

The Synthesis and Chemistry of Azolenines.† Part 8.‡ The Paal-Knorr Reaction with Cyclic 2-(Acylmethyl)-2-alkyl-1,3-diketones: Isolation of 1-Acyl-1*H*-pyrroles *via* Rearrangement²

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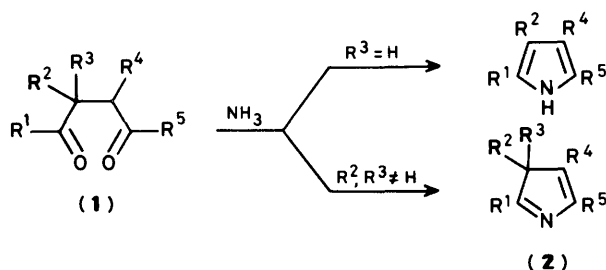
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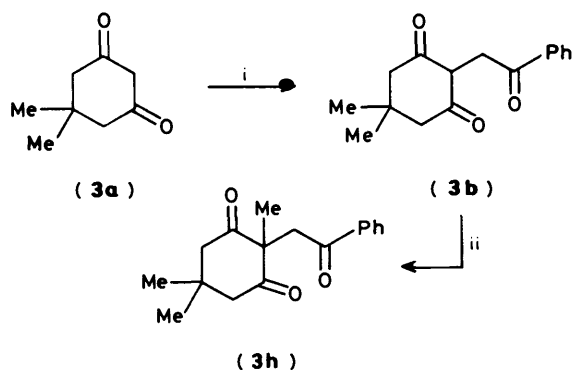
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Treatment of cyclic 2-acylmethyl-2-alkyl-1,3-diketones with ammonium acetate under reflux in acetic acid gives moderate to high yields of 1-acyl-1*H*-pyrroles by rearrangement. Some of the cyclic diketones react quantitatively with liquid ammonia to yield 2-hydroxy-3,4-dihydro-2*H*-pyrroles, which are converted in high yields into 1-acyl-1*H*-pyrroles by a number of methods. Possible mechanisms for the rearrangement are discussed, a process involving transannular interaction within an eight- or nine-membered ring being favoured. Improved methods for the mono- and bis-*C*-alkylation of cyclic 1,3-diketones are also described.

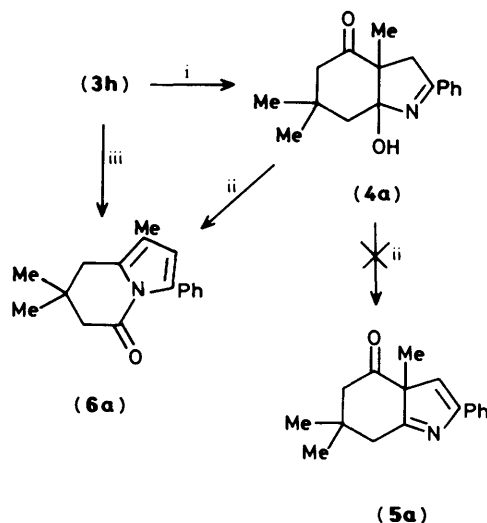
As part of a continuing search³ for new synthetic routes to the little-known 3*H*-pyrrole ring system (2),⁴ we were attracted by the, apparently unexplored, modified Paal-Knorr reaction between 2,2-disubstituted 1,4-diketones (1) and ammonia (Scheme 1). Structures of type (1) are in general not con-



veniently accessible; however, a straightforward approach to examples having $R^2 = \text{acyl}$ is the bis-alkylation of 1,3-diketones at C-2, one of the alkylating agents being an α -halogeno ketone or equivalent. Accordingly, dimedone (3a) was alkylated first with phenacyl bromide to give the triketone (3b),⁵ and then with methyl iodide, under conditions described by Ono⁶ for dialkylation of active methylene compounds, to yield the product (3h) which had the desired substitution pattern (Scheme 2). Treatment of the triketone (3h) overnight with



Scheme 2. Reagents: i, PhCOCH_2Br , K_2CO_3 , CHCl_3 ; ii, MeI, DBU, DMF



Scheme 3. Reagents: i, $\text{NH}_3(1)$; ii, various conditions; iii, AcONH_4 , AcOH, heat

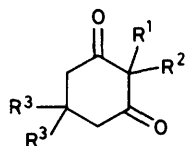
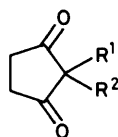
anhydrous liquid ammonia resulted in an essentially quantitative yield of the hydroxypyrroline (4a)† (Scheme 3). Dehydration to the 3*H*-pyrrole (5a) was attempted under a variety of conditions, including toluene-*p*-sulphonic acid in boiling benzene, hot acetic acid, dry HCl in ethanol, and 4A molecular sieves or Florisil in cold benzene. In all cases, only the isomeric 1-acyl-1*H*-pyrrole (6a) was isolated, cleanly and in high yield. Its structure was deduced from spectroscopic data, including the absence of diastereotopic groups, and the presence of a singlet at δ 6.04 in the ^1H n.m.r. spectrum. Subsequently, the same product was obtained on heating the precursor (4a) to its melting point, or simply by treating the triketone (3h) in boiling acetic acid with ammonium acetate. Compound (6a) appeared to be formed *via* a highly facile rearrangement, whose mechanism was worth investigating. Additionally, this was a novel synthetic route to 1-acyl-1*H*-pyrroles as well as to the indolizine ring system, which might usefully be extended. We report here some results on the scope and mechanism of this reaction.

† The term 'azolenines' refers to the non-aromatic isomers of the azoles.

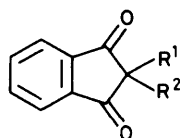
‡ U.v. absorption at 228 nm (EtOH) showed that the C=N bond was conjugated with the phenyl group.

Results and Discussion

Scope of the Reaction.—Preparation of ketones. A range of substituted cyclic 1,3-diketones (3), (7), (8), and (9) was selected, and preparative conditions sought for C-alkylation which

(3) R³ = Me(7) R³ = H

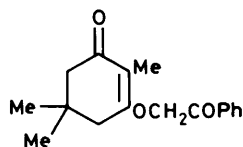
(8)



(9)

R ¹	R ²	R ¹	R ²
a	H	j	Me
b	H	k	Me
c	H	l	Me
d	H	m	Me
e	H	n	PhCH ₂
f	H	o	PhCH ₂
g	Me	p	PhCH ₂
h	Me	q	PhCH ₂
i	Me	r	PhCH ₂

minimised competing *O*-alkylation or ring-opening reactions. Thus, for example, reaction between the 3-methyl compound (3g) and phenacyl bromide using sodium hydroxide in ethanol, or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in dimethylformamide (DMF) led almost exclusively to the enol ether (10). For

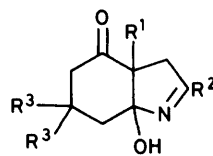
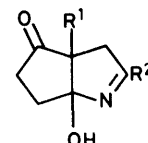


(10)

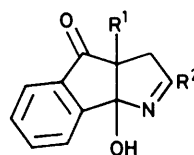
derivatives of the diketones (3a) and (7a), alkylation first with the appropriate halogeno ketone and then with the alkyl halide was found to be the most satisfactory approach. In the first step the reactants were stirred at 25 °C in chloroform in the presence of anhydrous potassium carbonate,⁵ the resulting triketone potassium enolate being precipitated, while any by-product enol ether remained in solution. The products (3b–f), (7b), and (7f), which existed predominantly in the enol form, were isolated by acidification of the potassium salts, and further alkylated with methyl iodide or benzyl bromide using DBU in DMF⁶ to give the ketones (3h–l), (3n–r), (7h), and (7l). Attempts to prepare the triketone (8h) *via* the precursor (8g) by a published procedure⁷ were unsuccessful; however, the methyl ketone analogue (8l) was obtained by Hg²⁺-catalysed hydrolysis⁸ of the prop-2-ynyl compound (8m).⁹ The indandiones (9h) and (9l) have been prepared previously from the methyl compound (9g) using the appropriate halogeno ketone and potassium hydroxide,¹⁰ but in our hands the method could not be extended satisfactorily to other analogues. However,

high yields of products were obtained from compound (9g) and a number of halogeno ketones using anhydrous potassium carbonate in acetone,¹¹ either under reflux overnight [products (9h), (9i), and (9l)], or on being stirred at 25 °C for 24 h [products (9j) and (9k)]. Physical and analytical, and i.r. and ¹H n.m.r. data for the triketones (3), (7), (8), and (9) are given in Table 1.

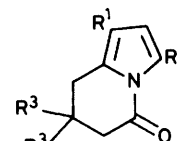
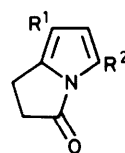
Reactions with Liquid Ammonia.—Treatment of the triketones (3h–l) with liquid ammonia overnight gave the corresponding hydroxypyrrolines (4a–e) in high yields, although the 4-nitro compound (4d) was always obtained in admixture with the triketone (3k). The ¹H n.m.r. spectra showed a number of diastereotopic groups: the *gem*-dimethyl group (δ 0.8 and 1.1), the pyrroline ring CH₂ (ABq, δ 2.8 and 3.6, *J* 17 Hz), and the CH₂ closest to the OH group (ABq, δ 2.1 and 2.5, *J* 13 Hz); the third CH₂ signal remained a singlet (δ 2.1) at 90 MHz. In contrast the benzyl triketones (3n–r) failed to react with liquid ammonia under the same conditions, starting materials being recovered unchanged. Compound (7h), however, was converted cleanly into the hydroxypyrroline (11a), although the methyl

(4) R³ = Me(11) R³ = H

(12)



(13)

(6) R³ = Me(14) R³ = H

(15)



(16)

R ¹	R ²	R ¹	R ²
a	Me	f	PhCH ₂
b	Me	g	PhCH ₂
c	Me	h	PhCH ₂
d	Me	i	PhCH ₂
e	Me	j	PhCH ₂

analogue (7l) gave a complex mixture. Hydroxypyrroline (12e) was obtained from the cyclopentanedione (8l), while in contrast, the indandiones (9h–l) failed to react with liquid ammonia, and compounds (13) could not be detected. The isolation of hydroxypyrrolines from these reactions is of particular interest, since only one other ring-fused example [compound (17)¹²] and two simple examples^{13,14} of this type (2-hydroxy-3,4-dihydro-2*H*-pyrroles) appear to have been reported previously. Samples were generally sufficiently stable for microanalyses to be obtained overseas, although this was not true for compounds

Table 1. Physical, analytical, i.r., and ^1H n.m.r. spectroscopic data for the triketones (3), (7), (8), and (9)

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found (%) (Required)			ν_{max} . (Nujol) (cm^{-1})	δ_{H} (CDCl_3)
				C	H	N		
(3b) ($\text{C}_{16}\text{H}_{18}\text{O}_3$)	88	Ethanol	182 ^a				2700—2100vbr, 1690, 1560, 1380, and 1355	1.04 (6 H, s), 2.31 (4 H, s), 4.00 (2 H, s), 7.3—7.6 (3 H, m), and 8.0—8.2 (2 H, m)
(3c) ($\text{C}_{16}\text{H}_{17}\text{BrO}_3$)	82	Ethanol	162	57.25 (57.0)	5.1 (5.1)		2700—2100vbr, 1685, 1600, 1385, and 1330	1.07 (6 H, s), 2.29 (4 H, s), 3.86 (2 H, s), 7.58 (2 H, m), and 7.84 (2 H, m)
(3d) ($\text{C}_{17}\text{H}_{20}\text{O}_4$)	68	Methanol	163	71.0 (70.8)	6.5 (6.95)		2700—2100vbr, 1680, 1600, 1385, and 1335	1.08 (6 H, s), 2.29 (4 H, s), 3.84 (3 H, s), 3.87 (2 H, s), 6.91 (2 H, m), and 7.96 (2 H, m)
(3e) ($\text{C}_{16}\text{H}_{17}\text{NO}_5$)	86	Ethanol- acetone	202	63.55 (63.35)	5.65 (5.65)	4.5 (4.6)	2700—2100vbr, 1695, 1565, 1530, 1385, and 1350	1.06 (6 H, s), 2.30 (4 H, s), 3.92 (2 H, s), 8.12 (2 H, m), and 8.27 (2 H, m)
(3f) ($\text{C}_{11}\text{H}_{16}\text{O}_3$)	80	Ethanol	134 ^b				2700—2100vbr, 1720, 1565, 1380, and 1355	1.10 (6 H, s), 2.17 (3 H, s), 2.35 (4 H, s), 3.43 (2 H, s), and 9.47 (1 H, s, br)
(3h) ($\text{C}_{17}\text{H}_{20}\text{O}_3$)	76	Ethanol	120	75.25 (75.0)	7.6 (7.4)		1730, 1690, 1225, and 1015	1.19 (3 H, s), 1.35 (3 H, s), 1.43 (3 H, s), 2.54 (2 H, d, J 15 Hz), 2.80 (2 H, d, J 15 Hz), 3.61 (2 H, s), 7.3—7.6 (3 H, m), and 7.8—8.1 (2 H, m)
(3i) ($\text{C}_{17}\text{H}_{19}\text{BrO}_3$)	72	Ethanol	139	58.05 (58.1)	5.55 (5.45)		1730, 1690, 1585, 1220, and 1010	1.17 (3 H, s), 1.32 (3 H, s), 1.40 (3 H, s), 2.50 (2 H, d, J 15 Hz), 2.81 (2 H, d, J 15 Hz), 3.54 (2 H, s), 7.56 (2 H, m), and 7.80 (2 H, m)
(3j) ($\text{C}_{18}\text{H}_{22}\text{O}_4$)	68	Methanol	92	71.5 (71.8)	7.3 (7.2)		1730, 1705, 1680, 1610, 1265, 1230, and 1015	1.19 (3 H, s), 1.36 (3 H, s), 1.42 (3 H, s), 2.56 (2 H, d, J 15 Hz), 2.78 (2 H, d, J 15 Hz), 3.58 (2 H, s), 3.83 (3 H, s), 6.89 (2 H, m) and 7.91 (2 H, m)
(3k) ($\text{C}_{17}\text{H}_{19}\text{NO}_5$)	75	Ethanol	123	64.3 (64.35)	5.85 (6.05)	4.4 (4.4)	1730, 1695, 1605, 1520, 1350, 1215, and 1015	1.17 (3 H, s), 1.21 (3 H, s), 1.48 (3 H, s), 2.34 (2 H, d, J 15 Hz), 3.10 (2 H, d, J 15 Hz), 3.62 (2 H, s), 8.22 (2 H, m), and 8.32 (2 H, m). [In (CD_3) ₂ SO]
(3l) ($\text{C}_{12}\text{H}_{18}\text{O}_3$)	76	Methanol	110	68.55 (68.55)	8.55 (8.6)		1730, 1715, 1695 and 1180	1.17 (3 H, s), 1.21 (3 H, s), 1.32 (3 H, s), 2.12 (3 H, s), 2.45 (2 H, d, J 15 Hz), 2.77 (2 H, d, J 15 Hz), and 3.06 (2 H, s)
(3m) ($\text{C}_{23}\text{H}_{24}\text{O}_3$)	72	Ethanol	177	79.65 (79.3)	6.95 (6.95)		1720, 1690, 1220, and 1005	1.19 (3 H, s), 1.38 (3 H, s), 2.60 (2 H, d, J 15 Hz), 2.87 (2 H, d, J 15 Hz), 3.10 (2 H, s), 3.48 (3 H, s), 6.9—7.1 (2 H, m), 7.2—7.5 (6 H, m), and 7.7—7.9 (2 H, m)
(3o) ($\text{C}_{23}\text{H}_{23}\text{BrO}_3$)	74	Ethanol	193	64.5 (64.65)	5.4 (5.4)		1720, 1685, 1585, 1215, and 1010	1.17 (3 H, s), 1.34 (3 H, s), 2.56 (2 H, d, J 15 Hz), 2.89 (2 H, d, J 15 Hz), 3.06 (2 H, s), 3.39 (2 H, s), 6.9—7.1 (2 H, m), 7.2—7.3 (3 H, m), 7.47 (2 H, m), and 7.65 (2 H, m)
(3p) ($\text{C}_{24}\text{H}_{26}\text{O}_4$)	62	Methanol	197	76.3 (76.15)	6.6 (6.9)		1725, 1695, 1670, 1600, 1265, 1230, and 1025	1.16 (3 H, s), 1.37 (3 H, s), 2.58 (2 H, d, J 15 Hz), 2.85 (2 H, d, J 15 Hz), 3.07 (2 H, s), 3.44 (2 H, s), 3.77 (3 H, s), 6.83 (2 H, m), 6.9—7.1 (2 H, m), 7.2—7.4 (3 H, m), and 7.80 (2 H, m)
(3q) ($\text{C}_{23}\text{H}_{23}\text{NO}_5$)	73	Ethanol	208	69.95 (70.2)	5.86 (5.9)	3.25 (3.55)	1725, 1690, 1520, 1350, 1210, and 1015	1.25 (3 H, s), 1.35 (3 H, s), 2.62 (2 H, d, J 15 Hz), 2.95 (2 H, d, J 15 Hz), 3.14 (2 H, s), 3.44 (2 H, s), 6.9—7.1 (2 H, m), 7.2—7.4 (3 H, m), 7.96 (2 H, m), and 8.23 (2 H, m)
(3r) ($\text{C}_{18}\text{H}_{22}\text{O}_3$)	78	Ethanol	162	75.25 (75.5)	7.85 (7.75)		1710, 1685, 1380, 1170, and 1080	1.17 (3 H, s), 1.25 (3 H, s), 2.04 (3 H, s), 2.53 (2 H, d, J 15 Hz), 2.85 (2 H, d, J 15 Hz), 2.91 (2 H, s), 2.98 (2 H, s), 6.9—7.1 (2 H, m), and 7.1—7.4 (3 H, m)
(7b) ($\text{C}_{14}\text{H}_{14}\text{O}_3$)	53	Ethanol	157 ^c				3100—2500vbr, 1685, 1670, 1600vs, and 1380vs	1.8—2.1 (2 H, m), 2.39 (4 H, t, J 6 Hz), 3.85 (2 H, s), 7.4—7.6 (3 H, m), and 7.9—8.1 (2 H, m)
(7f) ($\text{C}_9\text{H}_{12}\text{O}_3$)	68		<i>d</i>				3100—2500vbr, 1705, 1610vs, and 1380vs (film)	1.8—2.2 (2 H, m), 2.13 (3 H, s), 2.47 (4 H, t, J 6 Hz), 3.39 (2 H, s), and 7.3 (1 H, s, br)
(7h) ($\text{C}_{15}\text{H}_{16}\text{O}_3$)	82	Ethanol	125 ^e				1730, 1695, 1675, 1225, and 1025	1.33 (3 H, s), 2.0—2.6 (2 H, m), 2.75 (4 H, t, J 6 Hz), 3.79 (2 H, s), 7.3—7.6 (3 H, m), and 7.8—8.0 (2 H, m)
(7l) ($\text{C}_{10}\text{H}_{14}\text{O}_3$)	64	Methanol	65 ^f				1700 and 1690	1.19 (3 H, s), 2.03 (3 H, s), 1.9—2.3 (2 H, m), 2.4—2.7 (4 H, m), and 3.15 (2 H, s)
(8l) ($\text{C}_9\text{H}_{12}\text{O}_3$)	75		<i>g</i>				1720 and 1710 (film)	1.05 (3 H, s), 2.08 (3 H, s), 2.89 (4 H, s), and 3.17 (2 H, s)
(9h) ($\text{C}_{18}\text{H}_{14}\text{O}_3$)	80	Ethanol	117 ^h	77.55 (77.7)	4.95 (5.05)		1745, 1710, 1680, 1220, and 1000	1.34 (3 H, s), 3.82 (2 H, s), 7.3—7.6 (3 H, m), 7.8—8.0 (2 H, m), and 7.93 (4 H, m)
(9i) ($\text{C}_{18}\text{H}_{13}\text{BrO}_3$)	85	Ethanol	122	60.8 (60.5)	3.7 (3.65)		1745, 1705, 1680, 1220, and 1010	1.32 (3 H, s), 3.77 (2 H, s), 7.53 (2 H, m), 7.71 (2 H, m), and 7.92 (4 H, m)

Table 1 (continued)

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found (%) (Required)			ν_{\max} . (Nujol) (cm^{-1})	δ_{H} (CDCl_3)
				C	H	N		
(9j) ($\text{C}_{10}\text{H}_{16}\text{O}_4$)	84	Methanol	130	74.25 (74.0)	5.35 (5.25)		1 740, 1 710, 1 665, 1 260, 1 235, and 995	1.31 (3 H, s), 3.78 (2 H, s), 6.85 (2 H, m), 7.83 (2 H, m), and 7.90 (4 H, m)
(9k) ($\text{C}_{18}\text{H}_{13}\text{NO}_5$)	86	Ethanol- acetone	167	66.45 (66.85)	4.2 (4.05)	4.15 (4.35)	1 750, 1 710, 1 690, 1 520, 1 355, 1 220, and 1 000	1.37 (3 H, s), 3.84 (2 H, s), 7.96 (4 H, m), 8.04 (2 H, m), and 8.27 (2 H, m)
(9l) ($\text{C}_{13}\text{H}_{12}\text{O}_3$)	76	Methanol	139 ⁱ	72.2 (72.2)	5.65 (5.6)		1 750, 1 705, 1 200, and 1 020	1.21 (3 H, s), 2.06 (3 H, s), 3.26 (2 H, m), 7.89 (4 H, m)

^a Lit.,⁵ 180–182 °C. ^b Lit. (H. J. Schaeffer and R. Vince, *J. Org. Chem.*, 1962, **27**, 4502), 134–136 °C. ^c Lit. (H. Stetter and E. Seihnhold, *Chem. Ber.*, 1955, **88**, 271), 158.5 °C. ^d Oil; analytical data have been reported (H. Stetter and R. Lauterbach, *Justus Liebig's Ann. Chem.*, 1962, **652**, 40). ^e Lit.,⁷ 124–125 °C. ^f Lit.,⁸ 62–64 °C. ^g Oil; analytical data have been reported (T. Yanami, A. Ballatore, M. Miyashita, M. Kato, and A. Yoshikoshi, *Synthesis*, 1980, 407). ^h Lit.,¹⁰ 118 °C. ⁱ Lit. (G. N. Gheorghiu, *J. Prakt. Chem.*, 1936, **146**, 193), 136–137 °C.

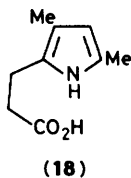
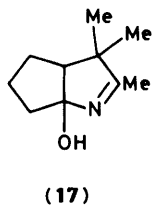
Table 2. Physical, analytical, i.r., and ¹H n.m.r. spectroscopic data for the hydroxypyrrolines (4), (11), (12), and (13)

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found (%) (Required)			ν_{\max} . (Nujol) (cm^{-1})	δ_{H} (CDCl_3)
				C	H	N		
(4a) ($\text{C}_{17}\text{H}_{21}\text{NO}_2$)	98	Ethanol	163	75.6 (75.25)	8.1 (7.8)	5.15 (5.15)	3 140, 1 715, 1 610, 1 279, and 1 050	0.78 (3 H, s), 1.04 (3 H, s), 1.35 (3 H, s) 2.10 (2 H, s), 2.13 (1 H, d, <i>J</i> 13 Hz), 2.49 (1 H, d, <i>J</i> 13 Hz), 2.76 (1 H, d, <i>J</i> 17 Hz), 3.59 (1 H, d, <i>J</i> 17 Hz), 5.80 (1 H, s, br), 7.3–7.5 (3 H, m), and 7.65–7.85 (2 H, m)
(4b) ($\text{C}_{17}\text{H}_{20}\text{BrNO}_2$)	85	Ethanol	155	<i>a</i>			3 160, 1 705, 1 610, 1 280, and 1 055	0.79 (3 H, s), 1.10 (3 H, s), 1.31 (3 H, s), 2.10 (1 H, d, <i>J</i> 13 Hz), 2.13 (2 H, s), 2.53 (1 H, d, <i>J</i> 13 Hz), 2.79 (1 H, d, <i>J</i> 17 Hz), 3.61 (1 H, d, <i>J</i> 17 Hz), 5.41 (1 H, s), 7.55 (2 H, m), and 7.72 (2 H, m)
(4c) ($\text{C}_{18}\text{H}_{23}\text{NO}_3$)	91	Ethanol	164	71.9 (71.75)	7.45 (7.7)	4.55 (4.65)	3 125, 1 715, 1 610, 1 280, 1 270, and 1 055	0.80 (3 H, s), 1.06 (3 H, s), 1.35 (3 H, s), 2.10 (2 H, s), 2.14 (1 H, d, <i>J</i> 13 Hz), 2.50 (1 H, d, <i>J</i> 13 Hz), 2.74 (1 H, d, <i>J</i> 17 Hz), 3.58 (1 H, d, <i>J</i> 17 Hz), 3.85 (3 H, s), 5.53 (1 H, s), 6.89 (2 H, m), and 7.71 (2 H, m)
(4e) ($\text{C}_{12}\text{H}_{19}\text{NO}_2$)	92	Methanol	136	69.0 (68.85)	8.8 (9.15)	6.4 (6.7)	3 150, 1 715, 1 650, 1 250, and 1 145	0.79, (3 H, s), 1.06 (3 H, s), 1.22 (3 H, s), 1.97 (3 H, s), 2.18 (2 H, s), 2.06 (1 H, d, <i>J</i> 13 Hz), 2.33 (1 H, d, <i>J</i> 17 Hz), 2.43 (1 H, d, <i>J</i> 13 Hz), 3.13 (1 H, d, <i>J</i> 17 Hz), and 4.91 (1 H, s, br)
(11a) ($\text{C}_{15}\text{H}_{17}\text{NO}_2$)	85	Ethanol	182	74.3 (74.05)	6.95 (7.05)	5.6 (5.75)	3 120, 1 705, 1 605, 1 275, and 1 050	1.37 (3 H, s), 1.4–2.0 (2 H, m), 2.0–2.7 (4 H, m), 2.85 (1 H, d, <i>J</i> 17 Hz), 3.68 (1 H, d, <i>J</i> 17 Hz), 5.62 (1 H, s, br), 7.3–7.5 (3 H, m), and 7.7–7.9 (2 H, m)
(12e) ($\text{C}_9\text{H}_{13}\text{NO}_2$)	81	Methanol	51	<i>a</i>			3 150, 1 730, 1 640, and 1 085	1.17 (3 H, s), 2.05 (3 H, s), 2.0–2.6 (4 H, m), 2.63 (1 H, d, <i>J</i> 14 Hz), 2.78 (1 H, d, <i>J</i> 14 Hz), and 4.72 (1 H, s, br)

^a Samples recrystallised and spectroscopically pure; satisfactory microanalyses could not be obtained (see text).

(4b) and (12e). Physical, analytical, and spectroscopic data are given in Table 2.

Preparation of 1-acyl-1H-pyrroles. The hydroxypyrrolines (4) were converted into the corresponding products (6) in high yields, either by stirring in benzene with 4A molecule sieves or Florisil, or by dry heating. Similar treatment of compound (12e), however, gave only complex dark mixtures.



1-Acyl-1H-pyrroles were prepared most simply by heating the appropriate triketone together with an excess of dry ammonium acetate under reflux in acetic acid. Thus, the triketones (3), (7), and (9) ($\text{R}^1 \neq \text{H}$) were converted into the corresponding pyrroles (6), (14), and (16) respectively in moderate to good yields. Attempts to prepare the pyrrolizine (15e) from the triketone (8l), however, gave complex mixtures in which the 1H-pyrrolecarboxylic acid (18) could be detected by ¹H n.m.r. spectroscopy. Related carboxylic acids, arising apparently from *N*-acyl cleavage of the products (6), (14), and (16), were also detected as by-products when wet ammonium acetate was used in reactions with the triketones (3), (7), and (9). The products (6) and (14) are 5,6,7,8-tetrahydroindolizin-5-ones, and do not appear to have been reported previously. The pyrrolo[2,1-*a*]isoindol-5-ones (16), however, are known,¹⁵ and like the structurally related 3H-pyrrolizin-3-ones¹⁶ are

Table 3. Physical, analytical, i.r., and ¹H n.m.r. spectroscopic data for the 1-acyl-1*H*-pyrroles (6), (14), and (16)

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found (%) (Required)			$\nu_{\max.}$ (Nujol) (cm ⁻¹)	δ_{H} (CDCl ₃)
				C	H	N		
(6a) (C ₁₇ H ₁₉ NO)	74	Ethanol	120	80.55 (80.6)	7.65 (7.55)	5.4 (5.55)	1 710, 1 355, 1 315, 762, and 695	1.05 (6 H, s), 1.96 (3 H, s), 2.45 (2 H, s), 2.58 (2 H, s), 6.04 (1 H, s), and 7.1—7.4 (5 H, m)
(6b) (C ₁₇ H ₁₈ BrNO)	68	Ethanol	113	61.55 (61.45)	5.45 (5.45)	4.2 (4.2)	1 705, 1 355, 1 292, and 820	1.06 (6 H, s), 1.97 (3 H, s), 2.47 (2 H, s), 2.58 (2 H, s), 6.04 (1 H, s), 7.21 (2 H, m), and 7.39 (2 H, m)
(6c) (C ₁₈ H ₂₁ NO ₂)	60	Methanol	123	76.7 (76.3)	7.55 (7.45)	5.0 (4.95)	1 710, 1 355, 1 310, 1 245, 1 030, and 830	1.09 (6 H, s), 1.98 (3 H, s), 2.48 (2 H, s), 2.61 (2 H, s), 3.81 (3 H, s), 6.00 (1 H, s), 6.85 (2 H, m), and 7.29 (2 H, m)
(6d) (C ₁₇ H ₁₈ N ₂ O ₃)	63	Ethanol-acetone	129	68.55 (68.45)	6.25 (6.1)	9.35 (9.4)	1 720, 1 510, 1 350, 1 335, and 865	1.04 (6 H, s), 1.97 (3 H, s), 2.60 (2 H, s), 2.68 (2 H, s), 6.39 (1 H, s), 7.95 (2 H, m), and 8.51 (2 H, m) [In (CD ₃) ₂ SO]
(6e) (C ₁₂ H ₁₇ NO)	62	Methanol	56	75.0 (75.35)	8.7 (8.95)	7.15 (7.3)	1 715, 1 360, 1 320, 805, and 800	1.05 (6 H, s), 1.90 (3 H, s), 2.48 (7 H, s, br), and 5.72 (1 H, s)
(6f) (C ₂₃ H ₂₃ NO)	72	Ethanol	78	84.05 (83.85)	7.2 (7.05)	4.15 (4.25)	1 715, 1 355, 1 300, 770 and 705	1.05 (6 H, s), 2.49 (2 H, s), 2.62 (2 H, s), 3.71 (2 H, s), 6.03 (1 H, s), and 7.1—7.3 (10 H, m)
(6g) (C ₂₃ H ₂₂ BrNO)	70	Ethanol	116	67.6 (67.65)	5.5 (5.45)	3.35 (3.45)	1 720, 1 360, 1 305, 820 and 714	1.08 (6 H, m), 2.51 (2 H, s), 2.66 (2 H, s), 3.72 (2 H, s), 6.04 (1 H, s), 7.21 (2 H, m), 7.24 (5 H, s), and 7.40 (2 H, m)
(6h) (C ₂₄ H ₂₅ NO ₂)	64	Ethanol	94	80.6 (80.2)	6.95 (7.0)	3.8 (3.9)	1 715, 1 360, 1 295, 1 250, 1 040, 835, and 735	1.08 (6 H, m), 2.50 (2 H, s), 2.65 (2 H, s), 3.73 (2 H, s), 3.79 (3 H, s), 5.99 (1 H, s), 6.84 (2 H, m), 7.23 (5 H, s), and 7.27 (2 H, m)
(6i) (C ₂₃ H ₂₂ N ₂ O ₃)	61	Ethanol-acetone	152	73.4 (73.75)	5.85 (5.9)	7.25 (7.5)	1 710, 1 505, 1 355, 1 340, 1 310, 1 290, 840, and 710	1.11 (6 H, s), 2.56 (2 H, s), 2.70 (2 H, s), 3.74 (2 H, s), 6.20 (1 H, s), 7.2—7.3 (5 H, m), 7.47 (2 H, m), and 8.13 (2 H, m)
(6j) (C ₁₈ H ₂₁ NO)	65	Methanol	66	80.45 (80.85)	7.9 (7.9)	5.1 (5.25)	1 705, 1 365, 1 320, 1 295, and 720	1.05 (6 H, s), 2.45 (5 H, s), 2.56 (2 H, s), 3.65 (2 H, s), 5.72 (1 H, s), and 7.1—7.3 (5 H, m)
(14a) (C ₁₅ H ₁₅ NO)	68	Ethanol	64	79.8 (80.0)	7.0 (6.7)	6.1 (6.2)	1 720, 1 355, 1 330, 1 305, 760, and 700	1.8—2.1 (2 H, m), 1.95 (3 H, s), 2.4—2.8 (4 H, m), 6.02 (1 H, s), 7.1—7.4 (5 H, m)
(16a) (C ₁₈ H ₁₃ NO)	52	Ethanol	90	83.4 (83.35)	5.3 (5.05)	5.55 (5.4)	1 775, 1 740, 1 355, 1 305, 895, 770 and 710	2.19 (3 H, s), 6.10 (1 H, s), and 7.0—7.85 (9H, m)
(16b) (C ₁₈ H ₁₂ BrNO)	54	Ethanol	144	63.85 (63.9)	3.55 (3.6)	4.05 (4.15)	1 780, 1 750, 1 365, 1 300, 895, 810, 760 and 705	2.21 (3 H, s), 6.13 (1 H, s), 7.9—7.7 (4 H, m), 7.49 (2 H, m), and 7.66 (2 H, m)
(16c) (C ₁₉ H ₁₅ NO ₂)	42	Methanol	140	78.65 (78.85)	4.6 (5.2)	4.65 (4.85)	1 780, 1 750, 1 355, 1 305, 1 265, 895, 820, 770, and 705	2.10 (3 H, s), 3.78 (3 H, s), 5.96 (1 H, s), 6.87 (2 H, m), 7.0—7.7 (4 H, m), and 7.71 (2 H, m)
(16d) (C ₁₈ H ₁₂ N ₂ O ₃)	44	Acetone	224	70.9 (71.05)	3.75 (3.95)	8.95 (9.2)	1 775, 1 740, 1 510, 1 340, 1 305, 895, 830, 760 and 705	2.25 (3 H, s), 6.35 (1 H, s), 7.1—7.7 (4 H, m), 7.97 (2 H, m), and 8.22 (2 H, m)
(16e) (C ₁₃ H ₁₁ NO)	42	Methanol	77	78.9 (79.15)	5.65 (5.6)	6.9 (7.1)	1 795, 1 730, 1 375, 1 300, 900, 770, and 705	2.10 (3 H, s), 2.34 (3 H, s), 5.61 (1 H, s), and 7.0—7.7 (4 H, m)

coloured orange to red. The i.r. spectra of all products showed a carbonyl frequency more typical for a ketone than an amide, as is generally the case with *N*-acylpyrroles. In the ¹H n.m.r. spectra, the pyrrole ring proton signal appeared as a singlet in the range δ 5.6—6.4, and was sensitive to the nature of R². Physical, analytical, and spectroscopic data for compounds (6), (14), and (16) are given in Table 3; yields are from the triketone precursor and ammonium acetate.

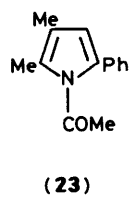
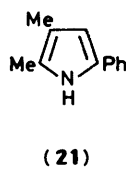
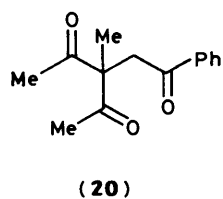
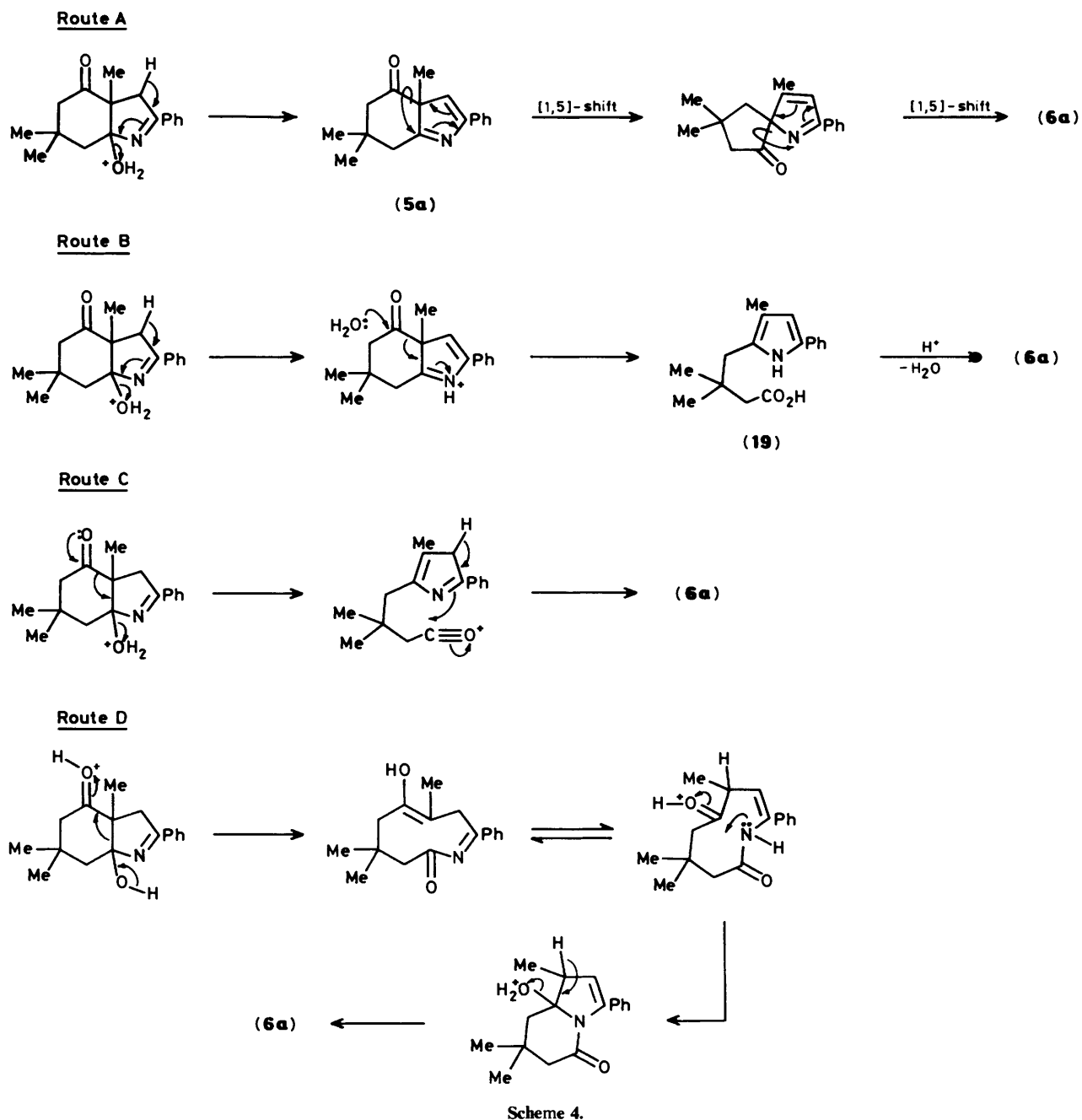
The Mechanism of the Rearrangement.—Since ammonium acetate in acetic acid has been reported to convert a precursor 1,4-diketone into compound (17),¹² and compounds (4) are readily transformed into the products (6) by a number of methods, it is reasonable to assume that hydroxypyrrolines (4), (11), and (13) are intermediates in the preparation of pyrroles (6), (14), and (16) respectively from triketones (3), (7), and (9). At least four different mechanisms can be envisaged for the rearrangement. These are shown for hydroxypyrroline (4a) in Scheme 4; it is possible for the dehydration step to precede, or be concerted with the rearrangements.

Route A is appealing, since [1,5]-sigmatropic shifts are reactions very characteristic of azolenines. For example, a rearrangement analogous to the final step of this pathway

has been observed for a spiro-3*H*-pyrazole.¹⁷ However, the formation of products (16) by this route would require highly strained spiro-benzocyclobutenone intermediates, and this is inconsistent with the ease by which the transformation takes place.

Teuber and co-workers proposed a mechanism analogous to route B for the conversion of the phenylhydrazone of 2-methylcyclohexane-1,3-dione into a 1,2,3,4-tetrahydropyrindo[1,2-*a*]indol-4-one, although they did not isolate any intermediates.¹⁸ We found that the acid (19), formed by hydrolysis of the indolizine (6a) with ethanolic sodium hydroxide followed by acidification, could not be converted back into (6a) on treatment with ammonium acetate in acetic acid, thus rendering this mechanism unlikely.

The fourth mechanism, route D, closely parallels the syntheses of benzopyrrolizinones,¹⁹ pyrrolizinones, and indolizinones²⁵ from 2-methylcyclopentane-1,3-dione, as described by Ban and co-workers, and referred to by them as 'crisscross annulation'.²⁰ The reaction is presumably mediated by trans-annular interaction between an amide nitrogen atom and a ketone carbonyl group within an eight- or nine-membered ring, and should fail with non-cyclic analogues where such an interaction would be much less favourable. The observation



that the triketone (20) yields the pyrrole (21) and acetamide, and not the pyrrole (22), on treatment with ammonium acetate and acetic acid, supports this prediction.²¹

At present we favour route D, although route C remains a strong contender; we are currently designing experiments to distinguish the two. Finally, all four rearrangement mechanisms are facilitated by the ketone carbonyl group in the hydroxypyrraline intermediate; we have recently shown that in the absence of such a group, hydroxypyrralines may be dehydrated successfully to give *3H*-pyrroles.²¹

Experimental

M.p.s are uncorrected, and were measured on a Reichert Thermovar hot-stage apparatus. I.r. spectra were recorded in Nujol on Perkin-Elmer 577 and 157G spectrometers, and were

calibrated against polystyrene. ^1H and ^{13}C N.m.r. spectra were recorded in CDCl_3 , unless indicated otherwise, on a JEOL FX-90Q spectrometer, with SiMe_4 as internal standard. Cyclic diketones (**3a**), (**7a**), and (**8g**) were purchased, while (**9g**) was prepared accordingly to Mosher's procedure.²²

Monosubstitution of Cyclic Diketones (3a) and (7a): General Procedure.—The cyclic 1,3-diketone (**3a**) or (**7a**) (0.1 mol), the appropriate α -bromo ketone (0.1 mol), and anhydrous K_2CO_3 (18 g, 0.13 mol), were stirred together in dry CHCl_3 (80 ml) for 12 h at 25 °C. The mixture was filtered and the residual potassium salt of the product was dissolved in water (60 ml), and the solution acidified with HCl. The crude product was filtered off, washed with water, and recrystallised from the appropriate solvent. Data for compounds (**3b–f**), (**7b**), and (**7f**), prepared by this method, are in Table 1.

Preparation of the Triketones (3h–l), (3n–r), (7h), and (7l): General Procedure.—DBU (15.2 g, 0.1 mol) was added to a stirred solution of the appropriate monosubstituted diketone (0.1 mol) in DMF (200 ml). With cooling, the alkyl halide (methyl iodide or benzyl bromide; 0.15 mol) was added dropwise during 15 min. The mixture was stirred at 25 °C for 12–14 h, poured into water (250 ml), and the solution extracted with CHCl_3 (3 \times 40 ml). The CHCl_3 extracts were washed with water (3 \times 50 ml), dried (MgSO_4), and evaporated to give the crude product, which was recrystallised from the appropriate solvent. Data are in Table 1.

Preparation of Cyclopentanedione Derivative (8l).—The diketone (**8m**)⁹ (7.5 g, 0.05 mol) in aqueous methanol (1:4) (200 ml) containing concentrated H_2SO_4 (2–3 drops) was stirred at 25 °C with mercuriated Dowex-50 resin⁸ (30 mg) for 24 h. The reaction mixture was filtered, the filtrate evaporated under reduced pressure, and the residue diluted with water (100 ml) and extracted with CHCl_3 (2 \times 50 ml). The extract was dried (MgSO_4), and evaporated to give the product as an oil.

Alkylation of 2-Methylindan-1,3-dione (9g): General Procedure.—The diketone (**9g**) (6.4 g, 40 mmol), the appropriate α -bromo ketone (40 mmol), and anhydrous potassium carbonate (6.9 g, 50 mmol) were mixed in dry acetone (80 ml). The mixture was stirred, either under reflux for 5 h [for the triketones (**9h**), (**9i**), and (**9l**)], or at 25 °C for 20 h [for the triketones (**9j**) and (**9k**)], and the solvent was evaporated under reduced pressure. The residue was acidified with 2M HCl, filtered, washed with water, and recrystallised. Data are in Table 1.

Reactions of the Triketones with Liquid Ammonia: General Procedure.—The triketone (**3**), (**7**), (**8**), or (**9**) (10 mmol) was dissolved in anhydrous liquid ammonia (70–80 ml) in an insulated container, and the ammonia allowed to evaporate slowly overnight. Where reaction occurred, the conversion was essentially quantitative, and the products were spectroscopically pure. They were recrystallised for microanalysis; data for hydroxypyrrolines prepared successfully are in Table 2. For the *p*-bromo compound (**4b**), δ_{C} 18.47 (q), 27.36 (q, 6-Me), 31.53 (q, 3a-Me), 32.02 (s, C-6), 42.85 (t, C-3), 46.86 (t, C-7), 50.16 (t, C-5), 57.80 (s, C-3a), 103.04 (s, C-7a), 125.19 (s, C-*p*), 129.20 (d, C-*o*), 131.48 (d, C-*m*), 133.20 (s, C-*i*), 171.89 (s, C-2), and 212.68 (s, C-4); for *p*-methoxy-compound (**4c**), δ_{C} 18.58 (q), 27.95 (q, 6-Me), 31.15 (q, 3a-Me), 32.18 (q, C-6), 43.93 (t, C-3), 47.94 (t, C-7), 50.49 (t, C-5), 55.42 (q, OMe), 57.69 (s, C-3a), 103.15 (s, C-7a), 113.87 (d, C-*m*), 126.44 (s, C-*i*), 129.80 (d, C-*o*), 162.36 (s, C-*p*), 173.08 (s, C-2), and 212.90 (s, C-4).

Preparation of 1-Acyl-1H-pyrroles.—From hydroxypyrrolines. The hydroxypyrroline (**4**) or (**11**) (5 mmol) was heated slowly

in an oil-bath to its melting point, and maintained at that temperature for 5 min. The cooled product was recrystallised. Alternatively, the hydroxypyrroline (5 mmol) was stirred at 25 °C in benzene (70 ml) in the presence of 4A molecular sieves, or Florisil (1–2 g), for 16 h. Filtration, followed by evaporation of the solvent, gave the product pyrrole essentially quantitatively.

From triketones: general procedure. The appropriate triketone (**3**), (**7**), (**8**), or (**9**) (5 mmol) and dry ammonium acetate (5.8 g, 75 mmol) were heated together under reflux in acetic acid for 4–5 h. The mixture was cooled, diluted with water (100 ml), neutralised with aqueous ammonia, and extracted with CHCl_3 (3 \times 30 ml). The CHCl_3 solution was washed with water (3 \times 50 ml), dried (MgSO_4), and the solvent removed under reduced pressure. The crude product was recrystallised; data are in Table 3. For the triketone (**8l**), the complex product contained the 1H-pyrrolicarboxylic acid (**18**); δ_{H} *inter alia* 1.92 (s, Me), 2.13 (s, Me), 2.3–2.8 (m, CH_2), 5.5 (d, J 2.5 Hz, ring CH), 8.05 (s, br, NH), and 8.9 (s, br, OH).

Hydrolysis of the 1-Acylpyrrole (6a) to the Carboxylic Acid (19), and Attempted Recyclization.—The pyrrole (**6a**) (1.27 g, 5 mmol) and 10% aqueous NaOH (15 ml) were refluxed in ethanol (60 ml) for 4 h, after which the mixture was cooled, and the ethanol evaporated under reduced pressure. The aqueous residue was acidified with 2M HCl and extracted with CHCl_3 (3 \times 30 ml). The CHCl_3 extracts were washed with water, dried (MgSO_4) and evaporated to give the essentially pure carboxylic acid (**19**); δ_{H} 1.07 (6 H, s), 2.05 (3 H, s), 2.28 (2 H, s), 2.59 (2 H, s), 6.30 (1 H, d, J 2.5 Hz), 7.0–7.5 (5 H, m), 9.25 (1 H, s, br), and 10.11 (1 H, s, br). Treatment of this product with ammonium acetate in acetic acid, under conditions described above for conversion of triketones into 1-acylpyrroles, gave a mixture containing some carboxylic acid (**19**), but none of compound (**6h**).

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