

# 183. Structural Factors Affecting the Basicity of $\omega$ -Pyridylalkanols, $\omega$ -Pyridylalkanamides and $\omega$ -Pyridylalkylamines

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(8. VI. 82)

## Summary

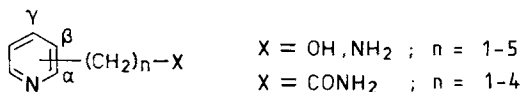
The present paper describes the preparation by conventional methods (when not available commercially) and the  $pK_a$ -determination of the  $\alpha$ -,  $\beta$ - and  $\gamma$ -isomers of pyridylethanamide, 3-pyridylpropanamide, 4-pyridylbutanamide, 5-pyridylpentanamide, pyridylmethanol, 2-pyridylethanol, 3-pyridylpropanol, 4-pyridylbutanol, 5-pyridylpentanol, pyridylmethanamine, 2-pyridylethanamine, 3-pyridylpropanamine, 4-pyridylbutylamine, and 5-pyridylpentylamine. While a field effect accounts for many variations in  $pK_a$  as a function of chain length, marked inductive effects are operative in some methyl and ethyl homologs. The  $pK_a$ -decreasing influence of an intramolecular H-bond is also apparent in some lower homologs belonging to the  $\alpha$ -series.

**1. Introduction.** – Central to QSAR (quantitative structure/activity relationships) methodology is the problem of describing molecular structure in terms of suitable descriptors such as connectivity indices, physicochemical parameters, and substituent constants.

The calculation of the partition coefficient by means of hydrophobic substituent (e.g. [1]) and fragmental constants (e.g. [1–3]), and the use of these constants to express variations in series of congeners, suffer from a number of limitations mainly due to our incomplete understanding of intramolecular interactions [3]. These effects indeed influence, and are in turn influenced by, such molecular properties as hydrophilic/lipophilic balance and ionization.

A thorough investigation of such intramolecular interactions is best undertaken using specifically designed compounds. We have selected a series of analogous, homologous and isomeric  $\omega$ -functionalized alkylpyridines depicted in *Scheme 1*.

Scheme 1. Compounds investigated



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Table 1. Survey of the synthesized compounds with their identification number (see Scheme 1)

	n	X								
		Cl	Br	phth	C≡N	malon	COOEt	CONH <sub>2</sub>	OH	NH <sub>2</sub>
α	1							1		
	2	2			3	8	4	6		
	3						9	10	5	7
	4	13 <sup>a)</sup>			14		15	17	12	11
	5								16	18
β	1							19		
	2							23	20	24
	3	25	33 <sup>b)</sup>	26	28	34	30	32		27
	4						35	37	31	29
	5								36	38
γ	1				39			42		
	2				44		45	46	41	43
	3	47	55 <sup>b)</sup>	48	50	56	52	54		49
	4						57	59	53	51
	5								58	60

a) As hydrochloride. b) As hydrobromide.

These compounds indeed can undergo simple or double protonation, and they are expected to display a number of bonded and non-bonded intramolecular interactions. In particular, an intramolecular H-bond is possible in some cases and sterically precluded in others. The model molecules thus appear as interesting tools

Scheme 2. General synthetic scheme. The first column refers to the number of C-atoms being added to the side-chain; the second column indicates the position of attachment to the ring (R = α-, β- or γ-pyridyl).

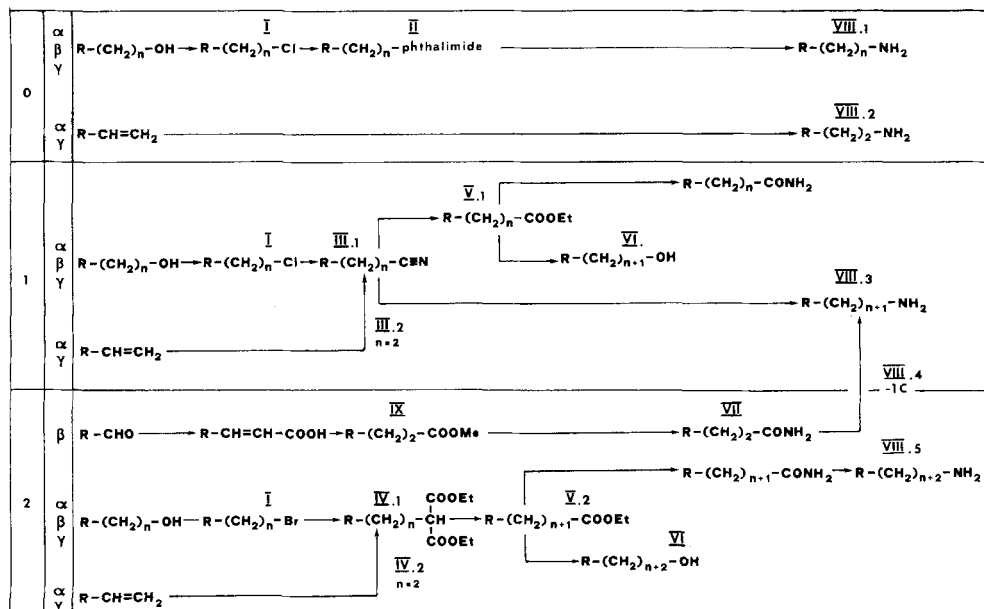


Table 2. Preparation of  $\omega$ -pyridylalkyl halides, phthalimides, cyanides and malonates (see Scheme 2, X = HCl, phthalimid residue, CN, CHCOOCH<sub>3</sub>)

No. <sup>a)</sup>	Name of the compound	From No.	Yield %	M.P. °C or b.p. °C/Torr	<sup>1</sup> H-NMR. (CDCl <sub>3</sub> )	Lit.
47	4-(3-Chloropropyl)pyridine	–	ca. 100		8.53 ( <i>d</i> × <i>d</i> , 2); 7.20 ( <i>d</i> × <i>d</i> , 2); 3.54 ( <i>t</i> , 2); 2.80 ( <i>t</i> , 2); 2.08 ( <i>m</i> , 2)	
2	2-(2-Chloroethyl)pyridine	–	90		8.63 ( <i>m</i> , 1); 7.77 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.24 ( <i>m</i> , 2); 3.90 ( <i>t</i> , 2); 3.21 ( <i>t</i> , 2)	
25	3-(3-Chloropropyl)pyridine	–	ca. 100		8.53 ( <i>m</i> , 2); 7.58 ( <i>m</i> , 1); 7.24 ( <i>d</i> × <i>d</i> , 1); 3.51 ( <i>t</i> , 2); 2.80 ( <i>t</i> , 2); 2.06 ( <i>m</i> , 2)	
13	2-(4-Chlorobutyl)-pyridinium chloride	12	84	81	8.62 ( <i>m</i> , 2); 8.07 ( <i>m</i> , 2); 3.66 ( <i>t</i> , 2); 3.39 ( <i>t</i> , 2); 2.05 ( <i>m</i> , 4)	
55a	4-(3-Bromopropyl)-pyridinium bromide	–	83	124	9.05 ( <i>d</i> , 2); 8.17 ( <i>d</i> , 2); 3.52 ( <i>t</i> , 2); 3.23 ( <i>t</i> , 2); 2.38 ( <i>m</i> , 2)	
33a	3-(3-Bromopropyl)-pyridinium bromide	–	89	108	9.00 ( <i>m</i> , 2); 8.60 ( <i>m</i> , 1); 8.22 ( <i>d</i> × <i>d</i> , 1); 3.50 ( <i>t</i> , 2); 3.17 ( <i>t</i> , 2); 2.33 ( <i>m</i> , 2)	[88]
48	N-[3-(4-Pyridyl)propyl]-phthalimide	47	75	116.5	8.53 ( <i>d</i> × <i>d</i> , 2); 7.82 ( <i>m</i> , 4); 7.20 ( <i>d</i> × <i>d</i> , 2); 3.79 ( <i>t</i> , 2); 2.77 ( <i>t</i> , 2); 2.10 ( <i>m</i> , 2)	
26	N-[3-(3-Pyridyl)propyl]-phthalimide	25	85	91.5	8.50 ( <i>m</i> , 2); 7.82 ( <i>m</i> , 4); 7.64 ( <i>m</i> , 1); 7.25 ( <i>d</i> × <i>d</i> , 1); 3.77 ( <i>t</i> , 2); 2.75 ( <i>t</i> , 2); 2.05 ( <i>m</i> , 2)	
50	4-(4-Pyridyl)butanenitrile	47	72	124/0.02	8.57 ( <i>d</i> × <i>d</i> , 2); 7.20 ( <i>d</i> × <i>d</i> , 2); 2.77 ( <i>t</i> , 2); 2.38 ( <i>m</i> , 2); 1.97 ( <i>m</i> , 2)	
28	4-(3-Pyridyl)butanenitrile	25	75	121/0.18	8.53 ( <i>m</i> , 2); 7.60 ( <i>m</i> , 1); 7.31 ( <i>d</i> × <i>d</i> , 1); 2.80 ( <i>t</i> , 2); 2.40 ( <i>m</i> , 2); 2.00 ( <i>m</i> , 2)	[88–90]
3	3-(2-Pyridyl)propanenitrile	2	69	87/2.0	8.59 ( <i>m</i> , 1); 7.69 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.20 ( <i>m</i> , 2); 2.99 ( <i>m</i> , 4)	[12][72]
39	4-Pyridylacetoneitrile	–	57	74/0.1	8.60 ( <i>d</i> × <i>d</i> , 2); 7.30 ( <i>d</i> × <i>d</i> , 2); 3.82 ( <i>s</i> , 2)	[37]
14	5-(2-Pyridyl)pentanenitrile	13	30	100/0.06	8.54 ( <i>m</i> , 1); 7.62 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.10 ( <i>m</i> , 2); 2.33 ( <i>t</i> , 2); 1.79 ( <i>m</i> , 4)	
44	3-(4-Pyridyl)propanenitrile	–		83/0.06	8.53 ( <i>d</i> × <i>d</i> , 2); 7.19 ( <i>d</i> × <i>d</i> , 2); 2.77 ( <i>m</i> , 4)	
34	Diethyl 3-(3-pyridyl)-propylmalonate	33	65	155/0.2	8.45 ( <i>m</i> , 2); 7.40 ( <i>m</i> , 1); 7.22 ( <i>d</i> × <i>d</i> , 1); 4.17 ( <i>qa</i> , 4); 3.36 ( <i>t</i> , 2); 2.64 ( <i>t</i> , 2); 1.23 ( <i>t</i> , 6)	
56	Diethyl 3-(4-pyridyl)-propylmalonate	55	68	152/0.15	8.54 ( <i>d</i> × <i>d</i> , 2); 7.17 ( <i>d</i> × <i>d</i> , 2); 4.18 ( <i>qa</i> , 4); 3.38 ( <i>t</i> , 1); 2.64 ( <i>t</i> , 2); 1.83 ( <i>m</i> , 4); 1.26 ( <i>t</i> , 6)	
8	Diethyl 2-(2-pyridyl)-ethylmalonate	–	90	138/0.2	8.60 ( <i>m</i> , 1); 7.67 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.19 ( <i>m</i> , 2); 4.20 ( <i>qa</i> , 4); 3.46 ( <i>t</i> , 1); 2.86 ( <i>d</i> × <i>d</i> × <i>d</i> , 2); 2.40 ( <i>m</i> , 2); 1.26 ( <i>t</i> , 6)	[22][70] [91]

for investigating the mutual influence of conformational, lipophilic and ionization factors. In addition, some of these molecules contain pharmacophoric patterns found in nicotinic, histaminergic and antihistaminic agents, and should prove of value in receptor binding studies.

The present paper summarizes the preparation by conventional methods of those compounds not commercially available, and reports a study of  $pK_a$ -values of all isomers and homologs in *Scheme 1*. A detailed study and interpretation of the partitioning behaviour of these compounds has been published [4].

**Synthetic work.** – A number of relevant syntheses have been described starting from picolines [5–25],  $\omega$ -halogenated alkylpyridines [26–44], formylpyridines [42] [43] [45–52], carboxylic acids and their derivatives [10] [41] [53–64], ketones [10] [65–67], and vinylpyridines [23] [68–73]. An extensive survey of this topic has been reported [74]. We have modified and/or lengthened existing and correctly positioned side-chains of pyridines, using available precursors. The synthesized compounds, listed with their identification numbers in *Table 1*, are subsequently referred to by these numbers in *Tables 2–6* which summarize the characteristics of their preparation.

The synthetic routes used are schematically presented in *Scheme 2*.

The Gabriel synthesis has been used [75] for the preparation without chain extension of the primary amines (*Scheme 2*, II and VIII.1; *Table 6*, **27**, **49**). 2-(4-Pyridyl)ethylamine (*Table 6*, **43**) has been obtained from 4-vinylpyridine without chain elongation (*Scheme 2*, VIII.2); the experimental conditions described by *Brady et al.* [69] minimized the formation of symmetrical dimer.

Chain extension by one carbon unit has been achieved by introduction of a cyano group (*Scheme 2*, III.1). The method of *Friedman* [76] (KCN in DMSO) allows much shorter reaction times than the classical conditions (EtOH/H<sub>2</sub>O) (*Table 2*, **3**, **28**, **50**). The halogenated derivatives potentially able to undergo quaternization (4-chloromethyl- and 2-(5-chloropentyl)pyridine) [36] [77–80] reacted as their hydrochlorides (*Table 2*, **39**, **14**). Starting from the nitriles were obtained either the ethyl esters

Table 3. Preparation of  $\omega$ -pyridylalkyl-alkanoates (see *Scheme 1*, X = OOC–R)

No.	Name of the compound	From No.	Yield %	M.p. °C or b.p. °C/Torr	<sup>1</sup> H-NMR. (CDCl <sub>3</sub> )	Lit.
<b>52</b>	<i>Ethyl 4-(4-pyridyl)-butyrate</i>	<b>50</b>	83	113/0.2	8.56 ( <i>d</i> × <i>d</i> , 2); 7.18 ( <i>d</i> × <i>d</i> , 2); 4.12 ( <i>qa</i> , 2); 2.66 ( <i>t</i> , 2); 2.31 ( <i>m</i> , 2); 1.94 ( <i>m</i> , 2); 1.23 ( <i>t</i> , 3)	
<b>30</b>	<i>Ethyl 4-(3-pyridyl)-butyrate</i>	<b>28</b>	76	111/0.2	8.52 ( <i>m</i> , 2); 7.58 ( <i>m</i> , 1); 7.25 ( <i>d</i> × <i>d</i> , 1); 4.10 ( <i>qa</i> , 2); 2.66 ( <i>t</i> , 2); 2.35 ( <i>m</i> , 2); 1.94 ( <i>m</i> , 2); 1.24 ( <i>t</i> , 3)	[89]
<b>45</b>	<i>Ethyl 3-(4-pyridyl)-propionate</i>	<b>44</b>	64	76/0.07	8.48 ( <i>d</i> × <i>d</i> , 2); 7.12 ( <i>d</i> × <i>d</i> , 2); 4.08 ( <i>qa</i> , 2); 2.76 ( <i>m</i> , 4); 1.20 ( <i>t</i> , 3)	
<b>4</b>	<i>Ethyl 3-(2-pyridyl)-propionate</i>	<b>3</b>	83	89/0.2	8.65 ( <i>m</i> , 1); 7.72 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.23 ( <i>m</i> , 2); 4.16 ( <i>qa</i> , 2); 3.00 ( <i>m</i> , 4); 1.22 ( <i>t</i> , 3)	
<b>15</b>	<i>Ethyl 5-(2-pyridyl)-pentanoate</i>	<b>14</b>	69	81/0.05	8.52 ( <i>m</i> , 1); 7.60 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.12 ( <i>m</i> , 2); 4.08 ( <i>qa</i> , 2); 2.80 ( <i>m</i> , 2); 2.32 ( <i>m</i> , 2); 1.74 ( <i>m</i> , 4); 1.20 ( <i>t</i> , 3)	
<b>57</b>	<i>Ethyl 5-(4-pyridyl)-pentanoate</i>	<b>56</b>	96	121/0.18	8.54 ( <i>d</i> × <i>d</i> , 2); 7.17 ( <i>d</i> × <i>d</i> , 2); 4.11 ( <i>qa</i> , 2); 2.62 ( <i>m</i> , 2); 2.29 ( <i>m</i> , 2); 1.67 ( <i>m</i> , 4); 1.23 ( <i>t</i> , 3)	
<b>35</b>	<i>Ethyl 5-(3-pyridyl)-pentanoate</i>	<b>34</b>	93	100/0.08	8.47 ( <i>m</i> , 2); 7.52 ( <i>m</i> , 1); 7.22 ( <i>d</i> × <i>d</i> , 1); 4.10 ( <i>qa</i> , 2); 2.63 ( <i>m</i> , 2); 2.31 ( <i>m</i> , 2); 1.70 ( <i>m</i> , 4); 1.20 ( <i>t</i> , 3)	
<b>9</b>	<i>Ethyl 5-(2-pyridyl)-pentanoate</i>	<b>8</b>	76	105/0.2	8.58 ( <i>m</i> , 1); 7.65 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.15 ( <i>m</i> , 2); 4.13 ( <i>qa</i> , 2); 2.85 ( <i>t</i> , 2); 2.21 ( <i>m</i> , 4); 1.24 ( <i>t</i> , 3)	[79] [92]
<b>40</b>	<i>Ethyl 4-pyridylacetate</i>	<b>39</b>	52	66/0.08	8.54 ( <i>d</i> × <i>d</i> , 2); 7.20 ( <i>d</i> × <i>d</i> , 2); 4.10 ( <i>qa</i> , 2); 3.60 ( <i>s</i> , 2); 1.20 ( <i>t</i> , 3)	[49]
<b>22</b>	<i>Methyl 3-(3-pyridyl)-propionate</i>	<b>21</b>	78	130/10		[49]

Table 4. Preparation of  $\omega$ -pyridylalkanol (see Scheme 1, X = OH)

No.	Name of the compound	From No.	Yield %	B.p. °C/ Torr	<sup>1</sup> H-NMR. (CDCl <sub>3</sub> )	MS.	Lit.
58	5-(4-Pyridyl)-pentanol	57	90	140/0.2	8.51 ( <i>d</i> × <i>d</i> , 2); 7.19 ( <i>d</i> × <i>d</i> , 2); 5.2 (br., 1); 3.62 ( <i>m</i> , 2); 2.63 ( <i>t</i> , 2); 1.58 ( <i>m</i> , 6)	165 (10), 164 (10), 118 (20), 106 (100), 105 (80), 93 (90)	
36	5-(3-Pyridyl)-pentanol	35	90	118/0.2	8.45 ( <i>m</i> , 2); 7.53 ( <i>m</i> , 1); 7.26 ( <i>d</i> × <i>d</i> , 1); 4.4 (br., 1); 3.65 ( <i>t</i> , 2); 2.63 ( <i>t</i> , 2); 1.61 ( <i>m</i> , 6)	166 (10), 164 (10), 106 (100), 93 (60), 92 (60)	
16	5-(2-Pyridyl)-pentanol	15	92	127/0.2	8.51 ( <i>m</i> , 1); 7.61 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.11 ( <i>m</i> , 2); 5.0 (br., 1); 3.62 ( <i>t</i> , 2); 2.81 ( <i>t</i> , 2); 1.64 ( <i>m</i> , 6)	120 (10), 106 (10), 93 (100)	
53	4-(4-Pyridyl)-butanol	32	87	128/0.2	8.49 ( <i>d</i> × <i>d</i> , 2); 7.20 ( <i>d</i> × <i>d</i> , 2); 4.7 (br., 1); 3.66 ( <i>t</i> , 2); 2.62 ( <i>m</i> , 2); 1.67 ( <i>m</i> , 4)	151 (15), 118 (15), 106 (20), 105 (100), 93 (40), 92 (40)	
31	4-(3-Pyridyl)-butanol	30	85	125/0.2	8.45 ( <i>m</i> , 2); 7.57 ( <i>m</i> , 1); 7.24 ( <i>d</i> × <i>d</i> , 1); 5.5 (br., 1); 3.67 ( <i>t</i> , 2); 2.63 ( <i>t</i> , 2); 1.73 ( <i>m</i> , 4)	106 (100), 105 (100), 93 (50), 92 (80)	[92]
12	4-(2-Pyridyl)-butanol	9	92	118/0.2	8.52 ( <i>m</i> , 1); 7.64 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.14 ( <i>m</i> , 4); 5.0 (br., 1); 3.68 ( <i>t</i> , 2); 2.83 ( <i>t</i> , 2); 1.71 ( <i>m</i> , 4)	120 (10), 106 (10), 93 (100)	[25][26]
5	3-(2-Pyridyl)-propanol	4	82	100/0.2	8.55 ( <i>m</i> , 1); 7.69 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.20 ( <i>m</i> , 2); 5.5 (br., 1); 3.75 ( <i>t</i> , 2); 2.98 ( <i>t</i> , 2); 2.00 ( <i>m</i> , 2)	136 (< 5), 120 (5), 106 (10), 93 (100), 79 (20)	
41	2-(4-Pyridyl)-ethanol	40	78	88/0.08	8.34 ( <i>d</i> × <i>d</i> , 2); 7.20 ( <i>d</i> × <i>d</i> , 2); 5.7 (br., 1); 3.82 ( <i>t</i> , 2); 2.82 ( <i>t</i> , 2)	123 (40), 93 (100), 78 (45), 77 (35)	[39][23] [93]
20	2-(3-Pyridyl)-ethanol	-	83	113/0.2	8.42 ( <i>m</i> , 2); 7.69 ( <i>m</i> , 1); 7.26 ( <i>d</i> × <i>d</i> , 1); 6.0 (br., 1); 3.89 ( <i>t</i> , 2); 2.83 ( <i>t</i> , 2)	122 (60), 93 (100), 92 (100)	[49][40] [94]

(Table 3, 4, 15, 30, 40) by alcoholysis (Scheme 2, V.1) or the amines (Table 6, 51, 29, 7) by reduction with LiAlH<sub>4</sub> in ether (Scheme 2, VIII.3).

Chain extension by two C-atoms involves alkylation to **34** and **56** (Table 2) of diethyl malonate by bromides (Table 2, 33, 55) (Scheme 2, IV.1) followed by decarboxylation (Scheme 2, V.2). The classical procedure of decarboxylation calls for diester hydrolysis, thermal decarboxylation, re-esterification of the monoacid, and necessitates the use of strong acids and bases and high temperatures. More direct and less drastic conditions have recently been described [81–86]. The method used here is that of Krapolio & Lovey [87]. By adding a N<sub>2</sub>-flow to eliminate CO<sub>2</sub>, a larger scale synthesis (several tens of grams) becomes possible (Table 3, 9, 35, 57).

In the synthesis of diethyl 2-(2-pyridyl)ethylmalonate (Table 2, 8) (Scheme 2, IV.2) the formation of pyridylethyl ethyl ether resulting from the addition of EtONa to vinylpyridine was decreased by the use of minimal quantities of ethanol. A large excess of diethyl malonate prevents the formation of a dimer in reaction IV.2. The esters (Table 3) were either reduced to alcohols (Table 4) in an ethereal suspension of LiAlH<sub>4</sub> (Scheme 2, VI) or transformed to amides (Table 5) by aminolysis in aqueous-methanolic medium (Scheme 2, VII). The amides (Table 5, 17, 37, 59) given their weak solubility in ether were reduced to amines by using a Soxhlet-extraction method (Scheme 2, VIII.5).

The Hofmann degradation of amides yields amines with a loss of one C-atom; this method was used for the synthesis of 2-(3-pyridyl)ethylamine (Table 6, 24) (Scheme 2, VIII.4). The necessary amide (Table 5, 23) was obtained from 3-formylpyridine by the reaction of Knoevenagel followed by double-bond reduction, esterification (Scheme 2, IX), and aminolysis. Excellent yields at each step justify this relatively long synthetic route.

Table 5. Preparation of  $\omega$ -pyridylalkanamides (see Scheme 1, X = CONH<sub>2</sub>)

No.	Name of the compound	From No.	Yield %	M.p. °C	<sup>1</sup> H-NMR. ((D <sub>6</sub> )DMSO/CDCl <sub>3</sub> )	MS.	Lit.
17	5-(2-Pyridyl)- pentanamide	15	78	73.2	8.54 (m, 1); 7.68 (d × d × d, 1); 7.16 (m, 2); 6.8–7.3 (br., 1); 6.5 (br., 1); 2.76 (m, 2); 2.20 (m, 2); 1.70 (m, 4)	150 (< 5), 134 (< 5), 120 (30), 106 (40), 93 (100)	
37	5-(3-Pyridyl)- pentanamide	35	86	74.5	8.45 (m, 2); 7.53 (m, 1); 7.23 (m, 1); 7.7–6.9 (br., 1); 6.67 (br., 1); 2.57 (m, 2); 1.62 (m, 4)	106 (100), 93 (18), 92 (15)	
59	5-(4-Pyridyl)- pentanamide	57	87	128.1	8.49 (d, 2); 7.22 (d, 2); 7.5–7.0 (br., 1); 6.75 (br., 1); 2.62 (m, 2); 2.19 (m, 2); 1.69 (m, 4)	150 (< 5), 134 (< 5), 120 (20), 106 (100), 93 (15), 92 (10)	
10	4-(2-Pyridyl)- butanamide	9	88	105.2	8.51 (m, 1); 7.66 (d × d × d, 1); 7.1 (m, 2); 7.4–7.0 (br., 1); 6.55 (br., 1); 2.85 (t, 2); 2.12 (m, 4)	120 (30), 106 (100), 93 (100)	
32	4-(3-Pyridyl)- butanamide	30	82	72.6	8.55 (m, 2); 7.65 (m, 1); 7.35 (d × d, 1); 6.47 (br., 2); 2.72 (t, 2); 2.12 (m, 4)	164 (< 5), 106 (100), 93 (18), 92 (10)	
54	4-(4-Pyridyl)- butanamide	52	85	128.1	8.53 (d × d, 2); 7.27 (d × d, 2); 7.5–7.1 (br., 1); 6.8 (br., 1); 2.66 (t, 2); 2.04 (m, 4)	164 (< 5), 163 (< 5), 120 (< 5), 106 (100), 83 (< 5), 82 (10)	
6	3-(2-Pyridyl)- propanamide	4	85	124.8	8.52 (m, 1); 7.64 (d × d × d, 1); 7.20 (m, 2); 8.0–7.0 (br., 1); 6.80 (br., 1); 3.04 (m, 2); 2.63 (m, 2)	150 (< 5), 106 (100), 79 (20)	[12] [95]
23	3-(3-Pyridyl)- propanamide	22	84	117.7	8.50 (m, 2); 7.73 (m, 1); 7.35 (d × d, 1); 7.5–7.3 (br., 1); 6.92 (br., 1); 2.85 (m, 2); 2.46 (m, 2)	150 (60), 106 (100), 104 (80), 93 (50), 92 (80)	
46	3-(4-Pyridyl)- propanamide	45	75	120.5	8.49 (d, 2); 7.30 (d, 2); 7.6–7.1 (br., 1); 6.9 (br., 1); 2.80 (m, 2); 2.40 (m, 2)	150 (80), 120 (< 5), 106 (100)	[14]
1	2-(2-Pyridyl)- ethanamide		75	120.5	8.58 (m, 1); 7.74 (d × d × d, 1); 7.28 (m, 2); 7.5–7.1 (br., 1); 6.9 (br., 1); 3.70 (s, 2)	136 (< 5), 93 (100), 79 (10)	[37]
19	2-(3-Pyridyl)- ethanamide		88	121.5	8.67 (m, 2); 7.93 (m, 1); 7.50 (d × d, 1); 7.7–7.4 (br., 1); 7.05 (br., 1); 3.60 (s, 2)	136 (20), 93 (100), 77 (20)	[37]
4	2-(4-Pyridyl)- ethanamide	40	90	142.5	8.52 (d × d, 2); 7.64 (br., 1); 7.33 (d × d, 2); 7.06 (br., 1); 3.44 (s, 2)	136 (50), 106 (100), 93 (100)	[37]

**Basicity studies.** – All pK<sub>a</sub>-values are presented in Table 7, and as a rule appear in good agreement with literature values. However, a completely meaningful comparison is not always possible since literature values are often extrapolated to I=0 or even refer to an unspecified ionic strength. The pK<sub>a</sub>-values of the basic primary amines range for 8.30 to 10.38 in the pyridylalkylamines as compared to 9.47 to 10.55 in the phenylalkylamines. As regards the pyridyl N-atom, its pK<sub>a</sub>-values are in the range 4.34 to 5.92 in pyridylalkanamides, 4.92 to 6.04 in pyridylalkanols, and 3.50 to 5.99 in pyridylalkylamines.

Plotting these pK<sub>a</sub>-values as a function of the number of CH<sub>2</sub>-groups in the side-chain (Fig. 1–3) allows to visualize the differences, within each series of

Table 6. Preparation of  $\omega$ -pyridylalkylamines (see Scheme 1, X = NH<sub>2</sub>)

No.	Name of the compound	From No.	Yield %	B.p. °C/ Torr	<sup>1</sup> H-NMR. (CDCl <sub>3</sub> )	MS.	Lit.
49	3-(4-Pyridyl)-propylamine	48	90	70/0.06	8.50 ( <i>d</i> × <i>d</i> , 2); 7.14 ( <i>d</i> × <i>d</i> , 2); 2.68 ( <i>m</i> , 4); 1.73 ( <i>m</i> , 2); 1.16 ( <i>s</i> , 2)	107 (100), 106 (100), 53 (10), 80 (50)	
27	3-(3-Pyridyl)-propylamine	26	86	122/0.2	8.45 ( <i>m</i> , 2); 7.52 ( <i>m</i> , 1); 7.19 ( <i>d</i> × <i>d</i> , 1); 2.69 ( <i>m</i> , 4); 1.72 ( <i>m</i> , 2); 1.15 ( <i>s</i> , 2)	120 (60), 107 (80), 106 (100), 93 (50)	[88]
43	2-(4-Pyridyl)-ethylamine	–	50	115/15	8.56 ( <i>d</i> × <i>d</i> , 2); 7.20 ( <i>d</i> × <i>d</i> , 2); 2.82 ( <i>m</i> , 4); 1.19 ( <i>s</i> , 2)	108 (< 5), 107 (< 5), 93 (100), 80 (< 5)	[68] [69]
51	4-(4-Pyridyl)-butylamine	50	90	76/0.05	8.49 ( <i>d</i> × <i>d</i> , 2); 7.10 ( <i>d</i> × <i>d</i> , 2); 2.60 ( <i>m</i> , 4); 1.53 ( <i>m</i> , 4); 1.10 ( <i>s</i> , 2)	150 (5), 107 (10), 106 (10), 93 (100)	
29	4-(3-Pyridyl)-butylamine	28	75	74/0.06	8.45 ( <i>m</i> , 2); 7.48 ( <i>m</i> , 1); 7.18 ( <i>d</i> × <i>d</i> , 1); 2.62 ( <i>m</i> , 4); 1.51 ( <i>m</i> , 4); 1.22 ( <i>s</i> , 2)	134 (20), 107 (35), 106 (36), 93 (100)	[88]
7	3-(2-Pyridyl)-propylamine	3	60	53/0.04	8.52 ( <i>m</i> , 1); 7.58 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.09 ( <i>m</i> , 2); 2.74 ( <i>qa</i> , 4); 1.83 ( <i>qa</i> , 2); 1.14 ( <i>s</i> , 2)	107 (10), 106 (30), 93 (100), 80 (< 5)	
24	2-(3-Pyridyl)-ethylamine	23	68	54/0.06	8.45 ( <i>m</i> , 2); 7.55 ( <i>m</i> , 1); 7.23 ( <i>d</i> × <i>d</i> , 1); 2.83 ( <i>m</i> , 4); 1.18 ( <i>s</i> , 2)	120 (60), 107 (60), 106 (100), 93 (50)	[49] [52] [96] [42] [50]
18	5-(2-Pyridyl)-pentylamine	17	91	75/0.02	8.59 ( <i>m</i> , 1); 7.64 ( <i>d</i> × <i>d</i> × <i>d</i> , 1); 7.14 ( <i>m</i> , 2); 2.74 ( <i>m</i> , 4); 1.62 ( <i>m</i> , 6); 1.13 ( <i>s</i> , 2)	164 (< 5), 150 (< 5), 136 (< 5), 122 (< 5), 107 (100), 93 (100)	
38	5-(3-Pyridyl)-pentylamine	37	92	73/0.05	8.43 ( <i>m</i> , 2); 7.49 ( <i>m</i> , 1); 7.18 ( <i>d</i> × <i>d</i> , 1); 2.60 ( <i>m</i> , 4); 1.49 ( <i>m</i> , 6); 1.13 ( <i>s</i> , 2)	164 (< 5), 134 (21), 107 (26), 106 (100), 95 (23), 93 (38)	
60	5-(4-Pyridyl)-pentylamine	59	94	79/0.05	8.50 ( <i>d</i> × <i>d</i> , 2); 7.12 ( <i>d</i> × <i>d</i> , 2); 2.60 ( <i>m</i> , 4); 1.50 ( <i>m</i> , 6); 1.23 ( <i>s</i> , 2)	164 (5), 100 (100), 93 (30)	
11	4-(2-Pyridyl)-butylamine	10	93	73/0.05	8.44 ( <i>m</i> , 2); 7.50 ( <i>m</i> , 1); 7.19 ( <i>d</i> × <i>d</i> , 2); 2.61 ( <i>m</i> , 4); 1.50 ( <i>m</i> , 6); 1.14 ( <i>s</i> , 2)	150 (< 5), 134 (30), 106 (100), 100 (< 5), 93 (80)	

analogs, between homologs and regioisomers. For the pyridylalkanamides (Fig. 1), the basicity of the  $\beta$ - and  $\gamma$ -isomers shows a parallel variation, with the former consistently less basic by  $0.34 \pm 0.03$  pK<sub>a</sub>-unit. In contrast, the  $\alpha$ -isomers display a distinct behaviour, with the shorter homologs being less basic than their regioisomers, and the higher homologs having intermediate basicity.

In qualitative terms, the same pattern is apparent for pyridylalkanols (Fig. 2), with the  $\beta$ -isomers less basic than the  $\gamma$ -isomers by  $0.33 \pm 0.04$  pK<sub>a</sub>-unit. The  $\alpha$ -isomers behave like the amide analogs, but in a less marked way.

As regards the first protonation step of the pyridylalkylamines (Fig. 3A), these compounds as a whole are less basic than their phenyl analogs (by 0.96 pK<sub>a</sub>-unit for  $n=1$ , 0.52 for  $n=2$ , 0.28 for  $n=3$ , 0.21 for  $n=4$  and  $n=5$ ). Only limited differences appear between the three regioisomeric series, with the basicity usually in the order  $\alpha > \beta > \gamma$ . In the second protonation step (Fig. 3B), a behaviour is apparent in the  $\beta$ - and  $\gamma$ -series which resembles that of the alcohols and amides;

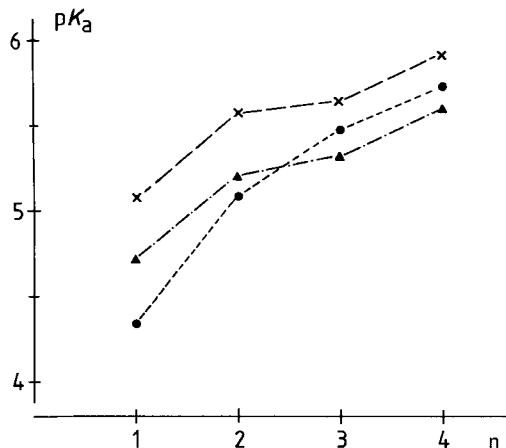


Fig. 1. The  $pK_a$ -values of pyridylalkanamides versus the number  $n$  of  $CH_2$ -groups in the side-chain (---●---  $\alpha$ -series; ---▲---  $\beta$ -series; ---×---  $\gamma$ -series)

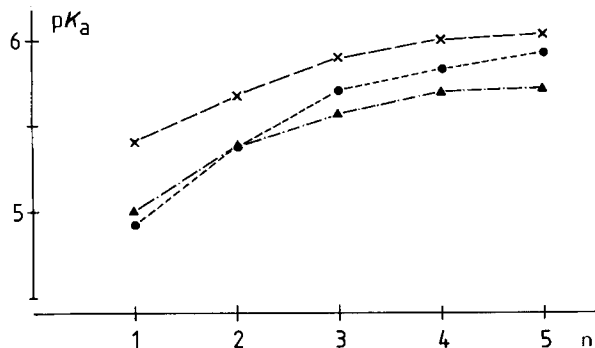


Fig. 2. The  $pK_a$ -values of pyridylalkanols versus the number  $n$  of  $CH_2$ -groups in the side-chain (---●---  $\alpha$ -series; ---▲---  $\beta$ -series; ---×---  $\gamma$ -series)

again the  $\beta$ -isomers are less basic by  $0.33 \pm 0.03$   $pK_a$ -unit than the  $\gamma$ -isomers. The  $\alpha$ -isomers display a deviant behaviour.

It is thus apparent from *Figures 1–3* that the variations of  $pK_a$  as a function of structure show some consistent trends in the series investigated. However, no interpretation can be deduced from *Figures 1–3* as to the nature of the intramolecular interactions underlying these variations.

The influence of polar substituents on a reactive center in a molecule is termed the polar effect and is thought to be transmitted by two modes, namely through the intervening bonds and atoms and through space (or solvent) [105]. For example, *Hoefnagel et al.* [106] have shown that the total effect of a substituent X on the  $pK_a$  of acids  $p\text{-X-C}_6\text{H}_4\text{-(CH}_2\text{)}_n\text{-COOH}$  can indeed be expressed as a function of a field and an inductive effect. In this model, the field effect  $\delta^B$  can be calculated using *Bjerrum's Equation 1* [107], where  $e$ ,  $k$ ,  $T$ ,  $D_E$  and  $r$  are the electric

$$\delta^B = e^2 / 2.3 k T D_E r \quad (1)$$



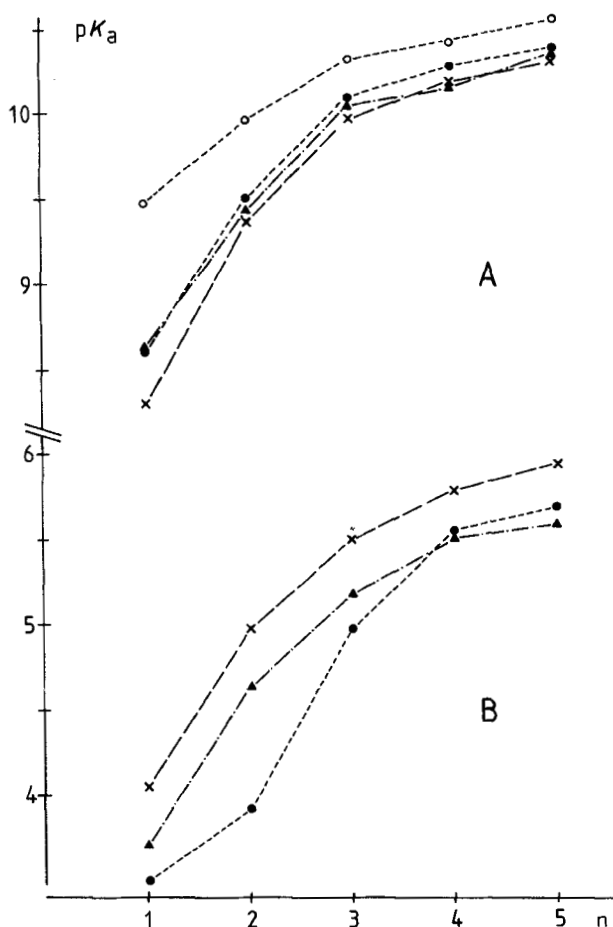


Fig. 3. The  $pK_a$ -values of pyridylalkylamines (same symbols as in Fig. 1) and phenylalkylamines (---○---) versus the number  $n$  of  $CH_2$ -groups in the side-chain. A: first protonation step ( $NH_2$ ); B: second protonation step ( $-N=$ ).

charge, Boltzmann's constant, absolute temperature, effective dielectric constant and direct distance, respectively. The approach of *Hoefnagel et al.* has been challenged [108], and the calculation of  $D_E$  is markedly influenced by the initial parameters [109–111]. For *Grob et al.* [112], the inductive model is merely an 'atomistic description of the role of the dielectric in the field model'. In this approach, plotting  $pK_a$  versus  $1/r$  should yield a linear correlation according to the field model.

We have attempted to plot the basicity of the pyridyl derivatives as a function of the reciprocal distance. The values of  $r$  were measured in *Dreiding* models. The many degrees of conformational freedom of the molecules generate a number of ambiguities in the measurement of  $r$  values. In order to minimize these ambiguities, we have arbitrarily assumed a fully extended conformation of the side-chain, and measured the distance between the functional group (carbonyl C-atom for amides,

Table 7. Apparent  $pK_a$ -values ( $I=0.1$ ;  $25^\circ$ ) of pyridylalkanamides, pyridylalkanols, pyridylalkylamines and phenylalkylamines<sup>a)</sup>

	n				
	1	2	3	4	5
A) Pyridylalkanamides					
$\alpha$	$4.34 \pm 0.03$	$5.09 \pm 0.03$	$5.48 \pm 0.03$	$5.73 \pm 0.03$	
$\beta$	$4.72 \pm 0.03$	$5.21 \pm 0.03$	$5.33 \pm 0.03$	$5.60 \pm 0.03$	
$\gamma$	$5.08 \pm 0.03$	$5.58 \pm 0.03$	$5.64 \pm 0.03$	$5.92 \pm 0.03$	
B) Pyridylalkanols					
$\alpha$	$4.92 \pm 0.03^b)$	$5.37 \pm 0.04^c)$	$5.71 \pm 0.03^d)$	$5.83 \pm 0.03$	$5.93 \pm 0.03$
$\beta$	$5.00 \pm 0.03^c)$	$5.38 \pm 0.03$	$5.57 \pm 0.03^f)$	$5.70 \pm 0.03$	$5.72 \pm 0.03$
$\gamma$	$5.41 \pm 0.03^g)$	$5.68 \pm 0.03^h)$	$5.90 \pm 0.03^i)$	$6.01 \pm 0.04$	$6.04 \pm 0.03$
C) Pyridylalkylamines ( $pK_{a1}$ )					
$\alpha$	$8.60 \pm 0.04^j)$	$9.51 \pm 0.03^k)$	$10.10 \pm 0.05$	$10.30 \pm 0.04$	$10.38 \pm 0.05$
$\beta$	$8.63 \pm 0.05^l)$	$9.44 \pm 0.03^m)$	$10.05 \pm 0.06$	$10.16 \pm 0.06$	$10.34 \pm 0.05$
$\gamma$	$8.30 \pm 0.04$	$9.37 \pm 0.03$	$9.98 \pm 0.04$	$10.18 \pm 0.07$	$10.30 \pm 0.06$
D) Pyridylalkylamines ( $pK_{a2}$ )					
$\alpha$	$3.50 \pm 0.05^j)$	$3.93 \pm 0.04^k)$	$4.98 \pm 0.04$	$5.56 \pm 0.03$	$5.70 \pm 0.03$
$\beta$	$3.71 \pm 0.04^l)$	$4.64 \pm 0.05^m)$	$5.19 \pm 0.03$	$5.52 \pm 0.05$	$5.61 \pm 0.03$
$\gamma$	$4.05 \pm 0.03$	$4.98 \pm 0.06$	$5.51 \pm 0.04$	$5.81 \pm 0.03$	$5.99 \pm 0.03$
E) Phenylalkylamines					
	$9.47 \pm 0.03^n)$	$9.96 \pm 0.03^o)$	$10.32 \pm 0.03^p)$	$10.42 \pm 0.03^q)$	$10.55 \pm 0.03^r)$

<sup>a)</sup> The reported errors are the cumulation of the calibration error ( $\pm 0.02$ ), the standard deviation of 3 determinations, and the error on the slope of the linearized titration curve (0.001–0.01). <sup>b)</sup> [97]: 4.86 (25°). <sup>c)</sup> [97]: 5.31 (25°). <sup>d)</sup> [97]: 5.61 (25°). <sup>e)</sup> [97]: 4.90 (25°). <sup>f)</sup> [97]: 5.47 (25°). <sup>g)</sup> [97]: 5.33 (25°). <sup>h)</sup> [97]: 5.60 (25°). <sup>i)</sup> [97]: 5.84 (25°). <sup>j)</sup> [98]: 8.51 and 3.1 (30°); [99]: 8.57 and 2.14 (25°,  $I=0.1$ ); [100]: 8.79 and 2.04 (20°,  $I=0.1$ ). <sup>k)</sup> [98]: 9.75 and 3.78 (20°); [98]: 9.52 and 3.84 (30°); [101]: 9.52 and 3.80 (25°). <sup>l)</sup> [102]: 8.58 and 3.42 (25°). <sup>m)</sup> [102]: 9.40 and 4.76 (25°). <sup>n)</sup> [103]:  $9.43 \pm 0.13$  ( $n=7$ ) (25°). <sup>o)</sup> [103]:  $9.84 \pm 0.04$  ( $n=5$ ). <sup>p)</sup> [104]: 10.16 (25°). <sup>q)</sup> [104]: 10.36 (25°). <sup>r)</sup> [104]: 10.44 (25°).

O-atom for alcohols, N-atom for amines) and the pyridyl N-atom arbitrarily considered proximal. For the phenylethylamines, the center of the aromatic ring was considered. The measured  $r$  and  $1/r$  values are listed in Table 8.

The reported  $pK_a$ -values depend upon polar effects, as well upon the influence of the C-chain itself. In order to better assess the former influence, a  $\Delta pK_a$  is defined – for the pyridine ring N-protonation:

$$\Delta pK_a = pK_a(n\text{-alkylpyridine}) - pK_a(\text{functionalized pyridine}) \quad (2)$$

– for the  $NH_2$ -protonation:

$$\Delta pK_a = pK_a(n\text{-alkylamine}) - pK_a(\text{arylalkylamine}) \quad (3)$$

Not all necessary  $pK_a$ -values of  $n$ -alkylpyridines are available. Since however these values vary with the position of the side-chain and very little with its length,

Table 8. Distances  $r$  (in Å) and reciprocal distances  $1/r$  (for an explanation see text)

		(CH <sub>2</sub> ) <sub>n</sub>				
		1	2	3	4	5
NH <sub>2</sub> and OH	$\alpha$	2.7	4.2	5.0	6.5	7.4
		0.370	0.238	0.200	0.154	0.135
	$\beta$	4.1	5.5	6.4	7.8	8.7
		0.244	0.182	0.156	0.128	0.115
	$\gamma$	5.1	6.4	7.4	8.8	9.8
		0.196	0.156	0.135	0.114	0.102
CONH <sub>2</sub>	$\alpha$	2.7	4.3	5.1	6.6	
		0.370	0.233	0.196	0.152	
	$\beta$	4.1	5.6	6.4	7.9	
		0.244	0.179	0.156	0.127	
	$\gamma$	5.1	6.5	7.4	8.8	
		0.196	0.154	0.135	0.114	
Phenylethylamines		3.7	5.1	6.1	7.5	8.6
		0.270	0.196	0.164	0.133	0.116

the following  $pK_a$  have been used: 1-(2-pyridyl)-*n*-alkanes  $5.96 \pm 0.03$  ( $n=14$ ); 1-(3-pyridyl)-*n*-alkanes  $5.65 \pm 0.08$  ( $n=10$ ); 1-(4-pyridyl)-*n*-alkanes  $6.02 \pm 0.07$  ( $n=13$ ) [103]. For the *n*-alkylamines, the following  $pK_a$ -values were used: methylamine 10.66; ethylamine 10.68; propylamine 10.72; butylamine 10.63; pentylamine 10.61 [103].

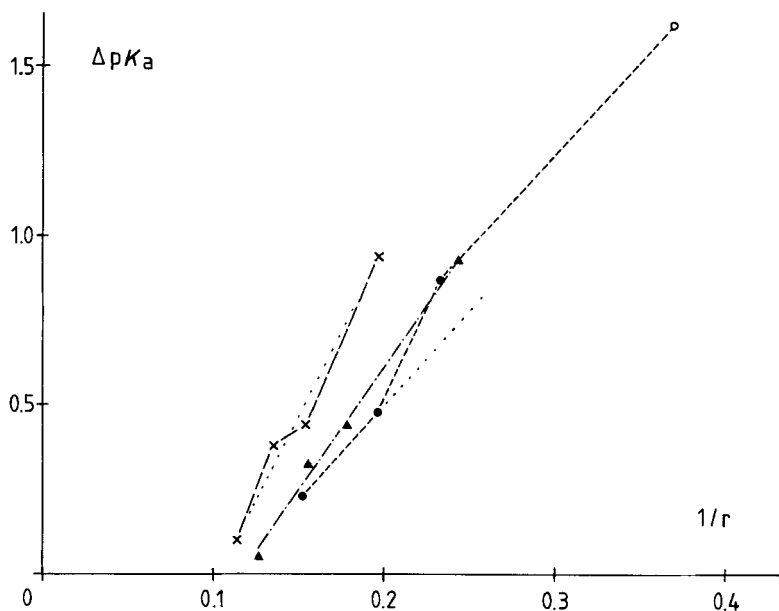


Fig. 4. The  $\Delta pK_a$ -values of pyridylalkanamides (see text) versus the reciprocal distance  $1/r$  (Table 8) (same symbols as in Fig. 1)

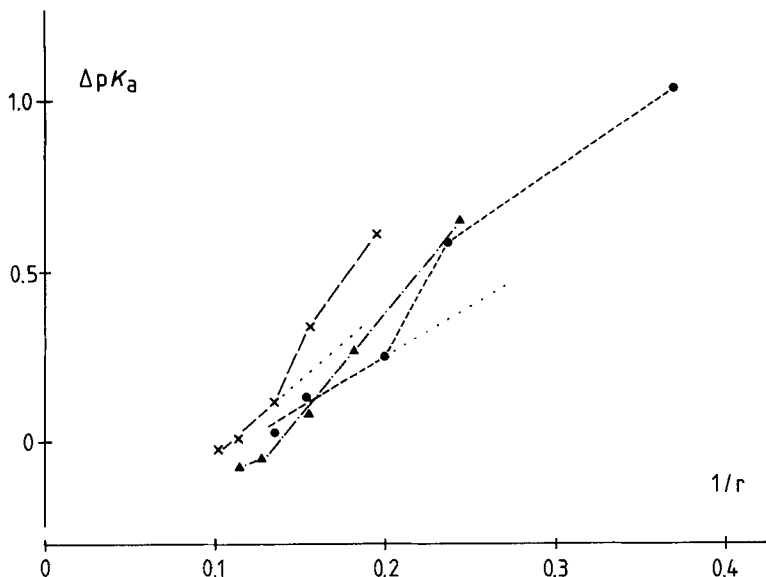


Fig. 5. The  $\Delta pK_a$ -values of pyridylalkanols (see text) versus the reciprocal distance  $1/r$  (Table 8) (same symbols as in Fig. 1)

The plot of  $\Delta pK_a$  versus  $1/r$  for the pyridylalkanamides is shown in Figure 4. In the  $\beta$ -series, the relationship is clearly a linear one ( $R^2=0.995$ ), indicating the absence of perturbative inductive effects. The plot of the  $\gamma$ -series is not revealing; a linear relationship is not conclusively apparent ( $R^2=0.976$ ), nor is an inductive effect apparent in the lower homologs. In the  $\alpha$ -series, (2-pyridyl)ethanamide and 3-(2-pyridyl)propanamide are somewhat less basic than expected on the basis of a pure field effect. Because an inductive effect would also occur in the  $\gamma$ -series, this suggests an intramolecular H-bond (Schemes 3A and 3B) which would decrease the probability of protonation.

The plot of  $\Delta pK_a$  versus  $1/r$  for the pyridylalkanols (Fig. 5) again reveals a linear correlation in the  $\beta$ -series, at least for the four lower homologs ( $R^2=0.997$ ); the case of 5-(3-pyridyl)pentanol is not clear. In contrast to the  $\beta$ -series, the  $\alpha$ - and  $\gamma$ -series have their methyl and ethyl homologs clearly less basic than expected on the basis of a pure field effect. This suggests a marked inductive effect of the OH-group. In addition, the  $pK_a$ -decrease appears somewhat more pronounced in the  $\alpha$ -series, suggesting the influence of an intramolecular H-bond (Schemes 3C and 3D).

The protonation of the  $NH_2$ -group in the arylalkylamines (Fig. 6A) certainly results in a linear correlation for the phenylalkylamines ( $R^2=0.994$ ) but not for the pyridyl derivatives. In the three series, the pyridylmethyamines and (2-pyridyl)-ethylamines point to a marked inductive effect. This effect appears strongest for (2-pyridyl)methylamine, but the similarity in the three series is striking. It is also interesting to note the similarities in  $pK_a$ -variations between the  $\omega$ -pyridylalkylamines (Fig. 6A), the (2-pyridyl)- and (4-pyridyl)alkanols (Fig. 5), and the

(2-pyridyl)alkanamides, despite the fact that the chemical group undergoing protonation differs.

When considering the second protonation step in pyridylalkylamines (Fig. 6B), large differences exist between the  $\alpha$ -series on one side, and the  $\beta$ - and  $\gamma$ -series on the other. Since the proton enters against a positive electrostatic potential, one

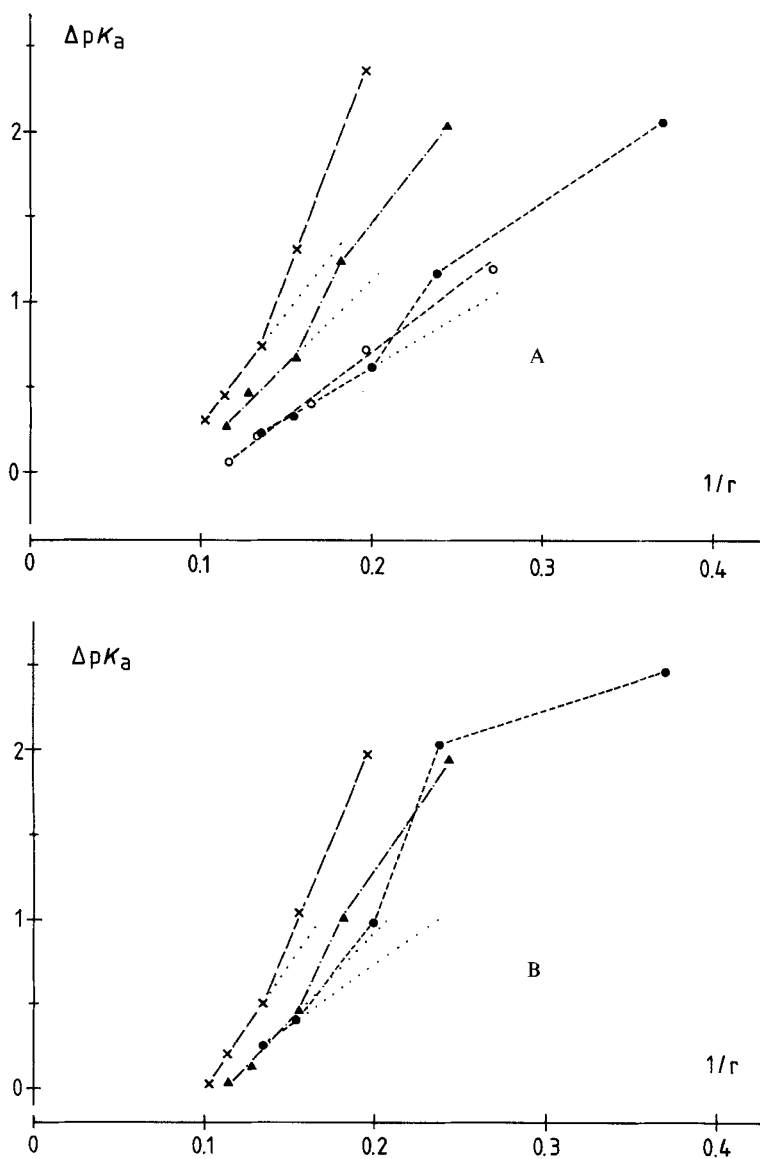
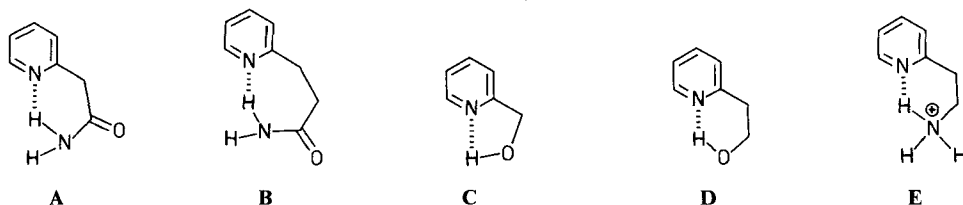


Fig. 6. The  $\Delta pK_a$ -values of pyridylalkylamines and phenylalkylamines (see text) versus the reciprocal distance  $1/r$  (Table 8) (same symbols as in Fig. 3). A: first protonation step ( $NH_2$ ); B: second protonation step ( $-N=$ ).

would expect the  $pK_a$ -variations to be influenced essentially or exclusively by a field effect. This expectation is contradicted by the three plots in *Figure 6B*. In the

Scheme 3. Postulated  $pK_a$ -decreasing intramolecular H-bonds



$\beta$ - and  $\gamma$ -series, the methyl and ethyl homologs appear to experience a perturbation of probable inductive origin. In the  $\alpha$ -series, the  $pK_{a2}$ -value 2-(2-pyridyl)ethylamine is much smaller than expected from its regioisomers (by approximately 0.8  $pK_a$ -unit, see *Fig. 3B*), while the  $pK_{a2}$ -value of (2-pyridyl)methylamine and 3-(2-pyridyl)-propylamine is also somewhat smaller than expected (by approximately 0.2–0.3  $pK_a$ -unit). It is reasonable to postulate that an intramolecular H-bond as shown in *Scheme 3E* acts to decrease the probability of protonation of the pyridine N-atom. This H-bond should be particularly strong in the 2-(2-pyridyl)ethylammonium cation (*Scheme 3E*).

**Conclusion.** – This study suggests that the  $pK_a$  of pyridylalkanamides, pyridylalkanols and pyridylalkylamines is influenced by a number of factors the contribution of which appears very difficult to quantitatively assess. In the context of existing theories [105] [106], and with the serious limitation that the effective distance  $r$  between interacting groups is unknown and must be arbitrarily defined, it appears that three intramolecular factors control the basicity in the investigated compounds. While for the higher homologs a field effect may account for most of the  $pK_a$ -variation, an additional effect of inductive nature is believed to exist in several methyl and ethyl homologs and to decrease their basicity, as seen in (2-pyridyl)- and (4-pyridyl)alkanols, pyridylalkyl-amines and -ammonium cations. In addition, an intramolecular H-bond is suggested to exist in, and to decrease the basicity of, (2-pyridyl)ethane- and -propanamide, (2-pyridyl)methanol and -ethanol, and the (2-pyridyl)methylammonium, -ethylammonium and -propylammonium mono-cations (*Scheme 3*).

The authors are indebted to the *Fonds national suisse de la recherche scientifique* for a grant, and to Dr. P. Seiler, Basle, for his interest and valuable advice.

**Experimental part.** – Melting points (m.p.) and boiling points were determined with a *Mettler FD5+FP51* instrument and are uncorrected. The presence of the correct functional group was checked by IR. spectroscopy, the results are published elsewhere [74]. The NMR. spectra were recorded on a 60 MHz *Varian EM-360* spectrometer; chemical shifts are expressed in ppm relative to TMS (multiplicity, number of protons). The mass spectra were recorded on a *HP 5980A* instrument at 70 eV with a temperature source of 180° ( $m/z$ , rel. intensity in %).

All lower homologs not listed in *Tables 4–6* are commercially available and have been purified by recrystallization or distillation under vacuum before use.

For the determination of  $pK_a$ -values, titration curves have been recorded using the following *Metrohm* equipment: *Dosimat E535*, potentiograph *E536*, combined glass electrode *EA 125*, temperature probe *EA 911-Pt-100*. The temperature was kept at  $25.0 \pm 0.1^\circ$  using a *Heto OIT 623* thermostat. All the water used was  $\text{CO}_2$ -deprived. The base (*ca.*  $7.5 \times 10^{-4} \text{ M}$ ) was titrated with  $\text{HCl}$   $0.01 \text{ N}$  (*Merck*);  $\text{KCl}$  (*pro analysi*, *Merck*) was added to reach a ionic strength of 0.1 at mid-titration.

The  $pK_a$ -values are calculated using the non-logarithmic linearization of the titration curve proposed by *Benet & Goyan* [113] and modified by *Leeson & Brown* [114] to circumvent the problem of dilution during titration. For the titration of a weak base by a strong acid, *Eqn. 4* applies:

$$Z' = B_0 - K_a^s \cdot \frac{Z'}{[H^+]} \quad (4)$$

where  $B_0$  = number of moles of weak base present at the beginning of titration

$K_a^s$  = stoichiometric dissociation constant

$Z' = X - H^+ + OH^-$

where  $X$  (amount of strong acid added),  $H^+$  and  $OH^-$  are in number of moles in solution.

For each titration curve, 15 to 30 points were calculated, and the slope ( $K_a^s$ ) and intercept ( $B_0$ ) in *Eqn. 4* obtained by linear regression. For each compounds, three titration curves were determined. All calculations were performed with a *Diehl Alphantronic* desktop calculator using a program written by *L. Anker* (unpublished). The errors on the  $pK_a$ -values result from the summation of errors on calibration ( $\pm 0.02$ ), of errors on the reading of points on the titration curve (0.001–0.01), and of the S.D. from 3 determinations. An attractive feature of the method is that the initial concentration of base does not need to be known accurately and is not a source of error.

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