and the ether was distilled off. The residue was distilled through a short path to yield 1.12 grams, b.p. 130–135° at 100 mm. Gas-liquid chromatography showed approximately 90–95% purity, and a center cut was collected for analysis. The NMR spectrum (100 m.c.s. in $CDCl_3$) had an octet centered at 2.25 $\tau$ (H at position 3) and a sextet centered at 3.04 $\tau$ (H at position 6) all of which were split ($J$ = ½ c.p.s.). Spin decoupling by irradiation at the median frequency of the peaks at 3.04 $\tau$ reduced the split peaks to sharp singlets.

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.5; H, 2.65. Found: C, 50.9; H, 2.60.

Saponification yielded an acid, m.p. 93–95°; 2,4,5-trifluorobenzoic acid (2) m.p. 97–98°.

Anal. Calcd. for $C_7H_3F_3O_2$: C, 47.7; H, 1.71. Found: C, 47.8; H, 1.77.

**4-Fluoro-3,5-dinitrotoluene (X).** To 11.6 grams (0.20 mole) of finely divided, anhydrous potassium fluoride was added 10.0 grams (46.3 mmoles) of 4-chloro-3,5-dinitrotoluene (Sherwin-Williams) and 30 ml. of dimethyl formamide. The reaction mixture was heated at 155° for 16 hours, chilled, and diluted with 150 ml. of water. The resulting mixture was partitioned between ether and water. The ether was washed with three 30-ml. portions of 1$N$ NaOH, three 30-ml. portions of 1$N$ HCl, three 30-ml. portions of water, dried, and evaporated in vacuo to dryness to yield a brown solid which was recrystallized from carbon tetrachloride to yield 0.850 gram (11%) of a yellow solid, m.p. 70–72°.

Anal. Calcd. for $C_7H_3FN_2O_4$: C, 42.0; H, 2.52; N, 14.0. Found: C, 41.7; H, 2.69; N, 13.7.

**3,5-Diamino-4-fluorotoluene (XI).** To 0.50 gram (2.5 mmoles) of 4-fluoro-3,5-dinitrotoluene was added 3.97 grams (21 mmoles) of stannous chloride, 4.3 ml. of concentrated hydrochloric acid, and 15 ml. of water. The mixture was stirred at reflux 2 hours, chilled, and evaporated in vacuo to dryness. The residue was recrystallized from benzene to yield 0.225 gram (64%) of a white solid, m.p. 75.5–77° C.

Anal. Calcd. for $C_7H_9FN_2$: C, 60.0; H, 6.47, N, 20.0. Found: C, 59.9; H, 6.47; N, 19.7.


## ACKNOWLEDGMENT

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# An Improved Preparation of Etioporphyrin I


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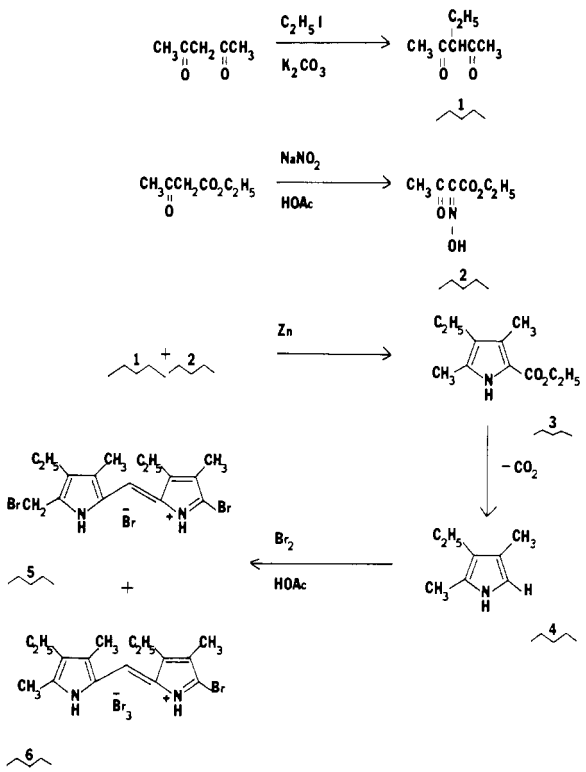
**A large quantity of highly purified etioporphyrin I was prepared by an improved method in an over-all yield of about 5% from 3-ethyl-2,4-pentanedione and ethyl acetoacetate.**


THE COLLECTION of reliable kinetic data on reactions of etioporphyrin I and its metallo derivatives requires substantial quantities of highly purified reactants. In following the preparative procedures described in the literature for the synthesis of etioporphyrin I, certain of the steps were unsatisfactory or inconvenient.

The authors have not been able to approach yields reported by Treibs and Schmidt (*15*) in the direct synthesis of 2,4-dimethyl-3-ethylpyrrole from ethyl 3,5-dimethyl-4-acetylpyrrole-2-carboxylate. Johnson and coworkers (*10*) report a yield of 8% for a comparable reaction. Yields of the order of 55 to 60% are obtained (*6, 13*) by effecting a high pressure, high temperature autoclave reduction, a procedure requiring special equipment and technique. The use of alkylated pentanediones (*2, 10, 11*) (2,4-pentanedione, Eastman) eliminates the troublesome reduction step. In the synthesis (*11*) of ethyl 3,5-dimethyl-4-ethylpyrrole-2-carboxylate from 3-ethyl-2,4-pentanedione and diethyl malonate, isolation of the intermediate oximinomalonate ester is required. A comparable yield of ethyl 3,5-dimethyl-4-ethylpyrrole-2-carboxylate was obtained by a direct reaction of 3-ethyl-2,4-pentanedione and ethyl acetoacetate by the procedure described herein.

Recently, new methods (*2, 9, 12*) have been described for the synthesis of etioporphyrin I. In two of these pro-



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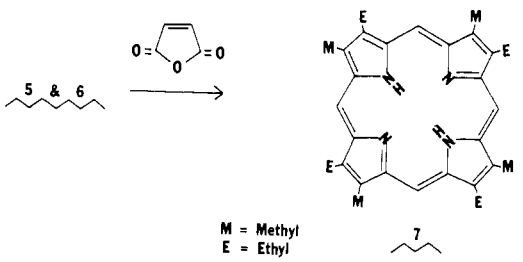


cedures (*2, 12*), the end product would likely contain isomeric etioporphyrins. In a third (*9*), a much lower overall yield resulted. The more conventional procedures (*5, 7*) have, in our hands, provided porphyrin in low yield and inadequate purity for our needs. Modifications have been made in the chemical procedures leading to the bromodipyrrylmethenes, their subsequent conversion to etioporphyrin I, and the isolation of the latter in analytical purity. These changes, while seemingly minor in most cases, influence yield and purity of the final product.

Some previously unreported analytical data are provided herein for etioporphyrin I and several of the intermediates.

## EXPERIMENTAL

Melting and boiling points are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Chemistry Department, University of Melbourne, Parkville, N. 2, Victoria. Infrared spectra were obtained on a Perkin-Elmer 421 spectrophotometer. The NMR spectra were obtained on a Varian A-60A spectrometer using tetramethylsilane as an internal standard. Visible spectra were obtained using a Beckman DU spectrophotometer equipped with a constant temperature bath (25.0° C.).

**Chemicals.** Alumina (neutral), M. Woelm, Eschwege, Germany. Ethyl iodide, Eastman, stored over mercury and distilled before use.

**3-Ethyl-2,4-pentanedione (1)** was prepared by the method of Johnson and coworkers (*10*) with the following modifications. The potassium carbonate filter cake was dispersed in water and the mixture extracted with ether to recover additional product. A tenfold increase in the amount of reactants gave a yield of 665 grams (79%) of product collected via a 2- × 45-cm. Vigreux column from 177–83° C., reported (*1*) 175–79° C. $\nu^{neat}$ 3410 (OH), 1723, 1695 (C=O); $\delta^{CCl_4}$ 5.51 (s, 0.10, OH), 3.60 [t, 0.90 $J$ = 7.0 c.p.s., $H$—C(Ac)$_2$Et], 1.95 (m, 2, $J$ = 7.0 c.p.s., —$CH_2$CH$_3$), 2.15 (s, 6, fine splitting, —CCH$_3$), 0.875 (t, 3, $J$ = 7.0 c.p.s., CH$_2$$CH_3$).

**Ethyl 3,5-Dimethyl-4-ethylpyrrole-2-carboxylate (3).** A method exactly analogous to Fischer's preparation (*6*) of ethyl 3,5-dimethyl-4-acetylpyrrole-2-carboxylate was employed. The oximino ester (2) was prepared as usual with ethyl acetoacetate (445 grams, Eastman), glacial acetic acid (1350 ml., Baker Analyzed Reagent), and a saturated solution of sodium nitrite (276 grams in about 500 ml. water). 3-Ethyl-2,4-pentanedione (500 grams) was substituted for acetylacetone. After addition of the zinc dust (500 grams; Merck Reagent, 94% Zn), the period of refluxing was limited to 30 to 45 minutes since the ester (**3**) is temperature sensitive. One recrystallization from 95% ethanol gave 436 grams (65%, based upon ethyl acetoacetate) of product, m.p. 84–5° C. Two recrystallizations gave white needles, m.p. 88–9° C, reported (*11*) 90–92° C. This product was identical to that resulting from the catalytic hydrogenation of the 4-acetyl analog. $\eta^{KBr}$ 1645 (C=O), 3290 (N—H); $\delta^{CCl_4}$ 4.30 (q, 2, $J$ = 7.0 c.p.s., —CO$_2$$CH_2$CH$_3$), 2.35 (m, 2, $J$ = 7.2 c.p.s., —$CH_2$CH$_3$), 2.24 (s, 6, $\alpha$—CH$_3$ and $\beta$—CH$_3$), 1.35 (t, 3, $J$ = 7.0 c.p.s., —CO$_2$CH$_2$$CH_3$), 1.02 (t, 3, $J$ = 7.2 c.p.s., —CH$_2$$CH_3$). Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66 H, 8.77 N, 7.17. Found: C, 67.53 H, 8.72 N, 7.51.

**2,4-Dimethyl-3-ethylpyrrole (Kryptopyrrole) (4).** A procedure similar to that of Gray and coworkers (*8*) was used. Our method is much shorter and more efficient. To a solution of 200 grams of dry KOH in 1 liter of freshly distilled ethylene glycol (b.p. 195° C.) were added 200 grams of the pyrrole ester (**3**). The orange mixture was refluxed for 2.5 hours while maintaining a gentle stream of nitrogen flowing through the system. After allowing the reaction mixture to cool, the kryptopyrrole layer was separated and stored in a stoppered flask under nitrogen. The cold ethylene glycol solution was extracted with ether and the ether extracts combined with the bulk of the product. The ether solution was washed with water, the ether removed in vacuo, and the sirupy residue (123 grams) vacuum distilled in a system well flushed with nitrogen. The yield of water-clear product collected at 56–57.5° C. (2–4 mm. McLeod gauge) was 113.4 grams (90%), reported (*6*) 85.5–87° C. (12.5 mm.); 92.5–94° C. (18 mm.). The infrared spectrum was identical to Sadtler No. 18498; $\delta^{CCl_4}$ 6.87 (s, broad, 1, N—H), 6.10 (s, 1, —H), 2.30 (q, 2, $J$ = 7.5 c.p.s., —$CH_2$CH$_3$), 1.99 (s, 6, fine splitting $J$ = 1.5 and 1.0 c.p.s., $\alpha$—$CH_3$ and $\beta$—$CH_3$), 1.02 (t, 2, $J$ = 7.5 c.p.s., —CH$_2$$CH_3$). Kryptopyrrole (mp. ca. 0° C.) is somewhat unstable and should be kept well protected from oxygen, light, and temperature. It can be stored under nitrogen in a freezer for a short time, but the following bromination should be performed as soon as possible.

**3,4′-Dimethyl-3′, 4-diethyl -5- bromoethyl-5′-bromodipyrrylmethene Hydrobromide (5) and 3,4′,5-trimethyl-monobromo hydroperbromide (6) (7).** Ten grams (11 ml.) of freshly distilled kryptopyrrole was mixed with 100 ml. of glacial acetic acid and immediately a solution of 31.2 grams (10 ml.) of bromine (Baker Analyzed Reagent) in 50 ml. of glacial acetic acid was added. The addition time was 3 to 5 minutes at room temperature. For the bromination of quantities of pyrrole considerably smaller than 10 grams, a 10-second addition time can be used. The bromination of quantities much larger than 10 grams is not recommended. The dark green mixture was allowed to stand overnight, and the precipitate was collected, washed thoroughly with cold ligroine, and dried in vacuo at room temperature. Further precipitate was obtained after allowing the mother liquor to stand for a week. When 110 grams of kryptopyrrole (10 separate brominations) was treated in the above manner, 134 grams of product was collected (50%, about 20% of **5**, and 30% of **6**). The mixture consisted of about 60% monobromo and 30% (by weight) of the dibromo salt. Separation may be achieved by stirring the mixture with chloroform. The dibromo compound is soluble and the monobromo compound insoluble in chloroform. However, the mixture gave the same yield of porphyrin in the subsequent condensation as did the separated dibromo compound. Other compounds in the mixture may be of the type proposed by Corwin (*3*). Pulverizing the bromodipyrryl methenes caused decomposition. The mixture showed a visible absorption maximum at about 485 m$\mu$ (acetone).

**Etioporphyrin I (7) (7).** One gram of the bromodipyrryl methenes and 2 grams of freshly distilled, pulverized maleic anhydride (Pfanstiehl, Waukegan, Ill.) were mixed together in a 15-cm. thin-walled test tube and heated in an oil bath at 190° C. for 30 minutes. After allowing the melt to cool, the test tubes were dried in a vacuum at 40° C., cut off above the melt line, and ground to a fine powder. The material was transferred to a Soxhlet thimble and extracted with boiling water to remove the carboxylic acid. A fast reflux rate was used when extracting with water to avoid blocking of the side tube. Foaming became severe after the initial overflow of water-soluble material; thus the water was replaced after the first few overflows and

the initial dark brown solution not allowed to reflux. After the brown color of the aqueous extract diminished, the thimble was removed and dried overnight in a vacuum oven at 75° C. The dried thimble and its contents were transferred to a new thimble and extracted with boiling chloroform until the extract was essentially colorless. Fresh chloroform was supplied to the Soxhlet apparatus every few hours, as the bulk of the porphyrin was removed during the first 8 hours. Apparatus containing porphyrin solutions were wrapped with metal foil to minimize introduction of light. The combined porphyrin solutions were washed with water until the water layer was colorless; the chloroform was evaporated in vacuo to dryness and the residue was washed onto a funnel with methanol. The solid was washed repeatedly with cold methanol until the filtrate was essentially colorless, then dried in a vacuum dessicator (yield 100 mg., 66%, based upon **5**). The methanol washing removed mainly unreacted starting material. Some etioporphyrin I may be recovered from the washings by column chromatography on neutral alumina using benzene and ether for elution of the porphyrin. The porphyrin was best purified by successive recrystallizations from benzene (for quantitative measurements, Baker Spectrophotometer Analyzed reagent was stored over sodium ribbon and distilled before use) until a constant spectrum and extinction coefficients were obtained for the four visible bands. Recrystallization was preferred over chromatography for purification of the bulk of the porphyrin. After three recrystallization steps, maximum purity was obtained. When 100 grams of the fresh bromodipyrrylmethenes were reacted in 100 separate test tube melts, utilizing five Soxhlet extractors for the work-up, the yield of thrice crystallized etio I was 6.6 grams (44%) of beautiful violet needles. $\lambda^{C_6H_6}$ 399 mμ slit 0.070, log ε 5.223; 498, 0.025, 4.170; 530, 0.025, 4.026; 568, 0.025, 3.833; 623, 0.07, 3.780. These absorptivity data agreed closely with those of Dean and Girdler (*4*). Other absorptivity values for etio I have been determined in chloroform (*2*) and dioxane (*14*) solutions. $\delta^{CDCl_3}$ 10.1 (s, 4, *meso* —H), 4.13 (q, 8, $J$ = 7.5 c.p.s., $-CH_2CH_3$), 3.68 (s, 12, $-CH_3$), 1.92 (t, 12, $J$ = 7.5 c.p.s., $-CH_2CH_3$), −3.67 (s, 2, N—H). Anal. Calcd. for $C_{36}H_{38}N_4$: C, 80.29 H, 800 N, 11.71 Found C, 80.19 H, 7.94 N, 11.66.


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# Reactions of Thioglycidaldehyde Diethylacetal


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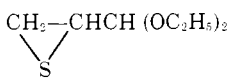
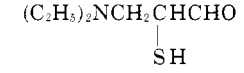
**A procedure has been developed for the isolation of pure products (3-substituted amino-2-thiolpropanal diethylacetals) from the reaction of thioglycidaldehyde with primary and secondary amines. Yields, physical constants, and analytical data are given for the products from diethylamine, ethylenimine, pyrrolidine, piperidine, and *tert*-butylamine.**

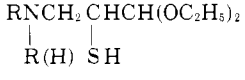

THE PREPARATION of thioglycidaldehyde diethylacetal (I)



was described in an article (*5*) on reactions of glycidaldehyde diethylacetal. It was reported that the reaction of I with diethylamine gave a product which decomposed on attempted distillation and that reaction of dilute hydrochloric acid with the crude product apparently gave a dimer of the hydrochloride of



Recent work in this laboratory has shown that the reaction products of amines and I can be prepared in good yield and are stable to distillation at reduced pressures sufficient to afford a reasonably low boiling point. The addition product of two molecules of I with one of piperazine, however, could not be distilled without decomposition—presumably because its boiling point was too high. These products have the general structure,



(II). Physical constants and analytical data are given in Table I. Several procedures were tried for hydrolysis of the addition compounds to the corresponding aldehydes, but even the use of 90% formic acid resulted in only polymeric material.