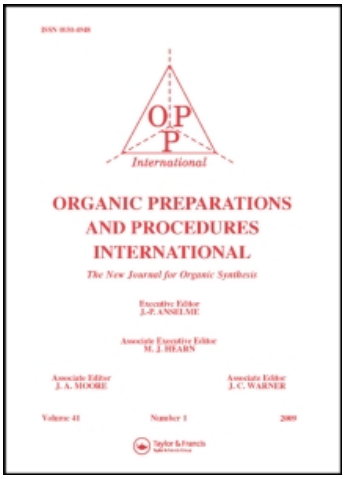

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IMPROVED PREPARATIONS OF SYMMETRIC PORPHYRINS

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IMPROVED PREPARATIONS OF SYMMETRIC PORPHYRINS

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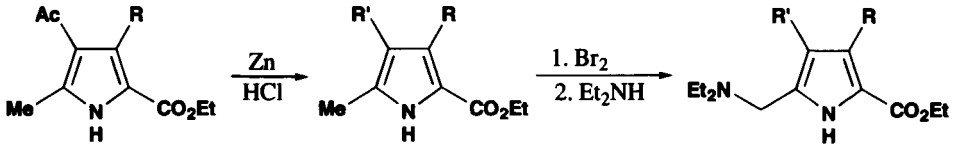
Symmetric porphyrins such as octaethylpocphyrin (**4a**), octamethylporphyrin and tetraphenylporphyrin have been synthesized via monopyrrole procedures.[1] The precursor of **4a**, ethyl 5-methyl-3,4-diethylpyrrole-2-carboxylate (**2a**), is usually obtained by diborane reduction of ethyl 4-acetyl-3-ethyl-5-methylpyrrole-2-carboxylate (**1a**). Other symmetric porphyrins, such as etioporphyrin I (**4b**), coproporphyrin I and uroporphyrin I, are reported to be synthesized *via* dipyrrylmethane or dipyrrylmethene procedures,[2] since they cannot be synthesized from monopyrroles because of the isomerization of the porphyrinogen in the strong mineral acid media used for the cyclization.[3] In our study of porphyrins, we have found that **2a** could be obtained in higher yield by zinc/hydrochloric acid reduction of **1a** in ethanol. Ethyl 4-acetyl-3-ethyl-5-methylpyrrole-2-carboxylate (**1a**) was obtained by the method of Paine *et al.*[4]

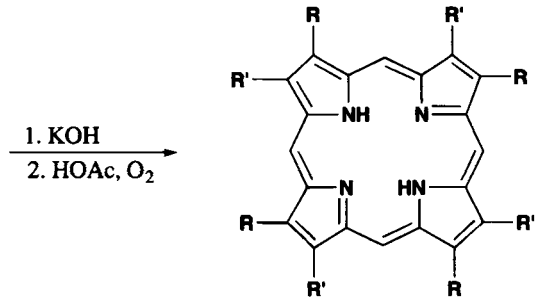
Although the porphyrinogen undergoes isomerization in strong mineral acid media, the type I porphyrins[5] can be formed under milder conditions from monopyrroles. The 5-methylpyrrole-2-carboxylates (**2**) were converted to pyrrylmethylamines (**3**) by bromination followed by diethylamination. The pyrrylmethylamines (**3**) which are amorphous solids or undistillable liquids, were saponified with ethanolic potash and then treated *in situ* with excess acetic acid and a stream of oxygen, the porphyrins (**4**) recrystallized after workup. Fine needles of **4** can be obtained by recrystallization. For porphyrins bearing carboxylic acid groups, such as coproporphyrin I, esterification in sulfuric acid/alcohol and then recrystallization yields better results. The precursor of etioporphyrin I (**4b**) in this study, ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (**2b**), was also obtained by zinc/hydrochloric acid reduction of the corresponding acetylpyrrole **1b**[6,7] in ethanolic solution. This is a relatively shorter route for the porphyrin synthesis and thus the overall yields of the porphyrins are improved considerably. For example, the overall yield of **4b** is 15% by this method starting from **1b** (obtained from 2,4-pentanedione and ethyl acetoacetate)[7] based on ethyl acetoacetate, while the highest yield



1 2 3

a) R = Et b) R = Me

a) R = R' = Et b) R = Me c) R' = $CH_2CH_2CO_2Et$



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a) R = R' = Et

b) R = Me, R' = Et

c) R = Me, R' = $CH_2CH_2CO_2Me$

reported in the literature for **4b** was 11% based on *t*-butyl acetoacetate starting from 2,4-pentanedione and *t*-butyl acetoacetate.[8] Furthermore, much more expensive reagents, such as *t*-butyl acetoacetate and ethyl iodide, were utilized in the literature procedures.

EXPERIMENTAL SECTION

Melting points were not corrected. Infrared spectra were recorded on a Perkin Elmer 983G IR spectrophotometer in KBr with absorption in cm^{-1}. ^1H NMR spectra recorded in ppm downfield from internal TMS were recorded on a Varian Unity 200 Instrument (200 MHz). All solvents and reagents were purchased from the Beijing Chemical Factory, Beijing. The solvents and liquid reagents were distilled before use. Given yields correspond to materials with the same purity as the samples used for analyses.

Ethyl 3,4-Diethyl-5-methylpyrrole-2-carboxylate (2a).- Into a 500 mL flask was placed crude ethyl 4-acetyl-3-ethyl-5-methylpyrrole-2-carboxylate (**1a**) (22.3 g, 0.083 mol, obtained by the procedures of Paine *et al.*[4] and containing 17% (molar ratio) of ethyl 3,5-dimethylpyrrole-2-carboxylate based on ^1H NMR measurement) under nitrogen. The pyrrole was dissolved in a minimum amount of anhydrous ethanol (about 200 mL). Zinc dust (19.5 g, 0.30 mol) was added to the flask with vigorous stirring at room temperature. Then, conc. hydrochloric acid (37%, 70 mL) was dripped in rapidly. The reaction proceeded vigorously for 40-50 min (temperature rose to 65-70°) and was then quenched by pouring the reaction mixture into 500 mL of ice-water. The white precipitate of the reduced pyrrole was collected and dissolved in 95% ethanol (90 mL) and the undissolved solid was removed by filtration. Into the ethanolic solution, diethylamine (6 mL) and trioxane (2.2 g) were added, followed by conc.

hydrochloric acid (about 1 mL). The mixture was refluxed overnight and evaporated to dryness. The residue was dissolved in ether and extracted with water and then with 5% hydrochloric acid until the washings remained acid. The ethereal solution was given a final wash with water, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallized from 70% methanol to give 16.0 g (92%) of **2a** as white crystals, mp 75-76° lit.[4] 75.5-76.6°. ^{1}H NMR ($CDCl_3$): δ 1.07 (t, 3H, J = 7.6Hz), 1.14 (t, 3H, J = 7.6Hz) 1.34 (t, 3H, J = 7.6Hz), 2.21 (s, 3H) 2.36 (q. 2H, J = 7.6Hz), 2.77 (q, 2H, J = 76Hz), 4.29 (q, 2H, J = 7.6Hz), 8.55 (br, 1H).

Ethyl 4-Ethyl-3,5-dimethylpyrrole-2-carboxylate (2b).- Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate (**1b**, 20.9 g, 0.1 mol)[7-8] obtained from the Knorr reaction of 2,4-pentanedione and ethyl acetoacetate was placed in a 500 mL flask. The pyrrole was dissolved in minor amount of anhydrous ethanol (200mL). Zinc powder (22.8 g, 0.35 mol) was then added to the vigorously stirring solution. With continued stirring under nitrogen gas, conc. hydrochloric acid (37%, 20 mL) was added dropwise and rapidly. The temperature of the reaction mixture rose rapidly upon addition of the hydrochloric acid. The temperature of the mixture was kept just below the boiling point of the alcohol (70°) by controlling the rate of hydrochloric acid addition. The solution was stirred for another 10 min. after addition and then was poured into ice-water (200 mL). The product which precipitated immediately as white needles, was collected and recrystallized from 70% methanol to yield 18 g (92%) of **2b**, mp 140-143°, lit.[7] 141-143°.

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.55; H, 8.76; N, 7.07

^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3H, J = 7.5Hz), 1.34 (t, 3H, J = 7.5Hz), 2.20 (s, 3H), 2.26 (q, 2H, J = 7.5Hz), 4.30 (q, 2H, J = 7.5Hz), 8.62 (br, 1H).

Ethyl 5-(Diethylaminomethyl)-3,4-diethylpyrrole-2-carboxylate (3a).- A solution of bromine (7.2 g, 0.044 mol) in dichloromethane (23 mL) was added dropwise and rapidly to a stirred solution of dry ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate (**2a**, 9 g, 0.043 mol) and potassium carbonate (0.1 g) in anhydrous ether (130 mL). After 30 min, the addition was complete. The mixture was stirred for a further 20 min. at room temperature. Diethylamine (16 mL, 0 15 mol) in anhydrous ether (50 mL) was added to the rapidly stirring solution causing the mixture change from deep red to pale yellow. After stirring for 30 min at room temperature, water (200 mL) was added. The organic phase was separated, washed with water (100 mLx5), and then extracted with 3.7% hydrochloric acid in ice-water (80 mL). The aqueous acid layer was washed rapidly with ether and added to 15% ammonium hydroxide (200 mL). The product oiled out immediately. The aqueous phase was extracted with ether. The organic layer was washed with water dried over anhydrous sodium sulfate and the solvent was removed under vacuum to yield 11.2 g (93%) of **3a**.

Anal. Calcd. for $C_{16}H_{28}N_2O_2$: C, 68.52; H, 10.08; N, 10.00. Found: C. 68.45; H, 10.27; N, 10.28

^{1}H NMR ($CDCl_3$): δ 1.00 (t, 6H, J = 7.2Hz), 1.05 (t, 3H, J = 7.5Hz), 1.12 (t, 3H, J = 7.5Hz), 1.32 (t, 3H, J = 7.5Hz), 2.38 (q, 2H, J = 7.5Hz), 2.48 (q, 4H, J = 7.2Hz), 2.70 (q, 2H, J = 7.5Hz), 348 (s, 2H), 4.26 (q, 2H, J = 7.5Hz), 9.43 (br, 1H).

Ethyl 5-(Diethylaminomethyl)-4-ethyl-3-methylpyrrole-2-carboxylale (3b).- This compound was

prepared as described above for ethyl 5-(diethylaminomethyl)-3,4-diethylpyrrole-2-carboxylate (**3a**) using ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (**2b**) (10 g, 0.051 mol). The product was obtained as a light-yellow amorphous solid (11.5 g, 85%).

^{1}H NMR ($CDCl_3$): δ 1.07 (t, 3H, J = 7.6Hz), 1.40 (t, 9H, J = 7.0Hz), 2.30 (s, 3H), 2.40 (q, 2h, J = 7.6Hz), 2.9- 3.2 (m, 4H), 4.08+4.11 (ss, 2H), 4.32 (q, 2H, 7.0Hz), 11.35+12.19 (ss, 1H).

Ethyl 2-Ethoxycarbonyl-5-(diethylaminomethyl)-3-methylpyrrole-4-propionate (3c).- This compound was prepared as described above for ethyl 5-(diethylaminomethyl)-3,4-diethylpyrrole-2-carboxylate (**3a**) using ethyl 2-ethoxycarbonyl-3,5-dimethylpyrrole-4-propionate (**2c**) (27 g, 0.1 mol). The product was obtained as an oil which solidified slowly on storage (18 g, 50%).

^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, J = 7.6Hz), 1.23 (t, 6H, J = 7.6Hz), 1.40 (t, 3H, J = 7.6Hz), 2.31 (s, 3H), 2.48 (t, 2H, J = 7.2Hz), 2.71 (K 2H, J = 7.2Hz), 295-3.15 (m, 4H), 4.06 (q, 2H, J = 7.6Hz), 4.21+4.24 (ss, 2H), 4.31 (q, 2H, J = 7.6Hz), 11.46+12.00 (ss, 1H).

Octaethylporphyrin (4a).- Ethyl 5-(diethylaminomethyl)-3,4-diethylpyrrole-2-carboxylate (**3a**, 5.6 g, 0.02 mol) was saponified in 95% ethanol (20 mL) with potassium hydroxide (2.7 g, 0048 mol). The mixture was heated to reflux for 3 hrs and then diluted to 40 mL with water. To the cooled mixture, acetic acid (40 mL) was added and then boiled while oxygen passed through it. After stirring for 1.5 hr, the solution was diluted with an equal volume of methanol. The product, which crystallized on cooling, was collected and recrystallized from toluene to give 1.2 g (45%) of **4a** as purple needles, mp. 317-318°, lit.[9] 318°.

Anal. Calcd for $C_{36}H_{46}N_4$: C, 80.84; H, 8.68; N, 10.48. Found: C, 80.85; H, 8.67; N, 10.25

^{1}H NMR ($CDCl_3$): δ -3.70 (br, 2H), 1.91 (t, 24H, J = 8.4Hz), 4. 12 (q, 16H, J = 8.4Hz), 10.14 (s, 4H).

Etioporphyrin I (4b).- Ethyl 5-(diethylaminomethyl)-4-ethyl-3-methylpyrrole-2-carboxylate (**3b**, 0.8 g, 3 mmol) was dissolved in 95% ethanol (5 mL) and the solution was saponified by refluxing with potassium hydroxide (0.4 g, 10 mmol) for 3 hrs. Upon cooling, the mixture was diluted with water to 10 mL and 10 mL of acetic acid was added. Then the mixture was stirred at room temperature for 6 hrs while oxygen gas passed through it. The solution was evaporated off about a half of the solvent and equal volume of methanol was added to the hot solution. The porphyrin crystallized upon cooling. The product was collected and recrystallized from toluene to give 0.1 g (28%) of **4b** as purple needles, mp. >350°, lit.[9] 380°.

Anal. Calcd. for $C_{32}H_{38}N_4$: C, 80.28; H, 8.01; N, 11.71. Found: C, 79.75; H, 7.92; N, 11.35

^{1}H NMR ($CDCl_3$): δ -3.48 (br, 2H), 1.90 (t, 12H, J = 7.4Hz), 3.68 (s, 12H), 4.11 (q, 9H, J = 7.4Hz), 10.10 (s, 4H).

Coproporphyrin I Tetramethyl Ester (4c).- Ethyl 2-ethoxycarbonyl-5-(diethylaminomethyl)-3-methylpyrrole-4-propionate (**3c**, 10 g, 0.026 mol) was dissolved in 95% ethanol (50 mL) and then solid potassium hydroxide (6.5 g, 0.12 mol) was added to the solution. The solution was heated to reflux for 4 hrs and then diluted to 100 mL with water. On cooling acetic acid (100 mL) was added and stirred while oxygen was introduced into the solution The reaction mixture was taken to dryness. The residue was dissolved in methanol (500 mL) then treated with suituric acid (to a concentration of

5%) for 5 hrs. The solvent was removed and the residue was dissolved in chloroform and chromatographed on a silicon gel column (50x200mm) (eluted with chloroform:ether = 4:1). The red band was collected and was taken to dryness on a vacuum rotary evaporator. The product was recrystallized from chloroform-methanol yielding 1.7 g (36%) of **4c**, mp. 252-254°, lit.[9] 254°.

Anal. Calcd. for $C_{40}H_{46}N_4O_8$: C, 67.58; H, 6.52; N, 7.88. Found: C, 67.11; H, 6.39; N, 7.70

^1H NMR ($CDCl_3$): δ -3.80 (br, 2H), 3.27 (t, 8H, J = 7.4Hz), 3.60 (s, 12H), 3.63 (s, 12H), 4.40 (t, 8H, J = 74Hz), 10.05 (s, 4H).

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