678. *The Reaction of Pyridine with Methyl Propiolate.*

By A. Crabtree, A. W. Johnson, and J. C. Tebby.

The adducts from pyridine, as well as β- and γ-picoline, and methyl propiolate have been formulated as dihydropyridines (III) containing *N*-β-acrylic ester and β-propiolic ester substituents. Hydrogenolysis of the pyridine adduct gives octahydro-3-oxoindolizine (V), and reaction with piperidine causes cyclisation to methyl (2-methoxycarbonylindolizin-1-yl)-acetate (VII) which has been degraded to octahydro-1-methylindolizine. The Diels rearrangement product of the pyridine–dimethyl acetylenedicarboxylate stable adduct, formed by the action of hot phenol or acetic acid, is formulated as methyl (1,2-dimethoxycarbonylindolizin-3-yl)acetate (X) and has been converted into methyl (2-methoxycarbonylindolizin-3-yl)-acetate (XI; R = Me) and octahydro-3-methylindolizine, both of which differed from the isomers formed in the propiolic ester series. The indolizine formed by reaction of pyridine and dimethyl acetylenedicarboxylate in methanol has been reformulated as methyl (1,2-dimethoxycarbonylindolizin-3-yl)methoxyacetate (XIII) because of its reduction to (X).

Several authors recently have re-examined the structure of the adducts derived from dimethyl acetylenedicarboxylate with pyridine and related compounds [1,2,3] which were originally described by Diels and his co-workers. There is fairly general agreement in regarding the adducts (*e.g.*, I or a valency tautomer, and II from pyridine) as derivatives of 4*H*- and 9a*H*-quinolizines, and in order to provide further examples of this remarkable reaction we examined the corresponding reactions with methyl propiolate. Pale yellow

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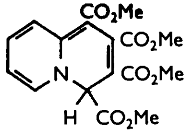
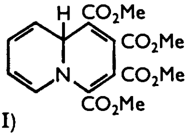
[1] Jackman, Johnson, and Tebby, *J.*, 1960, 1579.
[2] Acheson, Taylor *et al.*, *J.*, 1960, 1691; *Proc. Chem. Soc.*, 1960, 281.
[3] van Tamelen, Aldrich, Bender, and Miller, *Proc. Chem. Soc.*, 1959, 309.

crystalline adducts were obtained from both pyridine and β-picoline but the absorption spectra (max. at *ca.* 239, 297, and 342 mμ) and the low stability of these products suggested that they possessed a chromophore different from those of the adducts of dimethyl acetylenedicarboxylate.


(I)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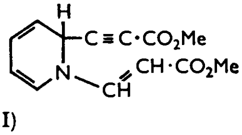
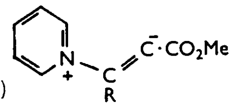

(III)

The pyridine–methyl propiolate adduct decomposed rapidly at 100°, and even at room temperature it decomposed after about six weeks. Analysis indicated that, like the dimethyl acetylenedicarboxylate adducts, each molecule of pyridine had combined with two molecules of the acetylenic ester and, moreover, like the 9a*H*-quinolizines, the adducts were non-basic. Oxidation of the pyridine adduct with hydrogen peroxide in acetic acid gave picolinic acid *N*-oxide, indicating that fission of the pyridine ring had not occurred. The nature of the adducts was revealed by their nuclear magnetic resonance spectra and in consequence structure (III) is advanced for the pyridine–methyl propiolate compound. The spectrum, which was measured and interpreted by Dr. L. M. Jackman, showed bands at 6·28 and 6·24 (methoxy-groups) and doublets at 4·89 and 2·58 ($J = 13{\cdot}4$ cycles/sec.; positions expressed as τ values) which were attributed to the two mutually interacting protons of the *cis*-acrylic ester grouping. Examination of the related adduct from γ-picoline showed a band at 8·0 which is attributed to a *C*-methyl group attached to a non-aromatic system. The ultraviolet and visible absorption is consistent[4] with the presence of a 1,2-dihydropyridine ring in the adduct, and the infrared spectrum showed the absence of an $>$NH grouping and the presence (band at 2235 cm.$^{-1}$) of an acetylenic bond.

In considering the mechanisms of the formation of the pyridine–acetylenic ester adducts (I), (II), and (III), the key intermediates are probably the ylids (IV; $R = H$ or CO_2Me) formed by nucleophilic addition of an equimolecular amount of the pyridine to the acetylenic ester. The ylid (IV; $R = CO_2Me$) from dimethyl acetylenedicarboxylate can then react with a second equivalent of the acetylenic ester to give a second ylid, which can cyclise to the quinolizine (II), as has been suggested previously.[1] In the case of the methyl propiolate adducts, the ylid (IV; $R = H$) reacts wth a proton formed by ionisation of another molecule of the acetylenic ester and the remaining acetylenic carbanion adds to the pyridinium ring to form the adduct (III).

In support of the formulation (III) for the propiolic ester adduct, hydrogenation under pressure over Raney nickel at 120° gave an oil which showed a strong infrared band at 1690 cm.$^{-1}$ indicative of the carbonyl group of an amide, and on this basis, coupled with the analytical figures, the hydrogenation product is formulated as octahydro-3-oxoindolizine (V). This amide[5] was shown to possess an infrared spectrum identical with that of the degradation product. Hydrogenolysis of the adduct (III) presumably involves loss of the acrylic ester side-chain and evidence for the presence of an aliphatic ester (methyl propionate?) in the volatile products from the reaction was obtained from the infrared spectrum (band at 1745 cm.$^{-1}$). Octahydro-3-oxoindolizine was further reduced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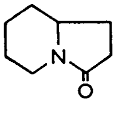
(V)

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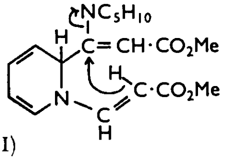
[4] Karrer *et al.*, *Helv. Chim. Acta*, 1957, **40**, 751; 1958, **41**, 2066; " Festschrift A. Stoll," Basel, 1957, p. 294.

[5] Tullock and McElvain, *J. Amer. Chem. Soc.*, 1939, **61**, 961.

by lithium aluminium hydride, to octahydroindolizine itself which was identified as the picrate.[6]

In an attempt to bring about interaction of the two side-chains of the adduct (III), by first hydrating the propiolic ester side-chain, piperidine was caused to react with the activated triple bond, a colourless crystalline compound, $C_{13}H_{13}NO_4$, being obtained. The hydrogen content of this indicated that a piperidyl group was not present and the ultra-violet absorption spectrum revealed that the product was an indolizine. Taking into account the most probable reaction sequence suggested in (VI), we represent the product as methyl (2-methoxycarbonylindolizin-1-yl)acetate (VII).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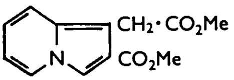
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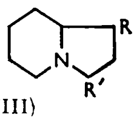
(VIII)

The dicarboxylic acid and anhydride corresponding to (VII) were also prepared and the acid decarboxylated to 1-methylindolizine which was hydrogenated to the octahydroindolizine (VIII; R = Me, R′ = H) and converted to the picrate.[7] This base should exist as two racemates depending on the relative configurations of the methyl substituent and the bridgehead hydrogen atom, but in this case a separation could not be achieved with the small quantity available. Consequently the melting point (184—189°; lit.,[7] 191°) of the picrate was not sharp, and the identity or otherwise of this base with the isomeric 3-methylindolizidines where the two forms have been separated[8] (picrates, m. p. 195—197° and 216°) remained in doubt until these compounds were prepared.

Condensation of α-picoline and propionic anhydride[9] gave, in low yield, 3-methylindolizine which was hydrogenated to octahydro-3-methylindolizine (VIII; R = H, R′ = Me), from which, however, only the lower-melting (190—193°) picrate could be isolated. Fortunately another sequence of reactions was discovered which left no doubt that the hydrogenation product from the rearrangement of the pyridine–propiolic ester adduct differed from octahydro-3-methylindolizine. Rearrangement of the stable adduct (I) from pyridine and dimethyl acetylenedicarboxylate by treatment with hot acetic acid or phenol is known[10,11] to yield a tricarboxylic ester which from its ultraviolet absorption curve is undoubtedly a derivative of indolizine. Since this manuscript was written, Acheson and Taylor[12] have reached a similar conclusion. Originally,[10] Diels and his co-workers thought that this ester was a derivative of quinolizine, but later, structure (IX) was preferred. By use of the sequence developed by Diels originally for the preparation of quinolizine itself (later shown to be an indolizine, however), the tricarboxylic ester, for which the modified structure (X) is suggested, was hydrolysed with aqueous potassium hydroxide, a dicarboxylic acid being obtained. Although Acheson and Taylor[12] suggest that this acid may be 3-methylindolizine-1,2-dicarboxylic acid rather than 2-carboxyindolizin-3-ylacetic acid (XI; R = H) on the grounds that the corresponding tetrahydro-derivative gives approximately one-sixth of the theoretical quantity of acetic acid in the Kuhn–Roth determination, we are adopting the latter structure on the grounds of the nuclear magnetic resonance spectrum kindly determined and interpreted for us by Dr. R. J. Abraham of the National Physical Laboratory, Teddington. Examination of the spectrum showed peaks associated with the methylene group as well as the single isolated aromatic

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[6] Clemo and Ramage, *J.*, 1932, 2969.

[7] Clemo and Metcalf, *J.*, 1937, 1518.

[8] Leonard and Pines, *J. Amer. Chem. Soc.*, 1950, **72**, 4931.

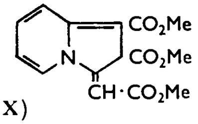
[9] Ochiai and Tsuda, *Ber.*, 1934, **67**, 1011.

[10] Diels, Alder, Friedrichsen, Klare, *et al.*, *Annalen*, 1932, **498**, 16; 1933, **505**, 103.

[11] Diels and Schrumm, *Annalen*, 1937, **530**, 68.

[12] Acheson and Taylor, *J.*, 1960, 4600.

proton, but peaks associated with an aromatic *C*-methyl group were absent. The corresponding dimethyl ester (XI; R = Me) was markedly different from the ester (VII) derived from the pyridine–propiolic ester adduct and emphasises the isomeric nature of the two series. Decarboxylation of the acid (XI; R = H) gave 3-methylindolizine, hydrogenated to the octahydro-compound (VIII; R = H, R′ = Me) which gave two distinct picrates corresponding to the two racemates.[8] Diels and Schrumm[11] reported only the lower-melting picrate; the higher-melting picrate, which Diels also obtained[10,11] but associated with octahydroindolizine itself, was possibly the derivative of the other racemate of octahydro-3-methylindolizine.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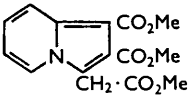
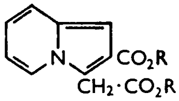
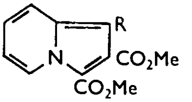
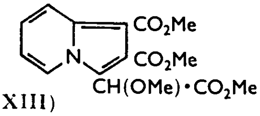

(X)


(XI)


(XII)


(XIII)

The formation of the tricarboxylic ester (X) emphasises the instability of the 4*H*-quinolizine ring and provides another example of the strong tendency to revert to the aromatic indolizine ring system. Recent interpretations[3,13] of the nuclear magnetic resonance spectra of 4*H*-quinolizines have in fact suggested that these compounds might be more correctly regarded as 2-pyridylbuta-1,3-dienes.

Another series of adducts from pyridines and acetylenic esters requires consideration in view of the above observations. Diels and Meyer[14] showed that pyridine and dimethyl acetylenedicarboxylate in cold methanol afforded a mixture of two indolizine tricarboxylic esters which were formulated as [XII; R = CO_2Me and CH(OMe)·CO_2Me]. We have now shown that the adduct of supposed structure [XII; R = CH(OMe)·CO_2Me] can be reduced with phosphorus and iodine in acetic acid solution to the diester of an indolizinetricarboxylic acid, which, when esterified with diazomethane, gives the tricarboxylic ester (X). Further, treatment of the ester (X) with phosphorus and iodine as before causes hydrolysis of one ester grouping and forms the same indolizinetricarboxylic acid diester. Consequently, Diels's formulation [XII; R = CH(OMe)·CO_2Me] of his adduct must be modified to (XIII). The precise intermediates in the formation of (XIII) have not yet been defined as it has not proved possible to rearrange ester (I) or (II) to (XIII) with methanol alone, with methanolic sodium methoxide, or with acidified methanol.

Adducts corresponding to (X), (XI), and (XIII) have been prepared from β-picoline and, as in the case of the corresponding quinolizine derivatives,[1] differences in chemical behaviour result from the position of the methyl group which can be a 6- or an 8-substituent. In the latter case, steric hindrance results from the proximity of the methyl and the 1-methoxycarbonyl group and this is revealed for example in the hydrolysis of the analogues of (X). With the 8-methyl compound, decarboxylation of the 1-carboxyl group is an easy reaction accompanying hydrolysis, and the product is a dicarboxylic ester, whereas with the 6-methyl isomer, the product is the diester of a tricarboxylic acid.

EXPERIMENTAL

Ultraviolet absorption spectra refer to ethanolic solutions and infrared spectra to potassium bromide discs except where otherwise stated.

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[13] Elvidge and Jackman, *J.*, 1961, 859.

[14] Diels and Meyer, *Annalen*, 1934, **513**, 129; see also Burrows and Holland, *J.*, 1947, 672.

Reaction of Pyridine and Methyl Propiolate.—Pure dry pyridine (0·5 g.) in dry ether (2 c.c.) was added dropwise to a solution of methyl propiolate [15] (1 g.) in ether (1 c.c.) at room temperature. The solution slowly darkened and was dark red after 1 hr. Next morning the crystalline adduct (III) [*methyl* cis-β-(1,2-*dihydro*-2-*methoxycarbonylethynyl*-1-*pyridyl*)*acrylate*] (0·8 g.) was separated and washed with a little dry ether. On crystallisation from cyclohexane, it was obtained as biscuit-coloured plates, m. p. 98° (decomp.), which were easily decomposed by heat (Found: C, 62·9; H, 5·5; N, 5·75. $C_{13}H_{13}NO_4$ requires C, 63·15; H, 5·3; N, 5·65%), $\lambda_{max.}$ 239, 297, and 342 mμ (log ε 3·90, 3·95, and 4·08 respectively), $\nu_{max.}$ 714, 909, 924, 972, 989, 1018, 1036, 1056, 1075, 1135, 1170, 1197, 1227, 1253, 1286, 1319, 1340, 1357, 1384, 1388, 1437, 1460, 1586, 1631, 1712, 1726, 2235, 2844, 2905, 2950, 2998, and 3060 cm.$^{-1}$.

Reaction of β-*Picoline and Methyl Propiolate.*—The *adduct* was obtained by a similar method except that the reaction mixture was kept for 2 days and the product was crystallised from methanol at −50°. It formed colourless needles which were unstable to heat; the m. p. varied considerably, 82° to 94°, with the rate of heating (Found: C, 64·1; H, 5·95; N, 5·2. $C_{14}H_{15}NO_4$ requires C, 64·35; H, 5·8; N, 5·35%). Light absorption: max. were at 238 and 339 mμ (log ε 4·05 and 4·04). This adduct was markedly less stable than those from either pyridine or γ-picoline.

Reaction of γ-*Picoline and Methyl Propiolate.*—Methyl propiolate (4 g.) in dry ether (10 c.c.) was added dropwise with stirring to γ-picoline (2 g.) in dry ether (10 c.c.) and kept at room temperature for 1 hr. The precipitate (2·5 g.) was separated, washed with dry ether (20 c.c.), and crystallised from cyclohexane, to give *methyl* cis-β-(1,2-*dihydro*-2-*methoxycarbonylethynyl*-4-*methyl*-1-*pyridyl*)*acrylate* as pale orange plates, m. p. 115—116° (Found: C, 64·6; H, 6·05; N, 5·15%), $\lambda_{max.}$ 244 and 337 mμ (log ε 3·94 and 4·12), $\nu_{max.}$ 745, 754, 772, 797, 816, 846, 922, 945, 977 984, 1000, 1029, 1038, 1052, 1082, 1153, 1170, 1188, 1202, 1238, 1275, 1314, 1346, 1380, 1434, 1444, 1461, 1486, 1582, 1597, 1633, 1674, 1715, 1722, 2225, 2857, 2920, 2960, 2977, 3018, 3050, and 3398 cm.$^{-1}$. The adduct was kept without decomposition for several months.

Oxidation of the Pyridine–Methyl Propiolate Adduct.—The adduct (2 g.) was dissolved in glacial acetic acid (40 c.c.) and 100-vol. hydrogen peroxide (20 c.c.) and the mixture heated on the steam-bath for 2 hr. The excess of solvent was then removed *in vacuo*, and the oily residue treated with a similar volume of glacial acetic acid and hydrogen peroxide and heated on the steam-bath overnight. The solvent was again removed and the residue extracted with boiling cyclohexane (5 × 20 c.c.). When the mixed extracts were cooled picolinic acid *N*-oxide was obtained as white needles, m. p. 166° (from methanol) not depressed on admixture with an authentic specimen [16] (Found: C, 51·6; H, 3·6; N, 10·0. Calc. for $C_6H_5NO_3$: C, 51·8; H, 3·6; N, 10·05%), $\lambda_{max.}$ 224, 264, and 311 mμ (log ε 4·28, 3·85, and 3·11 respectively).

Octahydro-3-*oxoindolizine* (V).—The pyridine–methyl propiolate adduct (3 g.) in methanol (300 c.c.) was shaken at room temperature with Raney nickel (0·2 g.) in an atmosphere of hydrogen (60 atm.) for 3 hr. The temperature was then raised to 120° for a further 10 hr., then the catalyst and solvent were removed and the residue was distilled at 70—80° (bath-temp.)/0·5 mm. to give octahydro-3-oxoindolizine as a colourless, slightly fluorescent oil (1 g.) (Found: N, 9·85. Calc. for $C_8H_{13}NO$: N, 10·05%). A hydrochloride [17] could be formed but was very deliquescent and sublimed at 140°/0·1 mm. Reduction of this amide with lithium aluminium hydride [18] gave octahydroindolizine (0·2 g.), b. p. (bath-temp.) 60—70°/15 mm., the infrared spectrum of which was identical with an authentic specimen prepared by reduction of authentic amide.[5,6] The picrate had m. p. 226° (lit.,[6] 226°).

In another experiment the pyridine–methyl propiolate adduct (2 g.) was hydrogenated in purified 2-methoxyethanol (40 c.c.) as in the previous experiment. After cooling, the hydrogen was blown off through a cold (−60°) trap and the small amount of liquid so collected in the trap was shown to possess a weak infrared band at 1745 cm.$^{-1}$ (saturated ester). The catalyst was removed from the main product and the first fraction (3 c.c.) from the solvent distillation was also shown to give this ester band.

Reaction of the Pyridine–Methyl Propiolate Adduct with Piperidine.—The adduct (1·5 g.) in dry benzene (20 c.c.) was added dropwise with shaking to piperidine (2 c.c.) in dry benzene (10 c.c.) and the mixture heated under reflux for 1 hr., becoming dark red. The solvents were

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[15] Wolf, *Chem. Ber.*, 1953, **86**, 735; Bielecki and Henri, *ibid.*, 1913, **46**, 2605.

[16] Emmert and Groll, *Chem. Ber.*, 1953, **86**, 205.

[17] Loffler and Kain, *Chem. Ber.*, 1909, **42**, 100.

[18] Galinovsky, Vogl, and Weisser, *Monatsh.*, 1952, **83**, 114.

removed and the residue was distilled, to give a yellow oil, b. p. (bath-temp.) 150—200°/0·1 mm., which slowly crystallised. Recrystallisation from cyclohexane gave colourless needles of *methyl* (2-*methoxycarbonylindolizin*-1-*yl*)*acetate* (VII), m. p. 88—89° (Found: C, 63·3; H, 5·3; N, 5·6. $C_{13}H_{13}NO_4$ requires C, 63·3; H, 5·3; N, 5·7%), $\lambda_{max.}$ 236, 295, 306, 352, 367, and 385 mμ (log ε 4·61, 3·34, 3·38, 3·41, 3·42, and 3·19 respectively), $\nu_{max.}$ 744, 755, 788, 806, 841, 896, 903, 937, 958, 989, 999, 1016, 1097, 1125, 1166, 1183, 1202, 1217, 1256, 1268, 1316, 1341, 1364, 1409, 1426, 1438, 1449, 1460, 1498, 1538, 1635, 1662, 1705, 1728, 1737, 2367, 2925, 2950, 2978, 3047, 3106, and 3140 cm.$^{-1}$. Alkaline hydrolysis gave the corresponding *acid*, which formed almost colourless needles, decomp. 210°, from 80% aqueous ethanol (Found: C, 60·0; H, 4·2; N, 6·55. $C_{11}H_9NO_4$ requires C, 60·3; H, 4·15; N, 6·4%), $\lambda_{max.}$ 236, 295, 306, 353, and 368 mμ (log ε 4·60, 3·33, 3·38, 3·42, and 3·42) (inflection at 390 mμ; log ε 3·15), $\nu_{max.}$ 745, 944, 960, 1105, 1135, 1165, 1175, 1192, 1212, 1229, 1258, 1280, 1300, 1318, 1356, 1403, 1417, 1448, 1469, 1498, 1543, 1632, 1650, 1681, 1699, 2600, 2658, 2940, 3125, and 3585 cm.$^{-1}$.

The acid (0·7 g.) was heated with acetic anhydride (1·5 c.c.) for 3 hr. at 140—150°; much charring occurred. After removal of the excess of solvent *in vacuo*, the residue was sublimed at 140°/0·05 mm., to yield the *anhydride* as a yellow solid (40 mg.), decomp. 200° (Found: C, 65·7; H, 3·75; N, 6·7. $C_{11}H_7NO_3$ requires C, 65·7; H, 3·5; N, 6·95%), $\lambda_{max.}$ (in *NN*-dimethylformamide) 258, 305, 357, 374, and 436 mμ (log ε 4·01, 3·52, 3·48, 3·46, and 3·06 respectively), $\nu_{max.}$ 1759s and 1780s cm.$^{-1}$ associated with the six-membered anhydride grouping.

Octahydro-1-*methylindolizine* (VIII; R = Me, R′ = H).—The foregoing dicarboxylic acid (6 g.) was intimately mixed with finely powdered calcium oxide (40 g.); the mixture, in small portions (3—4 g.), was heated strongly and the distillate collected. The combined distillates (3 c.c.) were mixed with 10% sodium hydroxide solution (5 c.c.) and steam-distilled. The rather unstable oil obtained in the distillate was isolated by extraction with ether and hydrogenated in methanol over Raney nickel at 180°/200 atm. After removal of the solvent, the residual oil (1 g.) was converted into the picrate which formed yellow plates, m. p. 184—189° (lit.,[7] 191°), from methanol.

Octahydro-3-*methylindolizine* (VIII; R = H, R′ = Me).—(i) 3-Methylindolizine was prepared by condensation of α-picoline and propionic anhydride by Ochiai and Tsuda's method.[9] The product was hydrogenated in methanol at 180°/200 atm. over Raney nickel. After removal of the catalyst and solvent, the resulting base was converted into the picrate which formed yellow needles, m. p. 190—193°. Attempted separation of the two forms of the base by chromatography on alumina (cf. ref. 8) yielded only one major fraction which gave a picrate, m. p. 194°, identical with the product described below. The higher-melting form was not obtained.

(ii) (2-Carboxyindolizin-3-yl)acetic acid (4·3 g.) (XI; R = H) was intimately mixed with powdered calcium oxide and distilled in six portions from a bulb tube. The combined distillates were extracted with ether, the solvent was then removed, and the residue distilled in steam. The distillate was extracted with ether and from the dried extract 3-methylindolizine was obtained as a pale yellow oil (1·5 g.), the infrared spectrum of which (in CCl_4) showed max. at 682, 702, 884, 958, 1000, 1020, 1070, 1113, 1145, 1235, 1267, 1295, 1310, 1350, 1370, 1390, 1440, 1490, 1615, 1670, 1715, 1745, 1810, 1880, 2850, 2910, 2990, and 3070 cm.$^{-1}$. The *picrate* formed blue needles, m. p. 95—96°, from ethanol (Found: C, 50·0; H, 3·5. $C_9H_9N,C_6H_3N_3O_7$ requires C, 50·0; H, 3·3%), $\lambda_{max.}$ 234, 282, 295, and 354 mμ (log ε 4·65, 3·91, 3·96, and 3·09 respectively).

The above base (1·5 g.) in methanol (100 c.c.) was hydrogenated overnight over Raney nickel (0·75 g.) at 180°/180 atm. After removal of the catalyst, the solvent was removed (fractionating column; product very volatile), leaving octahydro-3-methylindolizine as a pale yellow oil (0·15 g.), $\nu_{max.}$ 904, 1054, 1112, 1140, 1185, 1245, 1293, 1310, 1360, 1430, 1440, 2770, 2840, and 2925 cm.$^{-1}$. The picrate (0·25 g.), when crystallised from methanol, gave a first fraction (0·1 g.), m. p. 208—209°, as bright yellow needles and a second fraction (0·07 g.), m. p. 192—193°, as dull yellow prisms from the mother-liquors. The latter picrate was identical with the product obtained by method (i).

Methyl (1,2-*Dimethoxycarbonylindolizin*-3-*yl*)*acetate* (X).—Prepared by heating tetramethy-4*H*-quinolizine-1,2,3,4-tetracarboxylate with phenol [10] and crystallised from 50% methanol, this formed colourless needles, m. p. 70° (lit., 75°,[10] 68° [12]) (Found: C, 59·0; H, 5·2; N, 4·8; OMe, 31·2. Calc. for $C_{15}H_{15}NO_6$: C, 59·0; H, 4·9; N, 4·6; 3OMe, 30·5%), $\lambda_{max.}$ 219, 245, 293, 305, and 346 mμ (log ε 4·30, 4·40, 3·74, 3·89, and 3·86 respectively), $\lambda_{infl.}$ 335 mμ (log ε, 3·84),

$\nu_{max.}$ 700, 728, 742, 747, 771, 787, 837, 893, 937, 945, 975, 993, 1003, 1022, 1044, 1105, 1136, 1163, 1187, 1211, 1250, 1278, 1322, 1346, 1363, 1397, 1402, 1418, 1438, 1444, 1453, 1513, 1532, 1563, 1639, 1690, 1721, 1727, 2955, 3002, 3098, 3444, and 3557 cm.$^{-1}$.

Methyl (1,2-*Dimethoxycarbonyl*-8-*methylindolizin*-3-*yl*)*acetate*.—Tetramethyl 9-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate [1] (3·2 g.), m. p. 208°, one of the stable adducts from β-picoline and dimethyl acetylenedicarboxylate, was heated with glacial acetic acid (32 c.c.) for 20 min. The solvent was removed under reduced pressure, methanol (20 c.c.) was added, and the mixture cooled. The solid was separated, washed with methanol, and dried; it formed colourless cubes (2·55 g.), m. p. 105—106° [Found: C, 60·3; H, 5·6; N, 4·5%; *M* (Rast), 301. $C_{16}H_{17}NO_6$ requires C, 60·2; H, 5·3; N, 4·4%; *M*, 319], $\lambda_{max.}$ 241, 292, 303, 341, and 349 mμ (log ε 4·53, 3·60, 3·70, 3·66, and 3·65), $\nu_{max.}$ 1711 and 1737 (C=O) cm.$^{-1}$.

By a similar method, tetramethyl 7-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate [1] (1·5 g.), m. p. 224°, was rearranged with acetic acid and the product crystallised from 50% methanol to yield colourless needles of *methyl* (1,2-*dimethoxycarbonyl*-6-*methylindolizin*-3-*yl*)*acetate*, m. p. 110° (Found: C, 60·2; H, 5·1; N, 4·6; OMe, 28·8%), $\lambda_{max.}$ 220, 249, 296, 308, and 347 mμ (log ε 4·37, 4·48, 3·70, 3·83, and 3·93 respectively), $\lambda_{infl.}$ 335 mμ (log ε 3·90), $\nu_{max.}$ 1698 and 1728 (C=O) cm.$^{-1}$.

(2-*Carboxyindolizin*-3-*yl*)*acetic Acid* (XI; R = H).—Prepared by alkaline hydrolysis [10] of methyl (1,2-dimethoxycarbonylindolizin-3-yl)acetate, the acid formed colourless needles, m. p. 220° (decomp.) (lit.,[10] m. p. 229°), from 60% acetic acid (Found: C, 60·4; H, 4·5; N, 6·45. Calc. for $C_{11}H_9NO_4$: C, 60·3; H, 4·1; N, 6·4%), $\lambda_{max.}$ 235, 290, 301, 352, 364, and 385 mμ (log ε 4·64, 3·36, 3·40, 3·42, 3·42, and 3·19), $\nu_{max.}$ 725, 742, 767, 817, 851, 923, 980, 1015, 1100, 1139, 1174, 1215, 1247, 1283, 1325, 1346, 1370, 1397, 1428, 1449, 1526, 1556, 1674, 1707, 2348, 2370, 2607, 2640, 2675, 2757, 2860, 2937, 3030, 3076, 3130, and 3425 cm.$^{-1}$.

The dimethyl ester obtained therefrom by methanolic hydrogen chloride formed colourless prisms (from cyclohexane), m. p. 120—121° (Found: C, 63·3; H, 5·2; N, 5·6; OMe, 24·3. $C_{13}H_{13}NO_4$ requires C, 63·2; H, 5·3; N, 5·7; 2OMe, 25·0%), $\lambda_{max.}$ 235, 291, 302, 350, 365, and 384 mμ (log ε 4·66, 3·38, 3·44, 3·38, 3·42, and 3·19 respectively), $\nu_{max.}$ 1710 and 1732 (C=O) cm.$^{-1}$.

Methyl (1,2-*Dimethoxycarbonylindolizin*-3-*yl*)*methoxyacetate* (XIII).—Prepared [14] by reaction of pyridine (6 c.c.) and dimethyl acetylenedicarboxylate (11 c.c.) in methanol (30 c.c.), originally in an acetone–carbon dioxide bath and then allowed to warm slowly to 0°, this ester was kept at 0° for 2 days, after which the crystalline product (2·65 g.), m. p. 119—125°, was separated and crystallised repeatedly from methanol; it then had m. p. 139—140° (lit.,[13] 142—143°) (Found: C, 57·3; H, 5·25; N, 4·35; OMe, 37·6. Calc. for $C_{16}H_{17}NO_7$: C, 57·3; H, 5·1; N, 4·2; 4OMe, 37·0%), $\lambda_{max.}$ 218, 244, 269, 305, and 337 mμ (log ε 4·33, 4·48, 3·81, 3·97, and 3·92), $\nu_{max.}$ 693, 732, 747, 767, 774, 788, 826, 836, 899, 960, 990, 1022, 1042, 1097, 1116, 1188, 1213, 1223, 1247, 1282, 1301, 1336, 1362, 1400, 1427, 1438, 1465, 1517, 1567, 1700, 1719, 1754, 2600, 2840, 2955, 3008, 3290, and 3565 cm.$^{-1}$.

Methyl (1,2-*Dimethoxycarbonyl*-6-*methylindolizin*-3-*yl*)*methoxyacetate*.—Prepared by a similar method from β-picoline (9·6 g.) and dimethyl acetylenedicarboxylate (18 c.c.), the *adduct* formed colourless rods (1·1 g.), m. p. 159—160°, from methanol (Found: C, 58·6; H, 5·2; N, 4·1. $C_{17}H_{19}NO_7$ requires C, 58·5; H, 5·5; N, 4·0%), $\lambda_{max.}$ 218, 248, 308, and 339 mμ (log ε 4·34, 4·52, 3·88, and 3·95 respectively), $\nu_{max.}$ 1701, 1718, and 1747 (C=O) cm.$^{-1}$.

This adduct (0·65 g.) with 100-vol. hydrogen peroxide (6 c.c.) in glacial acetic acid (3 c.c.) at 100° for 1 hr., the solvent was removed *in vacuo*, and crystallisation of the residue from methanol (5 c.c.) gave 5-methylpicolinic acid *N*-oxide as colourless needles (0·07 g.), m. p. 160—161° alone and mixed with a specimen, m. p. 161—162°, prepared by a similar oxidation of tetramethyl 7-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate.[1] The oxide had $\lambda_{max.}$ 228 and 267 mμ (log ε 4·4 and 3·9) (Acheson and Taylor [2] gave 253 mμ, 3·85, by an error of transcription).

Methyl (1-*Carboxy*-2-*methoxycarbonylindolizin*-3-*yl*)*acetate*.—(i) Methyl (1,2-dimethoxycarbonylindolizin-3-yl)methoxyacetate (see above; m. p. 139—140°; 1·5 g.) was added to iodine (0·25 g.) and red phosphorus (0·75 g.) in glacial acetic acid (12·5 c.c.) and heated under reflux for 3 hr. The solid was separated from the hot solution, and the filtrate added to a solution of sodium dithionite (1·25 g.) in water (50 c.c.) and kept at 0° overnight. The product was separated, washed with hot methanol (5 c.c.), and crystallised from methanol as colourless needles (0·15 g.), m. p. 199—200°, identical with the product of the following experiment.

(ii) Methyl (1,2-dimethoxycarbonylindolizin-3-yl)acetate (see above; m. p. 65—66°; 1·5 g.) was treated as described in the previous experiment. The monocarboxylic *acid* again had m. p.

199—200° [Found: C, 57·3; H, 4·5; N, 4·5; OMe, 19·0%; equiv. (titration), 281. $C_{14}H_{13}NO_6$ requires C, 57·7; H, 4·5; N, 4·8; 2OMe, 21·3%; equiv., 291], $\lambda_{max.}$ 219, 250, 309, 337, 352, and 370 mμ, (log ε 4·28, 4·43, 3·83, 3·98, 4·08, and 3·92 respectively), $\nu_{max.}$ 725, 757, 777, 840, 877, 904, 950, 984, 992, 1031, 1040, 1113, 1157, 1178, 1218, 1244, 1254, 1294, 1357, 1386, 1405, 1438, 1456, 1483, 1500, 1523, 1552, 1604, 1637, 1712, 1728, 2315, 2450, 2501, 2580, 2850, 2958, 3001, 3030, 3092, 3123, 3143, and 3444 cm.$^{-1}$.

Methylation with diazomethane gave methyl (1,2-dimethoxycarbonylindolizin-3-yl)acetate, m. p. 64—65° not depressed when mixed with an authentic specimen (above). The ultraviolet and infrared spectra were identical with those of the previous sample.

Methyl (1-*Carboxy*-2-*methoxycarbonyl*-6-*methylindolizin*-3-*yl*)*acetate*.—Treatment of methyl (1,2-dimethoxycarbonyl-6-methylindolizin-3-yl)acetate, m. p. 110° (above), with iodine and phosphorus in acetic acid as in the preceding experiments gave the corresponding 1-*carboxylic acid*, m. p. 240—241°, as colourless needles (Found: N, 4·45; OMe, 19·4. $C_{15}H_{15}NO_6$ requires N, 4·6; 2OMe, 20·3%), $\lambda_{max.}$ 221, 253, 299, 312, 339, 353, and 371 mμ (log ε 4·33, 4·45, 3·61, 3·71, 3·98, 4·10, and 3·53 respectively), $\nu_{max.}$ 1713 and 1737 (C=O) cm.$^{-1}$.

A similar experiment with methyl (1,2-dimethoxycarbonyl-8-methylindolizin-3-yl)acetate caused decarboxylation as well as hydrolysis of the 1-methoxycarbonyl group and formed *methyl* (2-*methoxycarbonyl*-8-*methylindolizin*-3-*yl*)*acetate*, m. p. 130—132°, as colourless needles (methanol) (Found: C, 64·3; H, 5·7; N, 5·7; OMe, 23·0. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·7; N, 5·4; 2OMe, 23·8%), $\lambda_{max.}$ 236, 290, 301, 344, 360, and 378 mμ (log ε 4·72, 3·53, 3·59, 3·52, 3·55, and 3·37 respectively).

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