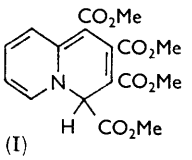
353. *Addition Reactions of Heterocyclic Compounds. Part XIII.* Hydrolysis of Tetramethyl* 4H-*Quinolizine*-1,2,3,4-*tetracarboxylate by Hydrochloric Acid.*

By R. M. Acheson, J. M. F. Gagan, and (in part) G. A. Taylor.

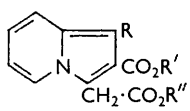
Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate with aqueous hydrochloric acid gave the monomethyl ester of 1,2-dicarboxyindolizin-3-ylacetic acid and 2-carboxy-1,4-dihydroquinolizinium chloride, which isomerised with alkali to the 3,4-dihydro-isomer. The structures of the quinolizines were derived from their ultraviolet and nuclear magnetic resonance spectra and their reduction to the same quinolizidinecarboxylic acid and its conversion into 2-hydroxymethylquinolizidine.

Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (I) is converted by formic acid, phenol, or potassium hydroxide into indolizines,[1] but in contrast hydrolysis with aqueous hydrochloric acid gives the chloride of a monocarboxylic acid [2] whose ultraviolet absorption spectrum [3] precludes the presence of an indolizine nucleus. Diels *et al.*[4] oxidised this chloride to picolinic acid and hydrogenation gave an octahydro-derivative,[2] indicating a bicyclic structure. The methyl ester of this octahydro-derivative formed a methiodide,[4] showing the presence of a tertiary nitrogen atom, and was reduced by sodium and ethanol to an alcohol [4] which differed from the two 1-hydroxymethylquinolizidines known at the time.

A re-examination of the hydrochloric acid hydrolysis showed that as well as the chloride (IV) some 1,2-dicarboxyindolizin-3-ylacetic acid monomethyl ester (II) was also formed. This monomethyl ester, when further refluxed with hydrochloric acid, lost the 1-carboxyl group, as it does in hot phenanthrene; [4] since the indolizinedicarboxylic acid (III) is stable in these conditions [3] the formation of the chloride (IV) through the intermediary of an indolizine is unlikely. The suggestion [1, 3] that the acid might be 3-methylindolizine-1,2-dicarboxylic acid has proved incompatible with its infrared absorption spectrum which shows a strong maximum at 8·31 μ, characteristic of the $CH_2 \cdot CO_2H$ group,[5] and with its nuclear magnetic resonance spectrum.[6]

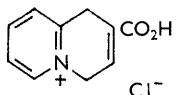


(I)

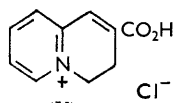


(II: R = CO_2H, R′, R″ = H, Me)

(III: R = R′ = R″ = H)



(IV)



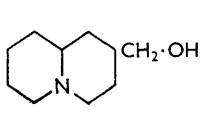
(V)

The ultraviolet absorption spectrum of the chloride (IV) was unchanged by acid but was instantly and irreversibly altered by sodium hydroxide or carbonate. All attempts to separate the organic product at various pH's from the inorganic salts failed. However, the spectral change was slowly but completely effected by repeatedly passing the aqueous chloride down a column of the hydroxide form of a cation-exchange resin, and subsequent addition of hydrochloric acid gave an isomer (V) of the original chloride. Both of these chlorides absorbed 4 mol. of hydrogen over Adams catalyst, giving the same octahydro-derivative, which was converted into an isomeric compound in boiling water. The reverse

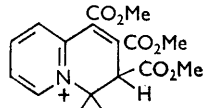
* Part XII, *J.*, 1963, 1008.

[1] Acheson and Taylor, *J.*, 1960, 4600.
[2] Diels, Alder, Kashimoto, Friedrichsen, Eckardt, and Klare, *Annalen*, 1932, **498**, 16.
[3] G. A. Taylor, D. Phil. Thesis, Oxford University, 1959.
[4] Diels, Alder, Friedrichsen, Klare, Winkler, and Schrum, *Annalen*, 1933, **505**, 103.
[5] Shimanouchi, Tsuboi, Takenishi, and Iwata, *Spectrochim. Acta*, 1960, **16**, 1328.
[6] Crabtree, Johnson, and Tebby, *J.*, 1961, 3497.

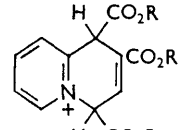
conversion was brought about by boiling acetic acid and the two reduced derivatives are possibly isomers involving the stereochemistry of the ring junction.[7] The octahydro-derivative on potentiometric titration against barium hydroxide gave [3] a curve very similar to that obtained with glycine hydrochloride, and with diazomethane gave an ester which was presumably the same as that obtained earlier [4] with methanol and hydrogen chloride. Reduction of this ester by lithium aluminium hydride yielded a compound which had the same properties [8] as 2-hydroxymethylquinolizidine (VI) and differed from all the other hydroxymethylquinolizidines.[9] The presence of a quinolizine ring in the chloride (IV) was confirmed as oxidation with *N*-bromosuccinimide gave 2-carboxyquinolizinium bromide which possessed an ultraviolet absorption spectrum very similar to that of quinolizinium iodide; [10] the isomeric chloride (V) was not oxidised under these conditions.



(VI)



(VII)



(R = H or Me) (VIII)

The ultraviolet absorption spectra of the chloride (IV) and its isomer (V) are very similar to those of the 2-hydroxy-1,2,3,4-tetrahydro- and -3,4-dihydro-quinolizinium cations, respectively [10] (cf. structure VIII; other analogies are also available [1]), which suggests that the chlorides are respectively pyridinium and 2-vinylpyridinium derivatives. A clear differentiation between pyridinium ($\lambda_{max.}$ 2580 Å; ε 4580) and 1-vinylpyridinium ($\lambda_{max.}$ 2580; ε 8380) [11] structures is not possible although the extinction coefficient (ε 4600) of the chloride (IV) indicates that it is probably of the former type. Diels *et al.*[4] oxidised the chloride (IV) with alkaline permanganate, conditions which would have caused initial conversion into the isomer (V), and obtained picolinic acid. This shows that the carboxyl-containing ring of the chloride (V) is degraded and presumably contains the vinyl group. The conclusion, that the chloride obtained on hydrolysis and its isomer have structures (IV) and (V), respectively, is in agreement with the nuclear magnetic resonance spectra of the compounds which were kindly measured by Mr. J. Kenworthy in trifluoroacetic acid at 29·91 Mc/sec. with cyclohexane as an internal standard. The first chloride (IV) showed a complex band centred on about 1·6 τ (4 aromatic protons), a singlet showing signs of splitting into a triplet at 2·4 τ (1 olefinic proton) and singlets (each 2 protons) at 4·2 τ (probably position 4) and at 5·5 τ corresponding to the two methylene groups. The isomeric chloride (V) possessed a complex band at 0·8—1·8 τ (5 aromatic and olefinic protons) and two triplets, each corresponding to two protons centred on 4·8 τ (probably position 4) and 6·5 τ. The τ values are all about 0·5 unit lower than those of similar groups in uncharged molecules and the results exclude all alternative double-bond isomers for (IV) and (V) based on the quinolizine system.

The protonation of tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate takes place largely at position 3, yielding the cation (VII), and it is therefore surprising that the chloride (IV) should be formed on decomposition with acid. If hydrolysis of the 3-ester group occurs, then loss of carbon dioxide is understandable as the product is a vinylogue of the readily decarboxylated 2-pyridylacetic acid.[12] Strain involving the 2- and 4-acid or ester groups now being relieved, the substituent at position 1 becomes the most hindered in the molecule. If therefore a proton moves to this position, giving the less

[7] Cf. Moynehan, Schofield, Jones, and Katritzky, *J.*, 1962, 2637.
[8] Leonard, Conrow, and Fulmer, *J. Org. Chem.*, 1957, **22**, 1445.
[9] Clemo, Morgan, and Raper, *J.*, 1937, 965; Lewis and Shoppee, *J.*, 1956, 313; Boekelheide, Linn, O'Grady, and Lamborg, *J. Amer. Chem. Soc.*, 1953, **75**, 3243; Ratuský, Reiser, and Šorm, *Coll. Czech. Chem. Comm.*, 1955, **20**, 798; Winterfeld and Müller, *Annalen*, 1953, **581**, 77.
[10] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832; see ref. 1 for other analogies.
[11] Duling and Price, *J. Amer. Chem. Soc.*, 1962, **84**, 578.
[12] Oparina, *per. Chem. Ztbl.*, 1935, **1**, 2536.

hindered cation (VIII), either during or subsequent to this decarboxylation, the formation of the acid (IV) can be understood. As this acid is stable to acids and gives an isomeric quinolizine with alkali, it appears that the formation of indolizines and quinolizines in the hydrolysis of the ester (I) proceed by separate paths.

Experimental

Infrared absorption spectra were measured in paraffin paste (P) or in chloroform (C); additional peaks occur outside the ranges given; ultraviolet absorption spectra are for methanol solutions, $10^{-4}\varepsilon$ being given in parentheses. Inflexions are marked with asterisks.

Tetramethyl 4H-*Quinolizine*-1,2,3,4-*tetracarboxylate* (I).—Freshly redistilled pyridine (40 g.) in dry ether (10 ml.) was added slowly with shaking to dimethyl acetylenedicarboxylate (100 g.) in dry ether (500 ml.) which had been cooled to 0° and the whole allowed to warm to room temperature overnight. The ether was decanted and the residual tar washed with ether and triturated with methanol (100 ml.). The solid, which was formed overnight, crystallised from 1 : 3 v/v nitroethane–methanol, yielding the quinolizine (45 g.) as yellow plates, m. p. 188°. Evaporation of the combined ether and methanol mother-liquors gave a tar which on treatment with methanol and crystallisation as above yielded further quinolizine (18 g.). Repeating this process with the mother-liquors gave a mixture of crystals from which Kashimoto's compound [1, 2] (pale yellow prisms with a purple sheen; m. p. 184°) were separated by hand-picking.

Tetramethyl 4H-*Quinolizine*-1,2,3,4-*tetracarboxylate with Hydrochloric Acid.*—(i) The quinolizine (20 g.) dissolved completely when refluxed with 2N-aqueous hydrochloric acid (130 ml.) for 1 hr. and much carbon dioxide was evolved. On cooling overnight a brown solid deposited and this, combined with another crop obtained by concentrating the filtrate, crystallised from methanol containing 15% of water; this yielded the monomethyl ester (II) of 1,2-dicarboxyindolizin-3-ylacetic acid (1·7 g.) as needles, m. p. 236°, alone or mixed with an authentic specimen (Found: C, 55·6; H, 4·0; N, 5·0. Calc. for $C_{13}H_{11}NO_6$: C, 56·3; H, 4·0; N, 5·05%); the infrared absorption spectra (P) of the specimens were identical. It gave the triester, m. p. and mixed m. p. 68°, with two mol. of diazomethane.

The above monomethyl ester (0·4 g.) was refluxed for 90 min. in 2N-hydrochloric acid, and, after cooling, unchanged ester (0·3 g.) crystallised. The filtrate was evaporated to dryness; the residual solid (70 mg.), on crystallisation from methanol, gave the monomethyl ester of 2-carboxyindolizin-3-ylacetic acid as prisms, m. p. 200° (decomp.) (Found: C, 62·2; H, 4·6; OMe, 12·6. Calc. for $C_{12}H_{11}NO_4$: C, 62·3; H, 4·8; OMe, 13·3%) [lit.,[4] m. p. 201—202° (decomp.)].

(ii) The quinolizine (I) (20 g.) was refluxed with 2N-hydrochloric acid (100 ml.) for 2 hr. and the cooled mixture extracted with chloroform (2 × 50 ml.); evaporation of the extract gave the indolizine monoester described under (i). The aqueous solution was evaporated to dryness *in vacuo* and the brown residue (8 g.) left overnight *in vacuo* over potassium hydroxide. Crystallisation (charcoal) from methanol containing 5% of water gave pale yellow 2-*carboxy*-1,4-*dihydroquinolizinium chloride* (IV), m. p. 222° (sealed tube) (Found: C, 56·6; H, 4·7; Cl, 17·1; N, 6·8. $C_{10}H_{10}ClNO_2$ requires C, 56·7; H, 4·7; Cl, 16·8; N, 6·6%), $\lambda_{max.}$ 2670 Å (0·46), $\nu_{max.}$ (P) 3·71, 3·96, 4·08, 5·55, 5·83, 5·91, 6·11, 6·28, 6·56, and 7·08 μ.

The chloride with hot methanolic picric acid gave the corresponding *picrate*,[3] yellow needles, m. p. 175—178° (Found: C, 47·9; H, 3·3; N, 13·6. $C_{16}H_{12}N_4O_9$ requires C, 47·5; H, 3·0; N, 13·8%). The *chloroplatinate*,[3] orange needles from water, darkened at 170° and had m. p. 185—188° (decomp.) [Found: Residue on ignition, 25·2. $(C_{10}H_9NO_2)_2,H_2PtCl_6$ requires Pt, 25·6%]. The *aurichloride*,[3] yellow needles from water, darkened at 160° and had m. p. 228—229° (decomp.) (Found: Residue, 39·1. $C_{10}H_9NO_2,HAuCl_4$ requires Au, 38·3%).

2-*Carboxyquinolizinium Bromide.*—2-Carboxy-1,4-dihydroquinolizinium chloride (IV) (1·2 g.) in dioxan (40 ml.) and water (5 ml.) was shaken with *N*-bromosuccinimide (1·8 g.) for 1 hr. at room temperature and subsequently refluxed for ½ hr. After cooling, 2-*carboxyquinolizinium bromide* (1 g.) separated; it crystallised from ethanol containing a trace of hydrobromic acid in pale cream needles, m. p. 307° (decomp.) (Found: C, 47·7; H, 3·3; N, 5·5. $C_{10}H_8BrNO_2$ requires C, 47·3; H, 3·2; N, 5·5%), $\lambda_{max.}$ 2690* (0·32), 2800* (0·29), 2940* (0·24), 3280 (1·08), and 3390 Å (1·52).

2-*Carboxy*-3,4-*dihydroquinolizinium Chloride* (V).—2-Carboxy-1,4-dihydroquinolizinium

chloride (0·5 g.) in water (50 ml.) was poured 35 times through a column of finely ground anion-exchange resin (5 g. of Amberlite IRA-400, HO^- form). The solution became yellow and the absorption at 2670 Å characteristic of the 1,4-dihydro-compound vanished. The solution was combined with aqueous washings (1 l.) of the column and evaporated to dryness; the residual gum (>0·45 g.) solidified in a vacuum-desiccator. After dissolution in 2N-hydrochloric acid and evaporation to dryness the resulting solid crystallised from methanol containing hydrochloric acid, and then from ethanol, yielding pale yellow 2-*carboxy*-3,4-*dihydroquinolizinium chloride* (V), m. p. 218° (sealed tube) (Found: C, 56·7; H, 4·7; Cl, 16·0; N, 6·5. $C_{10}H_{10}ClNO_2$ requires C, 56·7; H, 4·7; Cl, 16·8; N, 6·6%), $\nu_{max.}$ (P) 3·70, 4·15, 5·51, 5·90, 6·04, 6·17, 6·31, 6·58, 6·81, 6·88, and 7·05 μ, $\lambda_{max.}$ 2525 (0·73) and 3135 Å (1·20), and, basified, 2150 (0·86) and 3205 Å (1·18). The *picrate* separated from methanol in thick yellow needles, m. p. 190° (Found: C, 47·9; H, 3·15; N, 14·0. $C_{16}H_{12}N_4O_9$ requires C, 47·5; H, 3·0; N, 13·8%).

Quinolizidine-2-carboxylic Acid Hydrochloride.—2-Carboxydihydroquinolizinium chloride (0·5 g.) in (i) acetic acid (100 ml.) with platinic oxide (40 mg.) or (ii) water (100 ml.) with platinic oxide (40 mg.) or 10% palladium–charcoal was hydrogenated for 12 hr. at room temperature and 4 atm.; then the solution was filtered and evaporated, and the residue crystallised from ethanol. 1,4- and 3,4-Dihydro-2-carboxyquinolizine chloride gave the same product on the same treatment and it was separately shown that the 1,4-dihydro-compound was not isomerised under the hydrogenation conditions. From (i), *quinolizidine-2-carboxylic acid hydrochloride* A was obtained as prisms, m. p. 252° (Found: C, 54·7; H, 8·4; Cl, 16·1; N, 6·4. $C_{10}H_{18}ClNO_2$ requires C, 54·6; H, 8·2; Cl, 16·2; N, 6·4%), $\nu_{max.}$ (P) 3·78, 3·88, 5·81, 6·90, 7·01, 7·30, 7·43, 7·63*, 7·76, 7·88, 7·93, 8·13, 8·24, 8·43, 8·55, 8·72, 8·88, 9·19, 9·29, 9·49, 9·68, 9·86, 10·08, 10·52, 10·70, 10·94, 11·48, and 11·93 μ. From (ii), an *isomer B* was obtained as prisms, m. p. 248° (Found: C, 54·5; H, 8·3; N, 6·4%), $\nu_{max.}$ (P) 3·74, 3·86, 5·78, 6·86, 6·99, 7·10*, 7·28, 7·66, 7·86, 7·92, 8·04, 8·27, 8·45, 8·56, 8·70, 8·86, 9·17, 9·26, 9·41, 9·68, 9·78, 10·08, 10·39, 10·68, 10·84, 11·66, and 11·92 μ. Hydrochlorides A and B crystallised unchanged from ethanol when seeded with each other, but were interconverted in boiling water and acetic acid, respectively (Diels *et al.*[2] give m. p. 249—250°, but no specific structure). With aqueous sodium picrate they gave the same picrate, m. p. 184°.

2-*Hydroxymethylquinolizidine.*—Quinolizidine-2-carboxylic acid hydrochloride A (0·7 g.), dissolved in the minimum of methanol, was treated dropwise with diazomethane in ether until the yellow colour persisted. After 1 min. the excess was destroyed by 1 drop of acetic acid, and distillation gave methyl quinolizidine-2-carboxylate (0·6 g.), b. p. 160—165°/18 mm., n_D^{20} 1·4778, which gave a hydroxamic acid test (lit.,[4] b. p. 135—136°/20 mm.).

This ester (0·6 g.) in dry ether (100 ml.) was added dropwise to stirred lithium aluminium hydride (0·2 g.) in ether (200 ml.) in 45 min., and the mixture was then refluxed and stirred for 4 hr. A little ethyl acetate was next added, and followed by 2N-hydrochloric acid (100 ml.). The aqueous layer was combined with water-washings (2 × 100 ml.) of the ether solution, strongly basified with aqueous sodium hydroxide, and extracted with ether (5 × 100 ml.). Evaporation of the dried ($MgSO_4$) extract gave 2-hydroxymethylquinolizidine (0·42 g.) which separated from light petroleum (b. p. 40—60°) in prisms, m. p. 76° (Found: C, 71·3; H, 11·1; N, 8·4. Calc. for $C_{10}H_{19}NO$: C, 71·0; H, 11·3; N, 8·3%) (lit.,[8] m. p. 76°), $\nu_{max.}$ (C) 3·46, 3·52, 3·60, 3·66, and 3·77 μ (lit.,[8] very similar). The picrate separated from methanol in yellow needles, m. p. 144° (lit.,[8] m. p. 144—145°) (Found: C, 48·2; H, 5·7; N, 14·3. Calc. for $C_{16}H_{22}N_4O_8$: C, 48·3; H, 5·3; N, 14·1%).

Diels *et al.*[4] must have obtained 2-hydroxymethylquinolizidine from their reduction of the ester by sodium and alcohol for they report m. p. 75—76° and a correct analysis but they suggest no structure.

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