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THE SYNTHESIS AND CHEMISTRY OF AZOLENINES.[1] PART 18.[2] PREPARATION OF 3-ETHOXYCARBONYL-3H-PYRROLES *VIA* THE PAAL-KNORR REACTION, AND SIGMATROPIC REARRANGEMENTS INVOLVING COMPETITIVE ESTER MIGRATIONS TO C-2, C-4 AND N.[3]

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ABSTRACT: 3H-Pyrrole-3-carboxylic esters (4) have been prepared, in some cases together with isomers (5) and (6) having exocyclic double bonds, by cyclization of suitably substituted 2-ethoxycarbonyl-1,4-diketones (1) with liquid ammonia, followed by dehydration of the isolable 2-hydroxy-3,4-dihydro-2H-pyrrole intermediates (2) and (3) with aluminia in boiling solvents. Prolonged heating in toluene or p-xylene converts the 3H-pyrroles (4) quantitatively into isomeric 4-esters (11) and N-esters (13) of 1H-pyrroles *via* competitive [1,5]sigmatropic rearrangements. Isolable intermediate 2H-pyrrole-2-carboxylic esters (12) are converted similarly into the same products, under the same conditions. Detection of 3H-pyrroles (4) as intermediates in the latter reaction demonstrates for the first time the reversibility of the thermal 2H-pyrrole to 3H-pyrrole interconversion.

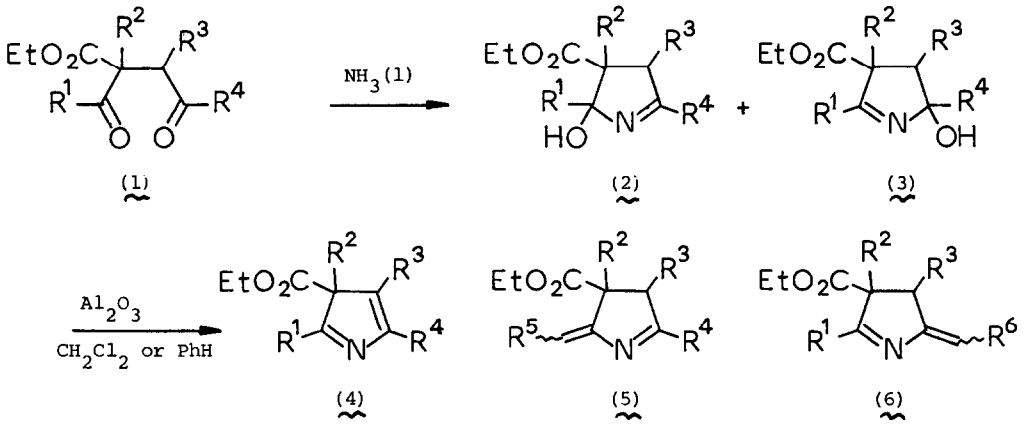
INTRODUCTION

As an extension to our recently-reported synthesis of 3H-pyrroles *via* the Paal-Knorr reaction,[4] we were interested in preparing examples having an ester group at C-3. Besides being a novel class of 3H-pyrrole, these compounds might undergo competitive thermal [1,5]sigmatropic rearrangements to isomeric 1H-pyrroles in a fashion analogous to the van Alphen-Hüttel rearrangements of 3H-pyrazoles.[5] Thermal [1,5]sigmatropic rearrangements of 2H-pyrroles to give ultimately 1H-pyrroles have been well documented, and sometimes pass through (unobserved) 3H-pyrrole intermediates;[6] likewise, during Diels-Alder cycloadditions, the 3H-isomers appear to exist in undetectably low concentrations in equilibrium with 2H-pyrroles.[7] In contrast, all known rearrangements starting from 3H-pyrroles have been reported to proceed by ionic mechanisms. Thus, McEwen and co-workers rationalised the observed 1H-pyrrole products from the rearrangement of 2,3,3,5-tetra-aryl 3H-pyrroles in strong acid, or on fusion with potassium hydroxide, in terms of cationic or anionic intermediates,[8] while Wong and co-workers showed by kinetics studies that the conversion of 2,3,3,4,5-penta-alkyl 3H-pyrroles into the 2H-isomers was irreversible, and proceeded *via* an acid-catalysed Wagner-Meerwein type mechanism.[9]

We now report the preparation of a series of 3-ethoxycarbonyl-3H-pyrroles, and a study of their thermal rearrangements.

RESULTS AND DISCUSSION

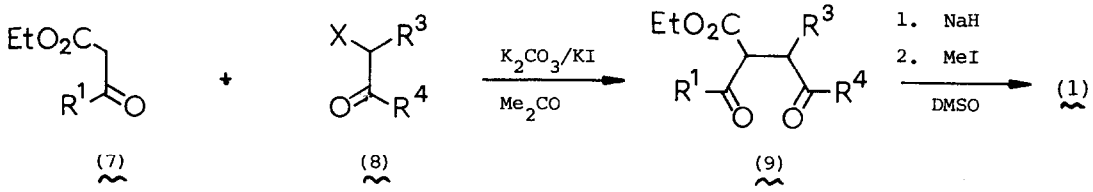
Preparation of 3H-Pyrroles. - A general route for the preparation of the desired 3-ethoxycarbonyl-3H-pyrroles (4) is shown in Scheme 1. The diketo-esters (1a)-(1i) were prepared by first alkylating a ß-keto-ester (7) (Scheme 2) with the appropriate haloketone (8) in the presence of potassium carbonate and potassium iodide in acetone[10] to give the diketo-esters



	R^1	R^2	R^3	R^4
a	Me	Me	H	Me
b	Me	Me	H	Ph
c	Ph	Me	H	Me
d	Ph	Me	H	Ph
e	Me	Me	H	Bu^t
f	Ph	Me	H	Bu^t
g	Me	Me	Me	Me
h	Me	Me	$[CH_2]_4$	
i	Me	Me	Me	Ph
j	Bu^t	Me	H	Me
k	EtO_2C	Me	H	Ph
l	$[CH_2]_4$		H	Me
m	$[CH_2]_4$		H	Ph

SCHEME 1

(9), which were further reacted with sodium hydride in dimethyl sulfoxide (DMSO) followed by methyl iodide to yield the products (1). Formation of compounds (9) (29-79%) by this method was more convenient than by that using sodium ethoxide in ethanol;[11] it was also regioselective, as was the second alkylation to give the diketo-esters (1a)-(1f). However, for alkylation of compounds (9) having $R^3 \neq H$, both C- and O-methylated products were isolated, the former predominating as a mixture of diastereomers. Attempts to methylate the 1-tert-butyl compound (9j) under the same conditions led not to the product (1j), but rather to the rearranged isomer (1e), formed presumably via a homo-enolate type mechanism analogous to that studied by Yates.[12] Compound (1j) was subsequently prepared by alkylating the ß-keto-ester (7c) sequentially with 3-bromopropyne and methyl iodide, followed by mercury(II)



	R^1
a	Me
b	Ph
c	Bu^t

	R^3	R^4	X
a	H	Me	Cl
b	H	Ph	Br
c	H	Bu^t	Br
d	Me	Me	Br
e	$[CH_2]_4$		Cl
f	Me	Ph	Br

	R^1	R^3	R^4
a	Me	H	Me
b	Me	H	Ph
c	Ph	H	Me
d	Ph	H	Ph
e	Me	H	Bu^t
f	Ph	H	Bu^t
g	Me	Me	Me
h	Me	$[CH_2]_4$	
i	Me	Me	Ph
j	Bu^t	H	Me

SCHEME 2

catalysed hydration[13] of the triple bond. Alkylation of diethyl 3-methyl-2-oxobutanedioate with the bromoketone (8b) gave the diketo-diester (1k) together with 30% of the O-phenacylisomer, while compounds (1l) and (1m) were prepared from ethyl 2-oxocyclohexanecarboxylate respectively by alkylation with 3-bromopropyne followed by mercury(II) hydration,[13] and by alkylation with the bromoketone (8b). Physical, analytical, IR, and ^{1}H NMR spectroscopic data for the diketo-esters (1), most of which are novel, are given in Table 1.

Previous experience had shown that, for 1,4-diketones (1) having the ester group replaced by alkyl or phenyl[4] or by an acyl group forming with R^1CO a cyclic 1,3-diketone moiety,[14] reaction with liquid ammonia gave mixed regioisomeric 2-hydroxy-3,4-dihydro-2H-pyrroles (hydroxypyrrolines). However, for analogues having an acetyl or benzoyl group in place of the ester, fragmentation occurred to give simpler 1,4-diketones together with acetamide or benzamide.[15] The diketoesters (1) proved to be intermediate in behaviour. Reaction overnight with liquid ammonia[4] gave high yields of mixed diastereomers of the regioisomeric hydroxypyrrolines (2) and (3) from examples (1a), (1b), (1e), (1g)-(1i), (1l), and (1m), while benzamide was formed from (1c), (1d), and (1f), trimethylacetamide from (1j), and the half ester - half amide of oxalic acid from (1k).

2,2-Dialkyl-1,4-diketones have been cyclized successfully to hydroxypyrrolines using ammonium acetate in acetic acid,[16] although we have found that this method can lead directly

Table 1. Physical, analytical, IR, and ^1H NMR spectroscopic data for the diketo-esters (1).

Compound (Formula)	Yield[a] (%)	B.p./mmHg or m.p. (^0C)	Found (%) (Required) C	H	$\nu_{C=0}$ (cm^{-1}) (Film)	δ_H ($CDCl_3$)
(1a) ($C_{10}H_{16}O_4$)	34	74/0.5	59.9 (60.0	8.3 8.05)	1740 and 1728	1.25(3H, t), 1.48(3H, s), 2.16 (3H, s), 2.26(3H, s), 3.07(2H, 3.07(2H, s), and 4.19(2H, q)
(1b) ($C_{15}H_{18}O_4$)	49	[b]	68.7 (68.7	7.15 6.9)	1740, 1720 and 1693	1.24(3H, t), 1.57(3H, s), 2.33 (3H, s), 3.65(2H, s), 4.20(2H, (2H, q) 7.3-7.6(3H, m), and 7.9-8.1(2H, m)
(1c) ($C_{15}H_{18}O_4$)	78	118-120 /0.05	68.9 (68.7	6.65 6.9)	1743, 1726 and 1690	1.13(3H, t), 1.66(3H, s), 2.15 (3H, s), 3.22(2h, s), 4.16(2H, q), 7.3-7.5(3H, m), and 7.7-7.9(2H, m)
(1d) ($C_{20}H_{20}O_4$)	68	66-67[c]	73.9 (74.05	6.25 6.2)	1740 and 1685	1.12(3H, t), 1.74(3H, s), 3.83 (2H, s), 4.17(2H, q), 7.4-7.6 (6H, m), and 7.6-8.0(4H, m)
(1e) ($C_{13}H_{22}O_4$)	79	63-65 /0.02	64.4 (64.45	9.25 9.15)	1735 and 1705	1.15(9H, s), 1.25(3H, t), 1.45 (3H, s), 2.29(3H, s), 3.16(2H s), and 4.19(2H, q)
(1f) ($C_{18}H_{24}O_2$)	84	120/0.07	71.15 (71.05	7.9 7.95)	1735, 1705 and 1685	1.09(9H, s), 1.12(3H, t), 1.63 (3H, s), 3.31 and 3.41(2H, ABq, J 18 Hz), 4.16(2H, q), 7.3-7.5(3H, m), and 7.7-7.9 (2H, m)
(1g) ($C_{11}H_{18}O_4$)	56[d]	[b]	61.8 (61.65	8.4 8.45)	1732 and 1713	1.15(3H, d), 1.24(3H, t), 1.49 (3H, s), 2.20(3H, s), 2.22(3H, s), 3.46(1H, q) and 4.16(2H, q); and 1.15(3H, d), 1.27(3H, t), 1.54(3H, s), 2.20(3H, s), 2.23(3H, s)[e] 3.46(1H, q), and 4.20(2H, q)[e]
(1h) ($C_{13}H_{20}O_4$)	48[f]	[b]	65.15 (65.0	8.55 8.4)	1732, 1720 and 1708	1.25(3H, t), 1.51(3H, s), 1.4-2.4(8H, m), 2.28(3H, s), 3.47 (1H, m) and 4.16(2H, q); and 1.23(3H, t), 1.44(3H, s), 1.4-2.4(8H, m), 2.21(3H, s)[e] 3.47 (1H, m), and 4.20(2H, q)[e]
(1i) ($C_{16}H_{20}O_4$)	49[g]	[b]	69.7 (69.55	7.3 7.3)	1736, 1712 and 1682	1.07(3H, t), 1.19(3H, d), 1.70 (3H, s), 2.25(3H, s), 4.04(2H, q), 4.45(1H, q), 7.4-7.6(3H, m), and 7.9-8.1(2H, m)[h]
(1j) ($C_{13}H_{22}O_4$	85	[b]	64.55 (64.45	9.2 9.15)	1720 and 1690	1.21(9H, s), 1.27(3H, t), 1.60 (3H, t), 2.17(3H, t), 2.85 and 3.08(2H, ABq, J 17 Hz), and 4.18(2H, q)
(1k) ($C_{17}H_{20}O_6$)	45[i]	[b]	63.8 (63.75	6.4 6.3)	1757, 1730 and 1685	1.23(3H, t), 1.35(3H, t), 1.58 (3H, s), 3.86 and 4.04(2H, ABq, J 18 Hz), 4.31(2H, q), 7.4-7.6(3H, m), and 7.9-8.1 (2H, m)
(1l) ($C_{13}H_{20}O_4$)	81	75-80[j] /0.02			1735, 1726 and 1710	1.27(3H, t), 1.72(5H, m), 1.9-2.9(3H, m), 2.19(3H, s), 2.86 (2H, s), and 4.22(2H, q)
(1m) ($C_{18}H_{22}O_4$)	60	92-93[k]			1716 and 1680	1.25(3H, t), 1.7-2.1(5H, m), 2.4-2.9(3H, m), 3.38 and 3.55 (2H, ABq, J 17 Hz), 4.23(2H, q), 7.3-7.6(3H, m), and 7.9-8.0(2H, m)

[a] From immediate precursor. [b] Oil; purified by column chromatography (SiO_2). [c] From 95% ethanol; IR spectrum in Nujol. [d] O-Methylated isomer (9%) also formed. [e] Mixed diastereomers; major isomer first. [f] O-Methylated isomer (6%) also formed. [g] O-Methylated isomer (10%) also formed. [h] Minor diastereomer *inter alia* δ_H 1.67(3H, s), and 2.23(3H, s). [i] O-Phenacyl isomer (10%) also formed. [j] Lit.[21] 85-90°C/0.1 mmHg. [k] Lit.[20] m.p. 94°C; IR spectrum in Nujol.

to 3H-pyrroles, or to isomeric 2H-pyrroles by rearrangement.[4] Again, the diketoesters (1) proved to be intermediate in behaviour, giving hydroxypyrrolines (2) and (3) in some cases, and in others 3H-pyrroles (4) alone, or in admixture with compounds (2) and (3). Results for both synthetic methods are summarized in Table 2. Where hydroxypyrrolines were isolated, the

Table 2. Products from the reaction of diketoesters (1) with liquid ammonia, or ammonium acetate and acetic acid.

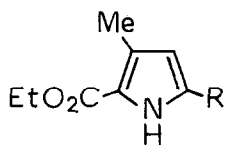
Compound	Conditions[a]	Product ratio[b] (2) : (3) : (4)	Other products
(1a)	A	3 : 1	
(1b)	A	7 : 3	
(1c)	A	0 : 0	$PhCONH_2$
	B	3 : 7 : 0	
(1d)	A	0 : 0	$PhCONH_2$
	B	0 : 0 : 1	
(1e)	A	7 : 3	
(1f)	A	0 : 0	$PhCONH_2$
	B	0 : 0 : 1	
(1g)	A	[c]	
(1h)	A	[c]	
(1i)	A	[c]	
(1j)	A	0 : 0	Bu^tCONH_2
	B	2 : 17 : 1	
(1k)	A	0 : 0	EtO_2CCONH_2
	B	19 : 0 : 1	
(1l)	A	19 : 1	
(1m)	A	19 : 1	

[a] A: Liquid NH_3, 16 h; B: $AcONH_4$, AcOH, 60-70°C, 16 h. [b] Determined from ^1H NMR integrals; isomers (2) and (3) as mixed diastereomers. [c] Complex mixture of isomeric hydroxypyrrolines (2) and (3).

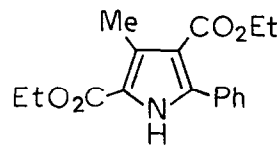
major regioisomer was the thermodynamically more stable one. Mixed diastereomers were observed in all cases, except for examples (2l) and (2m), where presumably only the isomers with cis-fused rings were formed. In most cases the major regioisomer could be obtained pure by recrystallisation, and could be distinguished by the coupling constant for the ^1H NMR AB quartet corresponding to the ring methylene group: J ca. 17 Hz for isomers (2) and ca. 14 Hz for isomers (3). Mixed diastereomers could not be separated.

Most hydroxypyrrolines were dehydrated successfully using basic alumina in refluxing dichloromethane, as described previously.[4] 3H-Pyrroles (4) were formed as the major products, together with exocyclic isomers (5) and/or (6) where substituents R^1 and R^4 bore an α-hydrogen atom ($R^5 = R^1 - CH_2$; $R^6 = R^4 - CH_2$). However, the mixed isomers (2c) and (3c) required prolonged refluxing in the higher-boiling benzene; and the regioisomer (3j) gave the mixed isomers (4j) and (6j) only on refluxing with acidic alumina in toluene for 24 h, or

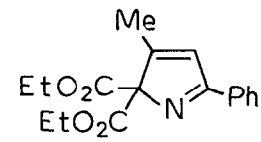
formed the de-tert-butyl-1H-pyrrole (10a) on heating with ammonium acetate in acetic acid. The hydroxypyrroline (2k) on prolonged heating with ammonium acetate in acetic acid yielded a small amount of the 3H-pyrrole (4k) together with the 1H-pyrroles (10b) and (11k), or on refluxing with acidic alumina in toluene for 48 h, gave a mixture of the three isomers (4k), (11k), and the 2H-pyrrole (12k). The isomers (11k) and (12k) must arise from migrations of the 3-ester group during the reaction. Details of isomer distributions are given in Table 3.



(10a) R = Me
(10b) R = Ph



(11k)



(12k)

Table 3. Products from the dehydration of hydroxypyrrolines (2) and (3).

Compounds	Conditions[a]	Product ratio[b] (4) : (5) : (6)
(2a), (3a)	C	50 : 45 : 5
(2b), (3b)	C	60 : 40
(2c), (3c)	D	75 : 25
(2e)	C	70 : 30
(2g), (3g)	C	98 : 2 : 0
(2h), (3h)	C	33 : 0 : 67
(2i), (3i)	C	98 : 2
(3j)	C,D,E	[c]
(2k)	E	[c]
(2l)	C	10 : 90 : 0
(2m)	C	70 : 30

[a] C: Basic Al_2O_3, CH_2Cl_2, reflux, 24 h; D: Basic Al_2O_3, PhH, reflux 48 h; E: $AcONH_4$, AcOH, 60-70°C, 12 h. [b] Determined from ^1H NMR integrals. [c] See text.

In contrast with 3H-pyrroles bearing only alkyl or aryl substituents,[4] the 3-ethoxycarbonyl compounds (4) could generally be separated from the exocyclic isomers (5) and (6) by rapid passage through a neutral alumina column using petroleum ether/diethyl ether as eluent; exceptions were compounds (4b) and (4e). Prolonged residence on the column resulted in loss of the 3-ester group, or hydration of the ring. 3H-Pyrroles prepared directly from the diketoesters (1) were likewise purified by column chromatography, or by pH partition. Exocyclic isomers (5) and (6) could not be obtained pure, but were readily identified from ^1H NMR signals in the 4-6 p.p.m. range. ^1H and ^{13}C NMR spectroscopic data for 3H-pyrroles

Table 4. ^1H and ^{13}C NMR spectroscopic data (δ; $CDCl_3$) for 3H-pyrroles (4).

Comp'd	δ_H	δ_C
(4a)	1.22(3H,t), 1.40(3H,s), 2.13(3H,d),[a] 2.22(3H,s), 4.11,4.12(2H,2q), 5.75 (1H,q)[a]	14.09(q), 16.14(2C,q), 18.53(q), 61.38(t), 66.80(s,C-3), 122.92(d,C-4), 153.75(s, C-5), 170.49(s), 182.30(s,C-2)
(4b)	1.21(3H,t), 1.51(3H,s), 2.33(3H,s), 4.12,4.14(2H,2q), 6.41(1H,s), 7.3-7.5 (3H,m), 7.8-7.9(2H,m)	14.03(q), 16.47(q), 18.80(q), 61.54(t), 67.45 (s,C-3), 121.29(d,C-4), 126.44(2C,d), 128.07 (d), 128.50(2C,d), 133.48(s), 155.21(s,C-5), 170.05(s), 182.40(s,C-2)
(4c)	1.08(3H,t), 1.53(3H,s), 2.27(3H,d), 4.08,4.11(2H,2q), 5.86(1H,q), 7.3-7.5 (3H,m), 7.7-7.9(2H,m)	13.87(q), 16.31(q), 19.17(q), 61.43(t), 64.96 (s,C-3), 124.82(d,C-4), 127.80(2C,d), 128.56 (2C,d), 130.40(d), 131.91(s), 154.45(s,C-5), 171.25(s), 179.26(s,C-2)
(4d)	1.06(3H,t), 1.65(3H,s), 4.08,4.13(2H, 2q), 6.48(1H,s), 7.3-7.5(6H,m), 7.9-8.1(4H,m)	13.92(q), 19.50(q), 61.70(t), 65.61(s,C-3), 122.71(d,C-4), 126.66(2C,d), 128.07(3C,d), 128.61(4C,d), 130.61(d), 132.19(s), 133.65(s), 155.75(s,C-5), 170.97(s), 179.10(s,C-2)
(4e)[b]	1.20(3H,t), 1.21(9H,s), 1.39(3H,s), 2.22(3H,s), 4.11(2H,q), 5.67(1H,s)	13.97(q), 16.24(q), 18.62(q), 28.43(3C,q), 32.93(s), 61.15(t), 66.15(s,C-3), 118.90(d, C-4), 167.22(s,C-5), 170.69(s), 181.36(s,C-2)
(4f)	1.07(3H,t), 1.29(9H,s), 1.50(3H,s), 4.08(2H,q), 5.77(1H,s), 7.3-7.5(3H,m), 7.7-7.9(2H,m)	13.87(q), 19.12(q), 28.55(3C,q), 33.26(s), 61.27(t), 64.41(s,C-3), 120.75(d,C-4), 127.85 (2C,d), 128.45(2C,d), 130.07(d), 132.46(s), 167.94(s,C-5), 171.62(s), 178.40(s,C-2)
(4g)	1.20(3H,t), 1.31(3H,s), 1.75(3H,d),[c] 2.05(3H,d),[c] 2.18(3H,s), 4.19(2H,q)	9.10(q), 13.76(q), 14.14(q), 16.20(q), 17.50 (q), 61.27(t), 68.10(s,C-3), 129.96(s,C-4), 147.13(s,C-5), 170.48(s), 179.15(s,C-2)
(4h)	1.20(3H,t), 1.33(3H,s), 1.7-1.8(4H,m), 2.02(3H,s), 2.3-2.5(4H,m), 4.19(2H,q)	14.08(q), 16.19(q), 17.49(q), 21.17,22.74, 22.91,25.13(4t), 61.10(t), 66.57(s,C-3), 133.31(s,C-4), 150.59(s,C-5), 170.31(s), 179.68(s,C-2)
(4i)	1.20(3H,t), 1.44(3H,s), 2.05(3H,s), 2.26(3H,s), 4.13(2H,q), 7.3-7.5(3H,m), 7.6-7.8(2H,m)	10.73(q), 14.09(q), 16.31(q), 17.55(q), 61.38 (t), 69.83(s,C-3), 127.52(s,C-4), 128.17(2C, d), 131.48(d), 134.73(s), 149.19(s,C-5), 170.05(s), 178.99(s,C-2)
(4j)	1.20(3H,t), 1.29(9H,s), 1.51(3H,s), 2.14(3H,d), 4.08(2H,t), 5.52(1H,q)	13.98(q), 16.25(q), 17.55(q), 29.85(3C,q), 37.54(s), 61.16(t), 66.47(s,C-3), 123.62(d, C-4), 153.42(s,C-5), 171.13(s), 191.34(s,C-2)
(4k)	1.15(3H,t), 1.42(3H,t), 1.70(3H,s), 4.07,4.15(2H,2q), 4.44(2H,q), 6.58 (1H,s), 7.3-7.5(3H,m), 7.8-8.0(2H,m)	13.97(q), 14.24(q), 17.44(q), 61.86(t), 61.97 (t), 67.11(s,C-2), 125.73(d,C-4), 126.70(2C, d), 128.65(2C,d), 129.14(d), 132.45(s), 155.74 (s,C-5), 160.62(s), 168.42(s), 172.97(s,C-2)
(4l)	1.22(3H,t), 1.2-1.8(4H,m), 2.16(3H,d), 2.1-2.9(4H,m), 4.12,4.15(2H,2q), 5.77 (1H,q)	
(4m)	1.22(3H,t), 1.2-1.8(4H,m), 2.1-3.0 (4H,m), 4.13,4.17(2H,2q), 6.45(1H,s), 7.3-7.4(3H,m), 7.8-8.0(2H,m)	14.14(q), 22.54,28.77,31.20,37.49(4t), 61.49 (t), 68.75(s,C-3), 120.26(d,C-4), 126.49(2C, d), 128.50(3C,d), 133.65(s), 156.29(s,C-5), 169.51(s), 185.16(s,C-2)

[a] $^4J_{HH}$ 1.3 Hz. [b] Inseparable mixture with exocyclic isomer. [c] $^5J_{HH}$ 0.9 Hz.

are in Table 4, and physical, UV, IR, and mass spectroscopic data for those obtained largely free from isomers are in Table 5. In most cases it proved impossible to remove all traces of impurities; only two examples were obtained analytically pure.

An attempt to characterize the 3H-pyrrole (4d) as a salt by treating with fluoroboric acid in diethyl ether led instead to the salt of the isomeric 2H-pyrrole (12d) by

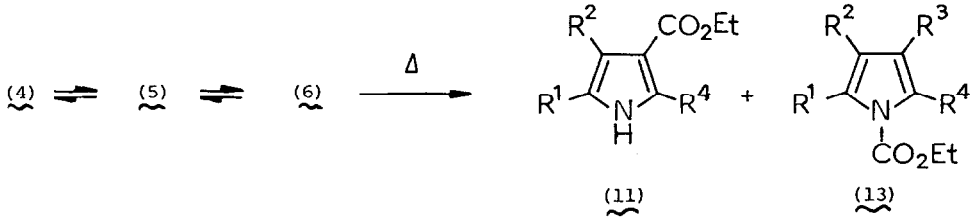
Table 5. Physical, UV, IR, and mass spectroscopic data for 3H-pyrroles (4).

Comp'd	Yield[a] (%)	M.p. (°C)	UV (95% EtOH) $\lambda_{max.}$/nm (log ε)	IR (Film) $\nu_{max.}$/cm^{-1}	M$^{+\cdot}$
(4a)	12	Oil		1735vs, 1628w, 1583w, 1228s, 1176s, 1086s, and 1001m	181
(4c)	33	Oil	214(4.00), 300(4.00)	1735vs, 1623m, 1545w, 1528m, 1220s, 1078s, 990m, 758m, and 668s	243
(4d)[b]	55	70-71[c]	218(4.27), 253(4.57) 321(3.78)	1727vs, 1589m, 1556w, 1528w, 1220vs, 1079s, 1000m, 756m, and 665s[d]	305
(4f)[e]	64	Oil	215(4.08), 300(4.02)	1728vs, 1604m, 1535m, 1234vs, 1102s, 1024m, 788m, and 698s	285
(4g)	47	Oil		1730vs, 1650w, 1589m, 1240s, 1109s, and 1025m	195
(4h)	20	Oil		1727vs, 1647w, 1580m, 1239vs, 1107s, and 1025m	221
(4i)	32	Oil	225(4.10), 275(3.69)	1730vs, 1618w, 1600m, 1491w, 1223vs, 1108s, 1022m, 777m, and 700s	257
(4j)	8	Oil	257(3.38)	1730vs, 1631m, 1550m, 1231s, 1101s, and 1027m	223
(4k)	11	Oil	245(4.39), 308(3.41)	1741vs, 1720vs, 1611w, 1598m, 1573m, 1233vs, 1080vs, 766s, and 700s	301
(4l)	14	Oil		1726vs, 1657m, 1234s, 1158s, and 1027m	207
(4m)	36	Oil		1726vs, 1602m, 1572w, 1221s, 1091m, 1025m, 760s, and 698m	269

[a] Isolated, pure product. [b] Found: C, 78.7; H, 6.45; N, 4.55. $C_{20}H_{19}NO_2$ requires C, 78.65; H, 6.25; N, 4.6%. [c] From light petroleum. [d] IR spectrum in Nujol. [e] Found: C, 76.05; H, 8.15; N, 4.75. $C_{18}H_{23}NO_2$ requires C, 75.75; H, 8.1; N, 4.9%.

rearrangement. 3H-pyrrole-3-carboxylic esters appear to rearrange more readily in this fashion under acid catalysis than do analogues having only alkyl or aryl substituents at C-3.[4]

Thermal Rearrangements of 3H-Pyrroles. - To eliminate possible ionic pathways for rearrangement, 3H-pyrroles were heated either in solvents of low polarity, or without solvent. Reaction of the mixture of isomers (4a), (5a), and (6a) in refluxing dry p-xylene under nitrogen for 48 h gave essentially quantitatively a mixture of only two products, which were shown from spectroscopic data to be the 1H-pyrrole isomers (11a) and (13a) in a ratio of 8:5 (Scheme 3). The same mixture was formed after 120 h in refluxing toluene. Other 3H-pyrroles, or their mixtures with exocyclic isomers, rearranged similarly; results are



(11) (13)

SCHEME 3

Table 6. Thermal rearrangement of 3H-pyrroles (4) and isomers (5) and (6).

3H-Pyrrole	Isomers	Conditions[a]	Time/h	Product ratio[b] (11) : (13)
(4a)	(5a),(6a)	I	120	8 : 5
		II	48	8 : 5
(4b)	(5b)	II	70	4 : 1
(4c)	(6c)	II	26	9 : 1
(4d)		I	72	24 : 1
		II	4	24 : 1
(4e)	(5e)	II	96	3 : 2
(4f)		II	24	17 : 3
(4g)		III	24	0 : 1
(4h)	(6h)	III	24	0 : 1
(4i)		II	48	0 : 1
(4k)		I	82	3 : 1
(4l)	(5l)	I	72	[c]
(4m)	(5m)	II	69	23 : 2

[a] I = reflux in dry toluene, under N_2; II = reflux in dry p-xylene under N_2; III = heat in absence of solvent at 140°C, under N_2. [b] From integrals of ^1H NMR spectra. [c] Complex mixture of products, including a small amount of 1H-pyrrole (111).

summarized in Table 6. The 1H-pyrroles were separated readily by column chromatography (SiO_2; eluent light petroleum/diethyl ether), the isomers being easily distinguished from IR and ^{13}C NMR spectra: for (11), $\nu_{max.}$ ca 3300(NH) and 1670 cm^{-1} (C=O), δ_C ca. 166 (C=O); and for (13), $\nu_{max.}$ ca. 1740 cm^{-1} (C=O), δ_C ca. 152 (C=O). The major isomers (11) were solids, being readily purified for microanalysis. However, the minor isomers (13) were obtained as oils in only milligram quantities; they are thus characterised by spectroscopic data. ^1H and ^{13}C NMR spectroscopic data are in Table 7.

Table 7. ^1H and ^{13}C NMR spectroscopic data (δ; $CDCl_3$) for the 1H-pyrroles (11) and (13).

Comp'd	δ_H	δ_C
(11a)	1.33(3H,t), 2.09(3H,s), 2.15(3H,s), 2.44(3H,s), 4.25(2H,q), 8.29(1H,br)	10.45(q), 10.94(q), 13.81(q), 14.57(q), 58.99(t), 110.73(s,C-4), 115.98(s,C-3), 122.16(s,C-2), 133.75(s,C-5), 166.69(s)
(11b)	1.14(3H,t), 2.16(3H,s), 2.20(3H,s), 4.12(2H,q), 7.26-7.50(5H,m), 8.14 (1H,br)	10.62(q), 10.83(q), 14.09(q), 59.27(t), 111.49(s,C-4), 117.34(s,C-3), 124.66(s,C-2), 127.53(d), 127.85(2C,d), 128.88(2C,d), 133.22(s), 135.17(s,C-5), 166.04(s)
(11c)	1.30(3H,t), 2.36(3H,s), 2.50(3H,s), 4.22(2H,q), 7.20-7.39(5H,m), 8.73 (1H,br)	11.86(q), 13.92(q), 14.46(q), 59.21(t), 112.08(s,C-4), 117.72(s,C-3), 127.52(s,C-2), 126.38(d), 127.36(2C,d), 128.50(2C,d), 132.87(s), 135.92(s,C-5), 166.69(s)
(11d)	1.16(3H,t), 2.41(3H,s), 4.16(2H,q) 7.23-7.52(10H,m), 8.34(1H,br)	11.70(q), 14.09(q), 59.43(t), 113.17(s,C-4), 118.91(s,C-3), 126.93(d), 127.47(2C,d), 127.96(3C,d), 128.72(2C,d), 128.99(2C,d), 129.53(s,C-2), 132.56(s), 132.89(s), 136.84 (s,C-5), 165.77(s)

Table 7. (cont'd)

Comp'd	δ_H	δ_C
(11e)	1.35(3H,t), 1.43(9H,s), 2.11(6H,s) 4.27(2H,q), 7.91(1H,br)	10.61(q), 11.32(q), 14.41(q), 29.25(3C,q), 32.88(s), 59.22(t), 110.62(s,C-4), 117.07 (s,C-3), 120.54(s,C-2), 143.13(s,C-5), 166.58(s)
(11f)	1.38(3H,t), 1.48(9H,s), 2.30(3H,s), 4.31(2H,q), 7.24-7.42(5H,m), 8.14 (1H,br)	12.19(q), 14.46(q), 29.36(3C,q), 33.10(s), 59.70(t), 112.57(s,C-4), 118.58(s,C-3), 126.11(s,C-2), 126.71(d), 127.63(2C,d), 128.77(2C,d), 133.15(s), 144.69(s,C-5), 166.69(s)
(11k)	1.13(3H,t), 1.29(3H,t), 2.60(3H,s), 4.16(4H,q), 7.27-7.55(5H,m), 9.77 (1H,br)	11.92(q), 14.03(q), 14.41(q), 59.70(t), 60.51(t), 114.20(s,C-4), 119.94(s,C-2), 127.96(2C,d), 128.66(d), 129.31(2C,d), 130.88(s,C-3), 132.13(s), 140.15(s,C-5), 161.92(s), 165.01(s)
(11l)	1.32(3H,t), 1.73(4H,m), 2.48(5H,s+m), 2.70(2H,m), 4.24(2H,q), 7.96(1H,br)	13.60(q), 14.57(q), 22.48,23.08,23.35,23.62 (4t), 58.94(t), 109.81(s,C-4), 118.75(s, C-3), 125.01(s,C-2), 134.08(s,C-5), 166.37 (s)
(11m)	1.13(3H,t), 1.75(4H,m), 2.46(2H,m), 2.72(2H,m), 4.07(2H,q), 7.21-7.49 (5H,m), 8.39(1H,br)	14.08(q), 22.47,22.91,23.39,23.50(4t), 59.15(t), 110.07(s,C-4), 120.04(s,C-3), 127.52(d), 127.79(2C,d), 127.89(s,C-2), 128.98(2C,d), 133.15(s), 135.80(s,C-5), 165.87(s)
(13a)	1.38(3H,t), 1.92(3H,s), 2.29(3H,s), 2.36(3H,s), 4.36(2H,q), 5.72(1H,s)	11.10(q), 13.11(q), 14.30(q), 16.14(q), 62.57(t), 113.82(d,C-4), 117.99(s,C-3), 126.60(s,C-2), 130.18(s,C-5), 153.23(s)
(13b)	0.97(3H,t), 2.01(3H,s), 2.36(3H,s), 4.11(2H,q), 6.02(1H,s), 7.18-7.35 (5H,m)	11.10(q), 12.55(q), 13.54(q), 62.83(t), 115.65(d,C-4), 118.47(s,C-3), 126.65(d), 127.73(2C,d), 128.22(2C,d), 128.55(s,C-2), 133.80(s,C-5), 135.21(s), 152.00(s)
(13c)	0.89(3H,t), 1.90(3H,s), 2.44(3H,s), 4.04(2H,q), 5.87(1H,s), 7.13-7.43 (5H,m)	11.42(q), 13.43(q), 15.32(q), 62.56(t), 113.65(d,C-4), 120.58(s,C-3), 126.65(d), 127.62(2C,d), 129.68(2C,d), 130.39(s,C-2), 131.85(s,C-5), 134.83(s), 151.79(s)
(13d)	0.76(3H,t), 2.00(3H,s), 3.94(2H,q), 6.17(1H,s), 7.26-7.44(10H,m)	11.47(q), 13.16(q), 63.10(t), 115.38(d, C-4), 120.74(s,C-3), 127.19(2C,d), 127.79 (4C,d), 128.65(2C,d), 130.01(2C,d), 133.64 (s,C-2), 135.32(2C,s), 151.62(s)
(13e)	1.35(9H,s), 1.40(3H,t), 1.93(3H,s), 2.17(3H,s), 4.38(2H,q), 5.82(1H,s)	11.05(q), 12.13(q), 14.03(q), 30.61(3C,q), 32.94(s), 63.27(t), 110.89(d,C-4), 116.36 (s,C-3), 126.22(s,C-2), 142.26(s,C-5), 153.53(s)
(13f)	0.78(3H,t), 1.41(9H,s), 2.00(3H,s), 3.94(2H,q), 5.93(1H,s), 7.21-7.40 (5H,m)	11.43(q), 13.00(q), 30.34(3C,q), 32.83(s), 63.49(t), 110.36(d,C-4), 118.10(s,C-3), 126.49(d), 127.96(2C,d), 128.82(2C,d), 131.15(s,C-2), 134.30(s), 143.72(s,C-5), 154.07(s)
(13g)	1.37(3H,t), 1.87(6H,s), 2.30(6H,s), 4.34(2H,q)	9.37(2C,q), 13.11(2C,q), 14.30(q), 62.35 (t), 118.86(s,C-3,C-4), 125.35(s,C-2,C-5), 152.23(s)
(13h)	1.37(3H,t), 1.72(4H,m), 1.86(3H,s), 2.32(5H,s+m), 2.77(2H,m), 4.33(2H,q)	8.78(q), 12.84(q), 14.30(q), 21.72,22.81, 23.84,25.46(4t), 62.19(t), 117.94(s,C-3), 121.73(s,C-4), 125.63(s,C-2), 128.39(s, C-5), 152.01(s)
(13i)	0.85(3H,t), 1.86(3H,s), 1.95(3H,s), 2.38(3H,s), 4.00(2H,q), 7.20-7.40 (5H,m)	9.26(q), 9.81(q), 12.46(q), 13.33(q), 62.30(q), 118.86(s,C-3), 121.24(s,C-4), 126.49(d), 127.20(s,C-2), 127.57(2C,d), 129.42(s,C-5), 129.69(2C,d), 135.05(s), 151.90(s)

Table 7. (cont'd)

Comp'd	δ_H	δ_C
(13k)	1.16(3H,t), 1.36(3H,t), 2.33(3H,s), 4.25(2H,q), 4.33(2H,q), 6.10(1H,s), 7.38(5H,s)	12.78(q), 13.54(q), 14.35(q), 60.51(t), 64.52(t), 114.03(d,C-4), 121.10(s,C-2), 128.12(2C,d), 128.34(d), 128.72(2C,d), 130.61(s,C-3), 131.64(s), 138.47(s,C-5), 151.85(s), 161.22(s)
(13m)	1.10(3H,t), 1.77(4H,m), 2.49(2H,m), 2.85(2H,m), 6.01(1H,s), 7.28(5H,s)	13.60(q), 22.97,23.19,23.51,24.97(4t), 62.62(t), 114.09(d,C-4), 121.29(s,C-3), 126.66(d), 127.58(2C,d), 128.55(2C,d), 131.53(s,C-2), 134.24(s,C-5), 135.22(s), 151.58(s)

Several observations can be made. First, with the exception of compounds (4g)-(4i), where $R^3 \neq H$, products from ester-migration to both C-4 and N are formed. This is the first time that competitive rearrangements of this type, common among 3H-pyrazoles,[5] have been observed with 3H-pyrroles. Second, where $R^3 = H$, migrations to C-4 to give the C-ester (11) are uniformly favoured over those that give the N-ester (13), the weighting being enhanced by bulky substituents, particularly at C-2, and less so at C-5. Third, within the limited accuracy of the ^1H NMR integrals, the product ratio appears to be independent of temperature; and fourth, the thermal equilibrium between 3H-pyrroles and their exocyclic isomers is again[17] demonstrated by the quantitative conversion of the mixtures of (4) with (5) and (6) to the products (11) and (13).

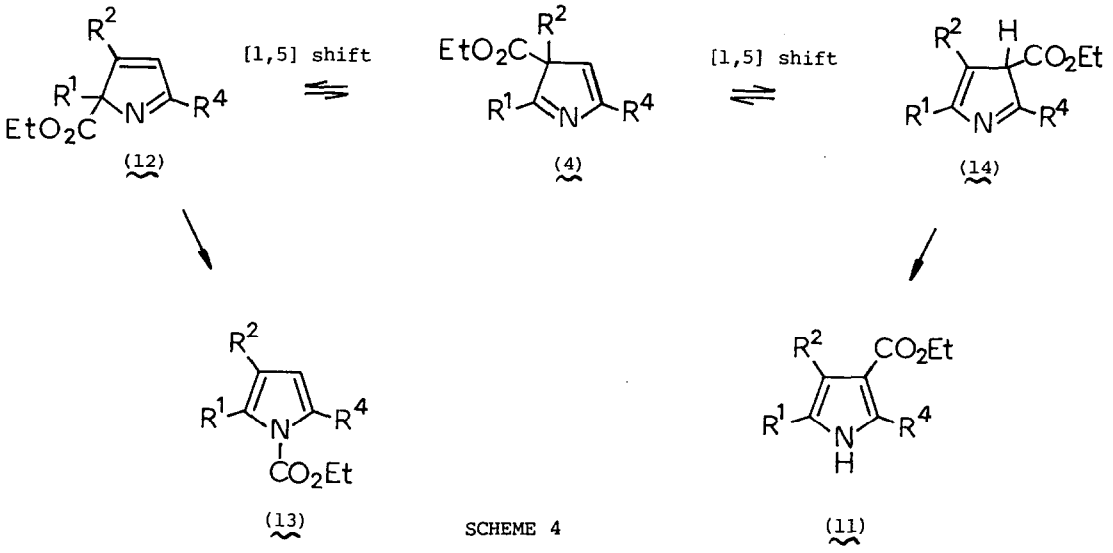
When reactions were stopped after ca. one third of the time shown in Table 6, additional ^1H NMR peaks corresponding to the 2H-pyrrole isomers (12) were frequently observed; notably, for R^2 = Me and R^3 = H, a doublet and a quartet were seen in the ranges δ 2.0-2.2 and 6.0-6.7 respectively, with $^4J_{HH}$ 1.3 Hz. Some 2H-pyrroles were separated successfully from 1H-isomers by pH partition, or by column chromatography, while others were present in too small amounts to be isolated. None was obtained analytically pure; however, their structures were confirmed spectroscopically. ^1H and ^{13}C NMR spectroscopic data for the 2H-pyrroles (12) are in Table 8.

Thermolysis of the pure 2H-pyrroles (12a) and (12b) in refluxing p-xylene also gave mixtures of the corresponding isomeric 1H-pyrroles (11) and (13) in essentially the same ratios as in Table 6. This demonstrates conclusively the intermediacy of the 2H-pyrroles in the transformation of the 3H-pyrroles (4) into the 1H-isomers (13), and suggests that the interconversion of the 2H- and 3H-pyrrole isomers is reversible under the reaction conditions. Proof for the latter was obtained from monitoring the thermolysis of 2H-pyrrole (12b) in refluxing toluene by ^1H NMR. After 2 h, peaks due to the 3H-pyrrole (4b) [δ_H 6.41(s)] and the exocyclic isomer (5b) [δ_H 5.01 and 5.45(2s)] were observable in addition to those for the 2H-pyrrole. These remained in roughly the same relative amounts as peaks due to the 1H-pyrrole isomers (11b) [δ_H 8.14(s,br)] and (13b) [δ_H 6.02(s)] appeared and grew in intensity. After 120 h, only the 1H-pyrroles (11b) and (13b) were present.

Table 8. ^1H and ^{13}C NMR spectroscopic data (δ; $CDCl_3$) for the 2H-pyrroles (12).

Comp'd	δ_H	δ_C
(12a)	1.23(3H,t), 1.49(3H,s), 2.04(3H,d), 2.24(3H,s), 4.14(2H,q), 6.03(1H,q)	13.00(q), 14.03(q), 18.80(q), 20.10(q), 61.32(t), 85.11(s,C-2), 126.44(d,C-4), 166.91(s,C-3), 170.27(s), 175.09(s,C-5)
(12b)	1.18(3H,t), 1.61(3H,s), 2.11(3H,d) 4.12,4.13(2H,2q), 6.62(1H,q), 7.4-7.5 (3H,m), 7.9-8.0(2H,m)	13.33(q), 14.03(q), 20.26(q), 61.38(t), 85.81(s,C-2), 123.36(d,C-4), 127.80(2C,d), 128.56(2C,d), 130.61(d), 133.76(s), 167.45 (s,C-3), 170.05(s), 173.84(s,C-5)
(12d)	1.28(3H,t), 2.17(3H,d), 4.29(2H,q), 6.66(1H,q), 7.28(5H,s), 7.4-7.5(3H,m), 8.0-8.1(2H,m)	14.09(q), 14.68(q), 61.92(t), 92.26(s,C-2), 123.73(d,C-4), 126.28(2C,d), 127.79(d), 128.07(2C,d), 128.61(4C,d), 130.94(d), 133.48(s), 136.63(s), 168.15(s,C-3), 169.18(s), 174.98(s,C-5)
(12e)	1.18(3H,t), 1.24(9H,s), 1.48(3H,s), 2.02(3H,d), 4.09(2H,q), 6.21(1H,q)	13.00(q), 13.98(q), 19.82(q), 28.12(3C,q), 34.89(s), 61.16(t), 84.56(s,C-2), 123.68 (d,C-4), 165.82(s,C-3), 170.59(s), 185.44 (s,C-5)
(12f)	1.25(3H,t), 1.32(9H,s), 2.05(3H,d), 4.24(2H,q), 6.22(1H,q), 7.26(5H,s)	
(12g)	1.22(3H,t), 1.45(3H,s), 1.85(3H,s), 1.89(3H,s), 2.21(3H,s), 4.41(2H,q)	9.96(q), 10.99(q), 13.97(q), 17.27(q), 19.98(q), 61.04(t), 83.63(s,C-2), 132.39 (s,C-4), 157.36(s,C-3), 170.69(s), 176.38 (s,C-5)
(12h)	1.22(3H,t), 1.46(3H,s), 1.73(4H,m), 1.89(3H,t,J 1.3 Hz), 2.39(2H,m), 2.65(2H,m), 4.12(2H,q)	
(12k)	1.30(6H,t), 2.31(3H,d), 4.28(4H,q), 6.77(1H,q), 7.4-7.5(3H,m), 7.9-8.1 (2H,m)	13.97(2C,q), 14.46(q), 62.46(2C,t), 92.91 (s,C-2), 126.82(d,C-4), 128.17(2C,d), 128.61(2C,d), 131.26(d), 132.94(s), 162.19 (s,C-3), 165.61(2C,s), 177.36(s,C-5)

These experiments confirm for the first time the reversibility of the thermal 3H-pyrrole to 2H-pyrrole interconversion, by producing mixtures of both species when heating either in the absence of the other. We also conclude from the conditions of these experiments, and from the intermediates and products observed, that the mechanism of the rearrangements involves a sequence of competitive [1,5]sigmatropic shifts. This is summarized in Scheme 4 for examples where R^3 = H. The interconversions between 3H-pyrroles (4), (unobserved) 3H-pyrroles (14), and 2H-pyrroles (12) are believed to be reversible under the reaction conditions, whereas the formation of 1H-pyrroles (11) and (13) may be taken to be irreversible, since the compounds lie in potential energy wells. Finally, since the 1H-pyrrole product (11) is favoured over its isomer (13), even when starting from the 2H-pyrrole (12), it appears that the aromaticity of the product (13) develops late in what must be a relatively higher energy transition state.



(12) (4) (14)

(13) (11)

SCHEME 4

EXPERIMENTAL

Details of spectroscopic measurements are as reported earlier.[4]

Preparation of the Diketoesters (9).[10] - To a solution of the ß-ketoester (7) (0.1 mol) [and potassium iodide (3.3 g, 0.02 mol) for haloketones (8; X = Cl)] in dry acetone (100 ml) was added slowly anhydrous potassium carbonate (27.6 g, 0.2 mol). The mixture was heated under reflux for a few minutes, and a solution of the appropriate haloketone (8) (0.11 mol) in dry acetone (30 ml) was added dropwise, and refluxing was continued for 48 h. The mixture was filtered, the residue was washed with acetone, and the combined filtrate and washings was evaporated. The residue was dissolved in diethyl ether (150 ml), and the solution was washed with water (3 x 100 ml), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on SiO_2 (eluent light petroleum/diethyl ether 2:1), or by vacuum distillation where the products were sufficiently stable.[11]

Prepared by this method were the known diketoesters (9a)[11], 55%, b.p. 66°C/0.03 mmHg (lit. 63-73°C/0.18 mmHg); (9b),[11] 41%; (9c),[11] 71%, b.p. 127-129°C/0.03 mmHg (lit. 141-150°C/0.43 mmHg); (9d),[11] 79%, m.p. 63-64°C (EtOH) (lit. 64°C); (9e),[18] 51%, b.p. 72-74°C/0.05 mmHg (lit. 98-100°C/0.8 mmHg); (9g),[11] 44% as mixed diastereomers; (9h),[19] 29%, b.p. 90-105°C/0.001 mmHg (lit. 129-145°C/2 mmHg), and (9i),[11] 51%; IR and ^1H NMR spectroscopic data matched literature values. Also prepared was ethyl 2-benzoyl-5,5-dimethyl-4-oxohexanoate (9f), 57%, b.p. 132°C/0.03 mmHg (Found: C, 70.4; H, 7.55. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.65%); $\nu_{max.}$ (Film) 1746, 1710, and 1693 cm^{-1}; δ_H ($CDCl_3$) 1.14(3H, t), 1.19(9H, s), 3.26(1H, d, J 7 Hz), 3.28(1H, d, J 7 Hz), 4.12(2H, q), 4.92(1H, t, J 7 Hz), 7.5-7.6(3H, m), and 8.0-8.1(2H, m); δ_C ($CDCl_3$) 13.76(q), 26.38(3C, q), 36.40(s), 43.82(t), 48.75(d), 61.43(t), 128.50(2C, d), 128.71(2C, d), 133.32(d), 136.19(s), 169.18(s), 194.75(s), and 212.57(s).

Preparation of the Diketoesters (1a)-(1i). - A solution of the appropriate diketoester (9) (0.045 mol) in dry DMSO (50 ml) was added to a suspension of sodium hydride (2.0 g; 60% in oil; 0.05 mol) in dry DMSO (50 ml) under N_2. The mixture was stirred at 25°C for 2 h, methyl iodide (9.4 g, 0.054 mol) as added dropwise, and stirring was continued at 25°C for a further 16 h. The mixture was diluted with water (100 ml), extracted with diethyl ether (3 x 60 ml), and the ether extracts were washed with water (3 x 100 ml), dried ($MgSO_4$) and evaporated. The residue was purified by vacuum distillation, or by column chromatography on SiO_2 (eluent light petroleum/diethyl ether, 2:1); physical, analytical, and IR and ^1H NMR data are in Table 1. Prior to distillation and recrystallisation, the crude product from the diketoester (9d) was triturated with 95% ethanol, giving a small amount of a byproduct 3-methyl-2,5-diphenylfuran; δ_H ($CDCl_3$) 2.15(3H, s), 6.74(1H, s), and 7.3-7.9(10H, m).

Preparation of the Diketoester (1i). - Reaction between ethyl 4,4-dimethyl-3-oxopentanoate (7c) (8.0 g, 0.047 mol) and 3-bromopropyne (6.0 g, 0.05 mol) under reflux in acetone for 24 h in the presence of anhydrous potassium carbonate, followed by work-up as for compounds (9), gave ethyl 4,4-dimethyl-3-oxo-2-(prop-2-ynyl)pentanoate, 8.5 g (87%), b.p. 61°C/0.05 mmHg (Found: C, 68.9; H, 8.7. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%); $\nu_{max.}$ 3384, 1737, 1709, and 1180 cm^{-1}; δ_H ($CDCl_3$) 1.21(9H, s), 1.25(3H, t), 2.02(1H, t, J 2.6 Hz), 2.67(1H, m), 2.74(1H, m), 4.15(3H, t), and 4.17(2H, q); δ_C ($CDCl_3$) 13.87(q), 19.07(t), 26.11(3C, q), 44.96(s), 51.30(d), 61.43(t), 70.10(d), 80.82(s), 167.99(s), and 208.19(s). Methylation with methyl iodide, using sodium hydride in DMSO, as for compounds (1a)-(1i) followed by column chromatography (SiO_2), gave ethyl 2,4,4-trimethyl-3-oxo-2-(prop-2-ynyl)-pentanoate, 61% (Found: C, 69.7; H, 9.0. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%); $\nu_{max.}$ (film) 3280, 1745, 1695, 1200, and 1020 cm^{-1}; δ_H ($CDCl_3$) 1.21(9H, s), 1.28(3H, t), 1.52(3H, s), 2.04(1H, t, J 2.6 Hz), 2.74(2H, d, J 2.6 Hz), and 4.21(2H, q), δ_C ($CDCl_3$) 14.0(q), 20.0(q), 26.9(t), 28.4(3C, q), 45.7(s), 57.9(s), 61.4(t), 71.8(d), 79.5(s), 171.7(s), and 210.1(s), together with a small amount of ethyl 2-tert-butyl-5-methylfuran-3-carboxylate, $\nu_{max.}$ (film) 1709, 1612, 1234, and 1110 cm^{-1}; δ_H ($CDCl_3$) 1.33(3H, t), 1.41(9H, s), 2.23(3H, d, J 1.3 Hz), 4.25(2H, q), and 6.26(1H, q, J 1.3 Hz); δ_C ($CDCl_3$) 12.62(q), 14.08(q), 28.11(3C, q), 34.18(s), 59.59(t), 108.18(d), 112.62(s), 147.57(s), 163.55(s), and 166.41(s). Mercury(II) - catalysed hydration of the triple bond using Stevens's method[13] gave the diketoester (1j), which was purified by chromatography on SiO_2 (eluent light petroleum/diethyl ether 2:1).

Preparation of the Diketoesters (1k) and (1m).[20] - The appropriate β-ketoester (0.1 mol) was alkylated with α-bromoacetophenone (0.1 mol) using sodium hydride in DMSO as for compounds (1a)-(1i) above. Products were purified by column chromatography on SiO_2.

Preparation of the Diketoester (1l). - The method of Beth and co-workers[21] was used. Alkylation of ethyl 2-oxocyclohexanecarboxylate with 3-bromopropyne gave the 1-(prop-2-ynyl) derivative (79%), b.p. 66-68°C/0.02 mmHg (lit. 74-77°C/0.1 mmHg) whose IR and ^1H NMR spectra matched those reported.[21] Mercury(II) catalysed hydration[13] yielded the diketoester (1l).

Preparation of Hydroxypyrrolines (2) and (3). - From diketoesters (1) and liquid ammonia. - The appropriate compound (1) (1 g) was dissolved in liquid ammonia (60-70 ml) in an insulated container, the solvent being allowed to evaporate slowly overnight. The last traces of ammonia were removed under reduced pressure, to give a crude mixture of hydroxypyrrolines (2) and (3). The ratio of products is given in Table 2. The diketoester (1a) gave compounds (2a) and (3a) as a mixture of four isomers, oil, 100%; $\nu_{max.}$ (film) 3250, 1735, 1652, 1265, 1140, 1080, and 1002 cm^{-1}; δ_C ($CDCl_3$) inter alia 21.12, 21.45, 21.88, 22.58(4q), 28.38, 28.60, 28.82, 29.52(4q), 84.35, 84.78, 98.76, 99.24(4s), and 172.76, 172.97, 173.14, and 173.25(4s); the diketoester (1b) gave initially a mixture of four isomers, which after recrystallisation from benzene yielded the two diastereomers of hydroxypyrroline (2b) (ratio ca. 11:8), 76% (Found: C, 68.85; H, 7.35; N, 5.4. $C_{15}H_{19}NO_3$ requires C, 68.95; H, 7.35; N, 5.35%); m/z 261 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 3150, 1737, 1621, 1616, 1300, 1160, 1136, and 1102 cm^{-1}; δ_H ($CDCl_3$) inter alia 2.79 and 3.97(2H, ABq, J 17 Hz), and 2.92 and 3.69(2H, ABq, J 17 Hz); δ_C ($CDCl_3$) major isomer 21.62(q), 23.57(q), 55.26(s), 60.78(t), 102.50(s), 173.41(s), and 173.90(s); minor isomer 20.04(q), 24.87(q), 56.34(s), 60.95(t), 101.31(s), 170.54(s) and 174.71(s); common 14.19(q), 45.72(t), 128.12(d), 128.45(d), 131.32(d), and 133.49; similarly, mixed diastereomers of compound (2e) (ratio ca. 11:9) were obtained from recrystallizing the initial product from the diketoester (1e), from light petroleum, 78% (Found: C, 64.8; H, 9.4; N, 5.65. $C_{13}H_{23}NO_3$ requires C, 64.7; H, 9.6; N, 5.8%); $\nu_{max.}$ (Nujol) 3195, 1729, 1632, 1301, 1165, 1131, and 1105 cm^{-1}; δ_H ($CDCl_3$) inter alia 2.37 and 3.47(2H, ABq, J 17 Hz), and 2.50 and 3.23(2H, ABq, J 17 Hz); δ_C ($CDCl_3$) major isomer 21.02(q), 23.57(q), 55.09(s), 60.51(t), 102.06(s), 174.00(s), and 185.00(s); minor isomer 19.50(q), 24.75(q), 56.12(s), 60.67(t), 100.60(s), 174.87(s), and 182.67(s); common 14.19(q), 27.74(q), 35.92(t), and 44.31(t); from diketoester (1l) was isolated a single product (2l) as only one diastereomer, 90%, m.p. 113-115°C (light petroleum-dichloromethane) (Found: C, 63.8; H, 8.45; N, 6.15. $C_{12}H_{19}NO_3$ requires C, 64.0; H, 8.5; N, 6.2%); $\nu_{max.}$ (Nujol) 3150, 1722, 1637, 1251, 1202, 1162, 1085, and 1040 cm^{-1}; δ_H ($CDCl_3$) 1.29(3H, t), 1.2-2.2(8H, m), 2.07(3H, s), 2.32 and 3.35(2H, ABq, J 17 Hz), and 4.20(2H, q); δ_C ($CDCl_3$) 14.19(q), 20.42(q), 21.18(t), 21.72(t), 34.35(t), 34.89(t), 49.35(t), 54.99(s), 60.62(t), 99.57(s), 173.84(s), and 178.28(s); and similarly the hydroxypyrroline (2m) was obtained as a single diastereomer, 95%, m.p. 128-131°C (light petroleum-dichloromethane) (Found: C, 70.95;

H, 7.4; N, 4.65. $C_{17}H_{21}NO_3$ requires C, 71.05, H, 7.35; N, 4.85%); $\nu_{max.}$ (Nujol) 3150, 1720, 1607, 1203, 1085, and 1029 cm^{-1}; δ_H ($CDCl_3$) 1.31(3H, t), 1.2-2.3(8H, m), 2.86 and 3.73(2H, ABq, J 17 Hz), 4.24(2H, q), 5.21(1H, br), 7.3-7.5(3H, m), and 7.8-7.9(2H, m); δ_C ($CDCl_3$) 14.25(q), 21.29(t), 21.83(t), 34.18(t), 35.16(t), 45.51(t), 54.72(s), 60.89(t), 99.79(s), 128.01(2C, d), 128.50(2C, d), 131.37(d), 134.08(s), 174.17(s), and 175.36(s).

From diketoesters (1) with ammonium acetate and acetic acid. The appropriate diketoesters (0.002 mol) and ammonium acetate (0.54 g, 0.007 mol) were heated in glacial acetic acid (1 ml) for 12 h in an oil bath at 60-70°C. The mixture was cooled, treated with aqueous ammonia (4 ml; 33%), and extracted with diethyl ether (2 x 15 ml). The ether extracts were dried ($MgSO_4$) and evaporated. Prepared by this method were a mixture of hydroxypyrrolines (2c) and (3c) each as two diastereomers, the mixture being separated by column chromatography on SiO_2 (eluent diethyl ether) to give mixed diastereomers of compound (3c) (ratio ca. 4:3), 25% (Found: C, 69.05; H, 7.45; N, 5.25. $C_{15}H_{19}NO_3$ requires C, 68.95; H, 7.35; N, 5.35%); $\nu_{max.}$ (Nujol) 1725, 1615, 1181, and 1142 cm^{-1}; δ_H ($CDCl_3$) major isomer 1.14(3H, t), 1.65(3H, s), 1.71(3H, s), 2.22 and 2.54(2H, ABq, J 14 Hz), 4.16(2H, q), 7.3-7.5(3H, m), and 7.7-7.8(2H, m); and minor isomer 1.19(3H, t), 1.55(3H, s), 1.68(3H, s), 2.13 and 2.64(2H,ABq, J 14 Hz), 4.19(2H, q), 7.3-7.5(3H, m), and 7.7-7.8(2H, m); δ_C ($CDCl_3$) major isomer 23.02(q), 30.07(q), 59.48(s), 61.54(t), 85.38(s), 130.34(d), and 168.86(s); minor isomer 24.00(q), 29.47(q), 59.92(s), 61.38(t), 85.27(s), 130.24(d), and 168.97(s); and common 13.92(q), 52.01(t), 128.07(d), 128.39(d), 132.84(s), and 174.66(s); mixed diastereomers of compounds (2j) and (3j), which on trituration with light petroleum gave the hydroxypyrroline (3j), 83% (Found: C, 64.75; H, 9.8; N, 6.05. $C_{13}H_{23}NO_3$ requires C, 64.7; H, 9.6; N, 5.8%); $\nu_{max.}$ (Nujol) 3195, 1729, 1631, 1282, 1162, and 1025 cm^{-1}; δ_H ($CDCl_3$) inter alia 1.94 and 2.43(2H, ABq, J 14 Hz), and 2.01 and 2.37(2H, ABq, J 14 Hz); δ_C ($CDCl_3$) major isomer 23.73(q), 29.65(q), 37.11(s), 52.22(t), 60.35(s), 61.05(t), 99.46(s), 174.60(s), and 182.46(s), minor isomer 22.59(q), 29.04(q), 37.22(s), 52.82(t), 60.78(s), 61.60(t), 99.03(s), 174.82(s), and 182.24(s), and common 13.92(q), and 29.80(q); and a single diastereomer of hydroxypyrroline (2k), which was separated from a small amount of 3H-pyrrole (4k) by column chromatography on SiO_2. Yield 70%, m.p. 111-112.5°C (Found: C, 64.15; H, 6.8; N, 4.35. $C_{17}H_{21}NO_5$ requires C, 63.95; H, 6.65; N, 4.4%); m/z 319 ($M^{+\cdot}$) $\nu_{max.}$ (Nujol) 3120, 1732, 1721, 1612, 1273, 1152, and 1037 cm^{-1}; δ_H ($CDCl_3$) 1.19(3H, t), 1.27(3H, t), 1.44(3H, s), 3.15 and 3.84(2H, ABq, J 17 Hz), 4.17(4H, q), 4.64(1H, br), 7.3-7.5(3H, m), and 7.8-8.0(2H, m); δ_C ($CDCl_3$) 13.87(q), 14.03(q), 22.43(q), 47.24(t), 50.39(s), 61.11(t), 62.52(t), 102.17(s), 128.12(2C, d), 128.55(2C, d), 131.75(d), 133.37(s), 171.78(s), 174.44(s), and 174.87(s).

Preparation of 3H-Pyrroles (4). - By dehydration of hydroxy-pyrrolines (2) and (3). The appropriate hydroxypyrroline, or mixed isomers, (0.002 mol) was refluxed in dichloromethane (50 ml) or benzene (50 ml) in the presence of base-washed Al_2O_3 (2 g; grade I), or for hydroxypyrrolines (3j) and (2k) in toluene using acid-washed Al_2O_3. Water was removed continuously with a Soxhlet apparatus filled with 4A molecular seives; the course of the reaction was monitored by ^1H NMR. Conditions, and product ratios are in Table 3. The solution was filtered and evaporated, and the residue freed from exocyclic isomers (5) and (6) by rapid column chromatography on neutral Al_2O_3 (eluent light petroleum/diethyl ether) [3H-pyrroles (4a), (4g), (4h), (4j), (4l), and (4m)], or by pH partition as described in ref. 4 [3H-pyrroles (4c) and (4i)].

From diketoesters (1d), and (1f), or hydroxypyrrolines (3j) and (2k), and ammonium acetate in acetic acid. As described for the preparation and isolation of hydroxypyrrolines above, only heating was continued for 16-24 h. Products were purified by rapid column chromatography on neutral Al_2O_3 (eluent light petroleum/diethyl ether).

Conditions and product ratios are in Tables 2 and 3, and spectroscopic, physical, and analytical data are in Tables 4 and 5. From hydroxypyrroline (3j) was isolated the 1H-pyrrole (10a), 60%, m.p. 123°C (95% EtOH) (lit.[22] 125°C); $\nu_{max.}$ (Nujol) 3310, 1660, 1275, and 1110 cm^{-1}; δ_H ($CDCl_3$) 1.34(3H, t), 2.24(3H, s), 2.30(3H, s), 4.30(2H, q), 5.78(1H, d, J 2.6 Hz), and 9.26(1H, br); and from hydroxypyrrolines (2k) the 1H-pyrrole (10b) 22%, m.p. 113-114 (light petroleum) (lit.[23] 114-115°C); $\nu_{max.}$ (Nujol) 3310, 1673, 1275, and 1112 cm^{-1}; δ_H ($CDCl_3$) 1.33(3H, t), 2.37(3H, s), 4.31(2H, q), 6.36(1H, d, J 2.6 Hz), 7.2-7.6(5H, m), and 9.66(1H, br).

Exocyclic isomers. Generally, exocyclic isomers were identified by ^{1}H NMR spectroscopy ($CDCl_3$); relevant signals being as follows: for (5a) δ_H inter alia 4.83 and 5.24(2s); for (6a) δ_H inter alia 4.76 and 5.20(2t); for (5b) δ_H 1.24(3H, t), 1.51(3H, s), 2.95 and 3.87(2H, ABq, J 18 Hz), 4.18(2H, q), 5.01(1H, s), 5.46(1H, s), 7.4-7.5(3H, m), and 7.9-8.0(2H, m); for (6c) δ_H inter alia 1.50(s), 4.80 and 5.40(2t, J 2 Hz); for (5e) δ_H 1.24(9H, s and 3H, t), 1.42(3H, s), 2.54 and 3.43(2H, ABq, J 18 Hz), 4.14(2H, q), 4.85(1H, s), and 5.29(1H, s); δ_C 13.98(q), 25.03(q), 28.01(3C, q), 36.13(s), 46.16(t), 50.44(s), 61.16(t), 102.50(t), 167.77(s), 174.17(s), and 188.52(s); for (6h) δ_H inter alia 1.33(3H, s), 2.00(3H, s), and 5.76(1H, m); for (6j) δ_H 1.26(9H, s and 3H, t), 1.46(3H, s), 2.51(1H, dt, J 17, 2 Hz), 3.05(1H, dt, J 17, 2 Hz), 4.16(2H, q), 4.76(1H, t, J 2 Hz), and 5.26(1H, t, J 2 Hz); for (5l) δ_H 1.22(3H, t), 1.2-2.8(8H, m), 2.15(3H, s), 2.51 and 2.97(2H, ABq, J 18 Hz), 4.12(2H, q), and 5.76(1H, t, J 4 Hz); and for (5m) δ_H inter alia 2.86 and 3.48(2H, ABq, J 18 Hz), and 6.00(1H, t, J 4 Hz).

Thermal Rearrangements of 3H-Pyrroles (4). - Isolation of 1H-pyrroles. The 3H-pyrrole (4), or its mixture with exocyclic isomers (5) and/or (6) (0.4 g) was heated under N_2 in refluxing toluene or p-xylene (20 ml), or without solvent on an oil bath, for various periods of time (Table 6); the progress of the reaction was monitored by ^{1}H NMR. The solvent was evaporated, and the residual 1H-pyrroles (11) and (13) were separated by column chromatography on SiO_2 (eleuent light petroleum/diethyl ether). ^{1}H and ^{13}C NMR data are in Table 7; additional data follow.

1H-Pyrrole-3-carboxylic esters (11). For ester (11a) yield 43%, m.p. 101-102°C (lit.[24] 100-105°C); m/z 181 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 3310, 1662, and 1255 cm^{-1}; for ester (11b) yield 45%, m.p. 108-109°C (80% MeOH) (lit.[25] 109.5-111.5°C); m/z 243 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 3295, 1665, and 1160 cm^{-1}; for ester (11c) yield 45%, m.p. 120-121°C (MeOH) (lit.[26] 120-121.5°C); m/z 243 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 3325, 1667, 1260, and 1115 cm^{-1}; for ester (11d) yield 55%, m.p. 112-113°C (95% EtOH) (Found: C, 78.65; H, 6.1; N, 4.6 $C_{20}H_{19}NO_2$ requires C, 78.65; H, 6.25; N, 4.6%); m/z 305 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 3270, 1666, 1262, and 1076 cm^{-1}; for ester (11e) yield 48%; $\nu_{max.}$ (film) 3370, 1675, 1275, and 1083 cm^{-1}; for ester (11f) yield 60%, m.p. 92-93°C (95% EtOH) (Found: C, 75.5; H, 8.25; N, 4.95. $C_{18}H_{23}NO_2$ requires C, 75.75; H, 8.1; N, 4.9%); $\nu_{max.}$ (Nujol) 3350, 1672, 1271, and 1097 cm^{-1}; for ester (11k) yield 39%, m.p. 113.5-114.5°C (80% EtOH) (Found: C, 67.9; H, 6.4; N, 4.85. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.35; N, 4.65%); m/z 301 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 3290, 1704, 1675, 1256, and 1068 cm^{-1}; for ester (11l) yield 5%, m.p. 127.5-129.5°C (lit.[27] 133°C); $\nu_{max.}$ (Nujol) 3340, 1662, 1268, 1155, and 1108 cm^{-1}; and for ester (11m) yield 40%, m.p. 111-112°C (95% EtOH) (lit.[28] 107°C); $\nu_{max.}$ (Nujol) 3270, 1662, 1281, and 1136 cm^{-1}.

1H-Pyrrole-N-carboxylic esters (13). For ester (13a) yield 16%, oil; m/z 181 ($M^{+\cdot}$); $\nu_{max.}$ 1748, 1310, 1132, and 1082 cm^{-1}; for ester (13b) yield 9%, oil; m/z 243 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1740, 1316, 1199, and 1078 cm^{-1}; for ester (13c) yield 6%, oil; m/z 243 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1746, 1312, 1200, and 1080 cm^{-1}; for ester (13d) yield 2%, oil; m/z 305 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1748, 1305, 1192, and 1040 cm^{-1}; for ester (13e) yield 24%, oil; m/z 223 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1743, 1332, 1265, 1190, and 1025 cm^{-1}; for ester (13f) yield 2%, oil; m/z 285 ($M^{+\cdot}$); $\nu_{max.}$ 1747, 1303, 1278, 1190, and 1060 cm^{-1}; for (13g) yield 40%, oil; m/z 195 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1730, 1263, 1146, and 1065 cm^{-1}; for ester (13h) yield 60%, oil; m/z 221 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1735, 1320, 1138, and 1070 cm^{-1}; for ester (13i) yield 38%, oil; m/z 257 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1737, 1327, 1202, and 1075 cm^{-1}; for ester (13k) yield 10%, oil; m/z 301 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1767, 1701, 1280, 1223, and 1088 cm^{-1}; and for ester (13m) yield 3%, oil; m/z 269 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1739, 1322, 1298, 1197, and 1045 cm^{-1}.

Isolation of 2H-pyrroles (12). The appropriate 3H-pyrrole (4), or its mixture with exocyclic isomers, was heated in refluxing toluene or p-xylene, until peaks arising from the 2H-pyrrole isomer in the ^{1}H NMR spectrum of the crude mixture reached maximum intensity. The solvent was removed, and the 2H-pyrrole was isolated by column chromatography for product (12a), or by pH partition for the remaining products. For 2H-pyrrole (12a) yield 35% (toluene 48 h), oil; m/z 181 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1728, 1635, 1553, 1249, and 1110 cm^{-1}; for (12b), yield 30% (p-xylene 20 h), oil; m/z 243 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1738, 1630, 1232, and 1088 cm^{-1}; for (12e) yield 38% (toluene 48 h), oil; m/z 223 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1731, 1632, 1545, 1249, and 1105 cm^{-1}; for (12f) yield 8% (toluene 8 h), oil; m/z 285 ($M^{+\cdot}$); for (12g)

yield 32% (toluene 24 h), oil; m/z 195 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1738, 1639, 1552, 1250, and 1105 cm^{-1}; and for (12h) max. yield after 48 h reflux in toluene. The 2H-pyrrole (12k) was obtained from the dehydration product of the hydroxypyrroline (2k), after refluxing in toluene with acid-washed Al_2O_3 for 48 h, by column chromatography on SiO_2; yield 5%, oil; m/z 301 ($M^{+\cdot}$); $\nu_{max.}$ (film) 1736, 1629, 1530, 1257, and 1060 cm^{-1}.

Preparation of 2H-Pyrrole (12d). - To a cooled solution of the 3H-pyrrole (4d) (0.2 g, 6.5 x 10^{-4} mol) in diethyl ether (5 ml) was added dropwise 48% HBF_4 in diethyl ether (1 ml), and the mixture was stirred at 25°C for 24 h. The solvent was evaporated, the residue was dissolved in water (5 ml), and the solution was extracted with dichloromethane (2 x 20 ml). The extracts were dried ($MgSO_4$) and evaporated to give the HBF_4 salt of 2H-pyrrole (12d) as a gum, 0.12 g, 46%, δ_H ($CDCl_3$) 1.26(3H, t), 2.26(3H, d, J 1.3 Hz), 4.30(2H, q), 7.03(1H, d, J 1.3 Hz), 7.2-7.6(8H, m), and 8.0-8.2(2H, m). The salt was redissovled in dichloromethane (30 ml), excess anhydrous K_2CO_3 was added, and the mixture was stirred at 25°C for 24 h. Filtration of the mixture and evaporation of the filtrate gave the 2H-pyrrole (12d), which solidified on trituration with diethyl ether; yield 26%, m.p. 115-117°C, m/z 305 ($M^{+\cdot}$); $\nu_{max.}$ (Nujol) 1719, 1634, 1236, and 1055 cm^{-1}.

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