Table I. ^1H and ^{13}C NMR Assignments of Prionitin (1)[a]

carbon	^1H	^{13}C
1-Hα	3.16 (ddd, 16.8, 4.2, 2.6)	26.64
1-Hβ	2.80 (ddd, 17.0, 12.3, 4.4)	
2-Hα	2.16 (dddd, 17.4, 12.1, 4.4, 2.5)	23.71
2-Hβ	1.66 (ddd, 17.4, 12.3, 4.5)	
3	3.34 (dd, 12.2, 4.6)	62.87
4		93.58
5		127.33
6		152.12
7		153.22
8		118.07
9		130.81
10		129.46
11	7.08 (d, 8.8)	126.07
12	7.68 (d, 8.8)	119.98
13		124.87
14		120.81
15	2.37 (s)	28.07
16	3.52 (sept, 6.7)	25.68
17	1.31* (d, 6.7)	21.33†
18	1.38* (d, 6.7)	21.53†
19	1.71 (ns)	21.95
20	1.17 (s)	18.89
OCH_3	3.88 (s)	47.74

[a] Spectra were recorded in $CDCl_3$. Proton chemical shifts are reported as δ values (ppm) from internal TMS at 300 MHz. Carbon chemical shifts are reported as δ values (ppm) at 90.8 MHz. (*,†) Interchangeable.

able, the use of one-bond or long-range HECTOR spectroscopic techniques were precluded. Magnetization transfer via irradiation of 3-H resulted in enhancements of δ 26.64, 129.46, and 152.12, which could be assigned as C-1, C-10, and C-6, respectively. Irradiation of 1-Hα enhanced the aliphatic methine carbon at δ 62.87, which should be C-3, and the aromatic quaternary carbons at δ 127.33 and 130.81. The latter two signals, C-5 and C-9, were distinguished through the irradiation of 2-Hα, which resulted in enhancements at δ 93.58 (C-4), 127.33 (C-5), and 129.46 (C-10). Selective INEPT irradiation of 12-H enhanced the signals at δ 130.81 (C-9) and 120.81, assigned as C-14, indicating that this latter carbon was substituted by the aromatic methyl group. CSCM 1D irradiation of the ^{13}C satellite of 12-H enhanced the signal at δ 119.98, permitting the assignment of C-12, and consequently the other aromatic methine carbon, C-11 (δ 126.07). Finally, selective INEPT irradiation of 11-H confirmed the assignment of C-10 (δ 129.46) and permitted the assignment of C-13 at δ 124.87. The complete assignment of the ^{13}C NMR spectra of prionitin (1) is shown in Table I. The relative location of the isopropyl, methyl, and methoxy groups was firmly established by a NOE experiment. Irradiation of the methyl singlet at δ 2.37 resulted in enhancement of the methoxyl (δ 3.88) and the isopropyl methyl groups (δ 1.31 and 1.38), thereby placing the aromatic methyl group at C-14.

Prionitin (1), which represents a novel diterpenoid skeleton, was evaluated in the P-388 cytotoxicity assay where an ED_{50} value at 9.2 μg/mL was observed. Compounds displaying an ED_{50} 4 μg/mL are regarded as active.[9] Studies of the remaining active compounds present in the plant are in progress.

Experimental Section

Melting point was determined on a Kofler-type hot-stage apparatus and is uncorrected. Optical rotation was measured with a Perkin-Elmer 241 polarimeter. Ultraviolet spectra were recorded with a beckman DU-7 spectrophotometer, and infrared spectra were obtained with a Nicolet MX-1 interferometer. Mass spectrum was determined on a Varian MAT 112S double-focusing mass spectrometer at 80 eV. The ^1H NMR spectra were obtained with a Nicolet NMC 360 instrument operating at 360 MHz. The ^{13}C NMR measurements were performed with a Nicolet NMC 360 instrument operating at 90.8 MHz. Tetramethylsilane (TMS) was used as the internal standard, and chemical shifts are reported as δ values (ppm).

Homonuclear COSY spectra were recorded at 1 K with a Varian XL-300 spectrometer. Standard Varian pulse sequences were used. The one-dimensional heteronuclear ^1H–^{13}C shift correlation (CSCM 1D) and selective INEPT experiments were performed on a Nicolet NMC 360 spectrometer. Data sets of 16K covering a spectral width of 10 000 Hz were acquired. Proton pulse widths were calibrated by using a sample of acetic acid in 10% $C6D_6$ (^1J = 6.7 Hz) in a 5-mm NMR tube. The radio frequency field strength for the soft proton pulse was on the order of 25 Hz in these experiments. For 1-Hα, 2-Hα, and 3-H protons, 4 Hz was used as the ^3J value and 6 Hz was used for the irradiation 11-H and 12-H. Twenty thousand acquisitions were accumulated in each irradiation.

Plant Material. The plant material of *S. prionitis* Hance was collected in the Jiang-Xi Province of China in June 1986 and identified by Dr. X.-L. Huang. A voucher sample is deposited in the herbarium of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, People's Republic of China.

Isolation of Prionitin (1). Dried and powdered roots of *S. prionitis* (11 kg) were extracted with EtOH (140 L), and the combined extracts were evaporated in vacuo. The residue was distributed between $CHCl_3$ (10 L) and H_2O (10 L), and the organic layer was washed with H_2O (2 × 2 L), dried, and evaporated to a residue (520 g), which was subjected to column chromatography on Si gel (3 kg), eluting with $CHCl_3$. The fractions were evaporated, examined by TLC, and purified further through preparative TLC to yield prionitin (5 mg, 0.001%) having the following physical and spectroscopic properties: mp 98–100 °C; IR (KBr) ν_{max} 2975, 2955, 1645, 1575, 1470, 1370, 1300, and 1100 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 254 (4.41) and 296 (3.56) nm; ^1H NMR, see Table I; ^{13}C NMR, see Table I; mass spectrum, m/z (relative intensity) 310 (M^+, 100), 295 (7), 267 (12), 253 (8), 237 (10), 195 (4), 165 (6).

Acknowledgment. The work was supported, in part, by a grant from the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. We thank the Research Resources Center of the University of Illinois at Chicago for providing NMR and mass spectroscopic facilities.

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Synthesis of Acylpyrroles via α-(Dimethylamino)-α-pyrrolylacetonitriles[1]

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Acylpyrroles are intermediates of considerable importance and numerous methods have been devised to provide synthetic access thereto. The 2-acyl compounds are most efficaciously prepared by the direct acylation of α-unsubstituted pyrroles with acid chlorides (in the presence or absence of a Lewis acid catalyst),[3] Vilsmeier–Haack

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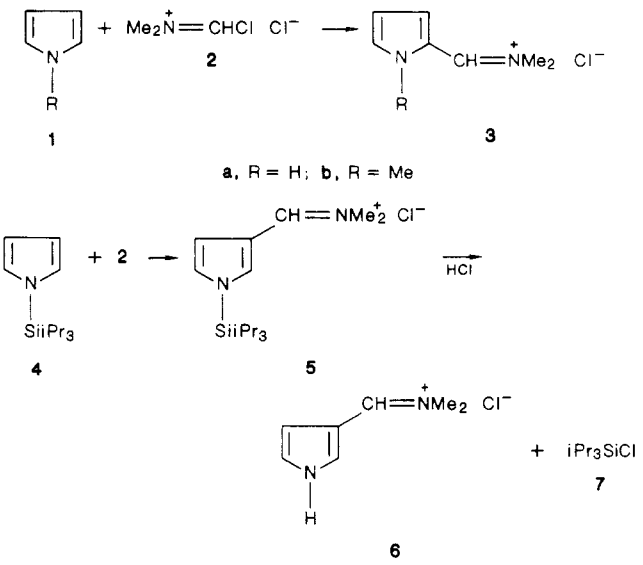
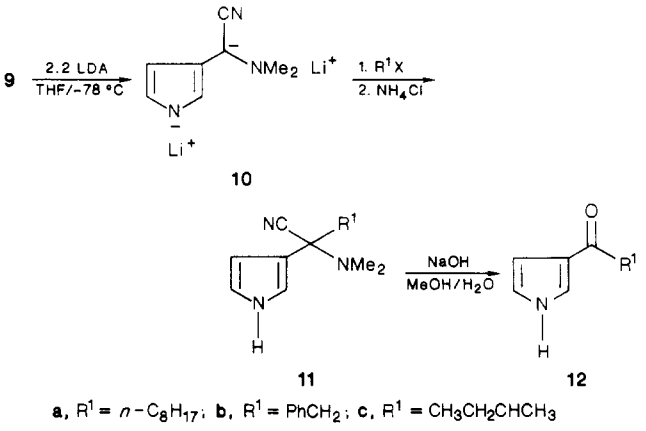
(2) Syntex Research Post-Doctoral Fellow, 1987–1988.

0022-3263/88/1953-6115$01.50/0

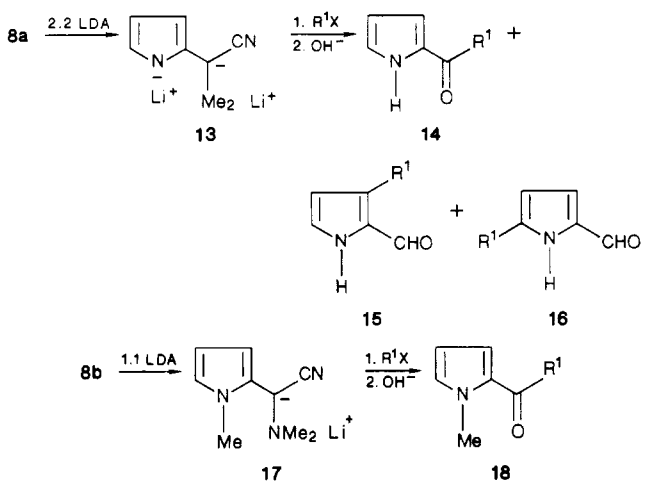
Scheme I



Scheme II



Scheme III



reagents,[3] nitrilium salts,[4] or activated esters[5,6]). The 3-acyl compounds are less easily obtained,[7] but several notably successful syntheses thereof have recently been developed based on the acylation of pyrroles bearing certain electronically perturbing[8] or sterically demanding[9,10] nitrogen substituents.

It occurred to us that α-(dialkylamino)-α-pyrrolylacetonitriles[11] would be particularly attractive precursors of alkyl pyrrolyl ketones. Such "Strecker type" nitriles[12] should, in principle, be readily available by the addition of cyanide ion to the iminium salts derived from pyrroles and dialkylformamides under Vilsmeier–Haack conditions.

The α-substituted *N,N*-dimethylformiminium chlorides **3** (Scheme I) were prepared from the corresponding pyrroles and *N,N*-dimethylchloroformiminium chloride (**2**). The ^{1}H NMR spectra (Table I, supplementary material) of these salts indicate that they exist in the anti conformation since the iminium proton is coupled to H-4 (J = 0.6–0.7 Hz) but not to H-5. This is unlike most pyrrole-2-carboxaldehydes for which the syn conformer predominates at room temperature ($J_{CHO,H5} \approx 1$ Hz) but analogous to that observed for certain 1-acylpyrrole-2-carboxaldehydes (see ref 3, pp 286–289, 474–475). It is also noteworthy that H-5 is coupled to the pyrrole *N*-methyl group in the iminium salt **3b**, which may, perhaps, be a reflection of the anti conformation of this salt. The β-substituted iminium salt **6** was prepared, in nearly quantitative yield and with excellent regioselectivity (**6**:**3a** $\geq$ 25),[13] by reaction of *N*-(triisopropylsilyl)pyrrole[9] (**4**) with the Vilsmeier–Haack reagent **2** in dichloromethane at reflux temperature. The high positional selectivity of this reaction and the absence of the silyl moiety in **6** indicate that the rate of formation of the primary product **5** must be considerably greater than the rate of hydrogen chloride induced desilylation of the starting material and probably of **5** as well.

As anticipated, the α-(dimethylamino)-α-pyrrolylacetonitriles **8** and **9** were easily synthesised, in excellent yields, by reaction of the corresponding iminium salts with a suspension of sodium cyanide in acetonitrile.[14] These compounds, isolated as low melting, chromatographically unstable solids, had weak IR C≡N stretching bands at 2232–2242 cm^{-1} and the ^{1}H NMR spectra (Table I, supplementary material) showed that the methine proton was long-range coupled (0.4–1 Hz) to the adjacent pyrrole proton (H-3 in **8** and H-2 in **9**).[15] The methine hydrogen of **8** was also coupled to H-5, which may imply the existence of two side-chain conformations in this molecule.

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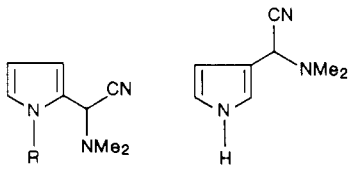
(13) This ratio was determined by alkaline hydrolysis (5 wt % NaOH in water) of the crude salt to a mixture (separated by column chromatography on silica gel), which consisted of pyrrole-3-carboxaldehyde (68.5%) and pyrrole-2-carboxaldehyde (2.7%). This β:α ratio (25.4) must be considered as the minimum in view of the high water solubility of the β-aldehyde.
(14) Compound **8a** was first synthesised by P. Hess in connection with another study.
(15) Such long-range coupling has been observed previously: Carpio, H.; Galeazzi, E.; Greenhouse, R.; Guzman, A.; Velarde, E.; Antonio, Y.; Franco, F.; Leon, A.; Perez, V.; Salas, R.; Valdes, D.; Ackrell, J.; Cho, D.; Gallegra, P.; Halpern, O.; Koehler, R.; Maddox, M. L.; Muchowski, J. M.; Prince, A.; Tegg, D.; Thurber, T. C.; Van Horn, A. R.; Wren, D. *Can. J. Chem.* **1982**, *60*, 2295 and references therein.



8a, R = H
b, R = Me

9

The alkylation of the β-substituted α-dimethylamino nitrile **9** was examined first. Thus, the putative dianion **10** (Scheme II) was generated with 2.2 equiv of lithium diisopropylamide in THF solution at −78 °C and after 2 h, it was reacted with 1.1 equiv of an alkyl halide (bromide or iodide). The crude α-alkylated product **11**, isolated after a 0.5-h reaction period (−78 °C/0.25 h, 0 °C/0.25 h), was hydrolyzed with aqueous methanolic sodium hydroxide to provide the 3-acylpyrroles **12a–c**, uncontaminated by products of N-alkylation.[16] It is noteworthy that these ketones were obtained in good yields even when the alkylation of **10** was effected with the secondary alkyl iodide 2-iodobutane (see Table II, supplementary material).[17] This process, therefore, would appear to be one of the most versatile routes to 3-acylpyrroles reported to date.

Alkylation of the dianion **13** (Scheme III), generated from **8a** in the manner described above, with *n*-octyl iodide and alkaline hydrolysis of the crude product, gave pure 2-nonanoylpyrrole (**14a**) in 63% yield. When the analogous reaction sequence was effected with benzyl bromide, the ketone **14b** was accompanied by a small amount (6%) of another product, the elemental analysis and ^{1}H NMR spectrum of which (Table I, supplementary material) were fully consistent with those expected for 3-benzylpyrrole-2-carboxaldehyde (**15b**). Utilization of 2-iodobutane as the alkylating agent produced a mixture of the ketone **14c** and the aldehyde **15c** in which the aldehyde predominated by a factor of 2. In contrast, the monoanion **17**, derived from **8b**, gave the ketone **18** as the only product, irrespective of the nature of the alkylating agent.

Several additional experiments were carried out to gain more insight into the factors that control the site of alkylation of the dianion **13**. Firstly, the monoanion of **8a** was inert to alkyl halides under the conditions that effected alkylation of the dianion. Secondly, with trimethylsilyl chloride, the dianion **13** reacted mainly, if not exclusively, at the side chain (presumably on the CN nitrogen atom), as determined from the ^{1}H NMR spectrum of the crude product before hydrolysis. Thus, the site at which alkylation of **13** took place seemed to be dependent on the "hardness" or "softness" of the alkylating agent used.[18] It was therefore predicted that α-methylbenzyl bromide, a particularly soft alkylating agent, would give a product mixture in which ring alkylation would strongly predominate over side-chain alkylation. Indeed, ketone **14d** was not formed at all and the product consisted of a 1.7:1 mixture of the aldehydes **15d** and **16d**!

The objective of this study was to ascertain if α-(dimethylamino)-α-pyrrolylacetonitriles were useful precursors of alkyl pyrrolyl ketones. It is evident from the data presented herein that such "Strecker type" nitriles do, in fact, have considerable utility for this purpose. It is also obvious that the course of alkylation of the dianion **13** is most unusual and merits further investigation, e.g., with other electrophilic reagents. Such studies will be undertaken in due course.

(16) Alkylation of the pyrrole nitrogen atom is unlikely to occur under these mild conditions (see ref 3, pp 173–175).
(17) The anions of α-dialkylamino nitriles are efficiently alkylated by secondary alkyl halides (ref 12, pp 3224–3225).
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Experimental Section

The melting points were determined in a Mel-Temp apparatus and are not corrected. The infrared spectra were measured as dispersions in KBr or as solutions in $CHCl_3$ on a Nicolet 5 PC FT infrared spectrophotometer. The ^{1}H NMR spectra were recorded with a Bruker WM-300 spectrometer, and the chemical shifts are given as parts per million (δ) from internal tetramethylsilane.

THF was distilled from sodium/benzophenone and diisopropylamine was distilled from calcium hydride. Anhydrous DMF (Aldrich) was stored over activated 4A molecular sieves before use and the alkyl halides were filtered through potassium carbonate. Reactions requiring anhydrous conditions were conducted in oven (130 °C) dried glassware under a positive pressure of dry nitrogen.

***N*,*N*-Dimethylpyrrole-2-formiminium Chloride (3a).** A solution of DMF (19.2 mL, 18.0 g, 246 mmol) in dry dichloromethane (20 mL) was added to a stirred solution of oxalyl chloride (19.4 mL, 28.0 g, 222 mmol) in dichloromethane (500 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and then a solution of pyrrole (15.0 g, 222 mmol) in dichloromethane (50 mL) was added over a 15-min period. Following this, the reaction mixture was stirred at room temperature for 20 min and then the solvent volume was reduced by 50% in vacuo. Dry ether (200 mL) was added and the precipitated salt was collected by filtration under a blanket of nitrogen. The solid was washed with anhydrous acetone and dried at reduced pressure to give a ^{1}H NMR pure white powder (33.0 g, 94% yield). ^{1}H NMR (DMSO-d_6): δ 3.56, 3.67 (s, NMe_2), 6.65 (ddd, $J_{3,4}$ = 4.30, $J_{4,5}$ = 2.32, $J_{4,CH}$ = 0.61, H-4), 7.45 (dd, $J_{3,4}$ = 4.30, $J_{3,5}$ = 1.26, H-3), 7.77 (dd, $J_{3,5}$ = 1.26, $J_{4,5}$ = 2.32, H-5), 8.81 (d, $J_{4,CH}$ = 0.61, CH=N), 10.55 (NH).

***N*,*N*-Dimethylpyrrole-3-formiminium Chloride (6).** The Vilsmeier–Haack reagent **2** was prepared, as described above, from DMF (10.0 mL, 9.40 g, 129 mmol) and oxalyl chloride (10.3 mL, 15.0 g, 118 mmol) in dry dichloromethane (510 mL). A solution of *N*-(triisopropylsilyl)pyrrole (**4**, 25.0 g, 112 mmol) in dry dichloromethane (20 mL) was added rapidly to the stirred suspension of the Vilsmeier–Haack reagent at 0 °C and then the mixture was placed in an oil bath preheated to 60 °C. The solid went into solution for a moment and then a precipitate formed again. The mixture was heated at reflux temperature for 0.5 h and cooled to 0 °C, and the precipitate was collected by filtration under a blanket of nitrogen. The solid was washed several times with dry ether before exposure to air and then it was dried in vacuo. A white powder (17.0 g, 97% yield) was obtained, which was pure, as judged by its ^{1}H NMR spectrum. ^{1}H NMR (DMSO-d_6): δ 3.55, 3.66 (s, NMe_2), 6.83 (dd, $J_{2,4}$ = 1.55, $J_{4,5}$ = 3.13, H-4), 7.21 (dd, $J_{2,5}$ = 1.77, $J_{4,5}$ = 3.13, H-5), 8.02 (t, $J_{2,4}$ = 1.55, $J_{2,5}$ = 1.77, H-2), 8.91 (s, CH), 11.00 (NH).

α-(Dimethylamino)-α-(pyrrol-2-yl)acetonitrile (8a). Compound **8a** was prepared as described for **9** (below) in 94% yield. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, NMe_2), 4.84 (m, CH), 6.17 (dd, $J_{3,4}$ = 3.56, $J_{4,5}$ = 2.81, H-4), 6.37 (m, $J_{3,4}$ = 3.56, $J_{3,5}$ = 1.55, $J_{3,CH}$ = 0.42, H-3), 6.81 (m, $J_{3,5}$ = 1.55, $J_{4,5}$ = 2.81, $J_{5,CH}$ = 1.13, H-5), 8.64, (NH).

α-(Dimethylamino)-α-(pyrrol-3-yl)acetonitrile (9). This procedure was used for all of the Strecker-type nitriles except that the sodium cyanide–iminium salt ratio was 5 for **8a** and **8b**. A mixture of sodium cyanide (0.85 g, 17 mmol) and the iminium salt **6** (0.55 g, 3.5 mmol) in acetonitrile (20 mL) was stirred at room temperature for 12 h. The mixture was poured into water (100 mL) and the product was extracted into ether. The ether extract was washed with saturated sodium chloride solution, dried over potassium carbonate, decolorized with activated carbon if necessary, filtered, and evaporated in vacuo. The light colored crystalline solid (0.49 g, 94% yield) was sufficiently pure to be directly used in the next step. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, NMe_2), 4.78 (d, CH), 6.26 (dd, $J_{2,4}$ = 1.72, $J_{4,5}$ = 2.94, H-4), 6.78 (dd, $J_{2,5}$ = 2.04, $J_{4,5}$ = 2.94, H-5), 6.91 (m, $J_{2,4}$ = 1.72, $J_{2,5}$ = 2.04, $J_{2,CH}$ = 0.97, H-2), 8.38 (NH).

Alkylation of the α-(Dimethylamino)-α-pyrrolylacetonitriles. Synthesis of 3-Nonanoylpyrrole (12a). A 1.6 M

solution of *n*-butyllithium in hexane (8.12 mL, 13.0 mmol) was added to a stirred solution of diisopropylamine (1.98 mL, 1.43 g, 14.2 mmol) in dry THF (100 mL) at −78 °C. After 10 min, a solution of the amino nitrile **9** (0.88 g, 5.9 mmol) in THF (10 mL) was added and the solution was stirred at −78 °C for 2 h. At this time, 1-iodooctane (1.17 mL, 1.56 g, 6.50 mmol) was added and after 15 min at −78 °C and 15 min at 0 °C, the solution was poured into an ice/aqueous ammonium chloride mixture. The product was extracted into ether, and the extract was washed with saturated sodium chloride solution, dried over potassium carbonate, and evaporated in vacuo. The residual heavy oil was dissolved in methanol (30 mL), 10 wt % aqueous sodium hydroxide solution (30 mL) was added, and the solution was stirred at room temperature for 1 h. The solution was diluted with water (150 mL), the product was extracted into ether, and the extract was washed with saturated sodium chloride solution and then dried over magnesium sulfate. The ether solution was evaporated in vacuo and the residue (1.5 g) was purified by flash chromatography on silica gel using hexane–ethyl acetate (3:1) as the eluting solvent. The pure ketone **12a** was obtained as a crystalline solid (1.01 g, 83% yield). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, CH_3), 1.29 (m, $(CH_2)_5$), 1.71 (m, CH_2CH_3), 2.76 (t, CH_2CO), 6.65 (dd, $J_{2,4}$ = 1.51, $J_{4,5}$ = 2.93, H-4), 6.78 (dd, $J_{2,5}$ = 1.92, $J_{4,5}$ = 2.93, H-5), 7.43 (t, $J_{2,4}$ = 1.51, $J_{2,5}$ = 1.92, H-2), 9.38 (NH).

Compounds **12b** and **12c** were prepared as described above except that the crude product was purified by crystallization.

The alkylation of **8a** with benzyl chloride or 2-iodobutane was effected as described for the synthesis of **12a** but the product mixtures were separated by column chromatography on activity II neutral alumina using 4:1 and 5:1 hexane–ethyl acetate mixtures for the benzyl bromide and 2-iodobutane reactions, respectively. The alkylation of **8a** with α-methylbenzyl bromide was carried out in the same way as when benzyl bromide was used except that the reaction was maintained at −78 °C for 0.5 h and 0 °C for 0.5 h after the addition of the alkyl halide. The product mixture (**15d** and **16d**) was separated by flash chromatography on silica gel using hexane–ethyl acetate (4:1) as the eluting solvent.

Alkylation of α-(Dimethylamino)-α-(1-methylpyrrol-2-yl)acetonitrile. Synthesis of *N*-Methyl-2-(2-methylbutyroyl)pyrrole (18c). The synthesis of this compound exemplifies the general procedure. The synthesis of the monoanion of **6** was effected in the usual way by using LDA, generated with 1.6 M *n*-butyllithium in hexane (4.20 mL, 6.75 mmol) and diisopropylamine (1.03 mL, 0.74, g, 7.36 mmol) in THF (100 mL). After being stirred at −78 °C for 10 min, the amino nitrile **8b** (1.00 g, 6.13 mmol) was added, stirring was continued for 1 h at the same temperature, and then 2-iodobutane (1.24 g, 6.75 mmol) in THF (10 mL) was added. The reaction mixture was agitated magnetically for 15 min at −78 °C and 15 min at 0 °C and thereafter it was worked up as described above for the synthesis of **12a**. The crude product was purified by column chromatography on activity II neutral alumina by using hexane–ethyl acetate (6:1) as the eluting solvent. The product (0.67 g, 67% yield) was obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, CH_3), 1.34 (m, $(CH_2)_5$), 1.69 (m, CH_2CH_3), 2.75 (t, CH_2CO), 3.93 (s, NMe), 6.11 (dd, $J_{3,4}$ = 4.08, $J_{4,5}$ = 2.48, H-4), 6.78 (m, $J_{3,5}$ = 1.69, $J_{4,5}$ = 2.68, H-5), 6.94 (dd, $J_{3,4}$ = 4.08, $J_{3,5}$ = 1.69, H-3).

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Registry No. **1a**, 109-97-7; **1b**, 96-54-8; **2**, 3724-43-4; **3a**, 75866-92-1; **3b**, 117068-08-3; **4**, 87630-35-1; **6**, 117067-97-7; **8a**, 117067-98-8; **8b**, 117068-07-2; **9**, 117067-99-9; **12a**, 117068-00-5; **12b**, 96999-24-5; **12c**, 117068-01-6; **14a**, 89631-85-6; **14b**, 13169-74-9; **14c**, 117068-03-8; **15b**, 117068-02-7; **15c**, 117068-04-9; **15d**, 117068-05-0; **16d**, 117068-06-1; **18a**, 117068-09-4; **18c**, 115045-72-2; DMF, 68-12-2; 1-iodooctane, 629-27-6; benzyl chloride, 100-44-7; 2-iodobutane, 513-48-4.

Supplementary Material Available: Table I containing the ^{1}H NMR spectra of the pyrrole derivatives (3 pages). Ordering information is given on any current masthead page.

Synthesis of a Novel Tetrahydrothieno[2,3-*b*]pyrrole[1]

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Esters of 1-[4′-(carboxy)phenyl]-3-pyrrolidinone (**1**)[2] have proven to be versatile intermediates for the preparation of a number of different types of fused heterocycles.[3,4] Although **1a** condenses normally under Knoevenagel conditions with cyanoacetamide (**2**) to give **4**,[5] an attempt to utilize cyanothioacetamide (**3**) as the active methylene partner with **1a** under the normal condensation conditions (reflux in benzene with added β-alanine and acetic acid) did not give the anticipated Knoevenagel product analogous to **4**, but instead yielded a compound whose spectral and chemical properties showed it to be the novel tetrahydrothieno[2,3-*b*]pyrrole **5a** (Scheme I). Analogous results were obtained with the ethyl and *tert*-butyl esters of **1**, leading to the bicyclic products **5b** and **5c**, respectively.

The presence of an *o*-aminonitrile functionality in **5** was indicated by IR absorptions at 3400, 3320, 3220, and 2170 cm^{-1} and confirmed by the conversion of **5a–c** with triethyl orthoformate or diethoxymethyl acetate to ethoxymethyleneamino derivatives **6**, which were then cyclized with ammonia to the fused 4-aminopyrimidine derivatives **8**.[6] The bicyclic tetrahydrothieno[2,3-*b*]pyrrole structure present in **5** was also evident from the NMR spectra of all three derivatives; the bridgehead hydrogen at C-3a appeared as a multiplet at ca. δ 4 and the bridgehead C-6a hydrogen as a doublet at ca. δ 6.0. A homonuclear decoupling experiment on the extremely soluble (dimethylamino)methylene derivative **7a** (prepared from **5a** with dimethylformamide dimethylacetal in the usual manner) also confirmed this structural assignment; irradiation at δ 2.3 (for the H-4 proton) resulted in conversion of the C-3a multiplet at δ 4.1 to a doublet, while irradiation at δ 4.1 resulted in collapse of the H-6a doublet at δ 6.0 to a sharp singlet.

(1) Presented in part at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, Canada, August 11–16, 1985 (Abstract P5-158).

(2) (a) Taylor, E. C.; McDaniel, K. F.; Skotnicki, J. S. *J. Org. Chem.* **1984**, *49*, 2500. (b) Taylor, E. C.; Ahmed, Z.; Kempton, R. J., manuscript in preparation.

(3) For a review of the preparation and utilization of 3-pyrrolidinols (from which pyrrolidinones are readily prepared), see: Flanagan, D. M.; Joullie, M. M. *Heterocycles* **1987**, *26*, 2247.

(4) For the conversion of the pyrrolidine enamine of **1a** to a "tied-back" deaza analogue of Methotrexate, see: Taylor, E. C.; Fletcher, S. R.; Fitzjohn, S. *J. Org. Chem.* **1985**, *40*, 1010.

(5) Taylor, E. C.; Fletcher, S. R.; Kempter, P., manuscript in preparation.

(6) These properties and reactions are characteristic of the *o*-aminonitrile functionality; see: Taylor, E. C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles*; Interscience: New York, 1970.

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