Heterocyclic Studies. Part XXXVIII.[1] Synthesis and Disproportionation of Pyrimido[4,5-*b*]quinolinium Salts

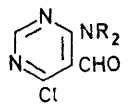
By **Jim Clark** * and **Bahman Parvizi**, The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

Treatment of 4-chloro-6-*N*-ethylanilinopyrimidine-5-carbaldehyde (3) with boiling water gave 10-ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride (7) together with 10-ethyl-5,10-dihydropyrimido[4,5-*b*]-quinolin-4(3*H*)-one (8) and 1-ethyl-1,2-dihydro-2-oxoquinoline-3-carbonitrile (6). The salt (7) underwent disproportionation at pH values greater than 9 to the 5,10-dihydro-compound (8) and 10-ethylpyrimido[4,5-*b*]-quinoline-4,5(3*H*,10*H*)-dione (25). The reaction was shown by deuterium-labelling studies, ionisation studies, and crossing experiments with a closely related 3-methylpyrimidoquinolinium salt (29) to involve a hydride ion transfer from the 5-position of one molecule of the compound, as its pseudo-base anion, to the 5-position of another molecule in the cation form. Several other pyrimidoquinolinium salts behaved similarly.

Reactions of the pyrimidoquinolines are described, including various oxidations, reductions, and disproportionations which enabled pyrimidoquinolines in the three possible oxidation states to be interconverted.

Pyrimidoquinolinium salts were attacked at the 5-position by *N*,*N*-dialkylanilines to give 5-(4-dialkylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinolines.

THE previous paper in this series [1] showed that when 4-chloro-6-dialkylaminopyrimidine-5-carbaldehydes (1; NR_2 = NMe_2, pyrrolidino, *etc.*) were heated with water or acid they readily underwent ring-cleavage and deformylation processes which led to 3-dialkylamino-3-iminopropiononitriles (2). However, similar treatment of 4-chloro-6-*N*-ethylanilinopyrimidine-5-carbaldehyde (3) gave



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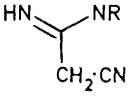


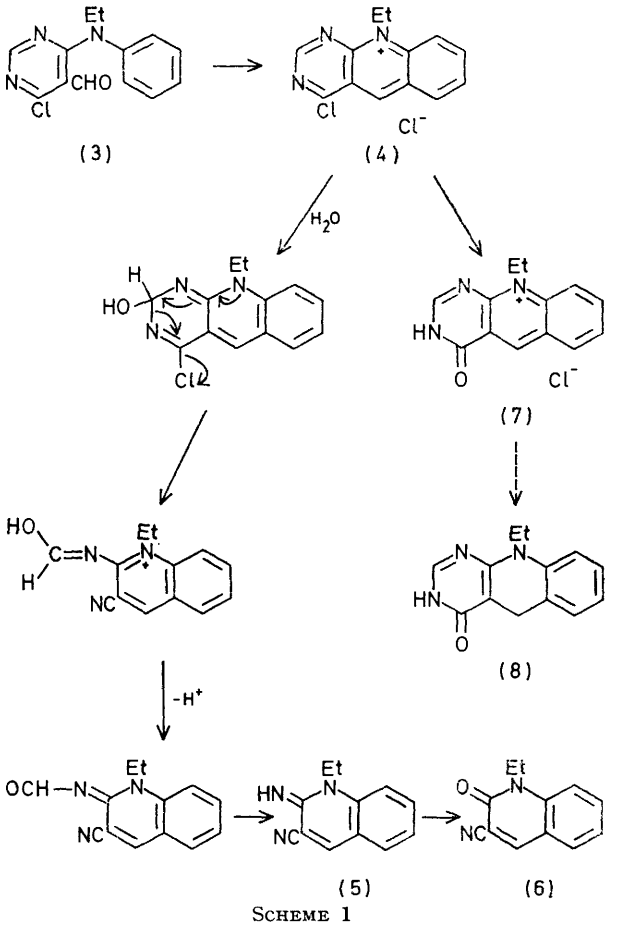
(2)

three products, none of which was the amidine (2; NR_2 = NEtPh). The first product was a weak acid which was filtered from the hot reaction mixture, the second a neutral compound which separated on thorough cooling of the filtrate, and the third a salt which was left on evaporation of the final mother liquor.

The neutral compound was assigned the 1-ethyl-2-oxoquinoline-3-carbonitrile structure (6) on the basis of its i.r. spectrum (ν_{CN} 2 240 cm^{-1}), its ^1H n.m.r. spectrum (signals for an *N*-ethyl group, four benzenoid protons, and one lower field aromatic proton), and its mass spectrum (M^+ 198.0792) ($C_{12}H_{10}N_2O$). The compound was synthesised unambiguously by ethylating the known 1,2-dihydro-2-oxoquinoline-3-carbonitrile [2] with ethyl iodide and sodium hydride.

The weak acid was identified as a dihydropyrimidoquinoline (8) by its i.r. spectrum [amide carbonyl (1 650 cm^{-1}) and NH signals], its ^1H n.m.r. spectrum [signals for four benzenoid protons, one lower field aromatic proton, and an *N*-ethyl group, and a 2-proton singlet at τ 6.2 (Figure 1a)], its mass spectrum (M^+ at 227.1052) ($C_{13}H_{13}N_3O$), and its ionisation constant (pK_a 9.96 $\pm$ 0.04), which was typical of a 2-aminopyrimidin-4(3H)-one.[3]

The third product was a hydrochloride whose ^1H n.m.r. spectrum (Table 2) showed signals for an *N*-ethyl group, four rather low field benzenoid protons, a lower field aromatic proton, and one still lower field proton at about τ 0. The last peak, together with a strong i.r. absorption at 1710 cm^{-1} suggested an aldehyde group, but the compound underwent none of the typical carbonyl reactions.



SCHEME 1

Its u.v. spectrum (Figure 2) led decisively to the assignment of the 10-ethylpyrimidoquinolinium structure (7), for the spectrum was almost identical with that of the

[1] Part XXXVII, J. Clark, B. Parvizi, and I. W. Southon, preceding paper.

[2] H. Janek, *Monatsh.*, 1963, **94**, 890.

[3] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965, p. 213.

cation of the known 10-unsubstituted pyrimidoquinolinone (9).[4] The close resemblance of the spectra (Figure 2) shows that the compounds have similar π-electron

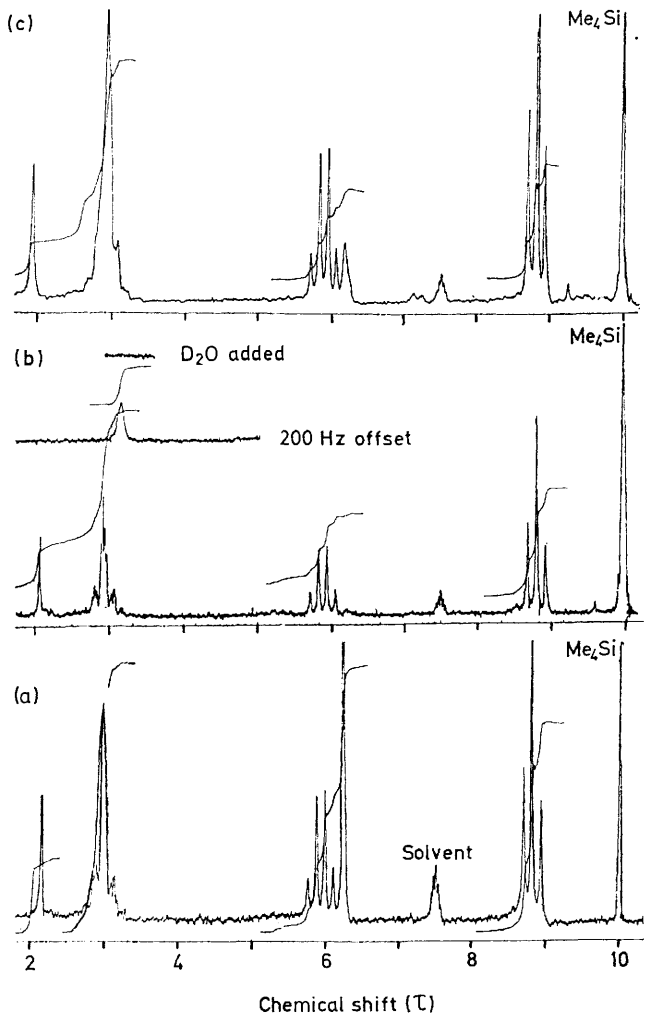


FIGURE 1 ^{1}H N.m.r. spectra [solvent $(CD_3)_2SO$] of (a) 10-ethyl-5,10-dihydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (8) (b) its 5,5-dideuterio-derivative, and (c) a specimen partially deuteriated at position 5

systems and this not only confirmed the structure of the new compound (7) but shows that the 10-unsubstituted compound (9) undergoes protonation at position 10.

N-Methyl analogues of the three compounds (6)—(8) were obtained when 4-chloro-6-*N*-methylanilinopyrimidine-5-carbaldehyde (1; NR_2 = NMePh) was treated with water in the same way as the ethylanilino-compound (3).

The origins of two of the three types of compound identified were clear (Scheme 1). The nitrile (6) resulted from cyclisation of the *N*-ethylanilinopyrimidine (3) to the pyrimidoquinolinium salt (4), which then underwent ring cleavage analogous to those undergone by simple 5-formyl-[1] or 5-nitro-pyrimidines.[5] The resulting imine (5) would be readily hydrolysed to the nitrile (6).

[4] E. Campaigne and G. Randau, *J. Heterocyclic Chem.*, 1971, **8**, 111.

Cyclisation must have preceded ring cleavage because the formylacrylonitrile (10), which would have been the product of an immediate cleavage,[1] undergoes deformylation rather than cyclisation to the quinoline (5) under acidic conditions.[6] Simple hydrolysis of the chloro-compound (4) accounted for the 4-oxopyrimidoquinolinium salt (7), but the origin of the product (8) was obscure because it was in an unexpected oxidation state. In view of this the reactions of the pyrimidoquinolines were investigated further.

The pyrimidoquinolinium salt (7) was obtained in quantitative yield and free from other compounds by treating the pyrimidine (3) with ethanolic hydrogen chloride. It was stable under aqueous acidic conditions but at pH values greater than 9 it changed into the dihydropyrimidoquinolone (8) already described (50%) and the corresponding quinoline-4,5-dione (25) (50%). The compounds, which were conveniently separated as 3-methyl derivatives (17) and (24), clearly came from a disproportionation reaction in which one molecule of the salt had been oxidised and another reduced. To check the generality of this type of reaction three more pyrimidoquinolinium salts (11)—(13) were synthesised and they all underwent disproportionation to appropriate dihydro- (18)—(20) and oxo- (26)—(28) compounds,

The relationships between the various pyrimidoquinolines were established as follows (Scheme 2). The salt (7) was reduced by ammonium formate to the dihydro-derivative (8) and this was oxidised by permanganate to the oxo-compound (25). The last two substances were converted by reaction with methyl iodide into 3-methyl derivatives, (17) and (24). The dihydro-methyl compound (17) was oxidised by triphenylmethyl perchlorate

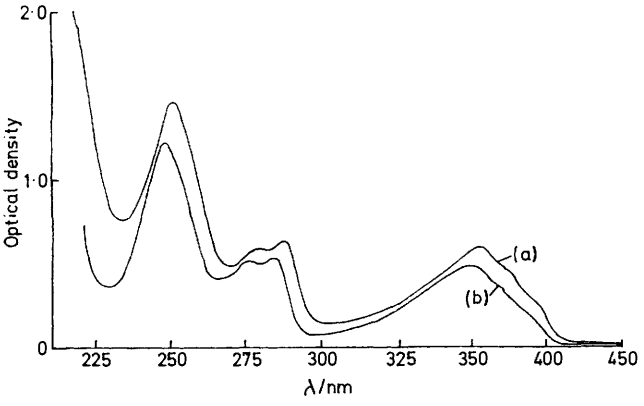


FIGURE 2 U.v. spectra of aqueous 5×10^{-5}M solutions of (a) 10-ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride (7) at pH 4.1 and (b) pyrimido[4,5-*b*]quinolin-4 (3*H*) -one (9) (cation) at pH 0.8

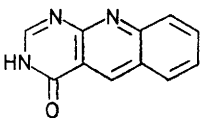
to the 3-methylpyrimidoquinolinium perchlorate (29), which underwent disproportionation at pH 9 to the dihydro- (17) and oxo- (24) compounds.

Reduction of the salt (7) with ammonium formate had been inspired by a report of a similar reduction of the

[5] J. Clark, I. Gelling, I. W. Southon, and M. S. Morton, *J. Chem. Soc.* (*C*), 1970, 494.

[6] B. Parvizi, Ph.D. Thesis, Salford University, 1974.

10-unsubstituted pyrimidoquinoline (9).[4] We prepared the latter very simply by treating 4-anilino-6-chloropyrimidine-5-carbaldehyde with polyphosphoric acid. It could not be made, like its 10-ethyl derivative (7), by treating the pyrimidine with ethanolic hydrogen chloride



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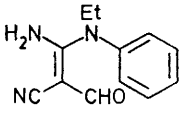

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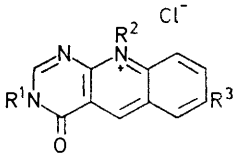
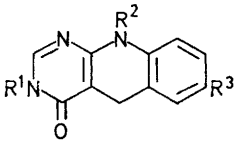
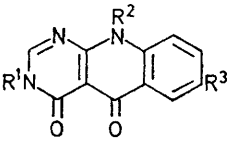


(11) R^1= R^3= H , R^2= Me
(12) R^1= H , R^2= Me , R^3= Cl
(13) R^1= H , R^2= Me , R^3= OMe



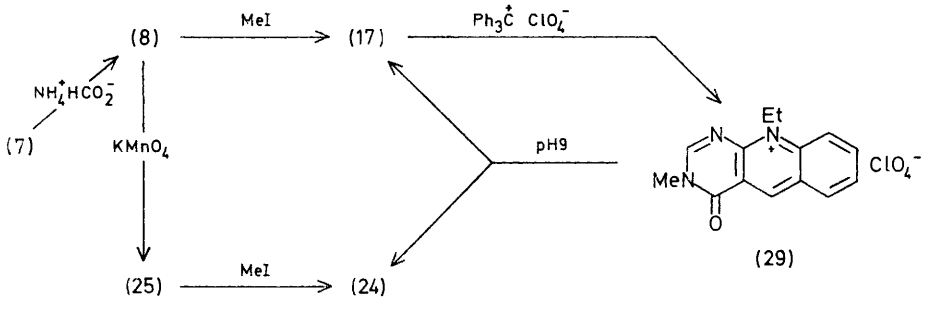
(14) R^1 = R^2= Me , R^3 = H
(15) R^1 = R^2= Me , R^3 = Cl
(16) R^1 = R^2= Me , R^3= OMe
(17) R^1 = Me , R^2= Et , R^3= H
(18) R^1 = R^3= H , R^2= Me
(19) R^1 = H , R^2= Me , R^3= Cl
(20) R^1 = H , R^2= Me , R^3= OMe



(21) R^1= R^2= Me , R^3= H
(22) R^1= R^2= Me , R^3= Cl
(23) R^1= R^2= Me , R^3= OMe
(24) R^1= Me , R^2= Et , R^3= H
(25) R^1= R^3= H , R^2= Et
(26) R^1= R^3= H , R^2= Me
(27) R^1= H , R^2= Me , R^3= Cl
(28) R^1= H , R^2= Me , R^3= OMe

because there occurred a ready deformylation initiated by protonation of the 5-position of the pyrimidine ring.[1] The 10-unsubstituted compound (9), pK_a 9.08 ± 0.05, showed no tendency to undergo disproportionation but it had been reported to undergo an ' unusual arylation ' when treated with phosphoryl chloride and diethylaniline.[4] Campaigne and Randau argued that this reaction, which led to the 5-*p*-diethylaminophenyl derivative acridinium salts,[7] xanthylium salts,[8] and thioxanthylium salts.[9] Treatment of the *N*-ethyl salt (30; R = Et) with diethylaniline in the presence of phosphoryl chloride gave (Scheme 3) the 10-ethyl analogue (32; R = Et) of the compound described by Campaigne and Randau, and simple refluxing of the salt (30; R = Et) with dimethylaniline resulted in a similar compound (33; R = Et) but, of course, without conversion into a chloro-compound. The last reaction suggests that phosphoryl chloride plays no part in the attacks by the dialkylanilines.

Mechanism of Disproportionation.—The origin of the extra hydrogen atom which appears at the 5-position of pyrimidoquinolinium salts during disproportionations



SCHEME 2

(32; R = H), went through a complex series of intermediates, but it now seems likely that it was formed by simple nucleophilic attack at the 5-position of the cation (31; R = H). There are many precedents for nucleophilic attacks, including some by dialkylanilines, at such electron-deficient positions, particularly the 9-position of

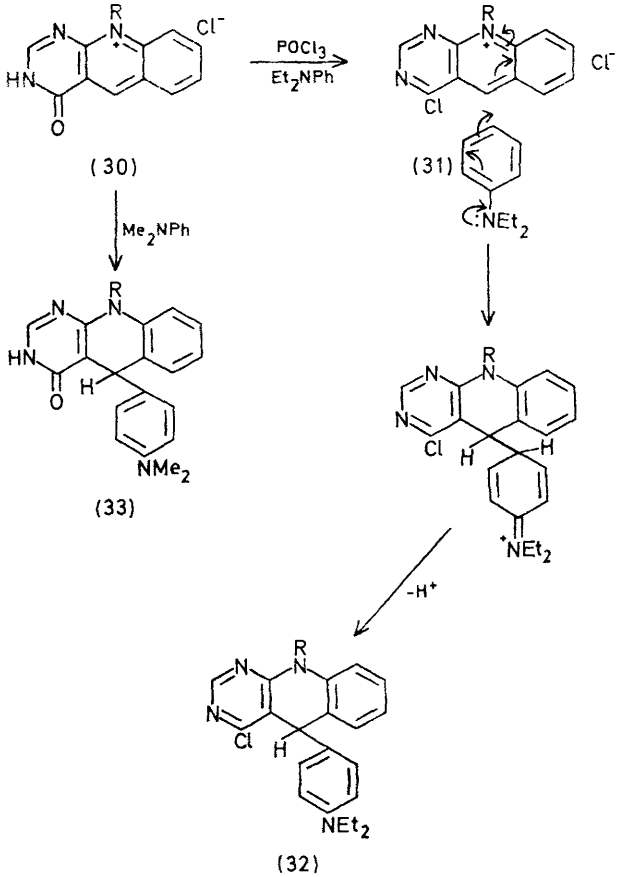
[7] I. A. Selby in 'Acridines,' 2nd edn., ed. R. M. Acheson, Interscience, New York and London, 1973, p. 437.
[8] S. Wawzonek in ' Heterocyclic Compounds, vol. 2,' ed. R. C. Elderfield, Wiley, New York, 1951, p. 477 *et seq.*

was established by deuteriation studies.[10] When the salt (7) disproportionated in a mixture of D_2O and NaOD, of suitable pH value, the dihydro-derivative produced (8) (Figure 1a) contained no deuterium, so the extra hydrogen had come from the organic compound. However the 5-deuterio-salt (35), made from the deuterioformylpyrimidine (34), gave, on disproportionation, an

[9] D. S. Tarbell in ref. 8, p. 546 *et seq.*
[10] Preliminary report, J. Clark and B. Parvizi, *J.C.S. Chem. Comm.*, 1974, 308.

isotopically pure 5,5-dideuteriopyrimidoquinoline (36) (Figure 1b). The reaction therefore involved a deuterium atom transfer from the 5-position of one molecule to the 5-position of another.

Since the salts (7) and (29) were stable under acidic conditions, the cations alone did not suffer disproportionation, so one or more other species must be involved. The



SCHEME 3

3-unsubstituted salt (7) had two easily accessible ionisation constants characterised by pK_a values of 6.12 ± 0.04 and 11.3 ± 0.07. The former was for ionisation of the 3-NH grouping to give the highly polar neutral molecule (37a) ⟷ (37b), and the second for pseudo-base anion (38) formation. The nature of the latter change, due to hydroxide ion attack at position 5, was revealed by the marked hypsochromic shift in the u.v. spectrum under alkaline conditions (Figure 3). Similar shifts are observed with 9-substituted acridines.[11] The 3-methylpyrimidoquinolinium salt (29), which lacks the ionisable 3-proton, had only one accessible pK_a value (8.31 ± 0.02), which was for pseudo-base (39) formation (Figure 4).

At this stage it seemed probable that disproportionation of the salt (7) occurred by transfer of a hydride ion from a good donor form such as (38) to a good acceptor form such as (7). Corresponding species for disproportionation of the 3-methyl compound (29) would be the pseudo-base (39) and the cation (29). This hypothesis was tested by mixing the 3-methyl (29) and 3-unsubstituted (7) compounds at pH 10.2. At this pH value the 3-unsubstituted compound consisted of about 5% of the good hydride ion donor (38) in equilibrium with 95% of the poor hydride ion acceptor (37) and about 0.01% of the good acceptor (7), whereas the 3-methyl compound consisted of about 98% of a moderately good donor (39) and

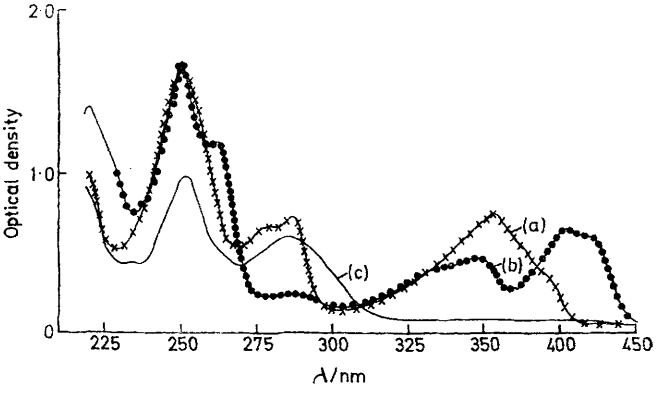


FIGURE 3 U.v. spectra of aqueous 5 × 10^{-5}M solutions of 10-ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride at (a) pH 4.1 (7), (b) pH 8.1 (37), and (c) pH 13.2 (38)

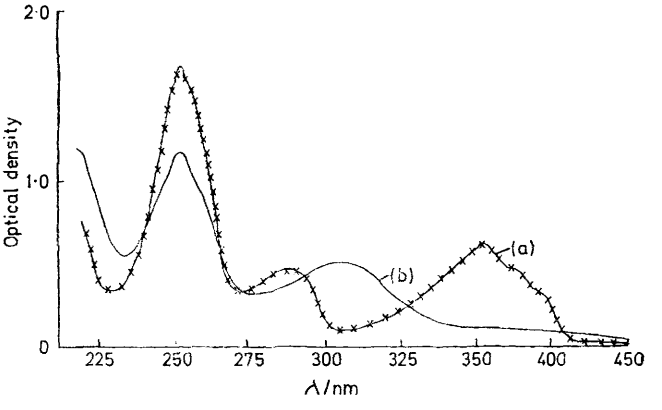


FIGURE 4 U.v. spectra of aqueous 5 × 10^{-5}M solutions of 10-ethyl-3,4-dihydro-3-methyl-4-oxopyrimido[4,5-*b*]quinolinium perchlorate at (a) pH 0.8 (29) and (b) pH 10.2 (39)

2% of the good acceptor (29). The result of this experiment was that the best acceptor present in appreciable quantity (29) was reduced by the best donor present (39) (Scheme 4) and there was little disproportionation. Thus the hydrogen atom is almost certainly transferred as a hydride ion. These reactions are reminiscent of related disproportionations of acridinium,[12] xanthylium,[13] thioxanthylium,[14] and other similar salts[15] but

[11] J. J. Dobbie and C. K. Tinkler, *J. Chem. Soc.*, 1905, 269; C. K. Tinkler, *ibid.*, 1906, 856.

[12] A. Albert, 'The Acridines,' 2nd edn., Arnold, London, 1966, p. 333; R. M. Acheson, 'Acridines,' ed. A. Weissberger, Interscience, New York, 1956, p. 239.

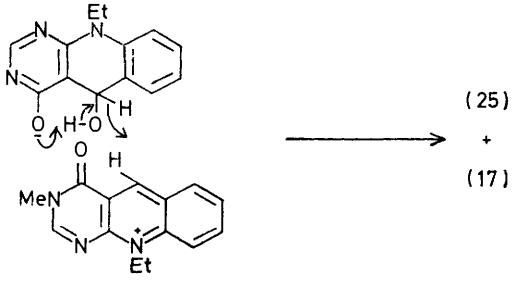
[13] F. G. Kny-Jones and A. M. Ward, *J. Chem. Soc.*, 1930, 535.

[14] C. V. T. Campbell, A. Dick, J. Ferguson, and J. D. Loudon, *J. Chem. Soc.*, 1941, 747; E. D. Amstutz and C. R. Neumoyer, *J. Amer. Chem. Soc.*, 1947, **69**, 1925.

[15] J. Ashby, M. Ayad, and O. Meth-Cohn, *J.C.S. Perkin I*, 1973, 1104.

in these cases no labelling evidence has been produced. Mixing of the salts (7) and (29) at pH 7.2 resulted mainly in disporportionation of the 3-methyl derivative (29), with the other compound (7) mostly unchanged. This confirms the hydride ion transfer theory because, under these conditions, less than 0.1% of the latter is present in a hydride ion donor form (38) while its good acceptor form (7), though present to the extent of about 8%, is swamped by the equally good acceptor (29) which is the form present to the extent of 93%.

The presence of the dihydro-derivative (8) in the reaction products from the pyrimidine (3) and water (Scheme 1), discussed at the start of this paper, cannot be completely explained by a disproportionation reaction because there was little of the corresponding oxo-compound (25). When the reaction was repeated with the deuterioformylpyrimidine (34) the dihydro-compound produced contained some hydrogen as well as deuterium at position 5

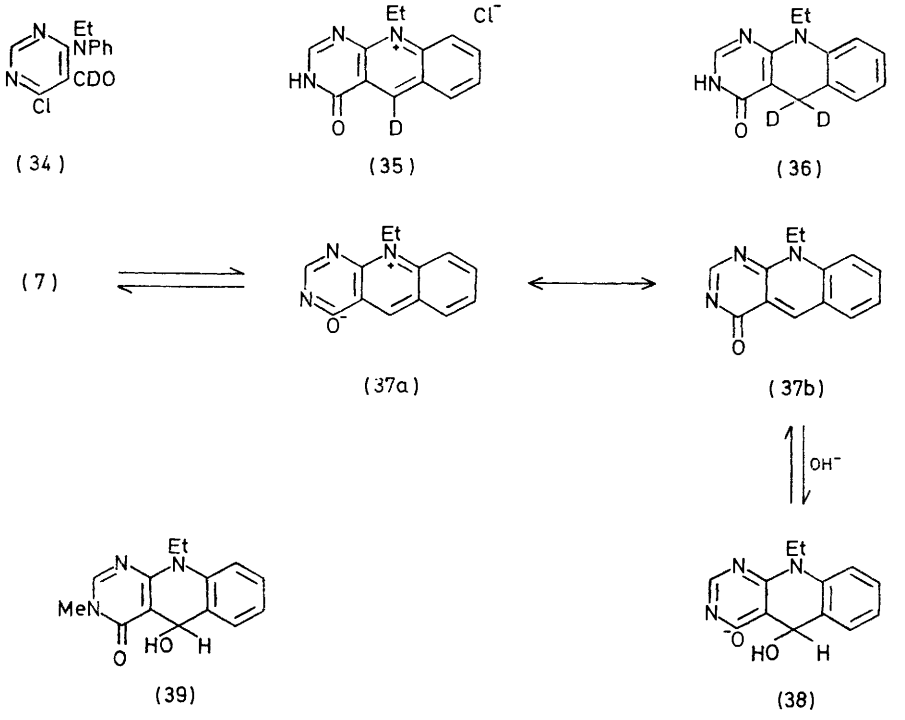


SCHEME 4

(Figure 1c). We argue that some of the salt (7) becomes reduced by the hydride ion donor formic acid, which comes from the ring-cleavage reaction (4) ⟶ (5), just as the salt (7) was reduced by formate to the dihydro-compound (8). The feasibility of this was illustrated by another experiment in which formic acid did indeed reduce the salt (7).

EXPERIMENTAL

Ionisation constants were measured, at 20 °C, by a rapid spectrophotometric method,[16] and u.v. spectra, for solutions in aqueous buffer, were recorded with a Unicam SP 800 instrument. Mass spectra were recorded with an A.E.I. MS 902S spectrometer (source temperature *ca.* 200 °C; accurate mass measurements made at a resolving power of 10 000)



^{1}H N.m.r. spectra were recorded with a Varian A60A instrument at normal probe temperature with tetramethylsilane as internal standard. I.r. spectra were recorded with a Perkin-Elmer 257 grating instrument for Nujol mulls.

Treatment of 4-*Chloro*-6-N-*ethylanilinopyrimidine*-5-*carbaldehyde with Water*.—The pyrimidine [1] (10 g) and water (30 ml) were heated under reflux for 3 h and the hot mixture was filtered to yield 10-*ethyl*-5,10-*dihydropyrimido*[4,5-b]-*quinolin*-4(3H)-*one* (8) (1.3 g), m.p. 210° (decomp.) (from aqueous dimethylformamide) (Found: C, 68.5; H, 5.6; N, 18.4. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.8; N, 18.5%) (^{1}H n.m.r. spectrum in Table 2).

The filtrate was thoroughly cooled and a solid (0.5 g) was filtered off, dissolved in chloroform, and eluted with chloroform from a silica column to yield 1-*ethyl*-1,2-*dihydro*-2-*oxoquinoline*-3-*carbonitrile* (6), m.p. 192—193° (from propan-2-ol), identical with a specimen synthesised as described below (Found: C, 72.7; H, 5.0; N, 14.2. $C_{12}H_{10}N_2O$ requires C, 72.7; H, 5.1; N, 14.1%), τ 8.60 (3 H, t, J 7.2 Hz) 5.58 (2 H, q, J 7.2 Hz), 2.97—1.97 (4 H, m), and 1.70 (1 H, s).

The cold mother liquor from the second filtration was

[16] J. Clark and A. E. Cunliffe, *Chem. and Ind.*, 1973, 281.

evaporated to dryness under reduced pressure and the oily residue triturated with acetone to yield 10-*ethyl*-3,4-*dihydro*-4-*oxopyrimido*[4,5-b]*quinolinium chloride* (7) (4.6 g), m.p. 249—251° (Found: C, 59.5; H, 4.8; N, 15.9. $C_{13}H_{12}ClN_3O$ requires C, 59.7; H, 4.6; N, 16.1%). This compound was best synthesised as described below.

Treatment of 4-*Chloro*-6-N-*methylanilinopyrimidine*-5-*carbonitrile with Water*.—The pyrimidine (5 g) was treated with water (20 ml) as described for the *N*-ethyl analogue. The products were 5,10-*dihydro*-10-*methylpyrimido*[4,5-b]*quinolin*-4(3H)-*one* (0.2 g), m.p. 200° (from propan-2-ol) (Found: C, 67.4; H, 5.2; N, 19.6. $C_{12}H_{11}N_3O$ requires C, 67.6; H, 5.2; N, 19.7%), 1,2-*dihydro*-1-*methyl*-2-*oxoquinolin*-3-*carbonitrile* (0.3 g), m.p. 214—216° (from propan-2-ol) (Found: C, 71.7; H, 4.3; N, 15.1. $C_{11}H_8N_2O$ requires C, 71.7; H, 4.4; N, 15.2%), and 3,4-*dihydro*-10-*methyl*-4-*oxopyrimido*-[4,5-b]*quinolinium chloride* (1.4 g), m.p. 258—260° (decomp.) (Found: C, 58.1; H, 4.1; N, 16.9. $C_{12}H_{10}ClN_3O$ requires C, 58.2; H, 4.1; N, 17.0%). The last compound was best synthesised as described below.

1-*Ethyl*-1,2-*dihydro*-2-*oxoquinoline*-3-*carbonitrile* (6).—1,2-Dihydro-2-oxoquinoline-3-carbonitrile [2] (0.15 g) was dissolved in dry dimethylformamide (5 ml) and stirred under under nitrogen. Sodium hydride (0.03 g) and ethyl iodide (0.2 g) were added and the mixture was stirred for 18 h. Insoluble matter was filtered off and the filtrate was evaporated to dryness under reduced pressure to yield the *N*-ethyl derivative (0.1 g), m.p. 190—191° (from water, identical with the specimen described above.

10-*Ethyl*-3,4-*dihydro*-4-*oxopyrimido*[4,5-b]*quinolinium Chloride* (7).—4-Chloro-6-*N*-ethylanilinopyrimidine-5-carbaldehyde (14.2 g) was dissolved in ethanolic hydrogen chloride (30%; 50 ml). After a few minutes an exothermic reaction occurred and the product separated as large yellow crystals (13.2 g), m.p. 248—251°, identical (i.r., u.v., and ^1H n.m.r. spectra) with the specimen described above.

3,4-*Dihydro*-10-*methyl*-4-*oxopyrimido*[4,5-b]*quinolinium Chloride*.— 4-Chloro-6-*N*-methylanilinopyrimidine-5-carbaldehyde (1 g) and ethanolic hydrogen chloride (30%; 15 ml) were heated under reflux for 2 h and the solution was then cooled and filtered to yield the product (1 g), m.p. 260—262° (decomp.), identical with the specimen described above.

3,4-*Dihydro*-7-*methoxy*-10-*methyl*-4-*oxopyrimido*[4,5-b] *quinolinium Chloride* (13).—4-Chloro-6-(4-methoxy-*N*-methylanilino)pyrimidine-5-carbaldehyde (3.5 g) and ethanolic hydrogen chloride (30%; 20 ml) were heated under reflux for 1 h. The dark yellow precipitate was filtered off and washed with ethanol to yield analytically pure *product* (3.4 g), m.p. 220—230° (decomp.) (Found: C, 56.3; H, 4.5; N, 15.3. $C_{13}H_{12}ClN_3O_2$ requires C, 56.2; H, 4.4; N, 15.1%).

7-*Chloro*-3,4-*dihydro*-10-*methyl*-4-*oxopyrimido*[4,5-b]-*quinolinium Chloride* (12) (4.2 g), similarly obtained from 4-chloro-6-(4-chloro-*N*-methylanilino)pyrimidine-5-carbaldehyde (4.5 g) and ethanolic hydrogen chloride (30%; 20 ml), had m.p. 230° (decomp.) (Found: C, 51.0; H, 3.4; N, 14.9. $C_{12}H_9Cl_2N_3O$ requires C, 51.1; H, 3.2; N, 14.9%).

Disproportionation of 10-*Alkyl*-3,4-*dihydro*-4-*oxopyrimido*-[4,5-b]*quinolinium Chlorides*.—The salt [(7), (11), (12), or (13)] was dissolved in water and 2N-sodium hydroxide solution added until the pH value reached 9. The solution was kept for 1—3 days and the mixture of products filtered off, washed with water, and dried at 100 °C. The solids were dissolved in potassium hydroxide solution (1 equiv.) and shaken for 48 h with methyl iodide (1 equiv). The mixture of methyl derivatives was filtered off, washed with water and extracted with chloroform. The chloroform-insoluble material was crystallised to yield the 10-*alkyl*-3-*methylpyrimido*[4,5-b]*quinoline*-4,5(3H,10H)-*dione* (21)—(24) (Table 1). The chloroform extract was dried ($MgSO_4$) and evaporated under reduced pressure, and the residue crystallised to yield the 10-*alkyl*-5,10-*dihydro*-3-*methylpyrimido*[4,5-b]*quinolin*-4(3H)-*one* (14)—(17) (Table 1).

10-*Ethyl*-5,10-*dihydropyrimido*[4,5-b]*quinolin*-4(3H)-*one* (8).—(*a*) 10-Ethylpyrimido[4,5-*b*]quinolinium chloride (1 g), formamide (25 ml), and ammonium formate (3 g) were heated under reflux for 1½ h. The solution was cooled and water (10 ml) was added to give a white precipitate which was filtered off, washed with water and ethanol, and crystallised from aqueous dimethylformamide. The product (0.75 g), m.p. 200° (decomp.), was identical with the specimen described above. (*b*) The same salt (1.3 g), formic acid (0.3 g), and water (15 ml) were heated under reflux for 3 h; the dihydro-derivative (0.4 g) was filtered off and purified as described above. (*c*) The same salt (1 g) was dissolved in water (10 ml) and treated with 2N-sodium hydroxide to pH 9. After 2 h the precipitate was filtered off and purified as above to give the dihydro-derivative (0.2 g).

The i.r. spectra of specimens produced by methods (*a*)—(*c*) were identical.

10-*Ethylpyrimido*[4,5-b]*quinoline*-4,5(3H,10H)-*dione* (25).—10-Ethyl-5,10-dihydropyrimido[4,5-b]quinolin-4(3*H*)-one (0.45 g) was dissolved in an excess of N-sodium hydroxide and treated with potassium permanganate (0.5 g) in water (20 ml). After 1 h the manganese dioxide was filtered off and the filtrate acidified with 6N-hydrochloric acid. The yellow precipitate was filtered off and crystallised from aqueous dimethylformamide to yield the *dione* (0.3 g), m.p. 247—249° (Found: C, 64.7; H, 4.7; N, 17.4. $C_{13}H_{11}N_3O_2$ requires C, 64.7; H, 4.6; N, 17.4%).

10-*Ethyl*-3-*methylpyrimido*[4,5-b]*quinoline*-4,5(3H,10H)-*dione* (24).—10-Ethyl-5,10-dihydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (0.2 g) was dissolved in 2N-sodium hydroxide and titrated with a slight excess of potassium permanganate solution. Manganese dioxide was filtered off and the filtrate shaken with methyl iodide (0.15 g) for 18 h to yield the product (0.12 g), m.p. 284—286° (decomp.) (from ethanol), identical with the specimen described in Table 1.

Synthesis and Disproportionation of 10-*Ethyl*-3,4-*dihydro*-3-*methyl*-4-*oxopyrimido*[4,5-b]*quinolinium Perchlorate* (29).—10-Ethyl-5,10-dihydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (0.35 g) in methylene chloride (15 ml) was stirred and treated with a solution of triphenylmethyl perchlorate (0.7 g) in methylene chloride (40 ml). After 0.5 h the precipitate was filtered off and washed with methylene chloride to yield the *salt* (0.4 g), m.p. 250—251° (Found: C, 49.6; H, 4.1; N, 12.4. $C_{14}H_{14}ClN_3O_5$ requires C, 49.5; H, 4.2; N, 12.4%).

This salt (1.2 g) was dissolved in water (30 ml) and the pH value of the solution adjusted to 9 with 2N-sodium hydroxide. The solution was kept for 24 h and the mixture of products was filtered off and dried. The solid was treated with chloroform (2 × 20 ml) and the chloroform-insoluble material crystallised from ethanol to yield 10-ethyl-3-methylpyrimido[4,5-*b*]quinoline-4,5(3*H*,10*H*)-dione (24) (0.3 g), m.p. 286° (decomp.). The chloroform extract was evaporated to yield 10-ethyl-5,10-dihydro-3-methylpyrimido[4,5-*b*]quinolin-4(3*H*)-one (17) (0.4 g), m.p. 178—180° (from aqueous ethanol). The products were identical with those described in Table 1.

Pyrimido[4,5-b]*quinolin*-4(3H)-*one*.—4-Anilino-6-chloro-

pyrimidine-5-carbaldehyde (2g) was added to polyphosphoric acid (30 g) and the mixture heated to 240° for 1½ h before being cooled and poured into ice–water. Insoluble matter was filtered off and the filtrate was basified with aqueous ammonia (*d* 0.88). The precipitate was filtered off, washed with water and then ethanol, and dried at 100 °C to yield the product (1.4 g), m.p. 324° (decomp.) [lit.,[4] 354° (decomp.)].

4-Chloro-5-(4-diethylaminophenyl)-10-ethyl-5,10-dihydropyrimido[4,5-b]*quinoline* (32; R = Et).—10-Ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride (1.3 g), phosphoryl chloride (20 ml), and *NN*-diethylaniline (1.5 g) were heated under reflux for 1½ h. The excess of solvent was removed under reduced pressure and water (15 ml) was added to the residue. The solution was extracted with chloroform (2 × 20 ml) and the extract dried ($MgSO_4$) and evaporated to give an oil which was triturated with propan-2-ol to yield the *product* (0.6 g), m.p. 131—132° [from light petroleum (b.p. 60—80°)] (Found: C, 70.4; H, 6.4; N, 14.2. $C_{23}H_{25}ClN_4$ requires C, 70.3; H, 6.4; N, 14.3%).

5-(4-Dimethylaminophenyl)-10-ethyl-5,10-dihydropyrimido[4,5-b]*quinolin-4*(3H)*-one* (33; R = Et).—10-Ethyl-3,4-dihydro-4-oxopyrimido[4,5-b]quinolinium chloride (0.65 g), ethanol (25 ml), and *NN*-dimethylaniline (0.61 g) were heated under reflux for 3 h and then the *product* (0.65 g), m.p. 262° (decomp.) (from aqueous dimethylformamide) was filtered off (Found: C, 72.6; H, 6.1; N, 16.3. $C_{21}H_{22}N_4O$ requires C, 72.8; H, 6.4; N, 16.2%).

Deuteriation Studies.—*4,6-Dichloropyrimidine-5-*[^{2}H]*carbaldehyde* was synthesised as described for its protium analogue [17] except that dimethyl[^{2}H]formamide was used (Found: M^+, 148.9550. $C_5H^{35}Cl_2DO$ requires *M*, 148.9545). *4-Chloro-6-N-ethylanilinopyrimidine-5-*[^{2}H]*carbaldehyde* (34) was synthesised as described for its protium analogue [1] except that the foregoing [^{2}H]aldehyde pyrimidine was used (Found: M^+, 262.0732. $C_{13}H_{11}{}^{35}ClDN_3O$ requires *M*, 262.0731). *10-Ethyl-3,4-dihydro-4-oxo*[5-^{2}H]*pyrimido*[4,5-b]*quinolinium chloride* was synthesised from the foregoing pyrimidine by treatment with ethanolic hydrogen chloride, as described for its protium analogue (above). The ^{1}H n.m.r. spectrum of the product was identical with that of the protium analogue except that it lacked a signal for the 5-proton.

The salt underwent disproportionation in aqueous solution at pH 9 as described for its protium analogue [method (*c*)] to give *10-ethyl*[5,5-$^2H_2$]*pyrimido*[4,5-b]*quinolin-4*(3H)*-one* (Found: M^+, 229.1180. $C_{13}H_{11}D_2N_3O$ requires *M*, 229.1184) (^{1}H n.m.r. spectrum Figure 1b). When 4-chloro-6-*N*-ethylanilinopyrimidine-5-[^{2}H]carbaldehyde was

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TABLE 1

Disproportionation and methylation of 10-alkylpyrimido [4,5-*b*]quinolinium chlorides

Starting material	Reaction time (days)	Structure	Yield (%)	Products (as 3-methyl derivatives) M.p. (°C)	Formula	Found (%) C	H	N	Required (%) C	H	N
(7)	1	(17)	35	178—180 *	$C_{14}H_{15}N_3O$	69.8	6.4	17.4	69.7	6.3	17.4
		(24)	43	286 (decomp.) †	$C_{13}H_{13}N_3O_2$	65.6	5.1	16.5	65.9	5.1	16.5
(11)	1	(14)	35	169—170 *	$C_{13}H_{13}N_3O$	68.5	5.4	18.5	68.7	5.8	18.5
		(21)	36	240 (decomp.) *	$C_{13}H_{11}N_3O_2$	64.5	4.5	17.4	64.7	4.6	17.4
(13)	2	(16)	15	138—140 *	$C_{14}H_{15}N_3O_2$	65.3	6.1	16.2	65.3	5.9	16.3
		(23)	29	145—146 †	$C_{14}H_{13}N_3O_3$	61.9	5.3	15.2	61.8	5.2	15.4
(12)	3	(15)	23	235 (decomp.) *	$C_{13}H_{12}ClN_3O$	59.7	4.6	16.2	59.7	4.6	16.1
		(22)	29	275 (decomp.) ‡	$C_{13}H_{10}ClN_3O_2$	56.6	3.5	15.3	56.6	3.7	15.2

* From aqueous ethanol. † From ethanol. ‡ From aqueous dimethylformamide.

TABLE 2

^{1}H N.m.r spectra of pyrimido[4,5-*b*]quinolines

Structure	Chemical shifts (τ values; *J* in Hz) 2-H [a]	3-Me [b]	5-Substituent	10-Substituent	Benzenoid	7-MeO [b]	Solvent
(9)	1.70		0.83 (1 H, s)		1.67—2.57 [c]		$(CD_3)_2SO$
(7)	1.10		0.17 (1 H, s)	8.37 (3 H, t) and 4.58 (2 H, q) (*J* 7.2)	1.47—2.17 [c]		D_2O
(11)	1.05		−0.15 (1 H, s)	5.05 (3 H, s)	1.25—1.80 [c]		$CF_3{\cdot}CO_2H$
(12)	1.15		0.05 (1 H, s)	5.10 (3 H, s)	1.40—1.65 [d]		$CF_3{\cdot}CO_2H$
(13)	1.15		0.05 (1 H, s)	5.10 (3 H, s)	1.50—2.20 [d]	5.80	$CF_3{\cdot}CO_2H$
(29)	1.18	6.12	0.06 (1 H, s)	8.26 (3 H, t) and 4.51 (2 H, q) (*J* 7.5)	1.39—2.04 [c]		$CF_3{\cdot}CO_2H$
(8)	2.12		6.23 (2 H, s)	8.82 (3 H, t) and 5.92 (2 H, q) (*J* 7.2)	2.67—3.27 [c]		$(CD_3)_2SO$
(14)	1.90	6.70	6.32 (2 H, s)	6.70 (3 H, s)	2.90—3.40 [c]		$(CD_3)_2SO$
(17)	2.12	6.53	6.03 (2 H, s)	8.77 (3 H, t) and 5.92 (2 H, q) (*J* 7.2)	2.62—3.25 [c]		$(CD_3)_2SO$
(18)	1.71		6.11 (2 H, s)	6.60 (3 H, s)	2.55—3.20 [c]		$(CD_3)_2SO$
(21)	1.30	6.15		5.55 (3 H, s)	1.50—3.20 [c]		$CF_3{\cdot}CO_2H$
(24)	1.30	6.15		8.33 (3 H, t) and 4.80 (2 H, q) (*J* 7.2)	1.12—2.28 [c]		$CF_3{\cdot}CO_2H$
(24)	1.55	6.60		8.75 (3 H, t) and 5.55 (2 H, q) (*J* 7.2)	2.00—3.00 [c]		$(CD_3)_2SO$
(25)	1.21			8.32 (3 H, t) and 4.73 (2 H, q) (*J* 7.2)	1.00—2.20 [c]		$CF_3{\cdot}CO_2H$
(32)	1.57		5.28 (1 H, s) [e]	8.62 (3 H, t, *J* 7.2) and 5.40—5.87 (2 H, m)	2.60—3.08 [c]		CCl_4

[a] 1 H, s. [b] 3 H, s. [c] 4 H, m. [d] 3, H, m [e] Also 3.03 and 3.52 (two halves of ABq, *J* 8.0, C_6H_4) and 6.75 (q) and 8.93 (t) (*J* 7.2, NEt_2).

treated with boiling water as described for its protium analogue the dihydropyrimidoquinoline (8) produced contained hydrogen as well as deuterium at position 5 (^{1}H n.m.r. spectrum Figure 1c).

Combined Disproportionations.—(*a*) A buffer solution was prepared by dissolving glycine (7.5 g) and sodium chloride (5.8 g) in water (200 ml) and adjusting the pH to 10.2 by addition of 2% sodium hydroxide solution. 10-Ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride (0.26 g) and 10-ethyl-3,4-dihydro-3-methyl-4-oxopyrimido[4,5-*b*]quinolinium perchlorate (0.34 g) were dissolved in some of the buffer solution (25 ml). After 16 h 10-ethyl-5,10-dihydro-3-methylpyrimido[4,5-*b*]quinolin-4(3*H*)-one (0.23 g), m.p. 175—178°, was filtered off and identified by its i.r. and ^{1}H n.m.r. spectra. Neutralisation of the filtrate gave 10-ethylpyrimido[4,5-*b*]quinoline-4,5(3*H*,10*H*)-dione (0.1 g), m.p. 247—249°, identified by its ^{1}H n.m.r. and i.r. spectra. (*b*) A buffer solution was prepared by dissolving potassium dihydrogen phosphate (5.44 g) and disodium hydrogen phosphate (21.48 g) in water (200 ml). 10-Ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride (0.52 g) and 10-ethyl-3,4-dihydro-3-methyl-4-oxopyrimido[4,5-*b*]-quinolinium perchlorate (0.68 g) were dissolved in the buffer solution (50 ml) and the pH was adjusted to 7.2 by addition of 4N-sodium hydroxide solution. The mixture was stirred for 24 h and filtered. The solid was dried and extracted with chloroform to give chloroform-insoluble 10-ethyl-3-methylpyrimido[4,5-*b*]quinoline-4,5(3*H*,10*H*)-dione (0.15 g), m.p. 286° (decomp.) (from ethanol) and chloroform-soluble 10-ethyl-5,10-dihydro-3-methylpyrimido-[4,5-*b*]quinolin-4(3*H*)-one (0.25 g), m.p. 178—180°. The u.v. spectrum of the aqueous filtrate was identical with that of 10-ethyl-3,4-dihydro-4-oxopyrimido[4,5-*b*]quinolinium chloride at pH 7.

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