(neat) 2960, 1460, 1410, 1180, 820 cm^{-1}.

3-*n*-Butyl-6,6-dichloro-1-methyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (2c): **1c**, 58, 13, 200, 4, 100/100, 100/120, 75/100, 75/100, 4, a and b, 22; oil; ^{31}P NMR ($CDCl_3$) δ +89.4; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 0.81-1.14 (m, 3 H, CH_2CH_3), 1.68 (s, CCH_3) overlapped by 1.24-3.69 (m, CH_2, CH), total int. 14 H; MS, *m/e* (relative intensity) 254 (M^+, 9), 219 (100), 115 (10), M^+ found 254.0358, $C_{10}H_{17}Cl_2OP$ requires 254.0394; IR (neat) 2930, 1460, 1410, 825 cm^{-1}.

6,6-Dichloro-3-methoxy-1-methyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (2d): **1d**, 103, 6.6, 250, 1, 75/90 7, a, 27; oil; ^{31}P NMR ($CDCl_3$) δ +88.1; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.53 (s, 3 H, CH_3), 1.59-2.83 (m, 5 H, CH_2, CH) 3.69 (d, 3 H, OCH_3, $^3J_{PH}$ = 11); MS, *m/e* (relative intensity) 228 (M^+, 29), 193 (100), 115 (58), M^+ found 227.9895, $C_7H_{11}Cl_2O_2P$ requires 227.9874; IR (neat) 2940, 1460, 1410, 1250, 1035, 895 cm^{-1}.

4,5-Dichloro-3,6-dimethyl-1-phenylphosphacycloheptа-2,4,6-triene 1-oxide (7a): **3a**, 39, 13.8, 200, 2, 115/115, 100/120, 4.5, a and c, 2; mp 141-142 °C; ^{31}P NMR ($CDCl_3$) δ +9.2; ^{13}C NMR, Table II; ^1H NMR ($CDCl_3$) δ 2.35 (s, 6 H, CH_3), 6.27 (d, 2 H, HC=, $^2J_{PH}$ = 11), 7.41-7.97 (m, 5 H, Ar), MS, *m/e* (relative intensity) 298 (M^+, 12), 174 (100), 139 (46), M^+ found 298.0044, $C_{14}H_{13}Cl_2OP$ requires 298.0081; IR (KBr disc) 2970, 1605, 1430, 1180, 840, 690 cm^{-1}.

Dichlorocarbene addition to 3d: **3d**, 6.3, 0.22, 20, 2, 5/5, 5/6, 4. A sample taken after the reaction with the second portion of sodium hydroxide solution was analyzed by ^{31}P NMR measurement, according to which product composition was 43% **4d**, 19% **8**, 24% **5d**, 7% **9**, and 7% **7d**. The changes on standing in the composition of the sample were also monitored. After 27 days standing at room temperature following the completion of the reaction, the mixture consisted of 42% **5d**, 52% **9**, and 6% **7d**.

4-Chloro-1,2-dihydro-1-hydroxy-3,5-dimethylphosphorin 1-Oxide (9), 4-Chloro-1,2-dihydro-1-methoxy-3,5-dimethylphosphorin 1-Oxide (5d), and 4,5-Dichloro-1-methoxy-3,6-dimethylphosphacycloheptа-2,4,6-triene 1-Oxide (7d). The previous reaction was run on a 10-fold scale. The crude product obtained after evaporating the solvent was allowed to stand for several weeks. Then the precipitated material was filtered, washed with ethyl acetate-*n*-hexane (1:1), and purified by column chromatography using silica gel and methanol as eluent to give **9**: 0.32 g, 3%; mp 145-146 °C (from ethyl acetate); ^{31}P NMR ($CDCl_3$) δ +32.5; ^{13}C NMR, Table II; ^1H NMR ($CDCl_3$) δ 2.10 (s, CH_3) partly overlapped by 2.17 (s, CH_3), total int. 6 H, 2.79 (d, 2 H, CH_2, $^2J_{PH}$ = 20), 6.02 (d, 1 H, HC=, $^2J_{PH}$ = 8), 10.5 (br s, 1 H, OH); MS, *m/e* (relative intensity) 192 (M^+, 98), 157 (8), 128 (13), 93 (100), M^+ found 192.0137, $C_7H_{10}ClO_2P$ requires 192.0108; IR (KBr disk) 2920, 2580, 1605, 1430, 1375, 1205 cm^{-1}.

The components of the filtrate obtained after removing the crude **9** were separated by repeated column chromatography on silica gel using benzene-acetone (4:6), chloroform-methanol (97:3), and acetone successively to give **5d** (1.45 g, 11%) and **7d** (0.15 g, 1%) as oils.

5d: ^{31}P NMR ($CDCl_3$) δ +32.8; ^{13}C NMR, Table II; ^1H NMR ($CDCl_3$) δ 2.13 (s, CCH_3) partly overlapped by 2.20 (s, CCH_3), total int. 6 H, 2.78 (d, 2 H, CH_2, $^2J_{PH}$ = 20), 3.72 (d, 3 H, OCH_3, $^3J_{PH}$ = 11), 6.03 (d, 1 H, HC=, $^2J_{PH}$ = 8); MS, *m/e* (relative intensity) 206 (M^+, 100), 171 (6), 128 (13), 93 (98), M^+ found 206.0291, $C_8H_{12}ClO_2P$ requires 206.0264; IR (neat) 2930, 1620, 1570, 1440, 1380, 1220, 1035 cm^{-1}.

7d: ^{31}P NMR ($CDCl_3$) δ +20.9; ^{13}C NMR, Table II; ^1H NMR ($CDCl_3$) δ 2.33 (s, 6 H, CH_3), 3.65 (d, 3 H, OCH_3, $^3J_{PH}$ = 12), 5.99 (d, 2 H, HC=, $^3J_{PH}$ = 11); MS, *m/e* (relative intensity) 252 (M^+, 16), 174 (100), 139 (35), M^+ found 251.9861, $C_9H_{11}Cl_2O_2P$ requires 251.9874; IR (neat) 2960, 1620, 1440, 1380, 1220, 1030, 850 cm^{-1}.

Acknowledgment. We thank the Hungarian Academy of Sciences for support.

Registry No. **1a**, 7564-51-4; **1b**, 62891-11-6; **1c**, 62891-09-2; **1d**, 695-59-0; **1d** (Y = Cl), 18874-22-1; **2a**, 109011-51-0; **2b**, 109011-52-1; **2c**, 109011-53-2; **2d**, 109011-54-3; **3a**, 710-89-4; **3d**, 697-29-0; **3** (Y = Cl), 873-16-5; **4d**, 109011-59-8; **5d**, 109011-56-5; **7a**, 109011-58-7; **7d**, 109011-57-6; **8**, 109011-60-1; **9**, 109011-55-4.

Regioselectivity of Pyrrole Synthesis from Diethyl Aminomalonate and 1,3-Diketones: Further Observations

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1,3-Diketones **1** react with diethyl aminomalonate (**2**) in boiling acetic acid to afford ethyl 2-pyrrolecarboxylates **6**. Considerable regioselectivity was noted for the following classes of diketone: 2-acylcyclohexanones **10a,b** [to give the 4,5,6,7-tetrahydroindoles **11a,b**], 2-acylcyclopentanones **10c,d** [to give the novel 2,4,5,6-tetrahydrocyclopenta[*c*]pyrroles **13a,b**], 1-phenyl-2-alkyl-1,3-alkanediones **17a-d** [to give the 3-phenylpyrroles **19a-d**], 3-phenyl-2,4-hexanedione (**21a**) [to give the 3-ethylpyrrole **23a**], 1-phenyl-3-alkyl-2,4-alkanediones **24a,b** [to give the 3-benzylpyrroles **25a,b**], and 2,2-dimethyl-3,5-alkanediones **29a,b** [to give the 5-*tert*-butylpyrroles **30a,b**]. The yields varied with the structural class, decreasing with increased steric hindrance. The product structure correlated with the structure of the enolized diketones in the case of the 2-acylcycloalkanones studied.

Introduction

Recently, we[2] reported *greatly* improved yields for the conversion of acyclic aliphatic 1,3-diketones **1** to ethyl alkyl-2-pyrrolecarboxylates **6** employing *preformed* diethyl aminomalonate (DEAM) (**2**) in boiling glacial acetic acid (Scheme I), instead of DEAM produced in situ by the Knorr-style dissolving-zinc reduction of diethyl oximinomalonate (**3**). These earlier conditions, discovered by Kleinspehn,[3] have been widely applied in pyrrole chemistry[4] but are not conducive to the survival of sensitive classes of dicarbonylic substrates or to the reaction of recalcitrant ones. Such substrates can be treated with a full equivalent of DEAM *all at once* and under a much

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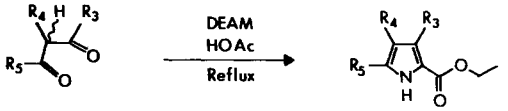
Table I. ^{13}C NMR Chemical Shifts Used in Structural Assignments of 30[a]

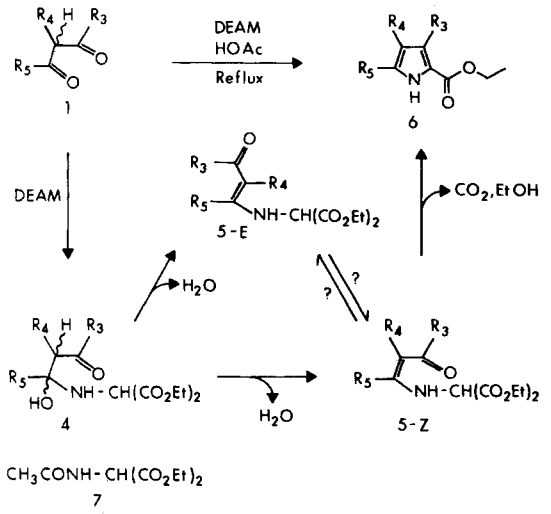


8a–d; 29a,b 9a–d; 30a,b

	R_5	R_3	C-2	C-3	C-4	C-5	R_5	R_3
9a	Et	Me	117.77	128.81	109.75	139.28	13.48, 20.94	12.98
9b	Me	Et	117.10	135.98	109.55	133.01	12.99	15.03, 20.48
9c	Me	Me	117.93	128.97	111.34	133.00	12.90*	12.90*
9d	Et	Et	117.00	135.68	107.89	139.62	13.55, 21.06	15.07, 20.65
30a	*t*-Bu	Me	117.83	128.29	108.13	146.49	30.12*, 31.64	13.06
30b	*t*-Bu	Et	117.18	135.11	106.24	146.70	30.18*, 31.75	15.01, 20.69

[a] Coincident or degenerate peaks are marked with an asterisk. R_4 = H for all compounds.

Scheme I. Pyrroles from 1,3-Diketones 1 and Diethyl Aminomalonate 2. Presumed Mechanism



wider range of conditions than afforded by zinc in acetic acid. The use of DEAM also allows a stepwise approach to the pyrrole, via the isolable intermediary enaminone **5**, as with the original synthesis of pyrrolnitrin.[5]

The substrates considered here, however, have proved to be quite stable to boiling glacial acetic acid, which we therefore continued to use exclusively as a one-pot one-step cyclization medium. DEAM, however, has only a limited lifetime under the reaction conditions since the yields of pyrroles with respect to it decrease as the diketone reactivity decreases, allowing it other modes of destruction. One byproduct that has been observed is diethyl acetamidomalonate (**7**). Since **7** is water-soluble, it has generally escaped notice in the usual workup procedure. Inasmuch as pyrrole formation requires the formation of CO_2, whereas the formation of **7** does not, gas evolution is a useful monitor of reaction progress and can be used to assess the efficacy of a delayed addition of excess DEAM to the boiling reaction mixture. Accordingly, the procedure was modified (for stable diketones) from the addition of a *mixture* of diketone and DEAM to boiling acetic acid to the gradual addition of DEAM alone to a boiling solution of the diketone in glacial acetic acid. Gas evolution was prompt and copious whenever good yields of pyrroles were obtained.

Unsymmetrical aliphatic 1,3-diketones **1** with a meso substituent (R_4 = alkyl) were generally found to give **6** under apparent kinetic control,[2] with the amine nitrogen of DEAM condensing predominantly with the less-hindered carbonyl of **1**. However, *meso unsubstituted* 1,3-diketones such as 2,4-hexanedione (**8a**) reacted unselectively,[2] even to the extent of favoring the 5-ethylpyrrole (**9a**) 2:1 over the 3-ethyl isomer (**9b**) (Table I)! Clearly, other structural classes of dicarbonylic compounds will require examination on a case-by-case basis to establish the extent and nature of regioselectivity in each system. Herewith we present some of our findings in that direction to help in the planning of future syntheses of potential users of this high-yielding and convenient approach to pyrroles.

Pyrroles from Alicyclic Diketones (Scheme II). 2-Acylcycloalkanones **10** are readily available from the acylation of the appropriate cycloalkanone (or enamine derivative) with aliphatic anhydrides,[6] esters,[6] or acid chlorides[7] and as such constitute attractive potential precursors for pyrroles. With DEAM, **10** would be expected to afford bicyclic pyrroles, but it would be difficult to extrapolate from acyclic diketones as to which carbonyl (exo- vs. endocyclic) would in fact prove the more reactive, either sterically or electronically, given the relatively rigid structures of **10** relative to acyclic analogs.

Scheme II summarizes our results with the 2-acetyl and 2-propionyl derivatives of cyclohexanone and cyclopentanone. The ^{13}C NMR chemical shifts that were most critical to the structural determination are shown and were assigned by direct comparisons among the homologues and acyclic analogues using the β and γ effects (replacing a methyl group by an ethyl substituent) upon the aromatic pyrrole carbons as the most important tool (2D NMR was unavailable to us at the time). Also diagnostic for these and other pyrroles (Schemes III–V) are the ^{13}C NMR chemical shifts of the ethyl substituents. A 5-ethyl group is quite polarized, with its methyl carbon being unusually far upfield (δ 13 to 14.5) and its methylene carbon being unusually far downfield (δ 19 to 21), compared to ethyl substituents at C_3 or C_4. The respective ranges for a 3-ethyl substituent are much closer: methyl between δ 15 and 16, methylene between δ 18 and 19. For 4-unsubstituted pyrroles (Scheme V, Table I, Table S-V of the supplemental material), ethyl group methylenes occur in the range of δ 20 to 21 in either the 3- or the 5-position, but the methyl carbons still occur in the above-mentioned ranges.

For both cyclohexanone derivatives **10a** and **10b**, product yields were high (80+%), and the reactions were rapid; zinc-Knorr conditions were also successful. The cyclo-

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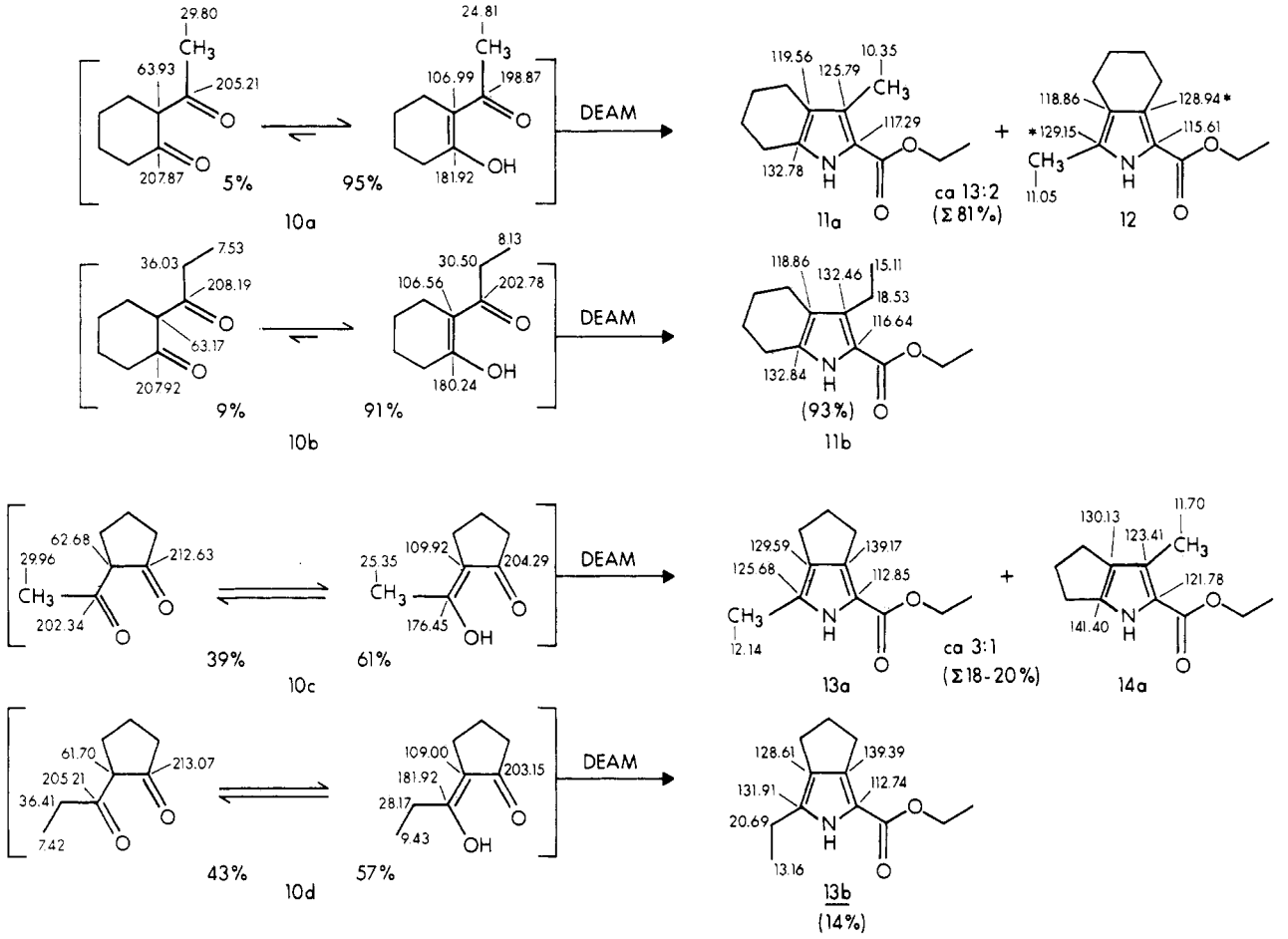
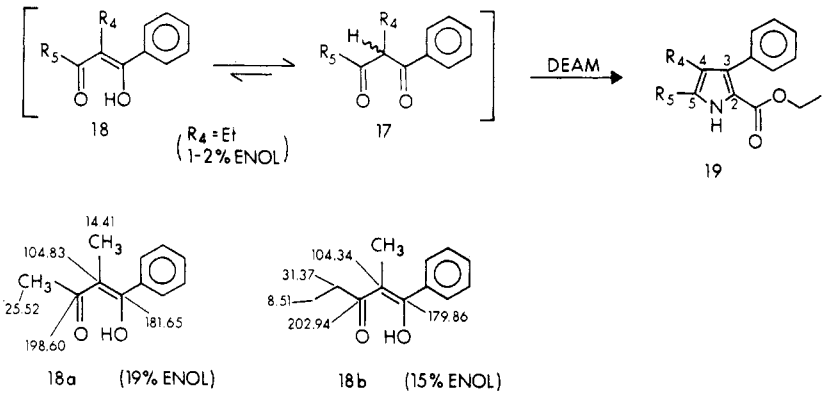
Scheme II. Pyrroles from 2-Acylcycloalkanones[a]



[a] Asterisks denote uncertain assignments.

Scheme III. Ethyl 3-Phenylpyrrole-2-carboxylates from Diketones

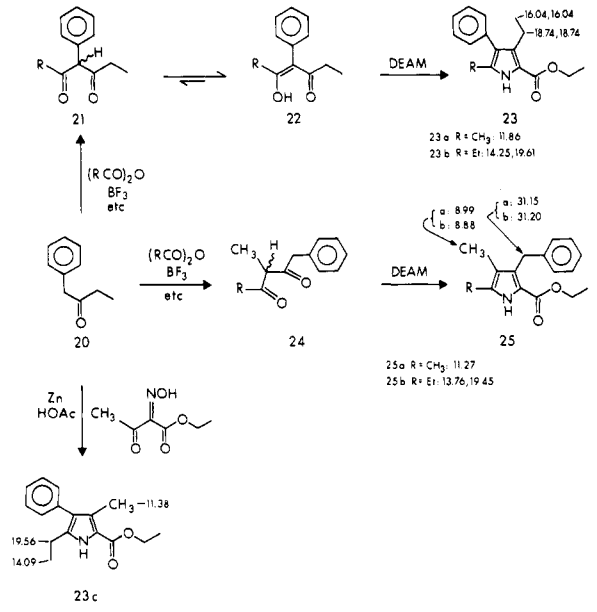


^{13}C NMR chemical shifts critical for structural assignment

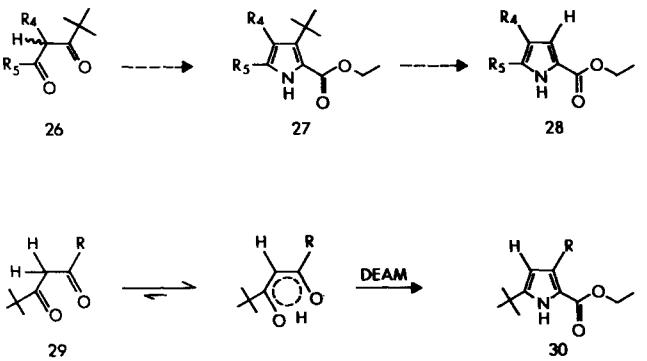
	R_5	R_4	C-2	C-3	C-4	C-5	R_5	R_4
19a	Me	Me	116.58	132.08	116.91	130.45	11.32	9.37
19b	Et	Me	116.48	132.02	116.10	135.60	13.49, 19.50	9.32
19c	Me	Et	116.58	131.70	123.90	129.80	11.38	15.71, 17.39
19d	Et	Et	116.75	131.64	123.14	135.98	13.98, 19.34	16.14, 17.23

pentanone derivatives **10c** and **10d** reacted far more slowly (at least at the cyclization step) and in much lower yield (14–21%); for these, zinc-Knorr conditions *failed*. Both *acetyl derivatives* **10a** and **10c** gave mixtures, the cyclohexanone derivative **10a** strongly favoring (by ca. 13:2) the product of an initial *endocyclic* condensation, **11a**. 2-Acetylcyclopentanone (**10c**), by contrast, strongly favored (by ca. 3:1) initial *exocyclic* condensation to give **13a** predominantly. The *propionyl* derivatives **10b** and **10d** both gave almost exclusively a single product, corresponding in structure to the dominant product of the *acetyl* analogues in both cases. For **10b**, this behavior was interpreted as being the result of increased steric hindrance about the exocyclic carbonyl acting to reinforce a natural preference for initial endocyclic reaction. Since **12** was sufficiently more polar than **11a** as to allow separation by column chromatography, it was disconcerting when first reacting **10b** to obtain nearly "single spot" product, since

Scheme IV. Ethyl 4-Phenylpyrrole-2-carboxylates or 3-Benzylpyrrole-2-carboxylates from 1,3-Diketones



Scheme V. *tert*-Butyl-Substituted Pyrroles (a, R = Me; b, R = Et)



this observation implied that the dominant products were the unwanted tetrahydroindoles (the tetrahydroisoindoles **12** were considered more desirable for potential porphyrin synthesis). The unanticipated *decrease* in "endocyclic" product (**14b**) upon increasing the steric hindrance about the exocyclic carbonyl for **10d** seemed perverse; it may be that the *cyclization* step is affected adversely in this instance. Compounds **11a,b** and **14a,b** have all been reported,[8,9] having been prepared in low yield by the Knorr reaction of the appropriate combinations of cyclohexanone or cyclopentanone with ethyl α-oximinoaceto(or propionyl)acetate. Products **12**, **13a**, and **13b** all appear to be novel; **13a** recently narrowly escaped synthesis when **10c** was reacted with excess glycine ethyl ester hydrochloride in boiling DMF.[10] Similar ratios of **11a** and **12** were also obtained from **10a** under zinc-Knorr conditions by using *either* diethyl oximinomalonate *or* ethyl α-oximinoacetoacetate. (The latter reagent gave byproduct diethyl 3,5-dimethyl-2,4-pyrroledicarboxylate as well.) The syntheses are practical for the dominant products, all of which can be obtained pure by recrystallization. The polarity difference between **13a** and **14a** is less pronounced than that for **11a** and **12**, requiring more efficient equipment for effective separation by chromatography. The isomers ring-fused at C-3 and C-4 (pyrrole numbering) were the more polar in both series.

The different preferences exhibited for initial condensation of the DEAM amine group with a diketonic carbonyl by the two ring sizes of diketone (**10c,d** vs. **10a,b**) are also reflected in the *specific enol* structures that dominate the time-averaged[11] composition of these diketones. The β effect of homologating an acetyl to a propionyl derivative *deshields* the exocyclic carbonyl by ca. 3 ppm for both keto and enol forms. This perturbation influences the upfield *enolic* carbonyl for **10c,d** but the downfield *keto* carbonyl for **10a,b**. Superimposed on this is a natural tendency for an ethyl substituent to stabilize an enol *keto* carbonyl more than a methyl group, an effect that influences the time-averaged position of the remote endocyclic carbonyl by about 1–2 ppm (in the shielding direction). A similar but opposite shift can be anticipated for the exocyclic carbonyl, so that the observed β effect for a propionyl group of an enolized diketone is thus the sum of a true β effect *plus* an additional contribution from a change in the time-averaged weighting which, being more ketonic, effects a further deshielding. The preferred enol structures are thus shown in Scheme II, 2-acetyl-1-cyclohexen-1-ol for **10a** and 2-(1-hydroxyethylidene)cyclopentanone for **10c**. These results confirmed conclusions reached elsewhere[12,13] by different (and less clear-cut!) means. The dominant pyrrolic products in both series are those whose enaminone precursors were the *aza analogues* of the preferred enols with the amine becoming bonded to what was the preferentially enolized carbonyl carbon.

It is unclear whether this correlation is a cause or an effect. It is unknown as to how reversible this reaction is at its early stages, which step is product determining, and whether this varies from system to system or is temperature-dependent. The behavior of the acyclic systems suggested kinetic control at high temperature but more thermodynamic control at lower temperatures. This implies extensive reversibility for the formation of the aminol **4** from precursors but less reversibility once the dehydration to the enaminones **5-E** or **5-Z** have been achieved. (The extent or mechanism of interconversion between **5-E** or **5-Z** is also unknown, but perhaps crucial.) For the alicyclic systems under discussion, a reactivity order of cyclohexanone > linear alkanone > cyclopentanone would explain the observed results. Data presented by Brown et al.[14] suggest an identical order of instability. Alternatively, a completely reversible aminol **4** formation might be directed by a preferred tendency for **4** to dehydrate if the arising enaminone **5** C=C double bond came to be placed in that location most preferred by the ring size at hand: endocyclic for cyclohexanes or semicyclic for cyclopentanes, as Brown[14] had observed in his classic report and as we have confirmed for the precursor diketones themselves. This preference even influences the *extent* of diketonic enolization in the two series (as observed in $CDCl_3$): the 2-acylcyclohexanones are 90% to 95% enolized, whereas the 2-acylcyclopentanones are enolized only

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to the extent of about 57% to 61%. The propionyl derivatives are slightly *less* enolized than their acetyl analogues in both series (another example of the slight ethyl preference for the carbonyl group).

A further effect noted by Brown et al.[14]—a general reluctance of exomethylene cyclopentanes to rehybridize from sp^2 to sp^3 geometry—may explain the low yields in the cyclopentane series. On the basis of TLC evidence, 2-acetylcyclopentanone (**10c**) reacts readily with stochiometric DEAM, yet gas evolution and pyrrole formation are both slow and incomplete. Upon aqueous workup, *only the pyrrolic products precipitate.* It is tempting to speculate that much of the diketone is diverted to give the *E* enaminone, which is unable, given the restraint above, to isomerize into the *Z* configuration required for cyclization to the pyrrole. The low yield would then derive from the considerable formation of a "dead-end" isomer of the reactive intermediate. The following paper[15] contains further evidence to support this view: a high yield of pyrrolic product formed *rapidly* under *zinc-Knorr* conditions, via spiro intermediates that could form independently of the *E* or *Z* configuration.

Other ring sizes were not examined. Structures of many other enolized cyclic diketones have been reported;[13,16] whether these correlate to potential pyrrolic products remains to be seen.

Phenyl-Substituted Diketones (Schemes III and IV). The first report of DEAM as such in pyrrole synthesis was by Umio et al.,[5] who reacted it with 1-phenyl-1,3-butanedione and its phenyl-substituted analogues so as to isolate the intermediary enaminones **5**. These were then cyclized to pyrroles in polyphosphate ester melts, an unattractive system if acetic acid would also succeed.

We wished to extend the reaction to the meso-alkyl substituted analogues, the 2-alkyl-1-phenyl-1,3-alkanediones **17a–d**, and determine the suitability of acetic acid as a one-step cyclization medium for the direct conversion of such diketones to pyrroles (Scheme III).

The four diketones **17a–d** were prepared conveniently, if in low yield, by the BF_3-induced acylation of propiophenone or butyrophenone with acetic or propionic anhydrides. (Higher yielding alternatives have been reported.[6,17]) These diketones were found to be only slightly enolized when examined by ^{13}C NMR (Table S-II of the supplementary material, Scheme III), with a decrease in enol content as steric congestion increased about the meso position (C-2). Thus only the 2-methyl homologues **17a,b** gave observable enol carbonyl resonances (enol contents of 15–19% vs. 1–2% for the 2-ethyl homologues). Since the β effect of homologating the alkane terminus deshielded only the downfield carbonyl, this class of diketone enolized specifically to 2-alkyl-1-hydroxy-1-phenyl-1-alken-3-ones **18**, a structure that maximizes π-overlap across the system. This enol structure did *not* correspond to that of what were the essentially exclusive pyrrolic products, viz. the 3-phenyl-2-pyrrolecarboxylate esters **10a–d**, whose structures follow from the NMR data (Scheme III, Tables S-III and S-IV of the supplemental data). The amine group of DEAM thus condensed preferentially with the more electrophilic alkyl-substituted carbonyl, rather than that deactivated by π-overlap with the aromatic ring. Steric hindrance effects at either the alkyl terminus or at the meso position were not observed. Product yields were good from this class of diketone (up to 70%), pure products being readily obtained by recrystallization, even when crude preparations of some of the diketones were employed.

The effect of a phenyl substitutent in the meso position was also investigated (Scheme IV). Commercially available 1-phenyl-2-butanone (**20**) was acylated (BF_3) with acetic or propionic anhydride. The resulting diketones, 3-phenyl-2,4-hexanedione (**21a**) and the novel 4-phenyl-3,5-heptanedione (**21b**), were found to be almost exclusively enolized, unlike their meso-alkyl analogues, displaying the "averaged" chemical shifts for the two carbonyls which imply rapid interchange of the two possible S-cis tautomers **22**. Evidently the increased π-overlap possible with the benzene ring when the meso carbon achieves sp^2 hybridization is responsible for this situation. Steric hindrance seemed to dominate the outcome of the reaction of **21a** with DEAM, the 3-ethylpyrrole **23a** forming the principal product. The minor amount of byproduct **23c** tended to persist in recrystallized **23a**, probably as a result of solid solution. Isomer **23c** could be prepared unambiguously in *low* yield (2.5%) from the Knorr reaction of **20** with ethyl α-oximinoacetoacetate.

Inasmuch as the acylation of **20** was not entirely selective, a fortuitous opportunity was provided to assess the influence of a terminal *benzyl* group on the reactivity of a β-diketone. Crude **21a** and **21b** contained variable amounts of 3-methyl-1-phenyl-2,4-pentanedione (**24a**) or 3-methyl-1-phenyl-1,4-hexanedione (**24b**), respectively, which reacted with DEAM to afford the 3-benzylpyrroles **25a** and **25b** which could be identified by NMR as impurities in the crude reaction mixtures (Scheme IV). Signals corresponding to the 5-benzylpyrrole isomers were not observed in either crude reaction mixture. Since the high-boiling fractions of **21b** were significantly enriched in **24b**, it proved possible to obtain **25b** in pure form without resort to chromatography, by simple crystallization. Since **24a** and **24b** occurred in the crude diketones largely in the *diketo* form, it is assumed that their behavior mimicked the usual aliphatic analogues, with steric hindrance being the principal influence on product distribution. Benzyl appears therefore to be more hindering than methyl or ethyl, and so 3-benzylpyrroles could be expected to be available from the appropriate diketones.

Pyrroles from Highly Hindered Diketones (Scheme V). The *tert*-butyl group is the classic example of a sterically hindering substituent and is of further interest in its own right, since when appended to an aromatic system it[9,19] is subject to (reversible) removal as isobutylene. It was therefore hoped that the pivaloyl group might serve as a bulky surrogate for the aldehyde function and that diketones with a terminal *tert*-butyl group might provide a product more regioselectively from DEAM than β-keto aldehydes appear to do generally.[2] In particular, it was hoped that 4-alkyl-2,2-dimethyl-3,5-alkanediones **26** might lead to the 3-*tert*-butylpyrroles **27**, which upon de-*tert*-butylation might afford 4,5-dialkyl-2-pyrrolecarboxylate esters **28**, an otherwise difficultly accessible class of compounds (Scheme V).

Pinacolone was acylated (BF_3) with acetic or propionic anhydrides to initiate investigations in this area. The resulting diketones **27a,b**, 80% to 85% enolized (unspecifically), were found to react only sluggishly with DEAM

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as evidenced by gas evolution. When the unreacted diketones were removed by steam-distillation, the pyrrolic products were also found to be steam-volatile and thus conveniently isolated in low yield (10–15%).

Even in crude form, these pyrroles proved to consist of but a single isomer, identified unambiguously by ^{13}C NMR comparison (Scheme V; Table S-V, supplemental material) with methyl and ethyl analogues **9a–d** as the 5-*tert*-butylpyrroles **30a,b**! The absolute regioselectivity displayed by **29a,b** was in sharp contrast to the usual lack of selectivity shown by earlier-examined[2] meso-unsubstituted diketones. The results seem to suggest that the cyclization step is even more sterically demanding than the initial condensation that generates the enaminone. The pivaloyl group is either too bulky to allow approach of the malonate moiety or else enforces the uncyclizable *E* configuration about the C=C double bond of that enaminone (**5**, R^3 = *t*-Bu, R_4 = H, R_5 = Me) most likely to form initially, for steric reasons. Only after the unlikely event of an initial condensation at the more hindered pivaloyl carbonyl can cyclization occur since the resulting enaminone (**5**, R^3 = Me, R^4 = H, R_5 = *t*-Bu) not only has unexceptional hindrance to cyclization but is probably constrained by the bulky *tert*-butyl group to exist in the favorable *Z* configuration. (It is possible that the product resulted from a condensation of the diketone with *2* equiv of DEAM; we have not explored this.) A recent experiment with dipivaloylmethane failed, since not even any enaminone formed: the bulky *tert*-butyl groups guarded *both* carbonyls from both front- and back-side attack! The low yields and contrary behavior of these prototypes persuaded us to abandon further investigations in this area.

In conclusion, we have established that a useful range of structural classes of 1,3-diketone can give pyrroles regioselectively with DEAM, often in good yield, and that many of the products can be obtained in pure form by simple crystallization, even when the regioselectivity was not absolute. Not all of the results were anticipated, however, since the outcomes were often the result of a complex struggle between steric effects and electronic reactivity, possibly at more than one stage of the reaction.

Other structural classes of 1,3-dicarbonylic compounds and related substances are under continuing investigation and will be reported in due course.

Experimental Section

Boron trifluoride gas was obtained from Matheson, and the remaining starting materials were obtained from Aldrich. A satisfactory atmospheric pressure hydrogenator reservoir of 17-L functional capacity was constructed from a pair of 20-L polyethylene aspirator bottles, joined at their tabulations by concentric plastic tubing. The gas bottle was secured against leakage by the use of silicone grease to seal the screw-cap. Hydrogen was conveyed from the *top* of this bottle via the inner tubing out of the overflow bottle to the apparatus.

Melting points (Thomas-Hoover oil immersion apparatus) are uncorrected. NMR data were obtained in $CDCl_3$ solution in 5-mm tubes (JEOL FX 90Q). Microanalyses were performed by Peter Borda of the University of British Columiba.

Diethyl Aminomalonate (DEAM) (2). Diethyl oximinomalonate[2] (**3**) (117.3 g, 100.5 mL, 0.62 mol), absolute ethanol (500 mL), and 10% Pd/C (0.9 g) were stirred under H_2 (1 atm, room temperature) until uptake (ca. 28 L) ceased. The Pd/C was filtered off and rinsed with ethanol. The ethanol was removed at 50 °C with a rotary evaporator, and the pale yellow residual oil distilled as rapidly as possible at full oil-pump vacuum with capillary bleed: bp 94–96 °C/1.2–1.4 Torr. Yield, 98.8 g (90.9% assuming pure **3**). The colorless oil was still satisfactory after 3 months of storage at −10 °C.

2-Acetylcyclopentanone (10c). A mixture of cyclopentanone (267 mL, 253.9 g, 3.02 mol) and acetic anhydride (604 mL, 652.3 g, 6.39 mol) was divided into three lots and separately saturated with BF_3 gas in dry ice–ethanol-cooled 1-L Erlenmeyer flasks. The internal temperature reached 50 °C; BF_3 uptake was close to 3 mol per mol of ketone and required 30 to 60 min. (The BF_3 was diluted with a small amount of N_2 to prevent backflow of liquid into the gas line.)

The reaction mixture was poured onto ice, causing the BF_2 complex to crystallize at once. The solids were filtered off, washed with water, and stored overnight in a beaker. Partial hydrolysis occurred on standing, causing the moist filter filter cake to liquify.

Each lot was treated with 4 M potassium acetate (400 mL) (prepared from aqueous KOH and a slight excess of acetic acid) and H_2O (100 mL) and distilled (with further addition of H_2O as needed) until no further oils condensed.

The oily phases (only 55% to 63% of the ultimate yield) were isolated, and the aqueous phase was extracted twice with CH_2Cl_2. The first extract afforded 27% to 37% of the total, the second one 8–10%. The combined extracts were concentrated and then distilled: bp 45–47 °C/0.7 Torr or 58 °C/3 Torr. Yield: 231.6 g (60.8%).

The foreruns, scavenged with copper(II) acetate, gave 10.6 g of chelate.

Remaining Diketones. The other diketones were prepared similarly, except that noncrystalline BF_2 complexes were extracted into CH_2Cl_2 before hydrolysis and the products were vacuum distilled afterwards if not steam-volatile. Several were purified as the copper(II) chelates, which are often a useful form in which to store the otherwise oxygen-sensitive 1,3-diketones.[20] Carbon-13 NMR chemical shifts are reported in Tables S-I and S-II (supplemental section) and in some cases were obtained from impure materials.

The previously unreported 4-phenyl-3,5-heptanedione (**21b**), which occurs totally enolized to 5-hydroxy-4-phenyl-4-hepten-3-one in $CDCl_3$, was prepared (BF_3) from 1-phenyl-2-butanone (**20**) and propionic anhydride and analyzed as its copper(II) chelate: mp 124.0–126.0 °C (from ethyl acetate–hexane). Anal. Calcd for $C_{26}H_{30}CuO_4$: C, 66.44; H, 6.43; Cu, 13.52. Found: C, 66.37; H, 6.36.

Free 1,3-diketone (enol only observed): ^1H NMR ($CDCl_3$) δ 1.00 (6 H, t, J = 7 Hz), 2.11 (4 H, q, J = 7 Hz), 7.09–7.49 (5 H, m), 16.78 (H, s); ^{13}C NMR ($CDCl_3$ at 77.36) δ 194.00 (3,5), 136.63 (Ar-1), 131.37 (Ar-2,6), 128.83 (Ar-3,5), 127.47 (Ar-4), 113.98 (4), 29.90 (2,6), 9.59 (1,7).

Ethyl 3-Methyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate (11a). Method A. Diethyl oximinomalonate[2] (**3**) (16.9 g, crude, 89.4 mmol maximum) and zinc dust (15 g, 229.5 mg atom) were added in portions over 11 min to a magnetically stirred solution of 2-acetylcyclohexanone (**10a**) (7.05 g, 50.3 mmol) in glacial acetic acid (50 mL). Water (13 mL) was added when zinc acetate began to crystallize. The reaction mixture reached a vigorous boil during the addition of reagents. After 10 min of additional stirring, the excess zinc was removed by decantation, rinsed with ethanol, and discarded. (*Caution*: the recovered zinc is pyrophoric and should be destroyed with dilute HCl or H_2SO_4 in a hood.) The supernatants and rinsings were diluted with H_2O (500 mL). When solidification was complete, the product was recovered by filtration, washed with H_2O, and dried; yield 8.30 g (79.7%). Traces of additional solids appeared in the filtrates overnight. The combined solids were recrystallized from aqueous ethanol in crops of 4.31 g (41.4%), 2.54 g (24.3%), and 1.38 g (13.3%), for a total of 8.23 g (79.0%): mp 105.5–107.0 °C (first crop), 96–108 °C (second crop) (lit.[8,21a] 110 °C). By NMR and TLC (CH_2Cl_2/silica G) the first crop was nearly pure; subsequent crops were mixtures of both isomers.

Method B. Diethyl aminomalonate (DEAM) (**2**) (12.0 g, 68.6 mmol) was added, dropwise, over 12 min, to a boiling solution of **10a** (7.03 g, 50.2 mmol) in glacial acetic acid (50 mL). Gas evolution was prompt and vigorous; reflux was maintained until this had ceased (ca. 90 min). The reaction mixture was diluted with H_2O (500 mL), and the precipitated solids were recovered

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by filtration, washed with H_2O, and dried. Yield: 8.39 g (80.7%). By TLC, this was a mixture indistinguishable in composition from the crude product of method A. Recrystallization from ethanol, first crop, 6.96 g (67.0% overall, or 83% recovery): mp 95–105 °C. Recrystallized again: 4.24 g, mp 104–108 °C. The later crops were chromatographed (see below).

Ethyl 3-Methyl-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (12). The subsequent crops of both A and B were chromatographed on silica gel (activity 1, 70–230 mesh, ICN) with dichloromethane and eluted with 1% and finally 2% (v/v) diethyl ether in CH_2Cl_2. The less polar tetrahydroindole **11a** eluted first, mp 107.0–108.5 °C (from aqueous ethanol) (lit.[8] mp 110 °C).

The considerable mixed fraction that followed was rechromatographed to give **12**, which was crystallized from aqueous ethanol: mp 144.0–145.5 °C.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.54; H, 8.24; N, 6.66.

Ethyl 3-Ethyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate (11b). Method A. **11b** was prepared similarly to **11a**, from 2-propionylcyclohexanone (**10b**) (50 mmol). Yield, first crop: 2.91 g (29.4%), mp 88.0–89.5 °C (lit.[8] mp 89 °C).

Method B. From **10b** (7.71 g, 50.1 mmol), DEAM (13.1 mL), and boiling glacial acetic acid (50 mL). The oils from the aqueous dilution soon solidified, 10.26 g (92.7%). First crop, from ethanol: 8.01 g (72.4%), mp 86.0–88.0 °C. Even the crude material showed only traces of the more polar tetrahydroisoindole by TLC (CH_2Cl_2/silica).

Ethyl 3-Methyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate (13a). DEAM [undistilled, from diethyl oximinomalonate[2] (**3**) (121.2 g, 0.641 mol)] was added over 35 min to a refluxing solution of 2-acetylcyclopentanone (**10c**) (80.8 g, 77.0 mL, 0.641 mol) in glacial acetic acid (504 mL). The mixture was refluxed 8 h, then diluted to 1.8 L with H_2O. The pale yellow sparkling granules were filtered off and washed with H_2O. Yield: 20.06 g (16.2%). On standing overnight, diluted to 3 L, a second crop (5.33 g, 4.3%) was obtained from the filtrates. Total 25.39 g (20.5%).

A repetition, from 128.5 g of oxime and 80.8 g of diketone, but refluxed only 4 h, gave crops of 16.26 g (13.1%) and 6.05 g (4.9%). Total 22.31 g (18.0%).

The first crops were separately twice recrystallized from ethanol, giving 12.05 + 8.68 g or 20.73 g total of pure material as spectacular folded (twinned) oscillating flat spears of multicentimeter size, mp 160–162 °C. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.50; H, 7.90; N, 7.25.

A second crop, 2.24 g, mp 151.5–157.5 °C, was obtained. The remainder, a mixture of both isomers, could not be further separated by crystallization.

Isolation of Diethyl Acetamidomalonate (7) as a Byproduct. 2-Acetylcyclopentanone (**10c**) 6.3 g, 50 mmol), DEAM (13.7 g, 12.4 mL, 78.3 mmol), and glacial acetic acid (50 mL) were refluxed for 2 h. The reaction was diluted with H_2O to give 1.08 g (11.1%) of pyrrolic product, after recrystallization from ethanol.

The filtrates were extracted with CH_2Cl_2. Upon evaporation, the resulting oils gradually crystallized in part. The crystals were filtered off, washed with 50% aqueous ethanol, and dried: yield, 1.92 g (11.3%); ^{1}H NMR ($CDCl_3$) δ 1.30 (6 H, t, J = 7 Hz), 2.08 (3 H, s), 4.27 (4 H, q, J = 7 Hz), 5.20 (H, d, J = 7 Hz), 7.05 (H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$ at 77.36) δ 170.05 (CH_3CONH), 166.59 (2 CO_2Et), 62.46 (2 CH_3CH_2O), 56.56 (CH), 22.54 (CH_3CO), 13.98 (2 CH_3CH_2O); ^{13}C NMR (authentic sample) 170.32, 166.66, 62.44, 56.59, 22.50, 14.01 (similar degeneracies).

Ethyl 3-Ethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate (13b). 2-Propionylcyclopentanone (**10d**) (7.02 g, 50.1 mmol) in boiling glacial acetic acid (51.5 mL) was treated, dropwise, over 40 min, with DEAM (13.5 g, 12.3 mL, 77.14 mmol). After 2.5 h, gas evolution had ceased. The mixture was diluted to 850 mL with H_2O depositing oils which soon solidified in part. After standing for 5 days, the oils had redissolved. The solids were filtered off and recrystallized from ethanol. Yield: 1.42 g (13.7%), mp 101.5–105.0 °C.

A sample, twice recrystallized from ethanol, was analyzed: mp 104–105 °C; remelted 104.5–106 °C. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.64; H, 8.17; N, 6.79.

Ethyl 4,5-Dimethyl-3-phenyl-2-pyrrolecarboxylate (19a). Bis(2-methyl-1-phenyl-1,3-butanedionato)copper(II) (**17a**, Cu chelate) (5.17 g, 12.5 mmol) was suspended in CH_2Cl_2 and shaken with excess cold aqueous H_2SO_4 until the greenish organic phase had faded to pale yellow. The organic phase was isolated and evaporated to give an oil (steam bath). The resulting diketone was added to boiling glacial acetic acid (40 mL) and treated, dropwise, over 25 min, with redistilled diethyl aminomalonate (DEAM) (8.7 g, 8.2 mL, ca. 50 mmol). Gas evolution had ceased after 90 min of reflux. The pale orange reaction mixture was diluted with H_2O to ca. 400 mL, and the precipitated solids (TLC, CH_2Cl_2–silica: single major product, trace of less polar impurity) were filtered off and recrystallized from 95% ethanol to give 4.26 g (70.0%) of large dense flat diamonds, mp 136.5–137.0 °C. These were recrystallized once from 95% ethanol for analysis, mp 136.5–137.5 °C. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.98; H, 7.12; N, 5.76.

Ethyl 5-Ethyl-4-methyl-3-phenyl-2-pyrrolecarboxylate (19b). Bis(2-methyl-1-phenyl-1,3-pentanedionato)copper(II) (**17b**, Cu chelate) (2.21 g, 5.01 mmol), DEAM (4.0 mL), and acetic acid (20.2 mL), as for **19a** gave **19b**. Snow white needles from ethanol: 1.69 g (65.7%), mp 99.0–99.5 °C. Recrystallized from ethanol for analysis, mp 99.0–100.0 °C (lit.[21a] mp 103 °C). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.44; H, 7.52; N, 5.39.

Ethyl 4-Ethyl-5-methyl-3-phenyl-2-pyrrolecarboxylate (19c). **19c** was prepared similarly from crude redistilled 2-ethyl-1-phenyl-1,3-butanedione (**17c**) (9.53 g, 50.2 mmole, DEAM (14.6 g, 13.2 mL, 83.4 mmol), and acetic acid (50 mL): 8.66 g (67.2%), mp 153.7–155.3 °C; remelted 159.0–160 °C. Recrystallized for analysis from 95% ethanol: mp partially at 153.7–154 °C, resolidified and melted 159.5–160.5 °C. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.50; N, 5.47.

Ethyl 4,5-Diethyl-3-phenyl-2-pyrrolecarboxylate (19d). **19d** was prepared from crude 2-ethyl-1-phenyl-1,3-pentanedione (**17d**) (7.20 g, ca. 65 mol % pure, 35.3 mmol nominal), DEAM (9.3 g, 8.2 mL, 53 mmol), and acetic acid (50 mL), as long large colorless needles from ethanol: 2.91 g (30.4% nominal); mp 113.5–115.5 °C. Recrystallized from ethanol for analysis: mp 114.0–115.0 °C. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.40; H, 7.86; N, 5.16.

Ethyl 3-Ethyl-5-methyl-4-phenyl-2-pyrrolecarboxylate (23a). Crude 3-phenyl-2,4-hexanedione (**21a**) (9.53 g, 50.14 mmol) (containing some 3-methyl-1-phenyl-2,4-pentanedione, **24a**) in boiling glacial acetic acid (52 mL) was treated with DEAM (14.0 g, 12.4 mL, 80 mmol) in portions: 7 mL in the first 9 min, the rest after 35 min. After 2 h of reflux, gas evolution had ceased. The product was precipitated by aqueous dilution, filtered off, and recrystallized from ethanol in several crops: first crop, 4.96 g (38.5%), mp 124.5–126.5 °C; second crop, 3.19 g (24.8%), mp 94–106 °C (by NMR, this contained 30–35% of ethyl 3-benzyl-4,5-dimethyl-2-pyrrolecarboxylate (**25a**), derived from the ketonic impurity). Total recovery, 8.15 g (63.3%). The first crop was recrystallized from ethanol for analysis, mp 127.0–128.0 °C. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.80; H, 7.44; N, 5.48.

Ethyl 3,5-Diethyl-4-phenyl-2-pyrrolecarboxylate (23b). **23b** was prepared from crude 4-phenyl-3,5-heptanedione (**21b**) (10.20 g, 50.0 mmol) (containing some 3-methyl-1-phenyl-2,4-hexanedione (**24b**)), DEAM (13.5 g, 12 mL, 77.1 mmol), and acetic acid (50 mL). First crop, as snow-white flakes from aqueous ethanol: 6.55 g (48.3%), mp 108.5–110.0 °C. Recrystallized for analysis, from ethanol, as white needles, mp 108.0–110.5 °C. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.39; H, 7.90; N, 5.16.

Ethyl 5-Ethyl-3-methyl-4-phenyl-2-pyrrolecarboxylate (23c). Ethyl acetoacetate (25.5 mL, 26.0 g, 0.2 mol) in glacial acetic acid (52 mL) was treated, dropwise, with a solution of $NaNO_2$ (15.3 g, 0.22 mol) in H_2O (40 mL). The resulting oxime solution and zinc dust (30.1 g, 0.46 mol) were added in portions to a solution of 1-phenyl-2-butanone (**20**) (14.83 g, 0.100 mol) in glacial acetic acid (104 mL). The reaction mixture reached the boiling point. After cooling, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The extracts were evaporated, and the residue was crystallized from aqueous ethanol. Yield 0.65 g (2.5%)

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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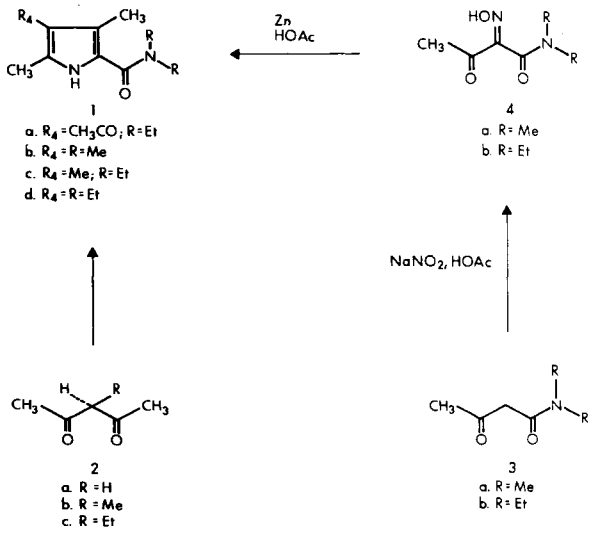
The mechanism of formation of *N,N*-dialkyl-2-pyrrolecarboxamides **1** from the reaction between *N,N*-dialkyl-2-(hydroxyimino)-3-oxoalkanamides **4** and meso-substituted β-diketones **2** upon treatment with zinc in acetic acid differs from the analogous reaction between 2-(hydroxyimino)-3-oxoalkanoate 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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