 (20 H, 4 × Ph); ^{1}H NMR (TFA-*d*–CDCl$_3$) δ 2.41 (8 H, 4 × CH$_2$C*H*$_2$CH$_2$), 3.70 (8 H, 4 × β-CH$_2$), 4.42 (8 H, 4 × meso-CH$_2$), 7.4–7.8 (20 H, 4 × Ph).

2,7,12,17-Tetraisopropyl-3,5:8,10:13,15:18,20-tetrapropano-porphyrin (21e). Only trace amounts of porphyrin were obtained from THI 10e. The product was isolated as an unstable green film: UV (CH$_2$Cl$_2$) λ$_{max}$ 432, 532, 574, 610, 672 nm.

2,7,12,17-Tetramethyl-3,5:8,10:13,15:18,20-tetrakis(3-methylpropano)porphyrin (28c). Prepared from 26c (2.30 g) by the method described for 21a. Crystallization from dichloromethane–methanol gave the title porphyrin[27] (51 mg; 3%) as purple crystals: mp >300 °C; FAB MS *m/e* 583 ([M + H]$^+$); HR FAB MS calcd for C$_{40}$H$_{46}$N$_4$ + H 583.3801, found 583.3781; UV (CHCl$_3$) λ$_{max}$ (log$_{10}$ ε) 422 (5.33), 520 (4.16), 554 (3.69), 595 (3.64), 641 (3.53) nm; ^{1}H NMR (CDCl$_3$) δ –3.05 (2 H, br, 2 × NH), 1.82–1.92 (12 H, m, 4 × CHC*H*$_3$), 2.77–2.81 (4 H, m), 3.0 (4 H, m) (4 × C*H*$_2$CH), 3.54 (12 H, s, 4 × porphyrin-CH$_3$), 3.7–4.0 (8 H, m, 4 × porphyrin-CH$_2$), 5.78 (4 H, m, 4 × C*H*CH$_3$).

Porphyrins with Exocyclic Rings. 2.[1] Synthesis of Geochemically Significant Tetrahydrobenzoporphyrins from 4,5,6,7-Tetrahydro-2H-isoindoles[2,3]

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Benzo- and tetrahydrobenzoporphyrins are widespread constituents of oil shales and petroleum. Although the origins of these materials are not known, a case is made for divinylchlorophyll a, a widespread pigment in marine algae, being the precursor to many of these geoporphyrins. Total syntheses of four tetrahydrobenzoporphyrins related to etioporphyrin III are described. Tetrahydroisoindoles were prepared by condensation of isocyanoacetates with 1-nitrocyclohexene in the presence of DBU or by reaction of aminomalonates with 2-formylcyclohexanone. Condensation of 3-unsubstituted 4,5,6,7-tetrahydro-2H-isoindoles 23c and 23d with (acetoxymethyl)pyrroles in the presence of Montmorillonite clay gave dipyrrylmethanes 28a and 36a in excellent yield. Hydrogenolysis of the benzyl esters and subsequent acid-catalyzed condensation with pyrrole aldehydes 37a and/or 37b gave a series of a,c-biladiene dihydrobromides. Copper(II) mediated cyclization of the a,c-biladienes 32, 33, 35, and 38, followed by demetallation with 15% sulfuric acid–trifluoroacetic acid, gave four isomeric tetrahydrobenzoporphyrins 10–13 in unusually high yield. This work provides a general route for the synthesis of these important porphyrin molecular fossils.

Introduction

Sedimentary deposits, such as oil shales, commonly contain complex mixtures of metalloporphyrins. Initially, there were thought to be two major groups of petroporphyrins: (1) the etioporphyrins, or polyalkyl porphyrins related to etioporphyrin III, and (2) cycloalkanoporphyrins related to deoxophylloerythroetioporphyrin (DPEP; 1). DPEP is believed to be a degradation product, or molecular fossil, of chlorophyll a (2a) and related biological pigments. On the other hand, the etioporphyrins are probably derived from both the hemes (e.g., protoheme (3)) and the chlorophylls. However, it is now known that many additional structural types are present in organic-rich sediments, and the origins of these materials is not always clear. In the 1960's, a minor family of petroporphyrins

with rhodo-type visible spectra were identified.[4,5] On the basis of mass spectrometry and IR data, Baker et al. suggested[5] that the compounds were benzoporphyrins 4. This proposal received additional support when synthetic monobenzoporphyrins were shown[6] to have electronic spectra similar to the sedimentary "rhodoporphyrins".

In 1984, Barwise and Roberts isolated[7] a "diDPEP" (porphyrin with two exocyclic rings) from El Lajjun oil shale (Jordan). On the basis of mass spectrometry and partial NOE difference proton NMR data, structure 5 was proposed for this compound. Subsequently, Maxwell and co-workers isolated[8] two benzoDPEP's (6a and 6b) from Boscan oil shale (Venezuela) and unambiguously demonstrated the structures of these petroporphyrins by NOE difference proton NMR spectroscopy. Structures 5 and

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