Synthetic Applications of *N*-*N* Linked Heterocycles. Part 8.[1] Regiospecific Synthesis of 4-(α-Acylalkyl)pyridines by Attack of Lithium Enolates of Ketones γ to *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts [2]

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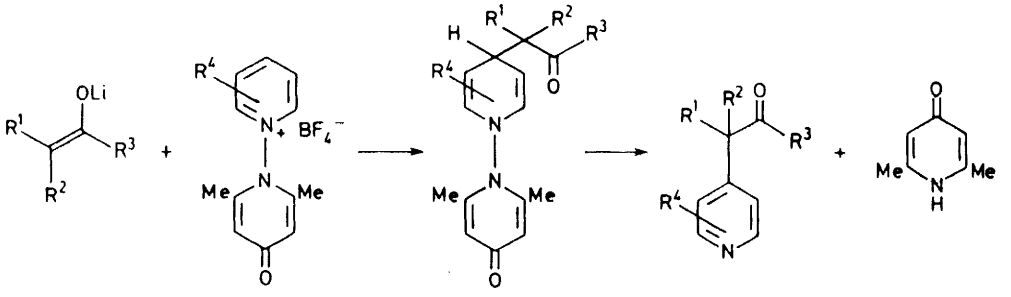
The addition of *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts (2)—(4) to lithium enolates (1) of ketones in tetrahydrofuran at low temperatures gives regiospecifically high yields of 1,4-dihydro-adducts (5)—(7). These are readily isolated and can be decomposed under free-radical conditions, also in high yield, to 4-(α-acylalkyl)-pyridines (8)—(10). Unsymmetrical dialkyl ketones give a mixture of two isomeric products, the ratio depending upon reaction conditions and steric factors. αβ-Unsaturated ketones, however, give products resulting from reaction exclusively at the position α′ to the carbonyl group.

RECENTLY we reported the versatility of the *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium cation (2) in the regiospecific synthesis of five classes of 4-substituted pyridines, including the 4-(α-acylalkyl)-derivatives (8).[2] The 2,6-dimethyl-4-oxopyridin-1-yl substituent, which can be attached to a pyridine nitrogen atom in two high-yield stages,[3] activates the pyridine ring to nucleophilic attack, and by sterically shielding the α-positions directs the nucleophile specifically to the γ-position to give a 1,4-dihydro-adduct [*e.g.* (5)]. It then serves as a leaving group to re-aromatise the ring.

We now report in full the synthesis by this method of 4-(α-acylalkyl)pyridines (8)—(10) [Scheme], a class of compounds of which relatively few examples have been recorded to date. With the exception of a route which is impracticable on the preparative scale,[4] previous syntheses have been achieved exclusively by acylation of alkyl-pyridines,[5] an approach which restricts considerably the range of compounds which can be prepared. Further, other methods for the synthesis of 2-(α-acylalkyl)pyridines have proved unsuitable for the preparation of the 4-isomers.[6]

This new method makes readily accessible for the first time acylalkyl-pyridines (8)—(10) with a wide range of substituents R^2, R^3, and R^4 in good overall yields.



(1) (2) R^4 = H; (3) R^4 = 2-Me; (4) R^4 = 3-Me (5) R^4 = H; (6) R^4 = 2-Me; (7) R^4 = 3-Me (8) R^4 = H; (9) R^4 = 2-Me; (10) R^4 = 3-Me (11)

SCHEME

RESULTS AND DISCUSSION

1,4-Dihydro-intermediates (5)—(7).—The oxopyridinyl-pyridinium salts (2)—(4) were added to solutions containing a 0.2 molar excess of lithium enolates (1) of ketones † in tetrahydrofuran, at −78 °C under nitrogen. Stirring at this temperature was continued for varying periods (see below) and, after the mixture had warmed to room temperature, the 1,4-dihydro-intermediates (5)—(7) were isolated by chromatography on alumina. Optimum yields (Table 1) were generally obtained by stirring at −78 °C for 5—15 min, but for benzylic and for αβ-unsaturated ketones 30 min was required. In most cases the intermediates (5)—(7) were too unstable to characterise by microanalysis, decomposing on standing, or on drying at 60 °C *in vacuo*, into the acylalkyl-pyridines (8)—(10) and the pyridone (11). They were however identified positively by ^{1}H n.m.r., and mass spectroscopy, and the relatively stable intermediate (5m) was analysed successfully. In no case was any product isolated resulting from attack at the 2-position of the pyridinium ring.

† Prepared by published procedures from lithium di-isopropylamide (LDA) and ketones,[7] except that 0.24M-solutions were used in place of the recommended 1.0M, to facilitate stirring after addition of the solid oxopyridinyl-pyridinium salt.

Unsymmetrical dialkyl ketones can theoretically give a mixture of two isomeric intermediates, arising from reaction respectively at the α- and α′-positions of the ketone. However, it has been shown [7] that formation of lithium enolates of ketones under kinetically controlled conditions gives predominantly the least-substituted isomer [*e.g.* (1; $R^1 = R^2 = H$) from methyl ketones]. Thus, formation of the lithium enolate of butan-2-one by dropwise addition of the ketone to a solution of LDA in tetrahydrofuran at −78 °C *during at least 5 min* gave,

TABLE 1

Yields (%) of intermediates (5)—(7) and products (8)—(10) [a]

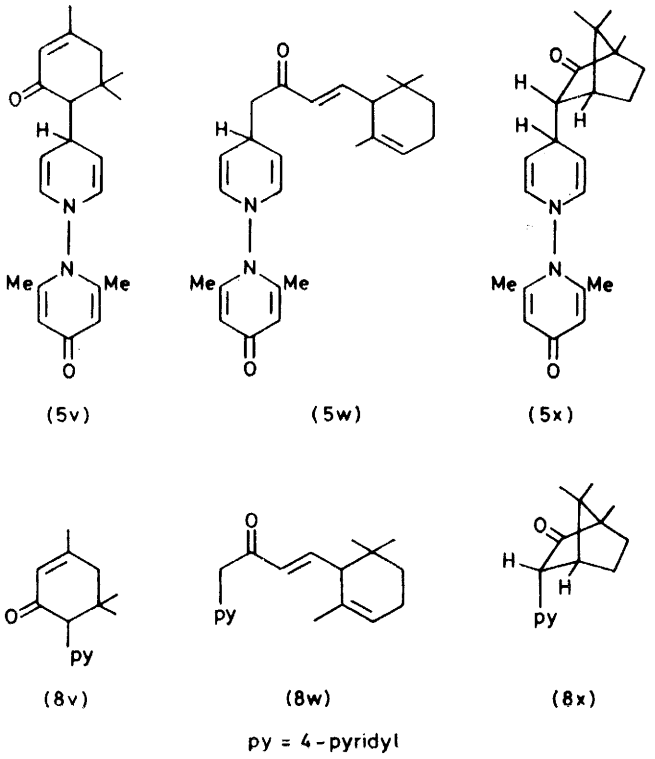
R^1	R^2	R^3	Intermediate	Yield [b]	Product	Yield [c]
H	H	Me	(5a)	23	(8a)	76
H	H	Et	(5b)	92 [d]	(8b)	72 [d]
H	H	Pr^i	(5c)	84	(8c)	100
H	H	Bu^n	(5d)	85 [d]	(8d)	92 [d]
H	H	Bu^i	(5e)	86	(8e)	85
H	H	Bu^t	(5f)	86	(8f)	91
H	Me	Et	(5g)	67	(8g)	99
Me	Me	Pr^i	(5h)	52	(8h)	77
H	$-(CH_2)_3-$		(5i)	72	(8i)	90
H	$-(CH_2)_4-$		(5j)	94	(8j)	91
H	$-(CH_2)_5-$		(5k)	84	(8k)	98
H	$-(CH_2)_3CHMe-$		(5l)	90	(8l)	92
H	H	Ph	(5m)	92	(8m)	89
H	Me	Ph	(5n)	79	(8n)	85
H	Ph	Me	(5p)	70	(8p)	82 [e]
H	Ph	Et	(5q)	75	(8q)	74
H	Ph	Pr^i	(5r)	72	(8r)	67
H	Ph	Ph	(5s)	70	(8s)	57 [e]
H	H	$Me_2:CCH-$	(5t)	84	(8t)	90
H	$-(CH_2)_2CH:CH-$		(5u)	71	(8u)	83
(Isophorone) [f]			(5v)	80 [g]	(8v)	90
(α-Ionone) [f]			(5w)	84	(8w)	68
(Camphor) [f]			(5x)	80	(8x)	80
H	H	Bu^t	(6f)	65	(9f)	93
H	Me	Et	(6g)	76	(9g)	76
H	$-(CH_2)_4-$		(6j)	88	(9j)	78
H	H	Ph	(6m)	86	(9m)	92
H	Ph	Me	(6p)	80	(9p)	62 [e]
H	H	Bu^t	(7f)	92	(10f)	80
H	Me	Et	(7g)	89	(10g)	95
H	$-(CH_2)_4-$		(7j)	75	(10j)	97
H	H	Ph	(7m)	85	(10m)	91
H	Ph	Me	(7p)	82	(10p)	71 [e]

[a] When a mixture is formed the substitution pattern refers to the major isomer. [b] Based on pyridinium salts (2)—(4). [c] Based on dihydro-intermediates (5)—(7). [d] Mixture of two isomers; see text. [e] Significant reversal to parent ketone also occurred; see text. [f] Parent ketone; structures of dihydro-intermediates and α-acylalkyl-pyridines are illustrated in the text. [g] 75% On ×5 scale.

after treatment with the oxopyridinyl-pyridinium salt (2), a mixture containing 75% of intermediate (5b) and 25% of the isomer (5b′) having $R^1 = H$, $R^2 = R^3 = Me$. The ratio was reduced to 55 : 45 when the ketone was added to the LDA solution all at once. Likewise, hexan-2-one gave a mixture containing 90% of intermediate (5d) and 10% of the isomer (5d′) having $R^1 = H$, $R^2 = Pr^n$, and $R^3 = Me$, the ratio again being reduced to 57 : 43 when the ketone was added rapidly.

Steric factors appear to be responsible for rendering the terminal enolate of hexan-2-one more favourable than that from butan-2-one. This is supported by the isolation of only one dihydro-intermediate (the one resulting from the least-substituted enolate anion) from the more sterically hindered ketones 3-methylbutan-2-one, 4-methylpentan-2-one, and 2-methylcyclohexanone [respectively (5c), (5e) and (5l)].* For camphor, only the *endo*-dihydro-intermediate (5x) was isolated, as evidenced from the ^1H n.m.r. spectrum of the pyridine (8x) [δ(H-3) 3.76 (1 H, d, J 4.6 Hz)].

With benzylic ketones, again only one dihydro-intermediate was observed, but for these ketones removal of one of the more acidic benzylic protons was the most favoured process, leading to compounds (5p—s).



SCHEME 2

Lee and his co-workers [8] have shown that for cyclic αβ-unsaturated ketones the rate of α′-proton abstraction is greater than that of γ-proton abstraction, and that alkylation of lithium enolates prepared from lithium amides under conditions of kinetic control occurs predominantly at the α′-position. We have found that for two cyclic and two non-cyclic αβ-unsaturated ketones, additions to the salt (2) *via* lithium enolates prepared as described above, took place essentially regiospecifically at the α′-positions of the ketones, giving rise to a single dihydro-intermediate in each case [respectively (5t—w)].* Lithium enolates formed by rapid addition of the ketones to LDA, however, gave a mixture of dihydro-intermediates, arising probably from addition at the α-, α′-, and γ-positions. No reaction took place with the lithium salt of 2,6-dimethylpyran-4-one

4-*Acylalkyl-pyridines* (8)—(10).—Although many di-

* It is possible that very small amounts of the isomeric dihydro-intermediates were formed, but they were not detected in the ^1H n.m.r. spectra of the isolated samples.

hydro-intermediates (5)—(7) decomposed slowly at room temperature in the solid state to give 4-acylalkyl-pyridines (8)—(10), they could be cleaved smoothly and cleanly in high yields (Table 1) by refluxing the intermediate in carbon tetrachloride for 16 h * in the presence of the free-radical initiator azobisisobutyronitrile. Thus 4-acylalkyl-pyridines can be prepared from 4-oxopyridinyl-pyridinium salts (2)—(4) in an average yield of 78%, and from the parent pyridines in an average yield of 50%.

A detailed study of the effect of solvent on the decomposition of intermediate (5m) was carried out, and the results are presented in Table 2. With the exception of the rather surprising observation with toluene, which may be due to the relatively high boiling temperature of that solvent, the results strongly support a free-radical mechanism. In the non-polar solvent carbon tetrachloride, and in the presence of initiators (deliberately added or present as peroxide impurities in ethers), decomposition was essentially complete in 16 h. In the absence of initiators, or when a quencher was added, however, the extent of decomposition was much reduced, and in many polar solvents it was negligible.

TABLE 2

Effect of solvent on the decomposition of the 1,4-dihydro-intermediate (5m)

Solvent	Reflux time (h)	Initiator [a]	Extent (%) of decomposition
Carbon tetrachloride	16	A	100
Carbon tetrachloride	16	B	100
Carbon tetrachloride	16	None	100
Carbon tetrachloride	16	A [b]	56
Tetrahydrofuran	16	None	100
Tetrahydrofuran	16 [c]	None	100
Tetrahydrofuran [d]	16 [c]	None	20
Dimethoxyethane	16	None	100
Dioxan	16	None	80
Chloroform	16	A	85
Chloroform	16	A [b]	10
Chloroform	16	None	0
CCl_4–Methanol (3 : 1)	16	None	100
Methanol [e]	16	None	10
Ethyl acetate	16	None	0
Ethanol	6	None	0
t-Butyl alcohol	6	None	0
Acetone	6	None	0
Diethyl ether	6	None	0
Toluene	6	None	100
Benzene	6	None	0

[a] A = Azobisisobutyronitrile; B = dibenzoyl peroxide. [b] Diphenylamine added as a free-radical quencher. [c] Room temperature reaction. [d] Purified to remove peroxides. [e] Absolute.

Intermediates (5p), (5s), (6p), and (7p) derived from benzyl ketones [though not intermediates (5q) and (5r)] gave, in addition to the acylalkyl-pyridines (8)—(10), 15—20% of the parent ketones based on the dihydro-intermediates, arising apparently from reversal of the initial addition reaction. Reversals of this type compete even more seriously with normal decomposition in the cases of dihydro-intermediates derived from the anions of β-dicarbonyl compounds and from certain azoles.[9] The phenomenon appears to be related to the strength of the bond formed between the attacking nucleophile and the pyridine ring, and is found to increase in effect with decreasing pK_a of the nucleophile conjugate acid, and with increasing steric crowding around the site of the bond. It can be minimised, though in our experience not entirely eliminated, by careful purification of the dihydro-intermediates, and by scrupulous exclusion of moisture and other proton sources during decomposition.

For reasons of economy, the relatively large number of preparations were performed on a small (2 mmol) scale. However, a reaction scaled up five times was carried out successfully without significant change in yield. Most of the acylalkyl-pyridines prepared were isolated as oils by chromatography on alumina followed by removal of solvent *in vacuo*; they were thus characterised more fully by ^{1}H n.m.r., i.r., and mass spectroscopy, and further as crystalline derivatives. Physical and analytical data for 8 known, and 23 previously unreported acylalkyl-pyridines and their derivatives are presented in Table 3. For known ketones, microanalytical data for derivatives have not been included unless the analyses were not previously reported, or unless observed melting points differ significantly from published values. 2,4-Dinitrophenylhydrazones or methiodides were prepared only when picrates did not form satisfactorily.

Spectroscopic Data.—*1,4-Dihydro-intermediates* (5)—(7). In the i.r. spectra of the dihydro-intermediates strong absorptions were observed for the ketone carbonyl group in the range 1 720—1 670 cm^{-1}, in addition to those characteristic of the pyridone moiety between 1 650—1 630 and 1 560—1 530 cm^{-1}, and the dihydropyridine ring near 1 680 cm^{-1}.

Integrals of ^{1}H n.m.r. spectra (in $CDCl_3$) showed the compounds to be essentially pure. The 2- and 6-methyl groups of the pyridone ring appeared near 2.0—2.2 p.p.m., often as two resolved singlets indicating restricted rotation about the N–N bond,[10] and the 3- and 5-protons as a broad singlet near 6.1 p.p.m. For the dihydro-pyridine ring, the 2- and 6-protons showed as a broadened doublet centred near 5.8—5.9 p.p.m., the 3- and 5-protons as a double doublet centred near 4.5—4.75 p.p.m., and the 4-proton as a multiplet centred in the range 3.3—4.0 p.p.m. Methyl-groups at the 2- or 3-positions, when present, appeared as broad singlets near 1.4—1.5 and 1.6—1.7 p.p.m. respectively. The remainder of the spectrum was characteristic for the acylalkyl substituent, and was used to confirm the substitution pattern.

Few dihydro-intermediates showed a molecular ion in the mass spectrum, the major fragmentation processes being (*a*) cleavage of the N–N bond to give the pyridone (11) (*m/e* 123) and the acylalkyl-pyridines (8)—(10); and (*b*) cleavage of the C–C bond joining the acylalkyl group to the dihydropyridine portion to give the oxopyridinyl-pyridinium fragment (*m/e* 201), followed by

* In some cases a shorter time sufficed.

further degradation to the pyridone (*m/e* 123) and pyridine (*m/e* 79).

4-(α-*Acylalkyl*)*pyridines* (8)—(10).—I.r. spectra were consistent with the proposed structures, the ketone carbonyl absorption appearing in the range 1 720—1 670 cm^{-1}.

A typical AA'XX' pattern was observed in the ^1H n.m.r. spectra of all acylalkyl-pyridines characteristic of 4-substitution in the pyridine, the two groups of lines being centred near 8.4—8.6 and 7.0—7.2 p.p.m.

Tetrahydrofuran (THF) was redistilled from $LiAlH_4$ before use. n-Butyl-lithium and di-isopropylamine were used as supplied by E. Merck Company. Hygroscopic ketones were dried and redistilled before use. The 4-oxopyridin-1-ylpyridinium tetrafluoroborates (2)—(4) were prepared as reported previously [3] and dried *in vacuo* before use. Light petroleum refers to the fraction b.p. 60—80 °C.

General Procedure for the Preparation of Dihydro-intermediates (5)—(7).—A solution containing LDA (2.4 mmol) was prepared by adding Pr^i_2NH (0.34 ml) to a mixture of 15% Bu^nLi in hexane (1.46 ml) and THF (10 ml) at −78 °C under dry N_2. The appropriate ketone (2.4 mmol) was added dropwise during at least 5 min, and the resulting clear solution stirred for a further 5 min. The tetrafluoroborate salt (2) (576 mg, 2 mmol) was added portionwise during 5—10 min to the latter, which was then stirred at −78 °C for 5—15 min (30 min for benzylic or αβ-unsaturated ketones), and finally allowed to warm to 0 °C. The solvent was removed under reduced pressure at 25 °C, the residue extracted into $CHCl_3$ (30 ml), the $CHCl_3$ extract evaporated, and the residue triturated with light petroleum to give the dihydro-intermediate sufficiently pure for proceeding to the next stage. The intermediate could be further purified by elution through a short (*ca.* 10 cm) alumina column (grade V; neutral) with $CHCl_3$.

Most intermediates were too unstable for characterisation by microanalysis, but the *dihydropyridine* (5m) gave yellow prisms as the monohydrate, m.p. 120—121 °C (CH_2Cl_2–light petroleum) (Found: C, 71.0; H, 6.55; N,

TABLE 3

Physical and analytical data for pyridine ketones (8)—(10) and their derivatives

Ketone	n_D (*t*/°C) Observed [a]	n_D (*t*/°C) Lit.	Derivative *	M.p. (*t*/°C) Observed	M.p. (*t*/°C) Lit.	Formula	Found (%) C	Found (%) H	Found (%) N	Requires (%) C	Requires (%) H	Requires (%) N
(8a)	1.5225(26)	1.5208(20) [b]	P	154	156—157.5 [b]	$C_{14}H_{12}N_4O_8$						
(8c)	1.5054(25)	1.5064(20 [b]	P	119—120	119—121 [b]	$C_{16}H_{16}N_4O_8$						
(8e)	1.5015(25)	1.5017(20) [b]	P	137—138	138.5—139.5 [b]	$C_{17}H_{18}N_4O_8$						
(8f)	1.5039(28)	1.5038(20) [b]	P	148—149 [c]	158.5—159.5 [b]	$C_{17}H_{18}N_4O_8$	50.3	4.3	14.0	50.2	4.5	13.8
(8g)	1.5028(26)		P	116—117		$C_{16}H_{16}N_4O_8$	49.1	4.2	14.4	48.9	4.1	14.3
(8h)	1.4990(24)		P	112—113		$C_{18}H_{20}N_4O_8$	51.4	4.4	13.3	51.4	4.8	13.3
(8i)	1.5406(26)		P	117—118		$C_{16}H_{14}N_4O_8$		*d*		49.2	3.6	14.4
(8j)	106—107 [c]	107—108.5 [c,f]	P	145—146		$C_{17}H_{16}N_4O_8$	50.2	4.1	13.6	50.5	4.0	13.9
(8k)	1.5288(26)		P	138—139		$C_{18}H_{18}N_4O_8$	51.7	4.4	13.2	51.7	4.3	13.4
(8l)	1.5215(26)		P	145—146		$C_{18}H_{18}N_4O_8$	51.7	4.5	13.4	51.7	4.3	13.4
(8m)	113—114 [c]	114—115.5 [c,f]	P	134—135 [c]	170—170.5 [f]	$C_{19}H_{14}N_4O_8$	53.3	3.3	13.2	53.5	3.3	13.1
(8n)	1.5620(26)	62.4—63 [c,g]	P	152—153	150—151 [g]	$C_{20}H_{16}N_4O_8$	54.5	3.7	12.7	54.5	3.7	12.7
(8p)	1.5612(26)		P	128—129		$C_{20}H_{16}N_4O_8$	54.2	3.7	12.6	54.5	3.7	12.7
(8q)	1.5640(26)		P	155—156		$C_{21}H_{18}N_4O_8$	55.7	4.2	12.5	55.5	4.0	12.3
(8r)	1.5455(29)		P	152—153		$C_{22}H_{20}N_4O_8$	56.6	4.5	11.8	56.4	4.3	12.0
(8s)	1.5542(27)		P	157—158		$C_{25}H_{18}N_4O_8$	59.7	3.7	11.1	59.8	3.6	11.2
(8t)	1.5210(26)		P	119—120		$C_{17}H_{16}N_4O_8$	50.3	4.2	13.6	50.5	4.0	13.9
(8u)	1.5298(25)		P	108—109		$C_{17}H_{14}N_4O_8$ [h]	55.7	5.3	10.5	55.8	5.4	10.8
(8v)	107—108 [c]		P	163—164		$C_{20}H_{20}N_4O_8$	54.1	4.6	12.8	54.1	4.6	12.6
(8w)	1.5362(28)		P	192—193		$C_{24}H_{26}N_4O_8$		*d*		57.8	5.3	11.2
(8x)	1.5245(23)		DNP	167—168		$C_{21}H_{22}N_5O_4$ [i]	57.4	6.2	16.8	57.1	5.9	17.0
(9f)	1.4912(24)		P	146—147		$C_{18}H_{20}N_4O_8$	51.5	5.0	13.4	51.4	4.8	13.3
(9g)	1.4953(26)		P	114—115		$C_{17}H_{18}N_4O_8$	50.4	4.5	13.7	50.2	4.5	13.8
(9j)	1.5307(25)		P	149—150		$C_{18}H_{18}N_4O_8$	51.7	4.5	13.3	51.7	4.3	13.4
(9m)	79—81 [c]	80.8—81,8 [c,j]	P	135—135.5 [c]	144—145.5 [j]	$C_{20}H_{16}N_4O_8$	54.3	3.8	12.7	54.5	3.7	12.7
(9p)	1.5168(27)		P	147—148		$C_{21}H_{18}N_4O_8$	55.4	4.0	12.1	55.5	4.0	12.3
(10f)	1.5028(24)		M	177—178		$C_{13}H_{20}NOI$	47.0	6.0	4.2	46.9	6.0	4.2
(10g)	1.5041(26)		P	95—96		$C_{17}H_{18}N_4O_8$	50.2	4.5	13.9	50.2	4.5	13.8
(10j)	1.5358(26)		P	123—124		$C_{18}H_{18}N_4O_8$	51.5	4.3	13.7	51.7	4.3	13.4
(10m)	1.5779(26)		P	168—169		$C_{20}H_{16}N_4O_8$	54.5	3.7	12.6	54.5	3.7	12.7
(10p)	1.5504(24)		P	137—138		$C_{21}H_{18}N_4O_8$	55.6	3.9	12.0	55.5	4.0	12.3

* P = Picrate, M = methiodide, DNP = 2,4-dinitrophenylhydrazone; all obtained as prisms.

[a] Most ketones isolated as oils by chromatography on Al_2O_3, and removal of solvent *in vacuo*. [b] Ref. 5*c*. [c] Large difference from literature value; composition confirmed by microanalysis. [d] Microanalysis unsatisfactory; structure confirmed by ^1H n.m.r. [e] Crystalline solid; m.p. (°C). [f] Ref. 4. [g] Ref. 5*a*. [h] Analyses with $1H_2O$. [i] Analyses with $1.5H_2O$. [j] Ref. 5*d*.

The proposed substitution pattern in the ketone portion was also verified, and where a mixture of isomers was found, the relative amounts were determined by integration.

A molecular ion was observed in the mass spectra of nearly all compounds studied. Major fragmentation pathways involved loss of the R^2 or R^3 group, followed respectively by loss of $R^3{-}C{\equiv}O^+$ or C=O. The azatropylium ion (*m/e* 92) was prominent in all spectra recorded.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 577 instrument as liquid films, or in Nujol; ^1H n.m.r. spectra as solutions in $CDCl_3$ on a Perkin-Elmer R-20 spectrometer using $SiMe_4$ as internal reference; and mass spectra on a Hitachi RMS-4 instrument.

8.4. $C_{20}H_{20}N_2O_2 \cdot H_2O$ requires C, 71.0; H, 6.55; N, 8.3%); $M^{+\bullet}$ 320; $\nu_{max.}$ 3 400br, 1 672, 1 635, and 1 550 cm^{-1}; $\delta(CDCl_3)$ 7.75 (5 H, m), 6.1 (2 H, s), 5.90 (2 H, d, *J* 8.3 Hz), 4.75 (2 H, dd, *J* 3.8, 8.3 Hz), 3.67 (1 H, m), 3.10 (2 H, d, *J* 6.8 Hz), and 2.28 (6 H, s).

General Procedure for the Decomposition of the Intermediates (5)—(7) *to the* 4-(α-*Acylalkyl*)*pyridines* (8)—(10).—The 1,4-dihydro-intermediate isolated from the previous stage was suspended in dry CCl_4 (25 ml) and a few crystals of azobisisobutyronitrile were added to the mixture; it was then heated under reflux for 16 h with protection from moisture. The solvent was evaporated under reduced pressure, and the residue eluted through an alumina column (grade V, neutral) with $CHCl_3$. The product emerged first, and was isolated as an oil by evaporation.

Picrates of Pyridines (8).—Difficulties were experienced in preparing a number of the picrates by standard procedures, but the following modified method proved to be satisfactory. The isolated pyridine, in conc. HCl (2 ml) was added dropwise with stirring to saturated aqueous picric acid (20 ml). The precipitated picrate was separated and recrystallised (95% EtOH).

Large-scale Preparation of Ketone (8v).—The preparation was carried out as described above, only both stages were scaled up five times. The *isophorone derivative* (8v) [(75%); based on salt (2)] was isolated as off-white prisms, m.p. 107—108 °C (light petroleum) (Found: C, 77.9; H, 8.15; N, 6.3. $C_{14}H_{17}NO$ requires C, 78.1; H, 7.95; N, 6.5%); $M^{+\bullet}$ 215; $\nu_{max.}$ 1 645br, 1 590, 1 550, and 810 cm^{-1}; $\delta(CDCl_3)$ 8.52 (2 H, m), 7.05 (2 H, m), 6.07 (1 H, s), 3.5 (1 H, s), 2.25 (2 H, s), 2.0 (3 H, s), 1.0 (3 H, s), and 0.9 (3 H, s).

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