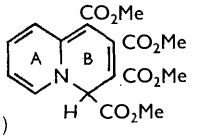
## 890. *Addition Reactions of Heterocyclic Compounds. Part VI.* The Hydrolysis of Tetramethyl* 4H-*Quinolizine*-1,2,3,4-*tetracarboxylate to Indolizines.*

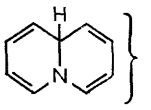
By R. M. Acheson and G. A. Taylor.

The hydrolysis of tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate by formic acid, phenol, or potassium hydroxide is shown to yield indolizines.

Pyridine and methyl acetylenedicarboxylate are known to give trimethyl indolizine-1,2,3-tricarboxylate [1] and tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate.[2] Diels and Alder found that the last compound (I), which at the time was thought to be the isomeric 9a*H*-quinolizine, on reaction with formic acid [3] or phenol [4] gave a trimethyl ester and a dimethyl ester of a tricarboxylic acid, for which structures (II) and (III) were suggested.[5] Further hydrolysis of either compound produced a monomethyl ester (IV), and saponification of any of these compounds (I—IV), with potassium hydroxide gave a dicarboxylic

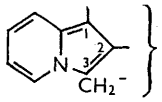



(I)




(II) R = R′ = R″ = $CO_2Me$
(III) R = R′ = $CO_2Me$, R″ = $CO_2H$
(IV) R = $CO_2Me$, R′ = R″ = $CO_2H$
(V) R, R′, R″ = H, $CO_2H$, $CO_2H$
(VI) R, R′, R″ = H, $CO_2Me$, $CO_2H$

acid to which structure (V) was assigned. Partial decarboxylation of the monomethyl ester (IV) produced a monomethyl ester of a dicarboxylic acid [4] which was thought to be (VI). Decarboxylation of the acid (V), followed by hydrogenation, gave a mixture of octahydroindolizine and its 3-methyl derivative,[5] which was earlier thought to have been octahydroquinolizine.[6] When these two reactions on the acid (V) were carried out in the reverse order, only octahydro-3-methylindolizine was obtained.[5] The quinolizine structures for all the hydrolysis products could therefore be questioned and it was of interest to discover at what stage the ring contraction took place.




(VII) R = R′ = R″ = $CO_2Me$
(VIII) R = R′ = $CO_2Me$, R″ = $CO_2H$
(IX) R = $CO_2Me$, R′ = R″ = $CO_2H$
(X) R, R′, R″ = H, $CO_2H$, $CO_2Me$
(XI) R, R′, R″ = H, $CO_2H$, $CO_2H$

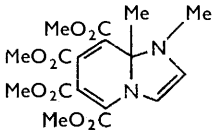
The hydrolysis products were all prepared as described by Diels and his co-workers, and their ultraviolet absorption spectra were measured. All the spectra closely resembled those of trimethyl indolizine-1,2,3-tricarboxylate [1] and other indolizines,[7] and differed markedly from that of the parent (I) and other 4*H*- and 9a*H*-quinolizines.[2] Conversion of the quinolizine into the indolizine system therefore occurs in the initial reaction with formic acid, potassium hydroxide, or phenol. Oxidation of the trimethyl ester with peracetic acid gave picolinic acid *N*-oxide indicating that ring A of the original quinolizine is intact in the indolizine. In view of the degradation of the trimethyl ester to octahydro-3-methylindolizine, this ester must have structure (VII), and the other hydrolysis products structures (VIII)—(XI).

On hydrogenation both the triester (VII) and the diacid (XI) give tetrahydro-derivatives whose ultraviolet absorption is of the pyrrole type, suggesting that the six-membered rings have been reduced.

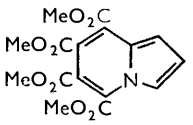
* Part V, *J.*, 1960, 2138.

[1] Wiley and Knabeschuh, *J. Org. Chem.*, 1953, **18**, 836.
[2] Acheson and Taylor, *J.*, 1960, 1691.
[3] Diels and Alder, *Annalen*, 1932, **498**, 16.
[4] Diels and Alder, *Annalen*, 1933, **505**, 103.
[5] Diels and Schrumm, *Annalen*, 1937, **530**, 68.
[6] Diels and Alder, *Annalen*, 1934, **510**, 87.
[7] Boekelheide and Feely, *J. Org. Chem.*, 1957, **22**, 589.

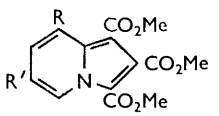
In the dicarboxylic acid (XI) it is likely that one carboxyl group is present at position 2, as indolizine-2-carboxylic acid is obtained by partial decarboxylation of the 1,2,3-tricarboxylic acid. The dicarboxylic acid (XI) gave no acetic acid in the Kuhn–Roth determination but a small amount was given by the tetrahydro-derivative. Although the quantity is much less than that required of one *C*-methyl group it is sufficient to suggest that the acid (XI) may be 3-methylindolizine-1,2-dicarboxylic acid rather than 2-carboxyindolizin-3-ylacetic acid.




(XII)




(XIII)




(XIV)

Diels *et al.*[8] have shown that dimethyl acetylenedicarboxylate and 1,2-dimethylimidazole yield a bright red adduct for which they proposed structure (XII) on the basis of a degradation to 2-methylpyridine. This structure is in agreement with the infrared (5—7 μ region) and ultraviolet absorption of the adduct (see Table). These are similar to those of tetramethyl 9-methyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate and its 7-methyl derivative which possess a similar chromophoric system. The nuclear magnetic resonance of the compound (XII) showed a more complex band in the ester-methyl region than was

*Absorption spectra of the indolizines.*

| Compound | Solvent | $\lambda_{max.}$ (Å) ($10^{-4}\varepsilon$ in parentheses) |
|---|---|---|
| (VII) | M | 3455 (0·81), 3055 (0·85), 2925 (0·61), 2435 (2·63), 2165 (2·18) |
| (VIII) | M | 3700 (0·78), 3515 (1·13), 3365 (0·91), 3090 (0·64), 2970 (0·47), 2480 (2·47), 2250 (1·91) |
| | B | 3460 (0·81), 3375 * (0·78), 3100 (0·88), 2690 (0·79), 2605 (0·85), 2325 (2·97) |
| (IX) † | M | 3425 (0·94), 3095 (0·68), 2300 (2·4) |
| | B | 3445 (0·98), 3120 (0·85), 2690 (0·66), 2605 (0·73), 2325 (2·8) |
| (X) | M | 3465 (0·97), 3140 (0·75), 2700 (0·64), 2625 (0·67), 2300 (2·58) |
| | B | 3465 (0·97), 3130 (0·66), 2700 (0·64), 2625 (0·67), 2265 (2·8) |
| (XI) | W | 3545 (0·24), 3015 (0·27), 2935 * (0·21), 2370 (3·75) |
| | A | 3545 (0·22), 2995 (0·29), 2870 (0·29), 2360 (3·85) |
| (XIV) R = R′ = H | M | 3225 (1·60), 2730 (1·44), 2640 (1·08), 2350 (2·66) |
| (XIV) R = Me, R′ = H | M | 3345 (1·37), 3210 (1·42), 2735 (0·92), 2655 (0·80), 2420 (2·85) |
| (XIV) R = R′ = Me | M | 3370 (1·48), 3240 (1·57), 2745 (0·97), 2645 (0·97), 2455 (3·47) |
| (XII) | M | 4550 (0·50), 2930 (1·55), 2175 (1·1) |
| (XIII) | M | 4155 (0·23), 3155 (0·34), 2730 (3·21), 2450 (1·61) |
| Tetrahydro- (VII) | M | 2680 (0·94) |
| Tetrahydro- (XI) | M | 2640 (1·66) |

* Inflexion. † Impure.
A = aq. NaOH; B = MeOH–NaOH; M = MeOH; W = $H_2O$.

expected, with six resolved peaks of widely differing intensity compatible with eight resonance bands of approximately equal intensity. This complexity may be due to the inversion of the nitrogen atom bearing the methyl group, as steric hindrance between the two adjacent methyl groups will be considerable when they are *cis* with respect to the 5-membered ring and negligible in the *trans*-position. The adduct (XII) is converted very rapidly into the indolizine (XIII) by acid.[8] The structure of the indolizine is consistent with its ultraviolet absorption spectrum and with its nuclear magnetic resonance spectrum which has been discussed earlier.[2]

## Experimental

*Methyl 1,2-Dimethoxycarbonylindolizin-3-ylacetate* (VII) *and its Hydrolysis Products.*—Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (I) was heated with phenol; [4] the product, on

[8] Diels, Alder, Winkler, and Peterson, *Annalen*, 1932, **498**, 1.

crystallisation from ethyl acetate–light petroleum and then aqueous methanol, gave the indolizine ester (VII) as needles, m. p. 68° (Found: C, 58·6; H, 4·9; N, 4·2. Calc. for $C_{15}H_{15}NO_6$: C, 59·0; H, 4·9; N, 4·6%). Heating the same quinolizine (I) with formic acid gave [3] the indolizine dimethyl ester (VIII) as needles (from methanol), m. p. 200° (Found: C, 57·6; H, 4·6; N, 4·8; OMe, 21·5. Calc. for $C_{14}H_{13}NO_6$: C, 57·7; H, 4·5; N, 4·8; 2OMe, 21·3%), and the monomethyl ester (IX), m. p. 236—237°.

Partial decarboxylation of this monomethyl ester (IX) gave another monomethyl ester (X) which separated from aqueous acetic acid in grey needles, m. p. 202—204° (decomp.) (Found: C, 61·7; H, 4·6; N, 6·0; OMe, 13·2. Calc. for $C_{12}H_{11}NO_4$: C, 61·8; H, 4·7; N, 6·0; OMe, 13·3%).

Saponification [3] of the 4*H*-quinolizine (I) with potassium hydroxide gave the indolizinedicarboxylic acid (XI) which separated from ethyl acetate in grey needles, m. p. 218—220° (decomp.) (Found: C, 60·2; H, 4·3; N, 6·6; *C*-Me, 0·0. Calc for $C_{11}H_9NO_4$: C, 60·3; H, 4·1; N, 6·4%).

*Oxidation of the Triester* (VII).—The trimethyl ester (VII) in acetic acid (40 ml.) containing 80% hydrogen peroxide (20 ml.) was heated at 100° for 5 hr. Similar further amounts of acetic acid and hydrogen peroxide were added and the heating was continued for a further 5 hr. Evaporation gave an oil, which with water (5 ml.) crystallised to a colourless solid, m. p. 157—158° alone or mixed with pyridine-2-carboxylic acid *N*-oxide.

*Methyl 5,6,7,8-Tetrahydro-1,2-dimethoxycarbonylindolizin-3-ylacetate*.—Methyl 1,2-dimethoxycarbonylindolizin-3-ylacetate (VII) (2·0 g.) was shaken with Raney nickel under hydrogen at 20°/2 atm. until absorption ceased. Filtration followed by distillation at 0·004 mm. (bath-temp. 135—140°) gave the *tetrahydroindolizine ester* as a wax, m. p. 71° (Found: C, 58·3; H, 6·2; N, 4·6; *C*-Me, 0·0. $C_{15}H_{19}NO_6$ requires C, 58·3; H, 6·2; N, 4·5%).

*Tetrahydro-derivative of the Dicarboxylic Acid* (XI).—The dicarboxylic acid (IX) (1·86 g.) in methanol (51 ml.) was hydrogenated at 110—120°/150 atm. for 5 hr. over palladium–charcoal. No reaction took place under similar conditions with Raney nickel. Filtration and evaporation gave a yellow oil, which was extracted with aqueous sodium hydroxide. After being shaken with ether the aqueous layer was acidified and the precipitate (0·47 g.) collected. Several recrystallisations from nitromethane and then aqueous ethanol, gave the tetrahydro-derivative as colourless needles, m. p. 207—208° (decomp.) (Found: C, 59·2; H, 6·0; N, 6·4; *C*-Me, 0·96, 1·24. Calc. for $C_{11}H_{13}NO_4$: C, 59·2; H, 5·8; N, 6·3; 1*C*-Me 6·7%).

*The 1,2-Dimethylimidazole–Dimethyl Acetylenedicarboxylate Adduct* (XII).—This was prepared as described [8] and separated from methanol in red needles, m. p. 166—167° (decomp.) (Found: C, 53·4; H, 5·3; N, 7·4; OMe, 32·6. Calc. for $C_{17}H_{20}N_2O_8$: C, 53·7; H, 5·3; N, 7·4; OMe, 32·6%), $\nu_{max.}$ (in $CHCl_3$) 5·76 and 6·96 μ.

*Tetramethyl Indolizine-5,6,7,8-tetracarboxylate* (XIII).—Rearrangement of the adduct (XII) in glacial acetic acid [8] gave this ester which separated from aqueous methanol in orange needles, m. p. 140° (Found: C, 55·0; H, 4·2; N, 4·3; OMe, 35·6. Calc. for $C_{16}H_{15}NO_8$: C, 55·0; H, 4·3; N, 4·0; 4OMe, 35·5%).

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