

NITROGEN BRIDGEHEAD COMPOUNDS. PART 82¹. AN UNEXPECTED RING TRANSFORMATION OF 6-HYDRAZONO-4-OXO-6,7,8,9-TETRAHYDRO-4H-PYRIDO[1,2-a]PYRIMIDINE-3-CARBOXYLATES²

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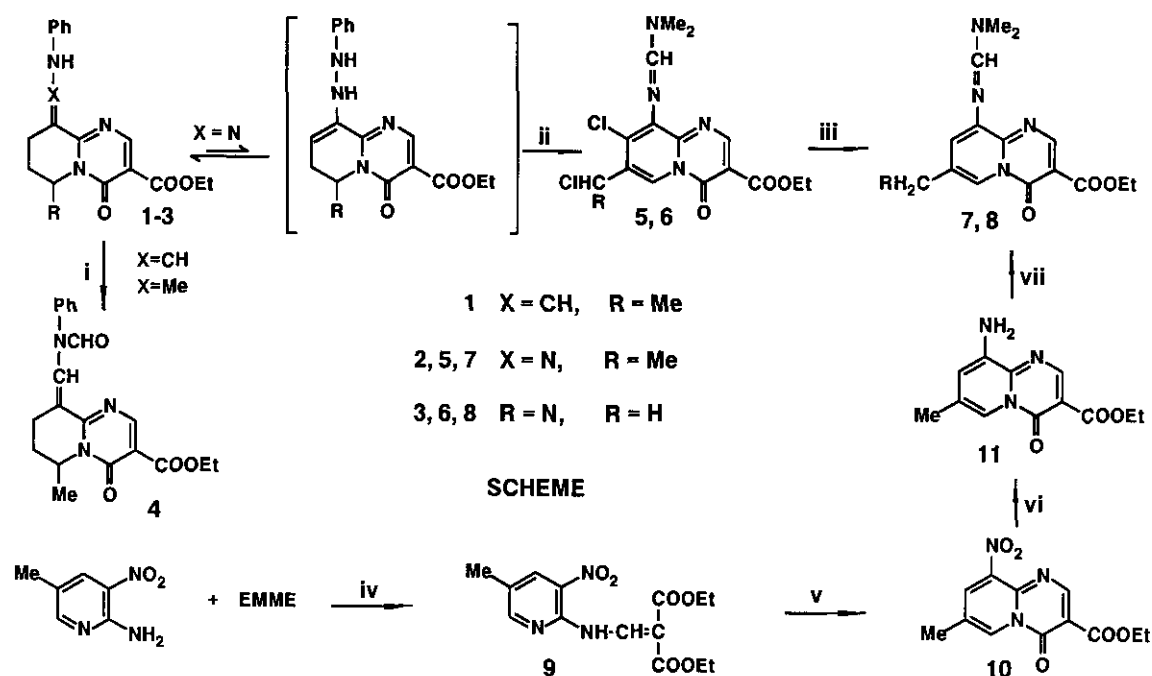
Abstract- Treatment of 9-hydrazono-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxylates with the Vilsmeier-Haack reagent gave unsaturated 7-substituted 9-amino-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylates in a degenerate ring transformation, probably through ring opening via the N(5)-C(6)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

Among the reactions of biologically active 4H-pyrido[1,2-a]pyrimidin-4-ones,³ the ring transformation of 6-substituted 4H-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 4H-pyrido[1,2-a]pyrimidin-4-one skeleton through ring opening via the N(1)-C(2) bond⁶ 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-4H-pyrido[1,2-a]pyrimidine-3-carboxylates.⁸

Whereas formylation of the antiallergic⁹ 9-anilinomethylene-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (1) with DMF-POCl₃ 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-4H-pyrido[1,2-a]pyrimidin-4-one derivative on the basis of its uv and 1H -nmr spectra.¹³ Following this, the compound obtained in the Vilsmeier-Haack formylation was described as a 8-chloro-7-(1-chloroethyl) derivative (5).



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-nitropyridine¹⁴ 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 cyclized¹⁵ 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 ¹H-nmr spectra were superimposable.

The 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones gave¹⁷ 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): $\lambda_{\max}$ 418nm. (log ϵ 3.50), 356 (4.24), 294nm. (3.76); ¹H-nmr(CDCl₃): δ (ppm) 1.33 (3H, t, *J* 7.4 Hz, CH₃); 1.37 (3H, d, *J* 6.0 Hz, 6-CH₃), 2.00 (2H, m, 7-H₂), 2.85 (2H, m, 8-H₂), 4.29 (2H, q, *J* 7.4 Hz, OCH₂), 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): $\lambda_{\max}$ 414nm. (log ϵ 3.63), 356 (4.28), 229 nm (3.79); ¹H-nmr: (CDCl₃) δ (ppm) 1.25 (3H, d, *J* 6.2 Hz, 6-CH₃), 1.38 (3H, t, *J* 7.4 Hz, CH₃), 1.75 (2H, m, 7-H₂), 1.95 (2H, m, 8-H₂), 4.35 (2H, q, *J* 7.4 Hz, OCH₂), 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 ϵ 4.27), 340 (4.14), 246nm (4.20); ir: (KBr) ν_{CO} 1720 and 1690 cm⁻¹; ¹H-nmr (CDCl₃): δ (ppm) 1.42 (3H, t, *J* 7.4 Hz, CH₃), 1.97 (3H, d, *J* 6.8 Hz, CH₃), 3.15 and 3.18 (6H, both s, NMe₂), 4.38 (2H, q, *J* 7.4 Hz, OCH₂), 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, ⁴*J*_{6,7CH} 0.5Hz, 6-H); ¹³C-nmr (CDCl₃): δ (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-NMe₂), 24.5 and 52.7 (7-CHCl-CH₃), 14.2, 60.7 and 164.6 (COOCH₂CH₃).

12. Uv (EtOH): $\lambda_{\max}$ 388 (4.27), 330 (4.32), 241 nm (4.10); ^1H -nmr (CDCl_3): δ (ppm) 1.33 (3H, t, J 7.8 Hz, $7\text{-CH}_2\text{CH}_3$), 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): δ (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 ($\text{COOCH}_2\text{CH}_3$), 14.4 and 26.2 ($7\text{-CH}_2\text{CH}_3$).
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16. The catalytic hydrogenation of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates generally affords 6,7,8,9-tetrahydro derivatives,²⁰ but the above results indicate that the presence of an amino group at position 9 of the pyridopyrimidinone skeleton prevents saturation of the double bonds of the pyridine moiety.
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