Tetrahedron Letters Vol. 21, pp 2097 - 2100 0040-4039/80/0515-2097$02.00/0

SYNTHESIS OF POLYSUBSTITUTED CIS- AND TRANS-2,5-DIHYDRONICOTINONITRILES

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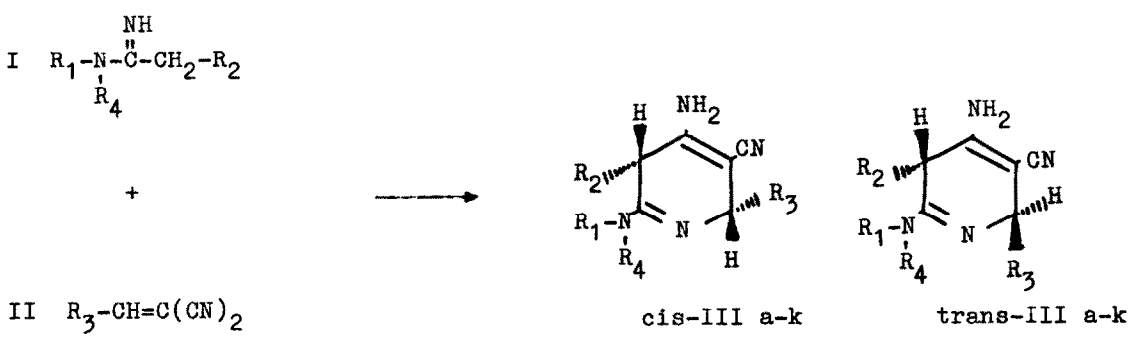
Summary: A method for synthesis of cis- and trans- polysubstituted 2,5-dihydronicotinonitriles III from N,N-disubstituted arylacetamidines I and ylidenemalononitriles II at room temperature in THF is reported.

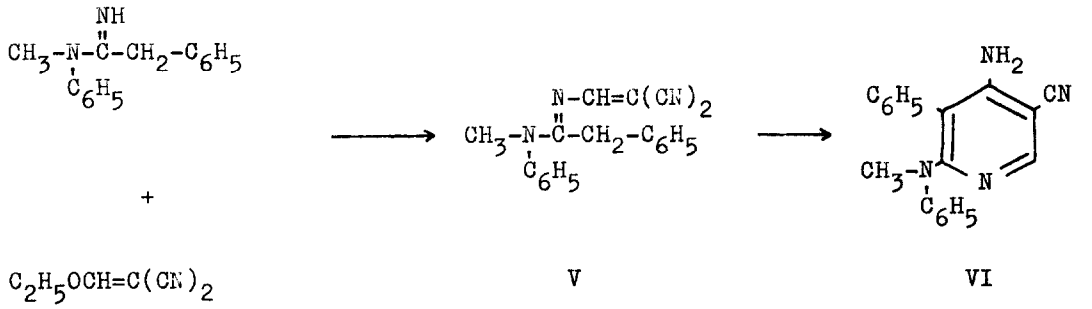
Derivatives of 1,4-dihydropyridine are well studied whereas 2,5-dihydropyridines are almost completely unknown. In the present communication we report the reaction of N,N-disubstituted arylacetamidines I and ylidenemalononitriles II at room temperature in tetrahydrofuran leading to the corresponding 6-(N-alkyl-N-aryl)-amino-4-amino-3-cyano-2,5-diaryl-2,5-dihydropyridines III which we have found to exist in stable cis- and trans- forms



The process goes through N-addition of I to II and a Thorpe cyclisation to III. The structure of III was ascribed on the basis of elemental microana-

lysis, spectral data and chemical behaviour: on boiling for 40-60 hours in toluene with palladised charcoal III underwent aromatisation giving the corresponding 6-(N-alkyl-N-aryl)-4-amino-3-cyano-2,5-diarylpyridines IV [1].

A model compound of IV was synthesised from N-methyl-N-phenyl-phenylacetamidine and ethoxymethylenemalononitrile via N-methyl-N-phenyl-N'-(2,2-dicyanovinyl)-phenylacetamidine V [2] which on boiling in quinoline was converted into 4-amino-3-cyano-6-(N-methyl-N-phenyl)-amino-5-phenylpyridine VI [3]



$C_2H_5OCH=C(CN)_2$ V VI

[5]

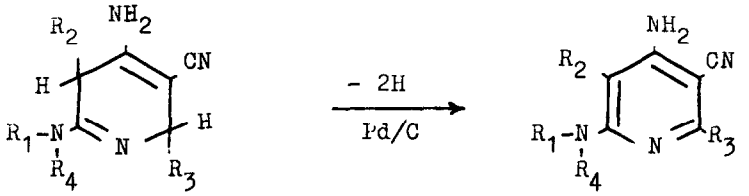
Table 1

	R_1	R_2	R_3	R_4	Cis-III mp C°	Trans-III mp C°	Total yield % (cis/trans
a	C_6H_5	C_6H_5	C_6H_5	C_2H_5	235	156	63(15:13)
b	C_6H_5	C_6H_5	C_6H_5	CH_3	237	157	68(15:10)
c	$2\text{-}CH_3C_6H_4$	C_6H_5	$2\text{-}C_2H_5OC_6H_4$	C_2H_5	179	166	72(26:23)
d	C_6H_5	C_6H_5	$4\text{-}C_6H_5C_6H_4$	CH_3	264	214	75(15:11)
e	$2\text{-}CH_3C_6H_4$	C_6H_5	$2\text{-}CH_3OC_6H_4$	C_2H_5	221	213	65(20:23)
f	C_6H_5	$4\text{-}ClC_6H_4$	C_6H_5	C_2H_5	240	178	77(16:11)
g	C_6H_5	$4\text{-}ClC_6H_4$	$2,4\text{-}(CH_3)_2C_6H_3$	C_2H_5	225	185	58(23:16)
h	C_6H_5	$4\text{-}ClC_6H_4$	$3,4\text{-}CH_2O_2C_6H_3$	C_2H_5	235	152	80(12:15)
i	C_6H_5	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	C_2H_5	233	215	73(18:14)
j	C_6H_5	$1\text{-}C_{10}H_7$	C_6H_5	C_2H_5	241	211	65(19:16)
k	C_6H_5	$4\text{-}ClC_6H_4$	$4\text{-isoPr-}C_6H_4$	C_2H_5	198	182	54(23:19)

The comparison of the UV-spectra of both IV and VI showed close resemblance; on the other hand the UV-spectra of IV and VI are markedly different from the alternative 3-cyano-2,6-diaminated pyridines whose formation might

be conceivable if a C-addition of I to II takes place first [4].

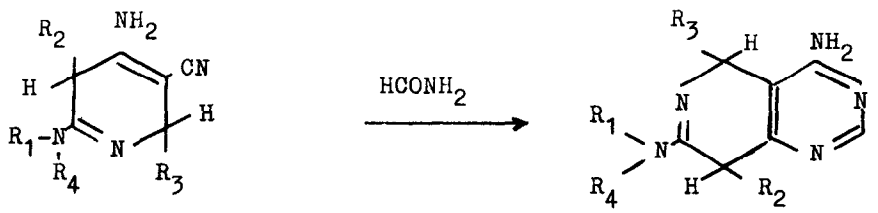
All compounds of type III were isolated in cis- and trans- forms which proved to be easily separable by means of fractional recrystallisation.



III IV

The H-2/H-5 protons in trans-III present ^{1}H nmr absorption maxima at higher fields (IIIa, trans-, 3,25 3,33 ppm) compared with the absorption pattern of the corresponding protons in the cis-forms (IIIa,cis-, 4,13 4,20 ppm) which is to be related to the diamagnetic shielding effect of the aryl groups when they are trans- positioned. Cis-III are readily convertable to trans-III by means of short time heating with acetic acid in ethanol(1:1). Some of trans-III underwent aromatisation on melting but no direct aromatisation of cis-III could be demonstrated under similar conditions which is evidence in favor of a trans-dehydrogenation mechanism during the aromatisation process of the dihydropyridine derivatives III.

When reacted with formamide,III gave 4-amino-7-(N-alkyl-N-aryl)-amino-5,8-diaryl-5,8-dihydropyrido[4,3-d]pyrimidines VII



III VII

In the course of our experiments with IIIf in boiling formamide we have isolated (according to the ^{1}H nmr data) only trans-VIIf irrespective whether the starting substance was cis- or trans-IIIf.

4-Amino-3-cyano-2,5-diphenyl-2,5-dihydro-6-(N-ethyl-N-phenyl)-aminopyridine IIIa. 2,38g(10 mmole) of N-ethyl-N-phenyl-phenylacetamidine Ia [6] and 1,54 g (10 mmole) of benzylidenemalononitrile IIa [7] were dissolved in 12 ml THF

and the reaction mixture was left at room temperature for 3 hours. The formed crystalline precipitate was filtered and washed with ethanol. It melted at 225-230°C and consisted mainly of cis IIIa (^{1}H nmr data showed cis-/trans- ratio to be 68:11). The filtrate was further treated with 5 ml 50% ethanol and after staying overnight an additional crop was collected with mp 145-155°C with cis-/trans- ratio 14:83. Cis-IIIa was purified by recrystallisation from acetonitrile and toluene. mp 234-235°C. UV(ethanol)247(4,30),337(3,94)lmax(log e nm;IR(nujol) 3460,3330,3215(NH),2170(CN) cm^{-1};^{1}H nmr 1,18(t,3H,CH_3)3,89(q,CH_2) 4,13 4,20(H-2,H-5)3,95(s,2H,exch,NH_2)6,50-7,40(m,15H,arom)ppm. Trans-IIIa melted at 154-156(ethanol). UV(ethanol)247(4,31)330(3,96)lmax(log e)nm;IR(nujol) 3475,3315,3210(NH),2170(CN) cm^{-1};^{1}H nmr 1,20(t,3H,CH_3)3,25 3,33(H-2,H-5)3,92 (q,2H,CH_2)4,01(s,2H,exch,NH_2)6,50-7,40(m,15H,arom)ppm. Total yield 2,46g(63%).

4-Amino-5-(4-chlorophenyl)-5,8-dihydro-7-(N-ethyl-N-phenyl)-amino-8-phenylpyrido/4,3-d/pyrimidine, trans-VIIf; mp 297-299°C(DMF);UV(ethanol)249(4,28)276 (4,09)312(4,16)lmax(log e)nm;IR(nujol)3450,3315,3120(NH)cm^{-1};^{1}H nmr 3,71 3,75 (H-5,H-8)4,92(s,2H exch,NH_2)6,75-7,50(m,14H,arom)8,37(s,1H,H-2)ppm.

REFERENCES AND NOTES

1. IVb: mp 182-184°C(toluene/hexane);UV(ethanol)237(4,33)266sh(4,20) 347(4,26) lmax(log e)nm;IR(nujol) 3435,3290,3140(NH),2210(CN) cm^{-1} IVh: mp 236-237°C(acetonitrile); IVk: mp 218-220°C(ethanol).
2. V: mp 116-118°C(ethanol);UV(ethanol)342(4,30)lmax(log e)nm;IR(nujol) 2220(CN) cm^{-1}.
3. VI melted at 172-173°C(toluene/hexane);UV(ethanol)243(4,26)266(4,20) 346(4,24)lmax(log e)nm;IR(nujol)3460,3360,3215(NH),2210(CN) cm^{-1}.
4. S.K.Robev, Heterocycles,(1980) in press.
5. Cis-III/trans-III ratio from ^{1}H nmr data (80 MHz, $\delta^{TMS}_{CDCl_3}$).
6. N,N-Disubstituted arylacetamidines were synthesised by the method of P.Oxley, M.Partridge, W.Short, J.Chem.Soc.(1947)1110.
7. A.J.Fatiady, Synthesis,(1978)178.

(Received in UK 11 March 1980)