

613. *Addition Reactions of Heterocyclic Compounds. Part XIX.*
A Theoretical Study of the H-Quinolizines and the Reduction of Some
Quinolizinium Salts.*

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A theoretical study of the quinolizines using the Hückel molecular orbital method has shown that the order of stability is $4H > 2H > 9aH$, and predictions have been made concerning probable positions of electrophilic and nucleophilic attack on the quinolizinium cation. Although the cation is not affected by sodium borohydride or dithionite, two 1,2,3,4-tetramethoxycarbonylquinolizinium salts are reduced by these reagents to the corresponding $4H$ -quinolizines.

A NUMBER of unsuccessful attempts have been made to prepare simple $4H$ -quinolizines. Lithium aluminium hydride and butylmagnesium bromide did not affect 4-quinolizone¹ and gave indefinable products with quinolizinium salts.² The hydrogenation of quinolizinium iodide over Adams catalyst rapidly gave quinolizidine³ whilst dehydrogenation of the last compound gave quinoline as the only identifiable product.⁴ Some 2-methylpyridine was obtained¹ from the Raney nickel desulphurization of 4-thioquinolizone and pyrolysis of 1,2,3,4-tetrahydro-2-hydroxyquinolizinium acetate caused a Hofmann elimination leading to 2-butadienylpyridine.³ In contrast, tetramethyl $4H$ - and $9aH$ -quinolizine-1,2,3,4-tetracarboxylates are easily obtained from various pyridines and dimethyl acetylenedicarboxylate.⁵

In view of the apparent difficulty in preparing simple quinolizines the Hückel molecular orbital method was used in a theoretical study of the $2H$ -, $4H$ -, and $9aH$ -isomers (III, IV, and I), of the quinolizinium cation (VII) and of 3-methylindolizine (X). Details of the method, which has its critics,⁶ are described elsewhere⁷ and illustrated by recent calculations on quinoline, isoquinoline, and their cations.⁸ With the aid of the programme for the "Dictionary of π -Electron Calculations," kindly supplied by Mr. M. D. Poole, and Oxford University's Mercury computer, we were able to use a wide range of the empirical variables: the Coulomb parameter (h), which is related to the electronegativity of the hetero-atom, and the resonance parameter (k), which expresses the ratio of carbon-nitrogen to carbon-carbon π resonance integral.

* Part XVIII, *J.*, 1964, 2676.

¹ Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.

² Richards and Stevens, *J.*, 1958, 3067.

³ Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.

⁴ Prelog and Balenovic, *Ber.*, 1941, **74**, 1508.

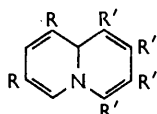
⁵ Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125.

⁶ McWeeny, *Ann. Reports*, 1961, **58**, 137.

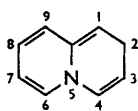
⁷ Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York and London, 1961.

⁸ Brown and Harcourt, *J.*, 1959, 3451; *Tetrahedron*, 1960, **8**, 23.

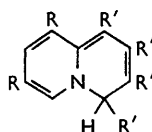
In order to compare the stabilities of the three quinolizine isomers, total π -electron energies (E_π) were calculated for parameter values in the range $h = 0.5-2$, $k = 0.5-1.5$.

(I: $R = R' = H$)

(II: $R = H$ or Me,
 $R' = CO_2Me$)

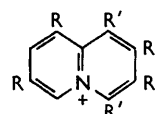


(III)

(IV: $R = R' = H$)

(V: $R = H$, $R' = CO_2Me$)

(VI: $R = Me$, $R' = CO_2Me$)

(VII: $R = R' = H$)

(VIII: $R = H$, $R' = CO_2Me$)

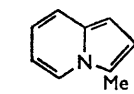
(IX: $R = Me$, $R' = CO_2Me$)

Delocalization energy values (DE_π) follow readily, and it was found that, for $k = 0.5-1.3$ and over the full range of h , the order of DE_π is $4H$ -(IV) $>$ $2H$ -(III) $>$ $9aH$ -quinolizine (I). Values of DE_π (units of β) at the pair of parameters suggested by Streitwieser⁷ to be most appropriate for these systems, namely $h = 1.5$, $k = 1$, are 2.47 for $4H$ -quinolizine, 2.26 for $2H$ -quinolizine, 1.83 for $9aH$ -quinolizine, and 3.16 for 3-methylindolizine. The results were calculated for planar π -electron systems: DE_π values would be expected to be lower for $9aH$ -quinolizine because this cannot be a planar molecule.

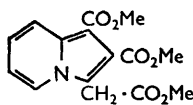
Assuming that the Kekulé forms of the structures (I), (III), and (IV) have the same energy, that relative stabilities are going to be determined by π -electron energies, and that the Hückel treatment gives the correct pattern of total π -electron energies, the order of stabilities predicted for the quinolizines is $4H$ (IV) $>$ $2H$ (II) $>$ $9aH$ (I); h and k parameters outside the range in which this order holds have not been used by previous workers.²

Although quinolizine itself has not yet been prepared this result is interesting in view of the known ready and irreversible isomerizations of $9aH$ -quinolizines of the type (II) to $4H$ -quinolizines (V) and (VI).⁵ No $2H$ -quinolizines are known at present.

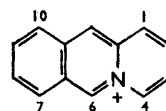
The Kekulé structure of 3-methylindolizine (X) has the same number of bonds of each kind as that of $4H$ -quinolizine (IV). Calculations show that DE_π for this system is greater than DE_π for the quinolizine for any pair of parameters in the range studied ($h = 0.5-2$, $k = 0.5-1.5$); one value is given above. This may be relevant to the observation that in the hydrolytic decarboxylation of the quinolizine (V), rearrangement to the indolizine system (XI) occurs¹⁰ under all but the most acidic conditions.



(X)



(XI)



(XII)

As a first approach to reactivities at the various ring positions of the quinolizinium cation (VII), electrophilic and nucleophilic localization energies (A_E and A_N) were calculated. Values of these quantities at $h = 2$, $k = 1$ are given in Table 1, together with figures for related cations. Since the Wheland transition state for nucleophilic attack at position 4, say, has the same π -electron system as $4H$ -quinolizine, it follows that the order of nucleophilic localization energies over the whole range $h = 0.5-2$, $k = 0.5-1.3$ is $A_N(9a) >$ $A_N(2) >$ $A_N(4)$.

The second approach involved calculation of the π -electron densities (q_i) at the ring positions. The order of the q_i values was insensitive to variation of h and k over the range studied ($h = 0.5-2.0$, $k = 0.5-1.5$). Table 2 presents q_i values at $h = 2$, $k = 1$. In keeping with other calculations,⁸ the variation of q_i at $h = 2$, $k = 1$ with a non-zero

⁹ Coulson and Streitwieser, "Dictionary of π -Electron Calculations," Pergamon, in the press.

¹⁰ Acheson, Gagan, and Taylor, *J.*, 1963, 1903, and unpublished data.

TABLE 1.

Localization energies for aromatic systems containing quaternary nitrogen ($h = 2, k = 1$).

Cation	Quinolizinium					Quinolinium *			
	1	2	3	4	9a	2	4	5	8
$A_B (-\beta)$	2.31	2.62	2.50	2.27	3.22	—	—	2.43	2.36
$A_N (-\beta)$	2.31	2.20	2.50	1.97	2.59	1.96	1.81	—	—

Cation	Isoquinolinium *				Pyridinium			Benzo[b]quinolizinium
	1	3	5	8	2	3	4	6
$A_B (-\beta)$	—	—	2.31	2.41	2.71	2.56	3.07	—
$A_N (-\beta)$	1.61	2.02	—	—	1.86	2.56	2.01	1.67

* Measured from graphs in ref. 8.

TABLE 2.

 π -Electron densities in the quinolizinium cation at $h = 2, k = 1$.

Position (i)	1	2	3	4	5	9a
$q_i (h' = 0)$	1.005	0.916	1.011	0.856	1.550	0.874
$q_i (h' = 0.2)$	0.956	0.917	0.952	0.946	1.523	0.937

auxiliary inductive parameter h' was followed. This was done using computed atom-atom polarizabilities for the molecule in Coulson's first-order perturbation treatment,¹¹ after having ascertained that this method reproduces the finite energy difference treatment given by Brown and Harcourt⁸ for the quinolinium ion. Values of q_i at $h' = 0.2$ are given in Table 2; other values may be obtained as desired by linear interpolation.

The figures in Tables 1 and 2 are compatible with nucleophilic attack on quinolizinium at position 4, unless it be assumed that the substrate is very reactive towards the attacking anion and also that h' is greater than 0.13, in which case attack would follow q_1 rather than A_N ⁷ and occur at position 2. If it is permissible to compare the magnitudes of localization energies within a series of similar heterocyclic molecules, nucleophilic attack on quinolizinium might be anticipated to be more difficult than at position 4 of quinolinium, position 6 of benzo[b]quinolizinium (XII) or position 1 of isoquinolinium.

Experimental results so far obtained concerning nucleophilic attack on the hetero-aromatic systems listed in Table 1 are mainly in agreement with the theoretical calculations. The hydroxyl anion appears¹² to add to the cation (XII) at position 6 and, although appreciable addition to the other systems has not been clearly demonstrated by physical methods, all the cations^{2,13,14} are oxidized by alkaline ferricyanide to the expected carbonyl derivatives, with the exception of the 1-methylquinolinium cation, which yields 1-methyl-2-quinolone; these reactions are usually considered to occur through the small concentrations of the pseudo-bases present in equilibrium. Cyanide ions, which do not react with the quinolizinium cation,² attack the benzo[b]quinolizinium cation¹² at position 6 and *N*-alkyl-quinolinium and -isoquinolinium salts at positions 4 and 1, respectively;^{13,15} phenylmagnesium bromide also attacks the benzo[b]quinolizinium¹² and 1-alkylisoquinolinium cations at positions 6 and 1, respectively, but the 1-alkylquinolinium cation again reacts at position 2.^{13,15} Although sodium borohydride reduces *N*-alkyl-quinolinium,¹⁶ -isoquinolinium,¹⁶ and -pyridinium cations¹⁷ it has now been found that neither this reagent nor sodium dithionite (which also reduces *N*-alkylpyridinium derivatives¹⁸) has

¹¹ Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **192**, 16.¹² Bradsher and Jones, *J. Amer. Chem. Soc.*, 1959, **81**, 1938.¹³ Acheson, "Introduction to the Chemistry of Heterocyclic Compounds," Interscience—John Wiley, New York and London, 1962.¹⁴ Paquette, *Chem. and Ind.*, 1962, 1292.¹⁵ Elderfield, "Heterocyclic Compounds," Vol. IV, John Wiley, New York, 1952.¹⁶ Torossian, *Compt. rend.*, 1952, **235**, 1312.¹⁷ Lyle, Nelson, and Anderson, *Tetrahedron Letters*, 1962, 553.¹⁸ *E.g.*, Mauzerall and Westheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 2261.

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any effect on quinolininium perchlorate or its 2-methoxycarbonyl derivative. However, the tetramethoxycarbonylquinolininium (VIII) and (IX) perchlorates gave the corresponding 4*H*-quinolizines, (V) and (VI), with both these reagents, and in methanol with alkali gave new ultraviolet absorption spectra which suggested¹⁹ that a hydroxyl anion had also added to position 4; the ease of nucleophilic attack is certainly due to the accumulation of electronegative ester groups.

There have been no experimental studies of electrophilic attack on the quinolininium ring system, although the magnitudes of A_E (Table 1) indicate that this should occur under the conditions used for quinoline and isoquinoline. Employing the generally used⁷ parameters $h = 2$, $k = 1$, A_E is lowest at positions 1 and 4, whilst q_i is higher at 1 than at 4 for $h' < 0.21$. As the substrate is already positively charged, the direction of attack would be expected to be governed by localization energies rather than by π -electron densities. It may well be that the high positive charge at the nitrogen (see Table 2), repelling an incoming cation, will be the factor which decides that attack will predominate at position 1; this effect is not normally accounted for in molecular orbital theories of chemical reactivity.

EXPERIMENTAL

1,2,3,4-Tetramethoxycarbonyl-7,9-dimethylquinolininium Perchlorate (IX).—Tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate was treated with bromine and perchloric acid as for tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate¹⁹ and gave the *perchlorate*, colourless prisms (31%), m. p. 186–187° (from methanol) (Found: C, 46.5; H, 4.1; Cl, 7.2; N, 2.8; OMe, 25.6. $C_{19}H_{20}ClNO_{12}$ requires C, 46.6; H, 4.0; Cl, 7.2; N, 2.7; 4OMe, 25.6%), λ_{max} . (in methanol containing a trace of perchloric acid) 252, 342, and 356 m μ ($\epsilon \times 10^{-4}$ 1.77, 0.81, and 0.87).

Reductions with Potassium Borohydride.—(i) Water (2 ml.) containing potassium carbonate (100 mg.) and potassium borohydride (25 mg.) was shaken with a suspension of finely powdered 1,2,3,4-tetramethoxycarbonylquinolininium (VIII) perchlorate (91 mg.) in water (2 ml.) for 30 min. at room temperature and the solid (64 mg.) collected. Recrystallisation from methanol gave tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (V), identical (m. p., mixed m. p., and ultraviolet and infrared absorption spectra) with an authentic specimen.

(ii) 1,2,3,4-Tetramethoxycarbonyl-7,9-dimethylquinolininium (IX) perchlorate, reduced similarly, required shaking for 1 hr. (disappearance of the quinolininium ultraviolet absorption), and gave tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (VI) (73%), identified as before.

Reductions with Sodium Dithionite.—(i) Potassium carbonate (150 mg.) and sodium dithionite (100 mg.) in water (2 ml.) were shaken with a suspension of 1,2,3,4-tetramethoxycarbonylquinolininium (VIII) perchlorate (103 mg.) in water (2 ml.) for 30 min., and the precipitated tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (70 mg.) was collected and identified as before.

(ii) The dimethyl analogue (IX) similarly gave tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (55%), identified as before.

2-Methoxycarbonylquinolininium Perchlorate.—Bromine in acetic acid (8 ml.; 10% w/v) was heated on a steam-bath with a suspension of 2-carboxy-3,4-dihydroquinolininium chloride (1.0 g.)¹⁹ in acetic acid (10 ml.) containing 70% perchloric acid (1 ml.) for 16 hr. On cooling the 2-carboxyquinolininium perchlorate separated; a further quantity was obtained on concentrating the filtrate (total yield 1.08 g.), and recrystallisation from methanol gave colourless prisms, m. p. 230–231° (decomp.) (Found: C, 43.9; H, 3.3; Cl, 13.2; N, 5.1. $C_{10}H_8ClNO_6$ requires C, 43.8; H, 2.9; Cl, 13.0; N, 5.1%).

Diazomethane in ether was added to the perchlorate (0.2 g.) in the minimum volume of methanol until a yellow colour persisted. Addition of more ether precipitated 2-methoxycarbonylquinolininium perchlorate (0.18 g.), prisms, m. p. 191–192° (from methanol) (Found: C, 45.4; H, 3.6; Cl, 12.8; N, 4.9; OMe, 11.4. $C_{11}H_{10}ClNO_6$ requires C, 45.9; H, 3.5; Cl, 12.4; N, 4.9; OMe, 10.8%), λ_{max} . (methanol) 238, 290, 315 inf., 328, and 343 m μ ($\epsilon \times 10^{-4}$ 1.98, 0.30, 0.65, 1.32, and 1.70).

¹⁹ Acheson and Taylor, *J.*, 1960, 1691.

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The ultraviolet spectrum of an aqueous solution of this perchlorate was not altered after treatment in the cold, or after refluxing, with alkaline solutions of potassium borohydride or dithionite.

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