Addition Reactions of Heterocyclic Compounds. Part 69.[1] Further Studies of Reactions between 2-Alkylquinolines and Dimethyl Acetylenedicarboxylate

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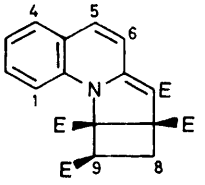
Dimethyl acetylenedicarboxylate (DMAD) has been treated with ethyl quinoline-2-acetate, other quinolines with activated 2-methyl groups, and 2-acetyloxyquinoline, and the products identified spectroscopically. The mechanism of the conversion of 2-methylquinoline to tetramethyl 7a,8,9,9a-tetrahydrocyclobuta[4,5]pyrrolo[1,2-*a*]-quinoline-7,*r*-7a,*c*-9,*c*-9a-tetracarboxylate, and derivatives, by DMAD has been investigated and mechanistic schemes proposed. Various reactions of this pyrroloquinoline have been re-interpreted on the basis of the new structure for this compound and ^{13}C n.m.r. spectra.

Our recent studies [2,3] concerning the nature of the products from dimethyl acetylenedicarboxylate (DMAD) and a number of heterocycles possessing ' active ' methyl or methylene groups have revealed that, in a number of cases, structures suggested previously were incorrect. In particular, quinolines containing 2-methyl or 2-methylene groups gave rise to cyclobutapyrroloquinoline



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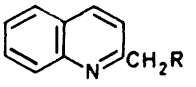


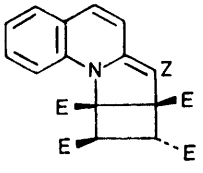
(2)

E = CO_2Me

derivatives such as (1) under most conditions.[2,4] In view of this we decided to examine further the reaction of DMAD with quinolines of type (2), and to study its reaction with 2-methylquinoline more closely.

RESULTS AND DISCUSSION

Ethyl quinoline-2-acetate with DMAD in ether gave no crystalline products, but in acetonitrile and methanol



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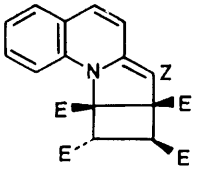
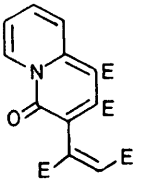


(4)

E = CO_2Me
Z = CO_2Et

the 1 : 2 molar adducts (3) and (4) were formed, respectively, and exclusively as shown by careful t.l.c. examination of the gross reaction products using pure (3) and (4) as comparison materials. The u.v. and mass spectra for (3) and (4) were almost identical, and the latter showed the loss of a fragment corresponding to dimethyl fumarate from the molecular ions to give the base peaks. The ethoxycarbonyl group was therefore not located at position 8 or 9.[3] The ^1H n.m.r. spectra for both showed similar AB systems for the 8- and 9-protons, and (3) showed normal-field ester-methyl and aromatic resonances. In contrast (4) possessed both a high-field ester-methyl group and an aromatic proton, these observations indicating the stereochemistry shown at position 9.[3] This contrasts with methyl pyridyl-2-acetate which with DMAD gave mixtures of the quinolizones (5) and (6),[5] while using the same conditions as for the corresponding quinoline ester, and methanol or acetonitrile as solvent, both (5) and (6) could be detected as reaction products by t.l.c. comparison with authentic materials.

2-Quinolylacetone with DMAD in acetonitrile produced a mixture of 1 : 1 adducts one of which was



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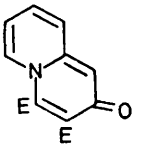
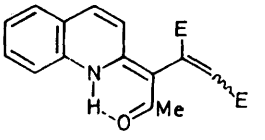


(6)

E = CO_2Me

characterised as (7). If acetonitrile–methanol was used as solvent then a 2 : 1 molar adduct was formed and identified as (8; R = Me), partly because of the high-



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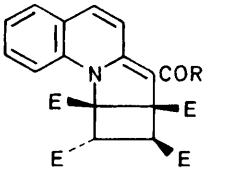


(8)

E = CO_2Me

field ester methyl group and aromatic proton in its ^1H n.m.r. spectrum, and the apparent loss of dimethyl fumarate in the mass spectrometer to give the base peak.

TABLE 1

N.m.r. spectra for the compounds prepared (deuteriochloroform solutions; recorded in δ from internal tetramethylsilane; J in Hz)

Compound		CO_2Me
(*a*) ^{1}H Resonances		
(3)	Ar-H, 6.80—7.45 (5 H, m); 5-H, 7.60 (d); 8-H, 4.66 (d);[a] 9-H, 4.06 (d);[a] OCH_2CH_3, 1.19 (t, J 7); OCH_2CH_3, 3.80—4.32 (m);[b] ($J_{5,6}$ 10; $J_{8,9}$ 9)	3.63, 3.65, 3.65, 3.74
(4)	Ar-H, 6.78—7.41 (4 H, m); 1-H, 6.44 (d); 5-H, 7.64 (d); 8-H, 3.86 (d);[a] 9-H, 5.02 (d);[a] OCH_2CH_3, 1.22 (t); OCH_2CH_3, 4.13 (q, J 7); ($J_{1,2}$ 8.5; $J_{5,6}$ 9; $J_{8,9}$ 10)	3.29, 3.66, 3.66, 3.71
(7)	Ar-H 6.90—7.70 (5 H, m); 1-H, 11.46:[c] 4-H, 6.58 (d);[d] COMe, 2.05; side-chain-H, 7.13; ($J_{1,2}$ 10)	3.60, 3.76
(8; R = Me)	Ar-H, 6.82—7.44 (4 H, m); 1-H, 6.65 (d);[d] 5-H, 7.90 (d); 7-$COCH_3$, 2.17; 8-H, 3.89 (d);[a] 9-H, 5.11 (d);[a] ($J_{1,2}$ 8; $J_{5,6}$ 9.5; $J_{8,9}$ 9.5)	3.29, 3.63; 3.67, 3.73
(8; (R = Et)[e]	Ar-H, 6.86—7.60 (4 H, m); 1-H, 6.53 (d);[d] 5-H, 7.91 (d); 7-$COCH_2CH_3$, 0.90 (t); 7-$COCH_2CH_3$, 2.05—2.77 (m); 8-H, 3.85 (d);[a,b] 9-H, 5.00 (d);[a] ($J_{1,2}$ 8; $J_{5,6}$ 9.5; $J_{8,9}$ 10)	3.30, 3.66, 3.66, 3.73
(11)	Ar-H, 7.40—7.82 (4 H, m); 1-H, 15.07;[c] 2-vinyl-H, 6.30; 3-H, 7.27 (d); 4-H, 8.01 (d); ($J_{3,4}$ 9.5)	3.78, 3.80
(12)	Ar-H, 7.23—8.24 (5 H, m); 4-H, 8.22 (d); ($J_{3,4}$ 9)	3.96, 3.96
(15)[f]	Ar-H, 7.60—8.36 (4 H, m); 3-H, 3.76 (d); 4-H, 8.65 (d); ($J_{3,4}$ 9)	3.47, 3.47, 3.62, 3.62
(16)	4a-CH_2Cl, 3.16 (d), 3.96 (d) (J 12); 5-H, 6.29 (d); 6-H, 6.54 (d);[d] 7,9-H_2, 6.82—7.10 (m); 8-Me, 2.31; 10-H, 7.22 (d); ($J_{5,6}$ 9; $J_{9,10}$ 8)	3.58, 3.68, 3.72, 3.80
(40)[g]	Ar-H 6.60—7.60 (11 H, m); 7-vinyl-H, 4.77; 8-H, 4.08; 9-CH, 4.62; 9-$CHOCH_3$, 3.20	3.50, 3.59, 3.59, 3.89
(*b*) ^{13}C Resonances (at 22.63 MHz)		
		CO_2CH_3 resonances
(37)[h]	34.6 (t); 59.8 (s), 79.1 (s); 120.3(d); 127.5 (d); 128.1 (s); 128.8 (d); 130.1 (d); 137.1 (d); 142.2 (s); 142.5 (s); 145.3 (s); 154.4 (s)	160.8, 52.1, 161.5, 52.1, 170.6, 52.8, 171.9, 52.8
(39)[h]	110.0 (s); 116.1 (d); 117.0 (d); 118.7 (s); 122.7 (s); 123.0 (d); 125.4 (s); 125.5 (d); 128.4 (d); 129.0 (d); 129.2 (d); 130.8 (s); 132.8 (s); 137.3 (s)	163.8, 51.9, 165.0, 51.9, 165.2, 52.8, 166.8, 53.4
(40)[h]	58.2 (d); 61.0 (q); 79.0 (s); 81.6 (d); 99.6 (s); 105.3 (d); 115.9 (d); 117.1 (d); 121.8 (d); 123.2 (s); 127.9 (d); 128.4 (d); 128.4 (d); 128.5 (d); 128.5 (d); 130.1 (d); 135.3 (d); 135.7 (s); 139.9 (s); 143.3 (s); 148.8 (s)	167.0, 50.9, 167.7, 51.8, 170.2, 52.7, 170.6, 53.2

[a] Assignments could be interchanged. [b] Partially obscured by OCH_3 resonances. [c] Broad and disappears on addition of D_2O. [d] Shows additional small coupling. [e] Mixture of epimers. [f] Solvent $(CD_3)_2SO$. [g] The resonances at 3.20 and 4.62 were absent, and the ester-methyls and the resonance at 4.77 were diminished in the deuteriated compound. [h] All ^{13}C—H attachments were confirmed by off-resonance decoupling experiments, and the multiplicities observed during decoupling are indicated.

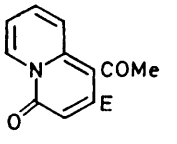
TABLE 2

U.v. spectra of the compounds prepared

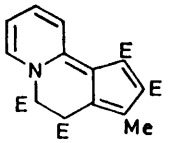
Compound	Solvent[a]	$\lambda_{max.}$/nm (10^{-4} ε in parentheses)
(3)	M	222 (2.19); 272 (1.51); 297 (1.81); 309[b] (1.75); 319 (1.15); 408[b] (0.72); 426 (0.96); 449 (0.93); 482[b] (0.48)
	P	246 (3.75); 276 (1.20); 298 (1.76); 301 (1.99); 316[b] (1.91)
(4)	M	220 (2.20); 268[b] (1.52); 277 (1.72); 296 (1.72); 308 (1.67); 321 (1.19); 404[b] (0.75); 425 (0.92); 451 (0.92); 481[b] (0.57)
	P	245 (3.89); 275 (1.24); 297 (1.83); 301 (2.06); 316[b] (1.97)
(7)	M	217 (2.85); 294 (1.13); 299[b] (1.13); 312[b] (0.99); 420 (1.10)
	A	220 (2.67); 241 (1.31); 284 (0.97); 321 (0.58); 384 (1.04)
(8; R = Me)	M	224 (2.67); 282 (1.31); 300 (1.45); 314 (1.91); 332[b] (1.75); 412 (0.82); 430 (1.19); 460 (1.23); 492[b] (0.86)
	A	227 (3.36); 293 (3.15); 410 (3.30)
(8; R = Et)	M	223 (2.38); 271[b] (0.85); 282 (1.08); 301[b] (1.27); 315 (1.63); 330 (1.56); 412[b] (0.97); 438 (1.37); 462 (1.43); 488 (0.88)
	A	225 (3.57); 284[b] (2.31); 293 (3.26); 406 (3.38)
(11)	M	225 (2.81); 295[b] (0.56); 306 (0.18); 368 (0.76); 370 (0.73); 421 (0.73); 440 (0.76)
	A	227 (2.90); 248[b] (0.74); 306 (0.71)
(12)	M	210 (2.25); 246[b] (1.97); 263 (2.23); 308 (1.16)
	P	270 (2.67); 348 (1.88)
(15)	M	221 (1.74); 231[b] (1.27); 264 (1.82); 293[b] (0.83); 340[b] (0.29)
	A	227 (1.19); 261 (1.43); 267[b] (1.34); 285[b] (0.83); 428 (0.67)
(16)	M	218 (2.03); 257 (1.93); 284[b] (0.64); 304[b] (0.39); 408 (0.54)
(40)	M	225 (2.09); 285 (1.00); 384 (3.47); 475 (2.75); 507 (2.51)
	A	205 (3.55); 270 (2.82); 361 (2.24)

[a] M = MeOH; A = MeOH with two drops 70% $HClO_4$ per cell; P = MeOH–70% $HClO_4$ (2 : 1 v/v). [b] Inflexion.

The reactions of 1-(2-quinolyl)butan-2-one were analogous to those of 2-quinolylacetone, but in contrast 2-pyridylacetone and 1-(2-pyridyl)butan-2-one gave rise to (9) and (10) respectively.[6]



(9)



(10)

E = CO_2Me

2-Nitromethylquinoline reacted with DMAD in acetonitrile, methanol, and mixtures of these, to give a single hydrogen-bonded 1 : 1 adduct which is probably the maleate (11). This compound did not react with an excess of DMAD, but on refluxing with acetonitrile under neutral or acidic conditions lost the elements of water. The product was identified as the oxazole (12), since the i.r. spectrum showed no absorptions characteristic of a nitro- or nitroso-group, the base peak in the mass spectrum corresponds to cleavage at (a), and the ^{1}H n.m.r. spectrum showed resonances typical of a 2-

TABLE 3

Mass spectra [a] of the compounds prepared

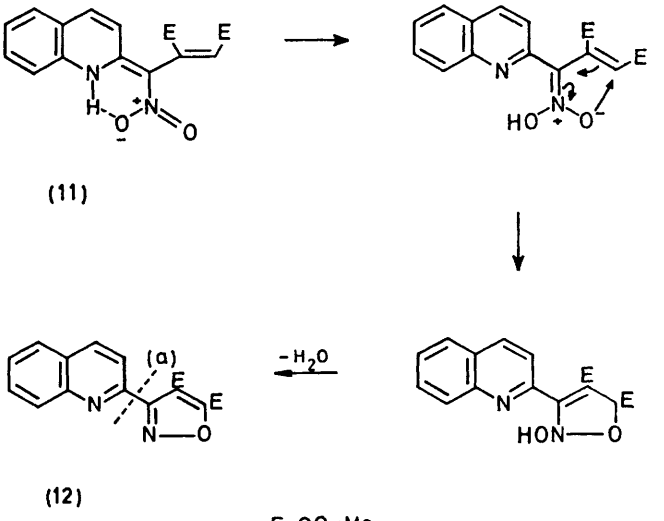
Compound	*m/e* (relative intensity in parentheses)
(3)	499 (M^+, 5); 408 (10); 394 (16); 356 (21); 355 (100); 310 (18); 252 (11); 113 (15)
(4)	499 (M^+, 3); 356 (23); 355 (100); 310 (13); 252 (9); 113 (12)
(7)	327 (M^+, 6); 269 (18); 268 (100); 252 (10); 237 (16); 236 (75); 226 (13); 194 (16); 180 (16); 167 (25); 128 (10). *m** 208 (268→236)
(8; R = Me)	469 (M^+, 5); 326 (22); 325 (100), 311 (17); 310 (86); 113 (12). *m** 296 (325→310)
(8; R = Et)	483 (M^+, 5); 340 (11); 339 (48); 311 (20) ; 310 (100). *m** 283.5 (339→310)
(11)	330 (M^+, 8); 285 (21); 284 (92); 283 (41); 271 (24); 254 (10); 253 (39); 252 (94); 240 (24); 239 (70); 226 (22); 225 (100); 224 (12); 223 (12); 212 (36); 211 (11); 209 (10); 197 (10); 196 (11); 195 (16); 194 (60); 182 (25); 181 (46); 180 (45); 168 (20); 167 (92); 166 (63); 165 (16); 164 (16); 155 (11); 154 (19); 153 (13); 140 (31); 139 (26); 129 (17); 128 (66); 101 (16). *m** 223.5 (352→284); 212 (239→225); 124 (252→167).
(12)	312 (M^+, 22); 237 (13); 223 (38); 156 (10); 142 (14); 140 (14); 129 (16); 128 (100); 101 (18). *m** 207 (312→254); 200 (253→225); 164 (312→226); 159.5 (312→223); 125 (226→168); 109 (223→156); 105 (312→181); 102.5 (312→179); 80 (128→101)
(15)	425 (M^+, 26); 395 (15); 394 (46); 363 (24); 362 (100); 304 (14); 245 (10); 165 (16). *m** 332.5 (394→362).
(16)	427 (26); 426 (100)
(16) [b]	478 ($M^+ + 1$, 4); 476 ($M^+ - 1$, 12); 446 (42); 445 (27); 440 (100); 427 (28). *m** 414→417 (broad), 478→446, and 476→444
(18)	583 (M^+,12); 440 (28); 439 (100); 380 (16); 349 (10). *m** 330.5 (583→439)
(40)	548 ($M^+ + 1$, 25); 547 (M^+, 60); 516 (17); 488 (21); 456 (10); 445 (38); 444 (100); 428 (13); 412 (32); 386 (12); 385 (31); 384 (92); 383 (12); 353 (17); 352 (61); 326 (21); 325 (26); 294 (15); 268 (13); 267 (40); 266 (18); 265 (18). *m** 360 (547→444); 332 (444→384)
(40) [c]	557 (25); 554 (31); 551 (26); 495 (15); 492 (19); 450 (48); 447 (74); 444 (58); 435 (13); 432 (19); 430 (10); 418 (15); 415 (29); 412 (26); 390 (44); 387 (100); 384 (91); 375 (34); 372 (31); 355 (54); 352 (76); 329 (20); 328 (43); 326 (35); 325 (46); 294 (36); 269 (21); 268 (38); 267 (96); 266 (45)

[a] Peaks with relative intensity ⩾ 10% usually recorded. [b] Chemical ionisation spectra. [c] Deuteriated sample; metastables correspond to those observed for the sample containing no deuterium.

substituted quinoline. It could be formed as shown in Scheme 1.

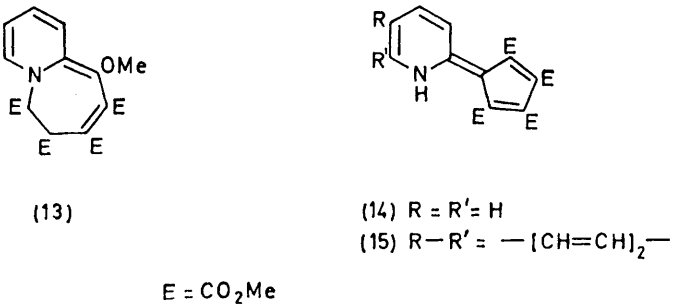
The reaction of 2-acetoxymethylquinoline with DMAD in DMF gave two products, one of which was identified as (15) from its spectra. The other product was an extremely insoluble powder, but its mass spectrum (electron impact and chemical ionisation) showed that its molecular weight corresponded to the addition of three moles of DMAD to the quinoline and loss of acetic acid, and that it was not a cyclobutapyrrole. 2-Acetoxymethylpyridine with DMAD under various conditions gives (13), converted into (14) by heat.[6] Attempts to detect the quinoline analogue of the deep red (13) by t.l.c. failed.

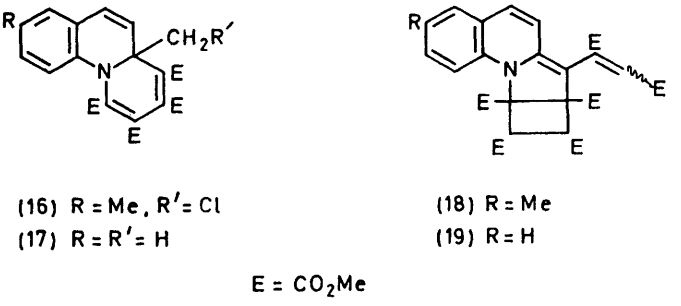
2-Chloromethyl-6-methylquinoline behaved differently from 2-acetoxymethylquinoline towards DMAD. In DMF only the quinolizine (16) was formed, while in methanol (16) was produced, along with a small amount of a red material whose mass spectrum suggested it to be (18). No trace of 2,6-dimethylquinoline could be detected in the starting material, and we assume that (18) arises from the chloromethylquinoline.



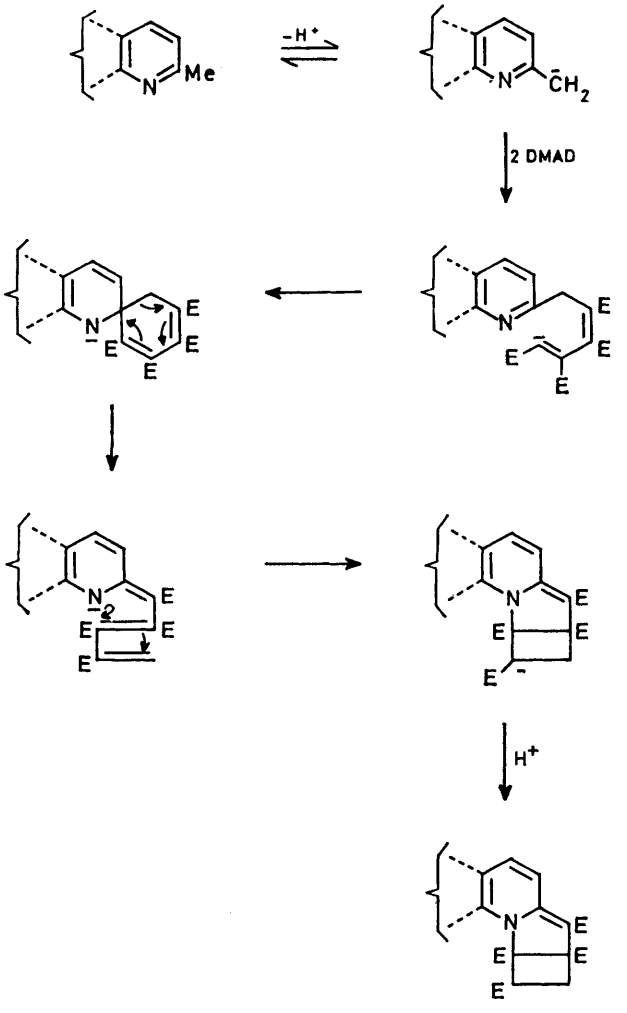
SCHEME 1

From these results it can be concluded that the products from the quinolines usually differ from those from the corresponding pyridines. It is perhaps significant that in the only similar case so far reported, the 2-acetyloxymethyl derivatives, the substituent on the methylene group is probably acting as a leaving group rather than as an 'activating' substituent. These differences have not been rationalised, nor has the fact that no cyclobutapyrroles have been isolated from any reactions of pyridines with DMAD.



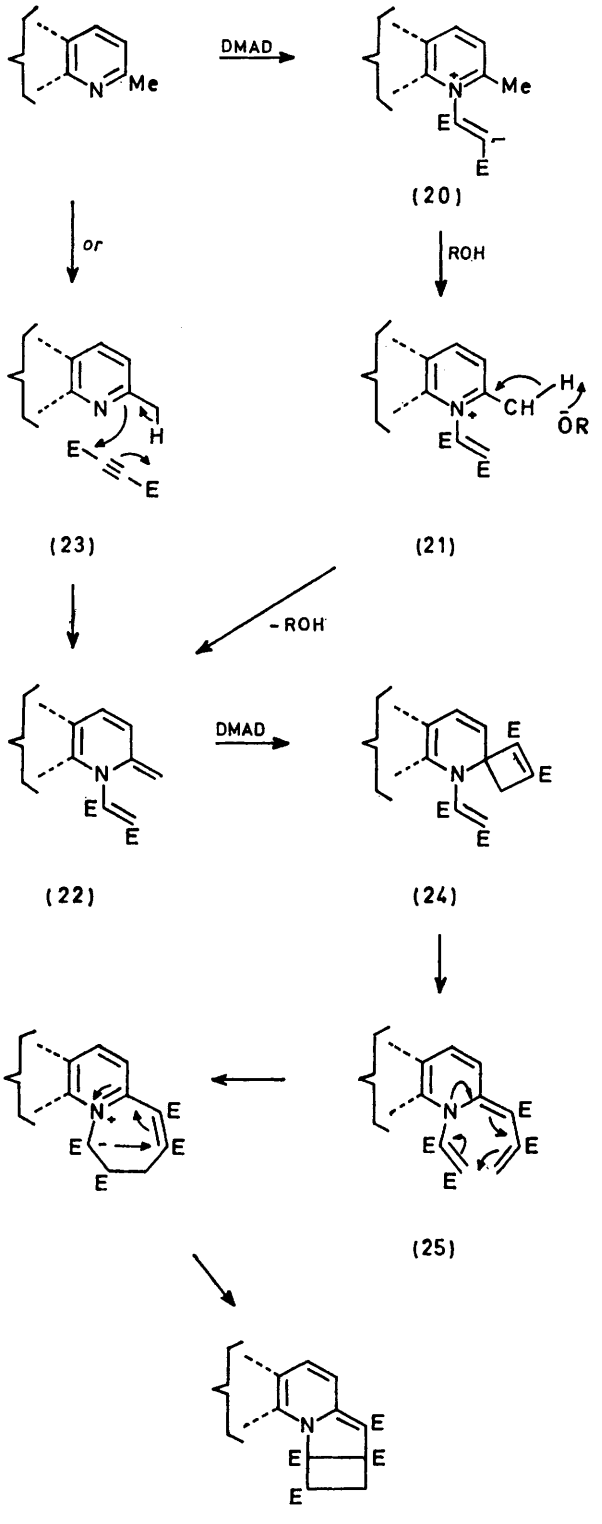


Elucidation of the mode of formation of the cyclobutapyrrole (1) from 2-methylquinoline and DMAD was the next objective, it being known from a ^{13}C tracer study that the methylene carbon atom of the product is that of the methyl group of the original quinoline.[7] Mechanistic studies of the reaction are complicated by the formation of tar and a mixture of products under all conditions examined. Schemes 2 and 3 account for the formation of the cyclobutapyrrole, Scheme 2 being a modification of an earlier suggestion.[2] If Scheme 2 was being followed then an exchange of deuterium for hydrogen, leading to incorporation of deuterium into unreacted 2-methylquinoline, could occur. However, no exchange took place in acetonitrile containing 5% [$^2H_4$]-methanol, and if insufficient DMAD was added for complete reaction and the basic fraction isolated from the mixture, no significant 2-methylquinoline could be recovered. So the unaided deprotonation of the 2-methylquinoline as shown (Scheme 2) does not occur, but the possibility that another competitive reaction



E = CO_2Me

SCHEME 2

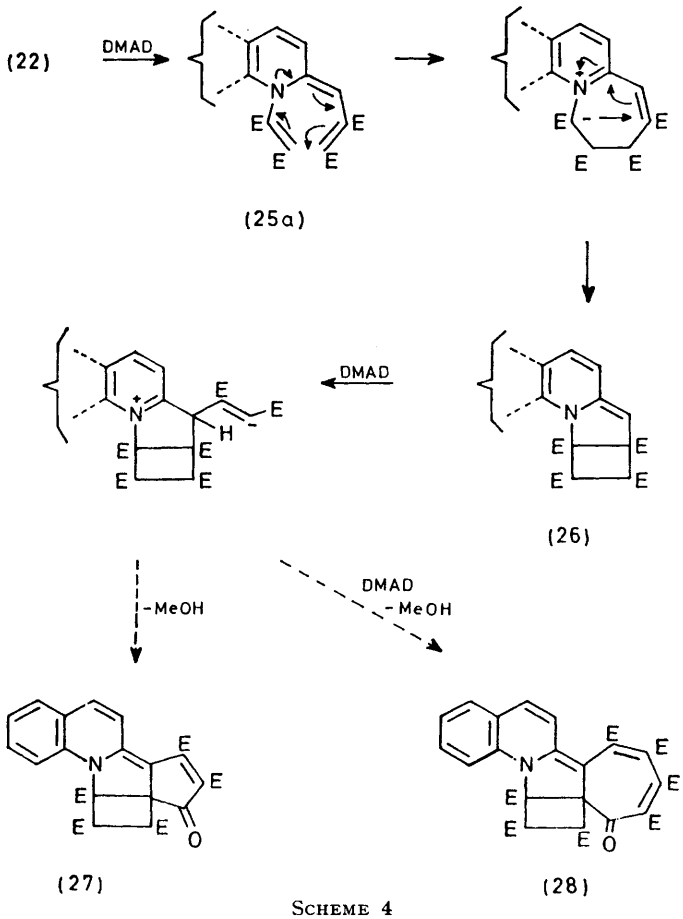


E = CO_2Me

SCHEME 3

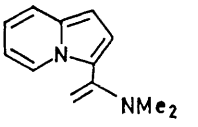
pathway exists, such as DMAD reacting at the nitrogen of the quinoline to give a carbanion [*e.g.* (20)] which could then cause the deprotonation, cannot be excluded.

If Scheme 3 were operative, then the key intermediate (22) could arise by several pathways. From 2-methylquinoline and DMAD in purified DMF only the quinolizine (17) was detectable as a product, while in the presence of 5% water, methanol, or nitromethane, no (17) appeared to be formed, but a mixture of (1), (19), (27), and (28). With 5% acetic acid the only product was a trace of the quinolizine (17). The reaction products were identified by t.l.c. comparison with authentic specimens. If structure (22) was built up *via* the mechanism indicated by (23), it is difficult to see why the addition of, for example, a little methanol to the medium should affect the nature of the products so drastically, but this is understandable if the route is *via* (20) and (21). The result with acetic acid suggests that the anion of the proton donor must be able to deprotonate (21). Neither the postulated intermediate (22), nor other intermediate compounds, could be detected by ^{1}H n.m.r. spectroscopy when the reaction was carried out in [$^2H_3$]acetonitrile with methanol or [$^2H_4$]methanol in the spectrometer at −20 to +35 °C. However, typical enaminic addition [8] to DMAD would give the cyclobutene (24), which by a well-known [8] ring-opening to (25) and cyclisation as



SCHEME 4

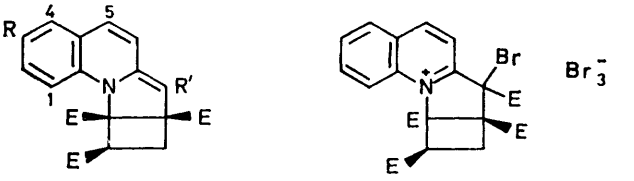
indicated could lead to the cyclobutapyrrole system (1). The intermediacy of (22) is also attractive as the best yields of adducts of types (19), (27), and (28) are obtained from reactions in methanol alone. Under these conditions addition of DMAD to the enamine (22) to give an ylide followed by protonation would give a normal type of Michael adduct (25a) leading to the compounds isolated as shown (Scheme 4), while a shortage of methanol would encourage the ylide to cyclise to the cyclobutene (24) and lead to compounds of type (1). A similar situation was observed for the reaction of (29) with DMAD in toluene or methanol.[9]



(29)

It was found that 2-methylquinoline with DMAD in acetonitrile containing 5% methanol gave a 37% yield of (1), compared with the 10% reported earlier. Using [$^2H_4$]methanol the cyclobutapyrrole was obtained containing atoms of deuterium, all of which were lost in the methyl acrylate fragment split off in the mass spectrometer, showing that deuterium was incorporated only at positions 8 and 9. Analysis of the ^{1}H n.m.r. resonances due to the 8- and 9-protons showed that most of the deuterium was located at position 9. A small quantity of (19) was also isolated, and contained deuterium at the 8- or 9-, and the vinyl position. These results are consistent with the mechanistic hypotheses suggested.

The cyclobutapyrrole (1) is remarkably stable, being recovered unchanged after melting *in vacuo* for 10 min, after photolysis in methanol for 2 d with a Hanovia medium-pressure u.v. lamp, and a flash-vacuum pyrolysis up to *ca.* 800 °C at 0.01 Torr. It was not epimerised by sodium methoxide in methanol, although complete deuterium exchange at position 9 was effected under these conditions. In contrast the bromo-derivative (31) gave a roughly 1 : 1 mixture of the 9-epimers under

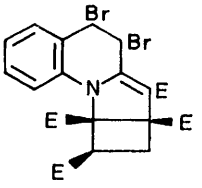


(30) R = H, R' = NO_2
(31) R = Br, R' = E
(32)
E = CO_2Me

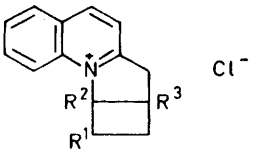
these conditions. A mixture of epimers is also obtained from 6-bromo-2-methylquinoline with DMAD, while only one of the possible epimers (1) is obtained from 2-methylquinoline.

Some reactions of the cyclobutapyrrole (1) have been described [10] and the spectra of the products [10] interpreted on the basis of an earlier suggested azepine structure,[10] and these are now summarised, and extended,

in terms of the new formulation. Catalytic hydrogenation reduces the 5,6-double bond, while electrophilic reagents attack the enaminic 7-position. Protonation occurs at position 7, nitric acid (2M) yields (30), while bromine in acetic acid gives (32). This last compound



(33)

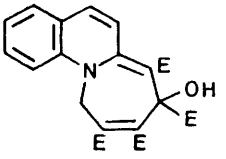


(34) $R^1,R^2,R^3 = 2 \times CO_2H + CO_2Me$

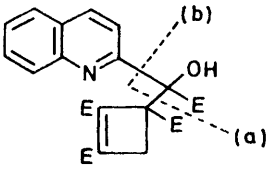
(35) $R^1 = R^2 = R^3 = CO_2H$

E = CO_2Me

on refluxing in methanol gives a mixture of (31) and (33). Hydrolysis of (1) with boiling aqueous hydrochloric acid yields (34), then (35). Oxidation with sodium dichromate in acetic acid gives a compound formulated [10] as (36), but the u.v. spectrum shows a quinoline chromophore. The ^{13}C n.m.r. spectrum resonances, reported here, are consistent with the presence of a quinoline ring system and compatible with (37), and the



(36)

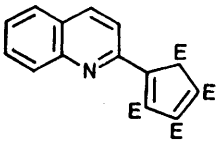


(37)

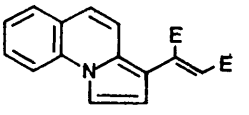
E = CO_2Me

mass spectrum shows a base peak corresponding to cleavage at (a), while cleavage at (b) also occurs. The formation of (37) from (1) can be readily envisaged by addition of, in essence, an electrophilic hydroxy at the 7-position followed by a Hoffmann elimination.

A red adduct from 2-methylquinoline and DMAD, now formulated as (19), on treatment with zinc and boiling acetic acid, or bromine in acetic acid followed by debromination, gave a product described [11] as (38) and



(38)

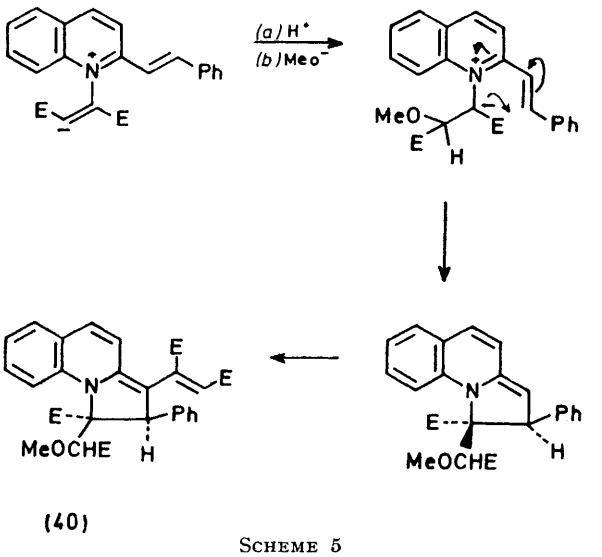


(39)

E = CO_2Me

formed through the apparent loss of dimethyl fumarate. This compound has now been obtained by melting (19) *in vacuo*; its ^{13}C n.m.r. spectrum shows no sp^3 carbon atoms except those of the ester-methyl groups, and the compound must therefore possess structure (39).

2-Styrylquinoline with DMAD in toluene or benzene gives [12,13] the yellow tetramethyl 4a-styrylbenzo[*c*]-quinolizine-1,2,3,4-tetracarboxylate, while in methanol a very deep red substance was obtained which analysed for, and possessed the molecular ion expected of, a 1 : 2 : 1 molar adduct from the reactants and solvent respectively. The adduct did not react with hydrogen peroxide, alkaline hexacyanoferrate(III), or diazomethane. Catalytic hydrogenation gave a mixture of di-, tetra-, and hexa-hydro-derivatives, identified by mass spectrometry, but none could be characterised. The ^1H n.m.r. spectrum showed six peaks in the δ 4.7—5.3 region, due to non-coupled protons, and seven distinct *O*-methyl resonances. It appeared now that the substance was a 1 : 1 mixture of two isomers, but all attempts at separation, using t.l.c. and fractional crystallisation, failed.[14] However, slow fractional crystallisation gave a sample of one isomer, of identical



(40)

SCHEME 5

u.v. and mass spectra to the mixture, but whose ^1H n.m.r. spectrum showed only three uncoupled mid-field resonances identical with three of those of the mixture. The mass spectrum showed a strong molecular ion, and the loss of *m/e* 103 to give the base peak. This could correspond to the scission of the styryl group, or of the substituent $CH(OMe)CO_2Me$. The red compound was prepared using $[^2H_4]$methanol, and although some ester exchange took place it was clear from the mass spectrum of the product that loss of $CD(OCD_3)CO_2Me$ gave rise to the base peak. The presence of this group in the compound was confirmed by the resonance at δ 81.6 in the ^{13}C spectrum. The u.v. spectrum was quite similar to that of (19) and showed a similar reversible hypochromic shift of the long-wavelength band from 507 to *ca.* 360 nm on acidification, comparable with the formation of a vinylquinolinium cation. Structure (40) accounts for these data, and also the ^{13}C n.m.r. spectrum, as the resonances due to the enaminic C-7 and vinylic CH are very similar to those of (19). In the pure isomer obtained the stereochemistry is probably as shown, for

there is no high-field ester-methyl group in the ^{1}H n.m.r. spectrum, and as the compound was unchanged on melting *in vacuo* the 2-hydrogen atom and 1-CH(OMe)-CO_2Me group are unlikely to be *cis*, for then elimination of methyl methoxyacetate would have been expected. Analogies exist for each stage of the synthetic route shown in Scheme 5.

EXPERIMENTAL

The instruments used here have been described in previous papers of the series. Alumina was Laporte Grade H, 100—200 mesh, deactivated by shaking with 5% (v/v) of 10% aqueous acetic acid and standing for at least 12 h. Silica gel was Hopkins and Williams MFC 100—200 mesh. Preparative layer chromatography was performed on 20 × 20 cm plates coated with PF_{254} Kieselguhr. Solvent A is toluene–ethyl acetate–light petroleum (b.p. 60—80 °C) 4 : 1 : 1 by volume.

Ethyl Quinoline-2-acetate.—2-Methylquinoline (15 g) in ether (100 ml) was added dropwise with stirring to a suspension of sodamide [from sodium (3 g)] in liquid ammonia (500 ml). After 30 min a solution of diethyl carbonate (11.8 g) in ether (100 ml) was added slowly, and 30 min later excess of ammonium chloride was added. When the ammonia had evaporated off water (500 ml) was added, the mixture extracted with ether, and the combined extracts shaken with 2N hydrochloric acid. The aqueous extract was neutralised with sodium bicarbonate, and the resulting oil collected with dichloromethane, and dried. Distillation gave ethyl quinoline-2-acetate (10.1 g, 44.8%) as a yellow oil, b.p. 118—120 °C at 0.1 mmHg (lit.,[15] b.p. 128—135 °C at 0.8 mmHg). Attempts to repeat the literature synthesis,[15] using lithiated 2-methylquinoline and diethyl carbonate, gave low and variable yields. The above procedure was quite reproducible.

2-*Quinolylacetone*.—2-Methylquinoline (8 g) in dry ether (50 ml) was added dropwise with stirring, under nitrogen, to butyl-lithium [from lithium (2.5 g) in dry ether (500 ml), at room temperature. After 30 min a solution of acetonitrile (6 g) in dry ether (50 ml) was added dropwise and the mixture stirred at room temperature for 1 h. The quinoline was isolated as above, except that chloroform was used for the extractions. Evaporation gave 2-quinolylacetone as bright yellow crystals (8 g, 69%) (from toluene), m.p. 68—70 °C [lit.,[16] 76 °C (from water) prepared by a different route].

1-(2-*Quinolyl*)*butan*-2-*one*.—This was synthesised in *ca.* 40% yield as for 2-quinolylacetone, except that propionitrile was used in place of acetonitrile. The product was an orange liquid, b.p. 150—154 °C at 2.0 mmHg, containing an unidentified impurity, which was not removed on a repeat distillation; good analytical data could not be obtained. The major (*ca.* 80%) component of this mixture showed ^{1}H n.m.r. and i.r. spectra consistent with that expected for the desired product; $\nu_{max.}$ (liquid film) 3 020(br), 2 960, 2 929, 2 860, 1 720, 1 630, 1 590, and 1 550 cm^{-1}; ^{1}H n.m.r. (p.p.m. from $SiMe_4$); CH_2CH_3, 1.18 (two very close triplets, J 8 Hz); CH_2CH_3, 2.20—2.78 m; keto-CH_2, 4.00; enol =C*H*, 5.32; enol-3-*H*, 6.58 (d, J 10 Hz); Ar-H, 6.83—8.50 (m).

Ethyl Quinoline-2-acetate with DMAD.—(*i*) DMAD (4 g) was added to a solution of the quinoline (50 ml), and the mixture set aside at room temperature for 6 d. Evaporation followed by preparative layer chromatography (solvent A, 30 plates) gave *tetramethyl* 7-*ethoxycarbonyl*-7a,8,9,9a-*tetrahydrocyclobuta*[4,5]*pyrrolo*[1,2-a]*quinoline*-r-7a,t-8,c-9,c-9a-*tetracarboxylate* (3) (R_F 0.15) (0.28 g, 6%), as orange crystals (from methanol), m.p. 203—204 °C (Found: C, 59.9; H, 5.0; N, 2.9. $C_{25}H_{25}NO_{10}$ requires C, 60.1; H, 5.0; N, 2.8%).

(*ii*) The reaction was carried out exactly as above, except that methanol was used in place of acetonitrile, the reaction was set aside for 11 d, and the deposited crystals filtered off. The supernatant liquid deposited more crystals on standing, and the combined solid product was crystallised from methanol to give *tetramethyl* 7-*ethoxycarbonyl*-7a,8,9,9a-*tetrahydrocyclobuta*[4,5]*pyrrolo*[1,2-a]*quinoline*-r-7a,c-8,t-9,c-9a-*tetracarboxylate* (4), (1.31 g, 28.2%) as orange crystals (from methanol), m.p. 157—158 °C (Found: C, 60.1; H, 5.0; N, 2.9. $C_{25}H_{25}NO_{10}$ requires C, 60.1; H, 5.0; N, 2.8%). No further crystalline products could be isolated by chromatography of the residues from the above crystallisations.

2-*Quinolylacetone with DMAD*.—(*i*) DMAD (4.6 g) was added to a solution of the quinoline (3 g) in acetonitrile (50 ml), and the mixture set aside at room temperature for 6 d. Evaporation gave a tar which was dissolved in toluene and applied to a silica column (350 ml). Elution with toluene–ethyl acetate (95 : 5, v/v) gave an orange tar, which was crystallised from methanol–ether to give a mixture of red chunks (major proportion) and fine yellow needles. The red chunks were separated by hand, to give *methyl* 4-[2-(1,2-*dihydroquinolinylidene*)]-3-*methoxycarbonyl*-5-*oxohex*-2-*enoate* (7), (0.18 g, 3.4%) as red crystals (from methanol), m.p. 112—114 °C (Found: C, 65.9; H, 5.1; N, 4.2. $C_{18}H_{16}NO_5$ requires C, 66.1; H, 5.2; N, 4.3%); $\nu_{max.}$ (CCl_4) 3 250(br), 3 000, 2 950, 2 820, 1 730, 1 635, and 1 480 cm^{-1}.

(*ii*) The reaction was carried out as above, except that acetonitrile–methanol (9 : 1, v/v) was used in place of acetonitrile, and the reaction was set aside for 15 d. The tar obtained on evaporation was taken up in toluene, and applied to an alumina column (400 ml) made up in toluene. Elution with toluene–ethyl acetate (95 : 5, v/v) gave a tar, which was crystallised from methanol to give *tetramethyl* 7-*acetyl*-7a,8,9,9a-*tetrahydrocyclobuta*[4,5]*pyrrolo*[1,2-*a*]*quinoline*-r-7a,-c-8,t-9,c-9a-*tetracarboxylate* (8; R = Me) (0.28 g, 3.7%), as orange crystals (from methanol), m.p. 222—223 °C (Found: C, 61.7; H, 5.0; N, 3.0. $C_{24}H_{23}NO_9$ requires C, 61.4; H, 4.9; N, 2.9%).

1-(2-*Quinolyl*)*butan*-2-*one with DMAD*.—This was carried out as in (*ii*) immediately above, and gave *tetramethyl* 7-*propionyl*-7a,8,9,9a-*tetrahydrocyclobuta*[4,5]*pyrrolo*[1,2-a]-*quinoline*-r-7a,c-8,t-9-c-9a-*tetracarboxylate* (8; R = Et), (0.33 g, 4.5%), as orange crystals (from methanol), m.p. 199—200 °C (Found: C, 62.0; H, 5.2; N, 2.6. $C_{25}H_{25}NO_9$ requires C, 62.1; H, 5.2; N, 2.9%).

2-*Nitromethylquinoline with DMAD*.—(*i*) DMAD (4.5 g) was added to a solution of the quinoline (3 g) [17] in acetonitrile (50 ml) and set aside for 5 d at room temperature. The solid was filtered off and crystallised from methanol to give *methyl* 4-[2-(1,2-*dihydroquinolinylidene*)]-3-*methoxycarbonyl*-4-*nitrobut*-2-*enoate* (11), (2.1 g, 39.9%) as yellow crystals (from methanol), m.p. 181—183 °C (Found: C, 58.1; H, 4.3; N, 8.5. $C_{16}H_{14}N_2O_6$ requires C, 58.1; H, 4.2; N, 8.5%); $\nu_{max.}$ (Nujol) 3 110(br), 1 720, 1 630, 1 530, and 1 345 cm^{-1}.

(*ii*) The reaction was carried out as above except that methanol was used in place of acetonitrile, and the reaction set aside for 4 d, to give (11) (2.5 g, 47.5%).

(*iii*) The reaction was carried out as above except that acetonitrile–methanol (9 : 1, v/v) was used in place of acetonitrile, and the reaction set aside for 15 d, to give (11), (1.19 g, 22.6%). Chromatography of the residues from the above reactions gave no crystalline products.

Dehydration of Methyl 4-[2-(1,2-*Dihydroquinolinylidene*)]-3-*methoxycarbonyl*-4-*nitrobut*-2-*enoate* (11).—A solution of (11) (0.3 g) in toluene (50 ml) was refluxed for 18 h, evaporated, and the residual solid crystallised (methanol) to give *dimethyl* 3-(2-*quinolyl*)*isoxazole*-4,5-*dicarboxylate* (12), (0.13 g, 45.8%) as colourless crystals (from methanol), m.p. 134—135 °C (Found: C, 61.4; H, 4.0; N, 8.9. $C_{16}H_{12}N_2O_6$ requires C, 61.5; H, 3.9; N, 8.8%); $\nu_{max.}$ (Nujol) 1 745, 1 735, 1 500, 1 430, and 1 238 cm^{-1}; $\nu_{max.}$ (CCl_4) 3 000, 2 960, 2 750, 1 430, and 1 227 cm^{-1}. The yield was not altered if a catalytic amount of toluene-*p*-sulphonic acid was employed, or if acetonitrile was used as solvent.

2-*Acetoxymethylquinoline with DMAD*.—DMAD (9.2 g) was added to a solution of the quinoline (6 g) [18] in dry dimethylformamide (100 ml), and set aside at room temperature for 2.5 d. The tar obtained on evaporation was dissolved in toluene and applied to an alumina column (1 000 ml) made up in toluene. Elution with toluene–chloroform (6 : 4 v/v) gave *tetramethyl* 1-[2-(1,2-*dihydroquinolinylidene*)]-*cyclopenta*-2,4-*diene*-2,3,4,5-*tetracarboxylate* (15) (0.30 g, 2.4%) as yellow crystals (from methanol), m.p. 198—200 °C (decomp.) (Found: C, 62.4; H, 4.5; N, 3.1. $C_{22}H_{19}NO_8$ requires C, 62.1; H, 4.5; N, 3.3%). The column was extruded, and the blue band extracted with methanol, to give an extremely insoluble blue solid (*ca.* 90 mg), m.p. 196—200 °C.

2-*Chloromethyl*-6-*methylquinoline with DMAD*.—(*i*) DMAD (3 g) was added to a solution of the quinoline (1.9 g) in dry dimethylformamide (50 ml) and the reaction set aside at room temperature for 3 d. The tar obtained on evaporation was dissolved in toluene and applied to an alumina column (500 ml) made up in toluene. Elution with toluene–ethyl acetate (99 : 1 v/v) gave *tetramethyl* 4a-*chloromethyl*-8-*methyl*-4a*H*-*benzo*[c]*quinolizine*-1,2,3,4-*tetracarboxylate* (16) (0.52 g 11.0%), as yellow crystals (from methanol), m.p. 153—155 °C (Found: C, 58.1; H, 4.7; N, 2.8. $C_{23}H_{22}ClNO_8$ requires C, 57.9; H, 4.8; N, 2.9%). Using acetonitrile 3.2% of (16) was obtained.

(*ii*) The reaction was carried out in acetonitrile–methanol (9 : 1, v/v) and (16) (0.09 g, 1.9%) was isolated as above. Elution of the column with toluene–ethyl acetate (9 : 1 v/v) gave a red compound (6 mg), m.p. 205—207 °C, thought to be (18).

2-*Methylquinoline with DMAD*.—DMAD (3 g) was added to a solution of 2-methylquinoline (1.5 g) in acetonitrile–methanol (95 : 5, 50 ml), and the mixture set aside at room temperature for 2 d. The tar obtained on evaporation was dissolved in toluene and applied to an alumina column (300 ml), made up in toluene. Elution with toluene–ether (95 : 5 v/v) gave tetramethyl 7a,8,9,9a-tetrahydrocyclobuta[4,5]pyrrolo[1,2-*a*]quinoline-7,*r*-7a,*c*-9,*c*-9a-tetracarboxylate (1) (1.65 g, 36.8%), m.p. 203—204 °C (methanol) (lit.,[10] 203—204 °C), identical with authentic material. Elution with toluene–ether (95 : 5, v/v) gave a small quantity (*ca.* 0.06 g, 1.0%) of the red 3 : 1 adduct (19), m.p. 228—230 °C (methanol) (lit.,[11] m.p. 230 °C) identical with authentic material. The reaction was repeated with CD_3OD in place of methanol, with essentially the same results, to give deuteriated samples of (1) (1.42 g) and (19) (*ca.* 0.05 g). A solution of deuteriated (1) (0.15 g) in methanol (50 ml) was refluxed with sodium hydride (*ca.* 0.005 g) for 20 h and the product isolated as in the epimerisation of (31) (below). It was identified as (1) (0.12 g), containing no deuterium (mass spectrometry and ^1H n.m.r.).

The Epimerisation of Tetramethyl 3-*Bromo*-7a,8,9,9a-*tetrahydrocyclobuta*[4,5]*pyrrolo*[1,2-a]*quinoline*-7,r-7a,c-9,c-9a-*tetracarboxylate* (31).—A solution of (31) (0.10 g), prepared by R. F. Flowerday,[7] in methanol (50 ml) was treated with sodium hydride (*ca.* 0.005 g) and the mixture refluxed for 20 h. Acetic acid (3 drops) was added to the cooled solution, and the solvent evaporated. The resulting solid was taken up in chloroform (100 ml), and the solution washed with water (50 ml), dried, and evaporated. The ^1H n.m.r. spectrum of this material showed it to be a mixture of (31) and the C-9 epimer in roughly equal proportions.

The Oxidation of Tetramethyl 7a,8,9,9a-*Tetrahydrocyclobuta*[4,5]*pyrrolo*[1,2-a]*quinoline*-7,r-7a,c-9,c-9a-*tetracarboxylate* (1).—The oxidation of (1) (2 g) was carried out essentially as described [10] to give *methyl hydroxy*-2-*quinolyl*-1,2,3-*trismethoxycarbonylcyclobut*-2-*enylacetate* (37) (0.19 g) as colourless crystals (from methanol–ether), m.p. 132—133 °C (lit.,[10] m.p. 133 °C).

Pyrolysis of the Red Adduct (19).—A sample of (19) (prepared by J. M. F. Gagan; [10] 1.0 g) was placed in a sublimation apparatus, and evacuated (water pump). The solid was heated until it melted, and this temperature was maintained for 10 min. The cooled solid was taken up in toluene–chloroform (2 : 1 v/v), and applied to an alumina column (200 ml) made up in this solvent. Elution of the yellow band with this solvent gave *dimethyl* 3-(1,2-*bismethoxycarbonylvinyl*)*benzo*[c]*indolizine*-1,2-*dicarboxylate* (39) (0.51 g) as yellow crystals, m.p. 138—140 °C (lit.,[11] m.p. 138—140 °C). Further elution gave unchanged starting material (*ca.* 0.05 g).

Methyl 3-[1-(1,2-*Bismethoxycarbonylvinyl*)]-r-1-*methoxycarbonyl*-t-2-*phenyl*-1,2-*dihydrobenzo*[c]*indolizine*-1-*methoxyacetate* (40).—2-Styrylquinoline [19] (2.5 g) was dissolved in warm acetonitrile (49 ml) and methanol (1 ml) and DMAD (2.9 g) was added. After refluxing for 2 h the solvent was removed and the residual tar (in toluene) chromatographed over alumina (600 ml) made up in toluene. Elution with toluene–ethyl acetate (9 : 2 v/v) gave a red tar which recrystallised (methanol) to give red crystals of the mixed isomer (0.35 g), m.p. 204.5—205 °C (Found: C, 65.8; H, 5.4; N, 2.6; OMe, 29.2. $C_{30}H_{29}NO_9$ requires C, 65.8; H, 5.3; N, 2.6; 5 × OMe, 28.3%). The crystals, in methanol, were set aside in an open flask at room temperature. The solid formed after 20 h was collected, and the filtrate allowed to evaporate further. The crystals from the third filtrate, after recrystallisation from methanol, yielded the indolizine (40) (70 mg), m.p. 123—124 °C. Repetition using [$^2H_4$]methanol gave deuteriated (40) (50 mg).

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