Quaternary Salts of Pyrido[1,2-*a*]pyrimidines

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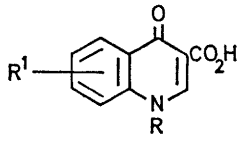
Ethyl 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylates undergo alkylation at the 1-position giving quaternary salts which decompose in alkaline solution yielding 2-alkylaminopyridines. Attack of the quaternary salts by ammonia occurs at the 4-position, opening the pyrimidine ring, but the 1-methyl-7-nitro-derivative is attacked at position 9a.

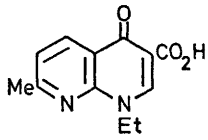
Some years ago A. R. Martin discovered that certain quinolones [1] with the general formula (1) had systemic antibacterial activity. Unfortunately, the most potent of them, the 6-nitro-derivatives, caused cataract in animals of several species and clinical use of these compounds was not possible. Following a similar observation, Lesher *et al.*[2] found a clinically useful compound in the naphthyridone (2). In both series of compounds the structural requirements for antibacterial activity are well defined: a lower alkyl group at position 1, carbonyl at 4, carboxy- or a group capable of metabolic transformation to carboxy- at 3, and some appropriate substituent at 6 or 7. These structural requirements should be satisfied by the quaternary salts (3) derived from 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylic acids.

The ethyl esters (4b), which are obtained from the anils derived from 2-aminopyridines and diethyl ethoxymethylenemalonate by thermal cyclisation [3,4] or by treatment with polyphosphoric acid,[5] were quaternised by heating with methyl or ethyl toluene-*p*-sulphonate at 120—160°. No reaction occurred, however, with ethyl 9-methyl-4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate; this recalls the resistance to quaternisation of 8-substituted quinolines. Acid hydrolysis of the quaternised esters caused degradation to 2-alkylaminopyridines, but careful treatment with hydrochloric acid gave the quaternary salts (3a) of the corresponding carboxylic acids. These could also be made by hydrolysis of the esters (4b) and quaternisation of the resulting acids in dimethylformamide. The antibacterial activity of these compounds was much inferior to that of the quinolones and naphthyridones.

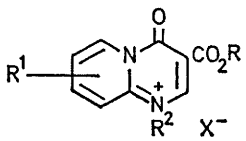
The stability of the pyrimidine ring to nucleophilic attack is greatly diminished by quaternisation. The unquaternised pyrido[1,2-*a*]pyrimidines are fairly stable, although drastic hydrolysis with alkali will degrade them to the parent aminopyridines.[2] With ammonia or hydrazine the esters yield the corresponding amides or hydrazides. On the other hand the quaternary derivatives are very unstable to alkali, giving deep yellow solutions from which the 2-methylamino- or ethylaminopyridines can be isolated after a short time. This provides a convenient preparative route to 2-alkylaminopyridines, since the products are not contaminated with unalkylated or dialkylated 2-aminopyridine. Because of this instability, attempts to reduce the quaternary salts with sodium borohydride were unsuccessful. Decomposition in the presence of ammonia is of particular



(1)

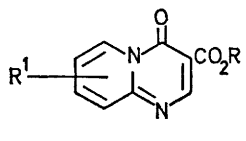


(2)



(3)

a; R = H
b; R = Et



(4)

a; R = H
b; R = Et

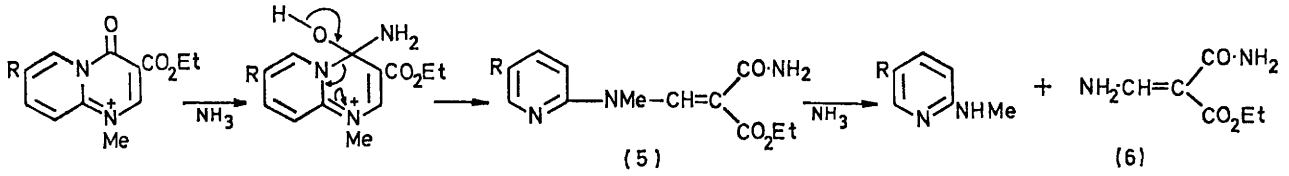
interest. When an aqueous solution of 3-ethoxycarbonyl-1-methyl-4-oxopyrido[1,2-a]pyrimidinium toluene-*p*-sulphonate is made alkaline with ammonia a precipitate of ethyl aminomethylenemalonamate (6) separates in a few hours, and 2-methylaminopyridine can be recovered almost quantitatively from the filtered solution. The aminomethylenemalonamate has previously been obtained by prolonged action of ammonia on tetraethyl propene-1,1,3,3-tetracarboxylate, diethyl aminomethylenemalonate being an intermediate.[6] The low reactivity of the carbonyl group in the latter compound towards ammonia contrasts strongly with the high reactivity of the carbonyl group in the 4-position of the quaternary salt, and suggests that the primary attack of ammonia is at this position (Scheme 1). This mechanism was confirmed by the isolation of the intermediate (5; R = Cl) from (3b; R^1 = Cl, R^2 = Me) and subsequent hydrolysis of this compound to 5-chloro-2-methylaminopyridine. With aqueous methylamine the

[1] B.P. 830,832.
[2] G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, and R. P. Brundage, *J. Medicin. Pharm. Chem.*, 1962, **5**, 1063.
[3] G. R. Lappin, *J. Amer. Chem. Soc.*, 1948, **70**, 3348.
[4] R. Adams and I. J. Pachter, *J. Amer. Chem. Soc.*, 1952, **74**, 5491.
[5] M. Shur and S. S. Israelstam, *J. Org. Chem.*, 1968, **33**, 3015.
[6] S. Ruhemann and R. S. Morell, *J. Chem. Soc.*, 1892, **61**, 791.

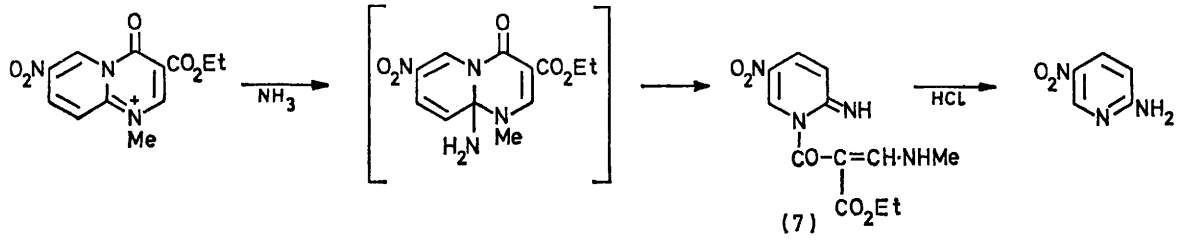
7-chloro-compound gave the corresponding methylamide.

The 7-nitro-derivative (3a; $R^1 = 7\text{-}NO_2$, $R^2 = Me$), on the other hand, reacts with ammonia to give a 1-acyl-1,2-dihydro-2-imino-5-nitropyridine (7), which on acid hydrolysis gives 2-amino-5-nitropyridine. In this case the initial attack is at the electron-deficient 9a-position (Scheme 2).

The difference between compounds (5; R = Cl) and (7) is shown by differences in the fragmentation patterns of their mass spectra: with (5; R = Cl) there is progressive breakdown of the side chain without fission at the pyridine ring, whereas with (7) there is a prominent ion of *m/e* 156 corresponding to the group CO·C(CO_2Et):CH·NHMe. Furthermore, the n.m.r. spectrum of compound (7) shows the vinyl proton coupled to NH (d, *J* 14 Hz), the coupling being lost on exchange with D_2O, whereas that of (5; R = Cl) shows =CH– and Me signals as narrow doublets attributable to restricted rotation about the N–C bond (the proportions of the rotamers varied with solvent and temperature).



SCHEME 1



SCHEME 2

EXPERIMENTAL

The ethyl 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylates have been described previously,[3-5] except for the 7-nitro-derivative. I am indebted to J. S. Morley for this preparation:

2-Amino-5-nitropyridine (82 g) and diethyl ethoxymethylenemalonate (127 g) were heated at 140° for 2 h, allowing ethanol (10 ml) to distil off, and the mixture was poured into ethanol (600 ml) while still warm. The solution was stirred and cooled, and the solid *diethyl 5-nitro-2-pyridylaminomethylenemalonate* was filtered off; yield 121 g, m.p. 163—165° (*from* benzene) (Found: C, 50·0; H, 4·8; N, 14·0. $C_{13}H_{15}N_3O_6$ requires C, 50·4; H, 4·9; N, 13·6%). The anil (10 g) was added to boiling diphenyl ether (100 g) and the mixture was boiled under reflux for 10 min, allowing ethanol to escape. The cooled mixture was diluted with light petroleum [350 ml (b.p. 60—80°)] and *ethyl 7-nitro-4-oxopyrido*[1,2-a]*pyrimidine-3-carboxylate* was filtered off; yield 5·5 g, m.p. 155—157° (from benzene) (Found: C, 50·3; H, 3·5; N, 16·4. $C_{11}H_9N_3O_5$ requires C, 50·2; H, 3·4; N, 16·0%).

Quaternisation of Ethyl 4-Oxopyrido[1,2-a]*pyrimidine-3-carboxylates.*—Ethyl 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate (25 g) and methyl toluene-*p*-sulphonate (25 g) were heated together to 120—130°; an exothermic reaction occurred, the temperature rising to 170°. When the temperature fell the mixture was heated at 140—150° for 15 min, then allowed to cool and triturated with acetone. *3-Ethoxycarbonyl-1-methyl-4-oxopyrido*[1,2-a]*pyrimidinium toluene-*p*-sulphonate* (42 g) was filtered off and crystallised from propan-2-ol. Quaternary salts made in this manner are listed in the Table.

Acid Hydrolysis of the Quaternised Esters.—The quaternised ester (5 g), conc. hydrochloric acid (15 ml), and water (10 ml) were boiled under reflux for 2 h; the solution was evaporated under reduced pressure and was finally taken to dryness in a vacuum desiccator over calcium chloride. The residue was triturated with acetone and the crystalline product was purified by dissolving in 2N-hydrochloric acid and reprecipitating with acetone. The following acids were made in this way: *3-carboxy-1-methyl-4-oxopyrido*[1,2-a]*pyrimidinium chloride*, m.p. 248—250° (Found: C, 49·7; H, 3·9; N, 11·8. $C_{10}H_9ClN_2O_3$ requires C, 49·9; H, 3·7; N, 11·6%); *3-carboxy-7-chloro-1-ethyl-4-oxopyrido*[1,2-a]*pyrimidinium chloride*, m.p. 223—224° (Found: C, 45·2; H, 3·8; N, 9·4. $C_{11}H_{10}Cl_2N_2O_3$ requires C, 45·7; H, 3·5; N, 9·7%); *3-carboxy-1-ethyl-7-methyl-4-oxopyrido*[1,2-a]*pyrimidinium chloride*, m.p. 235—236° (from methanol) (Found: C, 53·6; H, 4·8; Cl, 12·7; N, 10·1. $C_{12}H_{13}ClN_2O_3$ requires C, 53·6; H, 4·6; Cl, 13·2; N, 10·4%); and *3-carboxy-1,8-dimethyl-4-oxopyrido*[1,2-a]*pyrimidinium toluene-*p*-sulphonate*, m.p. 197° (decomp.) (from water) (Found: C, 55·3; H, 4·8; N, 7·2. $C_{18}H_{18}N_2O_6S$ requires C, 55·4; H, 4·6; N, 7·2%).

3-Ethoxycarbonyl-1-methyl-7-nitro-4-oxopyrido[1,2-*a*]-pyrimidinium toluene-*p*-sulphonate, however, was cleaved to give 2-methylamino-5-nitropyridine hydrochloride, m.p. 176—178°, which with alkali gave 2-methylamino-5-nitropyridine, m.p. 180—181° (lit.,[7] 181°) (Found: N, 27·0.

[7] A. E. Tschitschibabin and R. A. Konowalowa, *Ber.*, 1925, **58**, 1712.

Calc. for $C_6H_7N_3O_2$: N, 27·5%), and 7-chloro-3-ethoxycarbonyl-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium toluene-*p*-sulphonate gave *5-chloro-2-methylaminopyridinium toluene-p-sulphonate*, m.p. 165° (Found: C, 49·3; H, 4·6; Cl, 11·3; N, 8·7. $C_{13}H_{15}ClN_2O_3S$ requires C, 49·6; H, 4·7; Cl, 11·3; N, 8·9%); free *base*, m.p. 63—64° (from cyclohexane) (Found: N, 19·5. $C_6H_7ClN_2$ requires N, 19·7%).

5-Chloro-2-ethylaminopyridinium toluene-p-*sulphonate*, m.p. 159—160° (Found: C, 51·2; H, 5·5; N, 8·5. $C_{14}H_{17}ClN_2O_3S$ requires C, 51·1; H, 5·2; N, 8·5%), was isolated from the mother liquor from the acid hydrolysis of the quaternary salt by evaporation and treatment with acetone. With alkali it gave *5-chloro-2-ethylaminopyridine*, m.p. 67—68° (from cyclohexane) (Found: N, 18·1. $C_7H_9ClN_2$ requires N, 17·9%).

7-Methyl-4-oxopyrido[1,2-a]*pyrimidine-3-carboxylic Acid.*—Ethyl 7-methyl-4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate (5 g) and N-sodium hydroxide (500 ml) were shaken at laboratory temperature for 2·5 h, and the cloudy solution was extracted with ether. The clear aqueous layer was acidified and the *acid* (3·7 g) was filtered off, dried, and crystallised from dimethylformamide; m.p. 267—268° (Found: C, 59·3; H, 4·1; N, 13·7. $C_{10}H_8N_2O_3$ requires C, 58·8; H, 3·9; N, 13·7%). The acid (2·0 g) and methyl toluene-*p*-sulphonate (2·0 g) were dissolved in dimethylformamide and boiled under reflux for 15 min, cooled, and filtered from unchanged acid (0·45 g). The filtrate was concentrated to give *3-carboxy-1,7-dimethyl-4-oxopyrido*-[1,2-a]*pyrimidinium toluene*-p-*sulphonate* (2·4 g), which crystallised from ethanol–ethyl acetate as nodules, m.p. 190° (Found: C, 54·9; H, 4·4; N, 6·7. $C_{18}H_{18}N_2O_6S$ requires C, 55·4; H, 4·6; N, 7·2%). From water it gave a *monohydrate*, laminae, m.p. 140° (Found: C, 52·7; H, 4·9; N, 6·8; S, 7·7. $C_{18}H_{18}N_2O_6S,H_2O$ requires C, 52·9; H, 4·9; N, 6·9; S, 7·9%).

Alkaline Hydrolysis of the Quaternised Esters.—The quaternary salt (1 g) was dissolved in water (10 ml) and alkali was added to raise the pH to 10—11. The 2-alkylaminopyridine was extracted with ether and recovered by evaporation of the solvent or by precipitation as the picrate. The following were obtained: 2-methylaminopyridinium picrate, m.p. 188—194° (lit.,[8] 190°); *4-methyl-2-methylaminopyridinium picrate*, m.p. 224—225° (Found: C, 44·7; H, 3·9; N, 19·5. $C_{13}H_{13}N_5O_7$ requires C, 44·4; H, 3·7; N, 19·9%); *5-methyl-2-methylaminopyridinium picrate*, m.p. 200° (Found: C, 44·5; H, 4·2; N, 20·1%); and *2-ethylamino-5-methylpyridinium picrate*, m.p. 172—174° (Found: C, 46·2; H, 4·2; N, 18·7. $C_{14}H_{15}N_5O_7$ requires C, 46·0; H, 4·1; N, 19·2%).

Action of Ammonia on the Quaternary Salts.—(*a*) 3-Ethoxycarbonyl-1-methyl-4-oxopyrido[1,2-a]pyrimidinium toluene-*p*-sulphonate (50 g) was dissolved in cold water (100 ml) and the solution was made alkaline with concentrated aqueous ammonia. After 24 h ethyl aminomethylenemalonamate (12·6 g) was filtered off and washed with water. Crystallisation from ethyl acetate gave material, m.p. 172—176° (lit.,[6] 169—170°) (Found: C, 45·8; H, 6·9; N, 17·4. Calc. for $C_6H_{10}N_2O_3$: C, 45·6; H, 6·3; N, 17·7%). The aqueous filtrate was extracted with chloroform (3 × 100 ml) and the extract was evaporated. The residual *oil* was extracted with light petroleum (250 ml; b.p. 60—80°), leaving impure ethyl aminomethylenemalonate (1·5 g), and the petroleum was evaporated, leaving 2-methylaminopyridine (10·2 g) (picrate, m.p. 189—194°).

(*b*) 7-Chloro-3-ethoxycarbonyl-1-methyl-4-oxopyrido-[1,2-*a*]pyrimidinium toluene-*p*-sulphonate (14 g) was dissolved in water (140 ml) and treated dropwise with ammonia until just alkaline (pH 8). A bright yellow precipitate was formed after *ca.* 0·5 min, and was filtered off after 5 min and crystallised from ethanol to give *ethyl 5-chloro-2-pyridylmethylaminomethylenemalonamate* (3 g), cream prisms, m.p. 147° (Found: C, 51·2; H, 5·0; Cl, 12·7; N, 14·8. $C_{12}H_{14}ClN_3O$ requires C, 50·7; H, 4·9; Cl, 12·5; N, 14·8%). On boiling with dilute sodium hydroxide solution this compound gave 5-chloro-2-methylaminopyridine, m.p. 64°. Under similar conditions, with methylamine in place of ammonia, the *methylamide* was obtained as needles, m.p. 165° (from ethanol), showing an initial loss of CO·NHMe in the mass spectrometer and then a fragmentation like that of the amide (5; R = Cl) (Found: C, 52·5; H, 5·6; N, 14·1. $C_{13}H_{16}ClN_3O_3$ requires C, 52·4; H, 5·4; N, 14·1%).

(*c*) 3-Ethoxycarbonyl-1-methyl-7-nitro-4-oxopyrido[1,2-*a*]pyrimidinium toluene-*p*-sulphonate, treated similarly with aqueous ammonia, gave a cream precipitate of *1-(2-ethoxycarbonyl-3-methylaminoacryloyl)-1,2-dihydro-2-imino-5-nitropyridine* (7), needles, m.p. 206° (from 2-ethoxyethanol) (Found: C, 48·8; H, 4·6; N, 18·8. $C_{12}H_{14}N_4O_5$ requires C, 49·0; H, 4·75; N, 19·05%). When boiled with 5N-hydrochloric acid this compound gave 2-amino-5-nitropyridine, m.p. and mixed m.p. 187—188°.

4-Oxopyrido[1,2-a]*pyrimidine-3-carboxamide.*—A solution of ethyl 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate (5 g) in ethanol (200 ml) was made strongly alkaline with aqueous ammonia and was kept at laboratory temperature. After 48 h the *amide* (2·0 g) was filtered off and crystallised from ethoxyethanol; m.p. 264—268° (Found: C, 57·4; H, 4·0; N, 22·3. $C_9H_7N_3O_2$ requires C, 57·1; H, 3·7; N, 22·2%). In a similar experiment, with hydrazine hydrate (5 ml) instead of ammonia, *4-oxopyrido*[1,2-a]*pyrimidine-3-carbohydrazide* was obtained (3·0 g after 118 h); m.p. 218—220° (from ethanol) (Found: C, 53·4; H, 4·0; N, 27·2. $C_9H_8N_4O_2$ requires C, 52·9; H, 3·9; N, 27·4%).

Quaternary salts (3b; R = Et, X = *p*-MeC_6H_4·SO_3)

R¹	R²	Formula	M.p. *t*/°C	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
H	Me	$C_{19}H_{20}N_2O_6S$	167—170	56·8	5·1	6·85	56·5	4·9	6·9
7-Cl	Me	$C_{19}H_{19}ClN_2O_6S$	232—234	51·7	4·5	6·5	52·0	4·3	6·4
7-NO_2	Me	$C_{19}H_{19}N_3O_8S$	222—224	50·7	4·6	9·4	50·8	4·2	9·35
7-Me	Me	$C_{20}H_{22}N_2O_6S$	216—217	57·0	5·3	6·9	57·4	5·25	6·7
8-Me	Me	$C_{20}H_{22}N_2O_6S,H_2O$	116—117	54·9	5·6	6·2	55·0	5·5	6·4
7-Cl	Et	$C_{20}H_{21}ClN_2O_6S$	195—197	53·0	4·7	6·1	53·0	4·6	6·2
7-Me	Et	$C_{21}H_{24}N_2O_6S$	183—184	58·1	5·7	6·5	58·3	5·55	6.5

[8] A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *Ber.*, 1921, **54**, 814.

9-*Methyl*-4-*oxopyrido*[1,2-a]*pyrimidine*-3-*carbohydrazide*.—Ethyl 9-methyl-4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate (2·3 g), aqueous 40% hydrazine (1 ml), and ethanol (4 ml) were boiled under reflux for 1 h, and the solution was cooled. The *hydrazide* (1·8 g) was filtered off and crystallised from 2-ethoxyethanol; m.p. 238—239° (Found: C, 55·2; H, 4·8; N, 25·5. $C_{10}H_{10}N_4O_2$ requires C, 55·05; H, 4·6; N, 25·7%).

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