after recrystallization, mp 142.0–144.0 °C (lit.[21a] mp 147 °C). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.48; H, 7.38; N, 5.42.

Ethyl 3-Benzyl-5-ethyl-4-methyl-2-pyrrolecarboxylate (25b). **25b** was prepared from the "high cut" (bp 112–155 °C/1.1 Torr) of crude diketone, consisting of ca. 60% 3-methyl-1-phenyl-2,4-hexanedione (**24b**) (10.19 g, 49.9 mmol), DEAM (12.6 g, 12 mL, 72 mmol), and acetic acid (50 mL). After 2.5 h of reflux, the mixture was cooled and diluted with H_2O. After several weeks, the resulting oil crystallized in part. The oils were leached into aqueous ethanol, and the crystals were recovered by filtration: 2.70 g (20.0% nominal), mp 77–80 °C. Recrystallized from ethanol: 1.93 g (14.3%), mp 87.5–88.5 °C.

Ethyl 5-*tert*-Butyl-3-methyl-2-pyrrolecarboxylate (30a). 5,5-Dimethyl-2,4-hexanedione (**29a**) (7.1 g, 50 mmol) in boiling glacial acetic acid (30 mL) was treated, dropwise, with redistilled DEAM (12.0 g, 11.4 mL, 68.6 mmol) over 25 min. As gas evolution was slow, reflux was maintained for 27 h. The reaction mixture was diluted with H_2O (500 mL) and extracted with CH_2Cl_2. The extracts were distilled with water, the CH_2Cl_2, unreacted diketone, and pyrrolic product (which crystallized in the condenser) being collected separately. Yield of crude product: 1.81 g. This recrystallized from aqueous ethanol as pale yellow granules, 1.33 g (12.8%), mp 69–72 °C. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.99; H, 9.08; N, 6.73.

Ethyl 5-*tert*-Butyl-3-ethyl-2-pyrrolecarboxylate (30b). 2,2-Dimethyl-3,5-heptanedione (**29b**) (8.05 g, 51.5 mmol) in boiling acetic acid (50 mL) was treated, dropwise, with DEAM (15.4 g, 14.0 mL, 98.6 mmol) over 7 min. Reflux was continued for 7 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2 and the extracts were steam-distilled. The product-rich fractions (TLC, CH_2Cl_2/SiO_2) were combined and extracted with CH_2Cl_2. The resulting oil, obtained in low yield, gradually crystallized. It was not purified further and characterized only by NMR.

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Supplementary Material Available: ^1H and ^{13}C NMR chemical shift data for all of the pyrroles and ^{13}C NMR chemical shift data for **9**, **10**, and **17** (6 pages). Ordering information is given on any current masthead page.

Mechanism of the Formation of *N,N*-Dialkyl-2-pyrrolecarboxamides from 1,3-Diketones and *N,N*-Dialkyloximinoacetoacetamides

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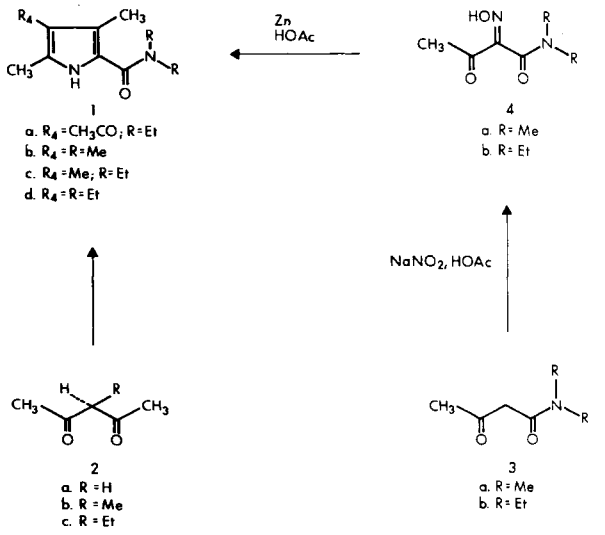
The mechanism of formation of *N,N*-dialkyl-2-pyrrolecarboxamides **1** from the reaction between *N,N*-dialkyl-2-(hydroxyimino)-3-oxoalkanamides **4** and meso-substituted β-diketones **2** upon treatment with zinc in acetic acid differs from the analogous reaction between 2-(hydroxyimino)-3-oxoalkanoate esters and **2**. The 3-substituent of **1** is found to be derived *exclusively* from **4**, not **2**. Parallel behavior was observed in the regioselectivity of reaction of 2-acylcycloalkanones **19** with **4** or with diethyl aminomalonate (**14b**). The strong preference of 2-acylcyclopentanones **19c,d** for initial reaction at the exocyclic carbonyl led to the formation of pyrrole-3-butanoic acids **22c,d** by ring-opening, in good yield. 2-Acylcyclohexanones **19a,b**, by contrast, gave good yields of a tetrahydroindole (**26**).

Some time ago, we[2] reported the Knorr-style synthesis of *N,N*-dialkyl-2-pyrrolecarboxamides **1a–c** from 1,3-diketones **2a,b** and *N,N*-dialkylacetoacetamides **3a,b**. Nitrosation of **3** afforded *N,N*-dialkyloximinoacetoacetamides **4a,b**, which were then reduced with zinc and acetic acid in the presence of **2** to give the pyrroles (Scheme I). The yields (ca. 45%) of pyrrolic products were entirely comparable to those obtained by Johnson et al.[3] from acetoacetate esters under similar conditions, and since the terminal substituents of both **2** and **3** were all methyl groups, there was no reason to suspect that the cyclization path might differ from that known[3,4] to be followed by the analogous esters.

That some significant chemistry lurked beneath the surface was only revealed when an attempt was made to prepare 3-ethyl-*N,N*,4,5-tetramethyl-2-pyrrolecarboxamide (**5a**) from 3-methyl-2,4-hexanedione (**6**) and **4a** (Scheme II). The product, isolated in 19% yield, consisted of

Scheme I



N,N,3,4,5-pentamethyl-2-pyrrolecarboxamide (**1b**), slightly contaminated by 5-ethyl-*N,N*,3,4-tetramethyl-2-pyrrolecarboxamide (**7a**). None of the anticipated **5a** was observed. A later attempt, with **6** and *N,N*-diethyl-

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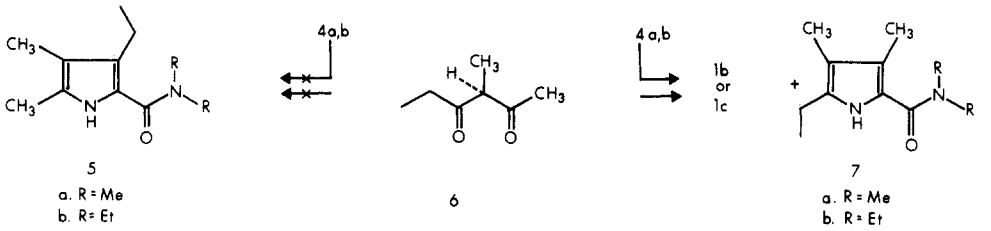
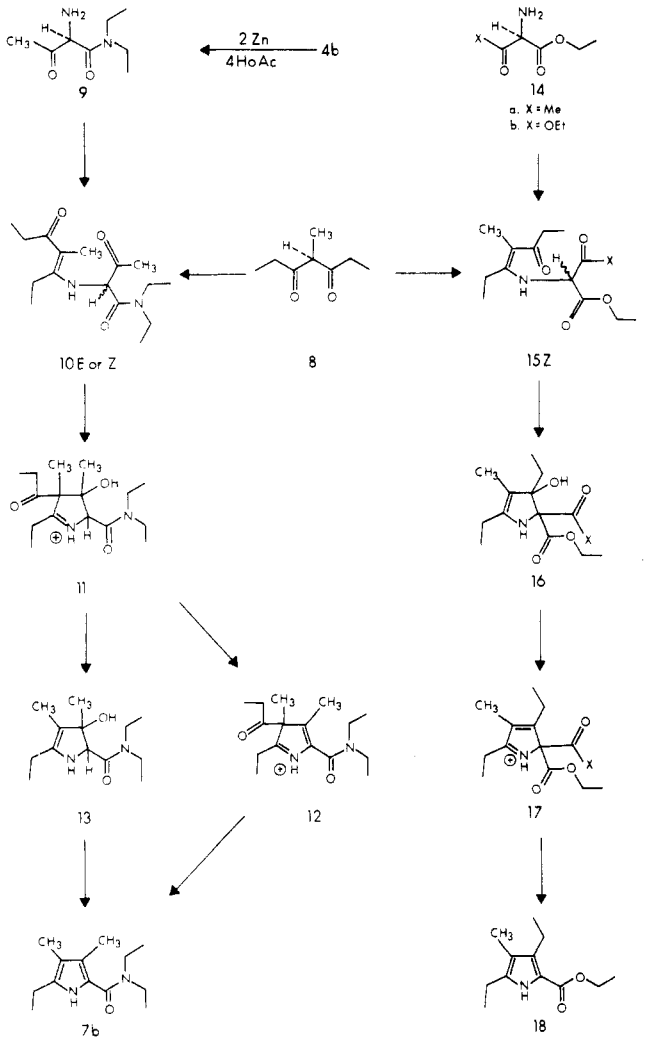
0022-3263/87/1952-3993$01.50/0

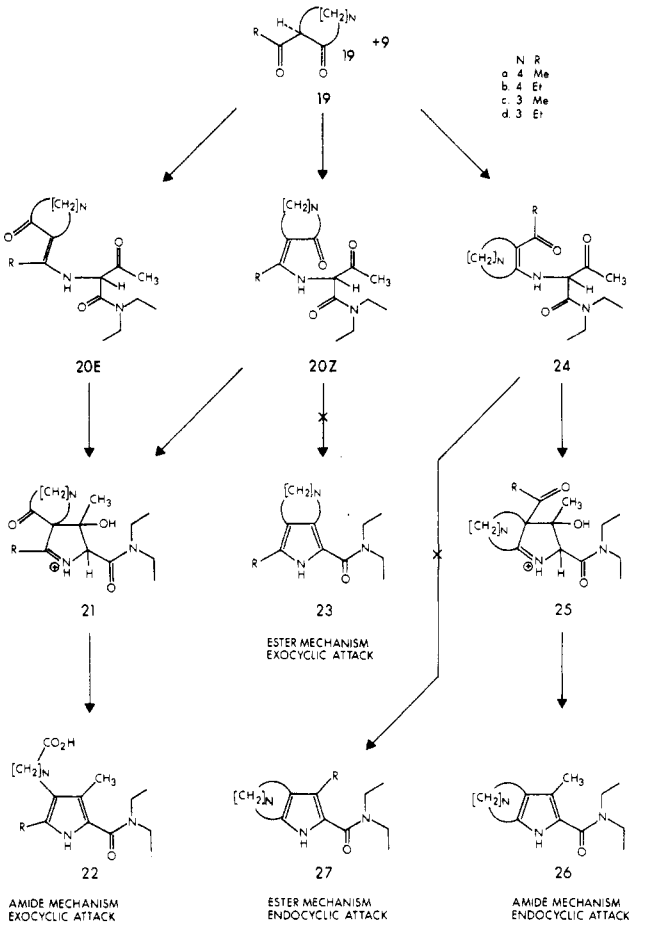
Scheme II



Scheme III



Scheme IV



oximinoacetoacetamide (**4b**), had a similar product distribution (**1c**, **7b**), but in 46% yield. Virtually all of the propionyl substituent from the diketone had "vanished"!

It appeared that an alternative mode of cyclization, shown by Harbuck and Rapoport[4] via isotopic labeling to have occurred to a slight (ca. 1%) extent in the ester systems, had with amides become the sole mode of reaction. Scheme III depicts the two mechanistic paths as they would operate on the symmetrical diketone, 4-methyl-3,5-heptanedione[5] (**8**). Evidently, the less electronegative amide function of **10** is unable to activate the adjacent methine proton sufficiently, to leave under the mildly acidic reaction conditions, and allow the "ester" mechanism to proceed. This leaves the way clear for the alternative pathway (hereafter called the "amide" mechanism) to occur, involving the acidity of the enaminone moiety. The "amide" mechanism is also that followed by esters in their reaction with meso-*un*substituted 1,3-diketones such as 2,4-pentanedione (**2a**), in the traditional Knorr reaction. Here, however, formation of the aromatic 1*H*-pyrrole system is temporarily blocked by the presence of two substituents at C-4. Whether the necessary deacylation step precedes or follows the dehydration step is not known, and likely to be difficult to establish. In any case, the deacylation, whether of **11** or **12**, seems to be comparable in facility to the corresponding deacylation observed with the 2*H*-pyrrole esters such as **17a**.

The "amide" mechanism readily explains the observed results. The amine function of **9** reacts preferentially as the less-hindered acetyl carbonyl of **6**, giving **1c** after loss of the propionyl group as propionic acid. The 5-ethylpyrrole byproduct, **7b**, results from an initial condensation of the amine function of **9** with the more hindered propionyl carbonyl.

Given that relatively subtle variations in the structure of 1,3-dicarbonylic compounds have had enormous consequences for product distribution of pyrroles in other systems,[5,6] we decided to examine whether the "amide" mechanism still operated with several 2-acylcycloalkanones

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19. Some of the consequences of this mechanism upon substrates of this connectivity can be seen in Scheme IV.

If the amine group of **9** condenses initially with the *exocyclic* carbonyl of **19**, an enaminone (**20**) results that can in principle adopt either the *E* or the *Z* configuration about the olefinic bond. Either of these should be capable of reacting through the amide mechanism to give one or more isomers of the intermediate spiroketone (**21**), whose deacylation will leave the departing carboxylic acid function still appended to the pyrrole. Base extraction would then allow the resulting terminal (carboxyalkyl)pyrrole **22** to be isolated in high recovery and purity.

Enaminone **20** is only able to react via the ester mechanism if in the *Z* configuration. The resulting product (**23**) would be fused at C-3 and C-4 (or "northside").

Initial condensation at the *endocyclic* carbonyl of **19** leads to an enaminone (**24**) that is necessarily constrained by the ring to exist in the *Z* configuration, essential for possible reaction via the ester mechanism, but a matter of indifference for possible reaction via the amide pathway. In both cases, ring-fusion at C-4 and C-5 ("westside") results. The identity of the substituent at C-3 would reveal the pathway followed, that part of **27** being derived from diketone **19**, whereas that of **26** being derived from the keto amide.

2-Acetylcyclohexanone (**19a**) showed a considerable preference for initial *endocyclic* condensation, a neutral product being isolated in at least 36% yield by crystallization. Since this was identical in all respects with the product obtained similarly from 2-propionylcyclohexanone (**19b**), the amide mechanism was proved to have operated in this system, and the product was necessarily the westside-fused tetrahydroindole (**26**). Isolated as an oil in 2.4% yield was an acidic byproduct whose NMR chemical shift data were entirely consistent with a structural assignment as *N,N*-diethyl-4-(4-carboxybutyl)-3,5-dimethyl-2-pyrrolecarboxamide (**22a**). 2-Propionylcyclohexanone (**19b**) led to a similar byproduct, **22b**, also as an oil, but in a yield of only 0.6%, reflecting the discouraging influence of increased steric hindrance about the exocyclic carbonyl upon initial condensation at that site. The isolation of this 5-ethyl-2-pyrrolecarboxamide allowed us to assign unambiguously the carbon-13 NMR chemical shifts among 2-pyrrolecarboxamides generally.

Since the strong preference of 2-acylcyclohexanones **19a,b** for initial endocyclic condensation with **9** had also been observed[6] in the reactions of **19a** or **19b** with diethyl aminomalonate (DEAM) (**14b**), we had reason to expect parallel behavior of the two amines **14b** and **9** in their reaction with 2-acylcyclopentanones **19c,d**. With DEAM, the 2-acylcyclopentanones had strong preference for reaction at the exocyclic carbonyl, but the ultimate yield of pyrrolic products had been low, only around 15% to 20%, compared with at least 80% yields obtained from 2-acylcyclohexanones. Although the increased strain of fusing a five-membered ring onto the aromatic pyrrole system undoubtedly slowed the formation of pyrrolic product from DEAM and **19c** or **19d**, the behavior of the reaction suggested that much of the enaminone (such as **15b**) formed in this system might have been of the uncyclizable *E* configuration, which might have been prevented from isomerizing to the *Z* configuration required for pyrrole formation by the general reluctance of five-membered rings to rehybridize from sp^2 to sp^3 geometry.[7]

By contrast with the reaction with DEAM, the enaminone (**20c,d**) to be expected from the exocyclic condensation of **19c,d** with **9** should be expected to give a spiroketone (**21c,d**) with much less strain than would be required for a ring-fusion, independently of the configuration about the olefinic bond of **20c,d**. High yields of pyrroles were anticipated, despite the increased lability of **9** compared to DEAM. This proved to be the case: the 4-(3-carboxypropyl)pyrroles **22c,d** were obtained in yields of 48% and 15%, respectively, from 2-acetyl- (**19c**) and 2-propionylcyclopentanone (**19d**). The lower yield of **22d**, relative to **22c**, again reflected the increased steric hindrance about the exocyclic carbonyl, and the limited lifetime of aminoacetoacetamide **9** under the reaction conditions. No neutral bicyclic product was isolated or detected by thin-layer chromatography.

As an illustration of the utility of the amide pathway for regioselective pyrrole synthesis from *acyclic* 1,3-diketones, **9** was reacted with the symmetrical 4-methyl-3,5-heptanedione (**8**),[8] which can only give a single pyrrole via the amide pathway. This (**7b**) was obtained, but in only 6% to 10% yield, due to steric hindrance. Most of the starting diketone **8** could be recovered unchanged by steam-distillation from the crude reaction product and isolated by chelation with copper(II). By contrast, when reacted with a longer lived amine such as DEAM, **8** gave a pyrrolic product (**18**) in yields approaching 70%.[5] As can be seen from Scheme III, **7b** is a derivative of 2-ethyl-3,4-dimethylpyrrole, a substitution pattern unavailable directly by "classical" ring-synthesis in any quantity. [3-Methyl-2,4-hexanedione (**6**) reacts with DEAM to afford almost exclusively the 3-ethyl-4,5-dimethyl-2-pyrrolecarboxylate ester.[5]]

This mechanistic pathway could be further exploited by use of *other* 3-oxo amides,[9] which might become available from acyl derivatives of Meldrum's acid,[10] or by alkylation of *N,N*-dialkylacetoacetamide *dianions*.[11] Since the yields with respect to the keto amide are often low, this synthesis will probably remain most useful in those cases where the commercially available acetoacetamides can be used directly. Otherwise, the traditional conversion[12] of 2-pyrrolecarboxylate esters to the corresponding amides would seem to be the most efficient route to such materials.

Experimental Section

N,N-Diethylacetoacetamide (**3b**) was obtained from Fluka AG. The β-diketones were prepared by standard boron trifluoride (Matheson) induced acylation of the appropriate ketone by acetic or propionic anhydride. Workup was modified[5] by using a stock solution of potassium acetate (prepared from KOH and acetic acid), instead of the sodium salt, to hydrolyze the BF_2 complexes, in order to avoid the separation of poorly soluble NaF. Melting points (Thomas-Hoover oil immersion apparatus) are uncorrected. NMR data were recorded with a JEOL FX 90Q spectrometer (5-mm sample tubes), in $CDCl_3$. Microanalyses were performed by Peter Borda of the University of British Columbia.

***N,N*-Diethyloximinoacetoacetamide (4b).**[13] A solution of $NaNO_2$ (35 g, 0.51 mol) in H_2O (70 mL) was added dropwise (hood!) to an ice-cooled, magnetically stirred solution of *N,N*-diethylacetoacetamide (**3b**) (78.6 g, 0.5 mol) in glacial acetic acid (100 mL), over ca. 30 min. Upon standing, the product crystallized.

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Water (100 mL) was added, and the solids were recovered by filtration, washed with H_2O, and dried. (The filtrates were discarded.) Yield: 65.3 g (70%), mp 116–118 °C. The dense white chunks proved indefinitely stable on storage at room temperature. A sample was recrystallized from aqueous ethanol for analysis, mp 116–120.5 °C, with partial recrystallization at 118.5 °C (lit.[13] mp 119 °C). Anal. Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.71; H, 7.50; N, 15.04. ^{1}H NMR ($CDCl_3$): δ 1.12* (3 H, t, J = 7 Hz), 1.22# (3 H, t, J = 7 Hz), 2.39 (3 H, s), 3.13* (2 H, q, J = 7 Hz), 3.52# (2 H, q, J = 7 Hz), 12.32 (1 H, br s). ^{13}C NMR ($CDCl_3$ at 77.25): δ 195.14 (3), 164.04 (1), 152.34 (2), 42.85* and 39.22# (NCH_2CH_3), 25.46 (4), 13.76 and 12.59 (NCH_2CH_3) (assignments tentative) [#, * on same ethyl group (selective decoupling)]. The nonequivalence of the ethyl groups and simplicity of the ^{13}C NMR spectrum suggest that this material consists of a single geometric isomer of fairly rigid constitution.

***N*,*N*-Diethyloximinoacetoacetamide (4b) stock solution**[2] was prepared as for the crystals from *N*,*N*-diethylacetoacetamide (**3b**) (235.7 g, 1.5 mol), acetic acid (400 mL), $NaNO_2$ (105.5 g, 1.53 mol), and H_2O (255 mL). Final total volume: 900 mL. This solution was supersaturated and began crystallizing after several days. It was employed as such for the first two preparations given herein.

Reaction of 3-Methyl-2,4-hexanedione (6) with *N*,*N*-Diethyloximinoacetoacetamide (4b) To Give 1c and 7b. An aliquot (90 mL, 0.15 mol) of **4b** as the crude nitrosation solution (supersaturated) and zinc dust (25.7 g) were added in portions over 15 min to a magnetically stirred solution of 3-methyl-2,4-hexanedione (**5**) (12.8 g, 0.1 mol) in glacial acetic acid (62.5 mL). The hot solution was kept for 15 min atop a steambath and then filtered to remove unreacted Zn, which was rinsed with ethanol and then H_2O. Upon dilution to 1 L with H_2O, the filtrates deposited oils which soon solidified. The solids were filtered off, washed with H_2O, and recrystallized from aqueous ethanol, after adding the oils resulting from the extraction of the aqueous filtrates with petroleum ether (bp 30–60 °C). The product formed broad white flakes, 9.75 g (46.4%), mp 109–114.5 °C (after prior sintering, above ca. 100 °C) (lit.[2] mp 116.5–118.0 °C). ^{1}H NMR ($CDCl_3$): δ 1.14 (6 H, t, J = 7 Hz, NEt), 1.88 (3 H, s, 4-Me), 2.00 (3 H, s, 3-Me), 2.12 (3 H, s, 5-Me), 3.53 (4 H, q, J = 7 Hz, NEt), 9.73 (1 H, br, NH), impurity 2.52 (q, J = 7 Hz, weak). ^{13}C NMR ($CDCl_3$ at 77.36): δ 166.04 (CON), 126.99 (5), 120.65 (2), 119.13 (3), 114.36 (4), 41.12 (2C: NCH_2CH_3), 13.60 (2C: NCH_2CH_3), 10.94 (2C: 3,5-CH_3), 8.83 (4-CH_3). Minor impurity peaks were noted at δ 133.00, 113.55, 19.23, 13.81; compare **7b**. An authentic sample of *N*,*N*-diethyl-3,4,5-trimethylpyrrole-2-carboxamide (**1c**) had afforded the following ^{13}C NMR data: ($CDCl_3$ at 77.38) δ 166.08, 127.09, 120.61, 119.11, 114.38, 41.06, 13.59, 10.95, 8.85, with similar degeneracies. The impurity content was estimated to be between 5% and 10% on the basis of NMR peak intensities.

***N*,*N*,4-Triethyl-3,5-dimethyl-2-pyrrolecarboxamide (1d).** *N*,*N*-Diethyloximinoacetoacetamide (**4b**) (0.15 mol of crude nitrosation solution, or slurry) and zinc dust (25 g) were added in portions over 14 min to a magnetically stirred solution of 3-ethyl-2,4-pentanedione (**2c**) (12.85 g, 0.1 mol) in glacial acetic acid (60 mL). The mixture was heated on a steambath for 25 min and then filtered, the zinc residue being washed with ethanol and then H_2O. The filtrates were diluted to 1 L with H_2O and extracted with petroleum ether (bp 30–60 °C) (2 × 100 mL). The extracts were evaporated, and the residue was crystallized from ethanol (10 mL)–H_2O (7 mL). After seeding, the mixture was left overnight in a freezer to crystallize. The white solids were rinsed with 50% (v/v) ethanol and then H_2O and dried. Yield: 7.42 g (33.3%). A sample was recrystallized for analysis, mp 77.0–78.5 °C. Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.19; H, 9.90; N, 12.50. ^{1}H NMR ($CDCl_3$): δ 1.03 (3 H, t, J = 7 Hz, 4-Et), 1.15 (6 H, t, J = 7 Hz, NEt), 2.03 (3 H, s, 3-Me), 2.12 (3 H, s, 5-Me), 2.34 (2 H, q, J = 7 Hz, 4-Et), 3.53 (4 H, q, J = 7 Hz, NEt), 9.72 (1 H, br, NH). ^{13}C NMR ($CDCl_3$ at 77.31): δ 166.10 (CON), 126.66 (5), 121.19 (4), 120.70 (2), 118.48 (3), 41.06 (2C: NCH_2CH_3), 17.50 (4-CH_3CH_2), 15.39 (4-CH_3CH_2), 13.60 (2C: NCH_2CH_3), 10.78 (2C: 3,5-CH_3). This compound was prepared to aid in the assignment of ^{13}C NMR chemical shifts.

***N*,*N*,5-Triethyl-3,4-dimethyl-2-pyrrolecarboxamide (7b).** *N*,*N*-Diethyloximinoacetoacetamide (**4b**) (9.3 g, 0.05 mol) and zinc dust (15 g) were added in portions to a magnetically stirred solution of 4-methyl-3,5-heptanedione (**8**)[5,8] (7.1 g, 0.05 mol) in glacial acetic acid (50 mL) such that the mixture boiled. When zinc acetate began to crystallize, H_2O (10 mL) was added. After being stirred for 10 min, the mixture was diluted with H_2O (400 mL) and extracted with CH_2Cl_2. The organic phase was filtered, isolated, and then steam-distilled to remove solvent and unreacted **8**. On cooling, the aqueous residue deposited crystals of **7b**, 0.65 g (6.3%), mp 89.5–92.0 °C. This was recrystallized for analysis from aqueous ethanol, mp 92.5–94.0 °C. Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 69.81; H, 9.88; N, 12.39. ^{1}H NMR ($CDCl_3$): δ 1.08 (3 H, t, J = 7 Hz, 5-Et), 1.15 (6 H, t, J = 7 Hz, NEt), 1.89 (3 H, s, 4-Me), 2.01 (3 H, s, 3-Me), 2.51 (2 H, q, J = 7 Hz, 5-Et), 3.53 (4 H, q, J = 7 Hz, NEt), 9.70 (1 H, br, NH). ^{13}C NMR ($CDCl_3$ at 77.31): δ 166.10 (CON), 132.94 (5), 120.59 (2), 119.13 (3), 113.55 (4), 41.12 (2C: NCH_2CH_3), 19.18 (5-CH_3CH_2), 13.65 (3C: 5-CH_3CH_2 and 2 NCH_2CH_3), 10.89 (3-CH_3), 8.72 (4-CH_3).

***N*,*N*-Diethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxamide (26). A.** *N*,*N*-Diethyloximinoacetoacetamide (**4b**) (9.34 g, 0.05 mol) and zinc dust (15 g) were added in portions to a magnetically stirred solution of 2-acetylcyclohexanone (**19a**) (6.99 g, 0.05 mol) in glacial acetic acid (50 mL), over 10–15 min. After 10 min of further stirring, the mixture was poured into H_2O (600 mL). Overnight, the oils crystallized. These were isolated, washed with H_2O, and dissolved in CH_2Cl_2. The solution was filtered, washed with aqueous Na_2CO_3, and evaporated to dryness. The residue was crystallized from aqueous ethanol (ca. 30 mL, 70%). The resulting sparkling snow-white granules were filtered off, rinsed with 50% aqueous ethanol, and dried. Yield: 4.24 g (36.3%), mp 121–122 °C. A sample was recrystallized for analysis from aqueous ethanol, mp 121.0–122.5 °C. Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.95; H, 9.30; N, 11.95. ^{1}H NMR ($CDCl_3$): δ 1.15 (6 H, t, J = 7 Hz, NEt), 1.66–1.82 (4 H, m, 5,6-CH_2), 1.98 (3 H, s, 3-Me), 2.34–2.48 (4 H, m, 4,7-CH_2), 3.54 (4 H, q, J = 7 Hz, NEt), 9.62 (1 H, br, NH). ^{13}C NMR ($CDCl_3$ at 77.25): δ 166.04 (CON), 129.96 (7a), 121.19, 117.72, 117.29, 41.06 (2C: NCH_2CH_3), 23.62, 23.24, 22.75, 21.34 (4C: 4,5,6,7), 13.65 (2C: NCH_2CH_3), 10.51 (3-CH_3).

B. The preceding preparation was repeated, using 2-propionylcyclohexanone (**19b**) (7.72 g, 0.05 mol) instead of the acetyl analogue. After aqueous dilution, the precipitated oils did not crystallize, so they were isolated by extraction into CH_2Cl_2. The extracts were washed with aqueous Na_2CO_3 and then steam-distilled to remove unreacted diketone (59%). The residue crystallized from aqueous ethanol. Yield: 2.52 g (21.5%), mp 120.0–122.0 °C. The ^{1}H NMR spectrum was identical with the previous preparation.

***N*,*N*-Diethyl-4-(4-carboxybutyl)-3,5-dimethyl-2-pyrrolecarboxamide (22a).** The aqueous filtrates from the isolation of crude **26** (preparation A) were extracted with CH_2Cl_2. The organic phase was extracted with aqueous Na_2CO_3; the aqueous phase was combined with the alkaline washings of the CH_2Cl_2 solution of **26** and acidified with 6 N HCl. The precipitated oil was extracted into CH_2Cl_2 and recovered by evaporation of the solvent. Yield: 0.35 g (2.4%). This was characterized only by NMR. ^{1}H NMR ($CDCl_3$): δ 1.16 (6 H, t, J = 7 Hz, NEt), 1.46–1.67 (4 H, m, chain: 2′,3′), 2.00 (3 H, s, 3-Me), 2.13 (3 H, s, 5-Me), 2.35 (4 H, t, J = 7 Hz, chain: 1′,4′), 3.54 (4 H, q, J = 7 Hz, NEt), 9.76 (1 H, s, NH), 10.55 (1 H, s, CO_2H). ^{13}C NMR ($CDCl_3$ at 77.20): δ 178.23 (COOH), 166.42 (CON), 127.85 (5), 120.05 (2), 119.56 (2C: 3 and 4), 41.39 (2C: NCH_2CH_3), 34.24 (4′), 30.28 (2′), 24.81 (3′), 24.00 (1′), 13.54 (2C: NCH_2CH_3), 11.16 (2C: 3,5-CH_3).

***N*,*N*,5-Triethyl-4-(4-carboxybutyl)-3-methyl-2-pyrrolecarboxamide (22b)** was isolated similarly to **22a** from the CH_2Cl_2 extracts of reaction B. The yield as an oil was 93.4 mg (0.61%). This was also only characterized by NMR. ^{1}H NMR ($CDCl_3$): δ 1.17 (9 H, split t, J = 7 Hz, 2 NEt, 5-Et), 1.56–1.67 (4 H, m, chain: 2′,3′), 2.00 (3 H, s, 3-Me), 2.34 (4 H, t, J = 7 Hz, chain: 1′,4′), 2.52 (2 H, q, J = 7.3 Hz, 5-Et), 3.53 (4 H, q, J = 7 Hz, NEt), 9.09 (1 H, br s, NH), 9.41 (1 H, s, CO_2H). ^{13}C NMR ($CDCl_3$ at 77.09): δ 177.96 (COOH), 166.32 (CON), 133.49 (5), 120.38 (2), 119.40 (3), 118.86 (4), 41.34 (2C: NCH_2CH_3), 34.18 (4′), 30.66 (2′), 24.92 (3′), 23.95 (1′), 19.18 (5-CH_3CH_2), 13.98 (5-CH_3CH_2), 13.60 (2C: NCH_2CH_3), 11.00 (3-CH_3).

***N*,*N*-Diethyl-4-(3-carboxypropyl)-3,5-dimethyl-2-pyrrolecarboxamide (22c).** *N*,*N*-Diethyloximinoacetoacetamide

(**4b**) (9.31 g, 0.05 mol) and zinc dust (15 g) were added in portions over 10–12 min to a magnetically stirred solution of 2-acetylcyclopentanone (**19c**) (6.28 g, 0.05 mol) in glacial acetic acid (50 mL) such that the solution reached reflux spontaneously. Water (10 mL) was added when zinc acetate began to separate. Stirring was maintained for 15 min; then the reaction mixture was diluted with H_2O (400 mL) and extracted with CH_2Cl_2. The product was extracted into aqueous Na_2CO_3 and back into CH_2Cl_2 after acidification with 6 N HCl. Upon evaporation of solvent, an oil was obtained that gradually crystallized solid upon standing in a warm location for several weeks. Yield: 6.72 g (48.2%). A sample was recrystallized from aqueous acetic acid for analysis, mp 98–99 °C. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.41; H, 8.70; N, 10.03. ^{1}H NMR ($CDCl_3$): δ 1.17 (6 H, t, J = 7 Hz, NEt), 1.69–1.91 (2 H, m, chain: 2′), 2.02 (3 H, s, 3-Me), 2.15 (3 H, s, 5-Me), 2.22–2.49 (4 H, m, chain: 1′,3′), 3.54 (4 H, q, J = 7 Hz, NEt), 9.85 (2 H, br s, NH, CO_2H). ^{13}C NMR ($CDCl_3$ at 77.31): δ 177.91 (COOH), 166.42 (CON), 128.01 (5), 120.16 (2), 119.56 (3), 118.80 (4), 41.39 (2C: NCH_2CH_3), 33.70 (3′), 25.84 (2′), 23.62 (1′), 13.49 (2C: NCH_2CH_3), 11.05 (2C: 3,5-CH_3).

***N*,*N*,5-Triethyl-4-(3-carboxypropyl)-3-methyl-2-pyrrolecarboxamide (22d)** was prepared similarly to **22c**, starting with 2-propionylcyclopentanone (**19d**) (6.94 g, 49.6 mmol), as an oil, 2.27 g (15.6%). Characterized only by NMR. ^{1}H NMR ($CDCl_3$): δ 1.17 (9 H, t, J = 7 Hz, 2 NEt, 5-Et), 1.67–1.94 (2 H, m, chain: 2′), 2.02 (3 H, s, 3-Me), 2.27–2.67 (6 H, m) [includes 2.34 (4 H, t, J = 7 Hz, chain: 1′,3′) and 2.54 (2 H, q, J = 7 Hz, 5-Et)], 3.54 (4 H, q, J = 7 Hz, NEt), 9.77 (1 H, s, NH), 10.19 (1 H, br s, CO_2H). ^{13}C NMR ($CDCl_3$ at 77.25): δ 177.91 (COOH), 166.42 (CON), 133.92 (5), 120.32 (2), 119.45 (3), 118.15 (4), 41.39 (2C: NCH_2CH_3), 33.80 (3′), 26.17 (2′), 23.62 (1′), 19.12 (5-CH_3CH_2), 14.03 (5-CH_3CH_2), 13.54 (2C: NCH_2CH_3), 10.94 (3-CH_3).

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Pteridines. 51. A New and Unequivocal Route to C-6 Carbon-Substituted Pterins and Pteridines[1]

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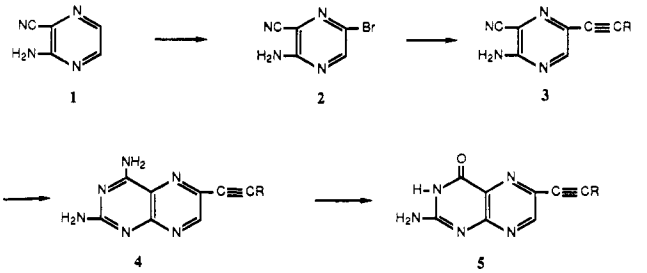
Coupling of terminal acetylenes with 2-amino-3-cyano-5-bromopyrazine in the presence of catalytic amounts of palladium(II) salts and Cu(I) gave a series of 5-ethynyl derivatives which were cyclized with guanidine to 2,4-diamino-6-ethynyl-substituted pteridines. Alkaline hydrolysis yielded 6-ethynyl-substituted pterins, which were prepared independently by analogous palladium-catalyzed coupling of the same terminal acetylenes with 2-pivaloyl-6-chloropterin, followed by alkaline removal of the 2-pivaloyl grouping.

A vast majority of biologically significant naturally occurring pterins and chemotherapeutically useful pteridine derivatives carry carbon substituents at position 6 (e.g., biopterin, folic acid, methotrexate). A major challenge in pteridine synthesis has been the unequivocal preparation of 6-substituted derivatives unaccompanied by 7-substituted isomers.[2] Several years ago we described a versatile solution to this problem which involved the preparation of 2-amino-3-cyano[and (ethoxycarbonyl)]-5-substituted pyrazines via their 1-oxides which were accessible by an unambiguous route by condensation of α-keto aldoximes with aminomalonitrile tosylate. Subsequent manipulation of these pyrazine intermediates and final annulation of the pyrimidine ring then led to 6-substituted pteridines and pterins.[3] Since its introduction, this procedure has been extensively used for the construction of a wide variety of C-6-substituted derivatives.[4] A potential drawback of this methodology, however, is the relative inaccessibility of complex α-keto aldoximes (the origin of the eventual C-6 substituents). We describe in this paper an alternative synthetic strategy which should permit the preparation of a wide diversity of pteridines carrying multifunctional carbon side chains at position 6.

Scheme I



	Yields, %		
	3	4	5
a, R = C_6H_5	75	88	87
b, R = $(CH_2)_3CH_3$	60	85	86
c, R = $C(CH_3)_3$	65	90	90
d, R = CH_2OCH_3	54	82	88

We have previously described the synthesis of 2-amino-3-cyano-5-(bromomethyl)[and (chloromethyl)]-pyrazine by condensation of aminomalonitrile tosylate with β-bromo(and β-chloro)pyruvaldoxime, followed by PCl_3 deoxygenation of the resulting 2-amino-3-cyano-5-(halomethyl)pyrazine 1-oxides.[5] Subsequent displacement of

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