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NITROGEN BRIDGEHEAD COMPOUNDS PART 12[1]. THE REACTION OF THE ETHYL 6-METHYL-4--OXO-6,7,8,9-TETRAHYDRO-4H-PYRIDO [1,2-a] PYRIMIDINE-3-CARBOXYLATE WITH IMINIUM CHLORIDES.

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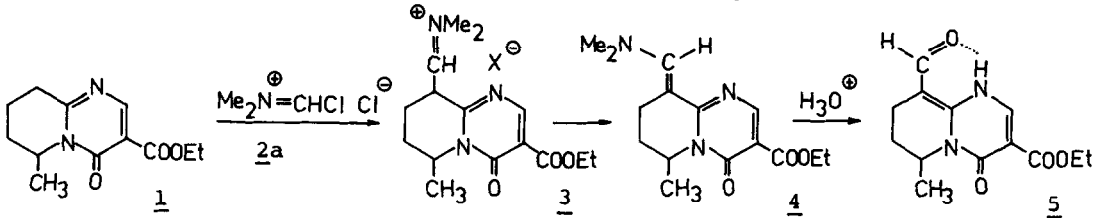
The 9-formyl- and 9-ester derivatives /5,9/ can easily be prepared from the title pyrido [1,2-a] pyrimidine /1/ with iminium chlorides /2a,b/ via the 9-/dimethyl--iminium-methyl/-derivatives /3,6/.

Pyrido [1,2-a] pyrimidines have increasing pharmacological significance[2]. Earlier we reported[3] that the title compound /1/ contains an activated methylene group in the 9-position. This observation offers the possibility of further chemical modification of the parent pyrido-pyrimidines of type 1 introducing different synthones into the 9-position. In this way we aimed to obtain new derivatives,possibly with favourable pharmacological properties.

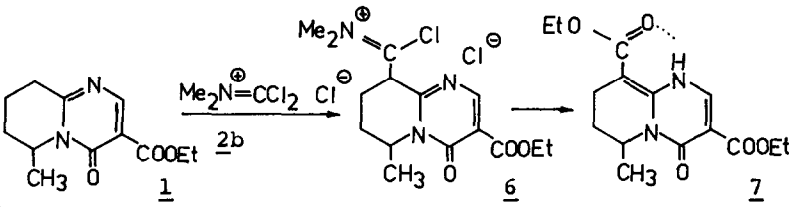
We have investigated the reactivity of the pyrido-pyrimidine /1/ towards iminium-chlorides /2a,b/. 1 with DMF and $COCl_2$ /molar ratio=1:1:1/ gave 3 in boiling anhydrous methylene chloride. Yield 93 %. /X=Cl mp:211°C decomp./ The 9--amino-methylene derivative /4/ was obtained from 3 with aqueous NaOAc. Yield 80%. 4 was also prepared treating 1 /1 mól/ with $POCl_3$ /2 mol/ and DMF /10 mol/ at ambient temperature for 2 hrs; yield 78%. [4 mp:136-7°C /EtOH/; uv /EtOH/: λ_{max} 397 /lgε 4,68/, 299 inf. /3,43/, 275 /3,49/, 230nm /4,23/].



According to ^{1}H-NMR the 9-amino-methylene derivative /4/ exists in $CDCl_3$-DMSO-d_6 only as the E isomer [$\delta_{Me_2N-CH=}$ 8,31ppm, triplett, $^4J_{=CH,C(8)H_2}$=1Hz]. The 6-methyl group is in quasiaxial position /$J_{6e7e} \approx J_{6e7a} \approx$ 3Hz/ because of 1,3-allylic strain[4,5].

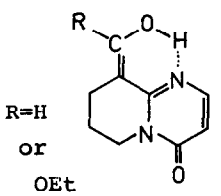
The 9-formyl-derivative /5/ [mp:130-1°C /EtOH/; yield 81%; uv /EtOH/ λ_{max} 358 /lgε4,34/, 315 inf. /3,86/, 265 /3,49/, 223nm /4,20/] was formed from 3 with water or from 4 with 5% aqueous HCl at 50°C.

1 smoothly reacted with phosgen iminium chloride[6] /2b/ in boiling anhydrous methylene chloride affording 6 /mp:181-3°C, yield 97%/.



6 treated with EtOH and NaOAc gave the 9-ester /7/ mp:144-6°C, yield 71%; uv /EtOH/ λ_{max} 335 /lgε 4,11/, 298nm /4,35/ .

Compounds 5 and 7 may exist in three tautomeric forms: enol—imine—enamine.



enol imine enamine

Recently the ethyl 2-methyl-4-oxo--tetrahydro-4H-pyrido [1,2-a] pyrimidine-9-carboxylate[7,8] and the 2-phenyl derivative[8] was found to exist in $CDCl_3$ and in DMSO-d_6 as a 20:80 mixture of the imine--enamine tautomers. With compounds 5 and 7 only the enamine tautomer could be detected in both solvents. The C(2)H proton gave rise to a doublet with $J_{N(1)H-C(2)H}$=5 and 7Hz, for 5 and 7 respectively. The enamine structure is stabilized by strong intramolecular hydrogene bonding /δ_{NH}=14,1ppm for 5 and 11,52ppm for 7/. The 6-methyl group is quasi-axial in both compounds.

These synthones can be useful also for protecting the 9-methylene group of compounds of type 1. The formyl derivative /5/ treated with 5% HCl readily and nearly quantitatively retransforms into the parent 1. The formyl and the ester groups can also be removed by treatment with 5% NaOH, when after acidification the 3-carboxyl derivative of 1 is gained.

^{1}H-NMR Chemical shifts, δppm, /Intensity/ JEOL-PS-100 /in $CDCl_3$-TMS/

Compound	2-H	6-H	7-CH_2	8-CH_2	6-Me	1-NH	=CH-	-OCH_2-	Me	NMe_2
4	8,41s /1H/	5,16m /1H/	1,6-2,05m /2H/	2,7-2,9m /2H/	1,28d /3H/	-	8,19t[a] /1H/	4,31q /2H/	1,39t /3H/	3,25s /6H/
5	8,23d[b] /1H/	5,00m /1H/	1,5-2,10m /2H/	2,4-2,85m /2H/	1,25d /3H/	14,5br /1H/	8,92d[c] /1H/	4,23q /2H/	1,42t /3H/	-
7	8,00d[d] /1H/	5,10m /1H/	1,55-2,1m /2H/	2,45-2,8m /2H/	1,23d /3H	11,52d /1H/		4,26q 4,31q /2x2H/	1,36t 1,40t /2x3H/	-

a/ $^4J_{CH-C(8)H_2} \approx$ 1Hz; b/ $^3J_{C(2)H-N(1)H} \approx$ 5Hz; c/ $^5J_{CH-N(1)H} \approx$ 1Hz; d/ $^3J_{C(2)H-N(1)H} \approx$ 7Hz

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