Synthesis of *N*-(Formylmethyl)protoporphyrin and *N*-(2-Hydroxyethyl)protoporphyrin IX Dimethyl Esters

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Received March 21, 1984

N-(Formylmethyl)protoporphyrin IX dimethyl ester zinc chloride and the corresponding dimethyl acetal were synthesized by the electrochemical reduction of *N,Co*-(formylmethylene)protoporphyrin IX dimethyl ester cobalt(III) chloride. This species, in which the cobalt and a porphyrin nitrogen are bridged by a single carbon atom, was prepared from the reaction of protoporphyrin IX dimethyl ester cobalt(II) with diazoacetaldehyde. *N*-(2-Hydroxyethyl)protoporphyrin IX dimethyl ester zinc chloride was obtained by the reduction of the corresponding *N*-formylmethyl complex with $LiAlH(O\text{-}t\text{-}C_4H_9)_3$. The free bases of all of the zinc complexes were obtained by acid-catalyzed demetalation.

It has recently been reported that the prosthetic heme of cytochrome P-450 monooxygenases is converted into abnormal green porphyrins during the metabolism of 1,4-dihydropyridine derivatives,[1-4] terminal olefins,[5] terminal acetylenes,[6,7] 1-aminotriazole,[8] and cyclopropyl amines.[9,10] *N*-Methylprotoporphyrin IX dimethyl ester with the *N*-methyl group specifically on ring A was characterized for the hepatically derived porphyrin biologically modified by 3,5-dicarbethoxy-1,4-dihydrocollidine on the basis of chemical synthesis and HPLC separation of four possible isomers of (*N*-methyl)-PPIXDME.[2,11,16] The electronic and stereochemical nature of the biological N-alkylation process with olefins and acetylenes seem to be different from those with 1,4-dihydropyridine derivatives since an oxygen atom, derived from dioxygen, is incorporated into the N-substituents and the site of N-alkylation is not usually on ring A. *N*-(2-Hydroxyethyl) and *N*-formylmethyl structures have been elucidated for the *N*-substituents of the heme biologically modified with ethylene[5] and acetylene,[6] on the basis of mass spectroscopic and NMR evidence. However, synthetic methods for the introduction of 2-hydroxyethyl and formylmethyl groups onto porphyrin nitrogen have only recently been reported.[12] The *N*-alkylprotoporphyrin IX dimethyl esters can serve as probes for the action of cytochromes P-450, which give rise to suicidal N-alkylation of the prosthetic heme and subsequent inhibition of ferrochelatase by the N-alkylated porphyrins.[11,13] We describe here the synthesis of these compounds from the reaction of cobalt protoporphyrin IX dimethyl ester with diazoacetaldehyde. Analysis of the high field ^1H NMR spectra of the synthetic materials, as mixtures of four possible ring isomers, provides a firm basis for their structural identification.

Results and Discussion

Cobalt(II) protoporphyrin IX dimethyl ester reacted with diazoacetaldehyde with a color change from red to brown. The progress of the reaction was monitored by the visible spectrum which showed a remarkable decrease in the intensity of the Soret band with four isobestic points at 373, 412, 515, and 573 nm. This spectral change is similar to that observed for the reaction of cobalt(II) octaethylporphyrin with diazoacetaldehyde.[12] The reaction product (1) was precipitated by the addition of diethyl ether to the reaction mixture. While an analytically pure sample of 1 was not obtained due to its labile nature, its spectral properties support the formulation as *N,Co*-(formylmethylene)-PPIXDMECo(III)Cl. Insertion of formylcarbene into a Co–N bond with peripheral vinyl groups remaining intact was verified by the ^1H NMR spectrum which shows signals due to internal and terminal vinyl protons at ~8.1 and ~6.2 ppm, respectively, along with absorptions due to the bridgehead methine proton of the formylmethylene moiety at ca. −0.5 and −1.0 ppm. The overall reaction is the insertion of formylcarbene accompanied by the simultaneous autoxidation of Co(II) to Co(III) with the chloride ligand being derived from the solvent. This parallels the reaction of cobalt(II) octaethylporphyrin with diazoacetaldehyde[12] and ethyl diazoacetate.[14] The adduct complex (1) was smoothly reduced electrochemically at −0.58 V vs. Ag/AgCl in the presence of acetic acid with a color change from brown to green. As the reduction product again proved to be too unstable to purify, the reaction mixture was treated with acid immediately after completion of the reduction, in order to remove cobalt from the porphyrin, which was finally purified as a zinc complex. Demetalation with 5% HCl in ethanol at 0 °C for 1 h, followed by treatment with zinc(II) acetate and sodium chloride, gave *N*-(formylmethyl)-PPIXDMEZn(II)Cl (2) in 21% overall yield from PPIXDMECo(II). The 400-MHz ^1H NMR spectrum of 2 shows signals due to the periphery of the porphyrin nucleus with the meso protons (4 H) at 10.5–10.2 ppm, internal vinyl protons (2 H) at 8.3–7.9 ppm, terminal vinyl protons (4 H) at 6.4–6.2 ppm, methyl protons (18 H) at 3.8–3.4 ppm,

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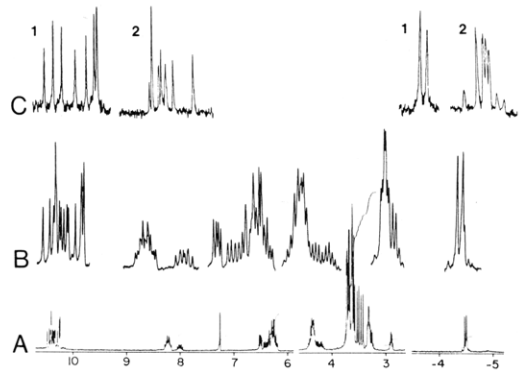

Figure 1. (A) 400-MHz ^1H NMR spectrum (δ, $CDCl_3$) of a mixture of the four isomers of *N*-(CH_2CHO)-PPIXDMEZn(II)Cl (**2**). (B) Expansion of A. (C) Ring A,B (**1**) and C,D (**2**) isomers after HPLC separation.

and methylene protons of the propionic acid side chains (8 H) at 4.4–4.1 and 3.3–2.9 ppm (see Figure 1). The ^1H NMR spectrum shows that all four possible N-alkylated isomers are present.

HPLC[15] resolved the mixture into two bands. The fast running component, band one, contained the ring A and B isomers (see below), while band two contained the ring C and D isomers. Eight meso protons are seen for each pair of isomers (Figure 1).

The difference in the magnetic environments experienced by the two vinyl groups at the 2- and 4-position is enhanced by N-alkylation at one of the two vinyl-substituted pyrroles, because the N-alkylated pyrrole ring is tilted out of the porphyrin plane. A ^1H NMR study of *N*-methylprotoporphyrin IX dimethyl ester showed that N-alkylation at the vinyl-substituted pyrrole caused the resolution of the two internal vinyl proton absorptions while N-alkylation at the propionic acid side chain substituted pyrrole gave rise to two distinct multiplets for the methylene protons next to the ester.[2] The signals due to the internal vinyl protons in the ^1H NMR spectrum of **2** appear at 8.2 and 8.0 ppm with integrals of 3:1 and those due to methylene protons adjacent to ester appear at 3.3, 3.26, and 2.9 ppm with a ratio of 2:1:1. This suggested that the vinyl-substituted pyrroles and the propionic acid side chain substituted pyrroles were N-alkylated in approximately equal amounts.

After chromatographic separation the ^1H NMR spectra of the ring A,B mixture exhibited two multiplets, centered at 7.95 and 8.2 ppm, for the internal vinyl protons while the ring C,D isomers showed only a single multiplet centered at 8.2 ppm. This behavior is similar to that of the four ring isomers of zinc *N*-methylprotoporphyrin IX dimethyl ester[2] where each of the pure ring A and B isomers show two sets of multiplets and the ring C and D isomers one set of multiplets for their internal vinyl protons. Similarly the exclusive in vivo ring A N-alkylated heme derived from the propyne-mediated destruction of cytochrome P-450[7] exhibited two sets of multiplets for the internal vinyl proton while the N-alkylated hemes derived from the N-alkylation with vinyl fluoride, 2,2,2-trifluoroethyl vinyl ether, and acetylene show only one set of multiplets in this region and are thus ring C,D isomers.

Table I. ^1H NMR Chemical Shifts of the N-Substituents of (*N*-Alkylporphyrin)zinc(II) Chlorides[a]

N-alkyl	ligand	N–C–H	O–C–H	OMe	OH
CH_2CHO	OEP[b]	−4.67 (s)	6.46 (s)		
	PPIXDME	−4.471 (s)	6.525 (s)		
		−4.504 (s)	6.510 (s)		
			6.497 (s)		
			6.484 (s)		
$CH_2CH(OMe)_2$	OEP	−5.08 (d)	1.40 (t)	1.95 (s)	
	PPIXDME	−4.94 (m)	1.48 (m)	2.080 (s)	
				2.053 (s)	
				2.027 (s)	
				1.997 (s)	
				1.975 (s)	
				1.964 (s)	
				1.941 (s)	
CH_2CH_2OH	OEP	−4.97 (t)	0.65 (q)		−0.80 (t)
	PPIXDME	−4.85 (m)	0.71 (m)		−0.67 (b)
					0.34 (b)

[a] Values are given in δ with Me_4Si as the internal standard in $CHCl_3$ solutions. [b] OEP data are taken from ref 12.

The ^1H NMR signals due to the N–CH_2CHO group of compound **2** appear as high field signals at ~−4.5 ppm and as four singlets at 6.53, 6.51, 6.50, and 6.48 ppm. We have shown that signals due to the N–CH_2CHO group of the octaethylporphyrin analogue appear at −4.67 and 6.46 ppm without observable spin–spin coupling between N–CH_2 and CHO protons. This may be the result of coordination of the formyl oxygen to the zinc(II) ion inhibiting free rotation around the C–C bond of the N–CH_2CHO group with the dihedral angle between the N–CH_2 protons and the CHO proton being fixed at 60°.[12] The signals due to the formyl proton at around 6.5 ppm are resolved into four singlets with approximately equal intensities, each of which is associated with one of the four possible ring isomers. After chromatographic separations the ring A,B isomers exhibited the 6.48 and 6.51 ppm singlets while the C,D isomers showed singlets at 6.50 and 6.53 ppm.

The ring A,B isomers show two slightly broad singlets at −4.49 and −4.52 ppm while the C,D isomers exhibit a multiplet (as the AB patterns begin to appear) centered around 4.5 ppm (Figure 1).

When the reaction mixture, after electrochemical reduction, was worked up with 5% H_2SO_4 in methanol at ambient temperature for 10 h, followed by the treatment with zinc(II) acetate and sodium chloride, *N*-(2,2-dimethoxyethyl)PPIXDMEZn(II)Cl (**3**) was obtained in 18% overall yield from PPIXDMECo(II). The ^1H NMR spectrum showed two multiplets at 8.2 and 8.0 ppm with relative intensities of 7:5. This means that compound **3** consists of the isomers with rings A or B or rings C or D N-alkylated, with a ratio of 5:1. Signals due to the *N*-alkyl groups appear at 2.1–1.9 (6 H, OCH_3), 1.48 (1 H, N–CH_2CH), and −4.94 ppm (2 H, N–CH_2). The methoxy proton signals associated with the two major isomers are resolved into four singlets at 2.08, 2.05, 2.03, and 2.00 ppm with equal intensities indicating that two methoxy groups in each isomer are magnetically nonequivalent and that the isomers with a N-substituent on ring A and ring B exist in approximately equal amounts. The methoxy proton signals due to the minor two isomers appear at 2.00 (overlapped), 1.98, 1.96, and 1.94 ppm. These chemical shifts are in excellent agreement with those observed for the

(15) After many unsuccessful attempts at separating the ring isomers of either compounds **2**, **3**, or **4** by HPLC we requested Professor K. M. Smith (U.C. Davis), who has considerable experience in these areas (see Smith, K. M.; Lui, J.-L. *J. Am. Chem. Soc.* **1984**, *106*, 5746–5748), to attempt a separation. He and his colleagues were successful in resolving **2** into two fractions containing the A,B and C,D isomers by using a Waters Associates HPLC system with a Model 6000A pump and a Perkin Elmer LC55B variable wavelength detector set at 429 nm. A 25-μL sample (in CH_3OH) was injected onto a Z module RP (C_{18}-5μ) column and eluted with 15% H_2O/CH_3OH at 2.0 mL/min. Two symmetric peaks, showing no additional resolution, even upon repeated recycling, were resolved.

(16) The abbreviations used are: PPIXDME, protoporphyrin IX dimethyl ester; (R)PPIXDME·H, an N-alkylated protoporphyrin IX dimethyl ester free base; OEP, octaethylporphyrin.

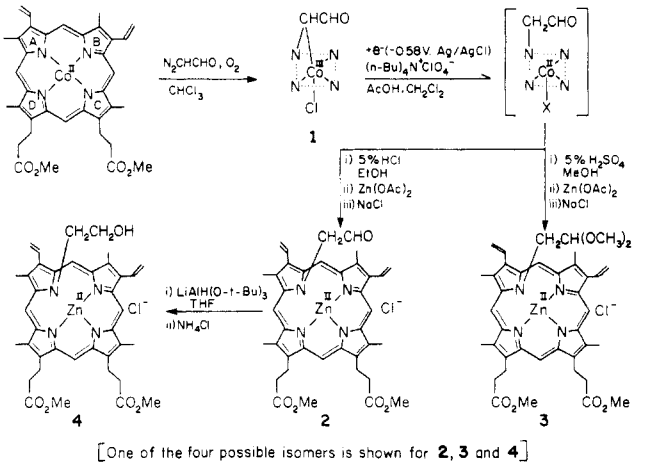

Figure 2.

N–$CH_2CH(OCH_3)_2$ group of the octaethylporphyrin analogue (see Table I).[13] Analysis of the ^1H NMR spectrum of **2** and **3** showed that, of the four possible isomers generated equally in the N-alkylation process, the isomers with a N-substituent on rings C and D were lost selectively during the prolonged acid treatment for dimethyl acetalization of the *N*-formylmethyl group. This can be rationalized in terms of a destructive intramolecular participation of the propionic acid side chain in the acid-catalyzed reaction of the *N*-formylmethyl group. From the cytochrome P-450 monooxygenase system inactivated with acetylene, Ortiz de Montellano et al.[6] isolated a mixture of *N*-alkylprotoporphyrin IX dimethyl esters, the N-substituents of which were determined as being formylmethyl and the corresponding dimethyl acetal groups on the basis of mass spectral studies. We have demonstrated that a similar mixture of *N*-formylmethyl and *N*-(2,2-dimethoxyethyl)protoporphyrin IX dimethyl esters are obtained when the acid treatment for demetalation of cobalt, after electrolysis, is carried out according to their method for esterification of the propionic acid side chains of the modified heme. The published ^1H NMR spectrum of the biological material showed signals due to the N–CH_2 protons at −4.5 and −5.0 ppm.[7] The latter had been associated with *N*-(CH_2CHO)PPIXDME, but we can now unambiguously assign it to the N–CH_2 proton of N-[$CH_2CH(OCH_3)_2$PPIXDME as a result of the chemical synthesis of **2** and **3**.

N-(Formylmethyl)-PPIXDMEZn(II)Cl (**2**) was reduced with LiAlH(O-*t*-$C_4H_9)_3$ in tetrahydrofuran to yield *N*-(2-hydroxyethyl)-PPIXDMEZn(II)Cl (**4**) in 57% yield. The 400-MHz ^1H NMR spectrum of **4** shows two multiplets due to the internal vinyl protons at 8.2 and 8.0 ppm with relative intensities of 7:4. This indicates that compound (**4**) is a mixture of isomers where N-substitution on vinyl-substituted pyrroles and on propionic acid substituted pyrroles occurs in a ratio of 8:3. A selective loss of the isomers with a N-substituent on rings C and D was observed in the hydride reduction of **2** to **4** again suggesting some participation of the propionic acid side chain residues in this reaction.

Signals due to the N–CH_2 and O–CH_2 protons of the N-substituents appear at −4.9 (2 H) and 0.71 ppm (2 H). These chemical shifts coincide with those observed for the biological materials isolated from cytochrome P-450 monooxygenase system inactivated with ethylene.[5] The hydroxy proton signal of **4** associated with the major isomers appears at −0.67 ppm, which is similar to the chemical shift of the OH proton of the octaethylporphyrin analogue[12] (see Table I), while the chemical shift (0.34 ppm) of the OH signal due to the minor two isomers is in accord with that observed for the biologically modified heme. The remarkable chemical shift difference between these two OH absorptions suggests that the hydroxy group in the isomers with the N-substituent on rings C and D is involved in hydrogen-bonding interactions with the propionic acid side chains. The analysis of the ^1H NMR spectrum of **4**, as discussed above, provides further evidence in support of the specific N-2-hydroxyethylation on ring C or D in the biological inactivation process of cytochrome P-450 with ethylene.

Experimental Section

Proton NMR spectra were recorded on Nicolet H-270 and Bruker WH-400 spectrometers with tetramethylsilane as internal standard in $CDCl_3$ solution. Visible spectra were measured in $CHCl_3$ with a Cary Model 17 spectrophotometer. Bulk controlled-potential electrolysis was performed in CH_2Cl_2 at platinum with a PAR Model 173 potentiostat with an Ag/AgCl couple as a reference. Kieselgel 60 F_{254} (Merck) and silica gel 60-H (EM Reagents) were used for preparative and column chromatography.

Reaction of PPIXDMECo(II) with Diazoacetaldehyde. To PPIXDMECo(II) (75 mg)[17] dissolved in chloroform (40 mL) was added dropwise a CH_2Cl_2 solution of diazoacetaldehyde[18] (ca. 10 molar excess) and the reaction was followed spectrophotometrically. The color of the solution turned brown in 1 h. The solution was concentrated by rotatory evaporation at room temperature and diethyl ether was added to give a black precipitate (67 mg) of *N,Co*-(formylmethylene)-PPIXDMECo(II)Cl (**1**). Anal. Calcd for $C_{38}H_{38}N_4O_5ClCo{\cdot}2H_2O$: C, 59.96; H, 5.56; N, 7.36. Found: C, 59.04; H, 5.23; N, 7.21.

Electrochemical Reduction of *N,Co*-(Formylmethylene)-PPIXDMECo(III)Cl (1) and Preparation of *N*-(CH_2CHO)-PPIXDMEZn(II)Cl (2). *N,Co*-(Formylmethylene)-PPIXDMECo(III)Cl (**1**) (67 mg) was placed in an H cell fitted with sintered glass frits and bulk electrolysis was carried out under argon at −0.58 V in CH_2Cl_2 (20 mL) containing acetic acid (0.1 mL) with tetra-*n*-butylammonium perchlorate as electrolyte (ca. 0.1 M). The color of the solution changed from brown to green in 40 min. The solvent was removed under reduced pressure and the residue was treated with 5% HCl/EtOH in an ice bath for 1 h. The acidic ethanol solution was then poured into cold water and the porphyrin extracted into chloroform. The chloroform layer was washed four times with water and then added to a methanolic solution of excess $Zn(OAc)_2{\cdot}2H_2O$. The resulting solution was partitioned between chloroform and water. The chloroform layer was washed with water and three times with saturated aqueous NaCl solution and then dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel with benzene–acetone (10:1). The green fraction following the first red band of PPIXDMECo(II) was collected and purified further by using preparative TLC with chloroform and acetone (3:1). Finally the green porphyrin was recrystallized from chloroform and *n*-hexane to give 17 mg of *N*-(CH_2CHO)-PPIXDMEZn(II)Cl (**2**) in 21% overall yield from PPIXDMECO(II). Anal. Calcd for $C_{38}H_{39}N_4O_5ClZn{\cdot}H_2O$: C, 60.80; H, 5.51; N, 7.46. Found: C, 60.77; H, 5.34; N, 7.03. Vis λ_{max} (ϵ) 380 (sh), 428 (128 500), 543 (9000), 586 (11 550), and 628 (3500) nm. The corresponding free base was easily obtained by treatment with cold 5% HCl/EtOH. The acidic solution was immediately poured into water and extracted with chloroform. The chloroform layer was washed four times with water, dried over anhydrous Na_2SO_4, and evaporated to give a brown residue which was then recrystallized from chloroform and *n*-hexane. *N*-(CH_2CHO)-PPIXDME·H was afforded in quantitative yield. Vis λ_{max} (ϵ) 415 (138 000), 509 (15 250), 541 (10 500), 590 (7500) and 648 (4130) nm; MS, 632 (M).

***N*-[$CH_2CH(OMe)_2$]-PPIXDMEZn(II)Cl (3).** The same procedure as described above was used except that acid treatment

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was carried out with 5% H_2SO_4/MeOH at room temperature for 10 h, instead of 5% HCl/EtOH at 0 °C for 1 h, to give the dimethyl acetal *N*-[$CH_2CH(OMe)_2$]-PPIXDMEZn(II)Cl (**3**) in 18% overall yield from PPIXDMECo(II). Anal. Calcd for $C_{40}H_{45}N_4O_6ClZn\cdot 2H_2O$: C, 58.97; H, 6.06; N, 6.88. Found: C, 59.31; H, 5.55; N, 6.50. Vis λ_{max} (ϵ) 380 (sh), 429 (108 000), 545 (7470), 588 (9690), and 630 (3490) nm. The corresponding free base *N*-[$CH_2CH(OMe)_2$]-PPIXDME·H was readily obtained, as described above, in quantitative yield. Vis λ_{max} (ϵ), 417 (129 000), 510 (14 280), 543 (9760), 591 (7020), and 649 (3860) nm; MS, 677 (M − 1).

Reduction of *N*-(CH_2CHO)-PPIXDMEZn(II)Cl (2) to *N*-(CH_2CH_2OH)-PPIXDMEZn(II)Cl (4). $LiAlH(O\text{-}t\text{-}C_4H_9)_3$ (34 mg) was added to a solution of *N*-(formylmethyl)-PPIXDMEZn(II)Cl (**2**) (34 mg) in tetrahydrofuran (20 mL) under argon and the reaction mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl solution was added and the porphyrin was extracted with chloroform. The chloroform layer was washed twice with saturated NH_4Cl and then with water. The solution was dried over anhydrous Na_2SO_4 and concentrated to give a residue which was chromatographed on silica gel preparative TLC with chloroform and acetone (7:3). The green band was collected and the porphyrin was extracted with acetone. The solvent was evaporated and the porphyrin was dissolved in chloroform and then dried over anhydrous Na_2SO_4. Recrystallization from chloroform and *n*-hexane gave 19 mg of *N*-(CH_2CH_2OH)-PPIXDMEZn(II)Cl (**4**) in 57% yield. Anal. Calcd for $C_{38}H_{41}N_4O_5ClZn\cdot H_2O$: C, 60.64; H, 5.76; N, 7.44. Found: C, 60.87; H, 5.54, N, 7.37. Vis λ_{max} (ϵ) 380 (sh), 430 (135 000), 546 (8510), 589 (12 100), 629 (3410) nm. The corresponding free base *N*-(CH_2CH_2OH)-PPIXDME·H was obtained as described above in quantitative yield. Vis λ_{max} (ϵ) 417 (120 000), 510 (13 200), 543 (9080), 591 (6500), 649 (3590) nm; MS, 634 (M).

Acknowledgment. This work was supported by the US National Institutes of Health (GM-29198) and the Canadian Natural Sciences and Engineering Research Council.

Registry No. 1 (Co III), 96633-03-3; 1 (Co II), 96633-06-6; 2, 96633-04-4; 2 (free base), 80829-76-1; 3, 96633-07-7; 3 (free base), 96633-08-8; 4, 96633-09-9; 4 (free base), 96633-10-2; PPIXDME-Co(II), 14932-10-6; N_2=CHCHO, 6832-13-9.

Synthesis of Alkylpyrroles by the Sodium Borohydride Reduction of Acylpyrroles[1]

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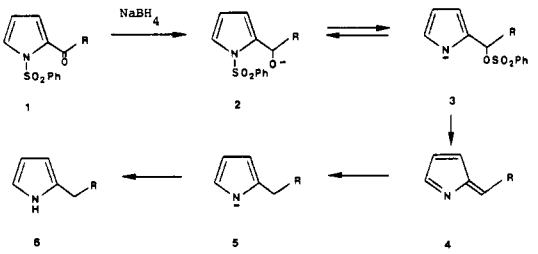
Received January 25, 1985

N-Unsubstituted alkylprroles are obtained by the reduction of the corresponding acylpyrroles with sodium borohydride in boiling 2-propanol. This reaction was demonstrated to proceed via the pyrrolylalkylcarbinol and was extended to the synthesis of a branched chain alkylpyrrole **25** from the tertiary alcohol **24**.

Alkylpyrroles can be prepared by a variety of methods, among which the reduction of the very readily available *C*-acylpyrroles is of particular importance. This reduction has been accomplished by the Wolff–Kishner method, with lithium aluminum hydride, with diborane, and by catalytic hydrogenation.[2] In addition, diverse 2-benzylpyrroles have been synthesized by the reduction of 2-benzoylpyrroles with sodium borohydride in boiling dioxane[3] and with lithium in ammonia[4] or by the lithium borohydride or sodium cyanoborohydride reduction of 6-aryl-6-(*N*,*N*-dialkylamino)-1-azafulvinium salts.[5] Of the reductive methods cited above, the Wolff–Kishner and lithium aluminum hydride processes are the most useful, but the vigorous nature and/or lack of selectivity thereof decreases their scope.

It occurred to us that the reduction of 2-acylpyrroles to the corresponding 2-alkylpyrroles would be more likely to take place, even with sodium borohydride, if the loss of the elements of water from the intermediate alcohol could be facilitated. Thus, it seemed not unreasonable that the alcoholate **2** (Scheme I) obtainable by the borohydride

Scheme I



reduction of the easily prepared 1-(phenylsulfonyl)-2-acylpyrrole (**1**)[6] would be in equilibrium with the sulfonate **3**, from which the elimination of benzenesulfonate should be particularly favorable. Hydride addition to C-6 of the azafuluene **4** thus obtained was expected[7] to occur with ease to generate the alkylpyrrole **6** via the highly stabilized pyrrolyl anion **5**. Indeed, when a 2-propanol[8] solution of 1-(phenylsulfonyl)-2-benzylpyrrole (**1**, R = Ph) containing excess sodium borohydride was heated at reflux temper-

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