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INTRAMOLECULAR 1,5-CYCLIZATION OF YLIDES
SYNTHESIS OF PYRAZOLO-[1,5-a]PYRIDINES AND INDOLIZINES

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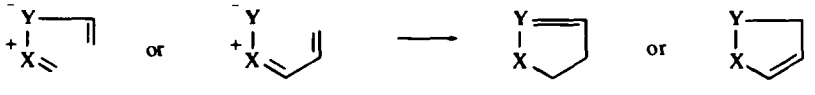
Abstract—N-(β-Acylvinyl)iminopyridinium betaines have been shown to cyclize in refluxing toluene to produce pyrazolo[1.5-a]pyridines. This intramolecular 1,5-cyclization reaction of ylides was extended to the synthesis of indolizine derivatives.

RECENTLY THE SYNTHESIS of heterocyclic compounds by the intramolecular 1,5-cyclization[1] of the ylides (I → II) has received considerable attention. Typical examples include the formation of oxadiazoles,[2] triazoles,[2] thiadiazoles,[2] thiophenes,[3] and indolizines.[4,5] Only one case[4] the ylide intermediate has been isolated. As part of our continuing interest in ylide chemistry we briefly reported on the synthesis of N-(β-acylvinyl)iminopyridinium betaines and their thermal intramolecular 1,5-cyclization to pyrazolo[1,5-a]pyridines.[6] We now describe the experimental details of the preliminary report and the extention of this reaction to the synthesis of indolizines.

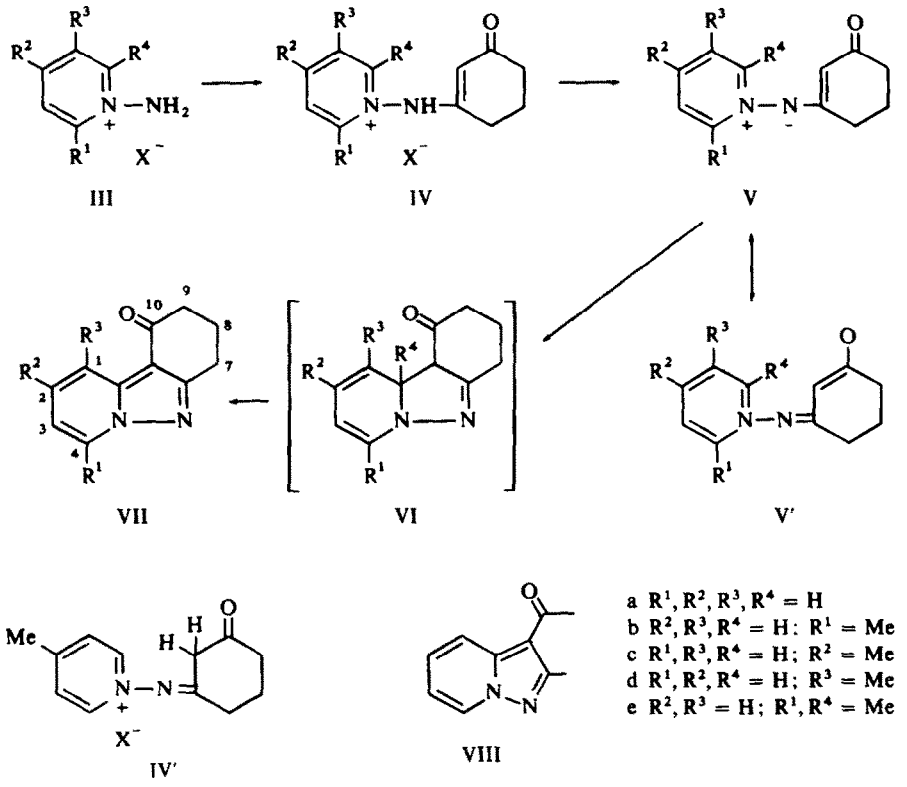


I II

Synthesis of pyrazolo[1,5-a]*pyridines*

Necessary N-(3′-oxocyclohexen-1′-yl)imino-4-methylpyridinium betaine (Vc) was conveniently prepared as follows. Readily available N-amino-4-methylpyridinium chloride[7] (IIIc) was treated with an excess of 3-chloro-2-cyclohexen-1-one to give quantitatively N-(3′-oxocyclohexen-1′-yl)amino-4-methylpyridinium chloride (IVc) as a hygroscopic crystalline solid. The structure was confirmed by its NMR spectrum (in DMSO-d_6), which shows a singlet at τ 4·98 due to an olefinic proton, a pair of doublets at τ 1·22 and 1·95 (J = 7 Hz) that were assigned to the pyridine ring hydrogens, and a Me singlet at τ 7·35. Since the olefinic proton signal was readily exchanged with deuterium by shaking with D_2O, the presence of tautomeric form IV′ as an intermediate is suggested.[8] The pyridinium salt IVc was transformed with Amberlite IRA-410 ion-exchange resin in EtOH or with aqueous K_2CO_3 to hygroscopic orange needles of the desired ylide (Vc). Its IR spectrum shows a characteristic band at 1505 cm^{-1}. The NMR spectrum in $CDCl_3$ exhibits a singlet at τ 5·91 attributable to an olefinic proton, a pair of doublets at τ 1·74 and 2·37 (J = 7 Hz) and a Me singlet at τ 7·40. The spectrum obtained immediately after Vc was dissolved in D_2O, exhibits no olefinic proton. This is again interpreted in terms of an amine–imine tautomerism (*c.f.* IVc ⇄ IV′). An unusually high-field shift of the olefinic proton in the NMR

spectrum of the ylide Vc as compared with that of the salt IVc may be ascribed to the delocalization (*c.f.* V—V') of the non-bonded electron pair on the imino nitrogen, which results in the increase of the electron density at C-2'.



SCHEME 1

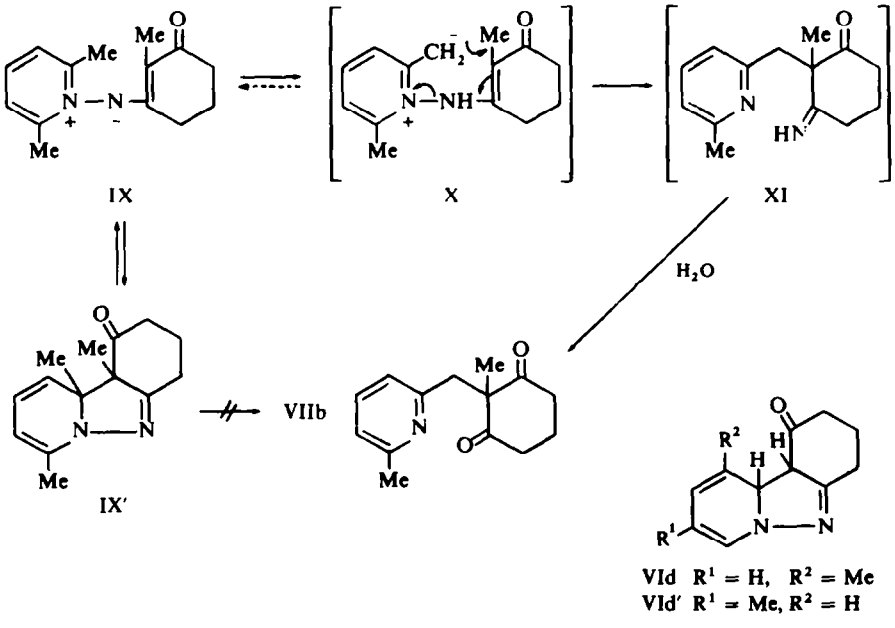
The ylide thus obtained, on heating in refluxing toluene until the orange color of the solution faded, afforded 56% yield of a colorless product of the molecular formula $C_{12}H_{12}N_2O$. The structure was assigned as 10-oxo-2-methyl-7,8,9,10-tetrahydropyrido[1,2-b]indazole (VIIc) on the basis of the following spectral evidence. Its IR spectrum shows characteristic bands at 1655 and 1630 cm^{-1}. The UV spectrum of VIIc closely resembles that of 3-acetyl-2-methylpyrazolo[1,5-a]pyridine (VIII).[9] The NMR spectrum exhibits a doublet at τ 1·75 (1H, J = 7 Hz) and a doublet–doublet at τ 3·30 (1H, J = 2 and 7 Hz) together with a broad singlet at τ 2·10 (1H) and a Me singlet at τ 7·52.

Similar conversion of the ylides (Va, b, d) to the corresponding pyrazolo[1,5-a]-pyridine derivatives (VIIa, b, d) was accomplished in moderate yields. The structures of VIIa, b, d were deduced from the elemental analysis and spectral data (Experimental). It should be noted that in the case of IIId the sole product of ring closure involving the more hindered side was obtained. Thus the NMR spectrum of VIId shows two doublets (J = 7 Hz) at τ 1·80 (H_4) and 2·95 (H_2), and a triplet (J = 7 Hz) at τ 3·25 (H_3), in accordance with the suggested structure. Similar results have also been

reported on the 1,3-dipolar cycloaddition reaction of N-imino-3-methylpyridinium betaine with dipolarophiles.[10]

As suggested in the preliminary communication,[6] the first step of this transformation may be explained in terms of a sigmatropic reaction (V → VI). However, attempts to obtain the possible intermediate VI were unsuccessful. Thus, when crystalline ylide Ve prepared in 60% yield from N-amino-2,6-dimethylpyridinium chloride (IIIe) and 3-chloro-2-cyclohexen-1-one, was subjected to cyclization in refluxing toluene for 7 hr, the product obtained in 46% yield was identical in all respects with VIIb. On the other hand, in contrast to the ylides described thus far, oily ylide IX prepared from IIIe and 3-chloro-2-methyl-2-cyclohexen-1-one, did not undergo cyclization but gave a Sommelet-type rearrangement product. Thus the ylide IX, on heating in boiling toluene for 7 hr, afforded white crystals, m.p. 141–142°. The elemental analysis and mass spectrum confirmed the molecular formula $C_{14}H_{17}NO_2$ (M^+, 231). Its UV spectrum is very similar to that of 2,6-lutidine and the IR spectrum shows carbonyl bands at 1720 (weak) and 1680 cm^{-1}. The NMR spectrum in $CDCl_3$ exhibits a triplet at τ 2·66 (1H, J = 6 Hz), a pair of doublets at τ 3·14 and 3·23 (J = 6 Hz) that were assigned to the pyridine hydrogens, a singlet at τ 6·46 (2H) due to methylene protons and two Me singlets at τ 7·63 and 8·66. These data can be readily accommodated in terms of structure XII, 2-(1′-methyl-2′,6′-dioxocyclohexyl)methyl-6-methylpyridine.

A possible mechanism for the rearrangement of IX to XII is outlined in Scheme 2. The reaction is assumed to be initiated by a hydrogen transfer from the α-Me group to the basic imino-nitrogen to yield betaine X, followed by rearrangement of the latter to intermediate XI. This is hydrolyzed during the working-up procedure to give XII. The sequence of steps (IX → X → XI) in Scheme 2 is closely related to the

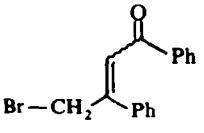


SCHEME 2

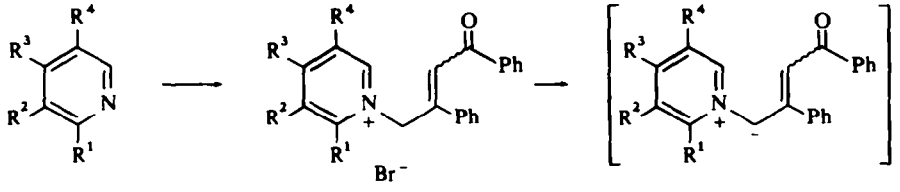
scheme proposed by Dimroth *et al.*[11] to account for the rearrangement of N-phenylimino-2,6-dimethylpyridinium betaine to 2-(2'aminobenzyl)-6-methylpyridine. The failure of IX to undergo cyclization may be explained if it is assumed that the cyclization step (IX ⇄ IX') is reversible and the rearrangement process (IX → X → XI) is more favorable than the aromatization step (IX' → VIIb) because the latter requires the cleavage of two C—C bonds in the intermediate IX'. The assumption of the presence of a rapid equilibrium in the cyclization step can also explain the preferential formation of VIId from Vd. The dihydropyridinium intermediate VId might be expected to get more resonance stabilization than VId', if one considers the effect of the 3-Me substituent which is capable of resonance interaction with the double bonds.[12] Further studies on this problem are in progress.

Synthesis of indolizines

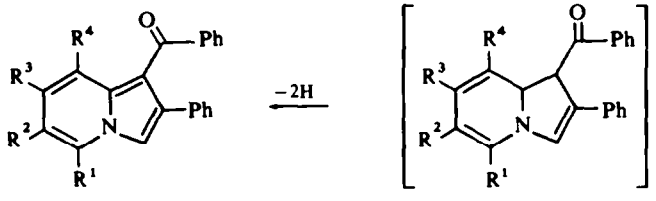
To explore the generality of this method for synthesizing heterocyclic compounds the reaction was investigated with the case of I (X = CH).



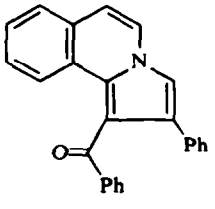
XIII



XIV XV



XVI



XVII

a R^1, R^2, R^3, R^4 = H
b R^2, R^3, R^4 = H; R^1 = Me
c R^1, R^2, R^4 = H; R^3 = Me
d R^1, R^3 = H; R^2, R^4 = Me
e R^1, R^2, R^4 = H; R^3 = CN

SCHEME 3

Thus pyridinium salt XIVa obtained from pyridine and readily available 4-bromo-1,3-diphenyl-2-buten-1-one (XIII),[13] was treated at room temp with anhyd. K_2CO_3 in EtOH to give yellow crystals, $C_{21}H_{15}NO$, m.p. 135–136°, in 95% yield. The structure was established as 1-benzoyl-2-phenylindolizine (XVIa) from its elemental analysis, spectral data and finally by direct comparison with an authentic sample prepared by the method of Melton and Wibberley.[14] This cyclization was shown to be effected by Et_3N or Amberlite IRA-410 ion-exchange resin in EtOH but in lower yield.

Similar treatment of XIVb–e gave the corresponding indolizine XVIb–e in high to moderate yields. The structures were established by the elemental analysis and comparison of the spectral data (Experimental). The same reaction was applied successfully to isoquinoline to give 1-benzoyl-2-phenylpyrrolo[2,1-a]isoquinoline (XVII).

This base-catalyzed transformation (XIV → XVI) under extremely mild conditions seems to proceed *via* a symmetry-allowed electrocyclic ring closure of the ylide intermediate XV, followed by loss of two hydrogen atoms under the reaction conditions, as suggested for the formation of pyrazolo[1,5-a]pyridines. The presence of the ylide intermediate XV is indicated by a transient red in the reaction mixture. A related case has been reported by Augstein and Krönke[4] with the formation of 7,9-dinitrobenzo[a]indolizine from N-(picryl-phenacyl)pyridinium betaine in which HNO_2 is eliminated.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra were determined with a Hitachi EPS-3T, IR spectra with a Hitachi EPI-G2, NMR spectra (TMS as internal standard) with a Hitachi R-20 spectrometer, and mass spectra with a Hitachi RMU-6D.

10-*Oxo*-2-*methyl*-7,8,9,10-*tetrahydropyrido*[1,2-b]*indazole* (VIIc). (Method A). A mixture of IIIc (0·72 g) and 3-oxocyclohexen-1-yl chloride (6 g) was warmed at 50° for 6 hr. The resulting pale-yellow solid was thoroughly washed with dry C_6H_6 and dry ether to give almost quantitatively hygroscopic crystals of IVc. The salt (IVc) was treated with Amberlite IRA-410 ion-exchange resin in EtOH and the solvent evaporated under reduced pressure below 50° to give quantitatively hygroscopic orange needles of the ylide (Vc). ν_{max}^{KBr} 1625 and 1505 cm^{-1}; NMR ($CDCl_3$) τ 1·74 (d, J = 7 Hz, H_2 and H_6), 2·37 (d, J = 7 Hz, H_3 and H_5), 5·91 (s, olefinic H) and 7·41 (s, Me). λ_{max}^{EtOH} 230 sh nm, 241 and 290.

After heating Vc (0·35 g) in boiling toluene (50 ml) for 2 hr, solvent was evaporated under reduced pressure. Recrystallization of the residual solid from petroleum ether gave white needles of VIIc (0·20 g; 56%), m.p. 107–108°: M^+, m/e 200; λ_{max}^{EtOH} 222 sh nm (log ε 4·42), 228 (4·58), 252 (3·79), 260 (3·84) 305 sh (4·05), 317 (4·16) and 328 sh (4·06); $\nu_{max}^{CHCl_3}$ 1655 and 1630 cm^{-1}; NMR (CCl_4) τ 1·75 (bd, J = 7 Hz, H_4), 2·10 (m, H_1), 3·30 (dd, J = 2 and 7 Hz, H_3) and 7·52 (s, Me). (Found: C, 71·92; H, 6·08; N, 13·77. $C_{12}H_{12}N_2O$ requires: C, 71·98; H, 6·04; N, 13·99%).

10-*Oxo*-4-*methyl*-7,8,9,10-*tetrahydropyrido*[1,2-b]*indazole* (VIIb). (Method B). (i) From IIIb—A mixture of IIIb (0·8 g) and 3-oxocyclohexen-1-yl chloride (1·6 g) was warmed at 50° for 6 hr, giving a red viscous oil, which was dissolved in 5 ml of water. The aqueous soln was washed with $CHCl_3$ (3 × 20 ml), neutralized with K_2CO_3, and extracted with $CHCl_3$ (4 × 20 ml). The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to a red oil (0·4 g; 36%) of Vb. After heating of Vb (313 mg) in boiling toluene (50 ml) for 4 hr, the solvent was evaporated under reduced pressure to give a pale-brown residue, which was chromatographed on alumina with C_6H_6 to remove a resinous substance, giving a white solid (45 mg; 14%). Recrystallization from petroleum ether gave white needles of VIIb, m.p. 100–101°; λ_{max}^{EtOH} 220 sh nm (log ε 4·55), 226 (4·65), 249 (3·90), 257·5 (3·94), 307·5 sh (4·24), 320 (4·42) and 331 (4·37); NMR ($CDCl_3$) τ 1·92 (bd, J = 8 Hz, H_1), 2·62 (dd, J = 6 and 8 Hz, H_2), 3·19 (bd, J = 6 Hz, H_3) and 7·22 (s, Me). (Found: C, 72·29; H, 5·89; N, 13·99. $C_{12}H_{12}N_2O$ requires: C, 71·98; H, 6·04, N, 13·99%). (ii) From IIIe—A mixture of IIIe (0·79 g) and 3-oxocyclohexen-1-yl chloride (6 g) was treated and worked up as described above to give an orange solid, recrystallized from EtOAc as hygroscopic pale-yellow needles (1·0 g; 60%) of Ve, m.p. 184–185°; NMR ($CDCl_3$) τ 2·00–2·65 (m, aromatic H), 6·19 (s, olefinic H), 7·41 (s, two Me). The olefinic proton disappeared when the spectrum was determined in D_2O. After heating of Ve (230 mg) in boiling toluene (100 ml) for 12 hr, working up as described above afforded white needles (0·1 g; 46%), m.p. 100–101°. This compound was shown to be identical with VIIb by m.m.p., TLC and IR spectra.

10-*Oxo*-1-*methyl*-7,8,9,10-*tetrahydropyrido*[1,2-b]*indazole* (VIId). Following the method B, yellow hygroscopic crystalline ylide Vd was obtained in 60% yield. $\nu_{max}^{CHCl_3}$ 1505 cm^{-1}. Cyclization of Vd was accomplished in 30% yield to give VIId, m.p. 95–96°; λ_{max}^{EtOH} 221·5 sh nm (log ε 4·19), 227 (4·23), 253 (3·41), 261 (3·46), 308 sh (4·13), 320·5 (4·15) and 332 (4·14); NMR (CCl_4) τ 1·80 (bd, J = 7 Hz, H_4), 2·95 (bd, J = 7 Hz, H_2), 3·25 (t, J = 7 Hz, H_3) and 7·13 (s, Me). The splitting pattern of the aromatic protons clearly eliminates the possibility of the 3-Me isomer. (Found: C, 72·18; H, 5·94; N, 13·85. $C_{12}H_{12}N_2O$ requires: C, 71·98; H, 6·04, N, 13·99%). GLC (5% SE-30, Column temp. 50°) of the crude reaction product indicated the presence of only a negligible amount of two unidentified products.

10-*Oxo*-7,8,9,10-*tetrahydropyrido*[1,2-b]*indazole* (VIIa). Following the method B, VIIa was obtained in 14% overall yield from IIIa, m.p. 113–114°. $\nu_{max}^{CHCl_3}$ 1655 and 1630 cm^{-1}; λ_{max}^{EtOH} 223 sh nm (log ε 4·67), 226·5 (4·57), 251 (4·04), 258·5 (4·09), 307 sh (4·20), 319 (4·31) and 331 sh (4·18); NMR (CCl_4) τ 1·61 (bd, J = 7 Hz, H_4), 1·88 (bd, J = 9 Hz, H_1), 2·65 (bt, J = 9 Hz, H_2) and 3·13 (bt, J = 7 Hz, H_3). (Found: C, 71·42; H, 5·30; N, 14·69. $C_{11}H_{10}N_2O$ requires: C, 70·95; H, 5·41; N, 15·05%).

2-(1′-*Methyl*-2′,6′-*dioxocyclohexyl*)*methyl*-6-*methylpyridine* (XII). A mixture of IIIe (2·0 g) and 2-methyl-3-oxocylohexen-2-yl chloride (4·0 g) was heated at 100° for 8 hr. After working up according to the method B, there was obtained a red oil of IX. $\nu_{max}^{CHCl_3}$ 1490 cm^{-1}. After heating IX in refluxing toluene (100 ml) for 7 hr, solvent was evaporated and the residue purified by prep. TLC (alumina/C_6H_6) to give white crystals (0·3 g), m.p. 141–142°. λ_{max}^{EtOH} 260·5 sh nm (log ε 3·17), 267 (3·19) and 273 sh (3·17). (Found: C, 72·67; H, 7·17; N, 5·98. $C_{14}H_{17}NO_2$ requires: C, 72·70; H, 7·41; N, 6·06%).

N-(2,4-*Diphenyl*-4-*oxo*-2-*butenyl*)-4-*methylpyridinium bromide* (XIVc). The general procedure used is illustrated by this example. A soln of γ-picoline (186 mg) and XIII (602 mg) in ether (5 ml) was allowed to stand at room temp for 30 hr. The precipitated crystals were collected and recrystallized from EtOH and ether to give white needles (400 mg; 50%) of XIVc, m.p. 175–176·5°; ν_{max}^{KBr} 1655 and 1605 cm^{-1}; NMR ($CDCl_3$) τ 0·48 (d, J = 6 Hz, H_2 and H_6), 1·8–3·0 (13H, m), 3·38 (s, methylene protons) and 7·39 (s, Me). (Found: C, 67·11; H, 5·11; N, 3·59. $C_{22}H_{20}NOBr$: C, 67·01; H, 5·11; N, 3·55%).

Similarly, XIVb, m.p. 175–176°, was obtained in 68% yield. (Found: C, 67·47; H, 5·60; N, 3·83. $C_{22}H_{20}NOBr$ requires: C, 67·01; H, 5·11; N, 3·55%). XIVa, m.p. 182–183°, was obtained in 63% yield. (Found: C, 66·39; H, 4·70; N, 3·58. $C_{21}H_{18}NOBr$ requires: C, 66·33; H, 4·77; N, 3·68%). XIVd, XIVe and N-(2,4-diphenyl-4-oxo-2-butenyl)isoquinolinium bromide were obtained as oils in 88, 55 and 84% yields, respectively, which were used for further reaction after washing with dry ether.

1-*Benzoyl*-7-*methyl*-2-*phenylindolizine* (XVIc). (Method A) To a soln of XIVc (100 mg) in EtOH (5 ml) was added anhyd. K_2CO_3 (35 mg) and the mixture stirred at room temp for 1·5 hr. The mixture was filtered and the solvent evaporated under reduced pressure to give a yellow solid which was purified by passing through a short column of alumina with C_6H_6. Concentration of the yellow fraction followed by recrystallization of the residue gave XVIa (76 mg; 95%), m.p. 143–144·5°; ν_{max}^{KBr} 1635 and 1595 cm^{-1}; λ_{max}^{EtOH} 247 nm (log ε 4·50) and 377 (4·10); NMR ($CDCl_3$) τ 2·01 (bs, H_8), 2·60 (d, J = 7 Hz, H_5), 2·5 (m, H_2' and H_6' of benzoyl group), 2·7–3·0 (m), 3·36 (dd, J = 7 and 2 Hz) and 7·64 (s, Me). (Found: C, 84·81; H, 5·51; N, 4·31. $C_{22}H_{17}NO$ requires: C, 84·86; H, 5·50; N, 4·50%). (Method B) A soln of XIVc (100 mg) in 1,2-dichloroethane (5 ml) and Et_3N (0·5 ml) was stirred overnight. Working up as described above gave yellow crystals (55 mg; 70%), m.p. 143–144°. (Method C) A soln of XIVc (215 mg) in EtOH was passed through a column of Amberlite IRA-410 ion-exchange resin and the ethanolic eluate was concentrated under reduced pressure below 40° to give a viscous oil which crystallized on standing. Recrystallization from EtOH gave yellow needles (122 mg; 72%), m.p. 143–144°.

The following indolizines (XVI) were synthesized according to the method A.

1-*Benzoyl*-2-*phenylindolizine* (XVIa), m.p. 135–136°, was obtained in 95% yield. ν_{max}^{KBr} 1630 and 1600 cm^{-1}; λ_{max}^{EtOH} 246 nm (log ε 4·61) and 375 (4·20). (Found: C, 84·76; H, 5·22; N, 4·72. $C_{21}H_{15}NO$ requires: C, 84·82; H, 5·09; N, 4·71%). This compound was identical with an authentic sample prepared by the method of Melton and Wibberley[14] by m.m.p. and IR spectra.

1-*Benzoyl*-5-*methyl*-2-*phenylindolizine* (XVIb), m.p. 134–135°, was obtained in 95% yield. ν_{max}^{KBr} 1630 and 1605 cm^{-1}; λ_{max}^{EtOH} 246·5 nm (log ε 4·63) and 375 (4·20). (Found: C, 84·82; H, 5·57; N, 4·40. $C_{22}H_{17}NO$ requires: C, 84·86; H, 5·50; N, 4·50%).

1-*Benzoyl*-6,8-*dimethyl*-2-*phenylindolizine* (XVId), m.p. 177–178°, was obtained in 42% yield. ν_{max}^{KBr} 1630 and 1595 cm^{-1}; λ_{max}^{EtOH} 250 nm (log ε 4·69) and 386 (3·95). (Found: C, 84·92; H, 5·76; N, 4·35. $C_{23}H_{19}NO$ requires: C, 84·89; H, 5·89; N, 4·30).

1-*Benzoyl*-7-*cyano*-2-*phenylindolizine* (XVIe), m.p. 233·5–235°, was obtained in 53% yield. ν_{max}^{KBr} 2210, 1600 and 1595 cm^{-1}; λ_{max}^{EtOH} 254 nm (log ε 4·58) and 389 (4·28). (Found: C, 82·05; H, 4·38; N, 8·51. $C_{22}H_{14}N_2O$ requires: C, 81·97; H, 4·38; N, 8·69%).

1-*Benzoyl*-2-*phenylpyrrolo*[2,1-a]*isoquinoline* (XVII), m.p. 161–162·5°, was obtained in 27% yield. M^+ *m/e* 347; ν_{max}^{KBr} 1635 and 1600 cm^{-1}; λ_{max}^{EtOH} 269 nm (log ε 4·65) and 363 (3·56). (Found: C, 86·16; H, 4·81; N, 4·04. $C_{25}H_{17}NO$ requires: C, 86·43; H, 4·93; N, 4·03%).

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