507. *Preparation of Indolizines from Ethyl 2-Pyridylacetate.*

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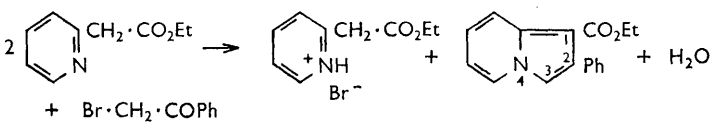
Ethyl alkyl- and aryl-indolizine-1-carboxylates have been prepared in one stage and in good yield by reaction of α-halogeno-ketones with ethyl 2-pyridylacetate. The structures of the products were confirmed by hydrolysis and decarboxylation to alkyl- and aryl-indolizines. The method was also successful with 3-chloropentane-2,4-dione and ethyl α-chloroacetoacetate, but with bromoacetaldehyde and ethyl α-bromoacetate there were also secondary reactions.

Alkyl- and aryl-indolizines can be prepared by Tschitschibabin's method [1] in which α-picoline or a derivative is quaternised with α-halogeno-ketones and then treated with aqueous alkali, preferably bicarbonate. We have found that when ethyl 2-pyridylacetate is refluxed with phenacyl bromide in ether ethyl 2-pyridylacetate hydrobromide separates instead of the quaternary salt and after filtration and concentration of the filtrate ethyl 2-phenylindolizine-1-carboxylate crystallises. Evidently part of the ester behaves as a base, removing hydrogen bromide and causing ring closure. The overall reaction can be expressed as follows:



The yield was greatly improved by using two mol. of ester and still further by using acetone as solvent. The method is of general application; α-bromoacetone, 3-bromobutan-2-one, α-bromopropiophenone, and α-bromobenzyl phenyl ketone each reacted with ethyl 2-pyridylacetate, forming indolizine esters. In this, as in the Tschitschibabin method, yields are higher from bromo- than from chloro-ketones,[2] and become progressively smaller as the α-hydrogen of the ketone is replaced by larger hydrocarbon residues.[2,3]

Borrows *et al.*[3,4] attempted to extend the Tschitschibabin method to the preparation of acyl and alkoxycarbonyl derivatives by using α-halogeno-β-diketones and α-halogeno-β-keto-esters. They failed owing to difficulties arising at the quaternising stage. By using our method which does not necessitate isolation of the quaternary salt, we have prepared ethyl 3-acetyl-2-methylindolizine-1-carboxylate and diethyl 2-methylindolizine-1,3-dicarboxylate from ethyl 2-pyridylacetate with 3-chloropentane-2,4-dione and ethyl α-chloroacetoacetate, respectively. The yields were small but increased ten-fold or more when the solvent was left out of the reaction mixture.

When two mol. of α-picoline were refluxed in acetone solution with one mol. of bromoacetone or phenacyl bromide only the quaternary salt could be isolated. This suggests that the facility with which indolizines are formed from ethyl 2-pyridylacetate is due to activation of the methylene group in the latter by the adjacent ethoxycarbonyl group. This activation was previously demonstrated by the authors in the condensation of ethyl 2-pyridylacetate with aromatic aldehydes and ketones.[5]

α-Halogeno-aldehydes may conceivably replace α-halogeno-ketones in the formation of indolizines, although it has been found difficult in practice when the other reagent is α-picoline; only bromoacetaldehyde reacts and then gives only a very small yield.[1] In an initial attempt to prepare ethyl indolizine-1-carboxylate, we applied our method to

[1] Tschitschibabin, *Ber.*, 1927, **60**, 1607; Tschitschibabin and Stepanow, *Ber.*, 1929, **62**, 1068; 1930, **63**, 470.
[2] Borrows, Holland, and Kenyon, *J.*, 1946, 1083.
[3] Borrows, Holland, and Kenyon, *J.*, 1946, 1069.
[4] Borrows and Holland, *J.*, 1947, 672.
[5] Bragg and Wibberley, *J.*, 1961, 5074.

ethyl 2-pyridylacetate and bromoacetaldehyde; however, one molecule of the solvent acetone condensed with two of the indolizine ester, giving diethyl 3,3′-isopropylidene-di(indolizine-1-carboxylate). Bromoacetal gave the same product but much more slowly.

Preliminary investigation of the reaction of α-halogeno-esters with ethyl 2-pyridylacetate has shown that an indolizine is formed when ethyl α-bromoacetate is used. The structure of the product has not been investigated yet but analysis suggests that it is not the expected ethyl 2-hydroxyindolizine-1-carboxylate but possibly a compound formed by further condensation of this substance.

All the derivatives of ethyl indolizine-1-carboxylate showed properties typical of indolizines: feeble basicity, strong fluorescence in dilute solution, an intense violet-to-blue colour on fusion with oxalic acid, and a dull purple colour in the pine-splint test. They are crystalline and stable to air and light, unlike some indolizines not having the ethoxycarbonyl group, notably 2-methylindolizine and 3-acetylindolizine, which darken on storage.

The indolizine-1-carboxylic acids obtained by alkaline hydrolysis of their esters were all decarboxylated a little above the melting point. The acetyl group of the 3-acetyl-ester was not removed by alkaline hydrolysis, as shown by decarboxylation of the resulting acid to 3-acetyl-2-methylindolizine. In most cases the decarboxylated products were conveniently purified by sublimation or distillation under reduced pressure.

Experimental

General Procedure for the Preparation of Ethyl Indolizine-1-carboxylates.—The α-halogeno-carbonyl compound (0·01 mole), ethyl 2-pyridylacetate (0·02 mole), and acetone (10·0 ml.) were refluxed together for the stated time. Acetone and any unchanged α-halogeno-carbonyl compound were removed by distillation at 15 mm. from a water-bath, and the oily residue was stirred with 2N-hydrochloric acid (10·0 ml.) and then extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal extract yielded the indolizine, and basification, with sodium carbonylate, of the acid fraction yielded the unchanged ethyl 2-pyridylacetate (0·005—0·013 mol.).

General Procedure for the Preparation of Indolizines from the Indolizine Esters.—The ethyl indolizine-1-carboxylate (0·5 g.) and potassium hydroxide (1·0 g.) in ethanol (10·0 ml.) were refluxed together for 16 hr. The ethanol was evaporated, the residue dissolved in water (10·0 ml.), and the solution acidified, to yield the indolizine-1-carboxylic acid. Without further purification, the acids were heated a little above the m. p. until effervescence ceased. The products were purified by sublimation or distillation under reduced pressure in most cases. The overall yield in all cases was greater than 75%.

Specific Cases.—α-Bromoacetone and ethyl 2-pyridylacetate (17 hr., reflux) yielded *ethyl 2-methylindolizine-1-carboxylate* (91%), prisms (from light petroleum), m. p. 43—44° (Found: C, 70·8; H, 6·6; N, 7·0. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·45; N, 6·9%). α-Chloroacetone gave the same product (56%) after 72 hours' refluxing. Hydrolysis produced 2-methylindolizine-1-carboxylic acid, m. p. 160—161° (decomp.), which was decarboxylated to 2-methylindolizine, m. p. (after sublimation) and mixed m. p. with a sample prepared by the method of Borrows *et al.*,[3] 59—60°.

Phenacyl bromide and ethyl 2-pyridylacetate (7 hr., reflux) yielded *ethyl 2-phenylindolizine-1-carboxylate* (85%), needles (from ethanol), m. p. 106—107° (Found: C, 77·0; H, 5·45; N, 5·5. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%). Hydrolysis followed by decarboxylation gave 2-phenylindolizine, m. p. and mixed m. p.[3] 213—214°. The carboxylic acid had m. p. 213—214° (decomp.) alone and with the authentic 2-phenylindolizine from which, however, it could be distinguished by its solubility in dilute alkali.

3-Bromobutan-2-one [6] and ethyl 2-pyridylacetate (17 hr., reflux) yielded *ethyl 2,3-dimethylindolizine-1-carboxylate* (45%), plates (from ethanol), m. p. 62—63° (Found: C, 71·9; H, 7·0; N, 6·5. $C_{13}H_{15}NO_2$ requires C, 71·9; H, 6·95; N, 6·4%). Hydrolysis of the ester gave the *carboxylic acid*, m. p. 169—170° (decomp.) (from ethanol) (Found: C, 69·8; H, 5·95; N, 7·1. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%), and thence 2,3-dimethylindolizine which was

[6] Catch, Elliot, Hey, and Jones, *J.*, 1948, 272.

purified by distillation *in vacuo* (plates, m. p. 40—41°; lit.,[7] 39·5—40·5°) (Found: C, 82·4; H, 7·6; N, 10·0. Calc. for $C_{10}H_{11}N$: C, 82·7; H, 7·6; N, 9·7%).

α-Bromopropiophenone [8] and ethyl 2-pyridylacetate (17 hr., reflux) yielded *ethyl 3-methyl-2-phenylindolizine-1-carboxylate* (38%), plates (from ethanol), m. p. 101—102° (Found: C, 76·9; H, 6·3; N, 4·8. $C_{18}H_{17}NO_2$ requires C, 77·4; H, 6·1; N, 5·0%). Hydrolysis yielded the acid, m. p. 172—174° (decomp.), which was decarboxylated to *3-methyl-2-phenylindolizine*. Sublimation at 15 mm. followed by crystallisation from ethanol gave plates, m. p. 97—98° (Found: C, 86·8; H, 6·4; N, 6·7. $C_{15}H_{13}N$ requires C, 86·9; H, 6·3; N, 6·8%).

α-Bromobenzyl phenyl ketone [9] and ethyl 2-pyridylacetate (17 hr., reflux) yielded *ethyl 2,3-diphenylindolizine-1-carboxylate* (24%), plates (from ethanol), m. p. 151—152° (Found: C, 80·4; H, 5·8; N, 4·0. $C_{23}H_{19}NO_2$ requires C, 80·9; H, 5·6; N, 4·1%). Hydrolysis yielded the acid, m. p. 196—198° (decomp.), which was decarboxylated to 2,3-diphenylindolizine. Sublimation at 15 mm. followed by crystallisation from ethanol gave prisms, m. p. 95—96° (lit.,[10] 94—95°) (Found: C, 89·5; H, 5·5; N, 5·0. Calc. for $C_{20}H_{15}N$: C, 89·2; H, 5·6; N, 5·2%).

3-Chloropentane-2,4-dione (prepared by the method used by Dey [11] for ethyl α-chloroacetoacetate) and ethyl 2-pyridylacetate (17 hr.) yielded *ethyl 3-acetyl-2-methylindolizine-1-carboxylate* (5%), plates (from light petroleum), m. p. 101—102°. The yield was 63% when the acetone was omitted (Found: C, 68·5; H, 5·6; N, 5·4. $C_{14}H_{15}NO_3$ requires C, 68·55; H, 6·2; N, 5·7%). Hydrolysis gave 3-acetyl-2-methylindolizine-1-carboxylic acid, m. p. 201—203° (decomp.), which was decarboxylated to 3-acetyl-2-methylindolizine, pale green needles (from light petroleum), m. p. 82—83°. The yellow benzylidene derivative had m. p. 103—104°. Borrows *et al.*[3] give m. p. 83° for 3-acetyl-2-methylindolizine and 102—104° for its benzylidene derivative.

Ethyl α-chloroacetoacetate [11] yielded *diethyl 2-methylindolizine-1,3-dicarboxylate* (6%), needles (from light petroleum), m. p. 112—113°; the yield was 61% when the acetone was omitted. (Found: C, 65·8; H, 5·65; N, 4·9. $C_{15}H_{17}NO_4$ requires C, 65·4; H, 6·2; N, 5·1%). Hydrolysis yielded the corresponding dicarboxylic acid, m. p. 170—172° (decomp.), which was decarboxylated to 2-methylindolizine, m. p. (after sublimation) and mixed m. p. with authentic sample [3] 59—60°.

Diethyl 3,3'-Isopropylidenedi(indolizine-1-carboxylate).—α-Bromoacetaldehyde, ethyl 2-pyridylacetate, and acetone (10 hr., reflux) yielded the *isopropylidene derivative* (22%), prisms (from ethanol), m. p. 159—160°. Bromoacetal gave the same product (33%) after 72 hours' refluxing [Found: C, 71·6; H, 6·2; N, 6·8%; *M* (Rast), 405. $C_{25}H_{26}N_2O_4$ requires C, 71·7; H, 6·3; N, 6·7%; *M*, 418]. Hydrolysis gave the carboxylic acid, m. p. 291—293° (decomp.), which was decarboxylated to *3,3'-isopropylindenedi-indolizine*. Sublimation at 15 mm. followed by crystallisation from ethanol gave pale yellow hexagonal plates, m. p. 206—207° (Found: C, 83·3; H, 6·65; N, 10·15. $C_{19}H_{18}N_2$ requires C, 83·2; H, 6·6; N, 10·2%). Scholtz [12] obtained an isopropylidene derivative of unspecified structure, m. p. 244—246°, by the reaction of indolizine with acetone in acetic acid.

Reaction of Ethyl α-Bromoacetate with Ethyl 2-Pyridylacetate.—Ethyl α-bromoacetate and ethyl 2-pyridylacetate (24 hr., reflux) yielded an unidentified indolizine (0·95 g.) which separated from methanol in yellow needles, m. p. 183—184° (Found: C, 68·9; H, 6·2; N, 7·1%).

Reaction of α-Bromoacetone or Phenacyl Bromide with Two Mol. of α-Picoline.—α-Bromoacetone (0·01 mole), α-picoline (0·02 mole), and acetone (10·0 ml.) were refluxed together for 6 hr. The oil which had separated was completely soluble in water and evaporation of the acetone solution at 15 mm. on the water-bath gave no residue. Thus 2-methylindolizine was not produced under these conditions.

A similar reaction with phenacyl bromide (17 hr., reflux) yielded 1-phenacyl-α-picolinium bromide, m. p. 213—214°, as the sole product in 96% yield.

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[11] Dey, *J.*, 1915, **107**, 1646.
[12] Scholtz, *Ber.*, 1912, **45**, 1718.