^{13}C NMR SPECTRAL AND STEREOCHEMICAL ANALYSIS OF PIPERIDINE DERIVED α-AMINONITRILES

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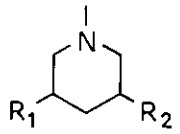
Abstract - Carbon-13 NMR spectra of several α-aminonitriles are reported, along with their preparation via the modified Polonovski reaction or the reductive cyanation of Fry. The substituent effects for the cyano group in the different nitrogen heterocycles were determined and stereochemical conclusions are made.

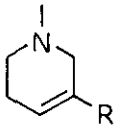
INTRODUCTION

The α-aminonitriles derived from piperidine derivatives have gained considerable attention during recent years, particularly because of their general utility in indole alkaloid synthesis.[1,2] We have recently synthesised the biochemically important isoquinuclidine ring system using α-aminonitriles as starting materials.[3] In connection with this synthetic work, and aware of the lack of ^{13}C NMR data in the literature, we prepared several 3- and/or 5-substituted 2-cyanopiperidines (piperidine derived α-aminonitriles) (compounds 3a-j), and recorded their ^{13}C NMR spectra. The results are listed in Table 1 (vide infra). Furthermore, knowledge of the preferential conformations of these compounds would allow a more accurate understanding of their reactions.

Compounds 3a-j were synthesised via the modified Polonovski reaction.[1,2] For stereochemical examination the corresponding N-methylpiperidines 1a-e were prepared and their ^{13}C NMR spectral data recorded (Table 1). New substituent increments for an axial cyano group in 3- and/or 5-substituted 2-cyanopiperidines (Table 3, vide infra) are reported.

Three corresponding 2-cyanotetrahydropyridines (4a-c) were synthesised via the reductive cyanation method of Fry.[4,5] These cyanotetrahydropyridines were then further reduced to give 2-cyanopiperidines 3a-e (vide supra).





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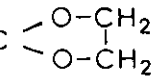
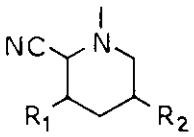
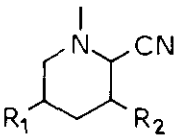
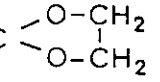
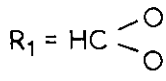
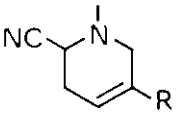
b	R_1=$CH_2CH_2CO_2Me$	R_2=H	b	R=$CH_2CH_2CO_2Me$	
c	R_1=$CH_2CH(CO_2Me)_2$	R_2=H	c	R=$CH_2CH(CO_2Me)_2$	
d	R_1=$CH_2CH(CO_2Me)_2$	R_2=Et			
e	R_1= 	R_2=H			





3a	R_1=Et	R_2=H	3b	R_1=Et	R_2=H
c	R_1=$CH_2CH_2CO_2Me$	R_2=H	d	R_1=$CH_2CH_2CO_2Me$	R_2=H
e	R_1=$CH_2CH(CO_2Me)_2$	R_2=H	f	R_1=$CH_2CH(CO_2Me)_2$	R_2=H
g	R_1=$CH_2CH(CO_2Me)_2$	R_2=Et	h	R_1=$CH_2CH(CO_2Me)_2$	R_2=Et
i	R_1= 	R_2=H	j	R_1= 	R_2=H

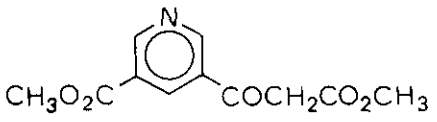


4a R=Et
b R=$CH_2CH_2CO_2Me$
c R=$CH_2CH(CO_2Me)_2$

For stereochemical examination the corresponding tetrahydropyridines 2a-c were prepared and their ^{13}C NMR data recorded (Table 1).

RESULTS AND DISCUSSION

Piperidines 1a-e were prepared from the corresponding pyridinium salts 15a-e by catalytic hydrogenation over PtO_2. The piperidines were then oxidised to the corresponding *N*-oxides, which were subjected to the modified Polonovski reaction conditions[1,2,6,7] followed by cyanide trapping to furnish the α-aminonitriles 3a-j. In most reactions the two possible α-aminonitriles were formed in approximately 1:1 ratio; the substituent in the 3 position of the piperidine ring seems to have some effect on the ratio; see experimental part compounds 3e,f and 3i,j.



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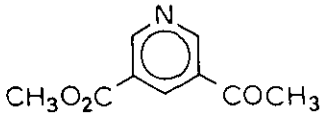

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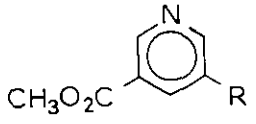

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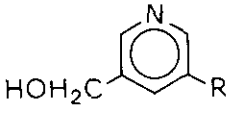

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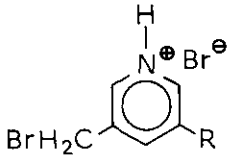

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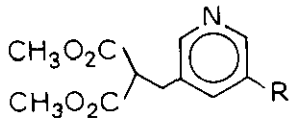

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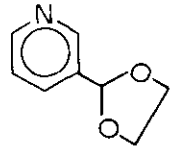

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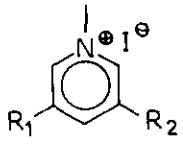


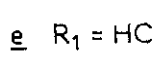
15 a R_1 = Et, R_2 = H
b R_1 = $CH_2CH_2CO_2Me$, R_2 = H
c R_1 = $CH_2CH(CO_2Me)_2$, R_2 = H
d R_1 = $CH_2CH(CO_2Me)_2$, R_2 = Et
e R_1 =  , R_2 = H

Table 1. ^{13}C NMR data of compounds 1-4.

C	1a	1b	1c	1d	1e	2a	2b	2c	4a	4b	4c
2	62.01	61.29	61.59	61.10	56.55	57.40	57.07	56.77	51.10	50.71	50.80
3	37.72	35.26	33.98	33.89	40.19	137.59	135.51	132.16	29.09	28.89	29.20
4	29.87	29.54	29.75	36.56	24.41	117.07	119.08	121.35	113.17	115.45	117.75
5	25.26	24.61	24.93	37.34	24.61	25.91	25.78	25.65	137.79	134.60	132.52
6	56.10	55.78	55.86	61.49	55.91	51.95	51.30	51.30	52.66	52.33	52.51
N-Me	46.43	46.04	46.42	46.04	46.49	45.84	45.65	45.57	43.18	43.31	43.22
CN									116.03	115.80	115.80
$\underline{CO_2}Me$		173.82	169.92(2C)	169.40(2C)			173.30	169.40(2C)		172.98	169.03(2C)
$CO_2\underline{Me}$		51.49	52.34(2C)	52.07(2C)			51.56	52.31(2C)		51.10	52.50(2C)
α-C		31.36	49.09	48.83			32.27	50.26		32.14	50.04
β-C		29.22	33.14	33.18			29.80	33.72		29.09	33.51
$-H\underline{C}\begin{matrix}O\\O\end{matrix}$					105.58						
$\begin{matrix}O-CH_2\\O-\underline{CH_2}\end{matrix}$					64.54(2C)						
$\underline{CH_3}-CH_2-$	11.04			11.04		12.08			11.69		
$CH_3-\underline{CH_2}-$	27.01			26.95		27.73			27.08		

C	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
2	59.67	54.21	59.63	54.00	59.74	54.02	59.37	59.70	55.19	53.96
3	39.87	28.31	37.44	28.03	36.17	28.05	36.13	39.65	42.72	27.60
4	25.97	25.84	25.76	25.76	25.78	25.78	32.55	32.55	20.58	20.58
5	24.48	37.01	24.27	34.71	24.28	33.37	36.78	33.27	23.76	39.61
6	50.32	56.23	50.03	55.93	50.06	55.91	55.86	55.91	50.00	50.97
N-Me	43.83	43.83	43.73	43.73	43.83	43.83	43.75	43.75	43.50	43.83
CN	114.47	115.84	114.20	115.60	114.21	115.47	114.52	114.52	114.20	115.77
$\underline{CO_2}Me$			172.60	173.04	169.21(2C)	168.88(2C)	169.59(2C)	169.59(2C)		
$CO_2\underline{Me}$			51.13	51.13	52.40(2C)	52.40(2C)	52.46(2C)	52.46(2C)		
α-C			30.67	30.63	48.57	48.70	48.70	48.70		
β-C			27.71	28.68	31.69	32.66	31.58	32.55		
$-H\underline{C}\begin{matrix}O\\O\end{matrix}$									103.82	104.80
$\begin{matrix}O-CH_2\\O-\underline{CH_2}\end{matrix}$									64.54(2C)	64.54(2C)
$\underline{CH_3}-CH_2-$	10.84	10.84					10.87	10.87		
$CH_3-\underline{CH_2}-$	25.65	26.62					26.43	25.45		

It can be assumed that the predominant conformation of the piperidine ring is such that the 3-substituent is equatorial in 1a, b, c, e. It is also safe to assume that in the 3,5-disubstituted compound 1d the substituents are cis to each other and occupy equatorial positions in the predominant conformation (same kind of β-effects in the 3,5-disubstituted piperidine as in the 3-substituted piperidines). A diaxial orientation would not be very probable. From this it can be predicted that in compounds 3a-j, too, the 3- and/or 5-substituents are in equatorial positions.

The stereochemistry of the cyano group in compounds 3a-j is somewhat more difficult to determine. Comparing data given in the literature (α-, β-, γ- and δ-effects for the cyano group)[8] with our values (Table 2), the results are somewhat ambiguous. Considering the positive β-effect (+2 - +3) one might justly assume that the cyano group is in equatorial position.[9,10] Yet looking at the α - and γ-effects, particularly the large negative γ-effect, the cyano group would seem to be in axial position.

Table 2. Observed substituent increments for the cyano group

Compound	α	β	γ_{CCC}	γ_{CNC}	δ
3a	-2.34	+2.15	-3.90	-5.78	-0.78
3b	-1.89	+3.05	-4.03	-5.78	-0.71
3c	-1.65	+2.18	-3.78	-5.75	-0.34
3d	-1.78	+3.42	-3.78	-5.36	-0.55
3e	-1.85	+2.19	-3.97	-5.80	-0.65
3f	-1.84	+3.12	-3.97	-5.68	-0.61
3g	-1.73	+2.24	-4.01	-5.63	-0.56
3h	-1.79	+2.31	-4.01	-5.19	-0.62
3i	-1.36	+2.53	-3.83	-5.91	-0.85
3j	-1.95	+2.99	-3.83	-5.58	-0.58
4a	-0.85	+3.18	-3.90	-4.74	-0.20
4b	-0.59	+3.11	-3.63	-4.74	-0.91
4c	-0.50	+3.55	-3.60	-4.26	-0.36
7a	-2.08	+2.15	-4.02	-5.52	-0.78
7b	-1.89	+2.92	-4.02	-5.39	-0.71

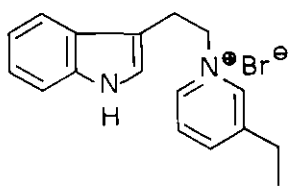
^{1}H NMR spectra of compounds 3a and 3c provide strong evidence that the cyano group is axially oriented in the predominant conformation of the ring. The coupling constants (J = 3.5 Hz) between C-2 and C-3 protons (combined with the assumption that the 3-substituent is equatorial, vide supra) definitively prove that the C-2 proton is equatorially oriented.

As a consequence we conclude that in compounds 3a-j the cyano group is axial in the predominant conformation and that the substituent increments for the cyano group given in the literature can not be used as such for this kind of compounds. Looking again at the values in Table 2, one sees that the α-, β-, γ- and δ-effects are strikingly similar for the different 2-cyanopiperidines. Even for the two indolic compounds 7a and 7b the values are of the same magnitude. Thus new average α-, β-, γ- and δ-effects can be determined for an axial cyano group in 2-cyanopiperidines. We would underline, however, that caution is needed in the application of the present results. Owing to the conformational equilibrium present, the "axiality" of the cyano group varies in the different piperidine derivatives. Moreover, the easy epimerization of the cyano group has to be kept in mind.

Table 3. Average substituent increments for an axial cyano group in 2-cyanopiperidines

α	-2
β	+2 - +3
γ_{CCC}	-4
γ_{CNC}	-5.5
δ	-0.5 - -1

In connection with our conformational study of the 1- and 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizines[11] we synthesised the nitriles 7a and 7b.



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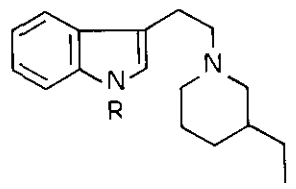
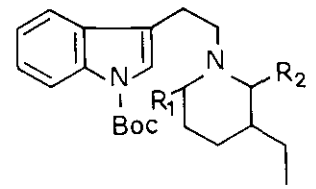


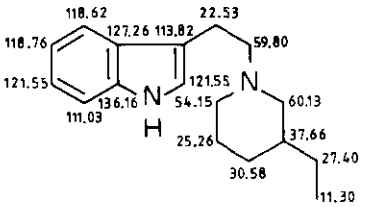
6a R=H
b R=Boc



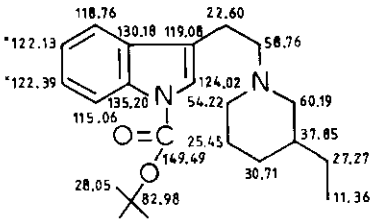
7a R_1=H R_2=CN
b R_1=CN R_2=H

Salt 5 was hydrogenated (PtO_2) to furnish the corresponding piperidine 6a, whose indole N was protected by the t-butyloxycarbonyl (Boc) group (6b).[12] The corresponding N-oxide was subjected to the modified Polonovski reaction conditions followed by cyanide trapping to furnish the nitriles 7a and 7b in 1:1 ratio.

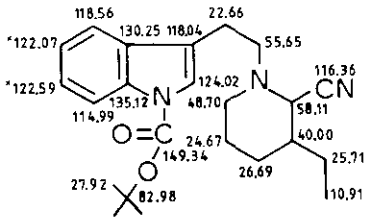
In compound 7a the coupling constant between the C-2 and C-3 protons of the piperidine ring was 3.5 Hz. On the basis of the present results (vide supra) we can assume that the ethyl group in this case is equatorial and the cyano group axial in the predominant conformation. Comparison of the substituent increments for the cyano group with our results above fully confirms our assumption. This indicates further that the stereochemistry in 7b is the same as in 7a.



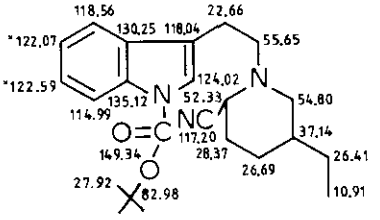
6a



6b



7a



7b

In the second part of this work compounds 4a-c were prepared by the reductive cyanation method ($NaBH_4$, KCN) of Fry.[4,5] The ^{13}C NMR data of these compounds are listed in Table 1. For stereochemical examination compounds 2a-c were prepared by reducing the corresponding pyridinium salts with $NaBH_4$.

We can assume that the ring itself in compounds 4a-c will be in a half-chair conformation which is the more stable one. The cyano group can adopt either axial (pseudoaxial) or equatorial (pseudoequatorial) position. Again the same kind of substituent increments as before will suggest that the cyano group is in axial position in the predominant conformation (vide supra).

The double bond in compounds 4a and 4b was then reduced (PtO_2) to give 3a and 3b, and 3c and 3d (appr. 1:1) respectively, where the cyano group had partly changed its place. The formation of two α-aminonitriles can be explained by the elimination of the cyanide ion followed by isomerisation of the iminium double bond and retrapping of the cyanide ion. Compound 4c yielded 3e as the only α-aminonitrile.

The present results provide valuable data for stereochemical considerations of 2-cyanopiperidines and should allow a more accurate picture of their reactions.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 Spectrophotometer using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. Bands yielding structural information are reported. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS as internal standard δ=0) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS where s, d, t, q and m designate singlet, doublet, triplet, quartet and multiplet, respectively. Coupling constants J are given in Hz. Mass spectrometry was performed on a Jeol JMS-D-100 apparatus and Kratos MS 80 RFA Autoconsole/DS 55 apparatus (high resolution). For column chromatography, Aluminium oxide Merck (act. II-III) and Silica Woelm TSC were used. TLC plates were coated with either Silica gel 60 $PF_{254+366}$ or Aluminium oxide $PF_{254+366}$ both from Merck. Dragendorff-Munier reagent was used to locate reaction components.

Methyl 5-methoxycarbonylacetylnicotinate 8

Sodium (1.8 g) and methanol (34 ml) were reacted to give sodium methoxide. Excess methanol was evaporated and drying was continued at 160-170°C for 2 h in high vacuum. After cooling, dry toluene (24 ml) was added and the mixture shaken thoroughly. Dimethyl 3,5-pyridinedicarboxylate (7.8 g, 40 mmol) and dry methyl acetate (12.7 ml, 161 mmol) were added and the reaction vessel was filled with nitrogen and closed. It was shaken for 2 days at rt. The solid orange mixture was dissolved in H_2O (20 ml) and neutralised with 6N HCl. A pale yellow precipitate was formed, which was filtered and dried. The product was pure ketoester 8. Mp 102°C (mp 102-103°C[13]). More of the desired product was formed by extracting the filtrate with ester. This fraction was contamined with a small amount of the unreacted dicarboxylate. The total yield of compound 8 was about 70%.

Methyl 5-acetylnicotinate 9

Ketoester 8 (4.5 g, 20 mmol) and 2N H_2SO_4 (33 ml) were refluxed for 75 min. The solution was neutralised with solid $NaHCO_3$ and extracted with ether. The organic phase was dried and ether evaporated. The desired product 9 was formed as pale yellow crystals (mp 86-88°C). During the reaction some ketoester 8 was hydrolysed to the corresponding acid. The acidified water phase was evaporated to dryness and methanol presaturated with dry HCl gas was added. More of compound 9 was formed. Y: 69%. IR ($CHCl_3$) 1740 (s) (CO_2CH_3), 1700 (s) (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.65 (3H, s, CH_3CO-), 3.98 (3H, s, CH_3O-), 8.72 (1H, t, J = 2 Hz, C-4-H), 9.28 (1H, d, J = 2 Hz), 9.35 (1H, d, J = 2 Hz). MS m/z 179 (M^+), 164 (100%), 148, 136. Found: C, 60.24; H, 5.00; N, 7.68. Calc. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82.

Methyl 5-ethylnicotinate 10a

Ester 9 (2.4 g, 13.8 mmol) and hydrazine hydrate (2.4 g) were warmed for 15 min on a boiling water bath. After cooling, 9 g of ground potassium hydroxide was added and the mixture was heated at 105-110°C for 1 h. The temperature was briefly allowed to reach 160°C, the mixture was cooled and 1.5 N HCl (20 ml) was added. Heating was continued for 1 h at 140°C. The mixture was made weakly acidic with conc. HCl and evaporated to dryness. MeOH/HCl was added and after the usual workup compound 10a was formed as a pale yellow liquid. Y: 75%. IR ($CHCl_3$) 1730 (CO_2CH_3) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz, $-CH_2\underline{CH_3}$); 2.66 (2H, q, J = 7.5 Hz, $-\underline{CH_2}CH_3$), 3.95 (3H, s, CO_2CH_3), 8.13-9.03 (3H, m, arom. H). MS m/z 165 (M^+), 164, 150, 134 (100%). Found: C, 65.30; H, 6.61; N, 8.32. Calc. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48.

Carbinols 11a and 11b

$LiAlH_4$ (0.90 g) and dry ether (50 ml) were refluxed for 30 min. Ester 10a (1.94 g, 11.8 mmol) in dry ether (20 ml) was added during 20 min to the cooled solution of $LiAlH_4/Et_2O$ (Ar-atm.). Stirring was continued at rt for 4 h. Water was added to destroy the complex. The organic phase was decanted and dried over Na_2SO_4 to give pure carbinol 11a. Y: 81%. ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.5 Hz, $-CH_2\underline{CH_3}$), 2.51 (2H, q, J = 7.5 Hz, $-\underline{CH_2}CH_3$), 4.68 (2H, s, $-\underline{CH_2}OH$), 7.56-8.27 (3H, m, arom. H). MS m/z 137 (M^+) (100%), 136, 119. Found: C, 69.89; H, 7.98; N, 10.02. Calc. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21.

Carbinol 11b was prepared from commercial methyl nicotinate in 85% yield. ^1H NMR ($CDCl_3$) δ 4.66 (2H, s, $-\underline{CH_2}OH$), 7.15-8.45 (4H, m, arom. H). MS m/z 109 (M^+) (100%), 108, 91. Found: C, 66.06; H, 6.40; N, 12.71. Calc. for C_6H_7NO: C, 66.04; H, 6.47; N, 12.84.

Salts 12a and 12b

47% HBr (4.5 ml) and carbinol 11a (0.368 g, 2.69 mmol) were refluxed (135-140°C, Ar-atm.) for 4 h. Water and excess HBr were evaporated under diminished pressure. The skin irritant product was immediately used in the next step. Y: 85%.

Salt 12b was prepared from carbinol 11b as described above. Y: 80%.

Malonates 13a and 13b

Dimethyl malonate (0.657 g, 5 mmol) was added during 45 min to a mixture of NaH (0.120 g, 5 mmol) and 8 ml of DMF (Ar-atm.). Stirring was continued for another 45 min. 12a (0.700 g, 2.5 mmol) in 15 ml DMF was added and stirring was continued for 1 h. The mixture was poured into 100 ml of cold water and extracted several times with CH_2Cl_2. The combined extracts were washed with conc. aq. NaCl and dried over Na_2SO_4. The crude product was purified through a silica column ($CHCl_3$/MeOH, 95:5) to give pure 13a as a yellow oil. Y: 82%. IR ($CHCl_3$) 1750 (s) (CO_2CH_3), 1735 (s) (CO_2CH_3) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 8.0 Hz, $-CH_2\underline{CH_3}$), 2.51 (2H, q, J = 8.0 Hz, $-\underline{CH_2}-CH_3$), 3.26 (2H, d, J = 8.3 Hz, β-C-H), 3.71 (1H, t, J = 8.3 Hz, α-C-H), 3.72 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 7.38 (1H, m), 8.32 (2H, m). MS m/z 251 (M^+). Found: C, 61.99; H, 6.75; N, 5.39. Calc. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57.

13b was prepared from salt 12b as described above. Y: 79%. IR ($CHCl_3$) 1750 (s) (CO_2CH_3), 1730 (s) (CO_2CH_3). ^1H NMR ($CDCl_3$) δ 3.21 (2H, d, J = 8.3 Hz, β-C-H), 3.71 (1H, t, J = 8.3 Hz, α-C-H), 3.72 (3H, s, CO_2CH_3), 3.75 (3H, s, CO_2CH_3), 7.25 (1H, m), 7.58 (1H, m), 8.48 (2H, m). MS m/z 223 (M^+). Found: C, 59.02; H, 5.77; N, 6.05. Calc. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27.

Acetal 14

Pyridine-3-carbaldehyde (0.99 g, 9.25 mmol) was dissolved in 20 ml of benzene. p-Toluenesulphonic acid monohydrate (1.80 g, 9.47 mmol) was added and the mixture was refluxed for 5 min. Redistilled ethylene glycol (0.63 g, 10.16 mmol) was added and refluxing was continued using a Dean and Stark apparatus for 4 h. By this time 0.4 ml of water had separated. The cooled mixture was shaken with 20 ml of 10% Na_2CO_3. Phases were separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4 and evaporated to give 14 as a pale yellow oil. Y: 87%. ^1H NMR ($CDCl_3$) δ 4.08 (4H, t, J = 0.8 Hz), 5.85 (1H, s), 7.19-8.70 (4H, m, arom. H). MS m/z 151 (M^+), 150, 106, 73 (100%). Found: C, 63.40; H, 5.85; N, 9.16. Calc. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27.

N-Methylpyridinium salts 15a-e

Salts 15a-e were prepared from methyl iodide and the corresponding substituted pyridines (3-ethylpyridine (Fluka), methyl azacinnamate[14], 13b, 13a, and 14) in good yields.

1-Methylpiperidine 1a

1-Methyl-3-ethyl pyridinium iodide (1.43 g, 5.74 mmol) was dissolved in 20 ml of MeOH and hydrogenated at rt over PtO_2 (0.10 g) under atmospheric pressure for 20 h. The catalyst was filtered off and MeOH evaporated in vacuo. The residue of 1a·HI was shaken with a saturated $NaHCO_3$ solution and the aqueous layer extracted several times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated to give 1a as a pale yellow oil. Y: 78%. ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s, NCH_3). Found: C, 75.49; H, 13.33; N, 10.81. Calc. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01.

1-Methylpiperidines 1b-e

Compounds 1b-e were prepared similarly to 1a in good yields.

1b. IR ($CHCl_3$) 1730 (s) (CO_2CH_3) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s, NCH_3), 3.66 (3H, s, CO_2CH_3). Found: C, 64.88; H, 10.29; N, 7.40. Calc. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56.

1c. IR ($CHCl_3$) 1750 (s) (CO_2CH_3), 1730 (s) (CO_2CH_3) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s, NCH_3), 3.72 (6H, s, CO_2CH_3). Found: C, 59.09; H, 8.51; N, 5.51. Calc. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76.

1d. IR ($CHCl_3$) 1760 (s) (CO_2CH_3), 1740 (s) (CO_2CH_3) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s, NCH_3), 3.81 (6H, s, CO_2CH_3). Found: C, 61.89; H, 9.10; N, 4.95. Calc. for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16.

1e. ^{1}H NMR ($CDCl_3$) δ 2.26 (3H, s, NCH_3), 3.87 (4H, m), 4.66 (1H, d, 5 Hz). Found: C, 62.97; H, 9.85; N, 7.92. Calc. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18.

1-Methyltetrahydropyridines 2a-c

The corresponding 1-methylpyridine salts were reduced with $NaBH_4$ in good yields.

2a. ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s, NCH_3), 5.50 (1H, br s, C-4-H). Found: C, 76.75; H, 11.94; N, 10.97. Calc. for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19.

2b. IR ($CHCl_3$) 1730 (s) (CO_2CH_3) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s, NCH_3), 3.67 (3H, s, CO_2CH_3), 5.48 (1H, br s, C-4-H). Found: C, 65.31; H, 9.20; N. 7.48. Calc. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64.

2c. IR ($CHCl_3$) 1755 (s) (CO_2CH_3), 1740 (s) (CO_2CH_3) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.35 (3H, s, NCH_3), 3.74 (6H, s, CO_2CH_3), 5.55 (1H, br s, C-4-H). Found: C, 59.81; H, 7.99; N, 5.60. Calc. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81.

Preparation of α-aminonitriles 3a-j using the modified Polonovski reaction

The desired compounds (3a-j) were prepared according to the following procedure, here exemplified by the preparation of 3a and b.

α-Aminonitriles 3a and 3b

Excess 30% H_2O_2 (1 ml) was added to a solution of 1a (0.547 g, 4.31 mmol) in 18 ml 1:1 CH_2Cl_2: MeOH and the resulting solution was stirred at 55°C for 2 days. Excess peroxide was destroyed by the addition of 40 mg 10% Pd/C and stirring at 55°C for 2 h. The mixture was filtered and concentrated. The residue was dissolved in 20 ml of CH_2Cl_2 and dried twice over Na_2SO_4. Filtration, evaporation and final drying in vacuum pump gave the N-oxide of 1a as white crystals (0.502 g, 82%). The N-oxide (0.502 g, 3.51 mmol) was dissolved in 7 ml of dry CH_2Cl_2, cooled to 0°C and stirred under an atmosphere of argon. Trifluoroacetic anhydride (1.2 ml, 8.78 mmol) was added dropwise over a period of 15 min. Stirring was continued at 0°C for 1 h and at rt for 15 min. Then an aqueous solution of KCN (0.342 g, 5.27 mmol) in 2 ml of H_2O was added and the pH of the aqueous layer adjusted to pH 5 by the addition of solid NaOAc. The mixture was stirred at rt for 30 min, basified to pH 10 with 10% aq. Na_2CO_3 and extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated to give a 1:1 mixture of 3a and b. Y: 80% (3a and b). IR ($CHCl_3$) 2240 (w) (CN) (both isomers) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.38 (3H, s, NCH_3) (both isomers), 3.77 (1H, d, J = 3.5 Hz, C-2-H) (3a). MS m/z 152 (M^+), 151, 137, 125, 123, 110 (100%) (both isomers). Found: C, 69.85; H, 10.34; N, 18.18. Calc. for $C_9H_{16}N_2$: C, 71.01; H, 10.59; N, 18.40.

α-Aminonitriles 3c and 3d

Compounds 3c and d were prepared similarly to 3a and 3b in 79% total yield (1:1). IR ($CHCl_2$) 2260 (w) (CN), 1740 (s) (CO_2CH_3) cm^{-1} (both isomers). ^1H NMR ($CDCl_3$) δ 2.38 (3H, s, NCH_3), 3.68 (3H, s, CO_2CH_3) (both isomers), 3.76 (1H, d, J = 3.5 Hz, C-2-H) (3c). MS m/z 210 (M^+), 184, 183, 150, 122, 110 (100%) (both isomers). Found: C, 62.69; H, 8.50; N, 13.09. Calc. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32.

α-Aminonitriles 3e and 3f

Compounds 3e (main compound) and 3f (minor compound) were prepared in 80% total yield (3:1). IR ($CHCl_3$) 2260 (w) (CN), 1755 (s) (CO_2CH_3), 1740 (s) (CO_2CH_3) cm^{-1} (both isomers). ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 3.75 (6H, s) (both isomers). MS m/z 268 (M^+), 242, 241, 122 (100%), 110 (both isomers). Found: C, 57.95; H, 7.39; N, 10.14. Calc. for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44.

α-Aminonitriles 3g and 3h

Compounds 3g and 3h were prepared in 80% total yield (1:1). IR ($CHCl_3$) 2255 (w) (CN), 1755 (s) (CO_2CH_3) cm^{-1} (both isomers). ^1H NMR ($CDCl_3$) δ 2.38 (3H, s, NCH_3), 3.75 (6H, s, CO_2CH_3) (both isomers). MS m/z 296 (M^+), 269, 254, 152 (100%), 138 (both isomers). Found: C, 60.70; H, 7.97; N, 9.30. Calc. for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.15; N, 9.45.

α-Aminonitriles 3i and 3j

Compounds 3i (minor compound) and 3j (main compound) were prepared in 80% total yield (1:3). IR ($CHCl_3$) 2250 (w) (CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.37 (3H, s, NCH_3), 3.88 (4H, m), 4.63 (1H, d, 5 Hz). MS m/z 196 (M^+), 170, 169, 123, 96, 73 (100%) (both isomers). Found: C, 61.01; H, 8.15; N, 14.00. Calc. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27.

Cyanotetrahydropyridine 4a

Hydrochloric acid (6N, 1.65 ml) was added dropwise to a stirred solution of 1.23 g of KCN (18.9 mmol) in 1.6 ml of H_2O, layered with 10 ml of Et_2O, and kept at 0°C. Then 2.5 ml of MeOH and 0.83 g (3.3 mmol) of the corresponding pyridinium salt were added, and 0.139 g (3.63 mmol) of $NaBH_4$ during 0.5 h. The mixture was stirred at rt for 4 h, the Et_2O layer was separated and the aqueous layer was extracted several times with Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give 4a as a yellow oil. The product was contaminated with a small amount of borane.[15] Y: 78%. IR ($CHCl_3$) 2240 (w) (CN), 1670 (w) ($RC{=}CR_2$) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.42 (3H, s, NCH_3), 5.41 (1H, br s, C-4-H). MS m/z 150 (M^+). Found: C, 71.71; H, 9.15; N, 18.39. Calc. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65.

Cyanotetrahydropyridines 4b-c

4b was prepared similarly to 4a in 66% yield. IR ($CHCl_3$) 2240 (w) (CN), 1730 (s) (CO_2CH_3), 1670 (w) ($RC=CR_2$), 840 (s) ($RC=CR_2$) cm^{-1}. ^1H NMR ($CDCl_3$) 2.44 (3H, s, NCH_3), 3.67 (3H, s, CO_2CH_3), 5.49 (1H, br s, C-4-H). MS m/z 208 (M^+). Found: C, 63.31; H, 7.52; N, 13.22. Calc. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45.

4c was prepared similarly to 4a in 77% yield. IR ($CHCl_3$) 2260 (w) (CN), 1760 (s) (CO_2CH_3), 1735 (s) (CO_2CH_3), 1680 (w) ($RC=CR_2$), 840 (s) ($RC=CR_2$) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.43 (3H, s, NCH_3), 3.74 (6H, s, CO_2CH_3), 5.45 (1H, br s, C-4-H). MS m/z 266 (M^+). Found: C, 58.49; H, 6.65; N, 10.28. Calc. for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52.

Preparation of α-aminonitriles 3a-e by reduction of compounds 4a-c

Cyanotetrahydropyridine 4a (0.200 g, 1.33 mmol) was dissolved in 20 ml of MeOH and hydrogenated at rt over PtO_2 (0.180 g) under atmospheric pressure for 4 h to give 3a and 3b (1:1) after purification by TLC. Y: 18%.

3c and 3d were prepared from 4b in 1:1 ratio by the method described for 4a. Y: 15%.

3e was prepared from 4c (3f was not formed). Y: 15%.

All the compounds were identical with those from the modified Polonovski reaction (compounds 3a-e). Moreover, considerable amounts of the corresponding piperidines were formed.[16]

Salt 5 and 1-[2-(3-indolyl)ethyl]-3-ethylpiperidine 6a

Alkylation of 3-ethylpyridine with tryptophyl bromide afforded the corresponding pyridinium salt 5, whose catalytic hydrogenation (PtO_2, 21 h) yielded compound 6a as a semisolid oil. Y: 98%. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 6.0 Hz, $-CH_2\underline{CH_3}$), 1.65 (2H, q, J = 6.0 Hz, $-\underline{CH_2}CH_3$), 6.89 (1H, s, ind.-H-2), 7.17-7.67 (4H, m, arom. H), 8.82 (1H, br s, NH). MS m/z 256 (M^+), 130, 126 (100%). Found: 256.1938 (mass spectrometry). Calc. for $C_{17}H_{24}N_2$: 256.1941.

1-[2-(3-(N-Boc)indolyl)ethyl]-3-ethylpiperidine 6b

50% aq. NaOH (5 ml) was added to compound 6a (0.5 g, 1.95 mmol) in 10 ml of toluene containing tetrabutylammonium hydrogen sulphate (0.2 g). The two phase system was stirred under argon for 15 min. Di-t-butyl dicarbonate (0.89 g, 4.0 mmol) in toluene (5 ml) was then added during 10 min and stirring was continued for another 10 min. The organic layer was separated and the aqueous layer

was washed with CH_2Cl_2 several times. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Y: 92%. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 5.5 Hz, $-CH_2-\underline{CH_3}$), 1.64 (9H, s, $C(CH_3)_3$), 7.41 (1H, s, ind.-H-2). MS m/z 356 (M^+), 341, 143, 130, 127, 126 (100%). Found: 356.0202 (mass spectrometry). Calc. for $C_{22}H_{32}N_2O_2$: 356.0210.

1-[2-(3-(N-Boc)indolyl)ethyl]-2-cyano-3(and 5)ethylpiperidines 7a and 7b

The corresponding N-oxide was readily prepared by reaction of compound 6b (0.80 g) with H_2O_2 (30%, 0.5 ml) in 8 ml of $CHCl_3$-MeOH (1:1) (55°C, 29 h). Excess peroxide was destroyed by the addition of 80 mg of 10% Pd/C and stirring of the mixture for 2 h. The mixture was then filtered and concentrated. CH_2Cl_2 was added and the solution was dried twice over Na_2SO_4 and evaporated to dryness. Y: 82%. The N-oxide was immediately used in the next step. N-Oxide (0.69 g, 1.85 mmol) in 3 ml of dry CH_2Cl_2 was stirred at 0°C (Ar-atm) and TFAA (0.65 ml, 4.63 mmol) was added during 15 min. Stirring was continued for 1 h at 0°C and thereafter 15 min at rt. KCN (0.16 g, 1.15 ekv) in H_2O (5 ml) was added and the pH of the aqueous layer was adjusted to pH 5 by the addition of NaOAc. The mixture was stirred at rt for 0.5 h, basified to pH 10 with 10% aq. Na_2CO_3 and extracted with CH_2Cl_2 several times. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Aminonitriles 7a and 7b were obtained as a mixture (3:2) by purification of the crude product through a short column of alumina (CH_2Cl_2-hexane 4:6). Y: 70%.

7a. ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 6.5 Hz, $-CH_2\underline{CH_3}$), 1.66 (9H, s, $C(CH_3)_3$), 3.92 (1H, br s, -CHCN), 7.46 (1H, s, ind. -H-2). MS m/z 381 (M^+), 354, 189, 151 (100%), 130, 124. Found: 381.2404 (mass spectrometry). Calc. for $C_{23}H_{31}N_3O$: 381.2418.

7b. ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 6.5 Hz, $-CH_2-\underline{CH_3}$), 1.66 (9H, s, $C(CH_3)_3$), 7.46 (1H, s, ind. -H-2). MS m/z 381 (M^+), 354, 189, 151 (100%), 130, 124. Found: 381.2405 (mass spectrometry). Calc. for $C_{23}H_{31}N_3O$: 381.2418.

REFERENCES AND NOTES

1. M. Lounasmaa and A. Koskinen, Heterocycles, 1984, 22, 1591, and references therein.
2. H. Volz, Kontakte (Darmstadt), 1984, (3), 14.
3. M. Lounasmaa, R. Jokela and T. Tamminen (née Ranta), Tetrahedron Lett., 1985, 26, 801.
4. E.M. Fry, J. Org. Chem., 1964, 29, 1647.
5. E.M. Fry and J.A. Beisler, J. Org. Chem., 1970, 35, 2809.
6 A. Koskinen and M. Lounasmaa, Tetrahedron, 1983, 39, 1627.
7. P. Potier, Rev. Latinoamer. Quim., 1978, 9, 47.

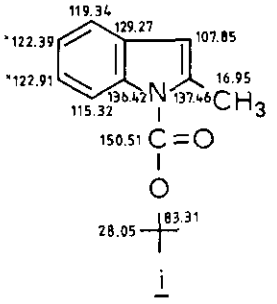
8. F.W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden and Son Ltd, London, 1978.

9. A. Koskinen and M. Lounasmaa, Heterocycles, 1983, 20, 563.

10. The present results indicate, that the earlier conclusions[9] leading to the equatorial preference for the cyano group were premature and should be reconsidered.

11. M. Lounasmaa, R. Jokela and T. Tamminen (née Ranta), Heterocycles, in press.

12. The correct ^{13}C NMR signal assignment for the indolic part of compounds 6a, 6b, 7a and 7b was confirmed by the spectrum of compound i.



i

13. M. Puhakka, Lic. Thesis, University of Oulu, Finland, 1977.

14. E. Wenkert, T. Halls, G. Kunesch, K. Orito, R. Stephens, W. Temple and J. Yadav, J. Am. Chem. Soc., 1979, 101, 5370.

15. M. Feliz, J. Bosch, D. Mauleón, M. Amat and A. Domingo, J. Org. Chem., 1982, 47, 2435.

16. J. Bosch, M. Feliz and M.-L. Bennasar, Tetrahedron, 1984, 40, 1413.

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