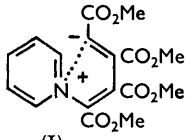
341. *Addition Reactions of Heterocyclic Compounds. Part IV.* Dimethyl Acetylenedicarboxylate and Some Pyridines.†*

By R. M. Acheson and G. A. Taylor.
[With an Appendix by P. Higham and R. E. Richards.]

The structure of the " stable yellow adduct " obtained by Diels and Alder, from pyridine and dimethyl acetylenedicarboxylate has been established as tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate. 3,5-Dimethylpyridine and the acetylenic ester give tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate which tautomerises when heated to the 4*H*-quinolizine. The products from 3-methylpyridine are the corresponding sterically unhindered 7-methyl-4*H*-quinolizine and the hindered 9-methyl-9a*H*- and -4*H*-quinolizine. Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate has been oxidised to quinolizinium salts, and to pyridine-2-carboxylic acid *N*-oxide. Degradation of both this 4*H*-quinolizine and the 9-methyl-9a*H*-quinolizine from 3-methylpyridine afforded pyridine-3,4,5-tricarboxylic acid. The structures of all the quinolizines, and their tetrahydro-derivatives, one of which is a 1,2-dihydropyridine, were deduced from the above data, coupled with a series of ultraviolet absorption spectrum and nuclear magnetic resonance comparisons.

The reaction between pyridine and dimethyl acetylenedicarboxylate was first investigated by Diels and Alder [1,2,3] who obtained isomeric labile (red) and stable (yellow) adducts, and a third material named " Kashimoto's compound " for which they suggested structures (I), (II), and (III) respectively. Structures (I) and (II) were based on the easy isomerisation of the labile (red) compound to the stable (yellow) adduct and on the oxidation of the latter to pyridine-2-carboxylic acid *N*-oxide. The bicyclic structure of (II) was not proved, nor was the significance of the dotted bond in structure (I) defined. Diels and Alder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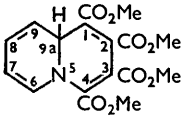
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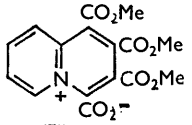
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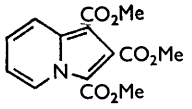

(IV)

subsequently published a number of papers describing the adducts from dimethyl acetylenedicarboxylate and quinoline,[1,3,5] isoquinoline,[5] acridine,[6] and phenanthridine [7] and based the structures of many of these adducts on the pyridine analogy, but the structures of some of the acridine [8] and phenanthridine [9] adducts were later revised.

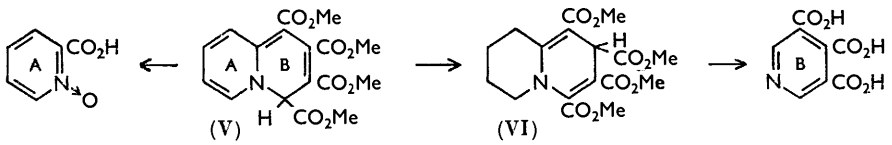
* Part III, Acheson and Jefford, *J.*, 1956, 2676.
† Cf. Acheson and Taylor, *Proc. Chem. Soc.*, 1959, 186.

[1] Diels and Alder, *Annalen*, 1932, **498**, 16.
[2] Diels and Alder, *Annalen*, 1933, **505**, 103.
[3] Diels and Alder, *Annalen*, 1934, **510**, 87.
[4] Diels and Kech, *Annalen*, 1935, **519**, 140.
[5] Diels and Harms, *Annalen*, 1936, **525**, 73.
[6] Diels and Thiele, *Annalen*, 1939, **543**, 79.
[7] Diels and Thiele, *J. prakt. Chem.*, 1940, **156**, 195.
[8] Acheson and Burstall, *J.*, 1954, 3240.
[9] Acheson and Bond, *J.*, 1956, 246.

Wiley and Knabeschuh [10] examined the pyridine reaction under somewhat different conditions and obtained only trimethyl indolizine-1,2,3-tricarboxylate (IV). In view of the interest a compound of structure (II) [or (I); cf. (XI)] would attract, if genuine, and the uncertainty of the structures of most of the compounds obtained by Diels and Alder, further studies seemed necessary.

Pyridine and dimethyl acetylenedicarboxylate combined exothermally in ether, depositing a tar which was then washed with the same solvent. The ether solutions, from which Wiley and Knabeschuh [10] obtained trimethyl indolizine-1,2,3-tricarboxylate in 20% yield, were discarded. The tar crystallised on trituration with methanol, and fractional crystallisation gave only Diels and Alder's stable (yellow) adduct, in 29% yield, with some of " Kashimoto's compound."

The stable pyridine adduct, the correct structure of which is (V), was oxidised by Diels and Alder to pyridine-2-carboxylic acid *N*-oxide. This oxidation, which has been confirmed, shows the presence of ring A. Proof of the formation of ring B has now been obtained. Hydrogenation of the stable adduct (V) to the tetrahydro-derivative (VI) followed by oxidation with nitric acid gave a tribasic acid, $C_8H_5NO_6$. Decarboxylation



then gave pyridine, and as the acid gave no colour [11] with ferrous sulphate it must be pyridine-3,4,5-tricarboxylic acid (derived from ring B), a formulation agreeing with its ultraviolet absorption spectrum and decomposition point. Pyridinepentacarboxylic acid is presumably formed first and subsequently decarboxylated.[12] The positions of the hydrogen atoms in the tetrahydro-derivative (VI) have been located by studies of the nuclear magnetic resonance, and the 1,4-dihydropyridine structure is confirmed by the similarity of the ultraviolet absorption spectrum to that of dimethyl 1,4-dihydro-2,4,6-trimethylpyridine-3,5-dicarboxylate,[13] the structure of which was also established by a nuclear magnetic resonance investigation.[14]

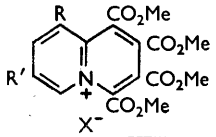
In confirmation of the bicyclic structure full hydrogenation of the stable adduct over Raney nickel gave an oily octahydro-derivative, which is presumably tetramethyl perhydroquinolizine-1,2,3,4-tetracarboxylate. This was basic and did not react with acetic anhydride or form crystalline salts or derivatives. Several attempts to degrade it to perhydroquinolizine by successive hydrolysis and decarboxylation failed.

Oxidation of the stable pyridine adduct by bromine in methanol by Diels's procedure [2] yielded a perbromide (VII; X = Br_3, R = R′ = H). This was converted into the perchlorate (VII; X = ClO_4, R = R′ = H) which was also obtained from the adduct and bromine in perchloric acid. The ultraviolet absorption spectra of these salts were almost identical and closely resembled that of the simple quinolizinium cation [15] in confirmation of both the 1,2,3,4-tetra(methoxycarbonyl)quinolizinium structures suggested earlier [2] and the bicyclic nature of the yellow adduct. Debromination of the perbromide (VII; X = Br_3, R = R′ = H) gave a simple bromide (VII; X = Br) instead of the " dibromide " or " methoxybromide " claimed earlier.[2] It is possible that Diels and Alder's " dinitrate," " hydroxynitrate," " dibromide," and " methoxybromide " are lattice compounds derived from simple salts of the quinolizinium cation (VII). The ultraviolet absorption spectrum of 1,2,3,4-tetra(methoxycarbonyl)quinolizinium perchlorate undergoes a reversible change

[10] Wiley and Knabeschuh, *J. Org. Chem.*, 1953, **18**, 836.
[11] Acheson and Taylor, *J.*, 1959, 4140.
[12] Weber, *Annalen*, 1887, **241**, 16.
[13] Kuss and Karrer, *Helv. Chim. Acta*, 1957, **40**, 740.
[14] Sims, *Proc. Chem. Soc.*, 1958, 282.
[15] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.

on the addition of alkali. The new spectrum is similar to that of the yellow pyridine adduct (V), which suggests that a pseudo-base (VIII) is formed.

Professor R. B. Woodward [16] has independently proved the bicyclic nature of the stable pyridine adduct by quantitative hydrogenation experiments. He has also shown that Kashimoto's compound is (IX) by a number of experiments including degradation to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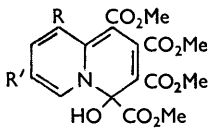
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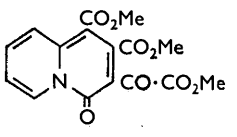
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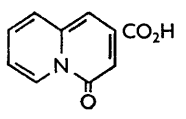

(X)

compounds identical with synthetic 4-oxoquinolizine-2-carboxylic acid (X) and its methyl ester. The infrared and ultraviolet absorption spectra of Kashimoto's compound, which were not reported by Woodward and Kornfeld, support structure (IX), and the ultraviolet absorption resembles that of quinolizin-4-one.[17]

Absorption spectra of the adducts and derivatives.

Compound			Solvent *	Absorption maxima (Å) ($10^{-4}\varepsilon$)			
Stable adducts (XIV)							
R	R′						
H	H		M	4410 (1·11)	3445 (1·11)	3060 (1·57)	2590 (0·98)
			P	3120 (1·21)			
H	Me		M	4450 (1·10)	3470 (1·16)	3070 (1·44)	2630 (0·91)
			P	3170 (1·16)	2535 (0·61) †		
Me	H		M	4390 (0·97)	3600 (1·3)	3110 (1·0)	2620 (0·74)
			P	3165 (0·07)	2725 (0·91)		
Me	Me		M	4420 (1·29)	3600 (1·82)	3100 (1·26)	2670 (0·97)
			P	3225 (0·12)	2705 (1·07)		
Labile adducts (XII)							
H	H		N	4270 (0·5) ‡	2800 (1·4) ‡		
Me	H		M	4410 (0·46)	2890 (1·48)	2350 (1·48)	
Me	Me		M	4440 (0·49)	2880 (1·51)	2335 (1·43)	
Reduced adducts							
(VI)			M	3730 (0·91)	2860 (1·52)	2250 (1·16)	
(XV)			M	4110 (0·58)	2860 (1·48)	2310 (1·20)	
Dihydro-derivative of (XII; R = R′ = Me)			M	4307 (0·78)	2715 (2·04)		
Quinolizinium salts (VII)							
R	R′	X					
H	H	ClO_4	M	3410 (1·21)	3280 (0·98)		
			B	4525 (1·15)	3535 (0·75)	2960 (1·36)	2660 (1·12)
H	Me	Br	A	3460	3335		
Me	H	Br	A	3520	3380		
Me	Me	Br	A	3555	3430		
Kashimoto's compound (IX)			M	4295 (2·15)	3430 (0·66)	2665 (1·32)	2165 (1·86)

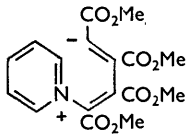
* Solvents: A = glacial acetic acid (containing *N*-bromosuccinimide); B = methanol basified with sodium hydroxide; M = methanol; N = neutral solution, solvent unspecified; P = methanol containing 8% of perchloric acid. † Inflection. ‡ Measured from diagram on p. 87 in ref. 3 [error ±100 Å (±0·2)].

Dimethyl acetylenedicarboxylate and 3-methylpyridine in cold ether or benzene gave two isomeric adducts, orange (XII; R = Me, R′ = H), m. p. 121°, and yellow (XIV; R = Me, R′ = H), m. p. 205°; a third, isomeric, yellow-brown adduct (XIV; R = H, R′ = Me), m. p. 221°, was isolated after a reaction carried out in hot benzene. The orange

[16] Professor R. B. Woodward, personal communication; E. C. Kornfeld, Ph.D. Thesis, Harvard, 1945.
[17] Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.

adduct (XII; R = Me, R′ = H), which corresponds to the labile (red) pyridine adduct, gave its stable yellow isomer (XIV; R = Me, R′ = H) on prolonged boiling in benzene. From 3,5-dimethylpyridine and the ester in cold benzene a labile (red) adduct (XII; R = R′ = Me) was obtained and heating this gave the stable (yellow) isomer (XIV; R = R′ = Me) which was also prepared from the reactants in boiling benzene. Attempts to isolate the labile (red) adduct of pyridine failed, although it was undoubtedly obtained by Diels and Alder. The ultraviolet absorption spectrum [3] for this compound is very similar to those of our other labile adducts (Table). The ultraviolet absorption spectra of all the stable adducts were also similar (Table) to each other, and this indicates a correspondence in structure. On oxidation with *N*-bromosuccinimide in glacial acetic acid both the stable and the labile adducts gave solutions with similar ultraviolet absorption which was characteristic of the quinolizinium cation (Table).

The charged structure (I) originally proposed for the labile (red) pyridine adduct suggests a type of quinquecovalent nitrogen atom and would now be interpreted as (XI). The labile adducts from both 3-methyl- and 3,5-dimethyl-pyridine are stable to methanol. The charged formulation (XI) is therefore improbable because addition of a proton to yield the corresponding pyridinium methoxide would be expected by analogy with results obtained with acridine,[8] benz[*b*]acridine,[18] and phenanthridine.[9] The cyclic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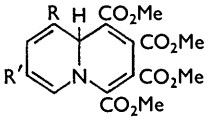
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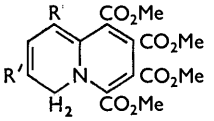
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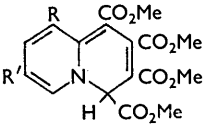
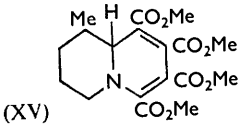

(XIV)

structure (XII) is attractive for the labile adducts as isomerisation to structures (XIII) or (XIV), which are fully conjugated, could account for the formation of the stable adducts. The ultraviolet absorption spectra (Table) of all the adducts is consistent with this type of isomerisation. The bicyclic nature of the labile adduct (XII; R = Me, R′ = H) from 3-methylpyridine, and hence that of the other labile adducts, has been proved by degradation. Hydrogenation over Raney nickel, which was separately shown not to convert the labile into the stable adduct, gave a tetrahydro-derivative (XV) and oxidation yielded pyridine-3,4,5-tricarboxylic acid. This conclusion is consistent with Diels and Alder's observations that the acid- and alkali-hydrolysis products of the labile pyridine adduct are (i) pyridine and some crotonaldehyde, and (ii) pyridine, oxalic and aconitic acid, respectively, although these authors argued that the pyridine moiety could only be attached through the nitrogen atom to the other atoms of the original molecule.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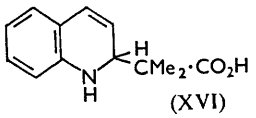

(XVI)

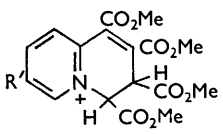
It is known that the 1,2-dihydroquinoline (XVI) splits [19] on alkali- or acid-hydrolysis to quinoline and isobutyric acid, in agreement with both our structure (XII) for the labile adduct and Diels and Alder's data. The structure of the tetrahydro-compound (XV) has been established from nuclear magnetic resonance measurements, and its ultraviolet absorption spectrum is almost identical with that [20] of diethyl 1,2-dihydro-1,2,4,6-tetramethylpyridine-3,5-dicarboxylate except that the long-wavelength absorption band has moved towards the visible region.

Four adducts (XII, XIV; R = R′ = H or Me) are possible products from the reaction

[18] Acheson and Jefford, *J.*, 1956, 2676.
[19] Staudinger, *Annalen*, 1910, **374**, 1.
[20] Traber and Karrer, *Helv. Chim. Acta*, 1958, **41**, 2066.

between 3-methylpyridine and dimethyl acetylenedicarboxylate. Steric interaction between the methyl and the ester groups is expected in one of the stable adducts (XIV; R = Me, R′ = H) but not in the other (XIV; R = H, R′ = Me). This is shown in the ultraviolet absorption spectra which closely resemble those of the corresponding adducts from 3,5-dimethylpyridine and pyridine respectively. On this basis, structures were allocated to the two stable adducts, and one of these (XIV; R = H, R′ = Me) has been confirmed by oxidation to a compound which was identical with authentic 5-methylpyridine-2-carboxylic acid. Since the labile pyridine adduct (XII) seems particularly unstable in comparison with the labile 3,5-dimethylpyridine adduct (XII; R = R′ = Me) it appears that steric hindrance near the ring junction stabilises the labile series of compounds. This supports the supposition that the mobile hydrogen atom is initially at position 9a and is in conformity with the isolation of only the hindered labile adduct (XII; R = Me, R′ = Me) from 3-methylpyridine; the unhindered labile adduct presumably rearranges rapidly, as does the labile pyridine adduct.

From the chemical and physical evidence presented above it is clear that both the labile and the stable adducts are bicyclic, and likely that the saturated ring carbon atom is at position 9a in the labile adducts. The more highly conjugated stable adducts could have the saturated atom at position 2, 4, 6, or 8. The positions of the hydrogen atoms in the labile and the stable adducts have been established as 9a and 4 respectively by the nuclear magnetic resonance study detailed in the Appendix; these structures were independently suggested, but not proved, by Professor R. B. Woodward.[16] Concurrently, infrared adsorption spectra of all the adducts and a number of other compounds were accurately measured in the 5—7 mμ region in the hope of resolving this problem, but the results merely confirmed the structural similarity between the individual members of the stable and the labile groups of adducts.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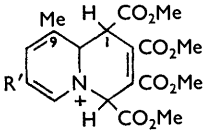
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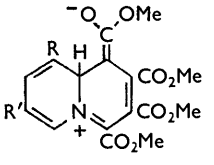
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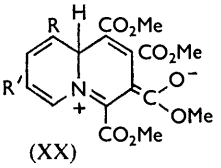

(XX)

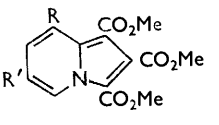
The ultraviolet absorption spectra of the stable adducts are altered very considerably on the addition of perchloric acid. Independently, Professor A. W. Johnson and Mr. J. C. Tebby showed that the stable adducts, but not the labile adducts, were basic to perchloric acid in glacial acetic acid and we have confirmed this observation. The addition of a proton to a stable adduct can take place at position 1, 3, 5, 7, or 9. If it occurred at position 5 the conjugation would be little affected and a marked change in the ultraviolet absorption spectrum would not be expected. Addition at position 7 or 9 is very unlikely as the conjugated system would be interrupted. The ultraviolet absorption spectra of the cations from both the stable pyridine adduct (XIV) and the unhindered stable 3-methylpyridine adduct (XIV; R = H, R′ = Me) are very similar and show strong absorption at *ca.* 3100 and 2330 Å. As 3,4-dihydroquinolizinium iodide has a very similar absorption [15] it appears that the proton has added to position 3 in these adducts, yielding (XVII) as the cation. The hindered stable adducts from 3-methyl- and 3,5-dimethyl-pyridine show strong absorption only at *ca.* 2700 Å; their absorption at *ca.* 3200 Å is very weak. This is consistent with an unconjugated pyridine structure and it therefore appears that the proton adds to position 1 to give (XVIII). It is difficult to account for this change in orientation of proton addition except on the basis that there is steric strain between the substituents at positions 1 and 9, that this is reduced by making the 1-carbon atom tetrahedral, and that the strain is so considerable as to make a reduction preferred to a retention of conjugation.

If the two isolated double bond systems of the classical formula for the labile adducts (XII) can conjugate, as is likely to some extent, zwitterionic structures such as (XIX) and (XX) will be produced. These charged structures were first suggested by Professor A. W. Johnson.[21] The apparent non-basicity of these labile adducts is understandable if they are considered as resonance hybrids to which such charged structures make a contribution, and the nuclear magnetic resonance measurements are consistent with this.

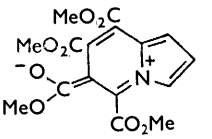
However, the ultraviolet absorption spectrum of the labile adduct (XII; R = Me, R′ = H) is similar to that of its tetrahydro-derivative (XV). The difference between the long-wavelength absorption bands of these compounds is not as great as the difference in the positions of the maxima might suggest, as both bands are very broad. This suggests that there can be little additional conjugation in the labile adduct and that the contribution of structures such as (XIX) and (XX) must be small.

The oxidation [1] of the stable pyridine adduct (XIV; R = R′ = H) to methyl indolizine-1,2,3-tricarboxylate has been confirmed. The mechanism proposed [1] for the oxidation included the " dinitrate " and " hydroxynitrate " as intermediates. The oxidation of 1,2,3,4-tetra(methoxycarbonyl)quinolizinium perchlorate to the indolizine is in agreement with the new formulation of these intermediates as solvated quinolizinium salts.

Oxidation of the labile 3-picoline adduct (XII; R = Me, R′ = H) with dilute nitric acid or chromic acid gives the corresponding indolizine compound (XXI; R = Me, R′ = H) which was identical with the product obtained by Johnson and Tebby [21] by oxidation of the hindered stable 3-picoline adduct (XIV; R = Me, R′ = H). Similarly, oxidation of both the labile and the stable adduct of 3,5-dimethylpyridine gave the same trimethyl dimethylindolizine-1,2,3-tricarboxylate (XXI; R = R′ = Me).



(XXI)



(XXII)

It is especially interesting in connection with our results that while quinolizinium salts are well known all attempts [15,17] to prepare quinolizine itself have so far failed. It is possible that the additional conjugation provided by the many ester groups stabilises the ring system in our compounds.

Appendix: *Nuclear Resonance Measurements.*

By P. Higham and R. E. Richards.

The high-resolution spectra were recorded on the apparatus which has been described previously.[22] The compounds were dissolved in chloroform or nitromethane and no important differences in the spectra were observed between these two solvents. The measurements were made at 29·92 Mc./sec. and the chemical shifts are quoted in parts per million (p.p.m.) from the chloroform solvent such that increased chemical shift corresponds to increased magnetic shielding. The results are shown in Figs. 1 and 2.

The group of lines in the adducts at 3·4—3·8 p.p.m. are due to the four ester-methyl groups. The resonances of the ring-methyl groups of the labile (XII; R = R′ = Me) and stable (XIV; R = R′ = Me) adducts are at 5·4 and 5·1 p.p.m. respectively. Resonances of methyl groups on aromatic systems occur at lower fields than on unsaturated ones, owing to the fields caused by ring currents. It may therefore be concluded that ring A [cf. (v)] of this labile adduct has lost its aromatic character but that in the stable adduct the aromatic character remains and the extra proton must be in position 2 or 4.

In the labile adduct (XII; R = R′ = Me) it could be at positions 6, 8, or 9a. At position 6 the resulting methylene resonance would appear as a doublet at about 3 p.p.m.,

[21] Johnson and Tebby, personal communication.
[22] Leane, Richards, and Schaefer, *J. Sci. Inst.*, 1959, **36**, 230.

being split by the C_8 proton. A methylene group in the 8-position would give the same spectrum. A proton on the 9a position would be split by the protons at C_6 and C_8, the resulting lines being at the limit of observation.

The absence of a doublet in the labile dimethylpyridine adduct which could be attributed to a methylene group indicates that the extra proton is in the 9a-position. An indistinct hump at 1·3 p.p.m. could be the resonance of this proton. The stable adducts (XIV; R = R′ = H or Me) give a sharp line at 1·3 p.p.m., and this must be due to a proton in the 2- or 4-position.

Additional evidence may be gained from the spacing of the ester-methyl resonances. The spectra of the reference compounds with two, three, or four methoxycarbonyl groups can be explained if the methyl resonances occur at higher fields when the methoxycarbonyl

FIG. 1. *Nuclear magnetic resonance spectra of substances* (*a*) (XIV; R = R′ = H), (*b*) (XII; R = R′ = Me), (*c*) (XIV; R = R′ = Me), and (*d*) —— (VI), - - - - (XV) *in chloroform.*

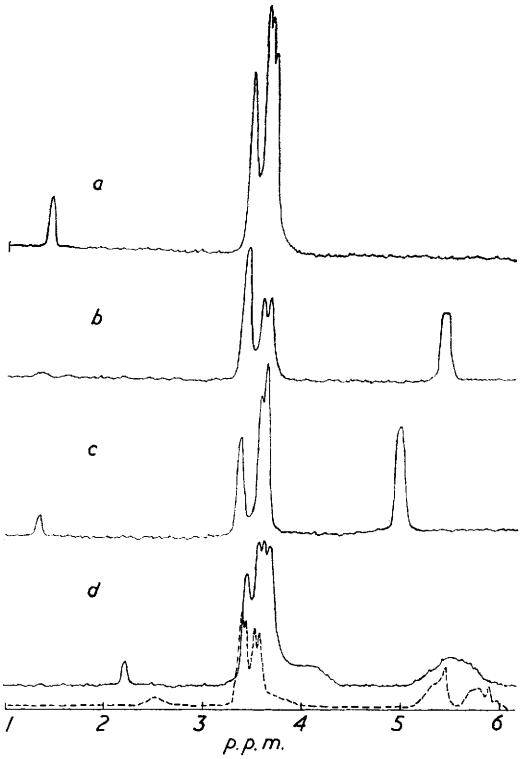
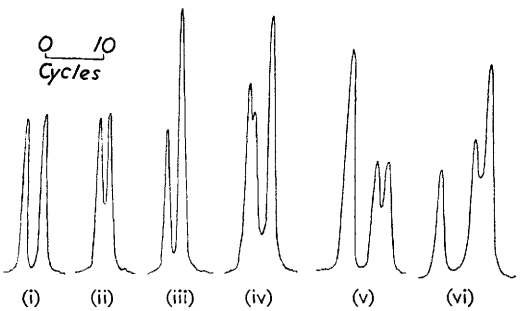


FIG. 2. *Ester-methyl resonances of* (i) *dimethyl itaconate,* (ii) *dimethyl pyridine-2,3-dicarboxylate,* (iii) *ester* (XXI; R = R′ = H), (iv) *ester* (XXII), (v) *ester* (XII; R = R′ = Me), *and* (vi) *ester* (XIV; R = R′ = Me) *in chloroform.*



group is on the carbon atom β or δ to the nitrogen atom. This is probably the result of transfer of negative charge from the nitrogen atom to these positions by resonance structures of type (XXII).

Thus, in trimethyl indolizine-1,2,3-tricarboxylate (XXI) charge can be transferred to the 1- and 2-methoxycarbonyl groups but not to that on $C_{(3)}$. The resonances of these two ester-methyl groups occur at higher fields than that of the 3-methoxycarbonyl, to give the spectrum shown in Fig. 2 (iii), the resonance at higher fields being of twice the intensity of the low field one (a 1–2 spectrum). In tetramethyl indolizine-5,6,7,8-tetracarboxylate charge can be transferred to the 6- and 8-methoxycarbonyl group but not to that on $C_{(5)}$ or $C_{(7)}$, so that the spectrum shown in Fig. 2 (iv) has two sets of resonances, one at high field ($C_{(6)}$, $C_{(8)}$) and the other at low field ($C_{(5)}$, $C_{(7)}$) of equal intensity. (Note that the intensity is measured by the area under an absorption curve, and not by the peak height.)

Further, the methyl resonance in $C{=}C{\cdot}CO_2Me$ appears at lower fields than in $-C-CH{\cdot}CO_2Me$, as shown by the spectra of itaconic ester [Fig. 2 (i)] and by mixtures of succinic and maleic ester. If, therefore, a hydrogen atom is added to the 2- or 4-position of the adducts, the methyl resonance of the methoxycarbonyl group in this position might be expected to shift to higher fields near the resonance of the 1- and 3-methoxycarbonyl groups which will not be appreciably affected, and a spectrum of the type 1–3 would be obtained with the high-field resonance three times as strong as the low-field resonance.

The labile adduct (XII; R = R′ = Me) gives a 2–2 spectrum in the ester-methyl region, confirming the absence of protons in the 2- or 4-position.

The stable adducts (XIV; R = R′ = H or Me) and the partially hydrogenated pyridine adduct (VI), on the other hand, have a 1–3 spectrum in the ester-methyl region. This shows that in these compounds there is an extra hydrogen atom at either the 2- or the 4-position and that the structures of the rings containing the methoxycarbonyl groups are otherwise the same in the two compounds. This means that the hydrogenated pyridine adduct (VI) is reduced in ring A. The resonance from the methylene groups occurs near 4·0 and 5·5 p.p.m.

The single resonance from the 2- or 4-hydrogen atom occurs at 2·2 p.p.m. in compound (VI) and 1·3 p.p.m. in the stable adducts. This large difference could not arise from the saturation of one ring in the hydrogenated product and so indicates that the hydrogen is at position 2 or 4 in this and at position 4 or 2 in the stable adducts. Resonance from the hydrogen atom adjacent to nitrogen is expected to occur at lower magnetic fields than the other one in the 2-position, and so we conclude that in the stable adduct the hydrogen is in the 4-position and in the hydrogenated product it is in the 2-position. The evidence of nuclear magnetic resonance therefore suggests that the labile and the stable adducts are best represented by (XII) and (XIV) respectively, and that the tetrahydro-derivative of the stable pyridine adduct has structure (VI).

The proton resonance spectrum of the tetrahydro-derivative (XV) of the labile 3-picoline adduct has a 2–2 spectrum in the ester-methyl region. A low hump at *ca.* 2·5 p.p.m. is probably due to a proton attached to the 9a-position, and is not at all like the sharp resonance observed with isolated protons (*i.e.*, at positions 2 and 4). The broad band due to a chain of methylene groups is also present, strongly suggesting that the correct structure for this compound is (XV).

We have also examined the stable quinoline adduct, to which an open-chain structure has been assigned,[23] and found that the grouping of the ester-methyl resonances differs from that observed in the adducts of the pyridine series.

Experimental

The ultraviolet absorption spectra were determined with a Carey recording spectrophotometer. The infrared absorption spectra were measured, unless otherwise specified, for chloroform (*ca.* 1 mg./ml.) solutions with a Perkin model 21 recording instrument, and the positions of the absorption maxima in the 5—7 μ region are recorded.

Tetramethyl 4H-*Quinolizine*-1,2,3,4-*tetracarboxylate* (XIV; R = R′ = H).—Pyridine (50 g.) was added to a solution of dimethyl acetylenedicarboxylate (125 ml.) in dry ether (700 ml.), a vigorous reaction ensuing. After 24 hr. the ether was decanted from the tarry precipitate which was washed with ether, the ether solution and washing being rejected. The tar was shaken with methanol (100 ml.) until crystallisation was complete. The orange solid was recrystallised twice from methanol (2 l.), giving the stable pyridine adduct, tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate as yellow plates (66 g., 29%), m. p. 187—188° (Found: C, 55·9; H, 4·95; N, 3·91; OMe, 33·3. Calc. for $C_{17}H_{17}NO_8$: C, 56·2; H, 4·68; N, 3·85; 4OMe, 33·9%), unchanged on recrystallisation from ethanol, $\nu_{max.}$ 5·75, 5·99, 6·13, 6·35, 6·73, and 6·95 μ.

Concentration of the mother-liquors from the first recrystallisation gave a mixture of yellow needles of the stable adduct and pale yellow plates with a purple sheen. The latter were separated mechanically and recrystallisation from aqueous acetic acid gave Kashimoto's

[23] van Tamelen, Aldrich, Bender, and Miller, *Proc. Chem. Soc.*, 1959, 309.

compound in yellow needles, m. p. 183—184° (Found: C, 55·0; H, 3·9; N, 4·15; OMe, 25·9. Calc. for $C_{16}H_{13}NO_8$: C, 55·3; H, 3·7; N, 4·0; 3OMe, 26·8%), $\nu_{max.}$ 5·74, 5·93, 6·13, 6·41, 6·79, and 6·96 μ.

When the reaction was performed in benzene, no precipitate was formed. The tarry product obtained by evaporation of the solution was treated as described above and gave the stable adduct (XIV). This adduct did not react with methyl iodide or sulphate at 100° in nitromethane; charring occurred with methyl sulphate in nitrobenzene at 140°.

Tetramethyl 6,7,8,9-*Tetrahydro*-2H-*quinolizine*-1,2,3,4-*tetracarboxylate* (VI).—Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (XIV) (20 g.) in methanol (4 l.) was shaken with Raney nickel under hydrogen at 1 atm. until absorption ceased. The solution was filtered, evaporated to small volume, and cooled to 0°. The product (VI) separated as a yellow solid which recrystallised from methanol in pale yellow prisms (11 g., 52%), m. p. 145—146° (Found: C, 55·8; H, 5·9; N, 3·8; OMe, 34·2. Calc. for $C_{17}H_{21}NO_8$: C, 55·6; H, 5·7; N, 3·9; 4OMe, 33·8%), $\nu_{max.}$ 5·76, 5·96, 6·28, 6·61, and 6·98 μ.

Evaporation of the mother-liquor left an oil identified as tetramethyl perhydroquinolizine-1,2,3,4-tetracarboxylate by comparison of its infrared absorption spectrum with that of an authentic sample.

Tetramethyl Perhydroquinolizine-1,2,3,4-*tetracarboxylate*.—Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (XIV; R = R′ = H) (5 g.), methanol (80 ml.), and Raney nickel were agitated for 8 hr. at 130° under hydrogen at 120 atm. After filtration the *perhydroquinolizine* was obtained as a pale yellow oil, b. p. 160—163°/0·01 mm. (Found: C, 54·8; H, 7·0; N, 3·4. $C_{17}H_{25}NO_8$ requires C, 54·9; H, 6·7; N, 3·8%).

Degradation of Tetramethyl 6,7,8,9-*Tetrahydro*-2H-*quinolizine*-1,2,3,4-*tetracarboxylate* (VI).—The ester (VI) (4 g.) and concentrated nitric acid (100 ml.) were mixed, with cooling, and heated at 100° for 18 hr. Water (100 ml.) was added and the heating continued for 10 hr. A white residue was obtained after filtration and evaporation *in vacuo*. Two recrystallisations from water gave colourless crystals of pyridine-3,4,5-tricarboxylic acid (*ca.* 0·5 g.) which charred without melting at 261° (Found, after drying at 60° *in vacuo*: C, 45·4; H, 2·7; N, 6·75%; equiv., 74. Calc. for $C_8H_5NO_6$: C, 45·5; H, 2·4; N, 6·6%; equiv., 70·3). The ultraviolet absorption spectrum showed one maximum at 2710 Å (ε 3200) and, on basification, 2710 Å (ε 2800).

A mixture of soda-lime (0·5 g.) and pyridine-3,4,5-tricarboxylic acid (83 mg.) was distilled in a slow stream of nitrogen, the products being trapped in cold dilute hydrochloric acid. When distillation was complete, the acid solution was evaporated to dryness, leaving a small amount of residue. The residue had an ultraviolet absorption spectrum with maxima at 2547 Å in acid solution, splitting into peaks at 2618, 2559, 2500, and 2441 Å in alkaline solution. The corresponding maxima for authentic pyridine are 2618, 2556, 2544, and 2500 Å respectively.

Addition of chloroauric acid to a solution of the residue precipitated a yellow solid having an infrared absorption spectrum and *X*-ray powder photograph identical with those of authentic pyridinium chloroaurate.

1,2,3,4-*Tetramethoxycarbonylquinolizinium Perchlorate* (VII; R = R′ = H, X = ClO_4).—A 10% w/v solution of bromine in glacial acetic acid (5 ml.) was added to tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (1·0 g.) suspended in glacial acetic acid (5 ml.) and 60% perchloric acid (1 ml.). After a few minutes' warming, water (10 ml.) was added, and the whole cooled to 0°. 1,2,3,4-Tetramethoxycarbonylquinolizinium perchlorate was deposited (1·12 g., 88%) as needles, m. p. 196°, unchanged on mixture with the compound obtained from the corresponding perbromide. Infrared maxima in the 5—7 μ region were at 5·75, 6·13, 6·29, 6·59, 6·88, 6·95 μ in Nujol mull.

1,2,3,4-*Tetramethoxycarbonylquinolizinium Bromide* (VII; R = R′ = H, X = Br).—1,2,3,4-Tetramethoxycarbonylquinolizinium perbromide (10 g.) and acetone (50 ml.) were boiled under reflux for 10 min., and on cooling to 0° a brown solid deposited. Two recrystallisations from methanol gave 1,2,3,4-tetramethoxycarbonylquinolizinium bromide as white needles (3 g., 41%), m. p. 113° (decomp.).

The picrate after recrystallisation from methanol was obtained as golden needles, m. p. 172—173° (decomp.); the styphnate had m. p. 187—188° (decomp.). A mixture of a hot methanolic solution of the bromide with chloroplatinic acid precipitated the *platinichloride* as orange needles, decomp. 195—200° [Found: C, 35·3; H, 2·7; Residue, 18·9. $(C_{17}H_{16}NO_8)_2PtCl_6$ requires C, 36·0; H, 2·8; Pt, 17·2%].

Tetramethyl 9-Methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (XII; R = Me, R′ = H) *and 7-Methyl-4H-quinolizine-1,2,3,4-tetracarboxylate* (XIV; R = H, R′ = Me).—A mixture of dimethyl acetylenedicarboxylate (120 ml.), 3-methylpyridine (50 ml.), and ether (500 ml.) was set aside at room temperature for 15 hr., after the initial vigorous reaction had subsided. The ether was then decanted, and the tarry residue shaken with methanol (100 ml.) until crystallisation was complete. The orange solid after two recrystallisations from methanol gave *tetramethyl 9-methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate* as orange needles (28 g., 14%), m. p. 121—122° (Found: C, 57·4; H, 5·05; N, 3·9%; *M*, 331. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·1; N, 3·7%; *M*, 377), $\nu_{max.}$ 5·75, 5·80—5·89, 6·20, 6·64, and 6·97 μ.

From a similar preparation in benzene, a small quantity of a yellow solid very sparingly soluble in methanol was obtained. Recrystallisation from methanol gave *tetramethyl 7-methyl-4H-quinolizine-1,2,3,4-tetracarboxylate* as yellow-orange needles, m. p. 223° (Found: C, 57·3; H, 5·1; N, 3·8. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·0; N, 3·7%).

Tetramethyl 9-Methyl-4H-quinolizine-1,2,3,4-tetracarboxylate (XIV; R = Me, R′ = H).—(i) Tetramethyl 9-methyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (5 g.) was refluxed for 15 hr. in benzene (50 ml.). The solvent was removed *in vacuo* and the residual solid recrystallised from methanol, affording *tetramethyl 9-methyl-4H-quinolizine-1,2,3,4-tetracarboxylate* as yellow-brown prisms (4·5 g., 90%), m. p. 205° (Found: C, 57·4; H, 4·95; N, 3·8; OMe, 32·6. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·0; N, 3·7; 4OMe, 32·9%), $\nu_{max.}$ 5·75, 5·99, 6·17, 6·35, 6·49, 6·83, and 6·97 μ.

(ii) Dimethyl acetylenedicarboxylate (25 ml.) in toluene (10 ml.) was added slowly to a boiling solution of 3-methylpyridine (1 ml.) in toluene (10 ml.) and boiling was continued for 15 min. The toluene was evaporated *in vacuo* and the residual tar shaken with methanol. The solid formed (0·86 g.) was recrystallised twice from methanol, affording almost pure tetramethyl 9-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate as irregular yellow-brown crystals, m. p. 201°.

Tetramethyl 6,7,8,9-Tetrahydro-9-methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (XV).—A solution of methyl 9-methyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (6·0 g.) in methanol (200 ml.) was shaken with Raney nickel under hydrogen at 2 atm. until rapid absorption ceased. The resulting solution was evaporated to dryness. The syrup, obtained on evaporation, slowly solidified. Recrystallisation from methanol afforded *tetramethyl 6,7,8,9-tetrahydro-9-methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate* as irregular yellow crystals (2·65 g., 44%), m. p. 132° (Found: C, 56·4; H, 6·0; N, 3·9. $C_{18}H_{23}NO_8$ requires C, 56·7; H, 6·0; N, 3·7%), $\nu_{max.}$ 5·75, 5·93, 6·23, 6·58, and 6·97 μ.

Oxidation of Tetramethyl 6,7,8,9-Tetrahydro-9-methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate.—The ester (1·0 g.) was added to cold concentrated nitric acid (40 ml.) and the mixture was heated on a steam-bath for 24 hr. After a further 18 hours' boiling, water (20 ml.) was added and boiling continued for 3 hr. Evaporation followed by cooling gave crystals of pyridine-3,4,5-tricarboxylic acid, which recrystallised from water, charred at 266° without melting (Found, after drying at 60° *in vacuo*: C, 45·3; H, 2·6%) and was identical in ultraviolet absorption spectrum with the same acid described above.

Oxidation of Tetramethyl 7-Methyl-4H-quinolizine-1,2,3,4-tetracarboxylate (XIV; R = H, R′ = Me).—A mixture of this ester (1 g.), 30% hydrogen peroxide (100 ml.), and glacial acetic acid (200 ml.) was heated at 100° for 15 hr. The solution was evaporated to dryness and the process was repeated twice more with the residue. The acetone-soluble fraction, after two recrystallisations from water, gave *5-methylpyridine-2-carboxylic acid N-oxide* as needles, m. p. 162—163° (Found: C, 54·7; H, 4·9; N, 9·5. $C_7H_7NO_3$ requires C, 54·9; H, 4·6; N, 9·15%), $\lambda_{max.}$ 2535 Å (ε 7000) in MeOH.

5-Methylpyridine-2-carboxylic Acid N-Oxide.—2,5-Dimethylpyridine (10 ml.), potassium hydroxide (5 g.), potassium permanganate (30 g.), and water (800 ml.) were stirred together at 30—35° for 3 days, by which time the purple colour had been discharged. After clarification with sulphur dioxide, the mixture was evaporated to 100 ml. The pH was adjusted to 4 by the addition of phosphoric acid and disodium hydrogen phosphate, after which the mixture was evaporated to dryness. The residue was extracted (15 hr.) with ethyl acetate in a Soxhlet apparatus. A white solid was deposited in the boiling solvent and was collected. The solid was dissolved in hot water (20 ml.), and the solution cooled to room temperature. The supernatant solution was evaporated to dryness, leaving a white solid (5 g.) which was very soluble in water and gave an orange colour with ferrous sulphate solution. This solid (1 g.), glacial

acetic acid (30 ml.), and 80% hydrogen peroxide (10 ml.) were heated at 100° for 6 hr., after which the mixture was evaporated to dryness. The residual syrup crystallised on being stirred with water (5 ml.), and the colourless solid (0·2 g.) recrystallised from water, affording 5-methylpyridine-2-carboxylic acid *N*-oxide as needles, m. p. 164°, unchanged by addition of the product obtained from (XIV; R = H, R′ = Me); the infrared absorption spectra of the two materials were identical.

Trimethyl 8-Methylindolizine-1,2,3-tricarboxylate (XXI; R = Me, R′ = H).—Tetramethyl 9-methyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (10 g.) and 2M-nitric acid (8 ml.) were warmed on a water-bath until the solid dissolved. The solution was diluted with hot water (12 ml.) and, on cooling, deposited a brown solid. Recrystallisation from aqueous methanol afforded trimethyl 8-methylindolizine-1,2,3-tricarboxylate as faintly yellow needles (0·35 g., 43%), m. p. and mixed [21] m. p. 109°, with the product obtained by Johnson and Tebby by oxidation of the corresponding 4*H*-quinolizine (Found: C, 59·4; H, 5·0; N, 4·05; OMe, 30·2. $C_{15}H_{15}NO_6$ requires C, 59·0; H, 4·9; N, 4·6; 3OMe, 30·5%), $\nu_{max.}$ 5·76, 5·89, 6·59, 6·71, and 6·93 μ.

*Tetramethyl 7,9-Dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate* (XII; R = R′ = Me).—3,5-Dimethylpyridine (10 ml.) in dry benzene (50 ml.) was added slowly to dimethyl acetylenedicarboxylate (20 ml.) in dry benzene (150 ml.), the temperature being kept below 20°. When addition was complete the mixture was left for 1 hr. and then evaporated *in vacuo*, the temperature being kept below 20°. The residue recrystallised from methanol (300 ml.), from which *tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate* was obtained as irregular red crystals (19 g., 52%), m. p. 141—142° (Found: C, 58·4; H, 5·5; N, 3·7; OMe, 31·2. $C_{19}H_{21}NO_8$ requires C, 58·3; H, 5·4; N, 3·6; 4OMe, 31·7%), $\nu_{max.}$ 5·75, 5·89, 6·22, 6·65, and 6·97 μ.

*Tetramethyl 7,9-Dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate* (XIV; R = R′ = Me).—(i) 3,5-Dimethylpyridine (10 ml.) in benzene (50 ml.) was added slowly to a boiling solution of dimethyl acetylenedicarboxylate (20 ml.) in benzene (50 ml.). The mixture was refluxed for 4 hr. and evaporated to dryness. The tarry residue was washed with methanol and recrystallised from methanol (600 ml.), affording *tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate* as bright yellow plates (14 g., 20%), m. p. 221° (Found: C, 58·0; H, 5·5; N, 3·7; OMe, 31·1. $C_{19}H_{21}NO_8$ requires C, 58·3; H, 5·4; N, 3·6; 4OMe, 31·7%), $\nu_{max.}$ 5·75, 6·01, 6·36, 6·49, 6·79, and 6·98 μ. A further quantity (4·5 g.) was obtained from the mother-liquors.

(ii) Tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (0·1 g.) was refluxed for 17 hr. in benzene (5 ml.). The residue, obtained on evaporation, when recrystallised from methanol, gave a product, m. p. 222°, identical with that described above.

Trimethyl 6,8-Dimethylindolizine-1,2,3-tricarboxylate (XXI; R = R′ = Me).—This *indolizine* was obtained from tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (1·0 g.) and 2M-nitric acid (4 ml.) by the method described for (XXI; R = Me, R′ = H) and recrystallised from aqueous methanol in pale yellow needles (0·36 g., 44%), m. p. 159° (Found: C, 60·4; H, 5·3; N, 4·5. $C_{16}H_{17}NO_6$ requires C, 60·15; H, 5·3; N, 4·4%), $\nu_{max.}$ 5·76, 5·90, 6·59, 6·68, 6·90, and 6·94 μ.

Oxidation of tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (1·0 g.) by an identical procedure gave the same product (0·43 g., 52%), m. p. and mixed m. p. 160°.

Tetramethyl Dihydro-7,9-dimethylquinolizine-1,2,3,4-tetracarboxylate.—Tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate was hydrogenated in conditions identical with those used for tetramethyl 9-methyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate. The resulting yellow *dihydroquinolizine*, recrystallised from methanol, had m. p. 114° (Found: C, 58·1; H, 5·9; N, 3·7. $C_{19}H_{23}NO_8$ requires C, 58·0; H, 5·85; N, 3·6%), $\nu_{max.}$ 5·75, 5·93, 6·23, 6·64, 6·87, and 6·97 μ.

Oxidation of the Adducts with N-Bromosuccinimide.—A freshly prepared solution of the adduct in cold glacial acetic acid was shaken with just sufficient *N*-bromosuccinimide to decolorise the solution. The solution was diluted with water and its ultraviolet absorption spectrum measured.

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