sulfite) in 50 ml of water, 65 g (0.65 mol) of 1-methylpiperazine was added over a period of 15 min. By cooling in an ice bath the temperature was not allowed to exceed 50°. After stirring at room temperature for 1 hr, the solution was poured into 500 ml of acetone. After cooling in ice, the precipitated product was collected at the filter and dried at 100° under reduced pressure (50 mm) for 48 hr. The product (105 g, 81% yield) was sufficiently pure for use in the next step. It could be recrystallized from dimethylformamide, mp 188–190° dec, but the best obtainable samples still were not quite analytically pure.

Anal. Calcd for $C_6H_{13}N_2NaO_3S$: C, 33.33; H, 6.06; N, 12.96. Found: C, 32.72; H, 6.24; N, 13.14.

In a similar manner were prepared the corresponding sodium salts derived from dimethylamine (61% yield, mp 197–200° dec), diethylamine[15] (67% yield), pyrrolidine (84% yield, mp >325°), piperidine (91% yield, mp >325°), and 1-methylhexahydro-1,4-diazepine (N-methylhomopiperazine) (71% yield, mp >325°). In D_2O, the NCH_2S peak in the A-60 nmr spectra of all these sodium salts fell within the range of 225–235 cps relative to TPS (sodium 3-trimethylsilyl-1-propanesulfonate).

1-(2′,2′-Diphenyl-2′-hydroxyethyl)-4-methylpiperazine (2, Ar = Phenyl, R_2N = 4-Methylpiperazino).—To a stirred suspension of sodium sand (3.5 g, 0.15 mol) in 50 ml of freshly distilled (from lithium aluminum hydride) 1,2-dimethoxyethane (DME) was added dropwise under an atmosphere of nitrogen, a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of DME. The temperature rose to 45° (no external cooling) and the color of the mixture went from blue to deep purple. After stirring for 1.5 hr at room temperature, the mixture was cooled to −50° by an acetone–CO_2 bath and 13.0 g (0.06 mol) of solid sodium 1-methyl-4-piperiazinomethanesulfonate was added in one portion. The cooling bath was removed and the mixture was stirred under nitrogen at room temperature for 19 hr. To the deeply colored mixture, still under nitrogen, was added dropwise with stirring 50 ml of water. (The first few drops decolorized the mixture.) The decomposed reaction mixture was then extracted with ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave 13.5 g (91%) of product that required only washing with pentane to give the pure amino carbinol, mp 81–83°, identical with an authentic[4a] sample. The dihydrochloride, mp 226–227°, also was identical with known material.[4]

Other compounds prepared by this method are listed in Table I. In several cases crystalline bases were not obtainable. Using ethereal or alcoholic solutions of appropriate acids they were converted into their corresponding crystallizable salts. In other cases distillation of the liquid bases followed by crystallization of the solidified distillates was required to effect purification. In some cases aqueous acid extraction of the original organic layer followed by reprecipitation of the base with excess aqueous alkali was necessary to separate the water-insoluble base from neutral and water-soluble by-products. The foregoing procedure probably does not represent optimum conditions for the preparation of all of the other compounds listed.

From a number of diaryl ketones no pure product could be isolated although spectral evidence indicated the presence of the desired material in the mixture. These ketones were *p*-chlorobenzophenone, anthrone, 2-benzoyl-, 3-benzoyl-, and 4-benzoylpyridine.

1-(2′,2′-Diphenyl-2′-aminoethyl)-4-methylpiperazine (4).—When diphenylketimine was substituted for benzophenone in the foregoing procedure, two fractions, bp 110–120° (0.5 mm) and bp 150–160° (0.1 mm), were obtained. The second fraction solidified and was recrystallized from hexane to give a 19% yield of **4**, mp 90–92°.[16]

Anal. Calcd for $C_{19}H_{25}N_3$: C, 77.25; H, 8.53; N, 14.22. Found: C, 77.15; H, 8.78; N, 14.25.

Registry No.—**1**, R_2N = 4-methylpiperazino, 16298-92-3; **4**, 16299-14-2.

Acknowledgment.—The authors wish to thank Mr. Orville Kolsto for the microanalyses, Mrs. Ruth Stanaszek for the nmr spectrometry, and Mr. W. H. Washburn for the infrared spectroscopy.

(15) E. Knoevenagel and E. Mercklin, *Ber.*, **37**, 4087 (1904).

(16) We are indebted to Dr. M. Winn for carrying out this experiment.

Octaethylporphyrin

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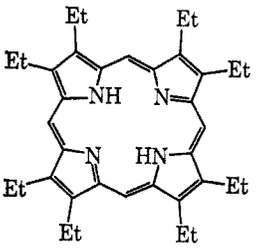
We wish to report a simple procedure for the synthesis of octaethylporphyrin (**1**). The procedure



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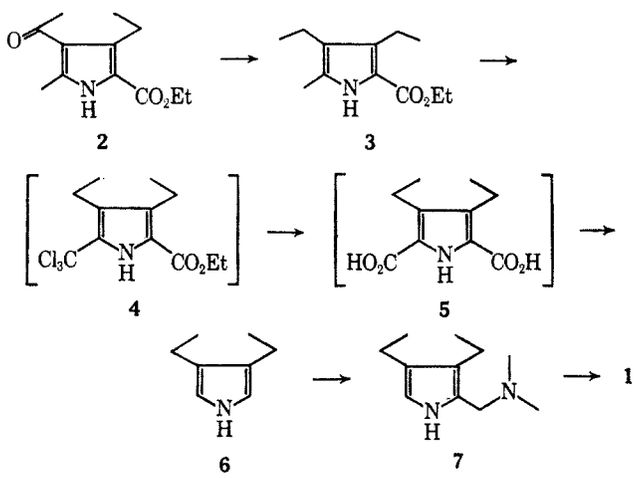
developed is basically an improvement of the synthesis of Eisner, Lichtarowicz, and Linstead.[1] The improvements have eliminated the need for high pressure equipment and chromatography, have resulted in the combination of several steps to minimize purification of intermediates and have raised the yield (40% from ethyl 4-acetyl-3-ethyl-5-methyl-pyrrole-2-carboxylate) of octaethylporphyrin to about three times that originally reported.[1] The synthesis is outlined in Scheme I. The improvements are as follows.

SCHEME I

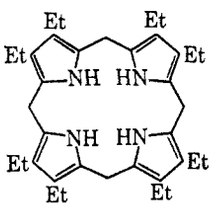


Conversion of 2 → 3.—Substitution of diborane reduction of **2** for catalytic hydrogenation gave a quantitative yield of **3**. No reduction of the carbethoxy group could be detected.

Conversion of 3 → 4 → 5 → 6 → 7.—Chlorination of **3** and subsequent hydrolysis to first the acid ester (originally isolated and purified by Eisner, *et al.*[1]) and then to diacid **5**, followed by decarboxylation of **5** in boiling quinoline containing barium-promoted copper chromite, was carried out without isolating and purifying intermediates. Entry of **6** into a Mannich reaction afforded a quantitative yield of oily **7**.

(1) U. Eisner, A. Lichtarowicz, and R. P. Linstead, *J. Chem. Soc.*, 733 (1957).

Conversion of 7 → 1.—Merely heating a solution of **7** in acetic acid to reflux while passing air or oxygen through the solution led to between 52 and 65% yields of **1**. The yield of porphyrin is relatively insensitive to variables such as the scale of the reaction, rate of bubbling, or purity of the Mannich base **7**. The most convenient procedure is to use crude Mannich base and isolate the porphyrin directly by crystallization from the reaction mixture. The above process is probably quite similar to that associated with the enzyme controlled cyclotetramerization of porphobilinogen[2,3] in the biosynthesis of porphyrins, but attempts to detect the cyclic tetrapyrrole **8** by omitting oxygen from the reaction mixture have so far been unsuccessful.[2-4]



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Porphyrin itself could not be detected as a product when 2-dimethylaminopyrrole was subjected to these reaction conditions.

Experimental Section

Ethyl 3,4-Diethyl-5-methylpyrrole-2-carboxylate (3).—In a 3-l., three-necked flask fitted with a dropping funnel, mechanical stirrer, and thermometer was placed, under nitrogen, 100 g (0.448 mol) of ethyl 3-ethyl-4-acetyl-5-methylpyrrole-2-carboxylate (**1**),[1] in 1 l. of purified tetrahydrofuran. The solution was stirred under nitrogen until the solid dissolved and was then cooled with stirring to 5°. To the above stirred solution were added 39.0 g (1.01 mol) of sodium borohydride. After the solid was completely dispersed 200 g (1.41 mol) of freshly distilled boron fluoride etherate was added dropwise at such a rate (1.5 hr) that the temperature of the solution remained near 10°. After addition was complete the solution was warmed to 25° and stirred at this temperature for 1 hr. The solution was then cooled in an ice bath to below 15° and 1 l. of cold 5% HCl was cautiously added dropwise to the solution so that the pot temperature remained below 35°. The resulting solution was added to a separatory funnel containing 500 cc of water, and the aqueous layer was extracted with ether. The fluorescent ether extracts were combined, washed with saturated salt solution, and dried over anhydrous potassium carbonate. Removal of the solvent afforded 95.0 g (100% yield) of **3** as pink crystals, mp 74.5°–75.5° (lit.[1] mp 77°).

The nmr spectrum of **3** ($CDCl_3$) showed a broad singlet at τ 0.85 (1 H), a quartet centered at 5.7 (2 H, J = 7 cps), two overlapping quartets centered at 7.27 (2 H, J = 7 cps) and 7.60 (2 H, J = 7 cps), a singlet at 7.80 (3 H), and a multiplet centered at 8.79 (9 H).

3,4-Diethylpyrrole (6).—In a 2-l. three-necked, round-bottomed flask, fitted with a dropping funnel, mechanical stirrer, and thermometer was placed 95.2 g (0.454 mol) of **3** in 800 cc of dry ether. The solution was cooled with stirring under nitrogen in an ice–salt bath and 111 cc (1.37 mol) of freshly distilled sulfuryl chloride was added dropwise (1.5 hr) so that the pot temperature remained below 0°. The dark solution was allowed to stand at 0° for 36 hr after which time 125 cc of ice water was added and the ether was evaporated *in vacuo*.

To the resulting oily residue was added a hot solution of 75 g of sodium acetate in 1500 cc of water, and the mixture was refluxed with stirring until a brown, lumpy precipitate appeared (0.5 hr). The precipitate was separated, dissolved in 570 cc of 10% aqueous sodium hydroxide, and the solution was extracted with ether and then heated under reflux for 2 hr. After reflux the solution was cooled in an ice bath to 15° and with stirring was acidified to congo red with hydrochloric acid. The solid was filtered, washed with water, and dried to afford 89.75 g (93.7%) of **5** as a light purple powder, mp 243–246° dec (lit.[1] mp 264° dec).

In a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, distilling head connected to a water cooled condenser, and a solids-addition device were placed 150 cc of quinoline and 1 g of barium-promoted copper chromite catalyst. The solution was heated under nitrogen with stirring to 190° and 89.75 g (0.425 mol) of crude **5** from above was added in small portions. After addition was complete the mixture was stirred at 190° until gas evolution ceased. The pot temperature was then raised and distillation was carried out until the head temperature was 238°. The distillate was added to a separatory funnel containing 1400 cc of cold 5% HCl and extracted with 500 cc of ether. The aqueous phase was separated, saturated with NaCl, and reextracted thrice with ether. The combined ether extracts were dried over anhydrous K_2CO_3 in the refrigerator and the ether was removed. The residue was distilled under nitrogen at 1 atm to afford 41.70 g (79.6%) of diethylpyrrole, bp 202°–205° (740 mm), which solidified in the freezer (lit.[1] mp 13°, bp 82° (9 mm)).

The proton nmr spectrum of **6** ($CDCl_3$) showed a broad singlet centered at τ 2.25 (1 H), a doublet centered at 3.50 (2 H, J = 2.5 cps), a quartet centered at 7.53 (4 H, J = 7.5 cps), and a triplet centered at 8.80 (6 H, J = 7.5 cps).

2-Dimethylaminomethyl-3,4-diethylpyrrole (7).—In a 2-l., three-necked, round-bottom flask fitted with a dropping funnel, thermometer, and a large magnetic stirrer was placed, under N_2, a solution of 41.70 g (0.338 mol) of **6** in 325 cc of methanol. The solution was cooled to −15° in a Dry Ice–acetone bath and a solution of 28.1 g (0.344 mol) of dimethylamine hydrochloride, 33.8 g (0.344 mol) of potassium acetate, and 27.8 g (0.343 mol) of 37% aqueous formaldehyde in 130 cc of water was added dropwise (1.75 hr). The pot temperature was kept between −15 and −10°. After addition the solution was stirred at −10° for 0.5 hr and was kept at 0° for 12 hr. Cold 5% hydrochloric acid (400 cc) was slowly added with stirring and the cold solution was extracted with ether. The aqueous layer was made basic by the slow addition of 500 cc of 2 *N* NaOH while stirring and cooling in an ice bath; the basic solution was extracted with three 500-cc portions of ether. The latter ether layers were combined and dried over anhydrous K_2CO_3, and the ether was removed *in vacuo* to afford 61.0 g (0.338 mol, 100%) of a brown oil which was substantially pure pyrrole (**7**) by nmr analysis.

The proton nmr spectrum of **7** ($CHCl_3$) showed a broad singlet at τ 1.18 (1 H), a doublet centered at 3.76 (1 H, J = 2.5 cps), a singlet at 6.65 (2 H), a multiplet (10 H) consisting of two overlapping quartets centered at 7.55 (J = 7.5 cps), a singlet at 7.78, and a pair of overlapping triplets centered at 8.80 and 8.92 (3 H, J = 7 cps and 3 H, J = 7.5 cps, respectively).

An analytical sample was prepared by molecular distillation (10 μ) at 30° on a high vacuum line.

Anal. Calcd: C, 73.28; H, 11.18; N, 15.54. Found: C, 72.93; H, 11.09; N, 15.86.

Octaethylporphyrin.—In a 500-cc, three-necked, round-bottomed flask fitted with a mechanical stirrer, reflux condenser, and a gas bubbler tube were placed 61.0 g (0.338 mol) of crude Mannich base (**7**) from the above in 500 cc of purified ($KMnO_4$) acetic acid. The solution was heated to reflux and refluxed 1 hr with rapid stirring while a strong stream of oxygen was bubbled through. Within minutes a dark precipitate appeared. The solution was cooled, the acetic acid was removed at reduced pressure, and 500 ml of methanol was added to the residue. The slurry was stirred and filtered, and the precipitate was washed with methanol until the filtrate was no longer brown. The

TABLE I

λ_{max}, mμ	ϵ	Lit.[1] λ_{max}, mμ	ϵ
399	163,500	400	159,000
497	14,150	498	14,500
530	10,590	532	10,800
568	6,800	568	6,800
596	1,510	596	1,500
623	6,220	622	5,800

(2) D. Mauzerall, *J. Amer. Chem. Soc.*, **82**, 2605 (1960).
(3) H. Fischer and R. Baumler, *Ann. Chem.*, **468**, 58 (1929).
(4) D. Mauzerall, *J. Amer. Chem. Soc.*, **82**, 2601 (1960).

purple crystals remaining were dried *in vacuo* to afford 24.1 g of crude octaethylporphyrin. Recrystallization from toluene afforded 23.51 g (52%) of pure octaethylporphyrin, mp 324–325° (lit.[4] mp 322°). Use of distilled Mannich base raised the yield to 60–65%. The visible spectrum in benzene is given in Table I.

Registry No.—1, 2683-82-1; 3, 16200-50-3; 6, 16200-52-5; 7, 16200-51-4.

Acknowledgment.—Partial support by the National Institutes of Health and the National Science Foundation is acknowledged.

The Synthesis of the Optically Active Cleland Reagent [(−)-1,4-Dithio-L$_g$-threitol]

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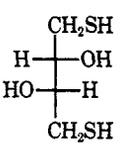
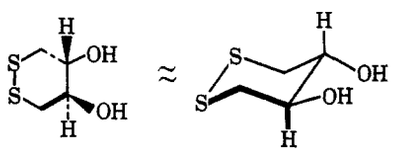
The introduction[2a] of *rac*-dithiothreitol (**1**) as a new reagent for the reduction of disulfide bonds and the protection of thiol groups has proved useful in a growing number of applications to the study of biologically active peptides.[3]

Since the available evidence[4-7] suggests that disulfide bridges in proteins may exist in asymmetric helical configurations which can, in some cases, have right-handed (in some cases left-handed) chirality, it occurred to us that an optically active form of Cleland's reagent should be expected to reduce right-handed and left-handed helical disulfide bridges at different rates, and that if the difference in these rates is sufficiently great,



1, racemic
2, $(R,R) \approx$ (L$_g$)-(−) isomer
(Rosanoff convention)



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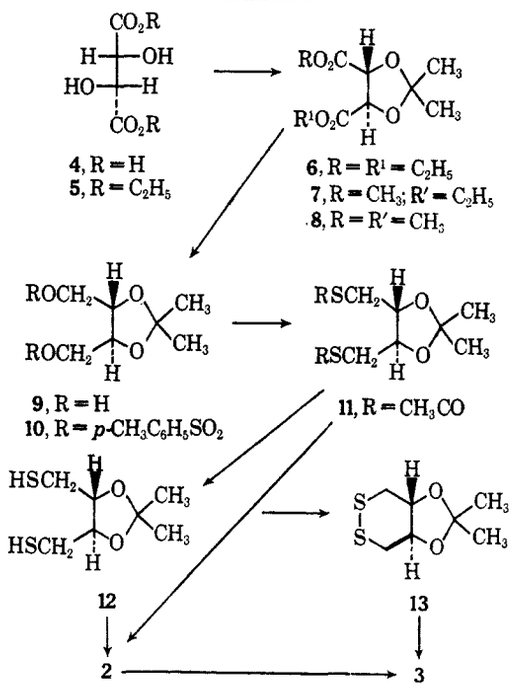
such a reagent would provide extremely interesting new possibilities for stereoselective reduction of individual disulfide bridges in complex molecules.

This paper describes the synthesis of L$_g$-(−)-1,4-dithiothreitol (**2**) from L$_g$-(+)-tartaric acid (**4**), whose absolute configuration was established by a direct X-ray method.[8,9]

We also desired the pure optical isomer of the oxidized form of dithiothreitol, 4,5-dihydroxy-1,2-dithiane (**3**), which has the same absolute stereochemical configurations as L$_g$-(+)-tartaric acid and could thus provide a reference standard relating the absolute helical sense of an asymmetric disulfide function to its observed circular dichroism (CD)[10] or optical rotatory dispersion (ORD). Compound **3** must have the 4*R*,5*R* configurations at the hydroxyl positions, and, in its presumably more stable chair conformation, would have the disulfide function in a right-handed (or P) helix.[11]

The synthetic reactions are shown in Scheme I. Compounds **4–6** and **8–10** have been described in the literature. Compounds **11–13** have not been previously prepared; racemic, but not optically active, forms of **2** and **3** have been described.

SCHEME I



Diethyl L$_g$-tartrate (**5**) was converted into the cyclic ketal ester **6** by reaction with 2,2-dimethoxypropane and a small amount of acidic catalyst.[12] Some ester interchange accompanied the formation of **6**, yielding esters **7** and **8**; the total yield of usable ester was nearly quantitative. Less satisfactory procedures for syn-

(1) (a) Publication No. 1546 from the Department of Chemistry, Indiana University. (b) To whom correspondence should be addressed. (c) From the doctoral dissertation research of C. J. Kelley, to be submitted to the Graduate School of Indiana University.

(2) (a) W. W. Cleland, *Biochemistry*, **3**, 480 (1964); (b) R. M. Evans, J. B. Fraser, and L. N. Owen, *J. Chem. Soc.*, 248 (1949).

(3) For a recent bibliography of uses, *cf.* "Biologics," No. 50, Calbiochem, Los Angeles, Calif., 1967, p 1.

(4) J. A. Schellman in "Optical Rotatory Dispersion. Applications to Organic Chemistry," C. Djerassi, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Section 15-4.

(5) L. Velluz and M. Legrand, *Angew. Chem. Intern. Ed. Engl.*, **4**, 838 (1965).

(6) S. Beychok, *Science*, **154**, 1288 (1966).

(7) M. Carmack and I. W. Stapleton, unpublished results; *cf.* I. W. Stapleton, Ph.D. Dissertation, Indiana University, 1966, p 149 ff, University Microfilms, Ann Arbor, Mich., Order No. 66-14,894; *Dissertation Abstr.*, **27B**, 4330 (1967).

(8) J. M. Bijvoet, A. F. Peerdeman, and A. J. Bommel, *Nature*, **168**, 271 (1951).

(9) For pertinent comments on the nomenclature relating to the stereoisomers of tartaric acid, *cf.* J. N. Baxter *J. Chem. Educ.*, **41**, 619 (1964), and E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co. Inc., New York, N. Y., 1962, pp 90–96.

(10) M. Carmack and L. A. Neubert, *J. Amer. Chem. Soc.*, **89**, 7134 (1967).

(11) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385, 391, and 406 (1966).

(12) An example of *trans*-ketalization with 2,2-dimethoxypropane has been well described by N. Lorette and W. Howard [*Org. Syn.*, **42**, 1 (1962)].