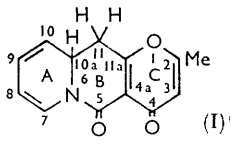
604. *Keten. Part I. The Reaction of Pyridine and Keten*

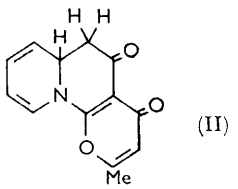
By G. A. Taylor

The product of the reaction of pyridine and keten has been shown to be 10a,11-dihydro-2-methylpyrano[2,3-*b*]quinolizine-4,5-dione (I). This has been degraded to 3-butylquinolizidine, which has been synthesised by an unambiguous route.

An investigation by Berson and Jones [1] of the product (Wollenberg's compound) of the reaction of pyridine and keten [2] resulted in the suggestion of alternative structures (I) and (II) for the compound. Similar products have been obtained from the reaction of quinoline and keten or diketen,[3] and here too no distinction could be made between the alternative structures corresponding to (I) and (II). Further investigation of Wollenberg's compound confirms the earlier conclusions,[1] and establishes the correct structure as 10a,11-dihydro-2-methylpyrano[2,3-*b*]quinolizine-4,5-dione (I).



(I)



(II)

The reaction of pyridine and keten, performed in the conditions previously described,[1] gave three products: one was identified as Wollenberg's compound, $C_{13}H_{11}NO_3$; dehydroacetic acid was isolated from the reaction mixture; and a third, orange substance, $C_{32}H_{26}N_2O_7$, which slowly crystallised out of the reaction residues, was obtained only in very small yield, and has not so far been investigated.

Oxidation of Wollenberg's compound with peracetic acid gave picolinic acid *N*-oxide, confirming the attachment of a carbon atom to position 2 of the pyridine ring. Previously, this conclusion was based [1] on the production of 2-picoline by distillation with zinc dust, during which migration of substituents from nitrogen to carbon may have occurred; [4] the mild conditions of the oxidation obviate this possibility.

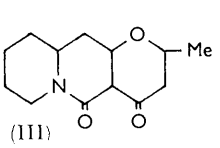
Catalytic reduction of Wollenberg's compound has been reported by both Wollenberg [2] and Berson.[1] Wollenberg isolated dihydro- and tetrahydro-derivatives, and also obtained a perhydro-derivative thought to be a hexahydro-compound. The first of these was

[1] J. A. Berson and W. M. Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 1625.
[2] O. Wollenberg, *Ber.*, 1934, **67**, 1675.
[3] T. Kato, T. Kitakawa, and Y. Yamamoto, *J. Pharm. Soc. Japan*, 1963, **83**, 267.
[4] O. Lange, *Ber.*, 1885, **18**, 3436.

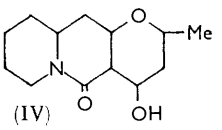
obtained by Berson, but neither of the other compounds has since been investigated. It appeared that a distinction between structures (I) and (II) might easily be made by examination of the perhydro-derivative, which should be an amide if derived from the structure (I). In addition, the whole carbon skeleton of the molecule could be confirmed by conversion of the perhydro-derivative into 3-butylquinolizidine.

Hydrogenation of Wollenberg's compound with a palladium catalyst resulted in the absorption of four moles of hydrogen. The product, whose analysis indicated an octahydro-derivative, showed infrared absorption at **1727** and **1639** cm.$^{-1}$, corresponding to the carbonyl absorption of ketone and amide groups, respectively. The octahydro-derivative gave a deep red colour with ferric chloride, suggesting a β-oxo-amide system, consistent with a weak infrared absorption at **3400** cm.$^{-1}$ attributed to a low concentration of the enol. These observations are compatible only with structure (I), which would give rise to an octahydro-derivative (III).

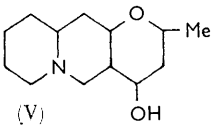
Catalytic hydrogenation of Wollenberg's compound or compound (III) with a nickel catalyst gave a decahydro-derivative (IV), which was reduced by lithium aluminium hydride to a strongly basic substance (V). Treatment of compound (V) with hydrogen bromide in acetic acid, followed by reduction of the crude product gave a small yield of a basic oil, which was identified as 3-butylquinolizidine (VI) by comparison with an authentic specimen.



(III)



(IV)



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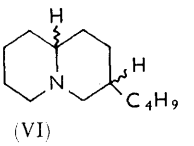
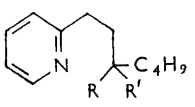
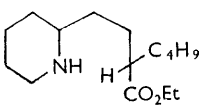


(VI)

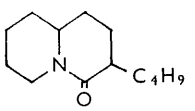
The synthesis of 3-butylquinolizidine was achieved by a route similar to that of Doering[5] and of Boeckelheide.[6] Sodium diethyl butylmalonate was added to 2-vinylpyridine, and the product (VII; R = R′ = CO_2Et) was converted into ethyl 2-[2-(2-pyridyl)ethyl]hexanoate (VII; R = H, R′ = CO_2Et) by standard methods. Hydrogenation of the monoester gave the corresponding piperidine (VIII), which was converted into the cyclic amide (IX). Reduction of the amide with lithium aluminium hydride gave 3-butylquinolizidine (VI).



(VII)



(VIII)



(IX)

The samples of 3-butylquinolizidine from Wollenberg's compound and from 2-vinylpyridine were compared by gas chromatography on Apizeon grease. The specimen synthesised from 2-vinylpyridine showed two equal peaks in the chromatogram, which presumably correspond to the racemic mixtures arising from the asymmetric centres at positions 3 and 10. Though the corresponding decalin would be expected to show four such peaks, it is probable that, with the quinolizidine, inversion at the bridgehead nitrogen occurs so readily under the chromatographic conditions, that isomerism from this source would not be observed. Gas chromatography of the amine from Wollenberg's compound showed two components of identical behaviour to those of the synthetic material, but in the proportion **3 : 1**, with the slower-moving component predominating. A mixture of the two samples of 3-butylquinolizidine was not resolved over a 50° range of temperature, and it was concluded that the compounds were chemically identical. This was subsequently

[5] W. E. Doering and R. A. N. Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2461.
[6] V. Boeckelheide and S. Rothchild, *J. Amer. Chem. Soc.*, 1949, **71**, 879.

confirmed by a mixed-melting-point determination on the picrolonate. Gas chromatography of a sample of the base recovered from an analytically pure specimen of the picrolonate showed only one peak, which corresponded to the faster-moving component in the original mixture.

The nuclear magnetic resonance spectrum of Wollenberg's compound confirms the arrangement of hydrogen atoms shown in (I). Singlets at τ 7·72 (3 protons) and 3·85 (1 proton) correspond to those observed in the spectrum of 2,6-dimethyl-4-pyrone,[7] and are assigned to the methyl group and hydrogen atom of ring C. A set of peaks at τ 7·21 (quartet, 1 proton), 6·70 (quartet, 1 proton), and 5·17 (multiplet, 1 proton) form an ABX system assigned to the 10a- and 11-protons. Multiplets corresponding to the protons of ring A occur at τ 4·5—4·9 (2 protons), 4·03 (1 proton), and 2·77 (1 proton). No other arrangement of hydrogen atoms on the carbon skeleton is consistent with this spectrum.

Experimental

10a,11-*Dihydro-2-methylpyrano*[2,3-b]*quinolizine-4,5-dione* (I).—This was obtained by the method previously described.[1] The crude product was washed with benzene and ether, and recrystallised from ethanol (22 ml. per g.) avoiding prolonged boiling of the solution. When the latter was cooled, the dione was obtained as yellow needles, m. p. 205—209° (decomp.) (Found: C, 67·9; H, 4·7. Calc. for $C_{13}H_{11}NO_3$: C, 68·1; H, 4·8%).

The benzene washings and the reaction residues were combined and set aside, when an orange precipitate slowly formed. This was collected, washed with hot ethanol, and extracted with chloroform in a Soxhlet apparatus. Microscopic orange prisms crystallised from the boiling solution, and were collected. This compound chars, without melting, between 300 and 330° (Found: C, 69·4, 69·7; H, 4·6, 4·7; N, 5·1, 5·2. Calc. for $C_{32}H_{26}N_2O_7$: C, 69·8; H, 4·7; N, 5·1%).

Oxidation of Compound (I) *with Peracetic Acid.*—A mixture of compound (I) (2 g.), acetic acid (75 ml.), and hydrogen peroxide (50 ml.; 30%) was heated at 100° for 18 hr., and evaporated to dryness. The oily residue crystallised on being shaken with water and, after recrystallisation from water, gave colourless needles (0·2 g. 16%), m. p. 161—163° (decomp.), undepressed on admixture with an authentic specimen of picolinic acid *N*-oxide.

Perhydro-2-methylpyrano[2,3-b]*quinolizine-4,5-dione* (III).—A solution of compound (I) in ethanol was hydrogenated with hydrogen (1 atm.) and a palladium–charcoal catalyst until absorption ceased (36 hr.). The solution was filtered and evaporated, leaving the *perhydro-dione* as a colourless oil, b. p. 142—144°/0·005 mm. (Found: C, 66·2; H, 8·3; N, 5·8. $C_{13}H_{19}NO_3$ requires C, 65·8; H, 8·0; N, 5·9%) $\nu_{max.}$ 3400, 1727, 1639 cm.$^{-1}$.

An identical product was obtained by hydrogenation of compound (I) with a platinum oxide catalyst under conditions similar to those described above.

Perhydro-4-hydroxy-2-methylpyrano[2,3-b]*quinolizin-5-one* (IV).—A solution of compound (I) (1 g.) in ethanol (100 ml.) was shaken with Raney nickel and hydrogen (1 atm.) until absorption of hydrogen ceased. (Vol. absorbed = 570 ml. Calc. for $5H_2$: 530 ml.). Filtration and evaporation of the solution left the *perhydroquinolizinone* as a syrupy liquid, which could not be purified further (Found: N, 6·0. $C_{13}H_{21}NO_3$ requires N, 5·9%) $\nu_{max.}$ (liquid film) 3397, 1612 cm.$^{-1}$.

Hydrogenation of compound (III) under similar conditions gave a product with an infrared spectrum identical to that of the compound previously described.

Perhydro-4-hydroxy-2-methylpyrano[2,3-b]*quinolizine* (V).—A solution of compound (IV) (10 g.) in tetrahydrofuran (200 ml.) was boiled under reflux with lithium aluminium hydride (4·3 g.) for 4 hr. Excess of lithium hydride was decomposed in the usual way, and the solution was filtered and evaporated. The residual brown oil was distilled under reduced pressure, when the *perhydroquinolizine* distilled as a colourless oil, b. p. 120°/0·02 mm., which was slowly oxidised to a red gum on exposure to air (Found: C, 69·7; H, 9·9. $C_{13}H_{23}NO_2$ requires C, 69·3; H, 10·2%).

3-*Butylquinolizidine* (VI).—A mixture of compound (V) (2·1 g.) and hydrogen bromide in glacial acetic acid (25 ml.; 50% HBr) was heated at 100° in a sealed tube for 18 hr. The product was evaporated under reduced pressure, leaving an oily brown residue, which was

[7] P. Beak and G. A. Carls, *J. Org. Chem.*, 1964, **29**, 2680.

dried *in vacuo* to constant weight (4·55 g.). The residue was extracted with tetrahydrofuran (100 ml.) and the extract added to a solution of lithium aluminium hydride (7 g.) in tetrahydrofuran (100 ml.). The mixture was boiled for 12 hr., after which excess of lithium aluminium hydride was decomposed, and the solution filtered. Evaporation of the filtrate left a small volume of brown oil, which on distillation gave 3-butylquinolizidine as the fraction boiling at 240—260° (2 ml.). Gas chromatography showed this to be identical with authentic 3-butylquinolizidine. The picrolonate was prepared by heating the base (0·3 ml.) and picrolonic acid (0·45 g.) in ethanol (20 ml.). After several recrystallisations from ethanol, 3-butylquinolizidinium picrolonate was obtained as yellow needles, m. p. 191—192° (decomp.), undepressed on admixture with an authentic specimen.

Diethyl Butyl-2-(2-pyridyl)ethylmalonate (VII; R = R′ = CO_2Et).—Sodium (12 g.) was dissolved in dry ethanol (250 ml.) and diethyl butylmalonate (120 g.) was added, followed by 2-vinylpyridine (50 g.). The mixture was boiled under reflux for 7 hr., acidified with hydrochloric acid, and extracted with ether, the extract being discarded. The aqueous layer was made alkaline and extracted with ether, and the extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was distilled under reduced pressure, the fraction b. p. 194—198°/10 mm. being collected. This fraction was redistilled, giving the diester as a colourless oil, b. p. 150°/0·05 mm. The *picrate* crystallised from ethanol as yellow prisms, m. p. 102° (Found: C, 52·1; H, 5·4; N, 10·3. $C_{18}H_{27}NO_4,C_6H_3N_3O_7$ requires C, 52·4; H, 5·5; N, 10·2%).

Ethyl 2-[2-(2-Pyridyl)ethyl]hexanoate (VII; R = H, R′ = CO_2Et).—A mixture of the foregoing diester (100 g.), sodium hydroxide (40 g.), water (150 ml.), and ethanol (100 ml.) was heated at 100° for 12 hr. The mixture was cooled, acidified with phosphoric acid to pH 5, and extracted with chloroform (3 × 50 ml.). The extract was washed with water, dried (Na_2SO_4), and the chloroform evaporated off, leaving a crystalline residue; a sample of this recrystallised from ethanol gave *butyl-2-(2-pyridyl)ethylmalonic acid* (VII; R = R′ = CO_2H) as colourless prisms, m. p. 137° (decomp.) (Found: C, 63·4; H, 6·9; N, 5·3. $C_{14}H_{19}NO_4$ requires C, 63·4; H, 7·2; N, 5·3%). The remainder of the crude product was heated under reduced pressure at 140° until evolution of gas ceased, leaving an oily residue of 2-[2-(2-pyridyl)ethyl]hexanoic acid (VII; R = CO_2H, R′ = H) (59 g., 86%). Esterification with ethanol and sulphuric acid by standard procedures gave the required *ester* as a colourless liquid, b. p. 169°/11 mm. (Found: N, 6·1. $C_{15}H_{23}NO_2$ requires N, 5·6%). The *picrolonate* crystallised from ethanol as yellow needles, m. p. 111° (decomp.) (Found: C, 58·4; H, 6·3; N, 13·7. $C_{15}H_{23}NO_2,C_{10}H_8N_4O_5$ requires C, 58·5; H, 6·0; N, 13·6%).

3-Butylquinolizidin-4-one (IX).—A solution of the foregoing ester (25 g.) in ethanol (300 ml.) and hydrogen chloride (20 g.) was shaken with platinum oxide and hydrogen (1 atm.) until absorption of hydrogen ceased. The solution was filtered on to solid sodium hydrogen carbonate and stirred until neutral. Filtration and evaporation of the neutralised filtrate left crude piperidine (VIII) as a colourless oily liquid. A mixture of this ester (10 g.), ethanol (100 ml.), and sodium methoxide (from 3·2 g. sodium) was boiled under reflux for several hours. The mixture was evaporated and the residue shaken with ether and dilute hydrochloric acid. The ethereal layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residual colourless oil was distilled under reduced pressure, giving *3-butylquinolizidin-4-one* b. p. 176°/14 mm. (7·5 g., 91%) (Found: C, 74·3; H, 11·1; N, 6·8. $C_{13}H_{23}NO$ requires C, 74·6; H, 11·0; N, 6·7%) $\nu_{max.}$ (liquid film) 1645 $cm.^{-1}$.

3-Butylquinolizidine (VI).—3-Butylquinolizidin-4-one (5·1 g.) was added to a solution of lithium aluminium hydride (2·5 g.) in ether (150 ml.) and the mixture was boiled under reflux overnight. Excess of lithium aluminium hydride was decomposed, and the solution was filtered and evaporated. The residual oil was distilled, when 3-butylquinolizidine was obtained as a colourless oil, b. p. 245° (4·5 g., 94%).

The *picrolonate* recrystallised from ethanol as yellow needles, m. p. 195—197° (decomp.) (Found: C, 60·2; H, 7·3; N, 15·5. $C_{13}H_{25}N,C_{10}H_8N_4O_5$ requires C, 60·1; H, 7·2; N, 15·3%).

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