# Heterocyclic Compounds with Bridgehead Nitrogen Atoms. Part III.[1,2] The Formation of Cyclopenta[*c*]quinolizines from 3-α-Dimethylaminovinylindolizines and Dimethyl Acetylenedicarboxylate

By W. K. Gibson and D. Leaver

2-Alkyl- and 2-aryl-indolizines react with *NN*-dimethylacetamide, in presence of phosphoryl chloride, to give 3-α-dimethylaminoethylideneindolizinium salts. The enamines derived from the salts by proton-loss react with dimethyl acetylenedicarboxylate in boiling toluene to give dimethyl cyclopenta[*c*]quinolizinedicarboxylates. The intermediate compounds in this rearrangement have been isolated and the substitution reactions of the cyclopenta[*c*]quinolizine nucleus have been studied.

HAFNER and his co-workers[3a] have shown that the enamine (I), obtainable from 4,6,8-trimethylazulene and *NN*-dimethylacetamide, can be converted into a derivative of cyclopenta[*ef*]heptalene (II). It seemed possible, therefore, that the enamine (IIIa) might be similarly converted into a derivative of cycl[4,3,2]azine (IV). It was found, however, that reaction of *NN*-di-

[1] Part II, D. Leaver and J. D. R. Vass, *J. Chem. Soc.*, 1965, 1629.

[2] Preliminary communication, W. K. Gibson and D. Leaver, *Proc. Chem. Soc.*, 1964, 330.

[3] (*a*) K. Hafner and K.-F. Bangert, *Annalen*, 1961, **650**, 98; (*b*) K. Hafner and J. Schneider, *ibid.*, 1959, **624**, 37.

methylacetamide with 5-methyl-2-phenylindolizine, in presence of phosphoryl chloride, gave, after a short time, a mixture of the 1- and the 3-α-dimethylaminoethylidene compounds * (Va) and (VIa), the former predominating. Longer reaction times gave only the 1-isomer (Va). The 3-isomer (VIa) was obtained pure, but in insufficient quantity for further reactions, by taking advantage of the difference in behaviour of the two isomers towards alkali. Treatment of the mixture of perchlorates with sodium hydroxide gave the 1-acetyl compound and the enamine (IIIa) which were separated by chromatography. The enamine was then reconverted into the perchlorate (VIa). The structures of the two isomers (Va) and (VIa) follow from the resemblance of their ultraviolet and visible spectra to those of the similarly prepared model compounds (Vb) and (VIb), respectively (Figure 1).

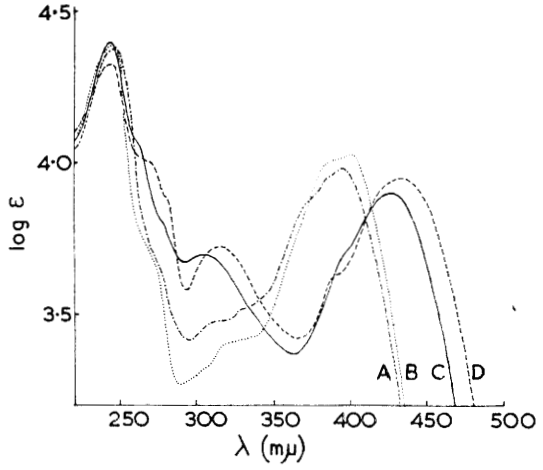
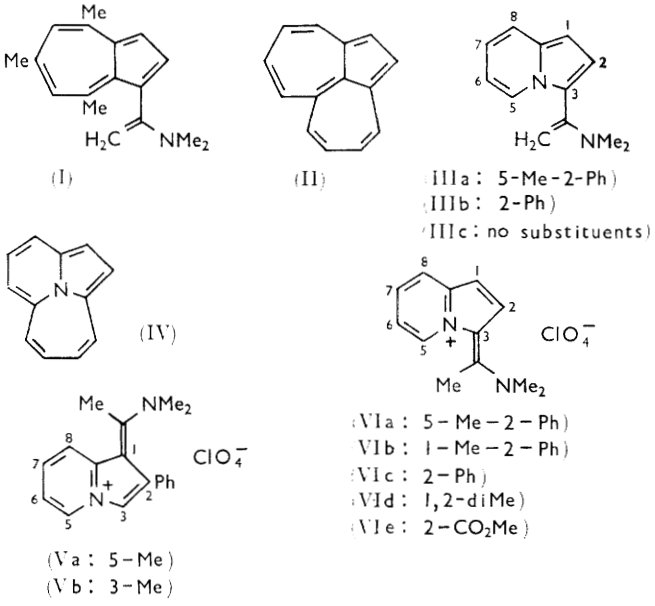


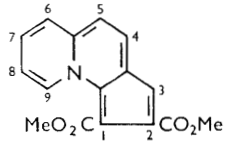

FIGURE 1 Ultraviolet and visible spectra, in ethanol, of α-dimethylaminoethylideneindolizinium perchlorates; (A) (Va); (B) (Vb); (C) (VIa); (D) (VIb)

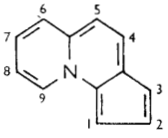



* The majority of such compounds were isolated as crystalline perchlorates.

Substitution in the 1-position of indolizines is unusual but the variation in product composition with time suggests that the reaction is reversible and that the 3-isomer, although formed initially, is the thermodynamically less-favoured product, probably owing to the steric effect of the 5-methyl group. Indolizines lacking a 5-substituent gave only the 3-dimethylaminoethylidene compounds.

Following the failure of this approach † to the synthesis of cycl[4,3,2]azines, we allowed the enamines (III) to react with dimethyl acetylenedicarboxylate in boiling toluene. Dimethylamine was evolved, suggesting that cyclisation had occurred, but the resulting orange diesters showed a low-field n.m.r. absorption (between −0·4 and 0·3 τ) which was attributable to the α-pyridine proton (position 5 in the original indolizine) since its multiplicity varied in the expected way with the position of methyl substitution in this pyridine ring. It was clear, therefore, that the compounds were not cycl[4,3,2]azines, but their properties can be accounted for on the basis of the cyclopenta[*c*]quinolizine formula (VII), rings A and B of which are iso-π-electronic with azulene. It was clear from the outset that, if the compounds were correctly represented by this ring system, the two ester groups must occupy adjacent positions in ring A. They were assigned to the 1- and 2- rather than the 2- and 3-positions since the abnormally low τ-value of the 9-proton (cf. the value of 1·5 for the α-protons in pyridine) could then be attributed to long-range deshielding by the 1-methoxycarbonyl group.




a: 4-Ph
b: 4-Me
c: 5-Me-4-Ph
d: 4,5-diMe
e: 4,6-diMe
f: 4,7-diMe
g: 4,8-diMe
h: 3,4-diMe
i: 4-$CO_2$Me

Boiling the 1,2-diesters with 6N-hydrochloric acid for 7 hr. caused hydrolysis and complete decarboxylation. The resulting parent compounds (VIII) showed ultraviolet and visible spectra similar to those of the diesters (Figure 2), indicating that no further rearrangement had taken place, and their n.m.r. spectra showed the expected upfield shift of the 9-proton signal (to $\tau = 1{\cdot}3$—$1{\cdot}6$) due to removal of the 1-methoxycarbonyl group. In acid solution, the ultraviolet spectra of the parent compounds (VIII) resembled those of the quinolizinium [4] and benzo[*c*]quinolizinium [5] ions (Figure 3) and were attributed to the protonated species (IX, or the 3*H*-isomers). Further evidence for the presence

† Other approaches, based on the work of Hafner [3b] in the azulene series, also failed to yield the desired ring system.

[4] V. Boekelheide and W. G. Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.

[5] E. E. Glover and G. Jones, *J. Chem. Soc.*, 1958, 3021.

of a quinolizine nucleus was afforded by oxidation of the triester (VIIi), with nitric acid, to the betaine (X). The latter compound has previously been obtained [6] by nitric acid oxidation of the 7,10-dimethoxybenzo[*b*]quinolizinium ion but we found it more convenient to prepare an authentic specimen by similar oxidation of the readily available [7] 2,3-di-(2-furyl)-quinolizinium ion.

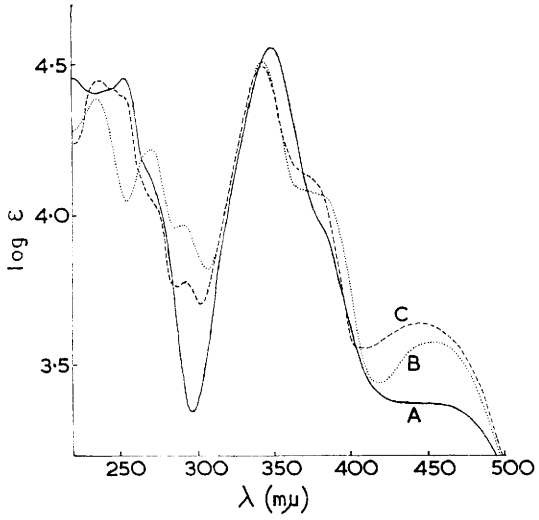



FIGURE 2 Ultraviolet and visible spectra, in ethanol, of cyclopenta[*c*]quinolizines; (A) (VIIIb); (B) (XVb); (C) (VIIb)

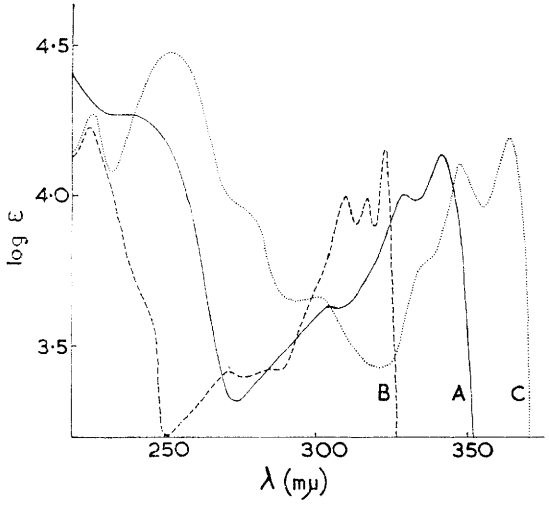
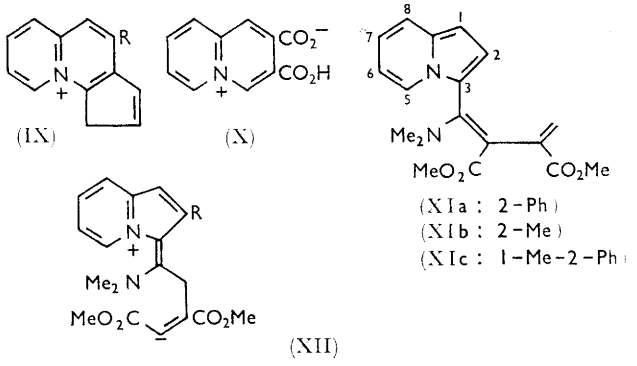



FIGURE 3 Ultraviolet spectra of (A) 4-methylcyclopenta[*c*]-quinolizine in ethanol containing 5% perchloric acid; (B) quinolizinium iodide [4] in water; (C) benzo[*c*]quinolizinium perchlorate [5] in water

Partial alkaline hydrolysis and decarboxylation of the 4-phenyl-diester (VIIa) gave a yellow and a red monoester. The ester groups in these compounds are assigned to the 1- and 2-positions, respectively, on the basis of the 9-proton τ-value which was low (−1·33) for the yellow ester and normal (1·2) for the red one. Hydrolysis of the same diester with acetic acid–hydrochloric acid for 3·2 hr. gave mainly the 2-carboxylic acid, convertible into the red monoester with methanolic hydrogen chloride. In the azulene series, 1-methoxycarbonyl substituents shift the visible absorption maxima hypsochromically whereas 2-methoxycarbonyl substituents cause bathochromic shifts.[8] Qualitatively similar effects are apparent in the cyclopenta[*c*]quinolizines and may be exemplified by the following values of $\lambda_{max.}$ (longest wavelength) for derivatives of the




4-phenyl compound (VIIIa): parent, 488; 1-methoxycarbonyl (yellow monoester), 445; 2-methoxycarbonyl (red monoester), 493; 1,2-dimethoxycarbonyl, 463 mμ.

The formation of the cyclopenta[*c*]quinolizines involves a rearrangement (indolizine to quinolizine) that is without precedent. It was of interest, therefore, to try to discover the nature of the intermediate compounds in the reaction sequence. In cold aprotic solvents, the enamine (IIIb) and dimethyl acetylenedicarboxylate gave a yellow 1 : 1 adduct which, when boiled in toluene, yielded the cyclopenta[*c*]quinolizine (VIIa) with loss of dimethylamine. The n.m.r. spectrum of the adduct, in the regions 1·8—2·0 and 3·0—3·6 τ, showed a pattern of multiplets (5 protons) that indicated the presence of an indolizine nucleus since it was almost identical with the corresponding pattern in the spectrum of the enamine (IIIb). On the basis of this evidence, and by analogy with the structures established [9] for related enamine–acetylenic ester adducts, the structure (XIa) was assigned to the compound. The remainder of its n.m.r. spectum showed a five-proton multiplet at τ 2·3—2·8 (phenyl), two three-proton singlets at τ 6·3 and 6·5 (OMe), a six-proton singlet at τ 7·35 ($NMe_2$), and two equivalent one-proton doublets ($J$ = 1·3 c./sec.) at τ 4·46 and 5·02 (=$CH_2$). The mechanism established [9] for related reactions led us to suppose that the adduct must have been formed by way of the zwitterion (XII) and the cyclobutene (XIII). By carrying out the reaction in methanol, the intermediacy of the zwitterion was rendered more apparent since it was then inter-

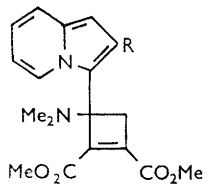
[6] C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, 1964, **29**, 452.

[7] O. Westphal, K. Jahn, and W. Heffe, *Arch. Pharm.*, 1961, **294**, 37.

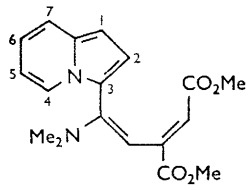
[8] M. Scholz and W. Treibs, *Z. Elektrochem.*, 1961, **65**, 120.

[9] G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, 1963, **28**, 1459; K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *ibid.*, p. 1464; C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, p. 3134.

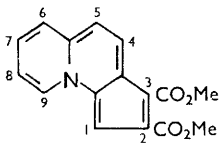
cepted by proton transfer to give the isomeric adduct (XIVa). The n.m.r. spectrum of this second adduct, in the low-field region, was very similar to that of the



(XIII)



(XIVa : 2-Ph)
(XIVb : 2-Me)
(XIVc : 1-Me-2-Ph)



(XV)

qualifying letters as for (VII)

first, but the signals due to the terminal methylene group were replaced by two barely resolved doublets ($J$ = 0·8 c./sec.), at $\tau$ 3·29 and 4·66, attributable to the differently situated olefinic protons of the side-chain. Conclusive evidence for retention of the indolizine nucleus was provided by recovery of 1-methyl-2-phenylindolizine after hydrolysis of the adduct (XIVc) with acetic acid–hydrochloric acid.

The second adduct was only slowly changed by boiling toluene but, after 24 hr. in boiling xylene, it gave a moderate yield of the cyclopenta[*c*]quinolizine 2,3-diester (XVa). The latter showed a 9-proton n.m.r. absorption at $\tau$ 1·3, consistent with the absence of a 1-methoxycarbonyl group, and was converted, by partial acid hydrolysis, into the 2-carboxylic acid, identical with the specimen obtained from the 1,2-diester (VIIa). A number of related 2,3-diesters were prepared and showed ultraviolet and visible spectra (Figure 2) similar to those of the 1,2-diesters.

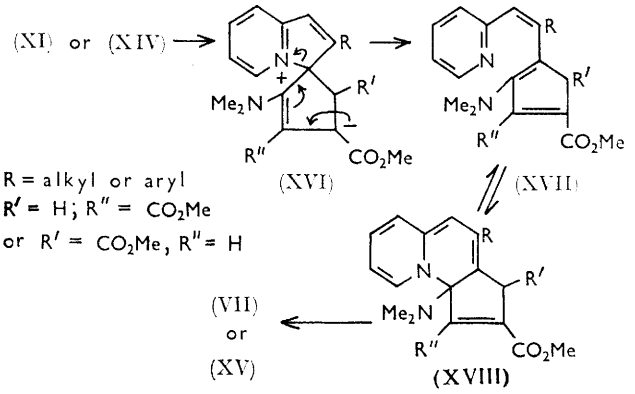
In an attempt to detect other intermediate compounds along the reaction pathway leading to the 1,2-diesters (VII), the adduct (XIb) was heated at 110° in tetrachloroethylene and the n.m.r. spectrum of the solution was examined at hourly intervals. No absorptions were observed that could not be attributed to the adduct, the final product, or dimethylamine. We conclude, therefore, that other intermediates have only a transitory existence. The most likely sequence of reactions, capable of accounting for the transformation, is that shown in the accompanying Scheme. It is suggested that the reaction is initiated by electrophilic attack of the terminal carbon atom of the side-chain at the 3-position of the indolizine nucleus. Charge neutralisation in the resulting spiro-zwitterion (XVI) would then lead to opening of the pyrrole ring. Valency tautomerisation [10] of compound (XVII) to the 4*H*-quinolizine (XVIII) and loss of dimethylamine complete the reaction.

[10] J. A. Elvidge and J. M. Jackman, *J. Chem. Soc.*, 1961, 859.
[11] A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Amer. Chem. Soc.*, 1953, **75**, 4980.

We are at present seeking experimental evidence to substantiate this mechanism.

The enamines (IIIa) and (IIIc) did not yield cyclopenta[*c*]quinolizines with dimethyl acetylenedicarboxylate in boiling toluene. Failure in the former instance may be due to the steric effect of the 5-methyl group but no explanation can be offered for the failure of the enamine (IIIc), derived from unsubstituted indolizine, to undergo the reaction. The enamine derived from 2-methylindolizine and *NN*-dimethylpropionamide reacted normally, although in poor yield, to give the diester (VIIh).

Electrophilic substitution in azulenes occurs under mild conditions in the 1- and 3-positions,[11] and the iso-π-electronic cyclopenta[*c*]thiopyrans react similarly




in the analogous 5- and 7-positions.[12] It was of interest, therefore, to compare the behaviour of the cyclopenta[*c*]quinolizines. The 4-methyl compound (VIIIb) reacted with acyl chlorides (acetyl and benzoyl) in the absence of a catalyst to give mono- and di-acyl derivatives, and with the *NN*-dimethylformamide–phosphoryl chloride reagent to give a diformyl compound. The 9-protons of the mono- and di-benzoyl and diformyl compounds showed $\tau$ values between −0·2 and −1·3, indicating the presence of an acyl group in the 1-position. Apparently the second acyl group had entered either the 3- or the 5-position since the 4-methyl groups of the diformyl and dibenzoyl compounds were deshielded ($\tau$ 7·01, 7·07) relative to those in the parent compound ($\tau$ 7·30) and its 1-benzoyl derivative ($\tau$ 7·33). The absence of a 5-substituent was shown, however, by the splitting of the methyl signal ($J$ = 0·5 c./sec.) of the dibenzoyl compound due to coupling with the 5-proton. A similar splitting of the methyl signal was shown by the 1,2-diester (VIIb) but not by its 3,5-dibromoderivative.

Two isomeric arylazo-compounds were formed when the 4-methyl compound (VIIIb) was allowed to react with either benzene- or *p*-bromobenzene-diazonium chloride. The 9-proton n.m.r. absorption of the lower-melting phenylazo-compound was observed at the very low $\tau$-value of −0·36 and showed that substitution had

[12] A. G. Anderson and W. F. Harrison, *J. Amer. Chem. Soc.*, 1964, **86**, 708.

occurred in the 1-position. The corresponding absorption in the higher-melting isomer was observed at τ 1·4, showing the absence of a deshielding substituent at the 1-position and indicating that substitution had occurred in the 3-position. Support for this conclusion was provided by the deshielding of the 4-methyl group (τ 6·94) in the 3-phenylazo-compound relative to that in the 1-phenylazo-compound (τ 7·33). The lower- and higher-melting *p*-bromophenylazo-compounds were *not* sufficiently soluble for examination by n.m.r. spectroscopy but positional assignments were possible for analysis from solvents (Table 1) containing a trace of perchloric acid.

Crystalline perchlorates were obtained, following this procedure, from 2-methyl- and 2,6-dimethyl-indolizine but they were not analysed. 2,7- and 2,8-Dimethylindolizines did not yield crystalline perchlorates and the product from 2-methylindolizine and *NN*-dimethylpropionamide was also non-crystalline.

When applied to 5-methyl-2-phenylindolizine, the foregoing procedure gave the 1-dimethylaminoethylidene compound but shortening of the reaction time to 5 min. gave a mixture of the 1- and 3-isomers. The mixed isomers were

TABLE 1

α-Dimethylaminoethylideneindolizinium perchlorates

| | | | Found (%) | | | | | Required (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | Solvent | M. p. | C | H | Cl | N | Formula | C | H | Cl | N |
| (Va) | $MeNO_2$ | 226° | 60·1 | 5·1 | 10·1 | 7·5 | $C_{19}H_{21}ClN_2O_4$ | 60·5 | 5·35 | 9·4 | 7·4 |
| (Vb) | AcOH | 249—250 | 60·6 | 5·6 | 9·6 | 7·5 | ,, | ,, | ,, | ,, | ,, |
| (VIb) | MeOH–AcOH | 236—237 | 61·0 | 6·0 | 9·8 | 7·1 | ,, | ,, | ,, | ,, | ,, |
| (VIc) | $MeNO_2$ | 237 | 59·6 | 5·1 | 9·8 | 7·9 | $C_{18}H_{19}ClN_2O_4$ | 59·5 | 5·2 | 9·75 | 7·7 |
| (VId) | MeOH | 163 | | | 10·7 | 8·75 | $C_{14}H_{19}ClN_2O_4$ | | | 11·3 | 8·9 |
| (VIe) | MeOH | 173—174 | 48·7 | 4·9 | 10·3 | 7·6 | $C_{14}H_{17}ClN_2O_6$ | 48·8 | 4·9 | 10·3 | 8·1 |

since their ultraviolet and visible spectra (Table 5) differed from each other but resembled those of the 1- and 3-phenylazo-compounds, respectively.

Treatment of the 4-methyl compound (VIIIb) with isopentyl nitrite and phosphoryl chloride afforded a green nitroso-derivative which, however, gave unsatisfactory analytical results for nitrogen. Attempted halogenation or nitration (even with tetranitromethane) of the quinolizine (VIIIb) led to decomposition, but the diesters (VIIa) and (VIIb) were readily brominated to give 3,5-dibromo-derivatives. Under the same conditions, the diester (VIId), in which the 5-position is blocked, yielded only a 3-monobromo-derivative.

## EXPERIMENTAL

Extracts were dried over anhydrous sodium or magnesium sulphates and all evaporations were carried out under reduced pressure. Nuclear magnetic resonance spectra were measured, for deuteriochloroform solutions, by means of a Perkin-Elmer R10 (60 Mc./sec.) spectrometer. Chromatographic separations were carried out on columns of alumina (Peter Spence, type H, untreated). Light petroleum refers to the fraction of b. p. 60—80° unless otherwise stated.

*α-Dimethylaminoethylideneindolizinium Perchlorates.*—The indolizine (0·05 mole) and *NN*-dimethylacetamide (0·052 mole) were dissolved in boiling anhydrous benzene (100 ml. or a larger volume if required to dissolve the indolizine) and phosphoryl chloride (0·054 mole) was added at such a rate that the reaction did not become too vigorous. The mixture was stirred and boiled for a further 15—30 min. and then cooled and diluted with ether. After decantation of the benzene–ether layer, the lower oily layer was dissolved in the minimum quantity of methanol, and perchloric acid (70%) was added, with cooling, until precipitation was complete. The yellow crystalline perchlorate was filtered off and washed with cold methanol and with ether. The salts (60—90% yield) were then sufficiently pure for further reactions but samples were recrystallised boiled with an excess of sodium hydroxide in aqueous ethanol for 2 hr. Extraction with ether then yielded a brown oil which was chromatographed on alumina. Elution with ether gave first an oily enamine and then 1-*acetyl*-5-*methyl*-2-*phenylindolizine*, needles, m. p. 111—112° [from light petroleum (b. p. 80—100°)] (Found: C, 81·9; H, 5·7; N, 5·3. $C_{17}H_{15}NO$ requires C, 82·0; H, 6·0; N, 5·6%), identical with a sample obtained by hydrolysis of the 1-dimethylaminoethylidene compound. The enamine, in methanol, was treated with perchloric acid to give 3-α-*dimethylaminoethylidene*-5-*methyl*-2-*phenylindolizinium perchlorate*, yellow needles, m. p. 209—210° (from acetic acid containing a trace of perchloric acid) (Found: C, 60·5; H, 5·25; Cl, 8·8; N, 7·2. $C_{19}H_{21}ClN_2O_4$ requires C, 60·5; H, 5·35; Cl, 9·4; N, 7·4%).

3-α-*Dimethylaminovinylindolizines.*—The dimethylaminoethylideneindolizinium perchlorate, or (when the perchlorate did not crystallise) the oil obtained after dilution of the initial reaction mixture with ether, was dissolved in the minimum quantity of acetonitrile (or *NN*-dimethylformamide) and treated with an excess of 2N-aqueous sodium hydroxide at 0° (for 2-aryl compounds) or at −7° (for 2-alkyl compounds). The liberated enamine was immediately extracted into ether and the extract was washed with cold water, dried, and evaporated. The enamines from 2-alkylindolizines were liquids and no attempt was made to purify them, but 2-phenyl- and 1-methyl-2-phenyl-indolizine gave crystalline enamines, 3-α-*dimethylaminovinyl*-2-*phenylindolizine*, m. p. 98—99° (from ethanol) (Found: C, 82·6; H, 7·0; N, 10·6. $C_{18}H_{18}N_2$ requires C, 82·6; H, 6·9; N, 10·7%) and 3-α-*dimethylaminovinyl*-1-*methyl*-2-*phenylindolizine*, m. p. 92—93° [from light petroleum (b. p. 100—120°)] (Found: C, 82·6; H, 7·2; N, 10·1. $C_{19}H_{20}N_2$ requires C, 82·9; H, 7·2; N, 10·2%).

3-(2,3-*Dimethoxycarbonyl*-1-*dimethylaminobuta*-1,3-*dien*-1-*yl*)*indolizines* (XI).—The 3-α-dimethylaminovinylindolizine and a slight excess of dimethyl acetylenedicarboxylate were dissolved in toluene, benzene, or ether and set aside for 24 hr. or more at room temperature. The solution was evaporated and the residual dark oil was chromatographed

on alumina. Elution with ether and collection of the main yellow zone gave the adduct in good yield. Details of the adducts are given in Table 2.

*3-(3,4-Dimethoxycarbonyl-1-dimethylaminobuta-1,3-dien-1-yl)indolizines* (XIV).—The 3-α-dimethylaminovinylindolizine and a slight excess of dimethyl acetylenedicarboxylate were boiled in methanol for 10 min. The solution was evaporated and the residual oil was chromatographed on alumina. Elution with ether and collection of the main yellow zone gave the adduct in good yield. Details of the adducts are given in Table 2.

*Dimethyl Cyclopenta[c]quinolizine-1,2-dicarboxylates.*—(*a*) The appropriate 3-α-dimethylaminovinylindolizine and dimethyl acetylenedicarboxylate (2—5% excess) were boiled in sulphur-free toluene (5—15 ml. per mmole enamine) under nitrogen for 24 hr. The solution was allowed to cool and the portion of product that crystallised was collected by filtration. The toluene solution was then evaporated and the residue was triturated with ethanol or methanol to induce further crystallisation.

(*b*) The appropriate 2,3-dimethoxycarbonylbutadienylindolizine was boiled in sulphur-free toluene, under nitrogen, for 24 hr. and the solution was worked up in the same way as in method (*a*).

Details of the diesters prepared in these ways are given in Table 3. All the esters formed yellow, orange, or red crystals from ethanol.

*Dimethyl Cyclopenta[c]quinolizine-2,3-dicarboxylates.*—The compounds were obtained in the same way as the 1,2-dicarboxylates [method (*b*)] by boiling the 3,4-dimethoxycarbonylbutadienylindolizines in sulphur-free xylene for 24—30 hr. Details of the esters are given in Table 3.

*Methyl 4-Phenylcyclopenta[c]quinolizine-1- and -2-carboxylates.*—Dimethyl 4-phenylcyclopenta[*c*]quinolizine-1,2-dicarboxylate (1 g.) was boiled with an excess of potassium hydroxide in methanol (100 ml.)–water (1 ml.) for 7 hr. The methanol was evaporated, the residue was treated with water, and the resulting aqueous solution was filtered to remove starting material (0·27 g.). The filtrate was acidified to pH 5 by addition of hydrochloric acid and the resulting red precipitate of methyl hydrogen dicarboxylates (0·59 g.) was filtered off and dried. Heating the mixture (2 g.) in a sublimation apparatus at 215°/0·03 mm. caused decarboxylation, and a mixture of monoesters was collected on the cold-finger. Chromatography on alumina in ether gave first *methyl 4-phenylcyclopenta*[c]*quinolizine-1-carboxylate* (0·7 g.), yellow plates, m. p. 159—160° [from light petroleum (b. p. 80—100°)] (Found: C, 79·15; H, 4·9; N, 4·8. $C_{20}H_{15}NO_2$ requires C, 79·6; H, 5·0; N, 4·65%), and then *methyl 4-phenylcyclopenta*[c]*quinolizine-2-carboxylate* (0·13 g.), red needles, m. p. 229—231°) from chloroform–light petroleum (Found: C, 79·6; H, 5·0; N, 4·7%).

*4-Phenylcyclopenta[c]quinolizine-2-carboxylic Acid.*—(*a*) Dimethyl 4-phenylcyclopenta[*c*]quinolizine-1,2-dicarboxylate (1 g.) was heated at 100° with acetic acid (20 ml.), concentrated hydrochloric acid (2 ml.), and water (0·5 ml.) for 3·5 hr., cooled, and diluted with water (50 ml.). The solution was adjusted to pH 5 by addition of sodium hydrogen carbonate and the resulting red precipitate (0·61 g.) was filtered off and dried. Crystallisation from ethanol–*NN*-dimethylformamide gave the *acid*, red needles, m. p. 264° (decomp.) (Found: C, 78·9; H, 4·8; N, 4·6. $C_{19}H_{13}NO_2$ requires C, 79·7; H, 4·5; N, 4·9%). Esterification, by boiling the acid for 2·5 hr. in methanol saturated with hydrogen chloride, gave methyl 4-phenylcyclopenta[*c*]quinolizine-2-carboxylate, m. p. 229—231°, infrared spectrum identical with that of the product obtained from the 1,2-diester by partial alkaline hydrolysis and decarboxylation.

(*b*) Dimethyl 4-phenylcyclopenta[*c*]quinolizine-2,3-dicarboxylate (0·2 g.) was boiled with 5N-hydrochloric acid

TABLE 2

Adducts of dimethylaminovinylindolizines and dimethyl acetylenedicarboxylate

| Adduct | Recryst. from * | M. p. | Found (%) C | H | N | Formula | equired (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (XIa) | L.P.–EtOAc | 143—144° | 71·1 | 5·8 | 7·1 | $C_{24}H_{24}N_2O_4$ | 71·3 | 5·9 | 6·9 |
| (XIVa) | EtOH | 133—134 | 71·5 | 6·0 | 7·4 | ,, | | | |
| (XIb) | $C_2Cl_4$ or L.P. | 103—104 | 66·5 | 6·2 | 8·3 | $C_{19}H_{22}N_2O_4$ | 66·6 | 6·5 | 8·2 |
| (XIc) | | Oil | 71·8 | 6·5 | 6·5 | $C_{25}H_{26}N_2O_4$ | 71·8 | 6·3 | 6·7 |
| (XIVc) | MeOH | 108—109 | 71·7 | 6·0 | 6·5 | ,, | | | |

* L.P. = Light petroleum.

TABLE 3

Dimethyl cyclopenta[*c*]quinolizinedicarboxylates

| Diester | Yield (%) * | M. p. | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (VIIa) | 70 | 175—176° | 73·2 | 4·6 | 4·5 | $C_{22}H_{17}NO_4$ | 73·7 | 4·5 | 3·9 |
| (XVa) | 45 | 196—197 | 73·7 | 4·4 | 3·7 | ,, | ,, | ,, | ,, |
| (VIIb) | 60 | 162—163 | 68·5 | 5·1 | 4·8 | $C_{17}H_{15}NO_4$ | 68·8 | 5·05 | 4·7 |
| (XVb) | 32 | 144—146 | 68·4 | 4·7 | 4·8 | ,, | ,, | ,, | ,, |
| (VIIc) | 73 | 162—163 | 73·8 | 5·1 | 3·8 | $C_{23}H_{19}NO_4$ | 73·9 | 5·1 | 3·8 |
| (XVc) | 44 | 215—216 | 73·8 | 4·8 | 3·7 | ,, | ,, | ,, | ,, |
| (VIId) | 63 | 193—194 | 69·9 | 5·4 | 4·5 | $C_{18}H_{17}NO_4$ | 69·45 | 5·5 | 4·5 |
| (VIIe) | 56 | 225—226 | 69·65 | 6·0 | 4·5 | ,, | ,, | ,, | ,, |
| (VIIf) | 8·5 | 218—220 | 69·4 | 5·1 | 4·5 | ,, | ,, | ,, | ,, |
| (VIIg) | 53 | 179—180 | 69·7 | 5·35 | 4·5 | ,, | ,, | ,, | ,, |
| (VIIh) | 12 | 166—168 | 69·7 | 5·35 | 4·7 | ,, | ,, | ,, | ,, |
| (VIIi) | 31 † | 188—189 | 63·2 | 4·3 | 4·2 | $C_{18}H_{15}NO_6$ | 63·6 | 4·4 | 4·1 |

* The yields reported for compounds (VII) are for preparation by method (*a*). † Prepared in boiling xylene.

for 7 hr. and the solution was cooled and diluted with water. The resulting red precipitate was filtered off and washed with methanol and then with ether. The material recovered from the washings was the 2-carboxylic acid, infrared spectrum identical with that of the sample obtained from the 1,2-diester. The main portion of the precipitate was dried and heated in an evacuated sublimation apparatus to give 4-phenylcyclopenta[*c*]quinolizine.

*Cyclopenta*[c]*quinolizines.*—(A) The dimethyl cyclopenta-[*c*]quinolizine-1,2-dicarboxylate was boiled with 6N-hydrochloric acid (10 ml. per g. diester) for 7—9 hr. The solution was cooled, made alkaline with sodium hydroxide, and extracted with ether. The extract was dried and evaporated and the residual solid was recrystallised from light petroleum (b. p. 60—80 or 80—100°).

During hydrolysis of the 4,6-dimethyl compound, a hydrochloride was precipitated and the reaction occurred much more slowly. After 28 hr. the remaining hydrochloride was filtered off and the quinolizine was recovered from the filtrate in the usual way. The quinolizines were red or deep orange crystalline solids, details of which are given in Table 4.

TABLE 4

Cyclopenta[*c*]quinolizines

| Compound | Yield (%) * | M. p. | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (VIIIa) | 50 | 111—112° | 88·8 | 5·5 | 5·75 | $C_{18}H_{13}N$ | 88·8 | 5·4 | 5·8 |
| (VIIIb) | 50 | 77—78 | 86·3 | 5·95 | 7·6 | $C_{13}H_{11}N$ | 86·2 | 6·1 | 7·7 |
| (VIIId) | 50 | 105—106 | 86·5 | 6·8 | 7·1 | $C_{14}H_{13}N$ | 86·3 | 6·7 | 7·2 |
| (VIIIe) | 35 | 138 | 86·0 | 6·5 | 7·1 | ,, | ,, | ,, | ,, |
| (VIIIf) | 42 | 85—86 | 85·4 | 6·3 | 7·1 | ,, | ,, | ,, | ,, |
| (VIIIg) | 44 | 89—90 | 86·6 | 7·0 | 6·6 | ,, | ,, | ,, | ,, |

* For preparation by method (A).

(B) Crude 4-phenylcyclopenta[*c*]quinolizine-2-carboxylic acid was heated, under 0·01 mm. pressure, in a sublimation apparatus until accumulation of red oil on the cold-finger was complete. Chromatography of the oil, in benzene, on alumina and crystallisation of the most rapidly eluted material from methanol gave 4-phenylcyclopenta[*c*]quinolizine identical with a specimen prepared by method (A).

1,3-*Diformyl*-4-*methylcyclopenta*[c]*quinolizine.* — Phosphoryl chloride (0·2 ml.) was added to 4-methylcyclopenta-[*c*]quinolizine (0·1 g.) in boiling *NN*-dimethylformamide (0·15 ml.) and the solution was boiled for a further 2 min. An excess of saturated aqueous sodium hydrogen carbonate was added, boiling was continued for 10 min., and aqueous sodium hydroxide was added. The resulting precipitate was recrystallised from ethanol to give the *dialdehyde* (0·085 g.), pale yellow needles, m. p. 209—211° (Found: C, 76·6; H, 4·6; N, 6·3. $C_{15}H_{11}NO_2$ requires C, 76·1; H, 4·65; N, 5·9%). The aldehydic protons gave rise to sharp signals at $\tau$ 0·03 and 0·33 in the n.m.r. spectrum.

*Acetylation of* 4-*Methylcyclopenta*[c]*quinolizine.*—The quinolizine (0·1 g.) and anhydrous sodium acetate (0·1 g.) were boiled in acetic anhydride (2 ml.) for 1 hr. Shaking the solution with an excess of aqueous sodium hydroxide gave a tarry material which was extracted with boiling ether. The extract was washed with water, dried, and evaporated. Chromatography of the residue, on alumina, in ether gave first 1-*acetyl*-4-*methylcyclopenta*[c]*quinolizine*, yellow needles, m. p. 110° (from light petroleum) (Found: C, 80·9; H, 6·1; N, 6·5. $C_{15}H_{13}NO$ requires C, 80·7; H, 5·8; N, 6·3%), and then 1,3-*diacetyl*-4-*methylcyclopenta*[c]*quinolizine*, pale yellow needles, m. p. 217—219° (from ethanol) (Found: C, 77·1; H, 5·8; N, 5·5. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%). The total yield of ketones was about 20%.

1-*Benzoyl*-4-*methylcyclopenta*[c]*quinolizine.* — 4-Methylcyclopenta[*c*]quinolizine (0·1 g.) was added to benzoyl chloride (2 ml.). A precipitate formed immediately and the mixture was shaken with aqueous sodium hydroxide to hydrolyse the excess of benzoyl chloride. Extraction with chloroform and evaporation of the dried extract gave an oil which was chromatographed on alumina, in ether, to give the *ketone* (0·085 g.), yellow needles, m. p. 196—197° (from ethanol) (Found: C, 84·6; H, 5·45; N, 5·0. $C_{20}H_{15}NO$ requires C, 84·3; H, 5·3; N, 4·9%).

1,3-*Dibenzoyl*-4-*methylcyclopenta*[c]*quinolizine.*—4-Methylcyclopenta[*c*]quinolizine (0·2 g.) was boiled in benzoyl chloride (3 ml.) for 3 min. Working up in the way described for the monobenzoyl compound gave the *diketone* (0·22 g.), yellow plates, m. p. 183—184° (from ethanol) (Found: C, 83·4; H, 4·9; N, 3·7. $C_{27}H_{19}NO_2$ requires C, 83·3; H, 4·9; N, 3·6%).

*Arylazocyclopenta*[c]*quinolizines.*—A solution of benzenediazonium chloride (from 0·26 g. aniline) was made alkaline (pH 10) with aqueous sodium hydroxide and added to 4-methylcyclopenta[*c*]quinolizine (0·5 g.) in the minimum volume of acetonitrile at 0°. The dark tarry precipitate which formed was chromatographed on alumina. Elution with ether gave a trace of starting material and then 4-*methyl*-1-*phenylazocyclopenta*[c]*quinolizine*, crimson needles, m. p. 156—157° (from ethanol) (Found: C, 80·6; H, 5·7; N, 14·4. $C_{19}H_{15}N_3$ requires C, 80·0; H, 5·3; N, 14·7%). Elution with ether containing methanol (4%) gave 4-*methyl*-3-*phenylazocyclopenta*[c]*quinolizine*, dark red needles, m. p. 181—182° (from nitromethane) (Found: C, 78·2; H, 5·3; N, 14·7%).

The solid mixture of products from a similar reaction with p-bromobenzenediazonium chloride was separated by (*a*) extraction with boiling benzene and recrystallisation of the soluble and insoluble portions from acetonitrile and *NN*-dimethylacetamide, respectively, or (*b*) chromatography on alumina in chloroform. The more-soluble, less strongly adsorbed isomer was 1-p-*bromophenylazo*-4-*methylcyclopenta*[c]*quinolizine*, red needles, m. p. 236—237° (Found: C, 62·7; H, 4·0; Br, 21·8; N, 11·6. $C_{19}H_{14}BrN_3$ requires C, 62·6; H, 3·85; Br, 22·0; N, 11·5%). The less-soluble, more strongly adsorbed isomer was 3-p-*bromophenylazo*-4-*methylcyclopenta*[c]*quinolizine*, dark red prisms, m. p. 251° (decomp.) (Found: C, 62·2; H, 4·15; Br, 21·6; N, 11·1%).

*Nitrosation of* 4-*Methylcyclopenta*[c]*quinolizine.*—Phosphoryl chloride (1 ml.) was added dropwise, with stirring, to the quinolizine (0·5 g.) and isopentyl nitrite (0·6 ml.)

TABLE 5

Ultraviolet and visible spectra of cyclopenta[*c*]-quinolizines (wavelengths in mμ)

| Compound | $\lambda_{max.}$ | log ε | $\lambda_{max.}$ | log ε | $\lambda_{max.}$ | log ε | $\lambda_{max.}$ | log ε |
|---|---|---|---|---|---|---|---|---|
| (VIIa) | (238) | 4·35 | 284 | 4·37 | 350 | 4·45 | 463 | 3·61 |
| | 251 | 4·41 | | | (380) | 4·0 | | |
| (XVc) | 234 | 4·44 | (285) | 4·2 | 354 | 4·57 | 480 | 3·59 |
| | 272 | 4·30 | | | (385) | 4·1 | | |
| (VIIb) | 236 | 4·46 | 288 | 3·78 | 342 | 4·50 | 445 | 3·64 |
| | (250) | 4·4 | | | (370) | 4·15 | | |
| | (270) | 4·05 | | | | | | |
| (XVb) | 253 | 4·04 | 288 | 3·97 | 342 | 4·52 | 453 | 3·58 |
| | 270 | 4·23 | | | (370) | 4·1 | | |
| (VIIi) | 242 | 4·43 | (280) | 4·1 | 360 | 4·31 | (480) | 3·5 |
| | (265) | 4·2 | | | (400) | 3·9 | | |
| (VIIIa-1-$CO_2$Me) | 236 | 4·37 | 275 | 4·56 | 348 | 4·42 | 445 | 3·48 |
| | | | | | (390) | 3·7 | | |
| (VIIIa-2-$CO_2$Me) | 235 | 4·39 | 294 | 4·32 | 362 | 4·47 | 493 | 3·51 |
| | 248 | 4·38 | | | (390) | 4·1 | | |
| (VIIIa) | 258 | 4·41 | (278) | 4·4 | 358 | 4·37 | 488 | 3·24 |
| | | | | | (390) | 3·8 | | |
| (VIIIb) | (242) | 4·4 | | | 348 | 4·55 | (445) | 3·4 |
| | 252 | 4·46 | | | (375) | 4·0 | | |
| | (267) | 4·1 | | | | | | |
| (VIIIb-1,3-diCHO) | 241 | 4·56 | | | 308 | 4·50 | 395 | 3·81 |
| | | | | | (320) | 4·5 | | |
| (VIIIb-1-Ac) | 236 | 4·57 | 299 | 4·12 | 348 | 4·47 | (410) | 3·6 |
| | (241) | 4·5 | | | | | | |
| | (258) | 4·1 | | | | | | |
| (VIIIb-1,3-diAc) | 242 | 4·50 | | | 310 | 4·44 | 405 | 3·73 |
| | (254) | 4·4 | | | (332) | 4·4 | | |
| (VIIIb-1-$PhN_2$) | 256 | 4·46 | | | (337) | 4·1 | 475 | 4·45 |
| | (266) | 4·4 | | | 344 | 4·17 | | |
| | | | | | 379 | 4·17 | | |
| (VIIIb-3-$PhN_2$) | (236) | 4·25 | | | 355 | 4·28 | 456 | 4·48 |
| | 256 | 4·20 | | | 390 | 4·37 | | |
| (VIIIb-1-$BrC_6H_4N_2$) | 260 | 4·47 | | | 336 | 4·10 | 488 | 4·50 |
| | 267 | 4·42 | | | 343 | 4·10 | | |
| | | | | | 381 | 4·04 | | |
| (VIIIb-3-$BrC_6H_4N_2$) | (240) | 4·1 | | | 349 | 4·14 | 467 | 4·40 |
| | 253 | 4·09 | | | 391 | 4·25 | | |

Values in parentheses refer to shoulders or inflexions.

in ether (15 ml.). The solution was stirred for a further 2 hr. and water was added to dissolve the precipitate which had formed. Non-basic material was removed by extraction with ether and the aqueous solution was made alkaline with sodium hydroxide and extracted with chloroform. A blue solid, insoluble in both phases, was filtered off but could not be recrystallised. Evaporation of the chloroform extract and crystallisation of the residue from nitromethane gave a 4-*methylnitrosocyclopenta*[c]*quinolizine* (0·15 g.), green plates, m. p. 215—216° (Found: C, 73·4; H, 4·8; N, 11·6. $C_{13}H_{11}NO$ requires C, 73·9; H, 4·8; N, 13·3%).

*Bromination of Dimethyl* 4-*Phenylcyclopenta*[c]*quinolizine*-1,2-*dicarboxylate*.—Bromine (0·16 g.) in dichloromethane (10 ml.) was added to the diester (0·18 g.) in dichloromethane (15 ml.) and the solution was set aside for 12 hr. Evaporation of the solvent gave a residue which was dissolved in acetic acid, precipitated with water, filtered off, dried, and recrystallised from benzene–light petroleum to give *dimethyl* 3,5-*dibromo*-4-*phenylcyclopenta*[c]*quinolizine*-1,2-*dicarboxylate*, yellow needles, m. p. 249—250° (Found: C, 50·8; H, 2·7; Br, 29·9; N, 2·9. $C_{22}H_{15}Br_2NO_4$ requires C, 51·6; H, 2·9; Br, 30·8; N, 2·7%).

*Bromination of Dimethyl* 4,5-*Dimethyl- and* 4-*Methyl-cyclopenta*[c]*quinolizine*-1,2-*dicarboxylates*.—Bromine (0·17 g., 2 moles) in dichloromethane (10 ml.) was added to the 4,5-dimethyl compound (0·16 g., 1 mole) in dichloromethane (15 ml.) and the solution was set aside overnight. The solvent was evaporated and the residue dissolved in methanol, neutralised with aqueous sodium hydroxide, and extracted into ethyl acetate. Evaporation of the washed and dried extract gave *dimethyl* 3-*bromo*-4,5-*dimethylcyclopenta*[c]*quinolizine*-1,2-*dicarboxylate*, yellow needles, m. p. 173° (from benzene–light petroleum) (Found: C, 56·0; H, 3·8; Br, 20·5; N, 3·6. $C_{18}H_{16}BrNO_4$ requires C, 55·4; H, 4·1; Br, 20·5; N, 3·6%). Similar treatment of the 4-methyl compound gave *dimethyl* 3,5-*dibromo*-4-*methylcyclopenta*[c]*quinolizine*-1,2-*dicarboxylate* (70%), yellow needles, m. p. 176° (from ethanol) (Found: Br, 34·5; N, 3·1. $C_{17}H_{13}Br_2NO_4$ requires Br, 35·1; N, 3·1%).

3-*Carboxyquinolizinium*-2-*carboxylate* (X).—(*a*) 2,3-Di-(2′-furyl)quinolizinium perchlorate [7] (0·7 g.) was heated at 100° with concentrated nitric acid (15 ml.) for 30 hr. The nitric acid was evaporated and the residual buff solid was boiled with acetic acid and filtered off. The resulting, almost colourless betaine, m. p. 262° (decomp.) [lit.,[6] 260° (decomp.)] (Found: N, 6·7. Calc. for $C_{11}H_7NO_4$: N, 6·5%), could not be easily recrystallised.

(*b*) The same procedure was followed for the oxidation of trimethyl cyclopenta[*c*]quinolizine-1,2,4-tricarboxylate and yielded the same betaine, m. p. and mixed m. p. 261—262°, infrared spectrum identical with that of the specimen prepared by method (*a*).

*Ultraviolet and Visible Spectra*.—The spectra were measured by using a Perkin-Elmer 137-UV spectrophotometer. Data for ethanol solutions of cyclopenta[*c*]quinolizines bearing a representative selection of substituents are listed in Table 5.

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