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A RING TRANSFORMATION OF 6,7-DIHYDRO-4*H*-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES[1]

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Abstract: Under the conditions of Vilsmeier-Haack formylation, nitrogen bridgehead ring systems containing a 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one moiety (which can isomerize into a tautomeric 6,7-dihydro form under the reaction conditions) or a 6,7-dihydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one moiety undergo a ring transformation to afford the same nitrogen bridgehead nitrogen ring systems containing an unsaturated 4*H*-pyrido[1,2-*a*]pyrimidin-4-one moiety. Some details of the ring transformation were investigated by using deuterated and optically active derivatives. In the first step, a 7-dimethylaminomethylene-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one species is formed, which is involved in the ring transformation. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

Vilsmeier-Haack formylation[2] has proved to be a versatile synthetic method for the functionalization of different bridgehead ring systems, among them pyrido[1,2-*a*]pyrimidines[3-7] with the aim of obtaining biologically active derivatives.

We recently reported[8] a ring transformation of antiallergic-antiasthmatic 9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[9] (**1**) under the conditions of Vilsmeier-Haack formylation to give unsaturated 4H-pyrido[1,2-*a*]pyrimidin-4-ones (**3**) (see Scheme 1). Since a 9-phenylaminomethylene derivative (**6**) yielded only an *N*-formylated product (**7**) as a separable mixture of *E* and *Z* isomers,[8] and Fischer indolization of **1** (e.g. R^1 = Me, R^2 = COOEt) afforded[10] tetracyclic 7,12-dihydropyrimido[1',2';1,2]pyrido-[3,4-*c*]indol-4(6*H*)-ones (e.g. **4**), it was assumed[8] that the enhydrazine tautomeric form **2** is involved in this rearrangement, which is the case in Fischer indolization.[11]

We now give an account of some mechanistic details of this ring transformation, obtained from an investigation of further 9-substituted-6,7,8,9-tetrahydro- and -6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

Results

The reactions of 9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-a]pyrimidine-4-one (**1**, R^1 = H, Me, R^2 = COOEt) in a mixture of DMF and phosphoryl chloride at 90-100 °C gave unsaturated 4*H*-pyrido[1,2-*a*]-pyrimidine-4-ones (**3**, R^1 = H, Me, R^2 = COOEt) in 51 and 93%. Similarly, the 3-methyl derivative (**1**, R^1 = R^2 = Me) afforded **3** (R^1 = R^2 = Me) in 40% yield.

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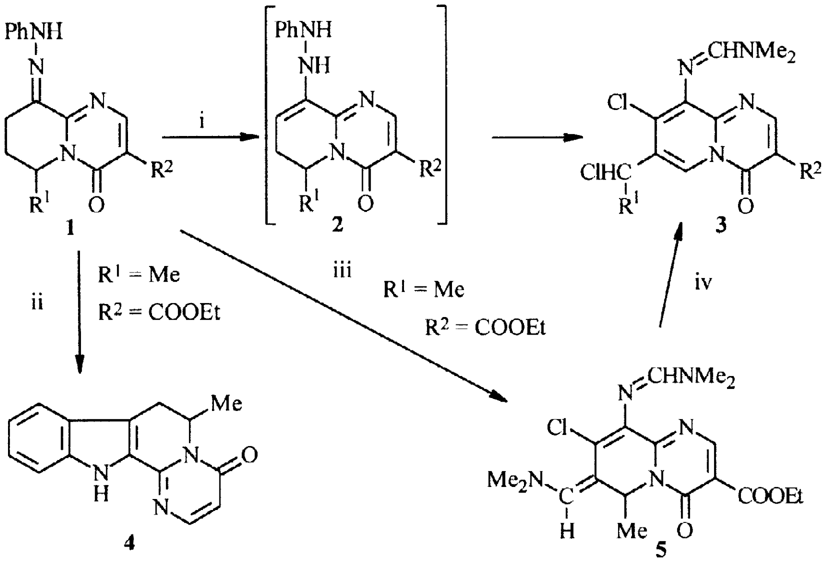
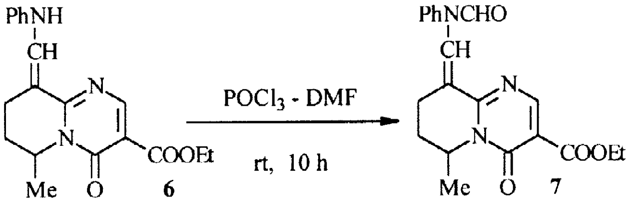


Scheme 1. i, $POCl_3$ / DMF, rt, 30 min, 60 °C, 2 h, then 100 °C, 30 min; ii, 85% H_3PO_4, 180-185 °C; iii, $POCl_3$ / DMF, 40-45 °C, 4 h; iv, $POCl_3$, 95 °C, 1 h.

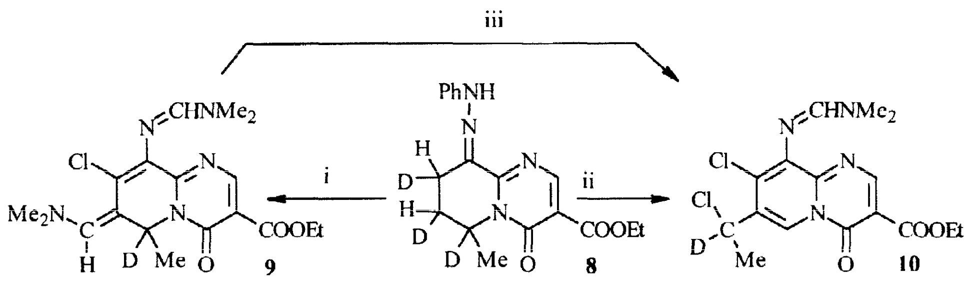
When the reaction mixture of **1** (R^1 = Me, R^2 = COOEt) in a mixture of DMF and phosphoryl chloride was stirred at only 40-45 °C, 9-(*N*,*N*-dimethylaminomethyleneamino)-8-chloro-7-(*N*,*N*-dimethylaminomethylene)-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-4-one (**5**) was isolated in 71% yield. Further heating of **5** in phosphoryl chloride at 95 °C for 1 h gave the rearranged product **3** (R^1 = Me, R^2 = COOEt) in 90% yield.



Starting from the deuterated hydrazone derivative **8**, the 6-deutero derivative **9** was obtained at 40-45 °C, whereas at higher reaction temperature the 7-(1-deutero-1-chloroethyl) derivative **10** was the product, which was also prepared from **9** (Scheme 2).

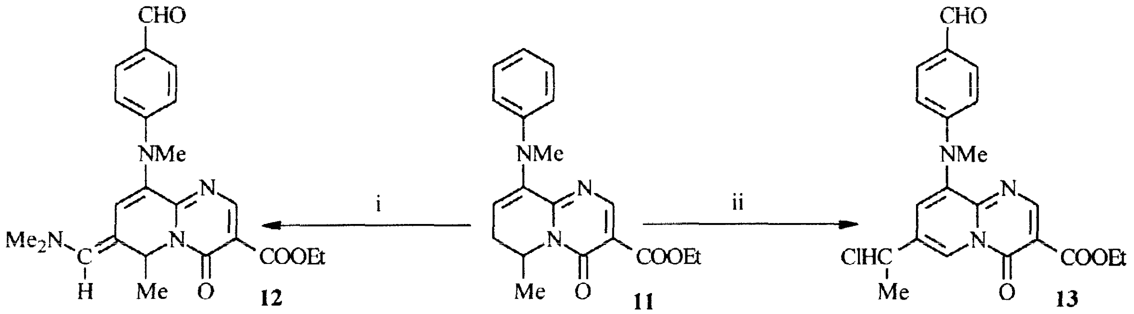
Table. Some characteristic ^{1}H-NMR data on **3** (R^1 = Me, R^2 = COOEt) and **6** and their deuterated derivatives **9** and **8** ($CDCl_3$)

	2-H	6-H	6-CH_3	7-CHCl	7-C(Cl)CH_3	$^3J_{6\text{-H},6\text{-Me}}$	$^3J_{7\text{-CH},\text{Me}}$	$^4J_{6\text{-H},7\text{-CH}}$
6	8.67s	6.63q	1.38d			7.0 Hz		
8	8.68s	-	1.38d			~1.2 Hz		
3	8.95s	9.13d		5.55dq	1.97d		~7.0 Hz	~0.5 Hz
9	8.99s	9.18s		-	1.95d		~1.2 Hz	



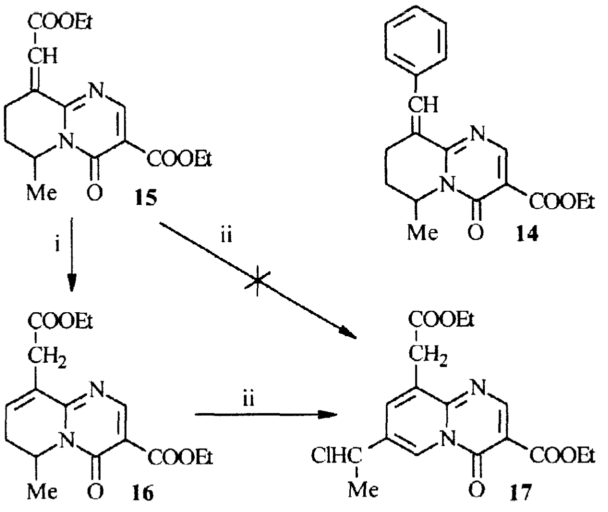
Scheme 2. i, $POCl_3$ / DMF, 40-45 °C, 4 h; ii, $POCl_3$ / DMF, 95-100 °C, 3 h; iii, $POCl_3$, 95 °C,1 h.

When the optically active 9-phenylhydrazono-6-methyl derivative of **1** (R^1 = Me, R^2 = COOEt) was similarly treated, optically active **5** was formed at 40-45 °C, but further heating in phosphoryl chloride at 95 °C led to an optically inactive unsaturated derivative (**3**, R^1 = Me, R^2 = COOEt) (Scheme 1).



Scheme 3. i, $POCl_3$ / DMF, 20-25 °C, 2 h; ii $POCl_3$ / DMF, 95-100 °C, 2 h.

Vilsmeier-Haack formylation of the antiallergic 9-(*N*-methyl-*N*-phenylamino)-6,7-dihydropyrido[1,2-*a*]pyrimidine-4-one[12] (**11**) yielded 7-(*N*,*N*-dimethylaminomethylene)-6-methyl-6,7-dihydro (**12**) and ring-transformed 7-(1-chloroethyl) derivatives (**13**) at lower and higher reaction temperatures, respectively (Scheme 3). In this case, the phenyl group was also formylated. 9-Benzylidene- and 9-ethoxycarbonylmethylene-6-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]-pyrimidine-4-ones[13,14] (**14** and **15**) were recovered unchanged from the reaction mixture of DMF and phosphoryl chloride at 95-100 °C. The 9-ethoxycarbonylmethylene-6,7,8,9-tetrahydro derivative (**15**) could be isomerized into the 9-ethoxycarbonylmethyl-6,7-dihydro derivative (**16**) by heating in Dowtherm at 250 °C. Vilsmeier-Haack formylation of **16** smoothly afforded the rearranged 9-ethoxy-



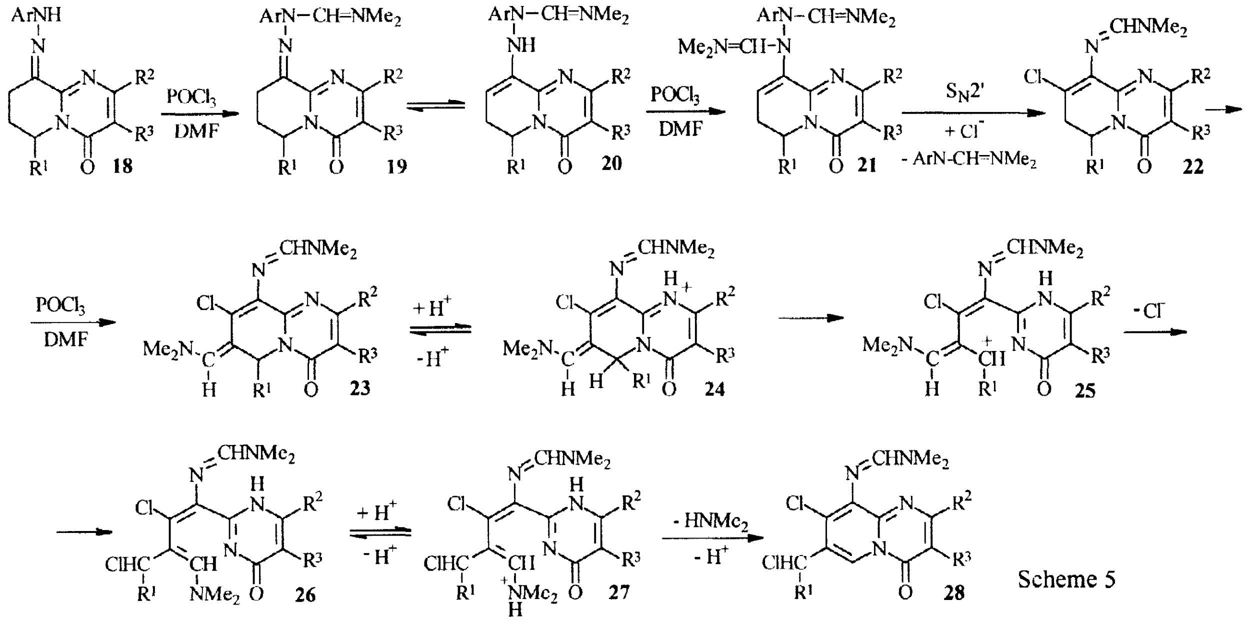
Scheme 4. i, Dowtherm A, 250 °C, 40 min; ii, $POCl_3$ / DMF, rt, 30 min, then 95-100 oC, 3 h.

carbonylmethyl-7-(1-chloroethyl) derivative (**17**) (Scheme 4).

Discussion

This ring transformation is characteristic of 6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. The 9-ethoxycarbonylmethylene-6,7,8,9-tetrahydro derivative (**15**), which could not isomerize into the 9-ethoxycarbonylmethyl-6,7-dihydro tautomer (**16**) under the given reaction conditions at 100 °C, did not undergo rearrangement, whereas the isomerized 9-ethoxycarbonylmethyl-6,7-dihydro derivative (**16**) smoothly afforded the ring-transformed product (**17**).

During the rearrangement of 9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**1**), similarly to the 9-phenylaminomethylene derivative (**6**), the amino group of the 9-phenylhydrazono moiety was first acylated by the Vilsmeier-Haack reagent (see Scheme 5). When the N(2) atom of the 9-hydrazono moiety bears an electron-withdrawing moiety, the equilibrium between the hydrazono (**19**) and enhydrazino (**20**) tautomers is shifted towards the enhydrazine form[15] (**20**). The enhydrazine form (**20**) reacted with a further 2 mol of the Vilsmeier-Haack reagent, at N(1) of the hydrazine moiety and at the allylic 7-CH_2 group. (N-N fission and chlorination of C(8) of the pyrido[1,2-*a*]pyrimidin-4-one skeleton probably occurred in a Lewis acid promoted S_N2' process and is independent of the rearrangement characteristic of 6,7-dihydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones.)



Scheme 5

After N(1) protonation of the pyrido[1,2-*a*]pyrimidine skeleton of 7-(*N*,*N*-dimethylaminomethylene)-6,7-dihydropyrido[1,2-*a*]pyrimidin-4-one (**23**), the C(6)-N(5) bond is heterolytically split to give a relatively stable conjugated carbocation **25**. In this step, the optically activity is lost. This carbocation **25** reacted with a chloride ion and, after protonation, the pyrimidine-4-one (**26**) formed cyclized to 7-(1-chloroethyl)-4*H*-

pyrido[1,2-*a*]pyrimidin-4-one (**28**) by elimination of dimethylamine. When sodium bromide was added to the reaction mixture of **1** (R^1 = Me, R^2 = COOEt) in a mixture of DMF and phosphoryl chloride at 100 °C, the presence of ethyl 7-(1-bromoethyl)-8-chloro-9-(*N*,*N*-dimethylaminomethylene)-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylate was detected in the product on an MS investigation.

This ring transformation can be extended to polycyclic nitrogen bridgehead ring systems containing a 6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one moiety, or its equivalent. For example, a tricyclic hydrazono-1,2,3,5,6,7,8,10-octahydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10-one derivative [**18**, Ar = 4-FC_6H_4, R^1 = Me, R^2, R^3 = $(CH_2)_3$] afforded a ring-transformed product [**28**, R^1 = Me, R^2, R^3= $(CH_2)_3$] on treatment with a mixture of DMF and phosphoryl chloride (Scheme 5).

Experimental

General: Melting points were measured in capillaries and are uncorrected. Yields were not maximised. UV and CD spectra were recorded in EtOH on a Unicam SP-800 spectrophotometer and a Rousell-Jouan Dichrogaph III. IR spectra were taken in KBr disks on a Pye Unicam SP-1100 IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on Bruker AC-200 equipment, at 200 MHz and 50 MHz, respectively. Samples were run in $CDCl_3$ solutions with tetramethylsilane as internal standard. Elemental analyses (C, H, N, F, Cl) were performed with a Perkin Elmer 2400 CHN Analyser.

Reactions of 6-Phenylhydrazino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (1) with DMF-$POCl_3$

8-Chloro-7-(1-chloroalkyl)-9-(N,N-dimethylaminomethylene)amino-4H-pyrido[1,2-a]pyrimidin-4-ones (3):

To a solution of a 6-phenylhydrazino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**) (10 mmol) in DMF (8 mL), phosphoryl chloride (4.6 g, 30 mmol) was added dropwise under cooling. The reaction mixture was stirred at ambient temperature for 30 min, then at 60 °C for 2 h, and finally at 100 °C for 30 min. The reaction mixture was poured onto crushed ice and the pH of the mixture was adjusted to 7 with 20% sodium carbonate solution. The crystals that precipitated out were filtered off and washed with water. The crude product was crystallised or was purified by column chromatography.

Ethyl 4-oxo-9-phenylhydrazino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[16] (**1**, R^1 = H, R^2 = COOEt) gave **3** (R^1 = H, R^2 = COOEt), yield 51%, after chromatography on a silica gel column with benzene as eluent; mp 175-176 °C (EtOH). Anal. Calcd for $C_{15}H_{16}Cl_2N_4O_3$ (371.225): C, 48.53; H, 4.34; N, 15.09; Cl, 19.10. Found: C, 48.23; H, 4.39; N, 14.92; Cl, 19.37.

Ethyl 6-methyl-4-oxo-9-phenylhydrazino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[9] (**1**, R^1 = Me, R^2 = COOEt) gave **3** (R^1 = Me, R^2 = COOEt), yield 93%; mp 192 °C (EtOH); λ_{max} 393 (log ε 4.27), 340 (4.14), 246 nm (4.20); ν_{max} 1720 (C=O, ester), 1690 cm^{-1} [C(4)O]; ^1H NMR ($CDCl_3$) δ 1.42 t ($CH_2C\underline{H}_3$), 1.97 d ($^3J_{H,Me,}$ ~7.0 Hz, $\underline{H}_3CCHCl$), 3.15 s and 3.18 s (Me_2N), 4.38 q (OCH_2), 5.55 dq (HCCl), 8.08 s (N=CH), 8.95 s (2-H), 9.13 d ($^4J_{6H,CH}$ ~0.5 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3$), 24.5 ($\underline{H}_3CCHCl$), 34.1 and 40.4 (NMe_2), 52.7 (CHCl), 60.7 (OCH_2), 104.2 (C-3), 118.9 (C-6), 131.6 (C-7), 134.2 (C-8), 143.1 (C-9), 148.3 (C-9*a*), 154.6 (C-4), 157.3 (N=CH-), 157.8 (C-2), 164.6 (COO). Anal. Calcd for $C_{16}H_{18}Cl_2N_4O_3$ (385.253): C, 49.88; H, 4.71; N, 14.54; Cl, 18.41. Found: C, 49.60; H, 4.79; N, 14.53; Cl, 18.29.

3,6-Dimethyl-9-phenylhydrazino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[17] (**1**, R^1 = R^2 = Me) gave **3** (R^1 = R^2 = Me), yield 40%; mp 190-191 °C (ethyl acetate); λ_{max} 366 inf (log ε 4.08), 352 (4.10), 260 inf (4.09), 217 nm (4.38); ν_{max} 1695 cm^{-1} [C(4)O]; ^{1}H NMR ($CDCl_3$) δ 1.98 d ($\underline{H}_3CCHCl$), 2.24 d ($^4J_{2\text{-}H,3\text{-}Me}$= ~0.8 Hz, 3-Me), 3.13 s and 3.18 s (NMe_2), 5.49 dq (CHCl), 8.00 s (N=CH-), 8.14 d (2-H), 8.91 d ($^4J_{6\text{-}H,CHCl}$ ~0.6 Hz, 6-H). Anal. Calcd for $C_{14}H_{16}Cl_2N_4O$ (327.215): C, 51.39; H, 4.93; N, 17.12; Cl, 21.67. Found: C, 51.38; H, 4.96; N, 17.19; Cl, 21.77.

The optically active (+)-(6*R*) derivative[18] of **1** (R^1 = Me, R^2 = COOEt) gave racemic **3** (R^1 = Me, R^2 = COOEt); yield 73%; mp 190-191 °C (EtOH), which and gave no mp depression mixed with an authentic sample.

The 6,7,8-trideutero derivative (**8**) (0.59 mmol), [prepared from ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylate[19] by reduction over 5% Pd/C catalyst in ethanol under D_2, and the oily 6,7,8-trideutero derivative of ethyl 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1**, R^1 = Me, R^2 = COOEt,), was reacted with benzenediazonium chloride[3a]] gave the 7-(1-chloro-1-deuteroethyl) derivative (**10**), yield 80%; mp 193-195 °C (EtOH); ^{1}H NMR ($CDCl_3$) 1.41 t ($CH_2C\underline{H}_3$), 1.95 d ($J_{D,CH3}$ 1.2 Hz, $\underline{H}_3CCDCl$), 3.15 s and 3.20 s (NMe_2), 4.43 q (OCH_2), 8.10 s (N=CH-), 8.99 s (2-H), 9.18 s (6-H).

Ethyl 8-Chloro-7-(N,N-dimethylaminomethylene)-9-[(N,N-dimethylaminomethylene)amino]-6-methyl-4-oxo-6,7-dihydro-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (5)

To a solution of **1** (R^1 = Me, R^2 = COOEt) (10 mmol) in DMF (8 mL), phosphoryl chloride (4.6 g, 30 mmol) was added dropwise under cooling. After stirring at 40-45 °C for 4 h, the reaction mixture was poured into crushed ice and the pH of the mixture was adjusted to 7 with 20% sodium carbonate solution. The crystals that precipitated out were filtered off and washed with water. After drying, compound **5** (5.59 g, 71%) was obtained, mp 160-162 °C; λ_{max} 499 (log ε 4.30), 313 (4.28), 282 (4.27), 221 nm (4.41); ν_{max} 1740 (C=O, ester), 1660 cm^{-1} [C(4)=O]; ^{1}H NMR ($CDCl_3$) δ 1.35 t ($CH_2C\underline{H}_3$), 1.38 d ($^3J_{H,CH3,}$ ~7.0 Hz, 6-Me), 3.07 s ($N{=}CH\text{-}N\underline{Me}_2$), 3.17 s [$C(7){=}CH\text{-}N\underline{Me}_2$], 4.35 q ($OCH_2$), 6.63 q (6-H), 6.83 s [$C(7){=}C\underline{H}\text{-}NMe_2$], 7.57 s ($N{=}C\underline{H}\text{-}NMe_2$), 8.67 s (2-H); ^{13}C NMR ($CDCl_3$), δ 14.4 ($CH_2\underline{C}H_3$), 20.6 ($6\text{-}CH_3$), 34 broad, and 40 broad ($N{=}CH\text{-}N(\underline{C}H_3)_2$), 44.0 (C-6 and $C(7){=}CH\text{-}N(\underline{C}H_3)_2$), 60.6 ($OCH_2$), 99.1 (C-7), 111.7 (C-3), 129.1 (C-9), 134.3 (C-8), 142.5 [$C(7){=}\underline{C}H\text{-}N(CH_3)_2$], 155.0 (C-9*a*), 157.0 [$N{=}\underline{C}H\text{-}N(CH_3)_2$], 157.6 (C-4), 158.8 (C-2), 164.4 (3-COO), $^3J_{\underline{C}\text{-}8,C(7)=C\underline{H}}$ ~10.4 Hz, $^3J_{\underline{C}\text{-}(8),6\text{-}\underline{H}}$

~7.9 Hz. Anal. Calcd for $C_{18}H_{24}ClN_5O_3$ (393.878): C, 54.89; H, 6.14; N, 17.78; Cl, 9.00. Found: C, 54.72; H, 6.08; N, 17.72; Cl, 8.94.

The optically active (+)-6$\underline{R}$) derivative of **1** (R^1 = Me, R^2 = COOEt) gave the optically active derivative of **5**, (R^1 = Me, R^2 = COOEt) (51%); mp 134-137 °C. CD λ_{max} 489 ($\Delta\varepsilon$ -15.45), 314 (+9.74), 279 (+9.33), 243 (-7.70), 217 nm (-16.09).

The 6,7,8-trideutero derivative (**8**) of **1** (R^1 = Me, R^2 = COOEt) (5 mmol) gave compound **9** (60%); mp 156-158 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 t ($CH_2C\underline{H}_3$), 1.38 d ($^3J_{6\text{-D},6\text{-Me}}$ ~1.2 HZ, 6-Me), 3.02 s (N=CH-N$\underline{Me}_2$), 3.12 s [C(7)=CH-N$\underline{Me}_2$], 4.35 q (OCH_2), 6.83 s [C(7)=C$\underline{H}$-NMe$_2$], 7.54 s (N=C$\underline{H}$-NMe$_2$), 8.68 s (2-H).

Ring Transformation of Ethyl 8-Chloro-7-(*N*,*N*-dimethylamino)-9-(*N*,*N*-dimethylaminomethylene)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (5)

A solution of compound **5** (0.39 g, 1 mmol) in phosphoryl chloride (3 mL) was stirred at 95 °C for 1 h. The reaction mixture was poured onto crushed ice and the pH of the mixture was adjusted to 7 with 20% sodium carbonate solution. The crystals that precipitated out were filtered off and washed with water to give **3** (R = COOEt, R^1 = Me) (0.35 g, 90%); mp 191-192 °C (EtOH), and it gave no mp depression mixed with a sample prepared as above.

Ethyl 7-(*N*,*N*-Dimethylaminomethylene)-9-[*N*-(4-formylphenyl)-*N*-methylamino]-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (12)

To a solution of ethyl 9-(*N*-methyl-*N*-phenylamino)-6-methyl-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[13] (**11**) (1.7 g, 5 mmol) in DMF (4 mL), phosphoryl chloride (2.3 g, 15 mmol) was added dropwise under cooling. The reaction mixture was stirred at ambient temperature for 2 h, and the reaction mixture was worked up as above to give compound **12** (1.65 g, 78%); mp 138-139 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 1.25 t ($CH_2C\underline{H}_3$), 1.38 d (6-CH_3), 3.23 s (C(7)=CH-N$\underline{Me}_2$), 3.35 s (NMe), 4.20 q (OCH_2), 6.50 q (6-H), 6.80 d (2-H and 6-H of Ph), 7.05 s (8-H), 7.73 d (3-H and 5-H of Ph), 8.38 s (2-H), 9.75 s (CHO). Anal. Calcd for $C_{23}H_{26}N_4O_4$ (422.489): C, 65.38; H, 6.20; N, 13.26. Found: C, 65.27; H, 6.13; N, 13.17.

Ethyl 7-(1-Chloroethyl)-9-[*N*-(4-formylphenyl)-*N*-methylamino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (13)

When a similar reaction mixture of compound **11** was stirred at 95-100 °C for 2 h, a similar work-up afforded compound **13** (1.65 g, 80%); mp 146-148 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.43 t ($CH_2C\underline{H}_3$), 1.96 d ($\underline{H}_3CHCl$), 3.55 s (NMe), 4.43 q (OCH_2) 5.23 dq (ClCH), 6.83 d (3-H and 5-H of Ph), 7.78 d (2-H and 6-H of Ph), 8.10 d ($^4J_{6H,8H}$ ~2.1 Hz, 8-H), 8.45 s (2-H), 9.20 dd ($^4J_{6H,CH}$ ~0.6 Hz, 6-H) 9.82 s (CHO). Anal. Calcd for $C_{21}H_{20}ClN_3O_4$ (413.864): C, 60.95, H, 4.87, Cl, 8.57, N, 10.15. Found: C, 61.05, H, 4.82, Cl, 8.47, N, 10.09.

Ethyl 3-Ethoxycarbonyl-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-9-acetate (16)

Ethyl 9-ethoxycarbonylmethylene-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[14] (**15**) (12.5 g, 5 mmol) was added to Dowtherm A (200 mL) at 250 °C. The reaction mixture was stirred at this temperature for 40 min. After cooling to ambient temperature, it was diluted with petroleum ether (400 mL), and extracted with 1:1 hydrochloric acid (2x150 mL and 1x100 mL). The combined acidic aqueous solution was treated with active charcoal and, after filtration, its pH was adjusted to 7 with 20% sodium carbonate solution. The aqueous solution was extracted with chloroform (2x150 mL and 1x100 mL). The combined organic phase was dried (over sodium sulfate) and evaporated to dryness in vacuo. The oily residue was chromatographed on a silica gel column with benzene as eluent to give compound **16** (3.5 g, 28%) as an oil; λ_{max} 341 (log ε 4.03), 253 (4.14), 213 (4.22); ^{1}H NMR ($CDCl_3$) δ 1.18 d (6-Me), 1.32 t and 1.40 t ($2xCH_2C\underline{H}_3$), 2.65 m ($7-CH_2$), 3.53 s [$C(9)-CH_2$], 4.15 q and 4.38 q ($2xOCH_2$), 5.34 m (6-H), 6.56 m (8-H), 8.61 s (2-H). Anal. Calcd for $C_{16}H_{20}N_2O_5$ (320.347): C, 59.99; H, 6.29; N, 8.74. Found: C, 60.12; H, 6.22; N, 8.84.

Ethyl 3-Ethoxycarbonyl-7-(1-chloroethyl)-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-acetate (17)

To a solution of 3-ethoxycarbonyl-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-9-acetate (**16**) (1.1 g, 3.4 mmol) in DMF (4 mL), phosphoryl chloride (1.54 g, 10 mmol) was added dropwise at 20-25 °C. The reaction mixture was stirred at ambient temperature for 30 min, then at 95-100 °C for 3 h. The reaction mixture was poured onto crushed ice, and the pH of the mixture was adjusted to 7 with 20% sodium carbonate solution. The aqueous mixture was extracted with benzene (3x30 mL). The combined organic phase was extracted with water (20 mL), the dried solution (over Na_2SO_4) was evaporated to dryness in vacuo, and the residue was chromatographed on a silica gel column, eluent: benzene and methanol, to give compound **17** (0.34 g, 27%); mp 130 °C (ethyl acetate); λ_{max} 372 (log ε 4.28), 362 inf (4.18), 314 (3.66), 260 (3.96), 254 inf (3.95); ν_{max} 1740 (CH_2CO), 1680 cm^{-1} [C(4)CO]; ^{1}H NMR ($CDCl_3$) 1.25 t and 1.38 t ($2xCH_2C\underline{H}_3$), 1.85 d ($\underline{H}_3CHCCl$), 4.08 s ($9-CH_2CO$), 4.20 q and 4.43 q ($2xCOCH_2$), 5.20 qd ($H_3CC\underline{H}-Cl$), 8.05 d ($^4J_{6H,8H}$ ~2.1 Hz, 8-H), 9.02 s (2-H), 9.23 dd ($^4J_{6H,CH}$ ~0.6 Hz 6-H). Anal Calcd for $C_{17}H_{19}ClN_2O_5$ (366.803): C, 55.67; H, 5.22; Cl, 9.67; N, 7.64. Found: C, 55.90; H, 5.20; Cl, 9.68; N, 7.75.

5-[2-(4-Fluorophenyl)hydrazono]-8-methyl-1,2,3,5,6,7,8,10-octahydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10-one (18, Ar = 4-FC_6H_4, R^1 = Me, R^2, R^3 = $(CH_2)_3$)

To a stirred solution of sodium acetate trihydrate (24 mmol, 3.3 g) and 4-fluorophenylhydrazonium chloride, prepared from 4-fluoroaniline (10 mmol, 1.12 g) with a solution of sodium nitrite (10 mmol, 0.7 g) in water (5 mL) at 0 °C by usual procedure,[20] 8-methyl-1,2,3,5,6,7,8,10-octahydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10-one[21] (10 mmol, 2.04 g) in 75% acetic acid (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and stored overnight in a refrigerator. The precipitated crystals (1.5 g) were filtered off, washed with water, dried, and crystallised from ethanol to give **18** (0.7 g, 21%); mp 184-186 °C. Anal. Calcd for $C_{18}H_{19}FN_4O$ (326.373): C, 66.23; H, 5.87; N, 17.17; F, 5.82. Found: C, 66.41; H, 5.78; N, 17.26; F, 5.97.

Ring Transformation of 5-[2-(4-Fluorophenyl)hydrazono]-8-methyl-1,2,3,5,6,7,8,10-octahydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10-one [18, Ar = 4-FC_6H_4, R^1 = Me, R^2, R^3 = $(CH_2)_3$]

To a solution of arylhydrazino derivative **18** [Ar = 4-FC_6H_4, R^1 = Me, R^2, R^3 = $(CH_2)_3$] (0.5 g, 1.5 mmol) in DMF (1.5 mL), phosphoryl chloride (1.15 g, 7.5 mmol) was added under cooling. The reaction mixture was stirred at 60 °C for 2.5 h, then at 95 °C for 1 h. The reaction mixture was poured onto crushed ice and the pH of the mixture was adjusted to 7 with 20% sodium carbonate solution. The crystals that precipitated out were filtered off and washed with water. The crude product was purified by column chromatography and finally recrystallised to give 6-chloro-7-(1-chloroethyl)-5-(*N*,*N*-dimethylaminomethylene)-1,2,3,10-tetrahydrocyclopenta[*d*]pyrido[1,2-a]pyrimidin-10-one [**28**, R^1 = Me, R^2, R^3 = $(CH_2)_3$] (0.1 g, 19%); mp 196-197 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.98 d ($^3J_{CH,Me,}$ ~6.8 Hz, $\underline{H}_3$CCHCl), 2.13 m (2-CH_2), 2.97 m (1- and 3-CH_2), 3.11 s and 3.18 s (Me_2N), 5.51 q (HCCl), 8.05 s (N=CH), 8.98 s (8-H). Anal. Calcd. for $C_{16}H_{18}Cl_2N_4O$ (353.270): C, 54.40; H, 5.14; N, 15.86; Cl, 20.07. Found: C, 54.69; H, 5.19; N, 16,12; Cl, 20.06.

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