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NITROGEN BRIDGEHEAD COMPOUNDS PART 14[1]. ACYLATION OF ETHYL 6-METHYL-4-OXO--6,7,8,9-TETRAHYDRO-PYRIDO(1,2-a)PYRIMIDINE-3-CARBOXILATE WITH ISOCYANATES

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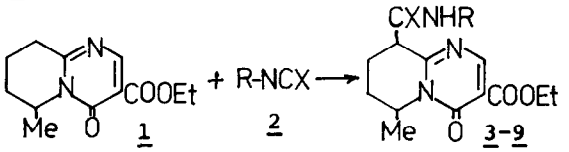
The 9-carbamoyl derivatives /3-9/ can be prepared from title compound /1/ with isocyanates /2/. 3-9 are mixtures of the cis /Z/ and trans /E/ imines and the enamine /e/. The equilibrium depends on the substituents R,X and on the solvent.

In the course of our pharmaceutical research work[2] we aimed to prepare new 6,7,8,9-tetrahydro-pyrido(1,2-a)pyrimidine derivatives by introducing different synthones into the reactive 9-position[3] of the ring. We have previously reported the reaction of the title compound /1/ with iminium chlorides[4].

Now we describe the reaction of 1 with isocyanates /2a-e/ and isothiocyanates /2f,g/ which are known to react with CH acidic compounds[5].



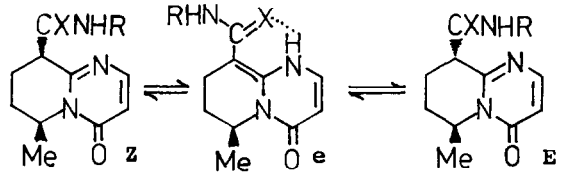
The aryl isocyanates /2a-e/ reacted with 1 at 80-90°C in 4-6 hrs /molar ratio 1:1,1/. The products crystallized on treating with EtOH /see Table 1/. Under similar conditions the alkyl isocyanates and isothiocyanates did not show reaction, even in the presence of tertiary amine catalyst. Using sodium hydride /in anhydrous benzene under argon atmosphere/, to generate the carbanion from the pyridopyrimidine, the isothiocyanates /2f,g/ readily reacted with 1, /at 25°C, in 2 hrs/ and yielded the 9--thiocarbamoyl derivatives 8,9. The sodium salts of 8,9 were precipitated from the reaction mixture with ether, and treated with AcOH.

Table 1.

Isocyanates	Product	R	X	Yield %	mp. °C
2a	3	Ph	O	72	198-9[a]
2b	4	3-Cl-Ph	O	70	193-5[a]
2c	5	4-Cl-Ph	O	81	206-8[a]
2d	6	3,4-Cl_2-Ph	O	78	208-9[a]
2e	7	4-Me-$-C_6H_5-SO_2$	O	72	178-9[b]
2f	8	Ph	S	56	173-5[b]
2g	9	Me	S	52	200-1[a]

recryst. from a/ EtOH; b/ MeCN.

The products 3-9 may exist in three forms: imine /cis and trans/ and enamine



cis imine enamine trans imine

form. Recently some examples have been reported[6] for the imine-enamine tautomerism of tetrahydro-pyridopyrimidines. No report however is to be found on the isomeric Z and E imines. The ^{1}H-NMR spectra of 3,8 and 9 /in $CDCl_3$ and in DMSO-d_6/ exhibit signals showing the presence of each of the above three tautomeric-isomeric forms. In $CDCl_3$ the enamine /stabilized by intramolecular hydrogen bonding/ is the predominant form, while in DMSO-d_6 the imines /Z and E/ predominate. In each form /Z,E,e/ the 6-methyl group is quasi-axial, due to A/1-3/ type allylic strain[6c,7]. Characteristic chemical shifts in DMSO-d_6 and isomeric ratios are presented in Table 2. ^{1}H-NMR signals of the isomeric imines do not allow structural assignament /to the cis or trans imine forms/. We carry on further study for correct assignement.

Table 2. ^{1}H-NMR chemical shifts; δ ppm; /Intensity/ in DMSO-d_6 Brucker WM-250

Compound	2-H	6-H	7-and 8-CH_2	6-Me	1-NH	NH-CO	9-H	R	OCH_2CH_3	Ratio in DMSO	Ratio in $CDCl_3$
3e	8,31d /0,4H/			1,09d /2,4H/	13,86d /0,4H/	8,86s /0,4H/	-	Ph 7,00-7,40 /3H/	4,14q 4,23q	40	92
3E or 3Z	8,32s /0,4H/	4,88m /1H/	1,55-2,80m /4H/	-	-	10,42s /0,4H/	4,1-4,4[a]	7,55-7,65 /2H/	1,23t 1,26t	40	8
	8,46s /0,2H/			1,36d /0,6H/	-	10,36s /0,2H/				20	
8e	?[b]			1,25[c] /?/	15,85d /0,25H/	9,82s /0,25H/	-	Ph 7,20-7,55 /3H/	4,17q 4,25q	25	75
8E or 8Z	8,48s	4,84m /0,55H/ 4,94m /0,45H/	1,60-2,80m /4H/	1,47d /1,65H/	-	12,09s /0,55H/	4,1-4,3[a]	7,75-8,00 /2H/	1,24t 1,26t	55	8
	8,46s			1,14d /0,6H/	-	11,93s /0,2H/	4,67m /0,2H/			20	17
9e										0	70
9E or 9Z	8,43s /1H/	4,80m /0,7H/ 4,92m /0,3H/	1,70-2,60m /4H/	1,43d /2,1H/	-	10,60m /0,7H/	4,1-4,3[a]	Me 3,02 /3H/	4,16q 4,24q	70	20
				1,07d /0,9H/	-	10,38m /0,3H/	4,37m /0,3H/		1,22t 1,26t	30	10

a/ overlap with OCH_2; b/ overlap with Ph /7,75-8,00/; c/ overlap with OCH_2-CH_3.

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