609. *Indolizines. Part II.*[1] *Preparation from Ethyl 2-Pyridylacetate and Related Compounds.*

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The synthesis of indolizines from ethyl 2-pyridylacetate and α-halogeno-ketones has been extended to the use of other 2-picolyl derivatives and other α-bromo-carbonyl compounds. It is now possible to synthesise directly indolizines with ester, acyl, or cyano-groups in position 1 or 3. The reaction of α-bromo-esters is shown to yield 2-hydroxyindolizines. The mechanism of this synthesis of indolizines is discussed.

In an earlier publication [1] we described the preparation of ethyl indolizine-1-carboxylates directly from ethyl 2-pyridylacetate and α-halogeno-ketones. In addition, Stepanow and Grineva [2] recently prepared 2-methylindolizine-1-carboxylic acid (VIII; R = CO_2H, R′ = Me, R″ = H) from α-chloroacetone and ethyl 2-pyridylacetate in boiling ethanol; they did not isolate an intermediate quaternary salt and state that treatment of the reaction mixture with sodium ethoxide caused cyclisation to the indolizine acid. We have repeated their preparation and have shown that ethyl 2-methylindolizine-1-carboxylate is produced directly under these conditions without the use of sodium ethoxide. Our previous synthesis of the acid through its ester remains the preferred method and we suggest that sodium ethoxide served only to hydrolyse the indolizine ester and did not effect cyclisation.

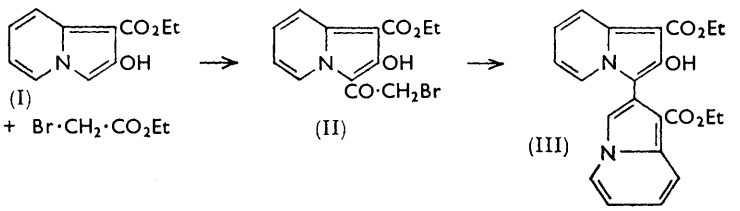
The scope of the method has now been extended to the reaction of ethyl 2-pyridylacetate with other α-bromo-carbonyl compounds and to the similar reaction of other picolyl derivatives with phenacyl bromide. Previous workers [3] have failed to introduce an acyl group at position 1 during synthesis, but phenyl 2-picolyl ketone (2·0 mol.) condensed in the expected manner with phenacyl bromide to yield 1-benzoyl-2-phenylindolizine (VIII; R = Bz, R′ = Ph, R″ = H). In a similar manner Mr. J. Hurst, in these laboratories, has prepared 1-cyano-2-phenylindolizine (VIII; R = CN, R′ = Ph, R″ = H). A 3-cyanoindolizine (VIII; R = CO_2Et, R′ = Me, R″ = CN), resulted from ethyl 2-pyridylacetate and α-bromo-α-cyanoacetone. Indolizine-2-carboxylic acid has been prepared [4] in 30% yield from α-picoline and ethyl bromopyruvate. The bromopyruvate and ethyl 2-pyridylacetate are now shown to give a 95% yield of diethyl indolizine-1,2-dicarboxylate (VIII; R = R′ = CO_2Et, R″ = H); traces of the 1-ethyl monoester acid were produced in this reaction, and considerably more if the initial exothermic reaction was not controlled. The same acid ester was produced by hydrolysis of the diester with dilute acid and its structure was established by decarboxylation. Alkaline hydrolysis yielded the diacid which was decarboxylated, as expected, to indolizine-2-carboxylic acid.

The complication, previously reported, which arises when bromoacetaldehyde replaces α-bromo-ketones in the reaction with ethyl 2-pyridylacetate was avoided by the omission of acetone from the reaction mixture, the expected ethyl indolizine-1-carboxylate being then obtained in 18% yield. Though low, this yield compares favourably with the 1% of indolizine itself previously obtained from α-picoline and bromoacetaldehyde. α-Bromopropionaldehyde and α-bromo-α-phenylacetaldehyde both gave the expected indolizine esters (VIII; R = CO_2Et, R′ = H, R″ = Me or Ph) in good yield in reactions carried out in acetone. Hydrolysis followed by decarboxylation yielded indolizine and 3-methyl- and 3-phenyl-indolizine, respectively.

α-Bromo-esters were also caused to react with ethyl 2-pyridylacetate, and a series of

[1] Cf. Bragg and Wibberley, *J.*, 1962, 2627, now regarded as Part I.
[2] Stepanow and Grineva, *Zhur. obshchei Khim.*, 1962, **32**, 1532.
[3] See Borrows and Holland, *Chem. Rev.*, 1948, **42**, 611.
[4] Borrows and Holland, *J.*, 1947, 672.

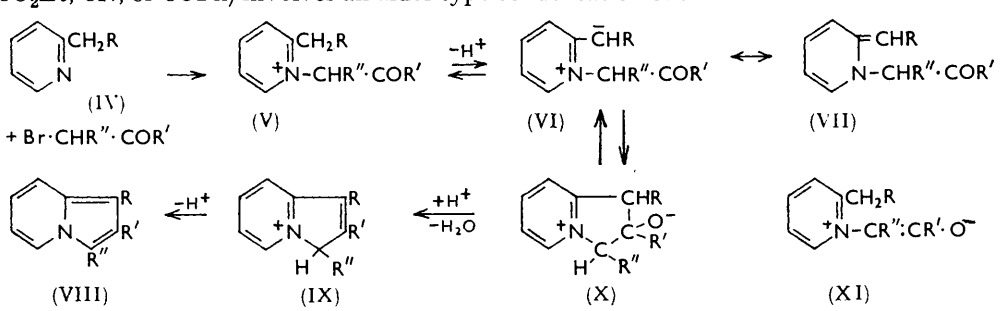
2-hydroxyindolizines was thus obtained. This seems to be the first synthesis of a hydroxyindolizine. Ethyl 2-hydroxy-3-methylindolizine-1-carboxylate (VIII; R = CO_2Et, R′ = OH, R″ = Me), the 3-phenyl analogue, and the diester (VIII; R = R″ = CO_2Et, R′ = OH) were prepared from ethyl α-bromopropionate, α-bromo-α-phenylacetate, and bromomalonate, respectively. The reactions are slower than those with the corresponding aldehydes or ketones and the solvent was omitted so as to raise the reaction temperature. In reactions of ethyl bromoacetate in the absence of solvent ethyl 3-ethoxycarbonylmethyl-2-hydroxyindolizine-1-carboxylate (VIII; R = CO_2Et, R′ = OH, R″ = $CH_2{\cdot}CO_2Et$), and ethyl 3-(1-ethoxycarbonylindolizin-2-yl)-2-hydroxyindolizine-1-carboxylate (III) were isolated. The first product is probably produced by alkylation of the expected ethyl 2-hydroxyindolizine-1-carboxylate (I) at the active 3-position with a further molecule of ethyl bromoacetate, such direct alkylation of indolizines being well established.[5] The second product probably arises by acylation of the ester (I) with ethyl bromoacetate and reaction of the bromo-ketone (II) with a second molecule of ethyl 2-pyridylacetate. Stepanow and Grineva [2] have shown that indolizines can be acylated in the 3-position



under similar conditions. Ethyl 2-hydroxyindolizine-1-carboxylate was prepared by reaction of ethyl 2-pyridylacetate and ethyl or methyl bromoacetate in ether with a modification of the normal isolation procedure.

All the 2-hydroxyindolizines gave colour reactions characteristic of indolizines and red or green colours with ferric chloride. Their structures were confirmed by formation of acetyl derivatives which no longer gave colours with ferric chloride. The presence of two carbonyl peaks, at 1735 (aliphatic ester) and 1670 $cm.^{-1}$ (indolizine ester), was further evidence for the structure of compound (VIII; R = CO_2Et, R′ = OH, R″ = $CH_2{\cdot}CO_2Et$). It is now considered that the compound previously prepared by us in the reaction of ethyl bromoacetate with ethyl 2-pyridylacetate in acetone may be the isopropylidene derivative of compound (III), but, in view of the complexity of the reaction, the posibility of other isopropylidene derivatives cannot be excluded.

No complete mechanism for the formation of indolizines by the Tschitschibabin method has yet been advanced, although in review articles [3,6] it is implied that an enol-betaine (XI) is involved. Such a compound is not in a form capable of cyclisation and we suggest that the formation of indolizines from α-picoline and from its derivatives (IV; R = CO_2Et, CN, or COPh) involves an aldol-type condensation outlined in the annexed scheme.



[5] Scholtz, *Ber.*, 1912, **45**, 1718.
[6] Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Interscience Publ., Inc., New York, 1961, Part I, p. 239.

Quaternary salts were never isolated in our syntheses from ethyl 2-pyridylacetate, but the facts that the latter is quaternised readily with methyl iodide and that both α-picoline and ethyl 4-pyridylacetate form similar salts with phenacyl bromide are strong evidence for their formation. Proton loss from the quaternary salt (V) to form the carbanion-betaine (VI) will be facilitated when the group R is electron-withdrawing, and so a second molecule of the picolyl base is an adequate catalyst when the group R is CO_2Et, CN, or Bz, but sodium hydrogen carbonate is required when R is H. After cyclisation of the intermediate (VI) by an intramolecular aldol-type reaction, removal of water from the product (X) would yield the indolizinium cation (IX). (There is recent evidence [7] that in its salts indolizine is protonated at position 3.) An excess of base would then liberate the indolizine (VIII).

Experimental

General Procedure.—Except where otherwise stated, the α-bromo-carbonyl compound (0·01 mole), the picolyl derivative (0·02 mole), and acetone (10·0 ml.) were refluxed together for the stated time and the indolizine was isolated by the method previously described. Hydrolysis of indolizine esters and decarboxylation of the acids formed were effected by methods previously described. 2-Hydroxyindolizines were acetylated with acetic anhydride.

1-*Benzoyl*-2-*phenylindolizine* (VIII; R = Bz, R′ = Ph, R″ = H).—Phenacyl bromide and phenyl 2-picolyl ketone (18 hr., reflux) yielded 1-*benzoyl*-2-*phenylindolizine* (67%), needles (from ethanol), m. p. 134—135° (Found: C, 84·55; H, 4·9; N, 5·0. $C_{21}H_{15}NO$ requires C, 84·8; H, 5·05; N, 4·7%). Hydrolysis with boiling dilute hydrochloric acid for 1 hr. produced 2-phenylindolizine, m. p. 213—214° alone and mixed with an authentic sample.

1-*Cyano*-2-*phenylindolizine* (VIII; R = CN, R′ = Ph, R″ = H).—2-Cyanomethylpyridine and phenacyl bromide (14 hr., reflux) yielded 1-*cyano*-2-*phenylindolizine* (48%), needles (from ethanol), m. p. 101—102° (Found: C, 82·7; H, 4·6; N, 12·9. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6; N, 12·8%).

Ethyl 3-*Cyano*-2-*methylindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = Me, R″ = CN).—Ethyl 2-pyridylacetate and α-bromo-α-cyanoacetone were heated together without solvent on the water-bath for 1 hr. and set aside for 24 hr., yielding the *nitrile* (15%), needles (from ethanol), m. p. 101—102° (Found: C, 68·4; H, 5·4; N, 12·5. $C_{13}H_{12}N_2O_2$ requires C, 68·4; H, 5·3; N, 12·3%).

Diethyl Indolizine-1,2-*dicarboxylate* (VIII; R = R′ = CO_2Et, R″ = H).—Ethyl bromopyruvate was added to ethyl 2-pyridylacetate with stirring and at such a rate that the temperature did not exceed 80°. The mixture was then heated for 10 min. on a water-bath, cooled, and shaken with water (10 ml.) to yield the *diester* (95%), needles, m. p. 83—84° (from ethanol), showing a blue fluorescence in ethanol (Found: C, 64·5; H, 5·7; N, 5·2. $C_{14}H_{15}NO_4$ requires C, 64·35; H, 5·8; N, 5·4%). The 1-*ethyl monoester* (VIII; R = CO_2Et, R′ = CO_2H, R″ = H), produced in the reaction (2%) and separated from the diester by means of its lower solubility in ethanol, crystallised from ethanol as needles, m. p. 228—229° alone and mixed with the product obtained in 95% yield by hydrolysis of the diester with boiling dilute hydrochloric acid (5 min.) (Found: C, 61·8; H, 4·9; N, 6·1%; equiv., 218. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·75; N, 6·0%; equiv., 233). The acid ester was decarboxylated when heated with half its weight of copper bronze at 3 mm.; the distillate had an infrared spectrum identical with that of ethyl indolizine-1-carboxylate. Hydrolysis of the diester with potassium hydroxide by the general procedure produced the *dicarboxylic acid* (VIII; R = R′ = CO_2H, R″ = H) (95%), needles (from ethanol), sublimed above 200°, m. p. 240—241° (with darkening above 215°) (Found: C, 58·7; H, 3·5; N, 6·7%; equiv., 98. $C_{10}H_7NO_4$ requires C, 58·5; H, 3·4; N, 6·8%; equiv., 102·5), and thence indolizine-2-carboxylic acid (VIII; R = R″ = H, R′ = CO_2H), m. p. 240—241° (with darkening above 215°) alone and with an authentic sample which had an identical infrared spectrum.

Ethyl Indolizine-1-*carboxylate* (VIII; R = R″ = H, R′ = CO_2Et).—Ethyl 2-pyridylacetate and bromoacetaldehyde were heated together without solvent on the water-bath for

[7] Fraser, Melera, Molloy, and Reid, *J.*, 1962, 3288.

22 hr., to yield the *ester* (18%), a pale yellow oil, b. p. 124°/3·0 mm., showing intense blue fluorescence in ethanol (Found: C, 70·1; H, 6·3; N, 7·3. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·85; N, 7·5%). Hydrolysis gave the *acid* (95%) as needles (from ethanol), m. p. 184—185° (decomp.) (Found: C, 67·1; H, 4·5; N, 8·6. $C_9H_7NO_2$ requires C, 67·1; H, 4·4; N, 8·7%), and thence indolizine, m. p. and mixed m. p. 74°.

Ethyl 3-*Methylindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = H, R″ = Me).—Ethyl 2-pyridylacetate and α-bromopropionaldehyde (16 hr., reflux) yielded the *ester* (76%) as a pale yellow oil, b. p. 138°/3·0 mm., having an intense violet fluorescence in ethanol (Found: C, 70·6; H, 6·5; N, 6·6. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·45; N, 6·9%). Hydrolysis gave the *acid* (95%) as needles (from ethanol), m. p. 187—188° (decomp.) (Found: C, 68·6; H, 5·2; N, 8·1. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%), and thence 3-methylindolizine, b. p. 230° (Found: C, 82·6; H, 6·75; N, 10·7. Calc. for C_9H_9N: C, 82·4; H, 6·9; N, 10·7%).

Ethyl 3-*Phenylindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = H, R″ = Ph).—Ethyl 2-pyridylacetate and α-bromo-α-phenylacetaldehyde (22 hr., reflux) yielded the *ester* (78%) as needles, m. p. 63—64° (from ethanol), showing a blue fluorescence in ethanol (Found: C, 76·6; H, 5·7; N, 5·4. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%). Hydrolysis produced the *acid* (90%) as prisms (from ethanol), m. p. 185—186° (decomp.) (Found: C, 76·35; H, 4·8; N, 5·8. $C_{15}H_{11}NO_2$ requires C, 75·9; H, 4·7; N, 5·9%), and thence 3-*phenylindolizine* as a viscous oil darkening at room temperature, b. p. 290° (Found: C, 86·6; H, 5·85; N, 7·7. $C_{14}H_{11}N$ requires C, 87·0; H, 5·7; N, 7·3%).

Ethyl 2-*Hydroxy*-3-*methylindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = OH, R″ = Me).—Ethyl 2-pyridylacetate and ethyl α-bromopropionate were heated together without solvent on the water-bath for 24 hr., to give the *hydroxy-ester* (48%) as yellow needles (from light petroleum), m. p. 51—52° (Found: C, 66·1; H, 6·2; N, 6·3. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%), and thence the *acetyl derivative* (VIII; R = CO_2Et, R′ = OAc, R″ = Me) prisms (from ethanol), m. p. 128—129° (Found: C, 64·25; H, 5·95; N, 5·1. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·8; N, 5·4%).

Ethyl 2-*Hydroxy*-3-*phenylindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = OH, R″ = Ph).—Ethyl 2-pyridylacetate and ethyl α-bromo-α-phenylacetate were heated together on the water-bath for 17 hr., to yield the *hydroxy-ester* (90%) as yellow needles (from ethanol), m. p. 75—76° (Found: C, 72·5; H, 5·3; N, 4·8. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·4; N, 5·0%), and thence the *acetyl derivative* (VIII; R = CO_2Et, R′ = OAc, R″ = Ph), needles (ethanol), m. p. 131—132° (Found: C, 70·2; H, 5·4; N, 4·4. $C_{19}H_{17}NO_4$ requires C, 70·6; H, 5·3; N, 4·3%).

Diethyl 2-*Hydroxyindolizine*-1,3-*dicarboxylate* (VIII; R = R″ = CO_2Et, R′ = OH).—Ethyl 2-pyridylacetate and diethyl bromomalonate were heated together on the water-bath for 12 hr., to yield the *hydroxy-diester* (30%) as prisms (from light petroleum), m. p. 124—125° (Found: C, 60·7; H, 5·45; N, 5·3. $C_{14}H_{15}NO_5$ requires C, 60·6; H, 5·45; N, 5·05%), and thence the *acetyl derivative* (VIII; R = R″ = CO_2Et, R′ = OAc), needles (from ethanol), m. p. 132—133° (Found: C, 60·05; H, 5·4; N, 4·3. $C_{16}H_{17}NO_6$ requires C, 60·2; H, 5·4; N, 4·4%).

Ethyl 3-(1-*Ethoxycarbonylindolizine*-2-*yl*)-2-*hydroxyindolizine*-1-*carboxylate* (III).—Ethyl 2-pyridylacetate and ethyl bromoacetate were heated together on a water-bath for 16 hr., cooled, and acidified with hydrochloric acid. The *ester* (III) was precipitated and after collection crystallised from benzene as prisms (38%), m. p. 177—178° (Found: C, 67·0; H, 5·3; N, 7·2. $C_{22}H_{20}N_2O_5$ requires C, 67·3; H, 5·1; N, 7·1%). The *acetyl derivative* crystallised from ethanol as needles, m. p. 180—181° (Found: C, 66·1; H, 5·1; N, 6·4. $C_{24}H_{22}N_2O_6$ requires C, 66·4; H, 5·1; N, 6·45%).

Ethyl 3-*Ethoxycarbonylmethyl*-2-*hydroxyindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = OH, R″ = $CH_2{\cdot}CO_2Et$).—The filtrate from the preparation of ester (III) was extracted with ether from which, by the general procedure, the *hydroxy-diester* (34%) was obtained as prisms (from ethanol), m. p. 106—107° (Found: C, 62·1; H, 5·7; N, 4·9. $C_{15}H_{17}NO_5$ requires C, 61·9; H, 5·9; N, 4·8%), $\nu_{max.}$ 1735s (aliphatic CO_2Et) and 1670s cm.$^{-1}$ (indolizine CO_2Et). The *acetyl derivative* formed prisms (from ethanol), m. p. 73—74° (Found: C, 61·2; H, 5·8; N, 4·3. $C_{17}H_{19}NO_6$ requires C, 61·25; H, 5·75; N, 4·2%).

Ethyl 2-*Hydroxyindolizine*-1-*carboxylate* (I).—Ethyl 2-pyridylacetate, ethyl bromoacetate, and dry ether were refluxed together for 48 hr. Dilute hydrochloric acid (5 ml.) was added and the aqueous solution was treated with 20% sodium hydroxide solution (15 ml.). The precipitated sodium salt was removed and suspended in ether (20 ml.) and water (5 ml.) into

which an excess of carbon dioxide was then passed. The ethereal solution was evaporated, to yield the *hydroxy-ester* (14%), yellow needles (from ethanol), m. p. 131—132° (Found: C, 64·6; H, 5·6; N, 6·9. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·8%). The *hydrochloride* crystallised from ethanol as yellow needles, m. p. 174—175° (Found: C, 54·9; H, 5·3; N, 5·5; Cl, 14·6. $C_{11}H_{12}ClNO_3$ requires C, 54·7; H, 5·0; N, 5·8; Cl, 14·7%). (When ethyl bromoacetate was replaced by methyl bromoacetate in the preparation a similar yield of the same product was obtained, as shown by the infrared spectrum and m. p. and mixed m. p. of the hydroxy-ester.) The ethereal extract of the hydrochloric acid solution, by the general procedure, yielded ethyl 3-ethoxycarbonylmethyl-2-hydroxyindolizine-1-carboxylate (25%), m. p. 106—107° alone and with an authentic sample, prepared as above, which had an identical infrared spectrum.

4-*Ethoxycarbonylmethyl*-1-*phenacylpyridinium Bromide*.—Ethyl 4-pyridylacetate (0·2 mole), phenacyl bromide (0·1 mole), and acetone (7 hr., reflux) yielded the quaternary *salt* (100%), prisms (from ethanol), m. p. 184—185° (decomp.) (Found: C, 55·9; H, 5·2; N, 4·1. $C_{17}H_{18}BrNO_3$ requires C, 56·0; H, 4·9; N, 3·8%).

Ethyl 2-*Methylindolizine*-1-*carboxylate* (VIII; R = CO_2Et, R′ = Me, R″ = H).—Ethyl 2-pyridylacetate (0·01 mole), chloroacetone (0·01 mole), and ethanol (7 ml.) were refluxed together for 14 hr. Ethanol and any unchanged chloroacetone were removed at 15 mm. on a water-bath, and the ester (36%) was isolated from the residue by the normal procedure; it had m. p. 43—44° alone and mixed with an authentic sample.[1]

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