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

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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, the ring transformation of 6-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones 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. Degenerate ring transformation of the 4H-pyrido[1,2-a]pyrimidin-4-one skeleton through ring opening via the N(1)-C(2) bond of the N(1)-C(9a) bond, 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. Whereas formylation of the antiallergic 9-anilinomethylene-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (1) with DMF-POCl₃ gave the expected 9-(N-formylaminomethylene) derivative (4) (yield 90%; mp 132-135 °C),
the similar reaction of its aza analogue (2) resulted in the formation of a product (5) (yield 92.7%; mp 192 °C, EtOH) whose mass spectrum indicated that it contained fewer carbon and hydrogen atoms (C_{14}H_{18}Cl_{2}N_{4}O_{3}) than the starting compound (2) (C_{18}H_{30}N_{4}O_{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) (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 \(^1\)H-nmr spectra. Following this, the compound obtained in the Vilsmeier-Haack formylation was described as a 8-chloro-7-(1-chloroethyl) derivative (5).

\[\text{Reaction conditions: i, DMF/POCl}_3, \text{ room temperature, 10 h; ii, DMF/POCl}_3; 60 ^\circ\text{C for 2 h and 90 ^\circ\text{C for 0.5 h; iii, H}_2/10\% \text{ Pd/C AcOH; iv, 150 ^\circ\text{C, 14 h; v, PP}\text{A, 115 ^\circ\text{C, 50 min; vi, H}_2/10\% \text{ Pd/C EtOH, vii, Me}_2\text{NCH(O\text{Me})}_2, acetone, reflux, 30 min.}\]
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-4H-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-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (8) was justified by an independent synthesis. 2-Amino-5-methyl-3-nitropyridine reacted with diethyl ethoxymethylene malonate (EMME) at 150°C for 14 h, and the aminomethylene malonate (9) (yield 75.5%; mp 195-197°C, MeCN) was then cyclized by heating in polyphosphoric acid at 115°C for 50 min to give 9-nitro-7-methyl-4-oxo-4H-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-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (11) (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-4H-pyrido[1,2-a]pyrimidin-4-ones gave 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-aminomethylene tetrahydropyridopyrimidinones could therefore be explained in that in the case of 9-hydrazono-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylates, similarly as in Fischer indolization, the reactive species are the tautomeric 9-hydrazino-6,7-dihydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylates.
REFERENCES AND NOTES


10. In the starting 9-anilinomethylene compound (1) there is a fast isomerization around \(\text{C}(9)=\text{CH-NH}\) double bond, giving a solvent dependent equilibrium mixture of \(E\) and \(Z\) isomers 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): \(\lambda_{\text{max}}\) 418 inf. (log \(\varepsilon\) 3.50), 356 (4.24), 294 inf. nm (3.76); \(^1\)H-nmr (CDCl\(_3\)): \(\delta\) (ppm) 1.33 (3H, \(t\), \(J\) 7.4 Hz, \(\text{CH}_3\)); 1.37 (3H, \(d\), \(J\) 6.0 Hz, 6-\text{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, =\text{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): \(\lambda_{\text{max}}\) 414 inf. (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-\text{CH}_3), 1.38 (3H, \(t\), \(J\) 7.4 Hz, \(\text{CH}_3\)), 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, =\text{CH}), 8.60 (1H, s, 2-H).

11. Uv (EtOH): \(\lambda_{\text{max}}\) 393 (log \(\varepsilon\) 4.27), 340 (4.14), 246nm (4.20); ir: (KBr) \(\nu_{\text{CO}}\) 1720 and 1690 cm\(^{-1}\); \(^1\)H-nmr (CDCl\(_3\)): \(\delta\) (ppm) 1.42 (3H, \(t\), \(J\) 7.4 Hz, \(\text{CH}_3\)), 1.97 (3H, \(d\), \(J\) 6.8 Hz, \(\text{CH}_3\)), 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=\text{CH-N}), 8.95 (1H, s, 2-H), 9.13 (1H, \(d\)), 4\(^{13}\)J\(_{6,7\text{CH}}\) 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=\text{CH-NMe}_2), 24.5 and 52.7 (7-CHCl-\(\text{CH}_3\)), 14.2, 60.7 and 164.6 (COOCH\(_2\)\(\text{CH}_3\)).
12. Uv (EtOH): $\lambda_{\text{max}}$ 388 (4.27), 330 (4.32), 241 (4.10); $^1$H-nmr (CDCl$_3$):
\[
\delta (\text{ppm}) 1.33 (3H, t, J 7.8 Hz, 7-CH$_2$CH$_3$), 1.41 (3H, t, J 7.6 Hz, CH$_3$),
2.77 (2H, qd, J 7.8 and 1.0 Hz, 7-CH$_2$), 3.15 and 3.20 (6H, both s, NMe$_2$),
4.44 (2H, q, J 7.6 Hz, OCH$_2$), 7.33 (1H, d, J 2.1 Hz, 8-H); 7.90 (1H, s, -N=CH-N),
8.87 (1H, dt, J 2.1 and 1.0 Hz, 6-H); 9.08 (1H, s, 2-H);
\]
$^{13}$C-nmr (CDCl$_3$): \[\delta (\text{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$_2$CH$_3$), 14.4 and
26.2 (7-CH$_2$CH$_3$).


16. The catalytic hydrogenation of 4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylates generally affords 6,7,8,9-tetrahydro derivatives, 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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