NITROGEN BRIDGEHEAD COMPOUNDS PART 15[1]. HALOGENATION OF 4-OXO-6,7,8,9-TETRAHYDRO-PYRIDO[1,2-a]PYRIMIDINE-3-CARBOXILIC ACIDS.

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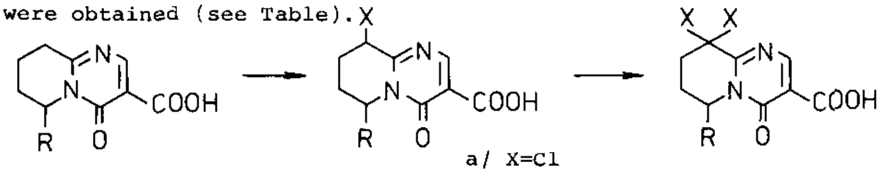
Abstract — 9-Monochloro- and 9,9-dichloro- and bromo-derivatives (3-6) can be prepared from title compounds. Stereochemistry of the halogenation and the product was studied.

As a continuation of our work aiming to introduce[2] different synthones into the reactive 9-position[3] of the 6,7,8,9-tetrahydro-pyrido[1,2-a]pyrimidin-4-ones, now we report the chlorination and bromination of the carboxylic acids 1 and 2 by use of NCS, SO_2Cl_2, NBS and Br_2. We have earlier prepared[4] the 9-bromo-derivative of the ester and the amide of 2, but the stereochemistry was that time not investigated.

The halogenation of 1 and 2 was carried out by treating 0,01 mol of the acid with 1 or 2 molar equivalent of the halogenating agents, i.e. $CHCl_3$ sol. of NCS or NBS in the presence of 0,1 g of benzoyl peroxide at boiling point for 2 hr; or Br_2 in AcOH sol. at 20° C for 0,5 hr; or SO_2Cl_2 in CH_2Cl_2 at boiling point for 4 hr. Depending on the molar ratio, the mono- (3, 4) or dihalogeno-derivatives (5, 6) were obtained (see Table).



1 R=H
2 R=Me

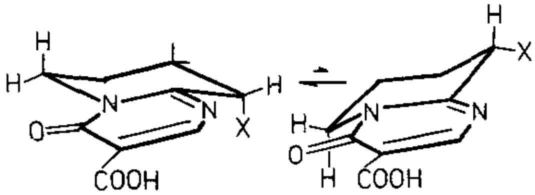
3 R=H
4 R=Me

5 R=H
6 R=Me

Pyrido-pyrimi-dine	Reagent	Mol ratio	Product[5]	Yield %	mp* °C	Pyrido-pyrimi-dine	Reagent	Mol ratio	Product[5]	Yield %	mp* °C
1	NCS	1:1	3a	77	139-40	1	NBS	1:1	3b	60	144-5
1	NCS	1:2	5a	91	159-60	1	NBS	1:2	5b	57	135-7
1	SO_2Cl_2	1:2	5a	80	158-60	1	Br_2	1:1	3b	59	144-5
2	NCS	1:1	4a	77x	130-2+	1	Br_2	1:2	5b	62	136-8
2	NCS	1:2	6a	68	128-9	2	NBS	1:1	4b	78x	151-2+
2	SO_2Cl_2	1:2	6a	70	127-8	2	NBS	1:2	6b	60	148-50
						2	Br_2	1:1	4b	76x	151-3+
						2	Br_2	1:2	6b	80	167-8

* recryst. from EtOH
x a mixture of cis and trans isomers in ratio ca. 1:4
+ m.p. of pure trans isomer

The monohalogeno-derivatives 3a,b may exist in two main conformations (A and B).



Conformer A Conformer B

The couplings between the 9-CH (appearing at δ=5,18t for 3a and 5,34t for 3b) and the 8-CH_2, have small and similar coupling constant values ($J_{8ax,9}\approx J_{8eq,9}\approx$ $\approx$3Hz) which refers to conformation A.

The predominance of conformer A, containing the halogen in axial position, may be explained — by analogy with the 2-halogeno-cyclohexanones[6,7] — by orbital interactions (arising between the occupied $\pi_{C=N}$ and the antibonding σ^{*}_{C-X}, or between the n_X and antibonding $\pi^{*}_{C=N}$ orbitals).

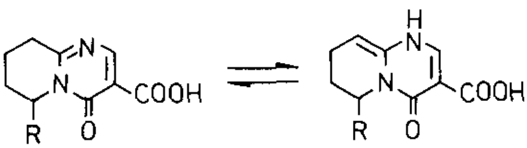
In the spectra of 3a,b the 6-H_{eq} and 6-H_{ax} protons give rise to two sets of multiplets (at δ=4,42; 3,90 for 3a and 4,50; 3,94 ppm for 3b). In the dihalogeno derivatives 5a,b the 6-CH_2 protons give rise to one triplet (at 4,18 and 4,22) which refers to rapid interconversion between the conformers.

In the 6-Me derivatives: 2[8], 4ab and 6ab the 6-Me group occupies quasi-axial position because of the $A^{1,3}$ allylic strain[9] (δ_{6H}=5,05 for 2[8]; 5,06 for 4a; 5,03 for 4b; 5,07 ppm for 6a,b; all multiplets with 1H intensity).

In the spectra of the crude 4a and 4b the two sets of doublets, appearing for the 6-Me group, with intensity ratio 4:1, indicate the presence of diastereomers (δ_{6Me}=1,43 and 1,47 for 4a; 1,48 and 1,68 for 4b). The major diastereomers proved to be the trans 6,9-isomers, which are in the trans diaxial conformation: 4a:δ_{9H}=5,17dd, $J_{8ax,9}$ $J_{8eq,9}$ 3Hz, $J_{6,7ax}\approx J_{6,7eq}\approx$3Hz; 4b:$\delta_{9H}$=5,28dd, $J_{8ax,9}\approx$3,5Hz, $J_{8eq,9}\approx$1,5Hz, $J_{6,7ax}\approx$1,0Hz, $J_{6,7eq}\approx$5,0Hz.

As the 6-Me group is in axial position, the minor diastereomer[10] must be in the cis-6-axial-9-equatorial-form (4a δ_{9H}=3,14m; 4b δ_{9H}=3,30m).

The ratio of the isomers in products 4a,b seems to be independent of the reagent used for the halogenation. The halogenation is therefore supposed to proceed from the enamine tautomeric form of 1,2. Further study is being carried out to get more information about the halogenation of the tetrahydro-pyrido-pyrimidines.



Imine 1,2 Enamine

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^{1}H nmr spectra were recorded in $CDCl_3$ JEOL FX-100 spectrometer

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