Reactivity of the Pyrido[1,2-*a*]pyrimidin-4-one Ring System

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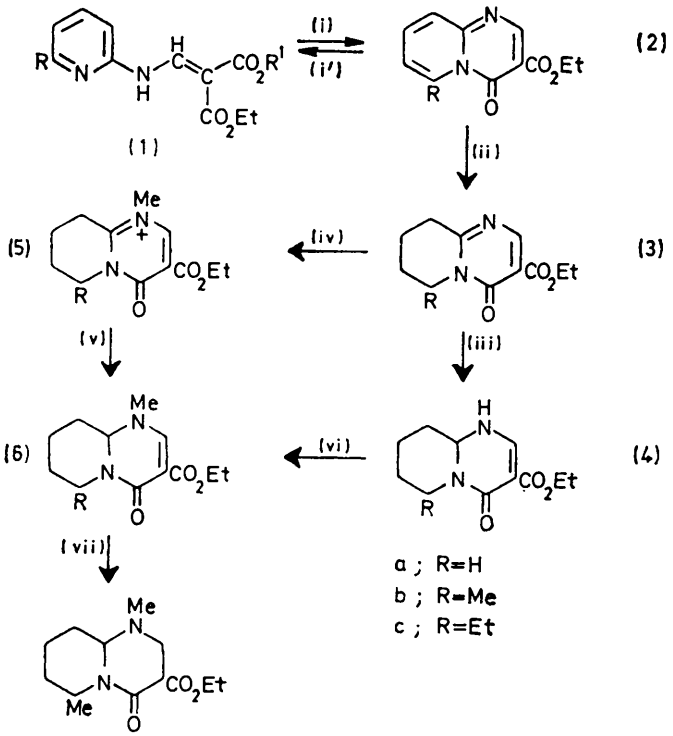
The reactivity of the pharmacologically active pyrido[1,2-*a*]pyrimidin-4-one ring system has been investigated, and its ring opening, catalytic hydrogenation, reduction by sodium borohydride, *N*-alkylation, and bromination are described. The hydrolysis, ammonolysis, and reaction with hydrazine of a 3-ethoxycarbonyl group are also discussed. The reactivity is compared with the charge distribution of the molecules calculated by quantum chemical methods.

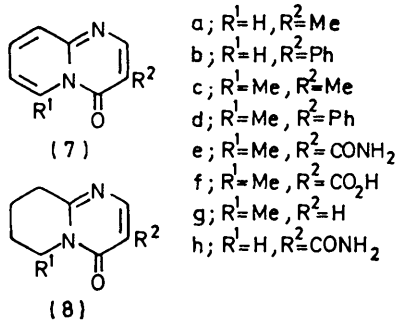
RECENTLY the synthesis of 3-ethoxycarbonyl-6-methylpyrido[1,2-*a*]pyrimidin-4-one (2b) was reported,[1] and this compound and several derivatives proved to be analgetically active.[2] We have investigated the reactivity of this ring system, and some of the reactions are summarized in Scheme 1. The reactivity was



SCHEME 1 Reagents: (i) $POCl_3$–polyphosphoric acid; R^1 = Et; (i') HCl–H_2O; R^1 = H; (ii) Pd–C/H_2; (iii) (v) $NaBH_4$ + H_2O; (iv), (vi) Me_2SO_4 + benzene; (vii) $NaBH_4$–H_2O–EtOH, 40—50°

correlated with the quantum mechanically calculated electron densities of the ring system. This method has been applied, with other compounds, by several authors.[3-6] It should be noted that inductive and mesomeric but not steric and solvent effects can be treated this way. The following reactions are discussed in detail.

Ring Opening.—Stirring the hydrochloride of compound (2a) at room temperature for one week leads to cleavage of the C(4)–N(5) bond,[1] to yield (1a; R^1 = H) (20%) (see Scheme 1). In the case of (2b), under the same conditions, 76% conversion is reached after one day. When a 3-methyl or 3-phenyl group is present (7a—d) no ring opening occurs. The instability of compounds



a; R^1=H, R^2=Me
b; R^1=H, R^2=Ph
c; R^1=Me, R^2=Me
d; R^1=Me, R^2=Ph
e; R^1=Me, R^2=$CONH_2$
f; R^1=Me, R^2=CO_2H
g; R^1=Me, R^2=H
h; R^1=H, R^2=$CONH_2$

(2a—b) is a consequence of the strain in the C(4)–N(5) bond. According to *X*-ray investigations[7] the C–N bond length in (2b) is 1·473 Å, corresponding to an aliphatic bond[8] (1·472 ± 0·005 Å). In the compounds (3), obtained through partial saturation, the bond length becomes 1·411 Å,[9] indicating a stronger bond: no ring opening was observed with these compounds.

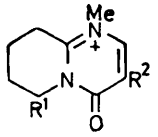
Catalytic Hydrogenation.—Reaction occurs over Pd–C or Raney nickel catalysts. Using the latter, (2a) yields (4a) directly with uptake of 3 moles of H_2.[1] In the case of (2b), only 2 moles of H_2 are absorbed to yield (3b),[1] and compounds (7a—d) behave similarly to give (8a—d).

Reduction with Sodium Borohydride.—Addition of $NaBH_4$ in an aqueous solution at 35—40 °C leads to saturation of the N(1)–C(9a) bond in compounds (3) and (8e—g) [see Scheme 1, (iii)].[1] No reaction occurs in the case of compounds (8a—d).

Reduction by borohydride starts with nucleophilic attack by the BH_4^- ion:[10] the most reactive atoms of the ring are: C-4 (0·400—0·418), C-9a (0·245—0·292), and C-2 (0·095—0·104), where the numbers in parentheses are the greatest and smallest values of the charges (in electrons) in the different molecules. Saturation of

[1] Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, *Arzneim.-Forsch.*, 1972, **22**, 815.
[2] J. Knoll, Z. Mészáros, P. Szentmiklósi, and S. Fürst, *Arzneim.-Forsch.*, 1971, **21**, 717.
[3] A. Streitwieser, 'Molecular Orbital Theory for Organic Chemists,' John Wiley, New York, 1961.
[4] J. O. Morley, *J.C.S. Perkin II*, 1972, 1223.
[5] S. Fliszár, *J. Amer. Chem. Soc.*, 1972, **94**, 1068.
[6] H. Sterk and W. Hoppels, *Z. Naturforsch.*, 1972, **27a**, 319.
[7] K. Sasvári, J. Csonka-Horvai, and K. Simon, *Acta Cryst.*, 1972, **B28**, 2405.
[8] L. E. Sutton, Tables of Interatomic Distances, *Chem. Soc. Special Publ.*, 1958.
[9] K. Sasvári and K. Simon, *Acta Cryst.*, 1973, **B29**, 1245.
[10] J. March, 'Advanced Organic Chemistry: Reactions, Mechanisms and Structure,' McGraw-Hill, New York, 1968.

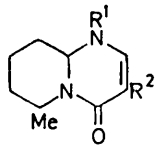
the 4-oxo-group does not occur as this group is part of a cyclic amide. Reaction occurs at position 9a which



(9)

a ; R^1 = H, R^2 = CO_2Et e ; R^1 = Me, R^2 = Ph
b ; R^1 = H, R^2 = $CONH_2$ f ; R^1 = Me, R^2 = Me
c ; R^1 = Me, R^2 = CO_2Et g ; R^1 = Me, R^2 = H
d ; R^1 = Me, R^2 = $CONH_2$ h ; R^1 = Me, R^2 = CO_2H

also has a considerable positive charge. Saturating the N(1)–C(9a) double bond causes C-2 to become more positive; in compounds (10) its charge is 0·180. Boro-



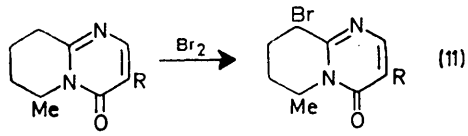
(10)

a ; R^1 = Et, R^2 = CO_2Et e ; R^1 = Me, R^2 = $CONH_2$
b ; R^1 = Pr^n, R^2 = CO_2Et f ; R^1 = Pr^n, R^2 = CO_2H
c ; R^1 = Bu^n, R^2 = CO_2Et g ; R^1 = Bu^n, R^2 = CO_2H
d ; R^1 = Me, R^2 = Ph

hydration then occurs at the C(2)–C(3) bond [Scheme 1, (vii)].[1] In the case of compounds (3a—c), (8a—e, g), and (9c, d) the outcome of the reaction depends on the net charge on C-9a. If this is not less than 0·258, reaction takes place. In the opposite case the initial products are regained. The only exception is (9e) where the C-9a net charge is lower (0·245) but reaction takes place. Compound (8g) reacts over a longer period (6 h) with a lower conversion (52%): here the net charge lies just at the limit (0·258). No experimental results are available for (8f) and (9a, b) but on the basis of their charges at C-9a (0·278, 0·292, and 0·291, respectively) it is considered that reaction should occur. For details of the reaction with (9d) and (9e), see the Experimental section.

Formation of Quaternary Ammonium Salts [*Scheme* 1, (iv) *and* (vi)].—This reaction always occurs at position 1. The conditions and the net charge on N-1 are summarized in the Table. Quaternization starts with the nucleophilic attack on the ring nitrogen,[10] and nucleophilicity, partly controlling the reactivity, is roughly proportional to the net charge.[3] Therefore the reactivity of N-5 is much more weaker because its net charge varies only between —0·096 and —0·157. We could find no reaction conditions under which alkylation occurs at N-5. The results in the Table demonstrate that decreasing the net charge on N-1 involves increasing reaction times.

Reactions of the 3-*Ethoxycarbonyl Group*.—The 3-EtO_2C group of compounds (2), (3),[1] (6),[1] (10a),[1] and (10b, c) can be hydrolysed. It also reacts with ammonia and hydrazine. These reactions are influenced by the ring structure and it is therefore reasonable to treat them separately. The net charge of the oxo-carbon atom is in all cases quite large (0·496—0·518), and this causes the increased reactivity. No parallelism was found here between reactivity and net charge.



(11)

a; R=CO_2Et b; R=$CONH_2$

SCHEME 2

Bromination.—Working in apolar solvents with bromine, substitution takes place at position 9 in the case of (3b) and (8e) (see Scheme 2).[1] This position shows high reactivity which is reflected by CNDO calculations. The hydrogen atoms attached to C-9 are very positive * and therefore easy to remove. Other hydrogen atoms of the molecule have smaller net charges (—0·013—0·010).

Reaction conditions for quaternization [1]

Compound	Reagent	Solvent	Reaction time (h)	Temperature †	Yield (%)	Net charge on N-1
(3a)	Me_2SO_4	Benzene	1	A	73	—0·282
	MeI		1	A	90	
(3b)	Me_2SO_4	Benzene	1	A	78	—0·282
	Et_2SO_4	Benzene	2	A	33	
(8f) *	Me_2SO_4	$CHCl_3$–MeOH	1	A	60	—0·282
(8e) *	Me_2SO_4	Dry benzene (suspension)	6	A	81	—0·275
(8g) *	MeI		1	B	88	
	Me_2SO_4	Benzene	12	B	69	—0·273
(8a)						—0·272
(8c) *	Me_2SO_4	Acetone	12	B	93	—0·272
(8b)						—0·270
(8d) *	Me_2SO_4	Acetone	36	B	75	—0·270

* For details see the Experimental section. † A = Reflux, B = room temperature.

THEORETICAL

The charge distribution of the molecules is approximated by the sum of σ and π charges. The former was

* The net charges are 0·022 and 0·029 electrons, respectively.

calculated according to Del Re's method [11] the latter by the Pariser–Parr–Pople procedure.[12] The calculation on the quaternary ammonium salts was performed on the basis of the σ-core polarization model of Nishimoto and his co-workers.[13] The details of the calculations as well as the empirical parameters used by us, are given in an earlier work.[14] CNDO Calculations were performed according to the standard procedure.[15]

EXPERIMENTAL

In this section, only novel reactions are described: the experimental details of other reactions discussed in this work are given in ref. 1.

I.r. spectra were measured for KBr pellets with a Zeiss UR-20 spectrometer, u.v. spectra were recorded in ethanolic solutions by means of Unicam SP 800 spectrometer, and n.m.r. data were determined with respect to a tetramethylsilane standard with a Perkin-Elmer R 12 spectrometer.

6-*Methyl*-4-*oxopyrido*[1,2-a]*pyrimidine*-3-*carboxylic Acid* (7f).—The pyridopyrimidinone (2b) (46·2 g) was stirred at room temperature in NaOH solution (2%; 600 ml) for 2 h. The deep orange solution was neutralized with 5% aqueous hydrochloric acid (pH 7). The precipitated ethyl hydrogen (6-methyl-2-pyridyl)aminomethylenemalonate [1] (1b; R^1 = H) (6·3 g, 12%) was filtered off. The filtrate was adjusted to pH 2. The *acid* (7f) formed pale yellow crystals (33·5 g, 82%), m.p. 180—182° (Found: C, 53·4; H, 4·7; N, 12·7. $C_{10}H_8N_3O_3$ requires C, 53·9; H, 4·5; N, 12·6%).

6-*Methyl*-4-*oxopyrido*[1,2-a]*pyrimidine*-3-*carboxamide* (7e).—The pyridopyrimidinone (2b) (23 g) was dissolved in a mixture of ethanol (150 ml) and conc. NH_4OH (450 ml). The solution was left at room temperature, and after *ca.* 40 min crystallization occurred. After 24 h the precipitated pale yellow *amide* (7e) (15·5 g, 76%) was filtered off, m.p. 259—260° (from dimethylformamide), $\lambda_{max.}$ 389 (log ε 4·18), 374 (4·15), and 255 nm (3·98) (Found: C, 59·4; H, 4·3; N, 20·9. $C_{10}H_9N_3O_2$ requires C, 59·1; H, 4·45; N, 20·7%).

4-*Oxo*-6,7,8,9-*tetrahydro*-4H-*pyrido*[1,2-a]*pyrimidine*-3-*carboxamide* (8h).—The tetrahydropyridopyrimidinone (3a) (6·66 g) was dissolved in conc. NH_4OH (30 ml). After 48 h the precipitated *amide* (8h) (4·7 g, 81%) was filtered off, m.p. 250—251° (from methanol) (Found: C, 56·1; H, 5·8; N, 21·7. $C_9H_{11}N_3O_2$ requires C, 56·0; H, 5·8; N, 21·7%).

Cyclization of Acrylic Acid Derivatives (*General Method*).—The acrylic acid derivative (0·1 mol) was held at 135—140° in phosphoryl chloride–polyphosphoric acid (45·6 g and 7 g respectively). After termination of the gas evolution (HCl) the mixture was broken up at 80—100° with ethanol (100 ml). The mixture was poured into water (150 ml), neutralized with 20% aqueous Na_2CO_3 solution, and shaken with chloroform. The dried (Na_2SO_4) solution was evaporated and the residue recrystallized.

Ethyl 2-methyl-3-(2-pyridylamino)acrylate gave 3-*methylpyrido*[1,2-a]*pyrimidin*-4-*one* (7a) (13·4 g, 90%) after 3 h reaction, as crystals, m.p. 120—122° (from propan-2-ol) (Found: C, 67·2; H, 5·9; N, 17·3. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%).

Ethyl 2-methyl-3-(6-methyl-2-pyridylamino)acrylate gave 3,6-*dimethylpyrido*[1,2-a]*pyrimidin*-4-*one* (7c) (15·7 g, 87%) after 3 h reaction, as pale yellow crystals, m.p. 73—74° (from ethyl acetate), $\nu_{max.}$ 1680, 1645, 1600, and 1500 cm^{-1}, $\lambda_{max.}$ 358 (log ε 3·98) and 247 nm (4·04), δ ($CDCl_3$) 2·16 (3H, s, 3-Me), 3·07 (3H, s, 6-Me), 6·65 (1H, t, 7-H), 7·3—7·5 (2H, m, 8- and 9-H), and 8·08 (1H, s, 2-H) (Found: C, 69·1; H, 5·6; N, 16·1. $C_{10}H_{10}N_2O$ requires C, 68·95; H, 5·8; N, 16·1%).

Ethyl 2-phenyl-3-(2-pyridylamino)acrylate gave 3-phenylpyrido[1,2-*a*]pyrimidin-4-one (7b) (15·2 g, 68%) after 6 h reaction, as pale yellow crystals, m.p. 167—168° (from ethanol) (lit.,[16] 166—167°).

Ethyl 2-phenyl-3-(6-methyl-2-pyridylamino)acrylate gave 6-*methyl*-3-*phenylpyrido*[1,2-a]*pyrimidin*-4-*one* (7d) (19·4 g, 82%) after 6·5 h reaction, as yellow crystals, m.p. 124—125° (from propan-2-ol) (Found: C, 75·9; H, 5·8; N, 11·7. $C_{15}H_{12}N_2O$ requires C, 76·25; H, 5·5; N, 11·9%).

3-*Methyl*-6,7,8,9-*tetrahydropyrido*[1,2-a]*pyrimidin*-4-*one* (8a).—The pyridopyrimidinone (7a) (16·0 g) was hydrogenated at atmospheric pressure in 10% aqueous hydrochloric acid (150 ml) over 10% Pd–C (3 g). After absorption of the theoretical amount of hydrogen the mixture was worked up to give the *ketone* (8a) (12·8 g, 87%) as crystals, m.p. 70—72° (Found: C, 65·9; H, 7·3; N, 17·0. $C_9H_{12}N_2O$ requires C, 65·8; H, 7·4; N, 17·1%).

3,6-*Dimethyl*-6,7,8,9-*tetrahydropyrido*[1,2-a]*pyrimidin*-4-*one* (8c).—Analogously to (8a), the pyridopyrimidinone (7c) gave (8c) (75%) as *crystals*, m.p. 67—68°, b.p. 130—135° at 0·3 mmHg, $\nu_{max.}$ 1660 cm^{-1}, $\lambda_{max.}$ 278 (log ε 3·98) and 231 nm (3·93), δ ($CDCl_3$) 1·36 (3H, d, 6-Me), 2·0 (4H, m, 7-H_2 and 8-H_2), 2·05 (3H, s, 3-Me), 2·9 (2H, m, 9-H_2), 5·0 (1H, m, 6-H), and 7·75 (1H, s, 2-H) (Found: C, 67·1; H, 8·2; N, 15·9. $C_{10}H_{14}N_2O$ requires C, 67·4; H, 7·9; N, 15·7%).

3-*Phenyl*-6,7,8,9-*tetrahydropyrido*[1,2-a]*pyrimidin*-4-*one* (8b).—Analogously to (8a), the pyridopyrimidinone (7b) yielded (8b) (77%) as yellow *crystals*, m.p. 168—169° (from propan-2-ol) (Found: C, 74·5; H, 6·3; N, 12·5. $C_{14}H_{14}N_2O$ requires C, 74·3; H, 6·2; N, 12·4%).

6-*Methyl*-3-*phenyl*-6,7,8,9-*tetrahydropyrido*[1,2-a]*pyrimidin*-4-*one* (8d).—Analogously to (8a), the pyridopyrimidinone (7d) gave (8d) (80%) as yellow *crystals*, m.p. 112—113° (from propan-2-ol). The same product was obtained when hydrogenation took place under 10 atm pressure, $\nu_{max.}$ 1675, 1610, 1540, and 1485 cm^{-1}, $\lambda_{max.}$ 302 (log ε 4·00), 245 (3·75), and 223 nm (3·72), δ ($CDCl_3$) 1·39 (3H, d, 6-Me), 1·9 (4H, m, 7-H_2 and 8-H_2), 2·9 (2H, m, 9-H_2), 5·1 (1H, m, 6-H), 7·3—7·85 (5H, m, 3-Ph), and 8·05 (1H, s, 2-H) (Found: 74·9; H, 6·5; N, 11·6. $C_{15}H_{16}N_2O$ requires C, 75·0; H, 6·7; N, 11·7%).

1,6-*Dimethyl*-4-*oxo*-6,7,8,9-*tetrahydro*-4H-*pyrido*[1,2-a]-*pyrimidinium Methyl Sulphate* (9g).—The tetrahydropyridopyrimidinone (8g) (16·4 g) was dissolved in dry benzene (50 ml). Dimethyl sulphate (13·2 g) was added and after 24 h the precipitated (9g) (21·3 g, 73%) was filtered off, as *crystals*, m.p. 163—164° (from ethanol), $\nu_{max.}$ 1735, 1660, 1530, and 1470 cm^{-1}, $\lambda_{max.}$ 266 (log ε 3·56) and 236 nm (3·94), δ (D_2O) 1·38 (3H, d, 6-Me), 2·1 (4H, m, 7-H_2 and 8-H_2), 3·75 (3H, s, $MeSO_4$), 3·85 (3H, s, NMe), 5·0 (1H, m, 6-H), 6·74 (1H, d, 3-H), 8·04 (1H, d, 2-H), 9-H_2

[11] G. Del Re, *J. Chem. Soc.*, 1958, 4031.
[12] R. Pariser and R. G. Parr, *J. Chem. Phys.*, 1953, **21**, 466, 767.
[13] K. Nishimoto, K. Nakatsukasa, R. Fujishiro, and S. Kato, *Theor. Chim. Acta*, 1969, **15**, 244.
[14] G. Náray-Szabó, E. Dudar, and G. Horváth, *Acta Chim. Acad. Sci. Hung.*, 1972, **74**, 281.
[15] J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.
[16] A. Halleux and H. G. Viehe, *J. Chem. Soc.* (*C*), 1970, 881.

exchangeable (Found: C, 45·3; H, 6·3; N, 9·7; S, 11·2. $C_{11}H_{18}N_2O_5S$ requires C, 45·5; H, 6·3; N, 9·7; S, 11·1%).

1,3,6-*Trimethyl*-4-*oxo*-6,7,8,9-*tetrahydro*-4H-*pyrido*[1,2-a]*pyrimidinium Methyl Sulphate* (9f).—The tetrahydropyridopyrimidinone (8c) (17·8 g) was dissolved in acetone (50 ml), and dimethyl sulphate (12·6 g) added. After 24 h the precipitated (9f) (28·4 g, 93%) was filtered off as *crystals*, m.p. 170—171° (from propan-2-ol) (Found: C, 47·1; H, 6·7; N, 9·2; S, 10·9. $C_{12}H_{20}N_2O_5S$ requires C, 47·4; H, 6·7; N, 9·2; S, 10·5%).

1,6-*Dimethyl*-4-*oxo*-3-*phenyl*-6,7,8,9-*tetrahydro*-4H-*pyrido*-[1,2-a]*pyrimidinium Methyl Sulphate* (9e).—Analogously to (9f) the tetrahydropyridopyrimidinone (8d) gave (9e) (85%) as *crystals*, m.p. 182—183° (from propan-2-ol), $\lambda_{max.}$ 295 (log ε 3·82) and 200 nm (4·04) (Found: C, 55·7; H, 6·1; N, 7·6; S, 8·8. $C_{17}H_{22}N_2O_5S$ requires C, 55·6; H, 6·3; N, 7·7; S, 8·9%).

3-*Carbamoyl*-1,6-*dimethyl*-4-*oxo*-6,7,8,9-*tetrahydro*-4H-*pyrido*[1,2-a]*pyrimidinium Methyl Sulphate* (9d).—The tetrahydropyridopyrimidinone (8e) (20·7 g) was suspended with dimethyl sulphate (13·2 g) in benzene (150 ml), refluxed for 6 h, and cooled. The *amide* (9d) (27 g, 81%) gave yellow crystals, m.p. 175—176° (from methanol), $\nu_{max.}$ 3415, 3200, 1720, 1650, 1595, 1520, and 1470 cm^{-1}, $\lambda_{max.}$ 354 (log ε 3·12) and 257 nm (4·08), δ (D_2O) 1·43 (3H, d, 6-Me), 2·1 (4H, m, 7-H_2 and 8-H_2), 3·75 (3H, s, $MeSO_4$), 3·98 (3H, s, NMe), 5·1 (1H, m, 6-H), and 8·82 (1H, s, 2-H), 9-H_2 and $-CONH_2$ exchangeable (Found: C, 43·3; H, 5·7; N, 12·6; S, 9·6. $C_{12}H_{19}N_3O_6S$ requires C, 43·6; H, 5·5; N, 12·5; S, 9·5%).

3-*Carboxy*-1,6-*dimethyl*-4-*oxo*-6,7,8,9-*tetrahydro*-4H-*pyrido*-[1,2-a]*pyrimidinium Methyl Sulphate* (9h).—The tetrahydropyridopyrimidinone (8f) (20·8 g) was dissolved in chloroform–acetone (100 ml and 25 ml respectively), dimethyl sulphate (26·4 g) was added, and the mixture was heated under reflux for 1 h. After 24 h the precipitated acid (9h) (20 g, 60%) was filtered off to give *crystals*, m.p. 177° (from ethanol), $\nu_{max.}$ 1745, 1715, 1665, 1525, and 1480 cm^{-1}, $\lambda_{max.}$ 366 (log ε 3·10) and 258 nm (4·22) (Found: C, 43·4; H, 5·4; N, 8·4; S, 9·7. $C_{12}H_{18}N_2OS$ requires C, 43·1; H, 5·4; N, 8·4; S, 9·6%).

1,6-*Dimethyl*-4-*oxo*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyrimidine*-3-*carboxamide* (10e).—The quaternary pyridopyrimidinone (9d) (33·3 g) was dissolved in water (350 ml), and a solution of $NaBH_4$ (4·1 g) in water (30 ml) added within 30 min while the reaction mixture was heated to 35—38°. The mixture was stirred for 1·5 h, adjusted with 1 : 1 hydrochloric acid to pH 3, neutralized with 5% aqueous $NaHCO_3$ solution, purified with charcoal, filtered, and extracted with chloroform. The dried extract was evaporated to give the *amide* (10e) (15·6 g), 70%), as crystals, m.p. 186° (from ethanol–ethyl acetate, 3 : 1), $\nu_{max.}$ 3350, 3180, 1670, 1615, 1570, 1560, and 1465 cm^{-1}, $\lambda_{max.}$ 319 (log ε 3·83) and 235 nm (4·31), δ ($CDCl_3$) 1·22 (3H, d, 6-Me), 1·8 (6H, m, 7-H_2, 8-H_2, and 9-H_2), 3·10 (3H, s, NMe), 4·7—5·3 (2H, m, 6-H and 9a-H), 5·7br (1H, NH), 7·90 (1H, s, 2-H), and 8·8br (1H, NH) (Found: C, 59·3; H, 7·7; N, 19·0. $C_{11}H_{17}N_3O_2$ requires C, 59·2; H, 7·7; N, 18·8%).

1,6-*Dimethyl*-3-*phenyl*-1,6,7,8,9,9a-*hexahydropyrido*[1,2-a]-*pyrimidin*-4-*one* (10d).—Analogously to (11e) the quaternary pyridopyrimidinone (9d) yields (10d) (80%) as *crystals*, m.p. 114—115° (from ethanol), $\nu_{max.}$ 1636, 1618, 1602, and 1490 cm^{-1}, $\lambda_{max.}$ 334 (log ε 3·76), 263 (4·08), and 223 nm (3·98) (Found: C, 74·8; H, 7·8; N, 10·8. $C_{16}H_{20}N_2O$ requires C, 75·0; H, 7·9; N, 11·0%).

Ethyl 6-*Methyl*-4-*oxo*-1-*n*-*propyl*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyrimidine*-3-*carboxylate* (10b).—The hexahydropyridopyrimidinone (4b) (24·0 g) was heated under reflux with n-propyl bromide (50 g) and K_2CO_3 (15 g) in ethanol (250 ml) for 12 h. The mixture was filtered and the filtrate evaporated and its residue dissolved in ethanol (50 ml). This solution was treated with charcoal, filtered, and 70% aqueous perchloric acid (10 ml) was added. After standing 24 h in a refrigerator, the precipitated 3-*ethoxycarbonyl*-6-*methyl*-4-*oxo*-1-*n*-*propyl*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyrimidinium perchlorate* (28·5 g, 70%) was filtered off as crystals (the base is a pale yellow oil), m.p. 110—111° (from ethanol) (Found: C, 47·6; H, 6·6; Cl, 9·1; N, 7·3. $C_{15}H_{24}N_2O,HClO_4$ requires C, 47·7; H, 6·6; Cl, 9·3; N, 7·4%).

Hydrolysis of (10b).—The pyridopyrimidinone (10b) (14·0 g) dissolved in 5% aqueous NaOH (120 ml) was stirred at 50—60° for 8 h and then extracted with benzene. The aqueous solution was acidified with 1 : 1 hydrochloric acid to pH 8, purified with charcoal, filtered, and acidified (pH 3). The precipitated 6-*methyl*-4-*oxo*-1-*n*-*propyl*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyrimidine*-3-*carboxylic acid* (10f) (9·3 g, 74%) was filtered off as crystals, m.p. 158—159° (from ethanol), $\nu_{max.}$ 1730, 1622, 1576, 1520, and 1450 cm^{-1}, $\lambda_{max.}$ 320 (log ε 3·81) and 241 nm (4·04), δ ($CDCl_3$) 1·00 (3H, t, $NCH_2CH_2CH_3$), 1·28 (3H, d, 6-Me), 1·5—2·0 (8H, m, 7-H_2, 8-H_2, 9-H_2, and $NCH_2CH_2CH_3$), 3·35 (2H, t, $NCH_2CH_2CH_3$), 5·0 (2H, m, 6-H and 9a-H), 7·94 (1H, s, 2-H), and 13·75 (1H, s, CO_2H) (Found: C, 61·8; H, 8·0; N, 10·9. $C_{13}H_{20}N_2O_2$ requires C, 62·0; H, 8·0; H, 11·0%).

Ethyl 1-*n*-*Butyl*-6-*methyl*-4-*oxo*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyrimidine*-3-*carboxylate* (10c).—Similarly to (11b) the hexahydropyridopyrimidinone (4b) yielded with n-butyl bromide 1-*n*-*butyl*-3-*ethoxycarbonyl*-6-*methyl*-4-*oxo*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyridinium perchlorate* (76%) as crystals (the base is a pale yellow oil), m.p. 135—137° (from ethanol) (Found: C, 48·8; H, 6·8; Cl, 9·1; N, 7·2. $C_{16}H_{26}N_2O_3,HClO_4$ requires C, 48·7; H, 6·8; Cl, 9·0; N, 7·1%).

Hydrolysis of (10c).—Working as above, the butylhexahydropyridopyrimidinone (10c) yielded 1-*n*-*butyl*-6-*methyl*-4-*oxo*-4,6,7,8,9,9a-*hexahydro*-1H-*pyrido*[1,2-a]*pyrimidine*-3-*carboxylic acid* (10g) (53%), as crystals, m.p. 112—113° (from ethanol) (Found: C, 62·8; H, 8·3; N, 9·3. $C_{14}H_{22}N_2O_3$ requires C, 63·0; H, 8·3; N, 9·3%).

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