# Synthesis of Indolizines by Intramolecular Cyclisation of Pyridinium Allylides [1-(1-Pyridinio)prop-2-enides]

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Pyridinium ethoxycarbonyl-(3-oxocyclohexen-1-yl)methylides (VII)—(IX) and 3,3-diacyl-1-ethoxycarbonylallylides (X)—(XIII) are prepared by the reaction of 1-ethoxycarbonylmethylpyridinium bromides (III) and (IV) with 3-chlorocyclohex-2-enones and 3-ethoxymethylenepentane-2,4-dione or diethyl ethoxymethylenemalonate, respectively. Refluxing the ylides (VII)—(IX) in xylene affords the ethyl 10-oxo-7,8,9,10-tetrahydropyrido[2,1-*a*]isoindole-6-carboxylates (XVI)—(XVIII), and the ylides (X) and (XII) give diethyl indolizine-1,3-dicarboxylate (XIX) and ethyl 1-acetylindolizine-3-carboxylate (XX), respectively. However, similar treatment of the ylides (XI) and (XIII) affords ethyl indolizine-3-carboxylate (XXVII) and the keto-ester (XX), respectively. The mechanisms for the formation of the indolizine derivatives are discussed.

In a series of papers,[1-5] we have reported that various types of pyridinium allylides (I; X = CR) and *N*-(1-pyridinio)vinylaminides (I; X = N) undergo intramolecular cyclisation to give indolizines (II; X = CR) and pyrazolo[1,5-*a*]pyridines (II; X = N), respectively. Since then other papers have appeared reporting similar reactions.[6-8] In continuation of our studies on the scope

(I) (II)

and mechanistic aspects of this reaction, we have investigated the thermochemical behaviour of pyridinium

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[8] T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *J.C.S. Perkin I*, 1973, 2089.

ethoxycarbonyl-(3-oxocyclohex-1-enyl)methylides (VII)—(IX) and 3,3-diacyl-1-ethoxycarbonylallylides (X)—(XIII).

Compounds (VII)—(IX) were synthesised by the reaction of the 1-ethoxycarbonylmethylpyridinium bromides (III) and (IV) with 3-chlorocyclohex-2-enone or 3-chloro-5,5-dimethylcyclohex-2-enone in ethanol in the presence of potassium carbonate at room temperature. Similarly, compounds (X)—(XIII) were obtained in good yields from (III) and (IV) and 3-ethoxymethylenepentane-2,4-dione or diethyl ethoxymethylenemalonate.

These ylides were characterised by analytical and spectral data. Compounds (VII)—(IX) are dark red crystals and exhibit two u.v. absorption maxima at 260—266 and 359—362 nm. The absence of i.r. carbonyl absorption bands above 1600 $cm^{-1}$ suggests that they have betaine-like structures with highly polarised carbonyl groups. The n.m.r. signal of the olefinic proton ($H_a$) is at $\tau$ 5·76—6·03 and this proton is readily exchanged with deuterium by adding one drop of deuterium oxide to a solution in deuteriochloroform, reflecting the increased electron density at this position.

Compounds (X)—(XIII) are red to yellow crystals and show spectral features essentially similar to those reported previously for the pyridinium 3,3-diacyl-1-benzoylallylides (XIV)—(XV):[2] the u.v. spectra have two absorption maxima at 260—287 and 337—343 nm, and the i.r. spectra show polarised carbonyl bands. In the n.m.r. spectra, the olefinic proton signal appears at $\tau$ 1·49—1·82.

When dark red solutions of the ylides (VII) and (IX) in xylene were refluxed until the colour of the solution faded to yellow, the indolizines (XVI) and (XVIII) were obtained in 10 and 29% yields, respectively. Similar treatment of (VIII), however, gave two products in 10 and 3% yields. The minor product was identical with (XVI). The structures of these compounds were readily established by elemental analyses and spectral data (Experimental section).

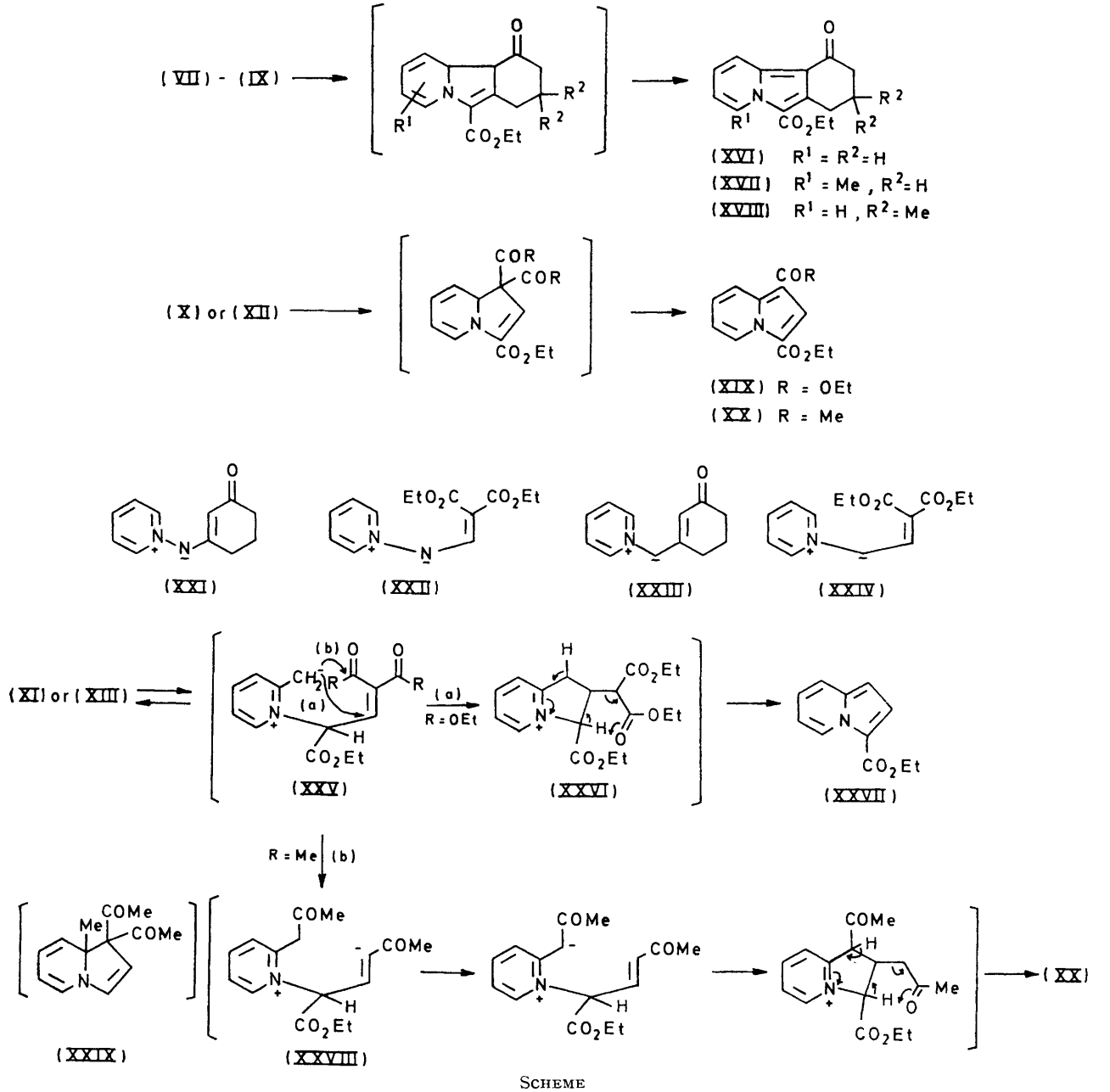
The ylides (X) and (XII) behaved similarly to give the indolizines (XIX) and (XX) in 25 and 3% yields, respectively.

The formation of the indolizine derivatives (XVI)—(XX) from (VII)—(X) and (XII) is thought to involve an electrocyclic reaction of the ylides followed by aromatisation of the resulting dihydroindolizine intermediates; such dihydroindolizine intermediates have been isolated in some cases.[6]

The aforementioned results are in accordance with the behaviour of the pyridinium 1-benzoylallylides (XIV) and (XV) and aminides (XXI) and (XXII), but are in contrast to that of the related unisolable allylides (XXIII)[5] and (XXIV)[8] which have been reported to give only intractable material. This difference is apparently a result of increased stability of the ylides (VII)—(X) and (XII), so that the 1,5-cyclisation reaction can compete with the decomposition of the ylides. The aminides (XXI) and (XXII) are also stable enough to be isolated.

In sharp contrast to the behaviour of (X) and (XII), the 2-methylpyridinium ylides (XI) and (XIII) reacted completely differently. Thus, refluxing ylide (XI) in xylene resulted in the formation of ethyl indolizine-1-carboxylate (XXVII) in 68% yield as an unstable oil, whose structure was deduced from its spectral data (Experimental section). Similar treatment of ylide (XIII) afforded (XX) in 50% yield.

The formation of these indolizines (XXVII) and (XX) may be rationalised as outlined in the Scheme. The initial step may be reversible proton shift to give (XXV). In the case of (XI), this step is then followed by Michael addition to lead to (XXVI) which undergoes carbon–carbon bond cleavage and aromatisation to afford (XXVII). In the case of (XIII) the carbanionic centre of (XXV) attacks an acetyl carbonyl group to give (XXVIII) which follows similar reaction sequences as in the formation of (XXVII) to give (XX). This proposal also rationalises the formation of a minor product, 1-acetyl-3-benzoylindolizine from 2-methylpyridinium 3,3-diacetyl-1-benzoylallylide.[2] An alternative explanation for the formation of (XX) from (XIII), that (XIII) undergoes a 1,5-cyclisation to afford (XXIX) followed by formal elimination of acetone, does not appear plausible in view of the facts that cyclisation occurs predominantly or exclusively at the non-substituted side of 2-methylpyridinium ylides.[5,7,8]




SCHEME

## EXPERIMENTAL

N.m.r. spectra were determined with a Hitachi R-20A spectrometer (tetramethylsilane as internal standard). I.r. spectra were recorded with a Hitachi EPI-G2 spectrophotometer and u.v. spectra with a Hitachi 124 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6D instrument with a direct inlet system operating at 70 eV.

Preparative layer chromatography (p.l.c.) was carried out on Merck alumina $PF_{254}$.

*Pyridinium Ethoxycarbonyl-(3-oxocyclohex-1-enyl)methylides* (VII)—(IX).—A solution of 3-chlorocyclohex-2-enone (10 mmol) or 3-chloro-5,5-dimethylcyclohex-2-enone (10 mmol) in ethanol (10 ml) was added to an ethanolic solution of a pyridinium ethoxycarbonylmethylide (V) or (VI) [prepared by stirring an ethanolic solution of a 1-ethoxycarbonylmethylpyridinium bromide (III) or (IV) (10 mmol) and potassium carbonate (1·38 g)]. The mixture was stirred at room temperature overnight and filtered to remove inorganic material. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography (alumina–$CHCl_3$). Concentration of a purple eluate gave dark red crystals or a dark red oil. *Pyridinium ethoxycarbonyl-(3-oxocyclohex-1-enyl)methylide* (VII) (69%) formed dark red plates, m.p. 161—162° (from acetone–ether) (Found: C, 69·3; H, 6·7; N, 5·6. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%); $\nu_{max.}$ ($CHCl_3$) 1570m and 1490s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 261 and 359 nm (log ε 4·02 and 4·84); τ ($CDCl_3$) 1·4—2·3 (5H, m, pyridine H), 5·76 (1H, s, vinyl H), 5·93 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 6·7—7·1 (2H, m, cyclohexenone H), 7·5—8·2 (4H, m, cyclohexenone H), and 8·85 (3H, t, *J* 7 Hz, $OCH_2CH_3$). 2-Methylpyridinium ethoxycarbonyl-(3-oxocyclohex-1-enyl)methylide (VIII) (29%) was obtained as a viscous oil; $\nu_{max.}$ ($CHCl_3$) 1560m and 1485s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 266 and 360 nm (log ε 3·68 and 4·67); τ ($CDCl_3$) 1·5—2·6 (4H, m, pyridine H), 5·93 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 6·03 (1H, s, vinyl H), 6·7—7·1 (2H, m, cyclohexenone H), 7·38 (3H, s, $CH_3$), 7·2—8·2 (4H, m, cyclohexenone H), and 8·85 (3H, t, *J* 7 Hz, $OCH_2CH_3$). *Pyridinium ethoxycarbonyl-(5,5-dimethyl-3-oxocyclohex-1-enyl)methylide* (IX) (20%) formed dark red crystals, m.p. 141—143° (decomp.) (from acetone–ether) (Found: C, 70·8; H, 7·5; N, 4·9. $C_{17}H_{21}NO_3$ requires C, 71·05; H, 7·4; N, 4·9%); $\nu_{max.}$ ($CHCl_3$) 1565m and 1490s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 260 and 362 nm (log ε 3·68 and 4·79); τ ($CDCl_3$) 1·4—2·3 (5H, m, pyridine H), 5·77 (1H, s, vinyl H), 5·93 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 7·02 (2H, s, cyclohexenone H), 7·88 (2H, s, cyclohexenone H), 8·86 (3H, t, *J* 7 Hz, $COH_3CH_3$), and 8·90 (6H, s, 2 × $CH_3$).

*Pyridinium 1,3,3-Trisethoxycarbonylallylides* (X) *and* (XI).—Using a similar procedure described for the preparation of (VII)—(IX), these ylides were obtained from (V) or (VI) and diethyl ethoxymethylenemalonate and purified by recrystallisation from ethanol–ether. *Pyridinium 1,3,3-trisethoxycarbonylallylide* (X) (55%) formed red plates, m.p. 99—101° (Found: C, 60·95; H, 6·4; N, 4·3. $C_{17}H_{21}NO_6$ requires C, 60·9; H, 6·3; N, 4·2%); $\nu_{max.}$ ($CHCl_3$) 1640s and 1620s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 260 and 337 nm (log ε 4·05 and 4·55); τ ($CDCl_3$) 1·49 (1H, s, vinyl H), 1·45—2·4 (5H, m, pyridine H), 5·6—6·4 (6H, m, 3 × $OCH_2CH_3$), 8·71 (3H, t, *J* 7·5 Hz, $OCH_2CH_3$), and 8·82 (6H, t, *J* 7·5 Hz, 2 × $OCH_2CH_3$). 2-*Methylpyridinium* 1,3,3-*trisethoxycarbonylallylide* (XI) (66%) formed red crystals, m.p. 89—90° (Found: C, 62·0; H, 6·8; N, 3·9. $C_{18}H_{23}NO_6$ requires C, 61·9; H, 6·6; N, 4·0%); $\nu_{max.}$ ($CHCl_3$) 1640s and 1530s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 265 and 340 nm (log ε 4·04 and 4·64); τ ($CDCl_3$) 1·56 (1H, s, vinyl H), 1·65—2·2 (4H, m, pyridine H), 5·6—6·3 (6H, m, 3 × $OCH_2CH_3$), 7·34 (3H, s, $CH_3$), 8·73 (3H, t, *J* 8 Hz, $OCH_2CH_3$), and 8·86 (6H, t, *J* 8 Hz, 2 × $OCH_2CH_3$).

*Pyridinium 3,3-Diacetyl-1-ethoxycarbonylallylides* (XII) *and* (XIII).—By using a procedure similar to that for the preparation of (VII)—(IX), these compounds were obtained from (V) or (VI) and 3-ethoxymethylenepentane-2,4-dione and purified by recrystallisation from ethanol–ether. *Pyridinium 3,3-diacetyl-1-ethoxycarbonylallylide* (XII) (58%) formed red crystals, m.p. 143—144° (Found: C, 65·35; H, 6·3; N, 4·8. $C_{15}H_{17}NO_4$ requires C, 65·4; H, 6·2; N, 5·1%); $\nu_{max.}$ ($CHCl_3$) 1660m, 1620w, 1590s, and 1510s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 287 and 343 nm (log ε 4·07 and 4·39); τ ($CDCl_3$) 1·5—2·4 (5H, m, pyridine H), 1·81 (1H, s, vinyl H), 5·76 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 7·74 (6H, s, 2 × $CO{\cdot}CH_3$), and 8·69 (3H, t, *J* 7 Hz, $OCH_2CH_3$). 2-*Methylpyridinium* 3,3-*diacetyl-1-ethoxycarbonylallylide* (XIII) (53%) formed yellow crystals, m.p. 116—118° (Found: C, 67·5; H, 5·7; N, 5·8. $C_{16}H_{19}NO_4$ requires C, 67·5; H, 5·7; N, 6·1%); $\nu_{max.}$ ($CHCl_3$) 1660m, 1640m, 1590s, and 1510s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 287 and 342 nm (log ε 4·05 and 4·33); τ ($CDCl_3$) 1·7—2·5 (4H, m, pyridine H), 1·82 (1H, s, vinyl H), 5·78 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 7·32 (3H, s, $CH_3$), 7·78 (6H, s, 2 × $COCH_3$), and 8·71 (3H, t, *J* 7 Hz, $OCH_2CH_3$).

*Thermal Reactions.*—(a) *Pyridinium ethoxycarbonyl-(3-oxocyclohex-1-enyl)methylide* (VII). A dark red solution of (VII) (200 mg) in xylene (25 ml) was heated under reflux until the solution turned yellow (*ca.* 1 h). The solvent was evaporated off under reduced pressure. The residue was purified by p.l.c. with benzene to give *ethyl* 10-*oxo*-7,8,9,10-*tetrahydropyrido*[2,1-a]*isoindole*-6-*carboxylate* (XVI) (20 mg, 10%) as pale yellow needles, m.p. 151—152° [from light petroleum (b.p. 60—80°)] (Found: C, 70·2; H, 6·0; N, 5·3. $C_{15}H_{15}NO_3$ requires C, 70·0; H, 5·9; N, 5·4%); $\nu_{max.}$ (KCl) 1675s and 1640s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 229, 257·5, 288, 331, and 349sh nm (log ε 4·22, 4·41, 4·03, 4·11, and 3·98); τ ($CDCl_3$) 0·43 (1H, d, *J* 7 Hz, 4-H), 1·58 (1H, d, *J* 9 Hz, 1-H), 2·4—3·2 (2H, m, 2- and 3-H), 5·59 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 6·80 (2H, t, *J* 6 Hz, 7-H), 7·2—8·0 (4H, m, 8- and 9-H), and 8·54 (3H, t, *J* 7 Hz, $OCH_2CH_3$).

(b) 2-*Methylpyridinium ethoxycarbonyl-(3-oxocyclohex-1-enyl)methylide* (VIII). Similar treatment of (VIII) (412 mg) in refluxing xylene (50 ml) gave two products, which were separated by p.l.c. (alumina–benzene). The major, oily product was identified as ethyl 4-methyl-10-oxo-7,8,9,10-tetrahydropyrido[2,1-*a*]isoindole-6-carboxylate (XVII) (41 mg, 10%), $M^+$ 271; $\nu_{max.}$ ($CHCl_3$) 1675s and 1640s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 231, 259, 287, 340, and 354 nm (log ε 4·20, 4·36, 3·92, 4·16, and 4·14); τ ($CDCl_3$) 1·55 (1H, d, *J* 7·5 Hz, 1-H), 2·64 (1H, dd, *J* 7·5 and 8·5 Hz, 2-H), 3·15 (1H, d, *J* 8·5 Hz, 3-H), 5·57 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 6·88 (2H, t, *J* 6 Hz, 7-H), 7·36 (3H, s, $CH_3$), 7·2—8·2 (4H, m, 8- and 9-H), and 8·53 (3H, t, *J* 7 Hz, $OCH_2CH_3$). The minor product was isolated as pale yellow needles, m.p. 151—152° (10 mg, 3%), and was identical with (XVI).

(c) *Pyridinium ethoxycarbonyl-(5,5-dimethyl-3-oxocyclohex-1-enyl)methylide* (IX). Similar treatment of (IX) (200 mg) in refluxing xylene (25 ml) gave *ethyl* 8,8-*dimethyl*-10-*oxo*-7,8,9,10-*tetrahydropyrido*[2,1-a]*isoindole*-6-*carboxylate* (XVIII) (58 mg, 29%) as pale yellow needles, m.p. 168—169° [from light petroleum (b.p. 60—80°)] (Found: C, 71·5; H, 6·7; N, 4·8. $C_{17}H_{19}NO_3$ requires C, 71·6; H, 6·7; N, 4·9%); $\nu_{max.}$ (KCl) 1675s and 1645s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 229, 256·5, 289, 333·5, and 350sh nm (log ε 4·40, 4·54, 4·17, 4·29, and 4·14); τ ($CDCl_3$) 0·41 (1H, d, *J* 7 Hz, 4-H), 1·57 (1H, d, *J* 8·5 Hz, 1-H), 2·45—3·2 (2H, m, 2- and 3-H), 5·56 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 6·93 (2H, s, 7-H), 7·57 (2H, s, 9-H), 8·53 (3H, t, *J* 7 Hz, $OCH_2CH_3$), and 8·85 (6H, s, 2 × $CH_3$).

(d) *Pyridinium 1,3,3-trisethoxycarbonylallylide* (X).—A solution of (X) (325 mg) in mesitylene (25 ml) was heated under reflux for 15 min. Work-up as described for (VII)

gave *diethyl indolizine*-1,3-*dicarboxylate* (XIX) (66 mg, 25%) as white needles, m.p. 130—131° [from light petroleum (b.p. 30—60°)] (Found: C, 64·5; H, 5·8; N, 4·95. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·8; N, 5·4%); $\nu_{max.}$ (KCl) 1670s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 220, 245, 273, and 328 nm (log ε 4·31, 4·55, 4·24, and 4·22); τ ($CDCl_3$) 0·52 (1H, d, *J* 7 Hz, 5-H), 1·70 (1H, d, *J* 9 Hz, 8-H), 2·07 (1H, s, 2-H), 2·5—3·4 (2H, m, 6- and 7-H), 5·62 (4H, q, *J* 7 Hz, 2 × $OCH_2CH_3$), and 8·57 (6H, t, *J* 7 Hz, 2 × $OCH_2CH_3$).

(e) 2-*Methylpyridinium* 1,3,3-*trisethoxycarbonylallylide* (XI). A solution of (XI) (339 mg) in xylene (25 ml) was heated under reflux for 4 h. Work-up as described for (VII) gave oily ethyl indolizine-3-carboxylate (XXVII) (129 mg, 68%) which appeared to be oxidised upon exposure to air, thus precluding elemental analysis; $M^+$ 189; $\nu_{max.}$ ($CHCl_3$) 1670s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 214·5sh, 218, 249sh, 253·5, 360, 364sh, and 369 nm (log ε 4·36, 4·44, 4·48, 4·56, 4·10, 4·11, and 4·13); τ ($CDCl_3$) 0·52 (1H, d, *J* 7 Hz, 5-H), 2·53 (1H, d, *J* 4 Hz, 2-H), 2·45—2·7 (1H, m, 8-H), 2·9—3·45 (2H, m, 6- and 7-H), 3·57 (1H, d, *J* 4 Hz, 1-H), 5·62 (2H, q, *J* 7 Hz, $OCH_2CH_3$), and 8·62 (3H, t, *J* 7 Hz, $OCH_2CH_3$).

(f) *Pyridinium* 3,3-*diacetyl*-1-*ethoxycarbonylallylide* (XII). A solution of (XII) (275 mg) in xylene (25 ml) was heated under reflux for 20 min. Work-up as described for (VII) gave *ethyl* 1-*acetylindolizine*-3-*carboxylate* (XX) (7 mg, 3%) as white needles, m.p. 145—146° (from ether) (Found: C, 67·5; H, 5·7; N, 5·8. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·7; N, 6·1%); $\nu_{max.}$ (KCl) 1680s and 1640s $cm^{-1}$; $\lambda_{max.}$ (EtOH) 223, 250, 287, and 330 nm (log ε 4·23, 4·53, 4·12, and 4·30); τ ($CDCl_3$) 0·45 (1H, d, *J* 7 Hz, 5-H), 1·40 (1H, d, *J* 8 Hz, 8-H), 2·10 (1H, s, 2-H), 2·4—3·2 (2H, m, 6- and 7-H), 5·59 (2H, q, *J* 7 Hz, $OCH_2CH_3$), 7·47 (3H. s. $CO{\cdot}CH_3$), and 8·58 (3H, t, *J* 7 Hz, $OCH_2CH_3$).

(g) 2-*Methylpyridinium* 3,3-*diacetyl*-1-*ethoxycarbonylallylide* (XIII). A solution of (XIII) (289 mg) in xylene (25 ml) was heated under reflux for 5 h. Work-up as described for (VII) gave (XX) (116 mg, 50%), m.p. 145—146°.

[4/2048 *Received*, 4*th October*, 1974]