Oxidation of Methyl 2-Hydroxy-3-methyl- and Methyl 2-Hydroxy-3-phenylindolizine-1-carboxylates

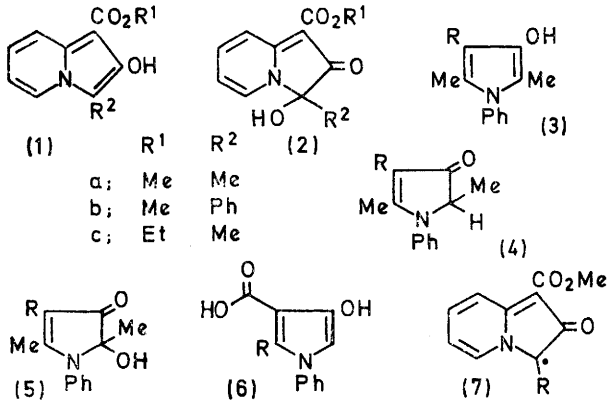
By **R. J. Bowers** and **A. G. Brown,*** Beecham Research Laboratories, Brockham Park, Betchworth, Surrey

Oxidation by air or potassium ferricyanide of methyl 2-hydroxy-3-methylindolizine-1-carboxylate and methyl 2-hydroxy-3-phenylindolizine-1-carboxylate gave methyl 2,3-dihydro-3-hydroxy-3-methyl-2-oxo and methyl 2,3-dihydro-3-hydroxy-2-oxo-3-phenylindolizine-1-carboxylate, respectively.

Bragg and Wibberley [1] have prepared 2-hydroxyindolizine esters of the type (1) by treatment of ethyl 2-pyridylacetate with α-bromo-esters, such as ethyl bromoacetate, ethyl α-bromo-propionate and ethyl α-bromophenylacetate. We have applied this procedure to the preparation of methyl 2-hydroxy-3-3-methylindolizine-1-carboxylate (Ia). When methyl 2-pyridylacetate and ethyl α-bromopropionate were heated at 100° for 24 hr. a compound A and trace

[1] D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 1963, 3277.

amounts of a compound B were obtained. Compound A, $C_{11}H_{11}NO_4$, m.p. 200—203° was a bright yellow crystalline solid, $\nu_{max.}$ 3165, 1700, and 1626 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 213, 268, 283, and 399 nm., τ ($CDCl_3$) 8·37 (3H, s, Me),



6·40 (3H, s, CO_2Me), 3·70—4·00 (1H, s, exchangeable, OH), and 1·77—3·23 (4H, m, 5-, 6-, 7-, and 8-protons of an indolizine ring). It was soluble in water and chloroform and insoluble in light petroleum (b.p. 60—80°), gave a red-brown colour with iron(III) chloride solution, but did not give a coloured melt with oxalic acid (colour reaction typical of indolizines [2]). With acetic anhydride compound A formed a mono-acetate.

When the reaction was repeated under nitrogen compound B was the main product, with traces of compound A. Compound B, $C_{11}H_{11}NO_3$, m.p. 96°, was a light yellow solid, $\nu_{max.}$ 3279, 1681, and 1631 cm.$^{-1}$, $\lambda_{max.}$ 231, 252, 274, 281, 325, and 349 nm., τ ($CDCl_3$) 7·72 (3H, s, aromatic Me), 6·07 (3H, s, CO_2Me), 2·08—3·42 (4H, m, 5-, 6-, 7-, and 8-protons of an indolizine ring), and 1·57 (1H, s, exchangeable, OH). Compound B gave a red-brown colour with iron(III) chloride solution and a coloured (green-blue) melt with oxalic acid. These properties indicated that it was methyl 2-hydroxy-3-methylindolizine-1-carboxylate (1a). At room temperature a solution of the 2-hydroxyindolizine (1a) in ethanol or chloroform was converted slowly into compound A. This oxidation was carried out more readily by treating methyl 2-hydroxy-3-methylindolizine-1-carboxylate (1a) with aqueous potassium ferricyanide solution at room temperature.

The n.m.r. spectrum of compound A indicated the presence of ester and hydroxy-functions together with four pyridyl protons and a methyl group attached to a fully substituted carbon atom, in agreement with its identification as methyl 2,3-dihydro-3-hydroxy-3-methyl-2-oxoindolizine-1-carboxylate (2a).

At 100° ethyl α-bromophenylacetate and methyl 2-pyridylacetate formed methyl 3-hydroxy-2-phenylindolizine-1-carboxylate (1b) only. No trace of the corresponding oxidised material (2b) was detected by t.l.c. However, in solution, slow oxidation to the oxo-ester (2b) occurred. Potassium ferricyanide readily converted the hydroxyindolizine (1b) into methyl 2,3-dihydro-3-hydroxy-2-oxo-3-phenylindolizine-1-carboxylate (2b) in good yield. The reaction of ethyl 2-pyridylacetate with ethyl α-bromopropionate gave only the 3-hydroxy-2-oxoindolizine (2c). Bragg and Wibberley [3] have also noted the formation of a compound which gave analytical figures corresponding to the ketone structure (2c).

The hydroxyindolizine (1) can be considered to be related to a substituted pyrrole of the type (3). Compounds of type (3) with R = H or CO_2H have been shown by Davoll,[4] using i.r. and u.v. spectroscopy to exist in the oxo-pyrroline form (4). Moreover these oxo-pyrrolines (4; R = H or CO_2H) were readily oxidised by air or potassium ferricyanide to the hydroxy-ketones (5; R = H or CO_2H).

In contrast, however, the spectroscopic properties (u.v., i.r., and n.m.r. in particular) of the indolizines (1a and b) indicate that they are enolic, at least in solution. Davoll [4] considered the existence of the pyrroles (3; R = H or R = CO_2H) in the oxo-form to be due to a loss of coplanarity of the phenyl ring with the pyrrole ring when positions 2 and 5 contain methyl substituents. The stable enolic form of the 4-hydroxypyrroles (3) was only present when position 5 had no substituent, as in the pyrroles (6; R = H or Me). In the indolizine system (1) the ring is of necessity planar and there is no steric interaction between position 5 of the indolizine and the 3-methyl group, so a situation similar to that present in the pyrroles (6; R = H or Me) exists.

The oxidation of the hydroxyindolizine (1) to the 3-hydroxy-2-ketone probably proceeds *via* a free-radical mechanism involving an intermediate radical (7).

EXPERIMENTAL

N.m.r. spectra were measured with a Varian A60-A instrument, with deuteriochloroform as solvent and tetramethylsilane as internal standard. I.r. spectra were recorded with a Perkin-Elmer 137 spectrophotometer, u.v. spectra with a Unicam SP 800 spectrophotometer, and mass spectra with an AEI MS12 spectrometer. M.p.s were determined with a Kofler hot-stage apparatus.

Methyl 2-Hydroxy-3-methylindolizine-1-carboxylate.—Methyl 2-pyridylacetate (3·02 g., 0·02 mole) and ethyl α-bromopropionate (1·81 g., 0·01 mole) were heated together at 100° under nitrogen for 24 hr. When cool the mixture was treated with 2N-hydrochloric acid (10 ml.) and extracted with ether several times. The combined extracts were dried ($MgSO_4$) and evaporated to a yellow oil (1·3 g.) which crystallised to form *methyl 2-hydroxy-3-methylindolizine-1-carboxylate* as yellow needles, m.p. 96—101° [from light petroleum (b.p. 60—80°)] (Found: C, 64·3; H, 5·5; N, 6·8. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·8%), $\nu_{max.}$ (Nujol) 3279, 1681, and 1631 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 231, 252, 274, 281, 325, and 349 nm. (ε 12,300, 16,400, 11,800, 11,600, 6850, and 6950), τ 1·57 (1H, s, exchangeable, OH),

[2] W. L. Mosby, 'Heterocyclic Systems with Bridgehead Nitrogen Atoms,' Interscience, New York, 1961, part 1, p. 239.

[3] D. G. Wibberley, personal communication.

[4] J. Davoll, *J. Chem. Soc.*, 1953, 3802.

2·03—3·42 (4H, m, 5-, 6-, 7-, and 8-protons of an indolizine ring), 6·07 (3H, s, CO_2Me), and 7·72 (3H, s, aromatic Me), M^+ 205.

When boiled with acetic anhydride for 20 min., methyl 2-hydroxy-3-methylindolizine-1-carboxylate formed an *acetate*, m.p. 100—104° (pale lime-green needles from ethanol) (Found: C, 62·8; H, 5·45; N, 5·6. $C_{13}H_{13}NO_4$ requires C, 63·15; H, 5·3; N, 5·65%), $\nu_{max.}$ (Nujol) 1773 and 1689 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 230, 258, 266, 300sh, 311, 335, and 345 nm. (ε 3360, 8150, 7650, 10,600, 9150, and 9400), M^+ 247.

Methyl 2-Hydroxy-3-phenylindolizine-1-carboxylate.—Methyl 2-pyridylacetate (3·02 g., 0·02 mole) and methyl α-bromophenylacetate (2·29 g., 0·01 mole) were heated at 100° for 16 hr. and the product was worked up as for methyl 2-hydroxy-3-methylindolizine-1-carboxylate to form *methyl 2-hydroxy-3-phenylindolizine-1-carboxylate* as a yellow oil (1·76 g.) which solidified and crystallised as yellow-brown cubes, m.p. 90—93° (from ethanol) (Found: C, 71·95; H, 4·95; N, 5·5. $C_{16}H_{13}NO_3$ requires C, 71·9; H, 4·9; N, 5·25%), $\nu_{max.}$ (Nujol) 3300 and 1667 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 231, 254, 281, 300sh, 325sh, and 350 nm. (ε 19,900, 18,000, 24,300, 12,700, 9345, and 8150), τ 1·20 (1H, s, exchangeable, OH), 1·60—3·47 (9H, m, 5-, 6-, 7-, and 8-protons of an indolizine ring and 5 aromatic protons), and 6·02 (3H, s, CO_2Me), M^+ 267.

The mother liquor, on concentration, yielded a small amount of methyl 2,3-dihydro-3-hydroxy-2-oxo-3-phenylindolizine-1-carboxylate (0·2 g.). Methyl 2-hydroxy-3-phenylindolizine-1-carboxylate formed an *acetate* with acetic anhydride which was purified on a silica gel column with ethanol–chloroform (1 : 9) as eluant. It crystallised as yellow cubes, m.p. 124—126° [from light petroleum (b.p. 60—80°)] (Found: C, 69·55; H, 5·0; N, 4·6. $C_{18}H_{15}NO_4$ requires C, 69·9; H, 4·9; N, 4·55%), $\nu_{max.}$ (Nujol) 1736 and 1691 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 225, 262, 294, 309sh, and 339sh nm. (ε 27,250, 21,450, 13,800, 11,100, and 7250), M^+ 309.

Methyl 2,3-Dihydro-3-hydroxy-3-methyl-2-oxoindolizine-1-carboxylate.—(*a*) Methyl 2-pyridylacetate (6·04 g., 0·04 mole) and ethyl α-bromopropionate (3·62 g., 0·02 mole) were heated together at 100° for 16 hr. to form a dark brown oil, which was shaken with 2N-hydrochloric acid (20 ml.) and extracted with ether (3 × 50 ml.). The ether solution was dried ($MgSO_4$) and evaporated to form a yellow solid (0·6 g.) which crystallised from ethyl acetate to yield *methyl 2,3-dihydro-3-hydroxy-3-methyl-2-oxoindolizine-1-carboxylate*, m.p. 200—203° (Found: C, 59·7; H, 5·15; N, 6·25. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%), $\nu_{max.}$ (Nujol) 3165, 1700, and 1626 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 213, 268, 283, and 399 nm. (ε 9850, 15,500, 17,500, and 5100), τ 1·77—3·23 (m, 5-, 6-, 7-, and 8-protons of an indolizine ring), 3·70—4·00 (1H, exchangeable, OH), 6·40 (3H, s, CO_2Me), acetic anhydride, this compound formed an *acetate*, m.p. 183—185° (Found: C, 57·3; H, 5·2; N, 5·05. $C_{13}H_{13}NO_5$,-$0·5H_2O$ requires C, 57·35; H, 5·15; N, 5·15%), $\nu_{max.}$ (Nujol) 1770 and 1720 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 210, 265, 283, and 402 nm. (ε 9000, 12,600, 13,150, and 4150), τ 1·65—3·35 (4H, m, 5-, 6-, 7-, and 8-protons of an indolizine ring), 6·17 (3H, s, CO_2Me), 7·90 (3H, s, OAc), and 8·32 (3H, s, aromatic Me), M^+ 263.

(*b*) To a suspension of methyl 2-hydroxy-3-methylindolizine-1-carboxylate (0·1 g.) in water (100 ml.) a solution of potassium ferricyanide (0·17 g.) in water (50 ml.) was added; the mixture was stirred for 6 hr. and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to produce methyl 2,3-dihydro-3-hydroxy-3-methyl-2-oxoindolizine (0·05 g.), identical (i.r. spectrum and m.p.) with that obtained in (*a*).

Ethyl 2,3-Dihydro-3-hydroxy-3-methyl-2-oxoindolizine-1-carboxylate.—Ethyl 2-pyridylacetate (6·6 g.) and ethyl α-bromopropionate (3·62 g.) were heated together at 100° for 24 hr. and the product (1·43 g.), isolated as in (*a*) produced the *ester*, m.p. 160—168° (yellow cubes from acetone) (Found: C, 61·25; H, 5·6; N, 5·95. $C_{12}H_{13}NO_4$ requires C, 61·25; H, 5·55; N, 5·95%), $\nu_{max.}$ (Nujol) 3015 and 1660 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 209, 267, 284, and 400 nm. (ε 13,550, 18,800, 21,250, and 5950), τ 1·68—3·23 (5H, m, 5-, 6-, 7-, and 8-protons of an indolizine ring and an exchangeable OH), 5·88 (q, J 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$), 8·36 (3H, s, aromatic Me), and 8·73 (3H, t, J 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$), M^+ 235.

The *acetate* had m.p. 236° (decomp.) (Found: C, 60·2; H, 5·5; N, 4·9. $C_{14}H_{15}NO_5$ requires C, 60·65; H, 5·45; N, 5·05%), $\nu_{max.}$ (Nujol) 1770 and 1710 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 210, 265, 285, and 404 nm. (ε 11,100, 15,800, 16,800, and 5250), τ 1·75—3·40 (4H, m, 5-, 6-, 7-, and 8-protons of indolizine ring), 5·69 (2H, q, J 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$), 7·90 (3H, s, OAc), 8·33 (3H, s, Me), and 8·64 (3H, q, J 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$), M^+ 277.

Methyl 2,3-Dihydro-3-hydroxy-2-oxo-3-phenylindolizine-1-carboxylate.—Methyl 2-hydroxy-3-phenylindolizine-1-carboxylate was oxidised with potassium ferricyanide as described for the 3-methyl analogue to form the *hydroxyketone*, m.p. 208—210° (decomp.) [yellow cubes from light petroleum (b.p. 60—80°)–ethyl acetate or acetone] (Found: C, 65·6; H, 4·65; N, 4·65. $C_{16}H_{13}NO_4$,$0·5H_2O$ requires C, 65·75; H, 4·8; N, 4·8%), $\nu_{max.}$ (Nujol) 3250, 1690, 1645, and 1620 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 206, 283, and 404 nm. (ε 17,900, 17,400, and 4450), M^+ 283.

The *acetate* had m.p. 260—263° (decomp.) (from ethanol) (Found: C, 66·2; H, 4·7; N, 4·3. $C_{18}H_{15}NO_5$ requires C, 66·45; H, 4·65; N, 4·3%), $\nu_{max.}$ (Nujol) 1775, 1695, 1675, and 1630 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 206, 279, and 412 nm. (ε 18,300, 17,600, and 4800), M^+ 325.

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