# New Types of Ester-shifts in the Formation of Azepines and Quinolizines

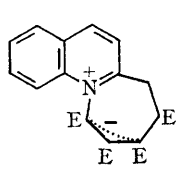
By R. M. ACHESON, R. T. APLIN, J. M. F. GAGAN, D. R. HARRISON, and G. R. MILLER

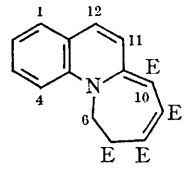
(*Department of Biochemistry and the Dyson Perrins and Physical Chemistry Laboratories, University of Oxford*)

QUINALDINE with dimethyl acetylenedicarboxylate yields[1] tetramethyl 11a-methyl-11a*H*-benzo[*c*]quinolizine-1,2,3,4-tetracarboxylate and a red isomer for which a structure possessing an angular methyl group was tentatively suggested.[2] Later, nuclear magnetic resonance studies[3] of the red isomer showed the absence of a *C*-methyl group and the presence of a single proton which was described as appearing as a high-field quartet centred at $\tau$ 7·4, the separation of the outer components being 29·8 c./sec., which was assumed to be the sum of the two coupling constants. The resonances of the two protons to which it was coupled were largely hidden by the ester-methyl absorption. It was concluded that a $-CH_2-CH<$ group was present and that the red isomer had structure (I).

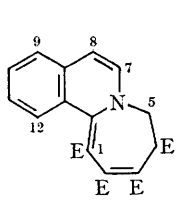
A new formulation (II) is now put forward for the red isomer; structure (I) is not consistent with all the published data. Analogous compounds have also been obtained from the acetylenic ester and 2,4-dimethylquinoline, 6- and 7-bromoquinaldine, 1-methylisoquinoline, and 6-methylphenanthridine, but not from 2-methoxymethylquinoline and 1-ethylisoquinoline where the activated alkyl group possesses only two replaceable hydrogen atoms. All these adducts have ultraviolet absorption spectra very similar to those of the corresponding 4*H*-quinolizines [*e.g.*, the spectrum of (III) resembles that of (XIII)], and in strongly acid solution the new spectra obtained closely resemble those of the protonated parent heterocycle suggesting that, for example, the protonation of (II) occurs largely at position 10; nuclear magnetic resonance spectra in trifluoroacetic acid support this interpretation.

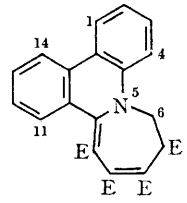
The nuclear magnetic resonance spectra of the adducts (III) and (IV) in deuterochloroform show low-field aromatic quartets due to the 12- and 11-protons respectively, deshielded by the neighbouring ester groups. This feature is absent from the spectrum of (II), where the 10-ester group now deshields the 11-proton so strongly that it appears below that at position 12. The general pattern of the saturated three-proton system, reported[3] for the red quinaldine adduct, was reproduced by all our analogous adducts, but the high-field proton appeared as six lines in the spectra of (III) and (IV) showing that the spectrum was not a simple first-order one as first supposed. To clear the 6$\tau$-region of ester group absorptions the ethyl ester analogue of (II) was synthesised and the three-proton multiplet was now clearly seen for the first time, being bracketed by the methylene and methyl resonances of the ethyl groups. The multiplet was examined at 30, 60, and 100 Mc./sec., and excellent agreement obtained between the observed and calculated spectra as regards both the line intensity and position for the parameters $H_A$ $\tau$6·373, $H_B$ $\tau$ 6·390, $H_C$ $\tau$ 7·380, $J_{AB} = 9{\cdot}2$, $J_{AC} = -12{\cdot}8$, and $J_{BC} = 10{\cdot}7$ c./sec. These values, and the negative coupling constant, now clearly establish that a $-CH_2-CH<$ group is present.





(I) E = $CO_2Me$ or $CO_2Et$ (II)

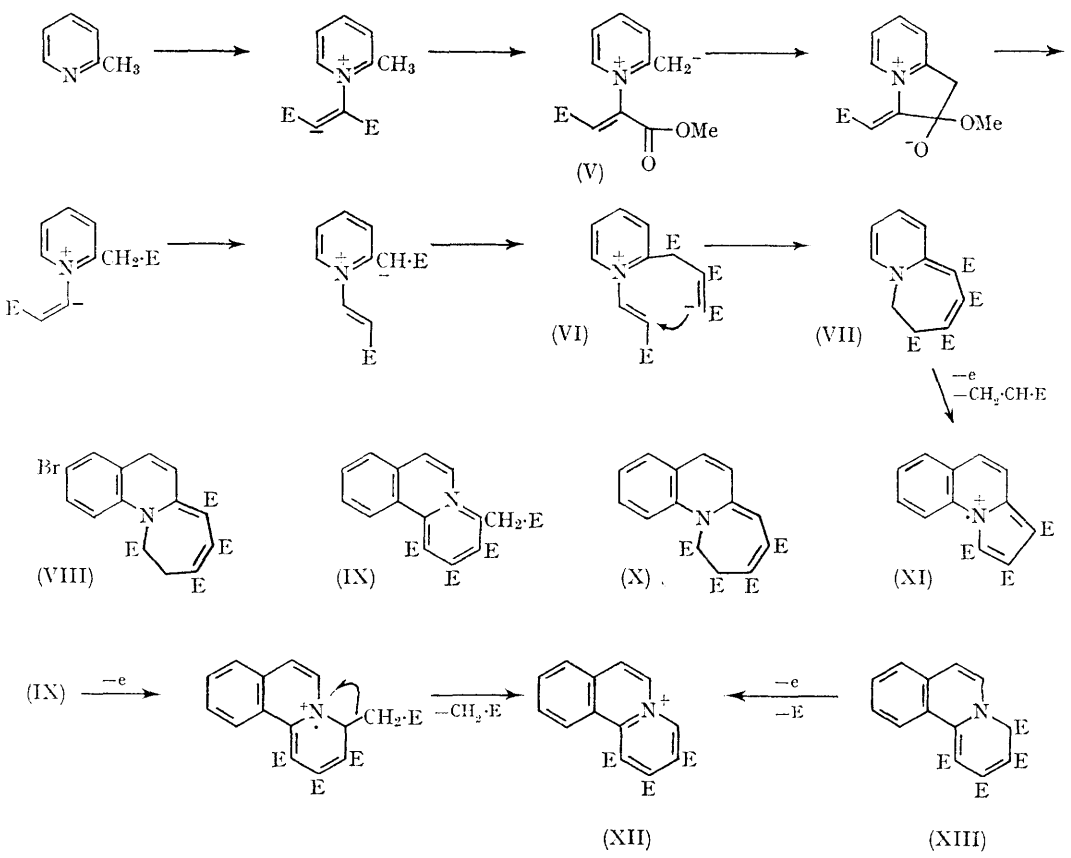




(III) E = $CO_2Me$ or $CO_2Et$ (IV)

Only two types of structure (VII and VIII) are consistent with all these observations. A reaction scheme in conformity with earlier suggestions[4] and accounting for the formation of (II) and its analogues is outlined below. The key feature is the migration of an ester group subsequent to nucleophilic attack; other examples of this type of rearrangement are known.[5] If the carbon atom bearing the negative charge of the intermediate (V) attacks the alternative *N*-vinyl-ester group the same scheme would lead to the isomeric azepine structure, exemplified by the adduct (VIII). From

6-bromoquinaldine and dimethyl acetylenedicarboxylate adducts corresponding to both structure (VII) and (VIII) were obtained. The spectra of one adduct (*cf.*, VII) are virtually identical to those of the adduct (II). The isomer (VIII) is again very similar except in its nuclear magnetic resonance spectrum where (a) the parameters for the saturated protons are $H_A$ $\tau$ 7·13, $H_B$ $\tau$ 5·44, $H_C\tau$ 6·68, $J_{AB}$ = 8·4, $J_{AC}$ = −13·5, and $J_{BC}$ = 10·5 c./sec.; (b) the proton at position 4 is shifted upfield because of its steric relation to the 6-carbonyl group; and (c) the 6-ester-methyl group is at higher field because of its situation above the aromatic carboxylic ring. A similar pair of adducts has been obtained from 2-methylquinoxaline and a number of adducts similar to (VII) have been obtained from various heterocycles with the correct structural characteristics.[6] A by-product from 1-methylisoquinoline and dimethyl acetylenedicarboxylate has structure (IX), and may be formed *via* the intermediate (VI) through attack of the negatively charged carbon atom at the α-carbon of the *N*-vinyl group. Its ultraviolet absorption spectrum is very similar to that of (XIII), and the parameters describing the saturated proton spectrum are $H_A\tau$ 4·12, $H_B\tau$ 6·75, $H_C\tau$ 7·52, $J_{AB}$ = 9·5, $J_{AC}$ = 3·0, $J_{BC}$ = 17·5 c./sec. A minor product from the quinaldine–diethyl acetylenedicarboxylate condensation is (X), the formation of which can be accounted for.[7]




The mass spectra[8] of the adducts of types (VII) and (VIII) show virtually identical fragmentation patterns. Expulsion of methyl acrylate gives ions, such as (XI), as the base peak. These are equivalent to the molecular ions of the corresponding benzoindolizines (*e.g.*, XI) whose spectra are identical with those of (II) and (III) below $M-86$. The fragmentation pattern for (IX) is quite different in type, the loss of the allylic $CH_2{\cdot}CO_2Me$ gives the base peak corresponding to (XII).

Subsequent fragmentation is similar to that of the quinolizine (XIII) after the initial loss of $CO_2Me$. A further mode of fragmentation is observed for (X) which proceeds by successive loss of the ester groups. Somewhat surprisingly there is no evidence of ring contraction of the type observed with the adducts (II) and (VIII).

(*Received, May 23rd,* 1966; *Com.* 348.)

[1] E. E. van Tamelen, P. E. Aldrich, P. Bender, and G. R. Miller, *Proc. Chem. Soc.*, 1959, 309.
[2] O. Diels and H. Kech, *Annalen*, 1935, **519**, 140.
[3] A. Crabtree, L. M. Jackman, and A. W. Johnson, *J. Chem. Soc.*, 1962, 4417.
[4] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125.
[5] R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1963, 1907.
[6] R. M. Acheson and M. W. Foxton, unpublished.
[7] R. M. Acheson, M. W. Foxton, and G. R. Miller, *J. Chem. Soc.*, 1965, 3200.
[8] Determined on an A.E.I. M.S.9 mass spectrometer using a direct insertion probe.