Heterocyclic Compounds with Bridgehead Nitrogen Atoms. Part V.[1,2] Pyrido[2,1,6-*de*]quinolizines (Cycl[3.3.3]azines)

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Alkyl quinolizin-4-ylideneacetates, obtainable in two stages from 4-chloroquinolizinylium perchlorate, react with alkyl propiolates in boiling nitrobenzene to give dialkyl cycl[3.3.3]azine-1,3-dicarboxylates. When t-butyl esters are used, the products can be thermolysed to give the parent cycl[3.3.3]azine or its 1-alkoxycarbonyl derivatives. The cyclazine diesters are readily hydrogenated to tetrahydro-derivatives, form Diels–Alder adducts with dimethyl acetylenedicarboxylate, and undergo electrophilic substitution in the 4- and 6-positions. The parent cyclazine is air-sensitive and is oxidised by halogens to a stable radical cation and to a dication; no substitution or addition products were obtained. Oxidation of diethyl cycl[3.3.3]azine-1,3-dicarboxylate gives an unstable radical cation which is readily converted into a derivative of 12c,14b-diazoniadibenzo[*cd,lm*]perylene. The ^{1}H n.m.r. spectra are discussed and it is concluded that cycl[3.3.3]azine is an antiaromatic system.

PYRIDO[2,1,6-*de*]QUINOLIZINE (1a) (cycl[3.3.3]azine) is of considerable theoretical interest,[3-5] being isoelectronic with the phenalenide anion and formally related to [12]annulene. There have been several reports[6] of attempted syntheses but, unlike cycl[3.2.2]azine[7] (2) which is similarly related to [10]annulene, cycl[3.3.3]-azine remained unknown until the present investigation.

Synthesis.—In Part IV[1] we described a synthesis of cyclopenta[*cd*]cycl[3.3.3]azines (3) by dehydrogenative cycloaddition of αβ-acetylenic esters to cyclopenta[*c*]-quinolizines (4). In order to extend this method to the synthesis of cycl[3.3.3]azines lacking the fused five-membered ring, we required a convenient source of 4-methylene-4*H*-quinolizines (5), and it seemed likely that such compounds would require to be stabilised by an electronegative substituent (R) on the methylene carbon atom.

Boekelheide and Gall[6a] reported the synthesis of the quinolizin-4-ylidenemalonate (5a) from 4-methylthio-quinolizinylium iodide (6a) and diethyl malonate, in the presence of triethylamine. Despite repeated attempts, however, we were unable to obtain more than traces of this compound by the published procedure, the main product being quinolizin-4-one together with a trace of the 4-thione. The required compound was finally obtained,† in good yield, by the reaction of 4-chloro-quinolizinylium perchlorate (6b) with diethyl sodio-malonate in tetrahydrofuran; its structure follows from its conversion, by heating with aqueous hydrochloric acid, into the 4-carboxymethylquinolizinylium salt (6c) which was decarboxylated to give (after exchange of anion) 4-methylquinolizinylium perchlorate, identical with an authentic specimen.[8] The same procedure was used to obtain the quinolizinylidenemalonates (5b—f) and the quinolizinylidenecyanoacetates (5g—i).

The n.m.r.‡ spectra of the malonates show a complex six-proton system (τ 1.8—2.9) together with a one-proton signal at low field (τ 0.8—1.1). The latter is clearly due to H-6 since it is present as a simple doublet ($J_{6,7}$ *ca.* 7 Hz) in the spectrum of the 8-methyl compound

† It became clear at this point that the oily product of Boekelheide and Gall[6a] could not have been the quinolizinylidenemalonate (5a), since our product had m.p. 179—180°. We believe that it was, in fact, an impure specimen of quinolizin-4-one which, in acidic solution, has a u.v. spectrum closely resembling that reported for the hydrochloride of the oily product but differing from that of the malonate (5a) in acid.

‡ All references to n.m.r. apply to ^{1}H spectra.

[1] Part IV, R. P. Cunningham, D. Farquhar, W. K. Gibson, and D. Leaver, *J. Chem. Soc.* (*C*), 1969, 239.

[2] Preliminary communication. D. Farquhar and D. Leaver, *Chem. Comm.*, 1969, 24.

[3] R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1959, **81**, 1459.

[4] R. D. Brown and B. A. W. Coller, *Mol. Phys.*, 1959, **2**, 158.

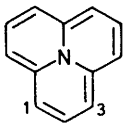
[5] M. J. S. Dewar and N. Trinajstic, *J. Chem. Soc.* (*A*), 1969, 1754.

[6] (*a*) V. Boekelheide and W. G. Gall, *J. Org. Chem.*, 1954, **19**, 499; (*b*) H. V. Hansen and E. D. Anstutz, *ibid.*, 1963, **28**, 393; (*c*) V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron*, 1964, **20**, 33; (*d*) D. Leaver and J. D. R. Vass, *J. Chem. Soc.*, 1965, 1629; (*e*) G. R. Underwood, *J. Org. Chem.*, 1968, **33**, 1313.

[7] A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1961, **83**, 453; V. Boekelheide and T. Small, *ibid.*, p. 462 and references cited therein.

[8] T. M. Moynehan, K. Schofield, R. A. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.

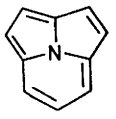
(5f), absent in that of the 6-methyl compound (5b), and shows additional *meta*-coupling ($J_{6,8}$ *ca.* 1 Hz) in those of the compounds lacking a methyl substituent.



(1)

a; parent

b; 1,3-$(CN)_2$



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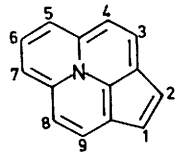
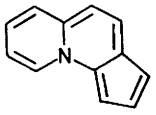


(3)

a; 3-Ph-6-Me

b; 3,9-Me_2



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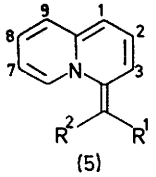


(5)

a; $R^1 = R^2 = CO_2Et$

b; $R^1 = R^2 = CO_2Et$; 6-Me

c; $R^1 = R^2 = CO_2Bu^t$

d; $R^1 = CO_2Bu^t$, $R^2 = CO_2Me$

e; $R^1 = CO_2Bu^t$, $R^2 = CO_2Et$

f; $R^1 = CO_2Bu^t$, $R^2 = CO_2Et$; 8-Me

g; $R^1 = CO_2Me$, $R^2 = CN$

h; $R^1 = CO_2Bu^t$, $R^2 = CN$

i; $R^1 = CO_2Me$, $R^2 = CN$; 6-Me

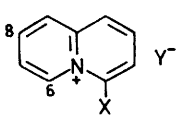
j; $R^1 = CO_2Me$, $R^2 = H$

k; $R^1 = CO_2Et$, $R^2 = H$

m; $R^1 = CO_2Et$, $R^2 = H$; 8-Me

n; $R^1 = CO_2Bu^t$, $R^2 = H$

o; $R^1 = CN$, $R^2 = H$



(6)

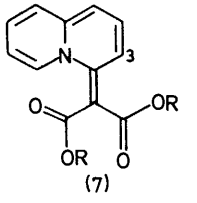
a; X = SMe, Y = I

b; X = Cl, Y = ClO_4

c; X = $CH_2{\cdot}CO_2H$, Y = Cl

d; X = Cl, Y = ClO_4; 6-Me

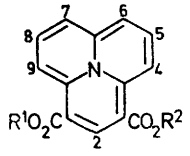
e; X = Cl, Y = ClO_4; 8-Me



(7)

The corresponding signal in the spectra of the cyanoacetates is shifted to higher field (τ 1.4—1.6), thus showing that the cyano-group, which has a less powerful deshielding effect than alkoxycarbonyl, is *cis* to C-6 (as might be expected from its smaller steric requirement).

The t-butoxycarbonyl groups were removed from the malonates (5d—f) and from the cyanoacetate (5h) by treatment with hydrogen chloride in benzene at 60 °C. Basification of the resulting oily hydrochlorides yielded the air-sensitive quinolizinylideneacetates (5j—m) and the much more stable quinolizinylideneacetonitrile (5o). Selective removal of one t-butoxycarbonyl group from the malonate (5c) was brought about by carefully controlled treatment with toluene-*p*-sulphonic acid in acetic acid. The n.m.r. spectra of the acetates show a singlet at τ 5.1—5.2, due to the exocyclic methine proton, and are noteworthy for the large upfield shift of the H-6 signal (to τ 2.2), recognisable by its characteristic *ortho*-coupling of *ca.* 7 Hz, and for the presence of a second low-field resonance (τ 1.5; J_{ortho} *ca.* 9 Hz) which is attributed to H-3. These features suggest (*a*) that the remaining alkoxycarbonyl group in the acetates is *cis* to C-3, and (*b*) that the corresponding alkoxycarbonyl group in the malonates is unable to exert its full deshielding effect on H-3 owing to lack of coplanarity with



(8)

a; $R^1 = R^2 = Me$; 2-Ph

b; $R^1 = Me$, $R^2 = Et$; 2-Ph

c; $R^1 = R^2 = Et$

d; $R^1 = R^2 = Bu^t$

e; $R^1 = Me$, $R^2 = Bu^t$

f; $R^1 = Et$, $R^2 = Bu^t$

g; $R^1 = R^2 = Et$; 5-Me

h; $R^1 = R^2 = Me$; 2-CO_2Me

i; $R^1 = R^2 = Et$; 4,5-$(CO_2Me)_2$

j; $R^1 = R^2 = Et$; 4-CHO

k; $R^1 = R^2 = Et$; 6-CHO

m; $R^1 = R^2 = Et$; 6-COMe

n; $R^1 = R^2 = Et$; 4-NO_2

o; $R^1 = R^2 = Et$; 6-NO_2

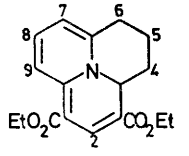
p; $R^1 = R^2 = Et$; 4,6-$(NO_2)_2$

q; $R^1 = R^2 = Et$; 4,7-$(NO_2)_2$

r; $R^1 = R^2 = Et$; 4,9-$(NO_2)_2$

s; $R^1 = R^2 = Et$; 6,7-$(NO_2)_2$

t; $R^1 = R^2 = Et$; 6-$CH_2{\cdot}NMe_2$



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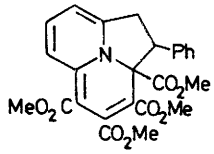

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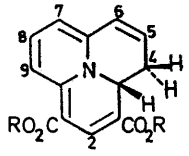
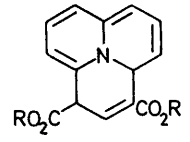


(11)

a; R = Et

b; R = Bu^t

c; R = Et; 5-Me



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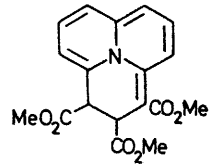

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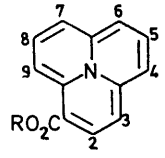


(14)

a; R = Me

b; R = Et

c; R = Bu^t

d; R = Et; 3-CHO

e; R = Et; 3-COPh

the ring-system and/or to a preferred conformation (7) in which the C=O system points away from H-3.

No identifiable product was obtained from the methyl quinolizinylideneacetate (5j) and methyl phenylpropiolate, in boiling benzene or toluene, in the presence of palladium–charcoal. In boiling nitrobenzene, however, two rings of the original quinolizine had become equivalent. Additional evidence for the formation of the cyclazine ring system was obtained by synthesis of the same ethyl methyl cyclazinedicarboxylate (8b) in two

TABLE 1

^{1}H N.m.r. data [a] of pyrido[2,1,6-*de*]quinolizines

Compd.	τ_1	τ_2	τ_3	τ_4	τ_5	τ_6	τ_7	τ_8	τ_9	Other data (J in Hz)
(8a)	(7.09)	(2.7—3.3)	(7.09)	5.01	4.43	5.46	5.46	4.43	5.01	$J_{4,5} = J_{5,6} = 8$, $J_{4,6}$ 2
(8c)	(6.01), (8.82)	2.91	(6.01), (8.82)	3.32	3.92	4.79	4.79	3.92	3.32	$J_{4,5} = J_{5,6} = 8.1$, $J_{4,6}$ 1.7
(8d)	(8.64)	3.05	(8.64)	3.43	4.03	4.87	4.87	4.03	3.43	
(1b) [b]		4.20		4.71	3.87	5.20	5.20	3.87	4.71	$J_{4,5}$ 8.4, $J_{5,6}$ 7.7, $J_{4,6}$ 1.5
(8g)	(5.99), (8.82)	2.67	(5.99), (8.82)	3.22	(8.35)	4.76	4.69	3.84	3.24	$J_{7,8} = J_{8,9} = 8.3$, $J_{4,6}$ 1.5, $J_{7,9}$ 1.6
(8h)	(6.55)	(6.40)	(6.55)	3.80	3.86	4.67	4.67	3.86	3.80	
(8i)	(5.91), (8.76)	2.57	(5.87), (8.76)	(6.45)	(6.26)	4.63	4.42	3.45	2.73	
(8j)	(5.84), (8.77)	2.20	(5.83), (8.72)	(1.59)	3.10	4.34	4.09	3.23	2.50	$J_{5,6}$ 9.0, $J_{7,8}$ 8.0, $J_{8,9}$ 8.5, $J_{7,9}$ 1.5
(8k)	(5.88), (8.75)	2.50	(5.88), (8.75)	3.51	3.24	(1.06)	2.33	3.33	2.67	$J_{4,5}$ 9.0, $J_{7,8}$ 8.0, $J_{8,9}$ 8.5, $J_{7,9}$ 1.5
(8m)	(5.89), (8.76)	2.58	(5.89), (8.76)	←— 3.25 —→		(7.84)	2.34	3.43	2.78	
(8n)	(5.82), (8.77)	2.13	(5.78), (8.71)		2.81	4.52	3.99	3.11	2.25	$J_{5,6}$ 9.8, $J_{7,8}$ 7.6, $J_{8,9}$ 8.7, $J_{7,9}$ 1.5
(8o)	(5.82), (8.73)	2.41	(5.80), (8.73)	3.26	3.16		2.23	3.16	2.58	$J_{4,5}$ 10.0, $J_{7,8}$ 8.5, $J_{8,9}$ 8.5, $J_{7,9}$ 1.5
(8p)	(5.78), (8.74)	1.84	(5.66), (8.63)		1.39		1.85	2.62	2.01	
(8q)	(5.78), (8.73)	2.03	(5.71), (8.66)		2.37	2.56		2.37	2.63	
(8r)	(5.76), (8.72)	1.91	(5.76), (8.72)		2.45	4.13	4.13	2.45		$J_{5,6} = J_{7,8} = 9.0$
(8s)	(5.73), (8.66)	2.02	(5.73), (8.66)	2.61	2.36			2.36	2.61	
(8t)	(5.99), (8.82)	2.77	(5.99), (8.82)	3.23	3.86	(7.46), (7.89)	4.28	3.65	3.05	
(14b) [c]	(6.16), (8.93)	4.40	6.44	5.69	4.73	6.10	5.65	4.49	3.94	
(14d)	(5.98), (8.81)	3.15	(1.45)	2.59	3.57	4.28	4.32	3.57	2.78	
(14e)	(6.11), (9.00)	3.07	(2.5—2.8)	2.54	3.61	4.37	4.44	3.66	3.00	
(16)	(5.97), (8.80)	2.81	(5.97), (8.80)	3.27	3.97	(8.16)	5.03	3.73	3.11	
(20)	(5.96), (8.80)	2.89	(5.96), (8.80)	3.40	4.20		4.77	3.77	3.22	
(9)	(5.84), (8.72)	2.18	(5.84), (8.72)	←— 6.7—8.3 —→			3.72	2.86	1.44	τ_{3a} 4.54, $J_{7,8}$ 7, $J_{8,9}$ 9.5
(11a)	(5.83), (8.71)	2.12	(5.83), (8.71)	6.65 7.61	3.40	3.71	3.71	2.79	1.30	τ_{3a} 4.45, $J_{7,8}$ 7, $J_{8,9}$ 9.5
(11c)	(5.81), (8.70)	2.10	(5.81), (8.70)	6.75 7.55	(8.00)	3.95	3.77	2.79	1.37	τ_{3a} 4.39
(13)	5.15 (6.41)	5.65 (6.42)	(6.28)	1.23	←————		2.6—3.7	———→		$J_{4,5}$ 9.5, $J_{4,6}$ 1.5
(15a)	5.00	(6.29)	(6.24)	(5.8), (8.7)	1.77	(5.8), (8.7)	1.55	2.9 [d]	3.55	τ 2.9—3.3 (etheno-bridge), $J_{7,8}$ 9.5, $J_{8,9}$ 7
(15b)	*e*	(6.27)	(6.18)	(5.9), (8.7)	1.90	(5.9), (8.7)	1.48	2.86	3.66	τ 6.9—8.2 (ethano-bridge), $J_{7,8}$ 9.5, $J_{8,9}$ 7

[a] In $CDCl_3$ unless otherwise stated; values in parentheses refer to protons in substituent groups. [b] In $(CD_3)_2SO$. [c] Assignments were made as follows: (i) H-2 and -3 give an AX system, the low-field component of which must be due to the proton (H-2) next to CO_2Et, (ii) the least shielded signal is due to H-9, (iii) H-5 and -8 show two *ortho*-splittings and are distinguished by the relative intensities of lines in the (four-line) multiplets (H-8 signal is between those of H-7 and -9; H-5 signal is downfield from those of H-4 and -6), (iv) H-6 is assumed to be more shielded than H-4 or -7 since it is further from CO_2Et, (v) the two remaining signals have almost the same chemical shift and the one with more nearly equal line intensities is assigned to H-7 since $\Delta\nu_{7,8} > \Delta\nu_{4,5}$. [d] H-8 signal partially obscured by that of the etheno-bridge protons. [e] H-1 signal obscured by *O*-alkyl signals or by those of the ethano-bridge protons.

the cycl[3.3.3]azine (8a) was formed in the absence of any dehydrogenating agent other than the solvent. The structure of this product was evident from the simplicity of its n.m.r. spectrum (Table 1), which showed that the ways: (*a*) by reaction of the methyl ester (5j) with ethyl phenylpropiolate and (*b*) by reaction of the ethyl ester (5k) with methyl phenylpropiolate.

Similar reactions of the quinolizinylideneacetates with

propiolate esters, and of the quinolizinylideneacetonitrile (5o) with propiolonitrile, yielded the cyclazine-dicarboxylates (8c—g) and the dicyanocyclazine (1b). Again, the structures of these products were evident from their n.m.r. spectra (Table 1 and *e.g.* Figure 1a). It is

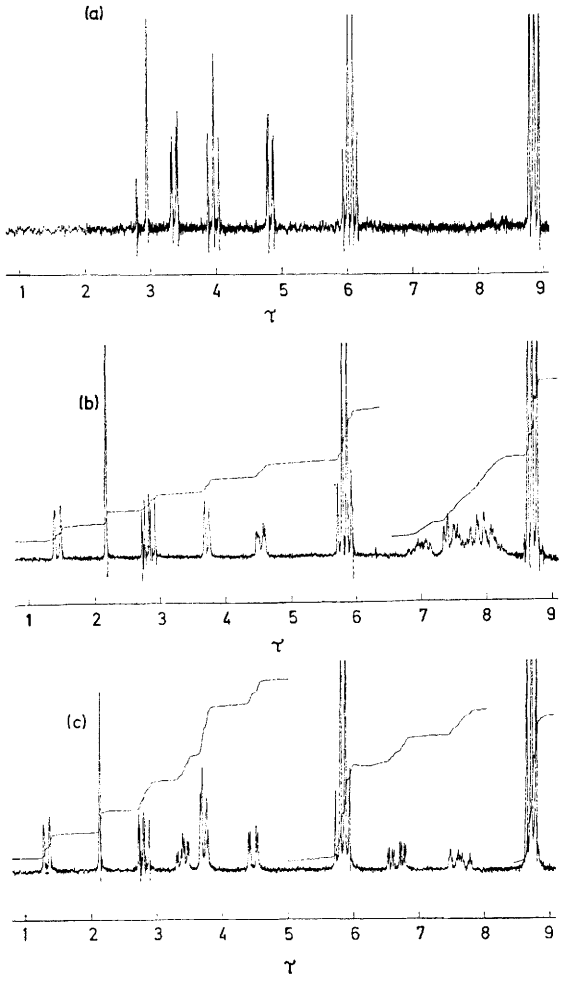


FIGURE 1 ^{1}H N.m.r. spectra of (a) diethyl pyrido[2,1,6-*de*]-quinolizine-1,3-dicarboxylate (8c), (b) the tetrahydro-derivative (9), and (c) the dihydro-derivative (11a)

noteworthy, in view of later structural inferences based on n.m.r., that the α-protons * at positions 4 and 9, which are *peri* to the alkoxycarbonyl groups, are deshielded by 1.4 p.p.m. relative to those at positions 6 and 7 and by 0.6 p.p.m. relative to the β-protons at positions 5 and 8.

During the course (*ca.* 6 min at 210 °C) of these reactions, the colour of the nitrobenzene solutions changed from the initial orange-red (quinolizines), through purple, to yellow-brown (cyclazines). Small amounts of the purple intermediates were occasionally obtained during work-up and, in a reaction of the ethyl ester (5k) with ethyl propiolate, the intermediate was isolated as the main product after 1 min at 160 °C. Catalytic hydrogenation of this purple compound (M^+ 313) gave, after absorption of 0.7 mol. equiv. of hydrogen, the cyclazine (8c) (M^+ 311) (16%) and a red compound (M^+ 315) (81%) which was also obtained, though much more slowly, by catalytic hydrogenation of the cyclazine (8c). These observations showed that the purple compound was a dihydrocyclazine and that the red compound, a tetrahydrocyclazine, was formed from it partly (*ca.* 70%) by addition of hydrogen and partly (*ca.* 15%) by disproportionation. Heating the purple compound in boiling nitrobenzene gave the cyclazine (8c) in high yield.

Structure (9), assigned to the tetrahydrocyclazine, follows from its electronic spectrum (Table 2), which is

TABLE 2

U.v. and visible spectra of di- and tetra-hydropyrido-[2,1,6-*de*]quinolizines in ethanol [$\lambda_{max.}$ (log ε)/nm] [a]

Compd.				
(9)	265 (4.02)	314 (4.39)	362 (3.96)	507 (3.95)
	272 (4.02)			
(10) [b]	272 (4.03)	312 (4.25)	362 (3.88)	470 (3.91)
(15a)	*270* (4.0)	*290* (4.2)	364 (4.01)	515 (3.85)
	281 (4.06)	307 (4.34)		
(15b)	*267* (4.06)	309 (4.36)	362 (3.88)	516 (3.84)
	275 (4.11)			
(11a)	*247* (4.0)	302 (4.47)	398 (4.05)	453 (3.65)
				530 (3.81)

[a] Italicised values refer to shoulders or inflections. [b] Data from ref. 9.

similar to that of the dihydrocycl[3.3.2]azine (10),[9] and from its n.m.r. spectrum (Figure 1b and Table 1) in which the signals due to H-2, -7, -8, and -9 were readily identifiable from their multiplicities and from the fact that H-9 is deshielded by the 1-ethoxycarbonyl group. The H-3a signal at τ 4.54 was also recognisable but the methylene protons gave a complex multiplet at higher field. The n.m.r. spectrum of the purple dihydrocyclazine (Figure 1c and Table 1) was consistent with the structure (11a), the signals due to H-2, -3a, -7, -8, and -9 being similar to the corresponding signals in the spectrum of the tetrahydro-compound. Two additional signals in the olefinic region were attributable to H-5 (τ 3.40) and H-6 (τ 3.71; superimposed on H-7 signal) and two high-field signals to the two methylene protons at position 4 (J_{gem} 18 Hz). Of these last two signals, the one at τ 7.61 showed a large coupling to H-3a (J 11.5 Hz), a small coupling to H-5 (J *ca.* 2 Hz), and allylic coupling to H-6 (J *ca.* 2 Hz), and the one at τ 6.65 showed a small coupling to H-3a (J 2.2 Hz) and a larger coupling to H-5 (J 7 Hz). From the known stereochemical dependence [10] of vicinal and allylic coupling constants, and by

* For the purpose of this discussion, the positions of cycl[3.3.3]-azine adjacent to ring junctions (*i.e.* 1, 3, 4, 6, 7, and 9) are designated α and those non-adjacent to ring junctions (2, 5, and 8) are designated β.

[9] R. M. Acheson and R. S. Feinberg, *J. Chem. Soc.* (*C*), 1968, 351; R. P. Cunningham and D. Leaver, unpublished observations.

[10] M. Karplus, *J. Phys. Chem.*, 1960, **64**, 1793; E. W. Garbisch, *J. Amer. Chem. Soc.*, 1964, **86**, 5561.

examination of a molecular model, these signals (τ 7.61 and 6.65) may be assigned unambiguously to the C-4 protons *trans* and *cis*, respectively, to H-3a. The electronic spectrum (Table 2) of the purple dihydrocyclazine was also consistent with the structure (11), being similar to that of the tetrahydrocyclazine (9) but displaced, in general, to longer wavelengths.

It is evident, from this structure, that the purple dihydrocyclazine cannot be the initial product of the reaction between the quinolizinylideneacetate and ethyl propiolate. If, as seems likely, the initial product is a 1,3a-dihydro-compound (12), then at least one hydrogen migration is required to give the observed 3a,4-isomer. We do not wish to comment on the mechanism of such a migration but suggest that the reason for its occurrence is related to the fact that unsubstituted 4*H*-quinolizines (as in the 1,3a-dihydrocyclazines) are unknown and probably unstable [11] whereas those bearing alkoxycarbonyl substituents in the dihydropyridine ring (as in the 3a,4-dihydrocyclazines) are well exemplified and stable.[12]

The methyl quinolizinylideneacetate (5j) reacted with dimethyl acetylenedicarboxylate, in benzene at room temperature, to give as the major product, a 1,2-dihydrocyclazine (13). The structure of this compound follows from its electronic spectrum, which was very similar to that of the quinolizinylideneacetate (5j), and from its n.m.r. spectrum (Table 1). The latter was generally similar to that of the quinolizinylideneacetate (5j) but differed in the absence of signals representing the quinolizine 6-position and the exocyclic methine proton; instead two doublets were present at τ 5.15 and 5.65, attributable to H-1 and -2 ($J_{1,2}$ 2.5 Hz). Heating the 1,2-dihydrocyclazine in boiling nitrobenzene gave, as the major product, the trimethyl cyclazine-1,2,3-tricarboxylate (8h).

The alkoxycarbonyl groups could not be removed from the cyclazinedicarboxylates by the usual hydrolytic–thermolytic procedures owing to the instability of the cyclazine system in protic media. Fortunately, however, the t-butyl esters lost isobutene and carbon dioxide above 220 °C. This procedure, in a nitrogen atmosphere, was first applied to the mono-t-butyl diesters (8e and f), thus yielding the air-sensitive alkyl cyclazine-1-carboxylates (14a and b). One t-butoxycarbonyl group was removed selectively from the di-t-butyl ester (8d) under similar conditions but removal of both ester groups required heating at a slightly higher temperature in a sealed, evacuated tube. All subsequent operations were conducted under nitrogen or in a vacuum and the parent cyclazine (1a) was sublimed from the thermolysis residue as a brown, crystalline solid which decomposed within minutes when exposed to air or when dissolved in chloroform, carbon tetrachloride, or hydroxylic solvents. Its identity was confirmed by the AX_2 pattern of its n.m.r. spectrum [in C_2Cl_4, C_6H_6, or $(Me_3Si)_2O$] and by an accurate mass measurement of its molecular ion.

Reactions.—(a) *Addition reactions.* Catalytic hydrogenation of the cyclazine diester (8c) over Adams catalyst occurred at atmospheric pressure and, as previously stated, gave a red tetrahydro-compound (9) containing a 1,3-bismethoxycarbonyl-4*H*-quinolizine system. Another example of the tendency to generate this type of residual conjugation is shown in the formation of the red Diels–Alder adduct (15a) by reaction of the diester (8c) with dimethyl acetylenedicarboxylate. The structure of this product is assigned on the basis of the following evidence. (i) The electronic spectrum of the adduct (Table 2) was very similar to that of the tetrahydrocyclazine (9). (ii) The n.m.r. spectrum of the adduct (Table 1), in the low-field region, was similar to that of the tetrahydrocyclazine, though the resonance of H-8 was partially obscured by that of the etheno-bridge protons and a signal due to the bridgehead proton was present at τ 5.07 (dd; X part of ABX). (iii) Catalytic hydrogenation of the adduct gave a red dihydro-derivative (15b) with only minor changes in the electronic

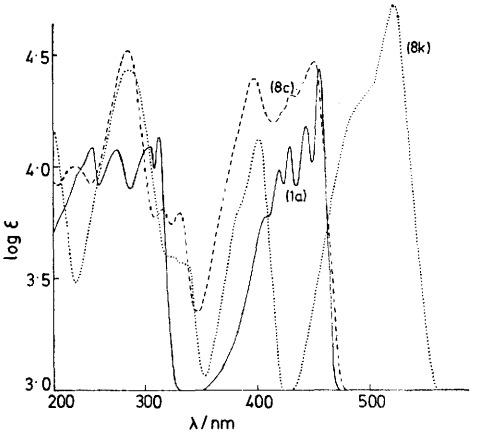


FIGURE 2 Electronic spectra of the pyrido[2,1,6-*de*]quinolizines (1a) (in cyclohexane), (8c) (in ethanol), and (8k) (in ethanol)

spectrum (Table 2). The n.m.r. spectrum (Table 1) of this compound indicated saturation of the etheno-bridge, the H-8 resonance now being clearly visible at the expected position. (iv) Heating the dihydro-derivative (15b) at 220—290 °C caused loss of ethylene (retro-Diels–Alder) and formation of a cyclazine-tetracarboxylic ester (8i) which was identified from its n.m.r. (Table 1) and electronic (Table 3) spectra; the latter showed the same characteristic shape (*e.g.* Figure 2) as those of all other cycl[3.3.3]azines.

Dimethyl acetylenedicarboxylate reacted rapidly with the cyclazine monoester (14b) and with the parent cyclazine (1a) but the products, as revealed by t.l.c., were numerous and none was formed in sufficient quantity for characterisation.

(b) *Substitution reactions.* Electrophilic substitution of the cyclazine diester (8c) gave 4- and/or 6-substituted

[11] V. Boekelheide and W. G. Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832; T. Miyadera, E. Ohki, and I. Iwai, *Chem. and Pharm. Bull (Japan)*, 1964, **12**, 1344; T. Miyadera and Y. Kishida, *Tetrahedron*, 1969, **25**, 397; F. Kröhnke and D. Mörler, *Annalen*, 1971, **744**, 65.

[12] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125.

derivatives. The evidence for this is derived from n.m.r. spectra (Table 1), typical examples of which are those of the two aldehydes (8j and k) obtained by Vilsmeier–Haack formylation.

The essential features of the spectra that reveal the identities of these two products are the relative positions of two signals which, because they show both *ortho*- and *meta*-coupling, are evidently due to the α-protons (H-7 and -9) of an unsubstituted ring. Relative to H-8 (triplet), both protons were deshielded in the case of the minor isomer, which was thereby identified as the 6-formyl compound (8k) containing no α-protons which are not *peri* to a carbonyl group, whereas the major isomer, identified as the 4-formyl compound (8j), had one proton shielded (H-7) and the other deshielded (H-9) relative to H-8. In the formyl-substituted ring, the upfield doublet of the AB system was assigned, in both isomers, to the α-proton but this was appreciably less shielded in the 6- than in the 4-isomer.

Vilsmeier acetylation of the diester (8c) gave the 6-acetyl compound (8m), the n.m.r. spectrum of which was similar to that of the 6-formyl compound.

Mononitration of the diester (8c) was achieved by brief treatment with copper(II) nitrate in acetic anhydride and gave the 4- and 6-nitro-derivatives (8n and o) in almost equal amounts. The n.m.r. spectra of these products (Table 1) were very similar to those of the two formyl compounds and the structures were assigned on the same basis. With tetranitromethane in pyridine, the diester (8c) gave a complex mixture from which the 6-nitro- (10%) and four dinitro-derivatives (total 50%) were isolated by preparative t.l.c. The dinitro-compounds were identified, in decreasing order of yield, as the 4,6- (two dd and one t, showing one unsubstituted ring), the 4,7- (two different but overlapping AB systems), the 4,9- (two superimposed AB systems; $\Delta\nu$ large), and the 6,7-isomer (two superimposed AB systems; $\Delta\nu$ small).

The reaction of the cyclazine diester (8c) with paraformaldehyde and bisdimethylaminomethane gave two products, the major one being a Mannich base and the minor a dicyclazinylmethane. The n.m.r. spectrum of the Mannich base showed an AB system, due to the protons of the monosubstituted ring, one doublet of which was close to the H-8 triplet, and therefore attributable to the β-proton (H-5); the other doublet, being down field, was due to an α-proton at position 4 rather than 6. Thus the product was identified as the 6-dimethylaminomethyl compound (8t) and similar evidence showed that the dicyclazinylmethane was the 6,6′-isomer (16).

The cyclazine monoester (14b) was much more reactive than the diester and electrophilic substitution was accompanied by extensive tar formation. Treatment with *NN*-dimethylformamide and phosphoryl chloride afforded two chromatographically mobile products which gave similar mass spectra showing parent ions corresponding to monoformyl derivatives. The minor product, an unstable red oil, could not be further characterised but the major product, a stable crystalline solid, was identified by n.m.r. (Table 1) as ethyl 3-formylcycl[3.3.3]-azine-1-carboxylate (14d). The milder formylating agent *NN*-dimethylformamide–benzoyl chloride [13] gave a better yield of this 3-formyl compound but none of the unstable isomer. An attempted acetylation of the

TABLE 3

U.v. and visible spectra [a] of pyrido[2,1,6-*de*]quinolizines [$\lambda_{max.}$/nm (log ε)] [b]

Compd.					
(1a) [c]	254 (4.09)	275 (4.08)	306 (4.10) 312 (4.14)	*410* (3.78)	422 (3.99) 431 (4.10) 446 (4.19) 458 (4.45)
(14a) [c]	247 (4.10)	282 (4.39)		404 (3.96)	451 (4.21) 467 (4.28) 476 (4.49)
(8c)	240 (4.00)	285 (4.53)	316 (3.81) 331 (3.81)	399 (4.40)	*430* (4.31) 453 (4.48)
(8a)	258 (4.18)	294 (4.49)		416 (4.15)	472 (4.39)
(1b)	*239* (3.83) *249* (3.88)	287 (4.65)		402 (4.20)	425 (4.23) 449 (4.36)
(8h)	250 (4.16)	288 (4.47)		407 (4.29)	450 (4.35)
(8i)		292 (4.45)	*328* (3.89)	413 (4.27)	488 (4.28)
(8j)	*253* (4.08)	286 (4.40)	*326* (3.76)	412 (4.30)	506 (4.24)
(8k)		285 (4.45)	*337* (3.57)	*382* (3.84) 400 (4.11)	*490* (4.29) 521 (4.73)
(8n)		279 (4.42)	350 (3.90)	413 (4.28)	581 (4.27)
(8o)		273 (4.29)	360 (3.68)	400 (3.81)	574 (4.59)
(8p)		267 (4.28) *293* (4.13)	366 (3.64)		462 (4.23) 532 (4.31)
(8q)		*275* (4.20) 292 (4.24)	*330* (3.8)		*516* (4.30) 548 (4.32)
(8r)		289 (4.28)	360 (3.87)		563 (4.34)
(8s)		284 (4.29)	*349* (3.84)		504 (4.50)

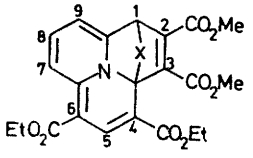
[a] In ethanol unless otherwise stated. [b] Italicised values refer to shoulders or inflections. [c] In cyclohexane.

[13] R. Chong, P. S. Clezy, A. J. Liepa, and A. W. Nichol, *Austral. J. Chem.*, 1969, **22**, 229.

monoester (14b), with *NN*-dimethylacetamide and benzoyl chloride, gave the 3-benzoyl derivative (14e), and attempted nitration with copper(II) nitrate–acetic anhydride gave a large number of highly coloured products (t.l.c.) none of which was produced in amount sufficient for characterisation.

Attempts were made to formylate (with $Me_2N{\cdot}CHO$–$POCl_3$) and to acetylate (with AcCl) the parent cyclazine (1a) but decomposition was extensive and, although t.l.c. showed traces of several mobile products, none was present in sufficient quantity for characterisation.

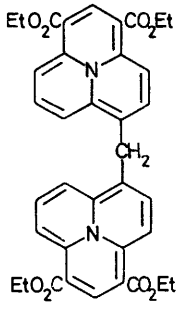
(c) *Oxidation reactions.* Solutions of the parent cyclazine (1a), in benzene, were greenish-yellow and stable in the absence of oxygen. Exposure to air gave an ill-defined brown gum but treatment with bromine vapour gave an air-stable blue solid which was identified as the cyclazine cation bromide (17) by its elemental



(15)

a; X = CH:CH

b; X = $CH_2{\cdot}CH_2$



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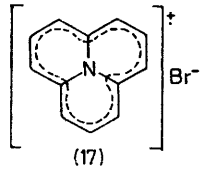
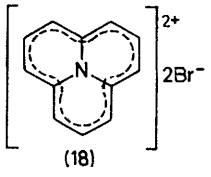
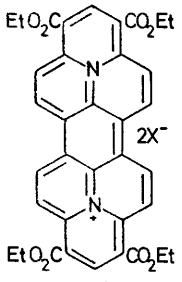


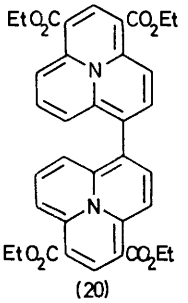
(17)



(18)



(19)



(20)

composition and by its conversion, on further treatment with bromine, into the greenish-brown dication dibromide (18). Blue solutions of the monocation, obtained by oxidation of the cyclazine with silver(I) perchlorate in acetonitrile, gave the expected e.s.r. signal * showing septet (α-H), quartet (β-H), and triplet (N) splittings.

The cyclazine dication dibromide, which was hygroscopic and could not be recrystallised, gave analytical results suggesting retention of an excess of bromine, probably as tribromide ion, but the dichloride, obtained by oxidation of the cyclazine with excess of chlorine, gave results which were acceptable in view of handling difficulties. The structure of the salts follows from the n.m.r. spectrum (Table 4) of the dibromide (in D_2SO_4),

TABLE 4

^{1}H N.m.r. data of phenalene and corresponding pyrido-[2,1,6-*de*]quinolizine species

	τ (doublet)	τ (triplet)	*J*/Hz	Solvent
(1a)	7.95	6.37	7.9	C_2Cl_4
Phenalenide ion [a]	4.83	4.09	7.5	Et_2O
(18)	−0.41	0.33	8.0	D_2SO_4 [c]
Phenalene cation [b]	0.7	1.52	7.2	$AsCl_3$

[a] Ref. 16. [b] Ref. 15. [c] $Me_4N^+BF_4^-$ (τ 6.90) as internal standard (N. C. Deno, H. G. Richey, N. Friedman, J. D. Hodge, J. J. Houser, and C. U. Pittman, *J. Amer. Chem. Soc.*, 1963, **85**, 2991).

which showed the expected A_2B system centred close to 0 τ.

Blue solids, presumed to be radical cation salts, were similarly obtained when the cyclazine diester (8c) was treated with bromine or with antimony pentachloride. These, however, were less stable than the parent radical cation salts and, on being heated gently in benzene–ethanol, became red. The red compounds were identified as salts of the diazoniadibenzo[*cd*,*lm*]perylene (19) by elemental analysis (of the hexachloroantimonate), mass spectrometry (M^+ 618, M^{2+} 309), and n.m.r., which showed three signals at low field—a singlet (τ 0.31, H-2 and -9) and two mutually coupled doublets (τ_A −0.31, τ_B 0.38, J_{AB} 10.0 Hz; H-4, -7, -11, and -14, and H-5, -6, -12, and -13). A minor product (M^+ 620), which remained in the benzene–ethanol solution, was identified by n.m.r. (Table 1) as the 6,6′-bicyclazinyl (20); it was obtained in better yield by oxidation of the diester (8c) with *N*-bromosuccinimide and was converted into the diazoniadibenzoperylene (19) by treatment of its solution in benzene with bromine followed by ethanol.

Discussion. The parent cyclazine (1a) and its radical cation (17) and dication (18) are formally isoelectronic with the phenalenide ion, the phenalenyl radical, and the phenalene cation, respectively. The increased positive charge of the cyclazine dication, relative to the isoelectronic hydrocarbon cation,[15] causes the expected downfield shift of the proton resonances but the opposite effect is observed in the neutral cyclazine which shows a large upfield shift relative to the phenalenide ion [16]

* We are indebted to Dr. I. R. Leith (University of Edinburgh) and Dr. I. Ritchie (University of St. Andrews) for the initial measurement and computer simulation of the e.s.r. spectrum which, however, was poorly resolved. Well resolved spectra of the radical cation and corresponding radical anion have since been obtained by Professor F. Gerson and his co-workers.[14]

[14] F. Gerson, J. Jachimowicz, and D. Leaver, *J. Amer. Chem. Soc.*, 1973, **95**, 6702.

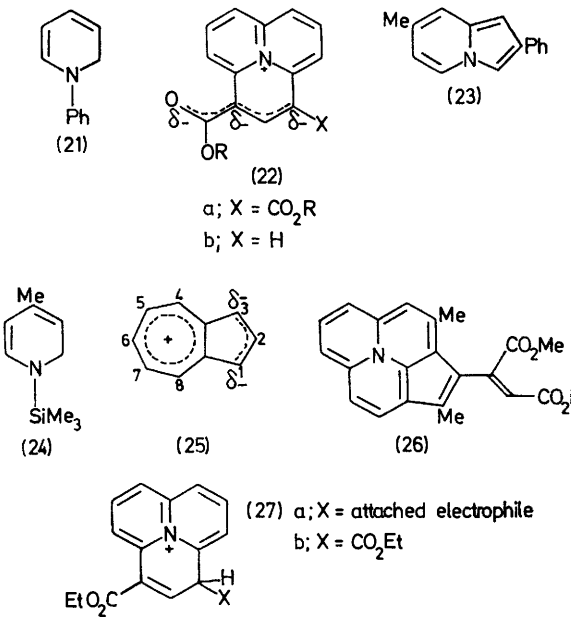
[15] H. Prinzbach, V. Freudenberger, and U. Scheidegger, *Helv. Chim. Acta*, 1967, **50**, 1087.

[16] V. Rautenstrauch and F. Wingler, *Tetrahedron Letters*, 1965, 4703.

(Table 4). This apparently anomalous result can only be due to a paramagnetic ring current in the antiaromatic 12π-perimeter of the cyclazine. Comparison with the non-aromatic model compound (21) [17] further supports this conclusion, the α- and β-proton resonances of the cyclazine being 2.8 and 2.2 p.p.m. upfield of their respective counterparts (H-5 and -4) in the spectrum of the 1,2-dihydropyridine. This high degree of shielding (among the highest yet reported for protons joined to trigonal carbon) is in marked contrast to the low-field ^{1}H resonance (τ 2.1—2.8) [18] of cycl[3.2.2]azine (2), which contains a 10π-perimeter and is typically aromatic. The recognition of cycl[3.3.3]azine as an antiaromatic system adds further interest to our previous conclusion,[1] based on n.m.r., that cyclopenta[*c*,*d*]cycl[3.3.3]azines (3) are aromatic, and highlights the importance of the fused five-membered ring in providing an essential link in the ring-current pathway.

Similarity to the corresponding hydrocarbon species is particularly marked in the radical cation (17), the e.s.r. spectrum [14] of which shows proton hyperfine splittings ($a_{\alpha\text{-H}}$ 6.45, $a_{\beta\text{-H}}$ 1.78) close to those reported [19] for the phenalenyl radical ($a_{\alpha\text{-H}}$ 6.29, $a_{\beta\text{-H}}$ 1.81). In addition, the small nitrogen hyperfine splitting (a_N 1.29) indicates a low spin density at the central atom, as is to be expected from the electron distribution [20] in the non-bonding orbital of phenalenyl. The conversion of the phenalenyl radical into dibenzo[*cd*,*lm*]perylene by oxidative dimerisation [21] finds its counterpart in the oxidation, *via* a radical cation species, of the cyclazine diester (8c) to the diazoniadibenzoperylene (19). The ease of oxidation to the radical cation accords well with the prediction [5] that the first ionisation potential of cycl[3.3.3]azine should be unusually low.

Electronegative substituents cause unusually large downfield shifts in the n.m.r. spectra of cycl[3.3.3]azines. The H-6 and -7 and H-5 and -8 absorptions of the diester (8c), for example, are shifted downfield by 3.2 and 2.5 p.p.m., respectively, relative to those of the α- and β-protons of the parent cyclazine. Since these protons are remote from the ester carbonyl groups, the effect cannot be due to the diamagnetic anisotropy of the latter but is probably the result of partial polarisation of charge in the cyclazine nucleus, as represented in formula (22a). The resonance contribution of such polarised structures must, nevertheless, be relatively small since the chromatographic mobility and solubility characteristics of the diesters (8a—g) are not consistent with a polar structure and the ^{1}H chemical shifts show no evidence of the aromaticity which would be associated with the quinolizinium system in the fully polarised structure (22a). The absence of a diamagnetic ring current in the diesters (8) is evident not only from the chemical shifts of their nuclear protons (particularly H-6 and -7) but also from that of the methyl protons (τ 8.35) in compound (8g). This value is *ca.* 0.6 p.p.m. upfield of the corresponding signals in the spectra of the cyclopentacyclazine (3a) (τ 7.70) and the indolizine (23)



(τ 7.75), which serve as representative aromatic analogues and is about the same as that of the *C*-methyl protons in the non-aromatic analogue (24) (τ 8.29).[22] Perhaps the most significant comparison is that with the 3a,4-dihydrocyclazine (11c), which shows a methyl signal at τ 8.00, the downfield shift of 0.35 p.p.m. caused by interruption of the peripheral conjugation being consistent with the presence of a paramagnetic ring current in the fully conjugated cyclazine. The Mannich base (8t) and the dicyclazinylmethane (16) provide further examples of unusually large shielding of protons in substituent groups; the methylene signal of the former compound occurs at τ 7.46 [*cf.* gramine,[23] τ (CH_2) 6.37; $=C-CH_2-N-$,[24] τ 6.21—7.08] and that of the latter at τ 8.16.

The most notable feature of the n.m.r. spectra of the cyclazine monoesters (14a—c) is the high-field position (τ 6.4) of the resonance due to H-3 which, despite its closeness to the electron-withdrawing alkoxycarbonyl group, is the most shielded of the protons joined to the cyclazine nucleus. This effect is probably a further manifestation of charge polarisation whereby both α-positions of the electronegatively substituted ring become electron rich at the expense of the other two rings [formula (22b)]. A similar effect is observed when

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an electronegative substituent (CHO, COMe, or NO_2) is introduced into the 4- or 6-position of the diester (8c); the remaining α-proton in the monosubstituted ring (H-6 or -4) then becomes the most shielded of the cyclazine protons, its signal being shifted only slightly downfield, and in some cases slightly upfield, with respect to the corresponding signal of the parent diester (8c).

This apparent shielding effect of electronegative groups on *meta*-situated protons appears not to have been reported previously but our unpublished observations in the azulene series show that it is not confined to cycl[3.3.3]azines. The H-3 resonance of 4,6,8-trimethylazulene, for example, is shifted upfield (by *ca.* 0.3 p.p.m.) and the H-2, -5, and -7 resonances downfield when an acetyl or ethoxalyl group is introduced into the 1-position; H-3 thus takes the place of H-5 and -7 as the most shielded of the nuclear protons. The shielding may again be attributed to enhancement, by the acyl group, of the charge polarisation (25) which has long been recognised [21,25] as a feature of the electronic ground state of azulenes.

The electronic spectra of cycl[3.3.3]azines (Table 3 and Figure 2) show several strong bands of which the two most characteristic are (*a*) in the u.v. at 280 ± 15 nm and (*b*) in the visible region at wavelengths varying with the extent of substitution. Surprisingly, in view of the large electronic perturbations revealed by n.m.r., electronegative groups in the 1- and 3-positions have little effect on the position of the main visible absorption maximum. Large bathochromic shifts are caused, however, by additional electronegative substituents in one or both of the other rings and this results in a change of solution colour from the bright greenish-yellow, characteristic of the parent cyclazine and the 1,3-diesters, to brown, purple, or blue in the acyl and nitro-derivatives of the latter.

The lack of aromatic character in cycl[3.3.3]azines, as revealed by physical evidence, is reflected in their chemical reactivity and particularly in the ease with which oxidation and addition reactions occur. These properties are in marked contrast to those of cyclopenta[*cd*]cycl[3.3.3]azines [1] which, even in the absence of electronegative substituents, are stable to oxygen and which react with dimethyl acetylenedicarboxylate by substitution rather than by addition. [The 3,9-dimethyl compound (3b) yields the maleate (26) as described in the Experimental section].

Substitution reactions in cycl[3.3.3]azines appear to be limited to those compounds already possessing one or more electronegative substituents. However, this is not necessarily an indication that such compounds are ' more aromatic ' than the parent cyclazine since even simple enamines are susceptible to electrophilic substitution. The fact that electrophilic substitution in the 1-ethoxycarbonylcyclazine (14b) takes place mainly in the 3-position, rather than in one of the unsubstituted rings, is related to the high-field proton chemical shift at this position and may be similarly explained in terms of a high electron density resulting from charge polarisation [as in (22b)]. An alternative, though entirely equivalent, explanation may be offered in terms of the stability of the Wheland intermediate (27a), which is the only one of the five possible α-substitution intermediates that has no electron-withdrawing group (CO_2Et) joined to the quinolizinium system. The same effect is seen in protonation of the 1,3-diester (8c) which, in trifluoroacetic acid, gives the 1*H*-cyclazinium ion (27b). The structure of the latter follows from its n.m.r. spectrum, which shows a six-proton multiplet (τ 1.2—2.1), due to the quinolizinium protons (H-4 to -9) and two mutually coupled doublets (*J* 7 Hz) at τ 4.32 and 2.35 due to H-1 and -2, respectively.

EXPERIMENTAL

^{1}H N.m.r. data were obtained at 60 or 100 MHz and, unless otherwise stated, refer to solutions in deuteriochloroform with tetramethylsilane as internal standard. I.r. data refer to Nujol mulls. Alumina for chromatography (Laporte type H) was deactivated by treatment with 10% aqueous acetic acid (0.1 cm^3 per g alumina). Silica for t.l.c. and p.l.c. was Merck Kieselgel G. For drying, tetrahydrofuran was kept over sodium and distilled from sodium hydride; benzene was kept over sodium; and nitrobenzene and dichloromethane were kept over Linde molecular sieve (type 4A). Light petroleum refers to the fraction of b.p. 60—80° unless otherwise stated. Extracts were dried over anhydrous magnesium sulphate and evaporated under reduced pressure.

8-*Methylquinolizin*-4-*one*.—Methyl 4-methyl-2-pyridylacetate (b.p. 82—86° at 0.2 mmHg) was prepared from 2,4-dimethylpyridine by a procedure described [26] for methyl 2-pyridylacetate. The identity of the product follows from the success of the subsequent reactions and from the ^{1}H n.m.r. spectrum, which showed no evidence of admixture with the isomeric 2-methyl-4-pyridylacetate.

Diethyl ethoxymethylenemalonate (16.5 g) in ethanol (50 cm^3) was added to an ice-cooled solution of the foregoing ester (11 g) in ethanol (50 cm^3) containing sodium ethoxide [from sodium (2 g)]. After 0.5 h the ice-bath was removed and the solution was kept at room temperature for 16 h. The resulting red-purple, semi-crystalline mass was diluted with water (100 cm^3), cooled to 0 °C, and neutralised with concentrated hydrochloric acid. The 1,3-bisalkoxycarbonyl-8-methylquinolizin-4-one (21 g) was filtered off and dried.

The crude diester (8.1 g) was boiled with potassium hydroxide (5 g) in methanol (70 cm^3)–water (50 cm^3) for 18 h and, after being cooled in ice, the solution was brought to pH 2 by dropwise addition of 6M-hydrochloric acid. The diacid (5.7 g) was filtered off, washed with water, dried, and heated in an evacuated (1 mmHg) sublimation apparatus at 230—240 °C for 30 min; gas (CO_2) was evolved and part of the product sublimed. Sublimation was completed at 170 °C and 0.01 mmHg to yield the *quinolizinone* (1.2 g), hygroscopic yellow prisms, m.p. 135° (from ether) (Found: C, 75.7; H, 5.9; N, 9.1. $C_{10}H_9NO$ requires C, 75.5; H, 5.7; N, 8.8%).

4-*Chloro*-8-*methylquinolizinylium Perchlorate* (6e).—A solution of 8-methylquinolizin-4-one (1.15 g) in phosphoryl

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[26] R. B. Woodward and E. C. Kornfeld, *Org. Synth.*, 1949, **29**, 44.

chloride (5 cm³) was heated at 90 °C for 10 min and the excess of phosphoryl chloride was evaporated off under reduced pressure. The solid residue was dissolved in water (10 cm³) and perchloric acid was added to precipitate the *perchlorate* (1.38 g, 69%), needles, m.p. 166—169° (from water containing a trace of perchloric acid) (Found: C, 43.3; H, 3.0; N, 5.0. $C_{10}H_9Cl_2NO_4$ requires C, 43.3; H, 3.3; N, 5.1%).

4-Chloro-6-methylquinolizinylium Perchlorate (6d).—A solution of 6-methylquinolizin-4-one (8.7 g) in phosphoryl chloride (16 cm³) was heated on a steam-bath for 30 min. The solid deposited was filtered off (glass sinter) and dissolved in water. Addition of perchloric acid precipitated the *perchlorate* (8.2 g, 54%), needles, m.p. 316° (decomp.) (from water) (Found: C, 43.2; H, 4.3; Cl, 25.8; N, 5.2. $C_{10}H_9Cl_2NO_4$ requires C, 43.3; H, 3.3; Cl, 25.3; N, 5.1%).

Dialkyl 4H-Quinolizin-4-ylidenemalonates and Alkyl 4H-Quinolizin-4-ylidenecyanoacetates.—The following procedure is typical. A solution of diethyl malonate (12.1 g, 0.076 mol) in dry, freshly distilled tetrahydrofuran (150 cm³) was stirred under dry nitrogen and powdered sodium hydride (1.82 g, 0.076 mol) (or the equivalent amount of oil-dispersed sodium hydride) was added in small portions. The solution was heated at 50 °C for 1 h to ensure complete reaction of the hydride. 4-Chloroquinolizinylium perchlorate (10.0 g, 0.038 mol) was then added in small portions (*ca.* 1 g) while the temperature was kept below 20 °C by cooling in ice. When the initial exothermic reaction had subsided, the resulting yellow suspension was stirred at 30 °C for 24 h and the solvent was then evaporated off under reduced pressure. Trituration of the residue with chloroform (100 cm³) and filtration yielded a solid from which 4-chloroquinolizinylium perchlorate (1 g) was recovered by recrystallisation from water. The filtrate was concentrated and applied to a column of alumina (380 × 44 mm). After elution with benzene to remove diethyl malonate, the product was eluted with chloroform as a broad yellow band. Recrystallisation gave *diethyl 4H-quinolizin-4-ylidenemalonate* (8.5 g), yellow needles (Table 5), $\nu_{max.}$ 1 700 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 211, 250, 310, and 422 nm (log ε 4.54, 4.39, 3.89, and 3.73), $\lambda_{max.}$ (EtOH–0.5% $HClO_4$) 213, 236, 290, 316, 322 sh, and 330 nm (log ε 4.44, 4.34, 3.53, 3.97, 3.95, and 4.17). The above procedure was used, essentially unchanged, for compounds (5d, e, f, h, and i) but was modified in other cases, as detailed below.

(i) The 6-methylquinolizinylidenemalonate (5b) was thermally unstable. The reaction mixture was not heated above room temperature and the final eluate from the column was evaporated at 20—25 °C. Recrystallisation was carried out by cooling a saturated solution of the compound to −20 °C. No significant impurities were revealed by n.m.r. but satisfactory analytical data were not obtained.

(ii) The di-t-butyl ester (5c) and the cyanoacetate (5g) were not isolated by chromatography. After removal of tetrahydrofuran from the reaction mixtures, water was added and the products were extracted into chloroform. The extracts were dried and evaporated and the residues were triturated with ether to yield the solid products which were purified by recrystallisation (Table 5). Small amounts of 4-chloroquinolizinylium perchlorate were recovered by evaporation of the aqueous solutions.

4-Carboxymethylquinolizinylium Chloride (6c) *and Perchlorate.*—A solution of diethyl 4*H*-quinolizin-4-ylidenemalonate (1 g) in aqueous 2M-hydrochloric acid (20 cm³) was heated under reflux for 1 h. The solution was evaporated under reduced pressure and the solid residue was recrystallised by precipitation from methanol with ether to yield the chloride (0.63 g, 81%), decomp. 168°. For analytical purposes, this was converted into the *perchlorate* (Found: C, 45.9; H, 3.8; N, 4.8. $C_{11}H_{10}ClNO_6$ requires C, 45.9; H, 3.5; N, 4.9%), $\lambda_{max.}$ (EtOH) 213, 234, 289, 318, 325, and 332 nm (log ε 4.43, 4.35, 3.63, 4.08, 4.07, and 4.28).

4-Methylquinolizinylium Perchlorate.—The foregoing chloride (0.57 g) was heated slowly to 200 °C in an open test tube. Vigorous effervescence occurred in the range 165—175 °C. After being cooled, the residue was dissolved in ethanol and treated with a few drops of perchloric acid. Addition of ether precipitated 4-methylquinolizinylium perchlorate (0.58 g, 94%), m.p. 207—209° (lit.,[8] 208—210°), i.r. spectrum identical with that of an authentic specimen.

Ethyl and Methyl 4H-Quinolizin-4-ylideneacetates (5k *and* j).—Hydrogen chloride was passed into a rapidly stirred suspension of t-butyl ethyl 4*H*-quinolizin-4-ylidenemalonate (5.0 g) in dry benzene (200 cm³). After 30 min, during which the suspended orange quinolizine was converted into a colourless, lower, liquid layer, the passage of hydrogen chloride was stopped, a few chips of porous pot were added, and the vessel was heated in a water-bath at 50 °C with occasional shaking. When gas (CO_2) evolution had ceased (*ca.* 50 min; longer heating causes de-esterification at the ethoxycarbonyl group), the mixture was cooled to 6 °C, the benzene layer was decanted off, and ice-cold carbon tetrachloride (150 cm³) was added. The vessel was placed in an ice–salt bath and the contents were stirred vigorously, under

TABLE 5

Dialkyl 4*H*-quinolizin-4-ylidenemalonates and alkyl 4*H*-quinolizin-4-ylidenecyanoacetates

Compd.	Yield (%)	M.p. (°C)	Solvent [a]	Found (%) C	H	N	Formula	Required (%) C	H	N
(5a)	88 [b]	179—180	EtOH	66.8	6.2	4.9	$C_{16}H_{17}NO_4$	66.9	6.0	4.9
(5b)	56	114—115	THF–LP	64.7	6.5	4.7	$C_{17}H_{19}NO_4$	67.8	6.4	4.7
(5c)	92 [b]	209 (decomp.)	MeOH	69.8	7.3	4.2	$C_{20}H_{25}NO_4$	69.9	7.3	4.1
(5d)	87 [b]	192—193	MeOH	67.3	6.3	4.8	$C_{17}H_{19}NO_4$	67.8	6.4	4.7
(5e)	86 [b]	187—188	MeOH	68.5	6.9	4.7	$C_{18}H_{21}NO_4$	68.5	6.7	4.4
(5f)	75	198—199	EtOH	68.1	7.5	4.1	$C_{19}H_{23}NO_4$	68.1	7.2	4.4
(5g)	89 [b]	198—199	EtOH	68.6	4.6	12.4	$C_{13}H_{10}N_2O_2$	69.0	4.5	12.4
(5h)	76	184—185	MeOH	71.5	5.9	10.5	$C_{16}H_{16}N_2O_2$	71.6	5.9	10.4
(5i)	75	197—198	PhH–LP	69.8	4.8	11.7	$C_{14}H_{12}N_2O_2$	70.0	5.0	11.7

[a] THF = tetrahydrofuran, LP = light petroleum. [b] Yields based on unrecovered quinolizinylium salt.

nitrogen, while ice-cold aqueous 6M-sodium hydroxide (10 cm³) was added dropwise during 15 min. The orange-red organic layer was separated and the aqueous layer (which should be strongly alkaline) was extracted with more carbon tetrachloride (2 × 50 cm³). The combined carbon tetrachloride solution was dried and evaporated at 25—30 °C. Prolonged scratching of the residual oil yielded crystalline *ethyl* 4H-*quinolizin*-4-*ylideneacetate* (2.4 g, 71%) sufficiently pure for conversion into cyclazine and stable for several weeks at −15 °C in nitrogen. Recrystallisation from benzene–light petroleum at a low temperature yielded orange-red plates, m.p. 80—81° (Found: C, 72.6; H, 5.9; N, 6.3. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%), $\nu_{max.}$ 1 665 cm^{-1} (C=O).

The same procedure was used to obtain (*a*) ethyl 8-methyl 4*H*-quinolizin-4-ylideneacetate (55%), which was not characterised other than by n.m.r., and (*b*) *methyl* 4H-*quinolizin*-4-*ylideneacetate* (72%), orange-red plates, m.p. 103—104° (Found: C, 71.8; H, 5.9; N, 7.2. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.9; N, 7.0%), $\lambda_{max.}$ (cyclohexane) 211, 233sh, 276, 286, 311, 322, and 451 nm (log ε 4.27, 3.91, 3.93, 3.98, 4.11, 4.18, and 4.08), $\lambda_{max.}$ (EtOH–0.5% $HClO_4$) 235, 290, 317, 324sh, and 330 nm (log ε 4.33, 3.64, 4.03, 4.0, and 4.21).

4H-*Quinolizin*-4-*ylideneacetonitrile* (5o).—The t-butoxycarbonyl group was removed from t-butyl 4*H*-quinolizin-4-ylidenecyanoacetate (5g) by the foregoing procedure except that (i) carbon tetrachloride was replaced by chloroform and (ii) the product was purified by chromatography on alumina in chloroform. The *quinolizine* (59%) was a red solid, m.p. 68—72° (decomp.) (Found: C, 78.7; H, 5.2; N, 16.0%; M^+, 168.0685. $C_{11}H_8N_2$ requires C, 78.6; H, 4.8; N, 16.7%; *M*, 168.0688), $\nu_{max.}$ 2 180 cm^{-1} (C≡N).

t-Butyl 4H-*Quinolizin*-4-*ylideneacetate* (5n).—A solution of di-t-butyl 4*H*-quinolizin-4-ylidenemalonate (5.6 g) and toluene-*p*-sulphonic acid (0.015 g) in acetic acid (50 cm³) was boiled for 6 min. (The disappearance of starting material, monitored by t.l.c. at 1 min intervals, was complete at this point and further heating caused progressive loss of the second t-butyl group.) The solution was cooled, stirred vigorously under nitrogen, and kept at 10 °C during addition of ice-cold, aqueous 6M-sodium hydroxide (160 cm³). Sodium acetate was filtered off and the orange-red product was extracted with carbon tetrachloride (2 × 100 and 2 × 50 cm³). Evaporation of the dried extract at 25—30 °C yielded a red oil which crystallised to yield the *quinolizine* (3.3 g, 83%), sufficiently pure for conversion into cyclazine. Recrystallisation of a sample from benzene–light petroleum at a low temperature yielded orange-red plates, m.p. 111—112° (Found: C, 74.2; H, 7.0; N, 5.4. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.0; N, 5.8%), $\nu_{max.}$ 1 650 cm^{-1} (C=O).

Dialkyl Pyrido[2,1,6-de]*quinolizine*-1,3-*dicarboxylates* (8a—g).—Dry nitrobenzene was distilled immediately before use. Acetylenic esters were distilled from anhydrous potassium carbonate immediately before use. The following procedure is typical. Ethyl 4*H*-quinolizin-4-ylideneacetate (1 g, 0.0046 mol) was dissolved in nitrobenzene (25 cm³) and, after purging of the solution with nitrogen, ethyl propiolate (0.6 g, 0.0061 mol), and anhydrous potassium carbonate (0.5 g) were added. The stirred solution was then heated rapidly, under nitrogen, and kept at the b.p. for 6 min. [The reaction time (5—8 min in general) is critical; the reactions were monitored by t.l.c. at 1 min intervals and heating was stopped when the intermediates (violet spots from propiolate esters or orange spots from phenylpropiolate esters) had been almost entirely replaced by the cyclazines (faster moving bright yellow spots).] Nitrobenzene was evaporated off at the lowest possible temperature (oil pump), the residue was dissolved in chloroform, and the solution was filtered through a short column (30 × 100 mm) of alumina to remove tarry by-products. The filtrate was evaporated and the residue was kept at 80 °C and 0.01 mmHg for 24 h. (This treatment removes residual nitrobenzene which otherwise interferes in the subsequent chromatography.) The residue, dissolved in the minimum volume of benzene, was applied to a column of alumina (25 × 500 mm) and eluted with benzene–light petroleum (initially 1 : 4, changing to 1 : 1 during 7 h). The first (bright yellow) band yielded *diethyl pyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (1.1 g, 75%), purplish brown needles (Table 6), $\nu_{max.}$ 1 660 cm^{-1} (C=O) and the second (violet) band yielded the 3a,4-dihydro-compound (0.12 g, 8%), obtained in better yield by the modified procedure outlined below.

TABLE 6

Dialkyl pyrido[2,1,6-*de*]quinolizine-1,3-dicarboxylates

Compd.	Yield (%)	M.p. (°C)	Solvent [a]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(8a)	26	215—216	THF	73.4	4.6	4.0	$C_{22}H_{17}NO_4$	73.5	4.8	3.9
(8b)	24	186—187	THF	73.9	5.4	3.7	$C_{23}H_{19}NO_4$	74.0	5.1	3.8
(8c)	75	145—146	THF	69.7	5.4	4.5	$C_{18}H_{17}NO_4$	69.4	5.5	4.5
(8d)	64	166—167	LP	72.3	6.7	4.1	$C_{22}H_{25}NO_4$	71.9	6.9	3.8
(8e)	62	156—157	EtOH	70.0	6.1	4.0	$C_{19}H_{19}NO_4$	70.1	5.9	4.3
(8g)	49	116—117	PhH–LP	70.1	5.7	4.7	$C_{19}H_{19}NO_4$	70.1	5.9	4.3

[a] See Table 5.

3a,4-*Dihydropyrido*[2,1,6-de]*quinolizines* (11a—c).—(*a*) The foregoing reaction was carried out at 160 °C for 1 min; otherwise the procedure was unchanged. Chromatography yielded (8c) (0.20 g, 14%) and *diethyl* 3a,4-*dihydropyrido*-[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (1.05 g, 72%), dark blue prisms, m.p. 99—100° (from light petroleum) (Found: C, 68.9; H, 6.0; N, 4.4%; M^+, 313. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%; *M*, 313), $\nu_{max.}$ 1 655 and 1 675 cm^{-1} (C=O).

(*b*) A similar reaction of t-butyl 4*H*-quinolizin-4-ylideneacetate with t-butyl propiolate yielded *di-t-butyl* 3a,4-*dihydropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (66%),

dark blue prisms, m.p. 144—145° (from light petroleum) (Found: C, 71.6; H, 7.2; N, 3.95. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.4; N, 3.8%).

(*c*) *Diethyl* 3a,4-*dihydro*-5-*methylpyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate*, m.p. 84—86° (Found: M^+, 327.1466. $C_{19}H_{21}NO_4$ requires M, 327.1470) was obtained as a minor product (6.5%) in the preparation of (8g) (8 min in boiling nitrobenzene).

Pyrido[2,1,6-de]*quinolizine*-1,3-*dicarbonitrile* (1b).—This compound was obtained from 4*H*-quinolizin-4-ylideneacetonitrile (0.7 g) and cyanoacetylene (0.3 g) by the general procedure described for the 1,3-diesters. Chromatographic purification was carried out on alumina in chloroform to yield the *dicyano-compound* (0.2 g, 23%) as purplish brown needles, m.p. 270—273° (from acetonitrile) (Found: C, 77.0; H, 3.3; N, 19.1. $C_{14}H_7N_3$ requires C, 77.4; H, 3.2; N, 19.4%), $\nu_{max.}$ 2 230 cm^{-1} (C≡N).

Diethyl 3a,4,5,6-*Tetrahydropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (9).—(*a*) The 3a,4-dihydro-compound (11a) (0.257 g) was hydrogenated, at atmospheric pressure, in ethanol (40 cm^3) containing Adams catalyst (0.035 g). Hydrogen (27 cm^3) was absorbed during 35 min and the colour of the solution changed from blue to red. The solution was filtered and evaporated and the residue was chromatographed on alumina, in benzene–light petroleum (7 : 3), to yield (i) diethyl pyrido[2,1,6-*de*]quinolizine-1,3-dicarboxylate (0.041 g, 16%) and (ii) the *tetrahydro-compound* (0.210 g, 81%), red needles, m.p. 104—105° (from light petroleum) (Found: C, 68.6; H, 6.7; N, 4.6%; M^+, 315. $C_{18}H_{21}NO_4$ requires C, 68.6; H, 6.7; N, 4.4%; M, 315), $\nu_{max.}$ 1 660 and 1 685 cm^{-1} (C=O).

(*b*) The cyclazine (8c) (0.060 g) was hydrogenated, at atmospheric pressure, in benzene (20 cm^3) containing Adams catalyst (0.015 g). After 3.5 h, more catalyst (0.015 g) was added and hydrogenation was continued for 3.5 h. The solution was then worked up as in (*a*) to yield the tetrahydro-compound (0.043 g, 72%) and starting material.

Trimethyl 1,2-*Dihydropyrido*[2,1,6-de]*quinolizine*-1,2,3-*tricarboxylate* (13).—Dimethyl acetylenedicarboxylate (1.8 g) in dry benzene (20 cm^3) was added to a rapidly stirred solution of methyl 4*H*-quinolizin-4-ylideneacetate (2.3 g) in dry benzene (80 cm^3) at 10 °C. After 2 h at room temperature, the solution was filtered, concentrated, and chromatographed on alumina. Elution with benzene removed a brown band leaving a number of more strongly adsorbed bands which were not completely resolved by further elution. The brown eluate was evaporated and the residue was dissolved in hot light petroleum containing a little benzene. After 24 h, a red solid which had been deposited was filtered off and the material from the filtrate was separated by dry-column chromatography (silica; ether) into (i) an unidentified yellow-brown oil (0.47 g) and (ii) more of the red solid. Recrystallisation of the red solid from benzene–light petroleum yielded the *dihydro-compound* (0.93 g, 23%), red prisms, m.p. 158—159° (Found: C, 62.6; H, 5.1; N, 4.2. $C_{18}H_{17}NO_6$ requires C, 63.0; H, 5.0; N, 4.1%), $\lambda_{max.}$ (EtOH) 212, 235sh, 283sh, 292, 326, and 452 nm (log ε 4.41, 4.00, 3.98, 3.04, 3.97, and 4.14), $\lambda_{max.}$ (EtOH–0.5%-$HClO_4$) 243, 296, 324, 332sh, and 337 nm (log ε 4.39, 3.62, 3.95, 3.94, and 4.19).

Trimethyl Pyrido[2,1,6-de]*quinolizine*-1,2,3-*tricarboxylate* (8h).—A solution of the foregoing dihydro-compound (0.25 g) in dry nitrobenzene (25 cm^3) was boiled for 10 min and the solvent was evaporated off under reduced pressure. The residue was chromatographed on alumina in light petroleum–benzene to yield (i) dimethyl pyrido[2,1,6-*de*]-quinolizine-1,3-dicarboxylate (0.014 g, 8%), brown needles, m.p. 220—221° (from ethanol), M^+ 283, identified by comparison of its n.m.r. spectrum with that of the corresponding diethyl ester, (ii) an unidentified compound (0.005 g), red needles, m.p. 175—176° (from ethanol), M^+ 341, and (iii) *trimethyl pyrido*[2,1,6-de]*quinolizine*-1,2,3-*tricarboxylate* (0.141 g, 57%), brown needles, m.p. 183—184° (from ethanol) (Found: C, 63.2; H, 4.3; N, 4.2%; M^+, 341. $C_{18}H_{15}NO_6$ requires C, 63.3; H, 4.4; N, 4.1%; M, 341).

Alkyl Pyrido[2,1,6-de]*quinolizine*-1-*carboxylates* (14a—c).—The t-butyl methyl ester (8e) (0.40 g) was placed in a cold-finger sublimation apparatus provided with a nitrogen-inlet tube which discharged immediately above the sample and with a side-arm which could be used either for addition of solvent (*via* pipette) or for vacuum take-off. The apparatus was heated in a Woods metal bath while being flushed slowly with dry nitrogen. Bubbles of gas started to appear from the molten sample at 220 °C. The temperature was then raised to 250 °C during 5 min and kept there for a further 5 min. The apparatus was cooled and, with continued flushing with nitrogen, the sublimate which had collected on the walls and cold finger was washed down by pipetting dry, deoxygenated ether through the side-arm. When the ether had evaporated, the cold finger was cleaned and the apparatus was evacuated (0.04 mmHg). After removal of volatile impurities (30 min at room temperature and 30 min while heating to 140 °C), the sample was sublimed during 1 h at 140 °C to yield *methyl pyrido*[2,1,6-de]*quinolizine*-1-*carboxylate* (0.17 g, 62%), brown needles, m.p. 118—119° (decomp.) (after resublimation) (Found: C, 74.8; H, 5.1; N, 6.1. $C_{14}H_{11}NO_2$ requires C, 74.6; H, 4.9; N, 6.2%). The ethyl and t-butyl esters were obtained similarly.

Pyrido[2,1,6-de]*quinolizine* (1a).—The di-t-butyl ester (8d) (0.2 g) was sealed, under vacuum, in a Pyrex Carius tube (120 × 6 mm int. diam.). The tube was placed for 8 min inside a heavy steel tube heated to 270 °C in a Carius furnace. (The temperature inside the steel tube fell initially to *ca.* 245 °C but rose again to 255—260 °C within 2 min of inserting the Carius tube.) After being cooled to 0 °C, the Carius tube was opened (blow-pipe flame) and placed immediately under dry nitrogen. All subsequent operations were conducted under dry nitrogen (dry bag) or in evacuated apparatus. The perforated end of the Carius tube was sheared off and the tube was placed in a sublimation apparatus designed to accommodate the tube in a snug-fitting well below the cold finger. Sublimation was carried out for 1 h at 120 °C and 0.01 mmHg to yield the *pyrido-quinolizine* (0.022 g, 24%), purplish-brown needles, m.p. 140—142° (sealed under N_2) (Found: M^+, 167.0727. $C_{12}H_9N$ requires M, 167.0735). The compound decomposed rapidly in air and the yield was estimated by dissolving in deoxygenated benzene containing a known weight of cyclohexane and integrating the n.m.r. spectrum.

4,6-*Diethyl* 2,3-*Dimethyl* 1,3a-*Dihydro*-1,3a-*ethenopyrido*-[2,1,6-de]*quinolizine*-2,3,4,6-*tetracarboxylate* (15a).—The diethyl ester (8c) (0.3 g) and dimethyl acetylenedicarboxylate (0.27 g) were heated under reflux in benzene (15 cm^3) for 16 h during which the colour changed from yellow to red. The solvent was evaporated off and the residue was chromatographed on alumina. Elution was carried out first with benzene (to remove the excess of acetylenic ester) and then with chloroform to remove the *adduct* (0.42 g, 96%), red prisms, m.p. 255—256° (from ethanol) (Found: C, 63.3;

H, 5.5; N, 3.0%; M^+, 453. $C_{24}H_{23}NO_8$ requires C, 63.6; H, 5.1; N, 3.1%; M, 453), $\nu_{max.}$ 1 670, 1 690, and 1 715 cm^{-1} (C=O).

4,6-*Diethyl* 2,3-*Dimethyl* 1,3a-*Dihydro*-1,3a-*ethanopyrido*-[2,1,6-de]*quinolizine*-2,3,4,6-*tetracarboxylate* (15b).—The foregoing adduct (0.345 g) was hydrogenated at atmospheric pressure in 2-methoxyethanol (80 cm^3) over Adams catalyst until 1 mol. equiv. had been absorbed (1.5 h). The catalyst was filtered off, the solution evaporated and the residue crystallised from ethanol to yield the *dihydro-adduct* (0.329 g, 95%), red prisms, m.p. 185—186° followed by solidification and remelting at 206—207° (i.r. spectrum of recovered material shows no chemical change) (Found: C, 63.3; H, 5.4; N, 3.2%; M^+, 455. $C_{24}H_{25}NO_8$ requires C, 63.3; H, 5.5; N, 3.1%; M 455), $\nu_{max.}$ 1 650 and 1 705 cm^{-1} (C=O).

1,3-*Diethyl* 4,5-*Dimethyl* *Pyrido*[2,1,6-de]*quinolizine*-1,3,4,5-*tetracarboxylate* (8i).—The foregoing dihydro-adduct (0.21 g) was heated at 220—290 °C under nitrogen for 10 min during which a gas was evolved. The product, part of which had sublimed on to the cooler parts of the vessel, was dissolved in the minimum volume of benzene and chromatographed on alumina. Elution with benzene gave (i) 1,3-diethyl 5-methyl pyrido[2,1,6-*de*]quinolizine-1,3,5-tricarboxylate (0.006 g, 3.5%), brown needles, m.p. 184—185° (from ethanol) (Found: M^+, 369. $C_{20}H_{19}NO_6$ requires M, 369), $\lambda_{max.}$ (EtOH) 244, 298, 330, 411, 452 sh, and 474 nm (log ε 4.13, 4.45, 4.01, 4.25, 4.2, and 4.38), τ 3.13 (1 H, s, H-2), 3.26 (1 H, d, H-4), 3.45 (1 H, dd, H-9), 4.04 (1 H, t, H-8), 4.52 (1 H, d, H-6), 4.94 (1 H, dd, H-7), and 1 × OMe and 2 × OEt signals, and (ii) the *tetraester* (0.135 g, 68%), reddish-brown needles, m.p. 226—228° (from ethanol) (Found: C, 61.8; H, 4.8; N, 3.2. $C_{22}H_{21}NO_8$ requires C, 61.8; H, 5.0; N, 3.3%).

Formylation of the Diester (8c).—*NN*-Dimethylformamide (0.076 g) and phosphoryl chloride (0.160 g) were mixed and stirred for 5 min at 5 °C and then for a further 20 min at room temperature. The viscous product was dissolved in dichloromethane (6 cm^3) and the solution was stirred and cooled to −5 °C. The diester (8c) (0.300 g) in dichloromethane (6 cm^3) was added and the solution was heated under reflux for 15 min. Aqueous sodium acetate (0.4 g in 15 cm^3) was added and heating was continued for 15 min with vigorous stirring. The product, which was obtained from the dichloromethane layer combined with chloroform extracts of the aqueous layer, was chromatographed on alumina. Elution with benzene gave (i) starting material (0.003 g) and (ii) *diethyl* 6-*formylpyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.039 g, 12%), brown needles, m.p. 181—182° (from ethanol) (Found: C, 67.2; H, 5.3; N, 4.0. $C_{19}H_{17}NO_5$ requires C, 67.25; H, 5.1; N, 4.1%), $\nu_{max.}$ 1 615 (formyl C=O) and 1 660 cm^{-1} (ester C=O). Elution with ether gave *diethyl* 4-*formylpyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.159 g, 51%), brown powder, m.p. 186—190° (not improved by repeated recrystallisation from ethanol) (Found: C, 67.0; H, 5.4; N, 4.3%), $\nu_{max.}$ 1 625 (formyl C=O) and 1 680 cm^{-1} (ester C=O).

Acetylation of the Diester (8c).—The foregoing procedure was repeated with *NN*-dimethylacetamide in place of *NN*-dimethylformamide. The crude product, dissolved in chloroform, was filtered through a short column of alumina to remove tarry by-products and then subjected to p.l.c. on silica [elution with benzene (97%)–ether (3%)]. The product extracted with chloroform from the main band (pink) was recrystallised from ethanol to yield *diethyl* 6-*acetylpyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.046 g, 16%), brown needles, m.p. 211—212° (Found: C, 67.6; H, 5.8; N, 3.9. $C_{20}H_{19}NO_5$ requires C, 68.0; H, 5.4; N, 4.0%), $\nu_{max.}$ 1 610 (acetyl C=O) and 1 680 cm^{-1} (ester C=O). Four other very faint bands (yellow or brown) were visible on the plate.

Nitration of the Diester (8c).—(a) *With copper*(II) *nitrate–acetic anhydride*. The diester (8c) (0.14 g), in acetic anhydride (25 cm^3), was added to a stirred solution of copper-(II) nitrate trihydrate (0.10 g) in the same solvent (10 cm^3). After being stirred at room temperature for 2 min, the solution was poured into ether and an excess of aqueous sodium carbonate. When all the acetic anhydride had been hydrolysed, the ether layer was separated, dried, and evaporated. The residue was chromatographed on alumina in benzene–light petroleum (1 : 2) to yield (i) *diethyl* 6-*nitropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.046 g, 29%), dark blue plates, m.p. 211—212° (from ethanol–benzene) (Found: C, 60.6; H, 5.2; N, 8.0. $C_{18}H_{16}N_2O_6$ requires C, 60.7; H, 4.5; N, 7.9%), $\nu_{max.}$ 1 680 cm^{-1} (C=O); (ii) *diethyl* 4-*nitropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.040 g, 25%), dark blue needles, m.p. 193—194° (from ethanol–benzene) (Found: C, 60.6; H, 4.5; N, 7.7%), $\nu_{max.}$ 1 680 cm^{-1} (C=O); and (iii) an unidentified dark blue-grey substance (0.009 g).

(b) *With tetranitromethane*. A solution of the diester (8c) (0.40 g) in dry pyridine (30 cm^3) was cooled to −5 °C and tetranitromethane (0.26 g) in pyridine (5 cm^3), also at −5 °C, was added with rapid stirring. The solution was allowed to come to room temperature during 30 min and the pyridine was evaporated off under reduced pressure (oil pump). The residue, dissolved in chloroform, was filtered through a short column of alumina and the filtrate was concentrated (to *ca.* 3 cm^3) and subjected to p.l.c. (six 20 × 20 cm plates) on silica [elution with benzene–ether (50 : 1)]. (The elution time was prolonged to 30 h by allowing the plates to protrude through slits in the lid of the tank so that solvent was able to evaporate from the upper edge of the adsorbent). Six blue or purple bands were present (together with a wide, relatively immobile band) but these were not resolved completely until the material from bands 3, 4, and 5 had been rechromatographed under the same conditions. Recovery of material from these bands by extraction with chloroform, and recrystallisation of each product from ethanol–benzene, yielded (i) unidentified light brown solid (0.003 g), (ii) *diethyl* 4,7-*dinitropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.087 g, 17%), blue-green needles, m.p. 153—154° (Found: C, 53.8; H, 3.9; N, 10.4%; M^+, 401. $C_{18}H_{15}N_3O_8$ requires C, 53.9; H, 3.8; N, 10.5%; M, 401), (iii) *diethyl* 6,7-*dinitropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.026 g, 5%), dark brown needles, m.p. 221—222° (Found: C, 54.1; H, 4.1; N, 10.5%; M^+, 401), (iv) *diethyl* 4,6-*dinitropyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (0.093 g, 18%), dark brown needles, m.p. 225—226° (Found: C, 54.7; H, 4.2; N, 10.5%; M^+, 401), (v) diethyl 6-nitropyrido[2,1,6-*de*]quinolizine-1,3-dicarboxylate (0.053 g, 10%), m.p. 211—212°, identical with the product obtained by method (a), and (vi) *diethyl* 4,9-*dinitropyrido*[2,1,6-de]-*quinolizine*-1,3-*dicarboxylate* (0.045 g, 9%), dark blue prisms, m.p. 233—234° (Found: C, 54.0; H, 3.9; N, 10.3%; M^+, 401).

Mannich Reaction of the Diester (8c).—Bisdimethylaminomethane (0.44 g) and paraformaldehyde (0.014 g) were heated in acetic acid (5 cm^3) until a clear solution was obtained. The solution was cooled and added dropwise, with stirring, to an ice-cold solution of the diester (8c)

(0.263 g) in dichloromethane (10 cm³), which was then kept overnight in a refrigerator. The solution was extracted with aqueous hydrochloric acid (30 cm³), which was then washed with dichloromethane, made alkaline with sodium hydroxide, and extracted with ether (2 ×). The extract was dried and evaporated and the residue was chromatographed on alumina. Elution with benzene yielded (i) *diethyl 6-dimethylaminomethylpyrido*[2,1,6-de]*quinolizine*-1,3-*dicarboxylate* (8t) (0.164 g, 54%), orange plates, m.p. 126—127° (from ethanol) (Found: C, 68.5; H, 6.4; N, 7.3%; M^+, 368. $C_{21}H_{24}N_2O_4$ requires C, 68.5; H, 6.5; N, 7.6%; *M*, 368), and (ii) *tetraethyl 6,6′-methylenebis*(*pyrido*[2,1,6-de]-*quinolizine*-1,3-*dicarboxylate*) (16) (0.054 g, 20%), orange needles, m.p. 248—250° (from benzene) (Found: C, 70.1; H, 5.3; N, 4.1%; M^+, 634. $C_{37}H_{34}N_2O_8$ requires C, 70.0; H, 5.4; N, 4.4%; *M*, 634).

Formylation of the Ester (14b).—(a) *With* NN-*dimethylformamide–phosphoryl chloride*. *NN*-Dimethylformamide (0.048 g) and phosphoryl chloride (0.105 g) were mixed and stirred for 5 min at 0 °C and then for a further 15 min at room temperature. Dichloromethane (3 cm³) was added and the solution was cooled to −78 °C and treated with the ester (14b) (0.155 g) in the same solvent (4 cm³). The solution was stirred at −78 °C for 10 min, allowed to come to room temperature, and heated under reflux with aqueous sodium acetate (0.4 g in 10 cm³) for 15 min. The aqueous layer was extracted with chloroform (3 × 15 cm³), and the extract and the dichloromethane solution were combined, dried, and evaporated. The residue was subjected to p.l.c. on silica (elution with chloroform) to yield (i) starting material (0.004 g), (ii) an unstable red oil (0.006 g), M^+ 267, probably a monoformylation product, and (iii) *ethyl* 3-*formylpyrido*[2,1,6-de]*quinolizine*-1-*carboxylate* (0.025 g, 15%), purplish brown needles, m.p. 260—262° (from ethanol–benzene) (Found: C, 71.9; H, 5.1; N, 5.1%; M^+, 267. $C_{16}H_{13}NO_3$ requires C, 71.9; H, 4.9; N, 5.2%; *M*, 267), $\lambda_{max.}$ (EtOH) 239, 281, 293sh, 323, 341, 372, 390, 431sh, and 452 nm (log ε 4.04, 4.42, 4.2, 3.58, 3.72, 4.07, 4.38, 4.21, and 4.38).

(b) *With* NN-*dimethylformamide–benzoyl chloride*.[13] Benzoyl chloride (0.095 g) was added dropwise to a stirred solution of the ester (14b) (0.150 g) in dry *NN*-dimethylformamide (5 cm³). The solution was stirred for 20 min at room temperature, diluted with dichloromethane (15 cm³), and heated under reflux with aqueous sodium acetate (0.6 g in 15 cm³) for 10 min. Water (100 cm³) was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 20 cm³). The combined dichloromethane solution was washed with water, dried, and evaporated and the residue was subjected to p.l.c. as in (a) to yield a single product, the 3-formyl compound (0.068 g, 41%), identical with the crystalline product obtained by method (a).

Ethyl 3-*Benzoylpyrido*[2,1,6-de]*quinolizine*-1-*carboxylate* (14e).—Benzoyl chloride (0.130 g) was added dropwise to a stirred, ice-cooled solution of the ester (14b) (0.220 g) in dry *NN*-dimethylacetamide (6 cm³). The solution was stirred for 5 min at 0 °C and then for a further 5 min while warming to room temperature. Dichloromethane (10 cm³) and aqueous sodium acetate (0.8 g in 10 cm³) were added and the mixture was heated under reflux for 10 min. Water (100 cm³) was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 20 cm³). The combined dichloromethane solution was washed with water, dried, and evaporated, and the residue was chromatographed on alumina. Elution with benzene gave (i) a trace of starting material, (ii) an unidentified purple substance (0.005 g), and (iii) the *benzoyl compound* (0.122 g, 39%), orange-brown needles, m.p. 185—186° (from ethanol–benzene) (Found: C, 76.8; H, 5.1; N, 4.1%; M^+, 343. $C_{22}H_{17}NO_3$ requires C, 77.0; H, 5.0; N, 4.1%; *M*, 343), $\lambda_{max.}$ (EtOH) 244, 283, 398, 435sh, and 458 nm (log ε 4.12, 4.43, 4.37, 4.2, and 4.42).

Pyrido[2,1,6-de]*quinolizine Cation Bromide* (17).—Bromine vapour, entrained in a stream of dry nitrogen, was passed over the surface of a gently stirred solution of pyrido-[2,1,6-*de*]quinolizine (0.02 g) in dry, oxygen-free benzene (3 cm³). A blue solid was rapidly deposited from the initially yellow-green solution, leaving a colourless supernatant liquid which was removed by pipette. The residue was washed with dry benzene and dried under vacuum over concentrated sulphuric acid to give the *cation bromide*, a dark blue powder, decomp. >300° (Found: C, 57.9; H, 3.6; N, 5.8. $C_{12}H_9BrN$ requires C, 58.3; H, 3.7; N, 5.7%).

Pyrido[2,1,6-de]*quinolizine Dication Dihalides* (18).—(*a*) The foregoing procedure was repeated but the passage of bromine vapour was continued until the initial blue precipitate had changed completely to a light brown oil. The supernatant benzene, containing the excess of bromine, was removed by pipette and the reaction vessel was kept at 0.005 mmHg over concentrated sulphuric acid for 16 h. The product had then become a greenish brown, hygroscopic solid which was shown by n.m.r. to be a dication salt. The mass spectrum showed peaks at *m/e* 167 (M^{2+} + e) and 83.5 (M^{2+}) but elemental analysis showed a small excess of bromine, probably present as perbromide ion.

(*b*) A solution of pyrido[2,1,6-*de*]quinolizine in dry benzene (for molecular weight determinations) was treated with chlorine entrained in dry nitrogen. The procedure was otherwise the same as described in (*a*) and yielded the *dication dichloride* as a hygroscopic greenish brown solid (Found: C, 61.4; H, 4.1; N, 5.5. $C_{12}H_9Cl_2N$ requires C, 60.6; H, 3.8; N, 5.9%). The analytical discrepancies are believed to be due to a trace of occluded benzene.

Tetraethyl Bi(*pyrido*[2,1,6-de]*quinolizin*-6-*yl*)-1,1′,3,3′-*tetracarboxylate* (20).—*N*-Bromosuccinimide (0.13 g) was added to a stirred solution of the diester (8c) (0.30 g) in dry dichloromethane (10 cm³) at −78 °C. The deep blue colour which appeared initially changed to orange-brown when the solution was allowed to come to room temperature. The solution was stirred for 10 min at room temperature and then concentrated and chromatographed on alumina. Elution with benzene gave (i) starting material (0.01 g) and (ii) the *bi*(*pyridoquinolizinyl*) (0.167 g, 58%), purplish brown plates, m.p. 313—314° (from ethanol) (Found: C, 69.7; H, 5.2; N, 4.8%; M^+, 620. $C_{36}H_{32}N_2O_8$ requires C, 69.7; H, 5.2; N, 4.5%; *M*, 620), $\lambda_{max.}$ (CH_2Cl_2) 248, 295, 327sh, 403, and 484 nm (log ε 4.25, 4.88, 4.0, 4.51, and 4.85).

Tetraethyl 12c,14b-*Diazoniadibenzo*[cd,lm]*perylene*-1,3,8,-10-*tetracarboxylate Salts* (19).—(*a*) An excess (2.5 equiv.) of antimony pentachloride in dry benzene (2 cm³) was added dropwise to a stirred solution of the diester (8c) (0.070 g) in dry benzene (10 cm³). A deep blue precipitate was formed immediately. Ethanol (1 cm³) was added and the suspension was heated briefly on a boiling water-bath, whereupon the blue solid turned red. The solid was separated by centrifugation, washed with benzene, and dried under vacuum to yield the *diazoniadibenzoperylene bishexachloroantimonate* (0.100 g, 69%), bright red powder, no melting below

350° (Found: C, 33.8; H, 2.4; N, 2.1. $C_{36}H_{30}Cl_{12}N_2O_8Sb_2$ requires C, 33.5; H, 2.3; N, 2.2%).

(*b*) Bromine vapour, entrained in dry nitrogen, was passed over the surface of a gently stirred solution of the diester (8c) (0.240 g) in dry benzene (10 cm³). The resulting blue suspension was treated with ethanol as in (*a*) to yield the diazoniadibenzoperylene dibromide (0.206 g, 68%), bright red powder, no melting below 350°, $\lambda_{max.}$ (H_2O) 204, 230sh, 235, 291, 303sh, 313sh, 326sh, 444sh, 471, 510, and 534sh (log ε 4.57, 4.43, 4.44, 4.58, 4.45, 4.37, 4.14, 4.39, 4.64, and 3.74). Addition of tetrafluoroboric acid to an aqueous solution of the dibromide precipitated the bistetrafluoroborate, *m/e* 618 (M^{2+} + e) and 309 (M^{2+}).

The mother liquor and washings from the dibromide were evaporated and the residue was subjected to p.l.c. on silica in chloroform to give the bi(pyridoquinolizinyl) (20) (0.027 g, 11%), identical with the product obtained by treatment of the diester (8c) with *N*-bromosuccinimide.

(*c*) A solution of the bi(pyridoquinolizinyl) (20) (0.027 g) in benzene was treated with bromine vapour and then with ethanol, as in (*b*), to yield the diazoniadibenzoperylene dibromide (0.020 g), identical with the product obtained directly from the diester (8c).

6-*Methyl*-3-*phenylcyclopenta*[ij]*pyrido*[2,1,6-de]*quinolizine* (3a) (with J. W. Dick).—Following the general procedures described in Part III,[27] 7-methyl-2-phenylindolizine was converted into *dimethyl* 7-*methyl*-4-*phenylcyclopenta*[c]-*quinolizine*-1,2-*dicarboxylate*, orange needles, m.p. 214—215° (from ethanol) (Found: C, 73.9; H, 5.1; N, 3.6. $C_{23}H_{19}NO_4$ requires C, 74.0; H, 5.1; N, 3.8%). Hydrolysis and decarboxylation then yielded 7-methyl-4-phenylcyclopenta[*c*]quinolizine as a red solid which was not purified. Reaction of this with ethyl propiolate in boiling nitrobenzene, following the general procedure described in Part IV,[1] yielded *ethyl* 6-*methyl*-3-*phenylcyclopenta*[ij]*pyrido*[2,1,6-de]-*quinolizine*-8-*carboxylate*, green needles, m.p. 164—165° (from ethanol) (Found: C, 81.5; H, 5.3; N, 3.9. $C_{24}H_{19}NO_2$ requires C, 81.6; H, 5.4; N, 4.0%). The ester was then hydrolysed [1] to yield 6-*methyl*-3-*phenylcyclopenta*[ij]*pyrido*-[2,1,6-de]*quinolizine*, green plates, m.p. 175—176° (from ethanol) (Found: C, 89.2; H, 5.4; N, 4.9. $C_{21}H_{15}N$ requires C, 89.7; H, 5.3; N, 5.0%).

Dimethyl 3,9-*Dimethylcyclopenta*[ij]*pyrido*[2,1,6-de]-*quinolizin*-1-*ylmaleate* (26).—The cyclopentapyridoquinolizine (3b) [1] (0.30 g) in dry benzene (10 cm³) was heated under reflux with dimethyl acetylenedicarboxylate (0.60 g) for 3 min. The solution was filtered and evaporated and the residue was chromatographed on alumina. Elution with light petroleum–benzene yielded (i) starting material (3b) (0.022 g) and (ii) an unidentified dark brown solid (0.017 g). Further elution with benzene yielded the *maleate* (0.198 g, 40%), dark brown needles, m.p. 156—157° (from ethanol) (Found: C, 73.6; H, 5.3; N, 4.0. $C_{22}H_{19}NO_4$ requires C, 73.1; H, 5.3; N, 3.9%), τ 2.87 (1 H, s, H-2), 2.65—3.25 (3 H, m, H-5, -6, and -7), 3.45 (1 H, s, H-4 or -8), 3.52 (1 H, s, H-8 or -4), 4.12 (1 H, s, olefinic),[1] 6.04 (3 H, s, OMe), 6.21 (3 H, s, OMe), 7.47 (3 H, s, CMe), and 7.59 (3 H, s, CMe).

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[27] W. K. Gibson and D. Leaver, *J. Chem. Soc.* (*C*), 1966, 324.