# NITROGEN BRIDGEHEAD COMPOUNDS. PART 82[1]. AN UNEXPECTED RING TRANSFORMATION OF 6-HYDRAZONO-4-OXO-6,7,8,9-TETRAHYDRO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINE-3-CARBOXYLATES[2]

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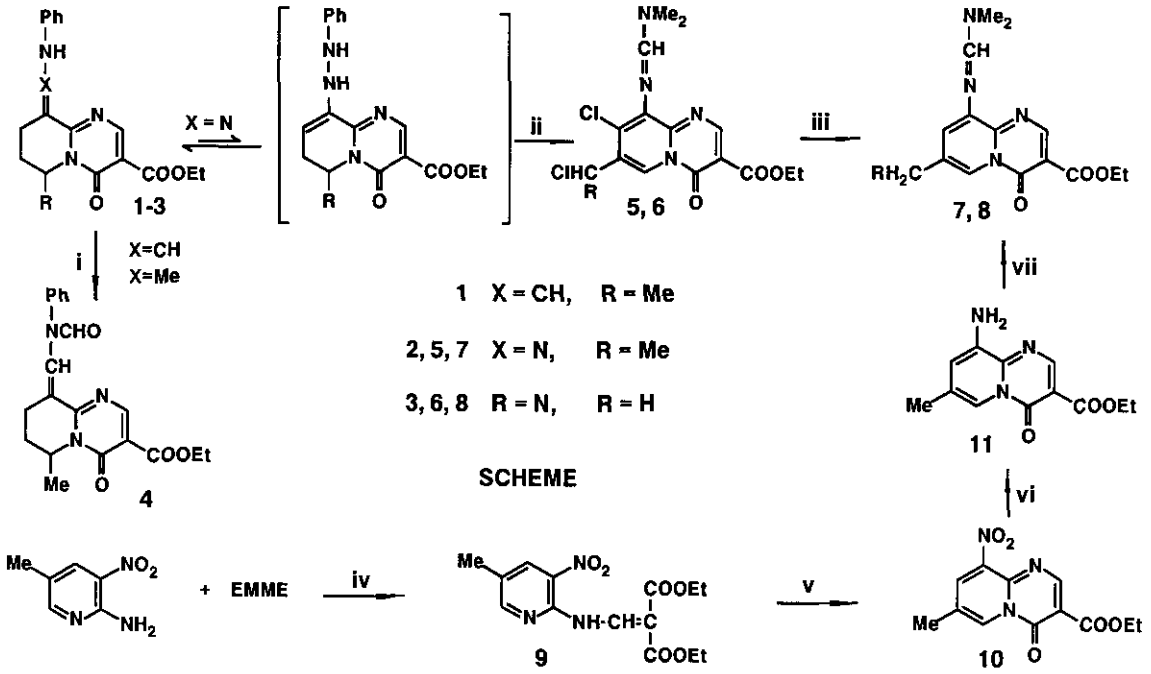
**Abstract-** Treatment of 9-hydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates with the Vilsmeier-Haack reagent gave unsaturated 7-substituted 9-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates in a degenerate ring transformation, probably through ring opening *via* the N(5)-C(6) bond.

Among the reactions of biologically active 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones,[3] the ring transformation of 6-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[2,4] through ring opening *via* the C(4)-N(5) bond affords 4-hydroxy-1,8-naphthyridines. Some of the latter are key intermediates in the synthesis of antibacterial nalidixic acid and its derivatives.[5] Degenerate ring transformation of the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton through ring opening *via* the N(1)-C(2) bond[6] of the N(1)-C(9a) bond,[7] has also been described.

We wish to report herein a new degenerate ring transformation of antiallergic 9-hydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates.[8]

Whereas formylation of the antiallergic[9] 9-anilinomethylene-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1**) with DMF-$POCl_3$ gave the expected 9-(*N*-formylaminomethylene) derivate (**4**)[10] (yield 90%; mp 132-135 °C),

the similar reaction of its aza analogue (**2**)[8] resulted in the formation of a product (**5**)[11] (yield 92.7%; mp 192 °C, EtOH) whose mass spectrum indicated that it contained fewer carbon and hydrogen atoms ($C_{14}H_{18}Cl_2N_4O_3$) than the starting compound (**2**) ($C_{18}H_{20}N_4O_3$), and that it also contained two halogen atoms. One of these is linked to an $sp^3$ carbon, and the other to an $sp^2$ carbon. Catalytic hydrogenation of the product (**5**) over Pd/C catalyst gave a simpler compound (**7**)[12] (yield 72.8%; mp 143 °C, EtOAc), which was identified as an unsaturated 9-(substituted amino)-7-ethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative on the basis of its uv and $^1$H-nmr spectra.[13] Following this, the compound obtained in the Vilsmeier-Haack formylation was described as a 8-chloro-7-(1-chloroethyl) derivative (**5**).




Reaction conditions: i, $DMF/POCl_3$, room temperature, 10 h; ii, $DMF/POCl_3$; 60 °C for 2 h and 90 °C for 0.5 h; iii, $H_2$/10% Pd/C AcOH; iv, 150 °C, 14 h; v, PPA, 115 °C, 50 min; vi, $H_2$/10% Pd/C EtOH, vii, $Me_2NCH(OMe)_2$, acetone, reflux, 30 min.

It was assumed that carbons of the 7-ethyl chain in **5** and **7** was identical with the carbon of 6-methyl group and ring carbon 6 of the starting hydrazone (**2**). If this is true, the 6-desmethyl-9-hydrazone derivative (**3**) should give 9-amino-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives (**6** and **8**). Indeed, the 7-methyl derivatives (**6**) (mp 175-176 °C, EtOH) and (**8**) (mp 147-148 °C, EtOAc) were obtained in 51% and 67.3% yields, respectively.

The structure of 9-amino-7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**8**) was justified by an independent synthesis. 2-Amino-5-methyl-3-nitropyridine[14] reacted with diethyl ethoxymethylenemalonate (EMME) at 150 °C for 14 h, and the aminomethylenemalonate (**9**) (yield 75.5%; mp 195-197 °C, MeCN) was then cyclized[15] by heating in polyphosphoric acid at 115 °C for 50 min to give 9-nitro-7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**10**) (yield 82%; mp 226-228 °C, MeCN). Catalytic hydrogenation of the 9-nitro derivative (**10**) over 10%-Pd/C catalyst afforded 9-amino-7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**11**)[16] (yield: 71%; mp 174-175 °C), which was treated with *N*,*N*-dimethylformamide diethyl acetal in boiling acetone for 30 min. Mixtures of this product (**8**) (yield 86%; mp 146-148 °C, EtOAc) and that obtained starting from **3** through **6** showed no melting point depression, and their uv, ir and $^1$H-nmr spectra were superimposable.

The 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones gave[17] indolopyridopyrimidinones under the conditions of Fischer indolization on heating in polyphosphoric acid, while the 9-arylmethylene derivatives did not. The difference in reactivity of 9-hydrazono- and 9-aminomethylenetetrahydropyridopyrimidinones could therefore be explained in that in the case of 9-hydrazono-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates, similarly as in Fischer indolization,[17,18] the reactive species are the tautomeric 9-hydrazino-6,7-dihydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates.

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10. In the starting 9-anilinomethylene compound (**1**) there is a fast isomerization the around C(9)=CH-NH double bond, giving a solvent dependent equilibrium mixture of *E* and *Z* izomers in solution,[19] whereas the presence of the formyl group on the amino group of **4** leads to an increase in the activation energy, which permits separation of the *E* and *Z* isomers of **4** by means of column chromatography (kieselgel 60; eluent: benzene-methanol=95.5 : 0.5).

(*Z*)-(**4**) yield 56%; mp 153-155 °C (EtOAc); uv (EtOH): $\lambda_{max}$ 418inf. (log $\varepsilon$ 3.50), 356 (4.24), 294inf. nm (3.76); $^1$H-nmr($CDCl_3$); $\delta$(ppm) 1.33 (3H, t, *J* 7.4 Hz, $CH_3$); 1.37 (3H, d, *J* 6.0 Hz, 6-$CH_3$), 2.00 (2H, m, 7-$H_2$), 2.85 (2H, m, 8-$H_2$), 4.29 (2H, q, *J* 7.4 Hz, $OCH_2$), 5.17 (1H, m, 6-H), 7.04 (1H, t, *J* 1.5 Hz, =CH), 7.20 (5H, m, Ph), 8.18 (1H, s, CHO), 8.35 (1H, s, 2-H).

(*E*)-(**4**) yield 27%; mp 185 °C (EtOAc), uv (EtOH): $\lambda_{max}$ 414inf. (log $\varepsilon$ 3.63), 356 (4.28), 229 nm (3.79); $^1$H-nmr: ($CDCl_3$) $\delta$(ppm) 1.25 (3H, d, *J* 6.2 Hz, 6-$CH_3$), 1.38 (3H, t, *J* 7.4 Hz, $CH_3$), 1.75 (2H, m, 7-$H_2$), 1.95 (2H, m, 8-$H_2$), 4.35 (2H, q, *J* 7.4 Hz, $OCH_2$), 5.12 (1H, m, 6-H), 7.1-7.7 (5H, Ph), 8.45 (1H, broad, CHO), 8.55 (1H, t, *J* 1.4 Hz, =CH), 8.60 (1H, s, 2-H).

11. Uv (EtOH): $\lambda_{max}$ 393 (log$\varepsilon$ 4.27), 340 (4.14), 246nm (4.20); ir: (KBr) $\nu_{CO}$ 1720 and 1690 cm$^{-1}$; $^1$H-nmr ($CDCl_3$): $\delta$(ppm) 1.42 (3H, t, *J* 7.4 Hz, $CH_3$), 1.97 (3H, d, *J* 6.8 Hz, $CH_3$), 3.15 and 3.18 (6H, both s, $NMe_2$), 4.38 (2H, q, *J* 7.4 Hz, $OCH_2$),5.55 (1H, qd, *J* 6.8 and 0.5 Hz 7-CHCl), 8.08 (1H, s, N=CH-N), 8.95 (1H, s, 2-H), 9.13 (1H, d, $^4J_{6,7CH}$ 0.5Hz, 6-H); $^{13}$C-nmr ($CDCl_3$): $\delta$(ppm) 157.8 (C-2), 104.2 (C-3), 154.6 (C-4), 118.9 (C-6), 131.6 (C-7), 134.2 (C-8), 143.1 (C-9), 148.3 (C-9a), 34.1, 40.4 and 157.3 (N=CH-$NMe_2$), 24.5 and 52.7 (7-CHCl-$CH_3$), 14.2, 60.7 and 164.6 ($COOCH_2CH_3$).

12. Uv (EtOH): $\lambda_{max}$ 388 ( 4.27), 330 (4.32), 241inf nm (4.10); $^1$H-nmr ($CDCl_3$): $\delta$ (ppm) 1.33 (3H, t, *J* 7.8 Hz, 7-$CH_2CH_3$), 1.41 (3H, t, *J* 7.6 Hz, $CH_3$), 2.77 (2H, qd, *J* 7.8 and 1.0 Hz, 7-$CH_2$), 3.15 and 3.20 (6H, both s, $NMe_2$), 4.44 (2H, q, *J* 7.6 Hz, $OCH_2$), 7.33 (1H, d, *J* 2.1 Hz, 8-H); 7.90 (1H, s, -N=CH-N), 8.87 (1H, dt, *J* 2.1 and 1.0 Hz, 6-H); 9.08 (1H, s, 2-H); $^{13}$C-nmr ($CDCl_3$): $\delta$ (ppm) 156.0 (C-2); 103.8 (C-3), 155.2 (C-4), 118.9 (C-6), 134.0 (C-7), 128.6 (C-8), 147.0 (C-9), 148.6 (C-9a), 34.5, 40.4 and 157.1 (=N-CH-$NMe_2$), 14.4, 60.5 and 165.1 ($COOCH_2CH_3$), 14.4 and 26.2 (7-$CH_2CH_3$).

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