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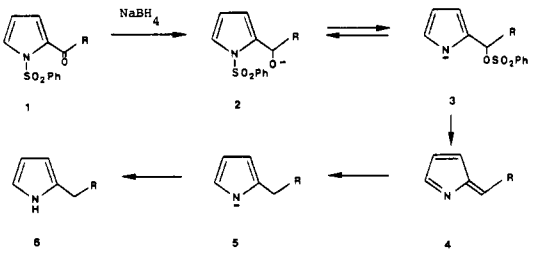
N-Unsubstituted alkylprroles are obtained by the reduction of the corresponding acylpyrroles with sodium borohydride in boiling 2-propanol. This reaction was demonstrated to proceed via the pyrrolylalkylcarbinol and was extended to the synthesis of a branched chain alkylpyrrole **25** from the tertiary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

(1) Contribution No. 683 from the Syntex Institute of Organic Chemistry.
(2) Jone, R. A.; Bean, G. P. "The Chemistry of Pyrroles"; Academic Press: London, 1977; pp 290–295.
(3) Dolby, L. J.; Nelson, S. J.; Senkowich, D. *J. Org. Chem.* **1972**, *37*, 3691.
(4) Schumacher, D. P.; Hall, S. S. *J. Org. Chem.* **1981**, *46*, 5060.
(5) McGillivary, G.; Smal, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 633.
(6) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214. Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1982**, *2*, 4899.
(7) Reference 2, pp 426–429.
(8) 2-Propanol was chosen as the solvent because sodium borohydride is appreciably soluble therein (8.8 g/L at 60 °C) and does not react measurably with this alcohol, even after extended periods at 60 °C; Brown, H. C.; Mead, E. J.; Subba, Rao, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 6209.

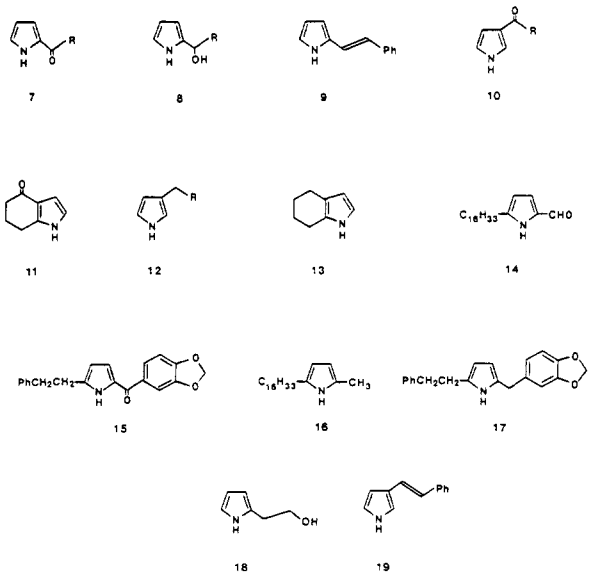
0022-3263/85/1950-2961$01.50/0

Table I. Synthesis of Alkylpyrroles from Acylpyrroles or Pyrrolylalkylcarbinols

starting material		reactn,	product				
compd	R	time, h	compd	yield, %	mp, °C	cryst solvent	purification process
7a	Ph	20	**6a**	99	oil		-[a]
7b	3,4-$(MeO)_2C_6H_3$	24	**6b**	98	94–95	CH_2Cl_2–hexane	cryst
7c	3,4-$(PhCH_2O)_2C_6H_3$	7	**6c**	88	54–55	CH_2Cl_2–hexane	cryst
7d	n-$C_{15}H_{31}$	20.5	**6d**	98	67–68	CH_2Cl_2–MeOH	cryst
7e	$PhCH_2$	21.5	**6e**	92	45–47[b]	Et_2O–hexane	cryst
7f	$CO_2(CH_2)_7CH_3$	29	**18**	22	oil[c]		CC;[d] EtOAc–hexane (3:7)
7g	H	30	**6f**	13	oil[e]		see text
8	$C_{15}H_{31}$	26	**6d**	99	67–68	CH_2Cl_2–MeOH	cryst
10a	Ph	53	**12a**	42	oil[f]		CC; EtOAc–hexane (5:95)
10b	$PhCH_2$	51	**12b**	65	oil		CC; EtOAc–hexane (5:95)
11		17	**13**	45	58–59[g]	hexane	CC; EtOAc–hexane (2:98)
14		6	**16**	73	72–73	hexane	CC; hexane
15		8	**17**	98	39–40	Et_2O–pentane	cryst
24		18	**25**	27	oil		CC;[h] EtOAc–hexane (4:96)

[a] Spectral characteristics of crude, TLC pure product identical with authentic specimen.[12] [b] Lit.[13] mp 40–42 °C. [c] Spectral properties identical with those reported.[14] [d] CC = Column chromatography; unless indicated otherwise the stationary phase was neutral alumina (Fluka, Act. II). [e] Low isolated yield because of difficulty in separation of 2-methylpyrrole:2-propanol azeotrope. [f] NMR spectrum identical with that reported.[15] [g] Lit.[16] mp 55 °C. [h] Stationary phase, silica gel.

ature (75 °C in Mexico City), 2-benzylpyrrole (**6**, R = Ph) was isolated in 36% yield. This reduction occurred via several intermediates, one of which had the same TLC mobility as phenyl-2-pyrrolylcarbinol (**8**, R = Ph). On the basis of this observation, and that of Dolby et al.,[3] it was not surprising that 2-benzoylpyrrole (**7a**), and the disubstituted 2-benzoylpyrroles **7b** and **7c** were reduced under the above conditions to the 2-benzylpyrroles **6a–6c**, albeit in very good yields and in considerably less time (Table I). It was very surprising, however, that 2-hexadecanoylpyrrole (**7d**) was also reduced in high yield to 2-hexadecylpyrrole (**6d**), since lithium aluminum hydride is the only metal hydride reported to be capable of effecting the complete reduction of 2-alkanoylpyrroles (ref 2, pp 292–3). 2-(Phenylacetyl)pyrrole (**7e**) also underwent reduction, but the expected product **6e** was admixed with an approximately equal amount of the styryl compound **9**. The formation of **9** was of mechanistic significance (see below), and only a minor inconvenience, because catalytic hydrogenation of the mixture (Pd–C/1 atm) provided 2-(2-phenylethyl)pyrrole in over 90% yield.



It is evident from the data in Table I that this reduction reaction has considerable generality. Thus, pyrrole-2-carboxaldehyde (**7g**), 3-acylpyrroles **10a**, **10b**, and **11**, and the 2-acyl-5-substituted-pyrroles **14**[9] and **15**, all gave the expected product. In contrast, 2-pyrrolylethanol (**18**) and not the expected ester (**6**, R = $CO_2C_6H_{17}$) was the major product isolated when an attempt was made to extend the process to n-octyl pyrrole-2-glyoxalate (**7f**). This result is analogous to that reported by Weston[10] for the reduction of 3-ethoxalylindole with sodium borohydride in boiling 2-propanol.

In addition to the formation of the styryl compounds **9** and **19**, several other observations were made during the course of this study which are relevant to the mechanism of the reduction reaction. Firstly, the reactions proceed via the corresponding carbinols. This was demonstrated unequivocally for 2-hexadecanoylpyrrole (**7d**). Thus, the alcohol **8** (R = $C_{15}H_{31}$), isolated from a reaction in which the reduction of **7d** to **6d** was ca. 50% completed, was converted into **6d** in near quantitative yield under the usual conditions. Secondly, the N-methyl compounds **20a** and **20b** were rapidly converted into the alcohols **21a** and **21b**, but reduction proceeded no further even after 48 h at reflux temperature. Therefore, as has been postulated previously for lithium aluminum hydride,[2] the reduction is successful when the formation of an azafulvene intermediate (e.g., **4**) is possible.[11] The formation of the styryl compounds **9** and **19** is thus merely a consequence of the competitive (i.e., with reduction) isomerization of the exocyclic azafulvene double bond to a thermodynamically

(9) 5-Hexadecylpyrrole-2-carboxaldehyde (**14**) has been isolated as one of the compounds, of a mixture of four 5-alkylpyrrole-2-carboxaldehydes, from the marine sponge *Laxosuberites* sp. [Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4980]. The NMR spectra of this mixture and **14** were essentially identical, except for intensity differences. In addition, the NMR spectra of **16** and that reported by Stierle et al. for the lithium aluminum hydride reduction product of the above mixture were virtually identical. This data strongly supports the structural assignment made by Stierle et al. for the natural product mixture.

(10) Weston, G. O. U. S. Patent 4 062 869, 1977.

(11) A curious exception to this generalization is known. It has been reported [Remers, W. A.; Roth, R. H; Gibs, G. J.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 1232] that 1-benzyl-4-oxo-5-phenyl-4,5,6,7-tetrahydroindole is reduced to 1-benzyl-5-phenyl-4,5,6,7-tetrahydroindole with sodium borohydride in boiling ethanol. A reexamination of this reaction would be worthwhile.

(12) Hobbs, C. F.; McMillin, C. K.; Papadopoulos, E. P.; Van der Werf, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 43.

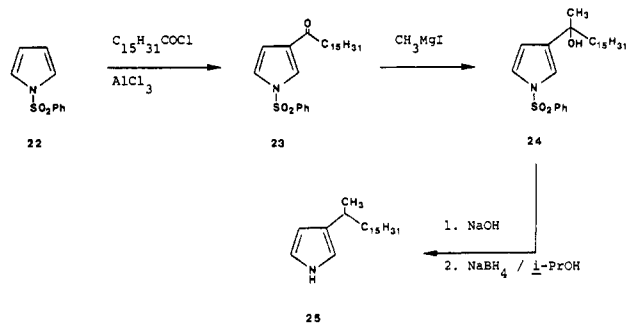
(13) Muchowski, J. M.; Solas, D. R. *Synth. Commun.* **1984**, *14*, 453.

(14) Moll, F.; Thoma, H. *Arch. Pharm. (Weinheim, Ger.)* **1968**, *301*, 872.

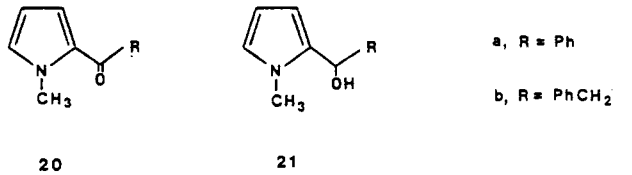
(15) Groves, J. K.; Anderson, H. J.; Nagy, H. *Can J. Chem.* **1971**, *49*, 2427.

(16) Patterson, J. M.; Soedigdo, S. *J. Org. Chem.* **1967**, *32*, 2969.

Scheme II



more stable system in which the double bond is in conjugation with two aromatic systems.



A predictable consequence of the mechanism of this reaction is that a pyrrolyldialkylcarbinol (i.e., an alcohol with no α-hydrogen atom) should be reduced. To test this prediction, *N*-(phenylsulfonyl)pyrrole (**22**, Scheme II) was acylated at C-3 with hexadecanoyl chloride ($AlCl_3$/CH_2Cl_2)[6] and the 3-acylpyrrole **23** was reacted sequentially with methylmagnesium iodide and aqueous methanolic sodium hydroxide. Reduction of the unstable tertiary alcohol **24**, under the usual conditions, gave the α-methyl compound **25** in 27% overall yield from **23**.

At this point, a moot question is, "why has this reduction not been observed previously?" A plausible rationalization is that sodium borohydride reductions are traditionally carried out, at room temperature or below, in methanol solution, a medium in which the reducing agent is very short-lived. It is probable that the energetics of the reduction are such that the generation of the azafulvene intermediate is slow under these conditions but relatively rapid at 75 °C. Thus the stability of the reagent in 2-propanol and the higher temperature achievable with this solvent both contribute to the success of the reaction.

In conclusion, N-substituted 2- or 3-acylpyrroles or alkyl-2- or -3-pyrrolylcarbinols are reduced to the corresponding alkylpyrroles with sodium borohydride in boiling 2-propanol. Alkylpyrrole-2-acetates are not, however, selectively obtained from alkyl pyrrole-2-glyoxylates. Instead, 2-pyrrolylethanol, the product of reduction of both carbonyl groups, is the major isolable product.

Experimental Section

The metling points were determined in a Mel-Temp apparatus and are corrected. The infrared spectra were measured in chloroform solution with a Perkin-Elmer Model 237 grating spectrophotometer. The NMR spectra were recorded with a Varian EM-390 spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane. The high resolution mass spectra were obtained with a Varian-MAT 311A mass spectrometer.

Unless indicated otherwise, the known pyrrolyl ketones were synthesized as described in the literature. Pyrrole-2-aldehyde was purchased from a commercial source.

The term "dried" signifies dried over anhydrous sodium sulfate throughout the Experimental Section. The elemental analyses and high resolution mass spectra (for new compounds), which are not given in the Experimental Section, are found in Table II. This data is available as supplementary material.

Sodium Borohydride Reduction of Acylpyrroles. General Procedure. A mixture of the acylpyrrole (1 part) and sodium borohydride (0.5 part) in 2 propanol (25–50 mL/g of acylpyrrole) was heated at reflux temperature with stirring for the time period indicated in Table I. The cooled mixture was diluted with water, the product was extracted with ether or ethyl acetate, the extract was washed with water (except where water solubility of the product was a problem, e.g., 2-methylpyrrole), and the solvent was removed in vacuo. The residue was then purified by the process indicated in Table I.

The IR and NMR spectra of the products were unexceptional and only a few representative examples are recorded below.

2-(2-Phenylethyl)pyrrole (6e). The reduction of **7e**, in the usual way, gave a 1:1 mixture of **6e** and the styryl compound **9**. The presence of **9** was supported by the NMR spectrum which showed (among other absorptions) two doublets for the olefinic protons at δ 6.60 (J = 16.7 Hz) and 6.9 (J = 16.7 Hz). The above mixture (4.45 g from 5.00 g of **7e**) was hydrogenated at 1 atm for 4 h in absolute alcohol (200 mL) containing 10% Pd–C (0.70 g). The mixture was filtered through Celite, the filtrate was evaporated in vacuo and the crystalline, TLC pure, residue (4.25 g) was recrystallized from ether–hexane to give **6e**, mp 45–47 °C.

2-Methylpyrrole (6f). When the reaction was completed the 2-propanol admixed with the product was directly distilled from the reaction mixture. This solution was redistilled and a fraction, bp 78 °C, was collected. This fraction was taken up in ether and washed with water and the ether was distilled off. The residual oil was 2-methylpyrrole (>95% pure by NMR).

Synthesis of the 2-Aroylpyrroles 7a–7c and 15. These compounds were prepared by the method of White and McGillivray[17] from the pyrrole, the appropriate arylmorpholide, and phosphorus oxychloride. Compounds **7b**, **7c**, **15**, and the morpholide precursors were not known, and a representative synthesis of each class of compounds is given below.

***N*-(3,4-Dimethoxybenzoyl)morpholine.** Morpholine (2.2 mol) was added dropwise to a stirred solution of 3,4-dimethoxybenzoyl chloride (1 mol) in anhydrous dichloromethane (5–10 mL/g of acid chloride) at 0 °C over a 2 h period. The mixture was washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by percolation through a column of silica gel using hexane–ethyl acetate (3:2) as the percolating solvent. The product (95% yield) had mp 72–73 °C after crystallization from dichloromethane–ether. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.57. Found: C, 62.15; H, 6.89; N, 5.46.

***N*-[3,4-Bis(benzyloxy)benzoyl]morpholine**: mp 82 °C (ether–methanol). Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.67; H, 6.52; N, 3.47.

***N*-(3,4-Methylenedioxybenzoyl)morpholine:** mp 83–84 °C, (dichloromethane–hexane). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.89; H, 5.60; N, 5.91.

2-(3,4-Dimethoxybenzoyl)pyrrole (7b). A mixture of the morpholide (1 equiv) and phosphorus oxychloride (2.5 equiv) was left at room temperature (occasional magnetic stirring), with strict protection from moisture, for 6 h. The pyrrole (1 equiv) dissolved in anhydrous dichloromethane (50 mL/g of pyrrole) was added and the reaction mixture was agitated magnetically for 18 h. At this time, the mixture was cooled to 0 °C, and a 10% aqueous sodium carbonate solution (25 mL/mL of $POCl_3$) was added cautiously with stirring. The vigorously stirred mixture was then heated at reflux temperature for 1 h. The dichloromethane phase was separated and combined with several extracts of the aqueous phase. The extract was dried and evaporated in vacuo. The residue was passed through a short column of a silica gel (10 g/g of mixture) by using dichloromethane as the solvent. The product (81% yield) on crystallization from methanol had mp 126–127 °C.

2-[3,4-Bis(benzoyloxy)benzoyl]pyrrole (7c): obtained in 77% yield as a solid mp 91–92 °C from dichloromethane–hexane.

2-(3,4-Methylenedioxybenzoyl)-5-(2-phenylethyl)pyrrole (15): prepared in 29% yield as a solid, mp 143–145 °C, from dichloromethane–acetone.

Synthesis of the 2-Alkanoylpyrroles. 2-Hexadecanoylpyrrole (7d). This compound was prepared by the uncatalyzed acylation[18] of pyrrole with palmitoyl chloride. A solution of pyrrole

(17) White, J.; McGillivray, G. *J. Org. Chem.* 1977, *42*, 4248.
(18) Carson, J. R. U.S. Patent 3 998 844 1976.

(2.0 g, 30 mmol) in anhydrous toluene (60 mL) was added dropwise over a 0.5-h period to a boiling solution of palmitoyl chloride (2.75 g, 10 mmol) in dry toluene (60 mL) maintained in a nitrogen atmosphere. The solution was heated at reflux temperature for an additional 5 h and then the solvent was removed in vacuo. The residue was subjected to column chromatography on silica gel (200 g) using hexane to elute the crystalline product (1.0 g, 33% yield) which had mp 78–79 °C after crystallization from dichloromethane–methanol.

2-(Phenylacetyl)pyrrole (7e). Prepared in 42% yield by the method used for **7d** except that the addition period was 2.5 h, and the reaction time thereafter was 3.5 h. After crystallization from ethyl acetate–hexane it had mp 94–96 °C.

***n*-Octyl Pyrrole-2-glyoxalate (7f).** A solution of pyrrole (13.4 g, 0.2 mol) in dry ether (50 mL) was added dropwise, in a nitrogen atmosphere, to a stirred solution oxalyl chloride (29.1 g, 0.21 mol) in anhydrous ether (250 mL) maintained at −50 °C. When the addition was completed (1 h), *n*-octanol (31 g, 0.24 mol), dissolved in dry ether (50 mL), was added dropwise over a 1-h period to the stirred solution of 2-oxalylpyrrole (at −50 °C). The solution was left to reach room temperature and after 1 h the ether was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute the product. The solid product, mp 42–43 °C after crystallizaiton from hexane (charcoal), was obtained in 89% yield.

***n*-Pentadecyl-2-pyrrolylcarbinol (8, R = $C_{15}H_{31}$).** The reduction of *n*-hexadecanoylpyrrole was effected in the usual manner except that the reaction was stopped at about 50% conversion to **6d** (TLC). After the usual workup the crude solid was washed with hexane in which **6d** is soluble. The insoluble residue was subjected to column chromatography on neutral alumina (Fluka, Act II) using hexane–ethyl acetate (4:1) to elute the product. This material had the following: mp 70–71°; IR 3605, 3480 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (m 3 H, CH_3, 1.31 (m, 26 H, $(CH_2)_{13}$), 1.82 (m, 2 H, CH_2), 4.67 (t, 1 H, J = 5.2 Hz, CH), (m, 2 H, H-3,4), 6.76 (dd, 1 H, $J_{4,5}$ = 2.3 Hz, $J_{3,5}$ = 1.3 Hz, H-5).

Synthesis of 3-(Phenylacetyl)pyrrole (10b). This compound was synthesized by the method of Kakushima et al.[6] Phenylacetyl chloride (6.48 g, 42 mmol) was added to a stirred suspension of anhydrous aluminum chloride (6 g, 45 mmol) in dry dichloromethane (75 mL). Ten minutes thereafter, a solution of *N*-(phenylsulfonyl)pyrrole (7.76 g, 37.5 mmol) in dry dichloromethane (15 mL) was added thereto and agitation was continued for 3 h. The reaction was quenched with ice–water; the dichloromethane phase was separated and combined with a dichloromethane extract of the aqueous phase. The extract was dried and evaporated in vacuo. The residual oil was dissolved in methanol (136 mL) 10% aqueous sodium hydroxide (136 mL) was added, and the solution was heated at reflux temperature for 3 h. The methanol was removed in vacuo and the residue was extracted with ethyl acetate. The extract was concentrated in vacuo and the residue was subjected to column chromatographic separation on silica gel (500 g) using hexane–ethyl acetate (4:1) to elute the product (4.3 g, 62% yield) which had mp 121–123 °C.

3-(2-Phenylethyl)pyrrole (12b). This compound, prepared in the same manner as described for **6e**, was obtained as an oil: IR 3500 cm^{-1}; NMR ($CDCl_3$) δ 2.87 (s, 4 H, $(CH_2)_2$), 6.08 (m, 1 H, H-4), 6.55 (m, 1 H, H-2 or H-5), 6.69 (m, 1 H, H-5 or H-2).

Synthesis of 5-Hexadecylpyrrole-2-carboxaldehyde (14). Phosphorus oxychloride (0.5 mL, 5.4 mmol) was added to a stirred solution of 2-hexadecylpyrrole (**6d**, 0.100 g, 0.34 mmol) in anhydrous dimethylformamide (4 mL) maintained in a nitrogen atmosphere. After 1 h, 10% aqueous sodium hydroxide was added, until a basic solution was obtained, and the product was extracted into ether. The extract was washed with water, dried, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (10 g) using hexane–ethyl acetate (96:4) as the eluting solvent. The solid aldehyde (0.075 g, 68%) had mp 70.5–71.5 °C after crystallization from methanol: NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.9 Hz, CH_3), 1.30 (m, 26 H), $(CH_2)_{13}$), 1.63 (m, 2 H, CH_2) 2.64 (t, 2 H, J = 7.6 Hz, CH_2), 6.07 (d, 1 H, J = 3.8 Hz, H-4), 6.88 (d, J = 3.8 Hz, H-3), 9.37 (s, 1 H, CHO).[9]

2-Methyl-5-*n*-hexadecylpyrrole (16): IR 3475 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3 H, $J \sim 6$ Hz, CH_3), 1.29 (m, 28 H, $(CH_2)_{14}$), 2.24 (s, 3 H, 2-CH_3), 2.53 (t, 2 H, J = 6.8 Hz, CH_2), 5.73, 5.76 (singlets, 2 H, H-3,4).[9]

***N*-Methyl-2-benzoylpyrrole (20a).** This compound was obtained as an oil, in 96% yield, from 2-benzoylpyrrole, as described below for *N*-methyl-2-(phenylacetyl)pyrrole. The NMR spectrum of this compound corresponded well to that reported by Pratt et al.[19]

***N*-Methyl-2-(phenylacetyl)pyrrole (20b).** A solution of 2-(phenylacetyl)pyrrole (**7e**, 7.17 g, 38.7 mmol) in dry dimethylformamide (50 mL) was added dropwise to a stirred suspension of sodium hydride (50% in mineral oil, 2.04 g, 42.6 mmol) in anhydrous dimethylformamide (50 mL). One-half hour thereafter, methyl iodide (6.5 g, 46 mmol) was added and after 3 h the reaction was quenched with water. The product was extracted into ether, and the extract was washed with water, dried, and evaporated in vacuo. The residue was subjected to column chromatography on neutral alumina (600 g, Fluka, Act II) using hexane–ethyl acetate (98:2) to elute the product (3.76 g, 49% yield). Compound **20b** was obtained as an oil: IR 1657 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (s, 4 H, CH_3), 4.06 (s, 2 H, CH_2) 6.12 (dd, 1 H, $J_{3,4}$ = 3.8 Hz, $J_{4,5}$ = 2.2 Hz, H-4), 6.77 (m, 1 H, H-5), 7.07 (dd, 1 H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.8 Hz, H-3), 7.32 (s, 5 H, C_6H_5).

Phenyl(*N*-methyl-2-pyrrolyl)carbinol (21a): obtained as an oil under the usual reduction conditions. It was not reduced further even after 41 h at reflux temperature.

Benzyl(*N*-methyl-2-pyrrolyl)carbinol (21b): prepared under the usual conditions and was not further reduced even after 48 h. This compound was an oil: IR 3595, 3460 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (m, 2 H, CH_2), 4.82 (d, 1 H, J_{AX} = 5.6 Hz, J_{BX} = 8.0 Hz, CH), 6.07 (dd, 1 H, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 2.5 Hz, H-4), 6.17 (dd, 1 H, $J_{3,4}$ = 3.6 Hz, $J_{3,5}$ = 1.8 Hz, H-3), 6.58 (t, 1H, H-5).

Synthesis of 1-(Phenylsulfonyl)-3-hexadecanoylpyrrole (23). Palmitoyl chloride (15.4 g, 56 mmol) was added to a stirred suspension of aluminum chloride (8.0 g, 60 mmol) in anhydrous dichloromethane (100 mL). A solution of *N*-(phenylsulfonyl)-pyrrole (10.4 g, 50 mmol) in dry dichloromethane (20 mL) was added 10 min thereafter and then agitation was continued for 19 h. Ice–water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was dried and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (900 g) using hexane–ethyl acetate (9:1) to elute the solid product (17.1 g, 77% yield). After crystallization from methanol, it had the following: mp 72–73 °C; IR 1672, 1385, 1188, 1178 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (m, 3 H, CH_3) 1.30 (m, 24 H, $CH_2)_{12}$), 1.67 (m, 2 H, CH_2) 2.72 (t, 2 H, CH_2CO), 6.70 (dd, 1 H, $J_{2,4}$ = 1.3 Hz, $J_{4,5}$ = 2.6 Hz, H-4), 7.15 (dd, 1 H, $J_{4,5}$ = 2.6 Hz, $J_{2,5}$ = 1.7 Hz, H-5), 7.56–8.00 (m, 6 H, H-3, C_6H_5).

3-(2-Methylhexadecyl)pyrrole (25). The ketone **23** (5.0 g, 11.2 mmol) was added, with stirring, to the Grignard reagent prepared from methyl iodide (5.0 g, 35.2 mmol) and magnesium (3.0 g) in anhydrous ether (100 mL). After 3 h the solution was decanted from the excess magnesium, and after evaporation of the solvent in vacuo, methanol (100 mL) and 10% sodium hydroxide solution (25 mL) were added to the residue. The mixture was heated at reflux temperature for 12 h, the methanol was removed in vacuo, and the product was extracted into ethyl acetate. The extract was dried and evaporated in vacuo, and the residue (4.5 g) containing the alcohol **24** was subjected to the general reduction conditions. After purification compound **25** was obtained as an oil: IR 3485 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (m, 3 H, 16′-CH_3), 1.17 (d, 3 H, H = 5.8 Hz, 2′-CH_3), 2.51 (sextet, 1 H, J = 5.8 Hz, CH), 6.10 (m, 1 H, H-4), 6.56 (m, 1 H, H-2), 6.70 (m, 1 H, H-5).

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Registry No. 1 (R = Ph), 86688-89-3; **6a**, 33234-48-9; **6b**, 96999-16-5; **6c**, 96999-17-6; **6d**, 96999-18-7; **6e**, 92454-16-5; **6f**, 636-41-9; **7a**, 7697-46-3; **7b**, 96999-19-8; **7c**, 96999-20-1; **7d**,

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96999-21-2; **7e**, 13169-74-9; **7f**, 96999-22-3; **7g**, 1003-29-8; **8** (R = Ph), 75400-63-4; **8** (R = $C_{15}H_{31}$), 96999-23-4; **9**, 35563-07-6; **10a**, 7126-41-2; **10b**, 96999-24-5; **10b** (*N*-phenylsulfonyl deriv), 96999-30-3; **11**, 13754-86-4; **12a**, 33234-57-0; **12b**, 97011-45-5; **13**, 13618-91-2; **14**, 75233-98-6; **15**, 93363-39-4; **16**, 75234-04-7; **17**, 96999-25-6; **18**, 22186-60-3; **19**, 96999-26-7; **20a**, 37496-06-3; **20b**, 93304-03-1; **21a**, 52293-26-2; **21b**, 86012-92-2; **22**, 16851-82-4; **23**, 96999-27-8; **24**, 96999-28-9; **25**, 96999-29-0; $NaBH_4$, 16940-66-2; $Me(CH_2)_{14}C(O)Cl$, 112-67-4; $PhCH_2C(O)Cl$, 103-80-0; 3,4-dimethoxybenzoyl chloride, 3535-37-3; *N*-(3,4-dimethoxybenzoyl)morpholine, 22792-13-8; 3,4-bis(benzyloxy)benzoyl chloride, 1486-54-0; *N*-[3,4-bis(benzyloxy)benzoyl]morpholine, 93363-32-7; 3,4-(methylenedioxy)benzoyl chloride, 25054-53-9; *N*-[3,4-(methylenedioxy)benzoyl]morpholine, 63916-59-6; pyrrole, 109-97-7; 2-pyrrolyloxalyl chloride, 3768-70-5.

Supplementary Material Available: Table of elemental analyses and high resolution mass spectra of pyrrole derivatives (1 page). Ordering information can be found on any current masthead page.

[2,3]-Sigmatropic Rearrangement of an in Situ Prepared Ylide and a Thioether to Thio Ester Conversion as Key Steps in Short Syntheses of Sarkomycin and Its Phenylthio Ester

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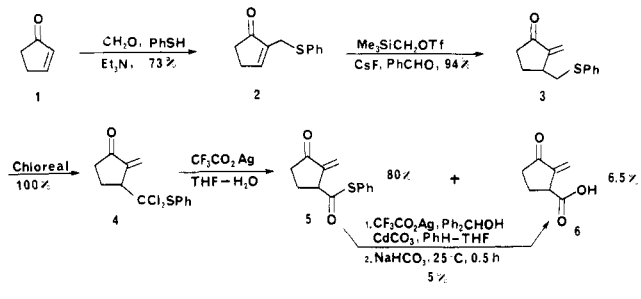
2-[(Phenylthio)methyl]cyclopent-2-en-1-one (**2**), which is readily available by the reaction of 2-cyclopentenone with thiophenol, formaldehyde, and triethylamine, is transformed, in high yield and moderate conversion by treatment with (trimethylsilyl)methyl triflate, cesium fluoride, and benzaldehyde, to 2-methylene-3-[(phenylthio)methyl]cyclopentanone (**3**), which, by the use of trichloroisocyanuric acid (Chloreal), can be quantitatively dichlorinated on the sulfur-bearing carbon atom to 3-[(phenylthio)dichloromethyl]-2-methylenecyclopentanone (**4**). This dichloro thioether could be hydrolyzed in good yield to a mixture of sarkomycin phenyl thio ester (**5**) and sarkomycin (**6**), containing mainly the former; an additional small amount of sarkomycin can be obtained by hydrolysis of the thio ester in the presence of silver trifluoroacetate and benzhydrol. This procedure represents one of the shortest extant syntheses of sarkomycin and a sarkomycin ester. Model studies of the dichlorination of *n*-octyl phenyl sulfide (**8**) to 1-(phenylthio)-1,1-dichlorooctane (**9**) and various transformations of the latter are also reported.

Our interest in the one-flask conversion of allylic phenyl thioethers to rearranged and homologated phenyl thioethers by means of the [2,3]-sigmatropic rearrangement of an in situ generated ylide[1] prompted us to attempt the synthesis of the antitumor antibiotic sarkomycin[2] (**6**) from 2-[(phenylthio)methyl]cyclopent-2-en-1-one (**2**)[3] (see Scheme I) which is readily available by a modification of the Petrow reaction[4] (see below). Although the carboxylic acid **6** is one of the simplest antitumor compounds known, the few syntheses[2,5,6] that were extant prior to 1984 are rather long, the shortest being at least eight steps, and the last step, the generation of the carboxylic acid itself, had proved troublesome.[5,7] The work reported by Thebtaranonth,[9] which largely overcomes these problems, appeared after the present work had been completed and prepared for submission.[10] We envisioned the dichlorination of **3** by the use of trichloroisocyanuric acid (Chloreal)[11] and the hopefully mild hydrolysis of **4** to sarkomycin (**6**).

Scheme I



When cyclopent-2-en-1-one (which is now available in one step from cyclopentene[12]) is treated with 1 molar equiv each of formaldehyde (as a 37% aqueous solution), thiophenol, and triethylamine in ethanol at 25 °C, a high yield of 3-(phenylthio)cyclopentanone, is produced in 2 h, but this material is gradually converted to **2**. The best yield

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