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An Improved Synthesis of Octaethylporphyrin

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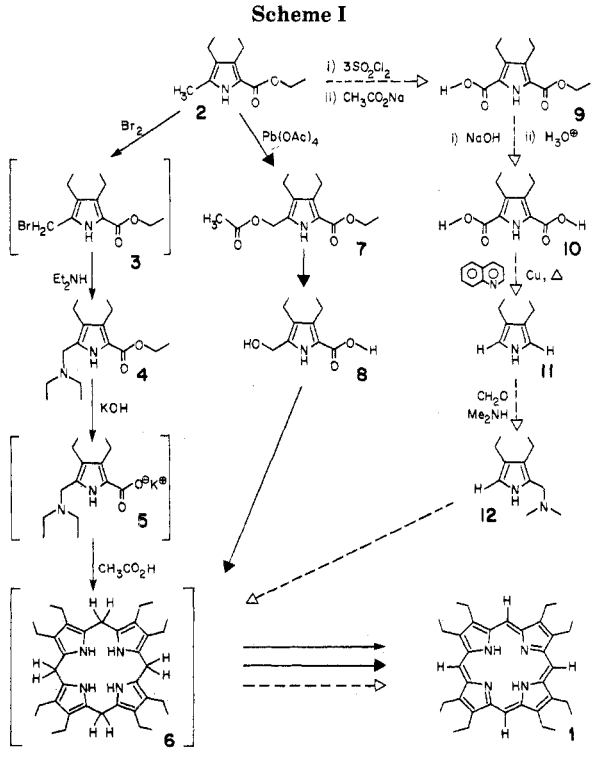
A convenient and economical synthesis of octaethylporphyrin, which proceeds via 2-*N*,*N*-diethylaminomethyl-5-ethoxycarbonyl-3,4-diethylpyrrole, is reported.

Octaethylporphyrin (OEP, **1**) is, by reason of its symmetry, high solubility, and stability, one of the more important and widely used models for the study of porphyrin chemistry. In the past, its synthesis has been tedious and erratic, particularly whenever more than a few grams were required. The usual syntheses, those of Inoffen et al.[1] and of Whitlock and Hanauer[2] (based on earlier work of Eisner, Lichtarowicz, and Linstead),[3] are summarized by Scheme I.

Scheme I



We report here an improved means of converting the common intermediate, 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (**2**), to OEP by procedures that are both facile and expeditious, which avoid the need to isolate overly sensitive intermediates such as **8**, **10**, **11**, or **12**, and which give improved overall yields. We also report procedures of improved convenience and reliability for the synthesis of the pyrrole **2** in especially high purity, using unpurified ethyl propionylacetate.

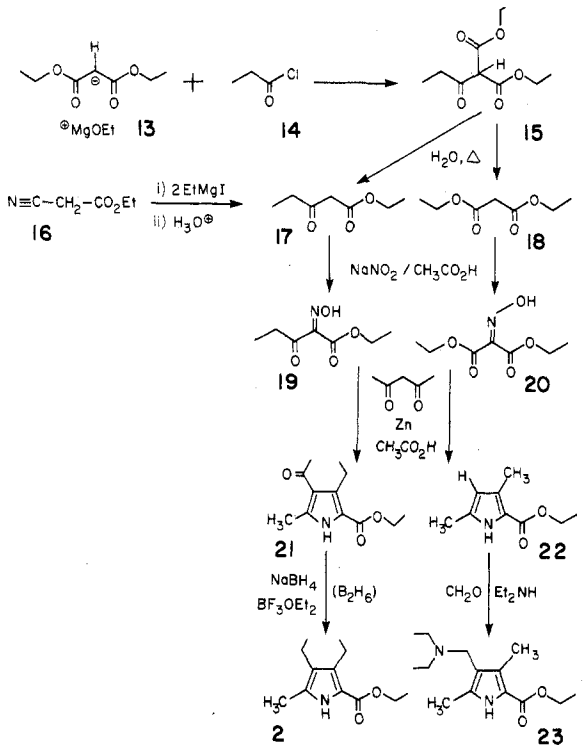
The Grignard synthesis of ethyl propionylacetate from ethyl cyanoacetate[4] requires a large excess of expensive ethyl iodide, some of which is wasted in formation of the cyanoacetate ester anion. The ethyl propionylacetate formed, however, is of high purity. An alternative synthesis has been devised by Kenner[5] and MacDonald:[6] Ethoxymagnesium diethyl malonate and propionyl chloride give diethyl propionylmalonate, which, after isolation in pure form by vacuum distillation, was hydrolyzed in boiling water. The hydrolysis gave ethyl propionylacetate, in moderately good yield, contaminated, however, by regenerated diethyl malonate, which was difficult to separate by distillation without an especillly efficient column. MacDonald,[6] unlike Kenner,[5] took note of this impurity and purified his ethyl propionylacetate via the bisulfite complex, not, however, without loss of yield.

We prefer to carry this impurity into the Knorr reaction with 2,4-pentanedione, and thereby maximize use of the ethyl propionylacetate. Nitrosation converts part of the diethyl malonate impurity to diethyl oximinomalonate which under the Knorr conditions with 2,4-pentanedione gives the otherwise useful 2-ethoxycarbonyl-3,5-dimethylpyrrole[7] (**22**).

Even when pure ethyl propionylacetate was used, pyrrole **22** was still generated via the Fischer–Fink[8] side reaction. As this impurity requires removal at a later stage in any case, purification of ethyl propionylacetate made from diethyl malonate was clearly superfluous for our purposes.

Although 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**) can be removed from the β-acetyl pyrrole (**21**) by several recrystallizations, considerable loss of product ensues, and so we have found it desirable to carry this impurity through the subsequent diborane reduction, which it survived intact. Treatment of the crude reduction product at reflux with ex-

cess diethylamine and formaldehyde effected quantitative conversion of the impurity (22) to the Mannich base[9] (23), which was then removed by acid extraction.



It should be noted in passing that the direct nitrosation of diethyl propionylmalonate (**15**) in the hope of obtaining ethyl oximinopropionylacetate (**19**), instead led exclusively to diethyl oximinomalonate (**20**).

Our synthesis of OEP, like Inhoffen's,[1] makes use of the α-methyl substituent of **2** to provide the porphyrin meso carbons, unlike Whitlock and Hanauer,[2] who amputated both pyrrolic α carbons only to replace one by a delicate Mannich reaction. Bromination of **2** generated the sensitive α-bromomethylpyrrole (**3**) which was not isolated, but instead immediately quenched with an excess of diethylamine. The pyrrylmethylamine (**4**) was then purified by extraction into ice-cold acid followed by prompt regeneration by basification with ammonia.

Conversions of α-methylpyrrole (**2**) to the amine **4** as high as 90% have been obtained. However, we have so far been unable to devise conditions which guarantee such high yields reproducibly, and hence this reaction should never be attempted on too large a scale. The pyrrylmethylamine (**4**) is an oil, indefinitely stable at room temperature, and a convenient and reliable precursor to OEP, into which it can be converted in 1 day, in 50+% yield. Saponification of the ester function with ethanolic potash gave the labile, aminomethylpyrrole carboxylate salt, which was treated in situ with excess acetic acid and warmed to reflux in a stream of air. The porphyrin crystallized as the reaction proceeded, occasionally contaminated by the crystalline intermediate octaethylporphyrinogen (**6**). Refluxing the crude product in toluene under air effected completion of the oxidation of this intermediate to OEP.

It has been claimed[10] that transition-metal halides could convert propionaldazine to 3,4-dimethylpyrrole at reflux temperatures. All attempts to repeat the synthesis, or to effect the analogous conversion of butyraldazine to 3,4-diethylpyrrole, proved fruitless. Instead, pyrazoles [3(5)-ethyl-4-methyl- and 3(5)-*n*-propyl-4-ethyl-] were obtained. These had undoubtedly arisen from the well-known[11] internal aldolization of the azine, followed by oxidation of the intermediary pyrazolines. No pyrroles were ever detected, either in the crude reaction mixture or after workup. The conversion of azines to pyrazolines is well documented,[11-13] and these have afforded the corresponding pyrazoles upon oxidation. Had the synthesis in fact succeeded, the resulting 3,4-diethylpyrrole would have greatly facilitated the large-scale production of OEP via the Whitlock–Hanauer route.[2]

Experimental Section

Diethyl Propionylmalonate.[5] Magnesium turnings (300 g, 12.34 mol) were placed in a 12-l. round-bottom flask equipped with a stirrer, addition funnel, gas inlet, and efficient condenser. A solution of diethyl malonate (1920 g, 12 mol) in absolute ethanol (960 ml) was prepared. Absolute ethanol (300 ml), followed by a portion of this solution (~300 ml), was added to the magnesium and with a slow stream of nitrogen passing through the apparatus, carbon tetrachloride (5 ml) was added to initiate the reaction. Stirring was begun as soon as the vigorously exothermic reaction set in. The remaining diethyl malonate solution was added cautiously so that the reaction proceeded vigorously, but not violently. If the malonate addition should be interrupted, even briefly, and then resumed, the reaction may not immediately restart. Instead, after an initial induction period the reaction may suddenly boil up and foam. To ensure that a buildup of unreacted diethylmalonate does not occur the mixture should be heated on a steam bath to maintain reflux temperature. As the reaction proceeded solid appeared and the reaction mixture became too thick to stir.

When the addition was complete the mixture was allowed to cool and absolute ether (3200 ml, 5 lb) was added. The mixture was then refluxed until only traces of metal remained. Freshly distilled propionyl chloride (1110 g, 12 mol) was slowly added to the stirred mixture, which was then allowed to stand overnight at room temperature.

Sulfuric acid (588 g, 6 mol) was poured onto excess crushed ice and diluted to 3500 ml with additional water. The cold acid was added dropwise to the stirred ethereal solution. The mixture was separated and the organic layer thoroughly washed with water. The solvent was removed and the remaining oil distilled under vacuum. The fraction boiling at 123–140 °C (20 mm) was collected. Yields varied in this reaction from 1800 to 2200 g.

^{1}H NMR δ_{Me_4Si} (CCl_4) (K = keto and E = enol tautomers) 1.04 (E, t, J = 7 Hz, CH_3CH_2CO), 1.26 (E + K, t, J = 7 Hz, CH_3CH_2O), 1.29 (K, t, J = 7.3 Hz, CH_3CH_2CO), 2.44 (E, q, J = 7.3 Hz, CH_3CH_2CO), 2.60 (K, q, J = 7.3 Hz, CH_3CH_2CO), 4.16 (E, q, J = 7 Hz, CH_3CH_2O), 4.19 (K, q, J = 7.5 Hz, CH_3CH_2O), 4.23 (E, q, J = 7.5 Hz, CH_3CH_2O), 4.42 (K, s, methine H), 13.35 (E, bs, OH). In CCl_4 the sample contains almost equal amount of the enol and keto tautomers.

Ethyl Propionylacetate.[5] A stirred mixture of diethyl propionylmalonate and water (2 ml/g) was slowly distilled at atmospheric pressure for 4.5 h. Additional water was occasionally added to replace that which had distilled over. After cooling, the distillate was combined with the still-pot residue. The mixture was separated and the aqueous phase extracted twice with ether. The organic layers were combined and the solvent removed. The remaining oil was then distilled at 26 mm. The fraction boiling at 90–115 °C was collected. NMR spectroscopy showed this material to contain approximately 75% ethyl propionylacetate and 25% diethyl malonate. Diethyl propionylmalonate (1 kg) was hydrolyzed in two equal lots, and the product collected as fractions boiling at 23.5–24 mm: bp 81–90 °C, 33.23 g; bp 90.5–96.5 °C, 339.88 g (by NMR consisting of 83% ethyl propionylacetate and 17% diethyl malonate); bp 96.5–110 °C, 162.03 g (by NMR 75% ethyl propionylacetate and 25% diethyl malonate). Total yield of crude distillate 535.14 g.

^{1}H NMR δ_{Me_4Si} (CCl_4) 1.01 (K + E, t, J = 7 Hz, CH_3CH_2CO), 1.23 (K + E + malonate, t, J = 7.5 Hz, CH_3CH_2O), 2.21 (E, q, J = 7.5 Hz, CH_3CH_2CO), 2.54 (K, q, J = 7.5 Hz, CH_3CH_2CO), 3.28 (malonate, s, $OCOCH_2COO$), 3.38 (K, s, $OCOCH_2CO$), 4.12 (K, q, J = 7.5 Hz, OCH_2CH_3), 4.15 (E or malonate, q, J = 7.5 Hz, OCH_2CH_3), 4.94 [E, s, $OCOCH{=}C(OH)$–], 12.08 (E, br, OH). Keto–enol ratio approximately 9:1; malonate content variable.

4-Acetyl-2-ethoxycarbonyl-3-ethyl-5-methylpyrrole[17] **(21).** The quantities given below are for a reaction on the molar scale. The reaction may be conveniently carried out on a 4–6-mol scale. The reaction vessel for the Knorr reaction requires 1.5–2 l./mol.

Into an ice-cooled Erlenmeyer flask equipped with a magnetic stirrer were placed crude ethyl propionylacetate (148 g) and glacial acetic acid (200 ml). A solution of sodium nitrite (69 g) in water (110 ml) was added dropwise to the stirred solution at such a rate as to

maintain the temperature below 45 °C. The solution was ready for the Knorr reaction as soon as the nitrite addition was complete.

Into a 200-ml three-necked round bottom flask, equipped with a mechanical stirrer and addition funnel, were placed 2,4-pentanedione (150 ml, 1.5 mol) and glacial acetic acid (200 ml). The ethyl oximinopropionyl acetate solution was added dropwise and zinc dust (260 g, 4 mol) was added in portions so as to maintain the temperature close to reflux. The zinc dust is best added as a thick aqueous slurry, which avoids much of the clumping the zinc otherwise suffers. Halfway through the addition additional 2,4-pentanedione (50 ml) and acetic acid (200 ml) were added. When the addition was complete the reaction was essentially over, and before the temperature fell below 100 °C the solution was decanted from the residual zinc which was washed with acetic acid. The combined supernatant and washings were diluted to four times their volume with water. The product oiled out and then crystallized.

When solid, the product was collected by filtration and thoroughly washed with water. The solid was dissolved in methylene dichloride, which caused the water present to separate. The two phases were filtered to remove any residual zinc. The organic phase was separated and washed with water. The methylene dichloride was removed on a steam bath and toward the end was replaced by hot hexane. Boiling was continued until all the methylene dichloride had been removed and the remaining hexane barely covered the crystallized solid. After cooling the product was collected by filtration, washed with hexane, and air dried to give the product (**21**) contaminated with 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**). The yield of **21** based upon the ethyl propionylacetate was 55%: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.20 (t, 3 H, J = 7.5 Hz), 1.38 (t, 3 H, J = 7.5 Hz), 2.48 (s, 3 H), 2.58 (s, 3 H), 3.11 (q, 2 H, J = 7.5 Hz), 4.36 (q, 2 H, J = 7.5 Hz), 10.58 (bs, 1 H).

The impurity 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**) had the following ^{1}H NMR spectrum in $CDCl_3$: δ 1.36 (t, 3 H, J = 7.5 Hz), 2.26 (s, 3 H), 2.31 (s, 3 H), 4.32 (q, 2 H, J = 7.5 Hz), 5.78 (d, 1 H, J = 3 Hz), 9.98 (br, 1 H).

2-Ethoxycarbonyl-3,4-diethyl-5-methylpyrrole. The reduction procedure of Whitlock and Hanauer[2] was used with a few modifications. For large-scale reactions less solvent was required, but the reaction mixture became viscous, and care had to be exercised while quenching the excess diborane with glacial acetic acid. The use of glacial acetic acid is superior to quenching with water since the volume of hydrogen liberated is reduced by two-thirds, and the final mixture is far less viscous.

Into an ice-cooled 12-l. round-bottom flask equipped with a mechanical stirrer, additional funnel, gas inlet, and condenser was placed, under nitrogen, crude 4-acetyl-2-ethoxycarbonyl-3-ethyl-5-methylpyrrole (1000 g). Tetrahydrofuran (5500 ml) was added, and the mixture stirred until the solid dissolved. Sodium borohydride (312 g, 8 mol) was added to the chilled solution, followed by the dropwise addition of boron trifluoride etherate (1600 g) so as to maintain the temperature at 10 °C. When the addition was complete the mixture was stirred for a further 1 h. An excess of glacial acetic acid was then cautiously added until gas evolution ceased, after which excess water was added. The aqueous phase was separated, and the organic layer filtered to remove boric acid, which was washed with ether. The combined THF/ether solution was taken down to dryness and the residue was dissolved in 95% ethanol (2000 ml).

Diethylamine (250 ml) and 37% aqueous formaldehyde (250 ml) were added, followed by concentrated HCl (5 ml). The mixture was refluxed overnight, the solution taken down to dryness, and the residue dissolved in ether. The ethereal solution was extracted with water, and then with 5% hydrochloric acid until the washings remained acid. Virtually all of the brown color passed into the acidic solution, from which the Mannich base, 2-ethoxycarbonyl-4-*N,N*-diethylaminomethyl-3,5-dimethylpyrrole, may be recovered by the addition of aqueous ammonia. The ethereal solution was given a final wash with water and the volume reduced to 1500 ml. On cooling the product crystallized. To this mixture was then added 70% aqueous methanol (2000 ml). The resulting slurry was filtered, and the product washed with 70% aqueous methanol and air dried: yield 740 g [85% based on the β-acetylpyrrole (**21**) in the starting material]; mp 75.5–76.5 °C (lit.[18] 75 °C); ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.04 (t, 3 H, J = 7.5 Hz), 1.13 (t, 3 H, J = 7.5 Hz), 1.33 (t, 3 H, J = 7.5 Hz), 2.20 (s, 3 H), 2.35 (q, 2 H, J = 7.5 Hz), 2.67 (q, 2 H, J = 7.5 Hz), 4.28 (q, 2 H, J = 7.5 Hz), 10.29 (br, 1 H).

5-*N,N*-Diethylaminomethyl-2-ethoxycarbonyl-3,4-diethylpyrrole. To an uncooled stirred solution of *dry* 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (104.5 g, 0.5 mol) in anhydrous ether (1500 ml), under dry nitrogen, was added, dropwise and rapidly, a solution of bromine (83 g, 0.52 mol) in dichloromethane (270 ml). The reaction was exothermic and the mixture refluxed. After 20 min the addition was complete and the mixture was stirred for a further 20 min. Diethylamine (175 ml, 1.69 mol) in absolute ether (500 ml) was added to the rapidly stirred solution over a period of 5 min causing the mixture to reflux and change from deep red to pale yellow. The mixture was stirred for a further 30 min. Water (1000 ml) was added and the mixture separated. The organic phase was washed with water, and then excess crushed ice added. The water was separated, and 37% hydrochloric acid (100 ml) was diluted to 1000 ml with ice and water and used to wash the organic phase. The aqueous layer was then quickly washed with ether and added to 30% ammonium hydroxide (100 ml) in water (100 ml). The product, which immediately oiled out, was extracted from the aqueous phase with petroleum ether (300 ml, bp 20–40 °C). The organic layer was washed with water, dried over sodium sulfate, and filtered, and the solvent removed under vacuum, yield 135 g (90%). Note, however, that yields of about 60% are obtained until the operator becomes familiar with the reaction! Prolonged contact of the product with aqueous solution of amine hydrochloride greatly reduces the yield by conversion to the dipyrromethane.

Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.52; H, 10.08; N, 10.00. Found: C, 68.47; H, 10.24; N, 10.32.

^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.00 (t, 6 H, J = 7 Hz), 1.05 (t, 3 H, J = 7 Hz), 1.12 (t, 3 H, J = 7 Hz), 1.32 (t, 3 H, J = 7 Hz), 2.38 (q, 2 H, J = 7 Hz), 2.48 (q, 4 H, J = 7 Hz), 2.70 (q, 2 H, J = 7 Hz), 3.48 (s, 2 H), 4.26 (q, 2 H, J = 7 Hz), 9.43 (bs, 1 H).

Octaethylporphyrin. 5-*N,N*-Diethylaminomethyl-2-ethoxycarbonyl-3,4-diethylpyrrole (28.0 g, 0.1 mol) in 95% ethanol (100 ml) was treated with a solution of potassium hydroxide (13.2 g, ~0.2 mol) in water (20 ml). The mixture was heated on a steam bath for 3 h and then diluted to 200 ml with water. The mixture was cooled in an ice bath and acetic acid (200 ml) was added. The mixture was then boiled with magnetic stirring. When the solution had become very dark, air was passed through it. After boiling for 1 h, by which time the solution was reduced to half its original volume, the solution was diluted with an equal volume of methanol; after cooling to room temperature, the product was collected by filtration, and washed with methanol to give 7.0 g (52%) of OEP.

Occasionally the product was a mixture of octaethylporphyrinogen and octaethylporphyrin. This mixture when heated under reflux in toluene (20 ml/g) was oxidized to the porphyrin and on cooling gives a high recovery of the pure product. The porphyrin itself can be recrystallized from toluene, with the aid of a Soxhlet extractor.

3(5)-Ethyl-4-methylpyrazole. Propionaldazine was prepared by dropwise addition of freshly redistilled propionaldehyde to ice-cooled hydrazine hydrate in stoichiometric amount, dried by extraction into toluene, and distilled at atmospheric pressure, bp 140–141.5 °C. The azine (50 g) and anhydrous nickel chloride (0.69 g, Alpha Inorganics, used without further purification) were refluxed under argon (heating mantle) for 24 h, and (after no pyrroles could be found) then refluxed in air for another 24 h. The crude reation mixture was then distilled at atmospheric pressure, mostly in the range of 202–232 °C. Main cut, bp 212–222 °C, 15.49 g, was slightly impure 3(5)-ethyl-4-methylpyrazole:[14] ^{1}H NMR[16] δ 1.21 (t, 3 H, J = 7.5 Hz), 1.98 (s, 3 H), 2.60 (q, J = 7.5 Hz, 2 H), 7.17 (5, 1 H), 13.13 (br, H). This spectrum agrees with the previously published spectrum, as does the infrared spectrum.[15]

3(5)-Propyl-4-ethylpyrazole. Butyraldazine, prepared similarly, bp 179–187 °C, led to 3(5)-propyl-4-ethylpyrazole, characterized by NMR: δ 0.94 (t, J = 7.5 Hz, 3 H), 1.18 (t, J = 7.5 Hz, 3 H), 1.66 (sextet, J = 7 Hz, 2 H), 2.42 (q, J = 7.5 Hz, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 7.26 (s, H), 12.22 (br, H).

This product was obtained by overnight reflux of the azine in *p*-xylene in the presence of such diverse catalysts as anhydrous cobalt iodide or ammonium chloride, and air.

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Registry No.—**2,** 16200-50-3; **4,** 60223-98-5; **14,** 79-03-8; **15** keto form, 21633-77-2; **15** enol form, 31575-85-6; **17** keto form, 4949-44-4; **17** enol form, 60223-99-6; **18,** 105-53-3; **19,** 35011-25-7; **21,** 37013-86-8; **22,** 2199-44-2; 2,4-pentanedione, 123-54-6; 3(5)-ethyl-4-methylpyrazole, 7231-33-6; propionaldazine, 15601-98-6; propionaldehyde, 123-38-6; 3(5)-propyl-4-ethylpyrazole, 60224-00-2; butyraldazine, 30020-59-8; butyraldehyde, 123-72-8; octaethylporphyrin, 2683-82-1.

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Characterization of Spiro-Bislactonic Phenolic Metabolites of Proteaceae by ^{13}C Nuclear Magnetic Resonance

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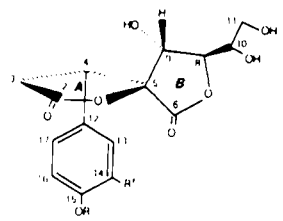
The ^{13}C NMR characteristics of a group of spiro-bislactonic phenolic metabolites of *Leucadendron* and *Leucospermum* species of the Proteaceae have been studied. The structure of a new member of this group, leudrin, has been established.

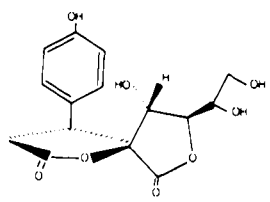
The great promise which ^{13}C NMR spectra have held for the characterization of natural products[2] has been richly fulfilled by the many studies now appearing. This tool has been used to establish the nature of alkyl chains unambiguously,[3] to demonstrate functional groups in puzzling circumstances,[4] to confirm or correct empirical formulas, and, in happy circumstances, to establish, together with ^1H NMR, the structures of surprisingly complex molecules without degradative or x-ray crystal studies.[5] However, in general, fruitful study of complex natural products has been possible only within the context of a series of closely related materials,[6] for knowledge of the factors which determine the chemical shifts of carbons in alicyclic and heterocyclic systems is still growing.[7] We describe here ^{13}C NMR studies of a group of plant phenolics not previously so studied which exemplify these problems, and which, with the support of the data of ^1H spectra taken at the field of a superconducting magnet, have led to the structure of a novel compound.

Previous studies on the phenolic constituents of the family Proteaceae have elucidated the structures and the stereochemistry[8] of leucodrin (**1**),[9] conocarpin (**4**),[10] conocarpic acid (**8**), and its methyl ester reflexin (**9**).[11] The structure and stereochemistry of leucodrin have been confirmed by an x-ray crystallographic study,[12] but those of the other compounds are based on interconversion and degradative studies, and on the spectral properties of the products. The configurations of C-4 in **1** and **4** have been established as *R* and *S*, respectively, by degradation of each to the corresponding *p*-methoxyphenylsuccinic acid, while that of C-10 is *S* in each case, as the chain of atoms C-8, C-10, and C-11 can be excised from both molecules in the form of L-glyceraldehyde. A key transformation in these studies is the conversion of conocarpin by bromine water to the spiroquinomethide ether (**5**), possible only for the configurations of C-4, C-5, and C-9 shown. The dienone–phenol rearrangement of **5** to a chroman such as **6** is attended by an upfield shift of H-8 in that compound,[10] which seems best accommodated by the configuration shown. Thus the configurations of all centers of the conocarpin series are firmly established with the exception of that at C-8. This paper particularly examines the ^{13}C NMR characteristics of this series of compounds.

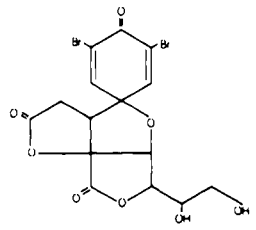
^{13}C Characteristics. The ^{13}C resonances observed in the ^1H noise-decoupled spectra are readily divided into several functional group categories[2] and methine and methylene carbons are readily recognized by off-resonance decoupled spectra. Within the aromatic group, C-15 is readily differen-



1. leucodrin, R = R′ = H
2. leucodrin methyl ether, R = CH_3, R′ = H
3. dimethylleudrin, R = CH_3, R′ = OCH_3



4. conocarpin



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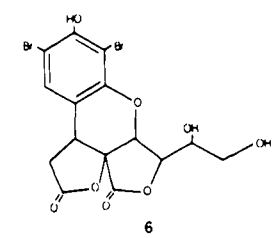

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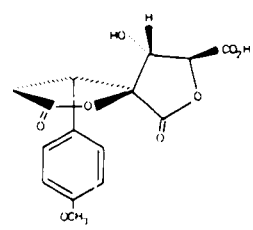
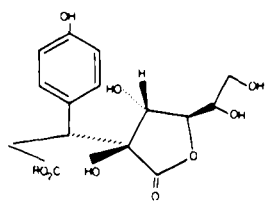


7. norleucodrinic acid methyl ether



8. conocarpic acid, R = H
9. reflexin, R = CH_3