Monatshefte für Chemie 115, 1219—1228 (1984)

Monatshefte für Chemie
Chemical Monthly

Selectivity of Hydrogenations. Part 4[1] 6- and 8-Substituted Quinaldines Yield of Tetrahydroderivatives and Basicities of Quinolines

Michael Hönel and **Friedrich W. Vierhapper***

Institut für Organische Chemie, Universität Wien, A-1090 Wien, Austria

(Received 25 July 1984. Accepted 9 August 1984)

Hydrogenation of 6- or 8-*R*-substituted quinaldines [*R* = H, CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, or CF_3] over platinum in trifluoroacetic acid gave higher yields (~ 90%) of 5,6,7,8-tetrahydroderivatives than hydrogenation of the corresponding quinolines. The *pKa*-values of 20 quinolines and quinaldines were determined by measuring the half-neutralization potentials in acetic anhydride. More basic quinolines gave higher yields of 5,6,7,8-tetrahydroproduct; exceptions are 6- and 8-methylquinoline and 8-*tert.* butylquinoline. Explanations for these observations are suggested.

(Keywords: Catalytic hydrogenation; PKa-Values; Quinaldines; Quinolines; 5,6,7,8-Tetrahydroquinolines, yields of)

Selektivität bei Hydrierungen. Teil 4[1]. 6- und 8-substituierte Chinaldine. Ausbeuten an Tetrahydroderivaten und Basizitäten von Chinolinen

Katalytische Hydrierung von 6- oder 8-*R*-substituierten Chinaldinen [*R* = H, CH_3, $CH(CH_3)_2$, $C(CH_3)_3$ oder CF_3] über Platin in Trifluoressigsäure ergab höhere Ausbeuten (~ 90%) an 5,6,7,8-Tetrahydroderivaten als die Hydrierung der entsprechenden Chinoline. Die *pKa*-Werte von 20 Chinolinen und Chinaldinen wurden durch die Messung der Halbneutralisationspotentiale in Essigsäureanhydrid bestimmt. Stärker basische Chinoline gaben höhere Ausbeuten an 5,6,7,8-Tetrahydroprodukten. Ausnahmen sind 6- und 8-Methyl- und 8-*tert.* Butylchinolin. Ein Versuch zur Erklärung der Beobachtungen wird unternommen.

* Dedicated to Prof. Dr. *K. Schlögl* on the occasion of his 60th birthday.

Introduction

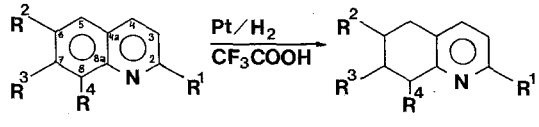
It has been demonstrated that the product distribution of the catalytic hydrogenation of benzenecondensed or -substituted pyridines can be determined by the choice of solvent[1,2]. The predominance of products hydrogenated in the benzene ring in strong acid was found to be quite general; however, if substituents were present in the benzene ring of quinoline (at C-6 or C-8), the ratio of benzene- to pyridine-hydrogenated product was often diminished, methyl substitution causing a reduction, but *tert.* butyl substitution an increase in hydrogenation of the benzene ring[2b].

Replacement of hydrogen by a methyl group at C-2 of quinoline had caused a tangible increase in the (already high) yield of 5,6,7,8-tetrahydro-product (in the sequel: 5,6,7,8-*THP*)[2a]. It was of interest to find out if this effect would also take place with quinolines substituted in the benzene ring, which had given only moderate amounts of 5,6,7,8-*THP* without the C-2 methyl group.

Methyl substitution in the α-position of pyridines is known to cause an increase in the *pKa*-value by a fairly constant increment[3], and substitution of the benzene part of quinolines also changes the basicity, partly because of inductive, and, in case of substitution at C-8, also because of steric reasons. To test for a possible correlation between hydrogenation behaviour (yield of 5,6,7,8-*THP*) and basicity, we determined the *pKa*-values of the quinolines and quinaldines of interest. Some literature values exist, but have been determined over the years by various methods in various solvents[4]. It seemed advisable to measure all values by the same technique. This way, even if the method did not provide absolutely correct values, they could be at least compared with reasonable confidence.

Results

The quinaldines **10**–**18**, and the quinolines **3**, **19** and **20** were hydrogenated in CF_3COOH over platinum at atmospheric pressure at carefully standardized conditions described previously[2b]. Together with these results, the data for corresponding quinolines[2b] are again reported for easy comparison. If yields of 5,6,7,8-*THP*'s were $\ll 90\%$ absolute, they are also reported as relative yields, with $\sum$ 1,2,3,4-*THP* + 5,6,7,8-*THP* = 100%.



1 — 20

The *pKa*-values of the bases were obtained by potentiometric titration in acetic anhydride with perchloric acid (0.1 *N* in acetic acid) and determination of the half-neutralization potentials (*HNP*). A linear correlation between *HNP*'s determined this way, and *pKa*'s (H_2O) over a considerable range of *pKa*-values has been demonstrated[5]. Heterocycles show somewhat large deviations from linearity, a fact that can at least partly be taken care of by the use of mainly heterocyclic compounds as standards.

The method has the advantage of simplicity, and succesful use for the determination of *pKa*'s of quinolines and pyridines has been reported[6]. However, at least in our hands the reproducibility of results was only moderate, although great care was taken to exclude experimental errors. We ascribe this in part to memory affects of the glass electrodes, and have tried to obtain accurate results by repeated titrations, rejecting data differing $\geqslant$ twice the standard deviation from the mean value; nevertheless in our experience the precision of the method is not higher than ± 10 mV (± 0.2 *pK*-units). The values for the 6- and 7-substituted compounds were checked using the *Hammett* equation (see Experimental).

The results are collected in Table 1.

Table 1. *PKa-values and yields of 5,6,7,8-tetrahydroproducts for quinolines and quinaldines*

Substituent R^2-R^4[a]	Quinoline ($R^1=H$) Compd.	*pKa*	5,6,7,8-*THP*, yield (%)[b,c]	Quinaldine ($R^1=CH_3$) Compd.	*pKa*	5,6,7,8-*THP*, yield (%)[b]
–	**1**	5.0	80[d] (93)	**10**	5.8	95
$R^2=CH_3$	**2**	5.2	59[d] (64)	**11**	5.9	91.5
$R^2=CH(CH_3)_2$	**3**	5.2	84.5 (88)	**12**	5.9	>95
$R^2=C(CH_3)_3$	**4**	5.5	86[d]	**13**	6.1	>95
$R^2=CF_3$	**5**	3.5	25[d] (26)	**14**	4.1	93
$R^4=CH_3$	**6**	4.8	51[d] (62)	**15**	5.6	91
$R^4=CH(CH_3)_2$	**7**	4.5	70[d] (88)	**16**	5.1	>95
$R^4=C(CH_3)_3$	**8**	3.4	85[d]	**17**	3.8	>95
$R^4=CF_3$	**9**	1.3	44[d] (61)	**18**	1.9	89
$R^3=CH_3$	**19**	5.3	85			
$R^3=C(CH_3)_3$	**20**	5.3	87			

[a] $R^2-R^4=H$ unless indicated.
[b] Determined by GC from the mixture of products (see Experimental).
[c] Values in parenthesis are yields of 5,6,7,8-tetrahydrocompounds, with total yield of tetrahydrocompounds as 100%.
[d] Data from Ref.[2b].

Discussion

The results in Table 1 show that introduction of a methyl group at C-2 of the quinoline ring system causes

(1) an increase in *pKa* of + 0.5 to + 0.8 *pK*-units. This compares well with data in the literature[3];

(2) an increase in the yield of 5,6,7,8-*THP* over 1,2,3,4-*THP*. Depending on the yield of the 2-H compounds (from **1**–**9**), this increase is between 15 and 65%.

The parallelity between the change in basicity and behaviour towards hydrogenation is likely to be not just coincidental. Based on the results of our earlier experiments[1,2], we had tried to show that the change in product distribution of hydrogenation of phenyl- and benzopyridines with the solvent must depend on at least two factors taking effect simultaneously:

(a) passivation of the pyridine ring by the high concentrations of strong acid (molar amounts of acid cause an activation[7]), and

(b) activation of the benzene part of the molecules.

We have rationalized term (a) with an increase of solvatization with rising concentration of acid[2b]. It seems likely that reducible acid-base pairs ($Qu \cdot H^+ - - - TFA^-$) are replaced by entities with higher ratios of *TFA*/quinoline, like the homoconjugate $Qu \cdot H^+ \cdots TFA^- \cdots H\text{-}TFA$ involving two molecules of acid[8,*]. These must be once more resistant towards hydrogenation of the pyridine moiety. Any factor making the quinoline more basic will then make the ion-paired TFA^- more basic (the hydrogen bond from the quinolinium ion being weaker) and hence favor the formation of acid-bound homoconjugates.

This hypothesis finds support by the results of hydrogenation of the quinoline and quinaldine series. The latter is less straightforward to interpret, because the yields of 5,6,7,8-*THP* are generally high. A linear correlation between *pKa*'s and yields of 5,6,7,8-*THP*'s could not be expected, since passivation of the pyridine moiety is only one of the factors influencing the hydrogenation behaviour, and *pKa* values measured in acetic anhydride are likely to correlate poorly with reaction yields obtained in strong acids. There is however a general trend: more basic quinoline – higher yield of 5,6,7,8-*THP*, with three notable exceptions (**2**, **6** and **8**).

The 6- and 8-methylquinolines (**2** and **6**) with *pKa*-values rather close* to the unsubstituted quinoline **1** show palpably reduced yields of 5,6,7,8-*THP*. It is interesting to note that 7-methylquinoline (**19**) with a *pKa*-value

---

* Since the hydrogenation behaviour changes in an identical manner for the quaternary *N*-methylquinolinium salts[1], other structures must also take part, but the principle will be the same.

not very different* from either **1** or **2** and **6** shows "normal" hydrogenation behaviour. The slightly higher *pKa* of this base has been rationalized[9b] by hyperconjugation superimposed on the inductive effect of the methyl substituent; hyperconjugation can increase the charge density at N in **19**, but not in **2** or **6**. A hyperconjugation phenomenon is probably the cause of the reduced yield of 5,6,7,8-*THP* in **2** and **6**. Since the yields are actually smaller than for **1**, it is not change caused in the pyridine, but a diminished activation of the benzene moiety [term (b); vide supra]. Support for this hypothesis comes from the result that for both **2** and **6** comparatively large (12%) amounts of starting material are found among the reaction products[2b]. Maybe the increase in charge density at the positions of the benzene ring influenced by the hyperconjugation of the 6- and 8-methyl groups disturbs the activating action of the acid.

The second exception is the 8-*tert.* butylquinoline, with a drastically reduced basicity, but with a very high yield of 5,6,7,8-*THP*. The cause for the low *pKa* is purely steric; the situation is similar to the much investigated 2,6-di-*tert.* butylpyridine[10], which has a ΔpKa to pyridine of -0.8, while on the basis of additivity of inductive effects it should be $+0.6$[10a]. Similarly, the ΔpKa for **8** (or **17**) compared to **1** (or **10**) is -1.6 (or -2.0, respectively). The size of the effect is understandable if *Dreiding* models of **8** and 2,6-di-*tert.* butylpyridine are compared. In optimally staggered conformations the distance of the nearest *tert* butylhydrogen to a proton on N is 0.6 Å shorter in **8**. Experimental evidence for the extreme steric hindrance was also found in attempts of N-methylation of **8**, where very forcing conditions had to be used[1].

Our argument why the diminution in *pKa* in **8** does not find a parallel in the yield of 5,6,7,8-*THP* (contrary to the situation in the CF_3-substituted compounds **5** and **9**) is as follows. The strong steric hindrance of the reaction of **8** with acid, similar to 2,6-di-*tert.* butylquinoline**, makes it a weaker basre. However, once the (hydrogenation-activating) protonation of the base has been forced by the high concentration of acid, the next step causing passivation of the pyridine (f.i. formation of homoconjugates with additional *TFA*) is no longer influenced by steric hindrance. The inductive effect of the *tert* butyl group leads to increased electron density at nitrogen (2,6-di-*tert.* butylpyridine is a stronger base than pyridine in the gas phase[10c]) so that the associates with the additional *TFA* will have higher stabilities than the ones for **5** or **9**, and stabilization

---

* See also the *pKa*-values reported by *Knight* et al.[9]: **1**, 4.79; **2**, 4.99; **6**, 4.75; **19**, 5.13.

** There has been some discussion if the low *pKa* of 2,6-di-*tert.* butylpyridine is caused by strain in the N^+-H bond, or by hindrance toward solvatization of the salt. Evidence exists now that the latter cause is at least the predominant one.

of the pyridine of 8-*tert.* butylquinolines will be equal to the 6-*tert.* butyl analogs in spite of the low *pKa*.

Finally, we want to emphasize that we do not want to overinterprete our data into a correlation basicity vs. product yield that does not exist, but that the observed parallelity agrees with the concept developed to explain the change in the yields of the hydrogenation products with the acidity of the solvent. Further insight into this phenomenon may be gained if not only the product distribution, but also the relative stabilities of the quinolines depending on their substituents will be available. Experiments to obtain this information are under way.

Acknowledgement

The authors are grateful to Mr. *W. Müller* for carrying out numerous potentiometric titrations. Financial support came from the *Fonds zur Förderung der Wissenschaftlichen Forschung*, Projects 3241 and 5155.

Experimental

Gas chromatography, melting point determinations and NMR-spectra were carried out or determined with the equipment previously described[1,2b]. Elemental (C, H) analysis were carried out by Dr. *J. Zak*, Institute of Physical Chemistry, Univ. Wien. All new compounds gave satisfactory elemental analysis.

Starting Materials. Synthesis and hydrogenation of quinolines **1**, **2**, and **4**–**9** has been previously reported[2]. 6-Isopropylquinoline[11] (**3**) was synthesized from 4-isopropylaniline by a standard *Skraup* procedure[2b] with As_2O_5 as oxidans.

For the synthesis of 7-methylquinoline[12] (**19**) and 7-*tert.* butylquinoline (**20**) *o*-nitrophenol and boric acid was used as suggested by *Manske* et al.[12]. Yields with this procedure were incomparably better.

7-Methylquinoline[12] (**19**)

m-Toluidine (120 g) was reacted by the procedure for 7-ethylquinoline[12]. Following steam distillation a mixture of *m*-toluidine (13.5%), 7-methylquinoline (64.5%) and 5-methylquinoline (22%) was obtained. The unreacted toluidine was separated after acetylation[2b] and the mixture of 5- and 7-methylquinoline was separated by repeated distillation on a spinning band column. Boiling point **19** 116°/10 mm. The product crystallized and could be recrystallized from ethanol at low temperature; m.p. 36° (lit.[13]: 39°). Boiling point 5-methylquinoline 122°/10 mm; crystallized in freezer (lit. m.p.[13]: 19°).

7-tert. Butylquinoline (**20**)

From 3-*tert.* butylaniline[14] by the above[12] procedure. Product mixture: 96% **20**, 4% 7-*tert.* butyl-1,2,3,4-tetrahydroquinoline. After separation of the byproduct via acetylation **20** was purified by distillation on a spinning band column; b.p. 145°/10 mm. The product crystallized, m.p. 56°. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-2, 8.30 (dd, 4.4, 1.8); H-8, 8.17 (s); H-4, 8.07 (dd, 9, 1.8); H-5, H-6, 7.67; H-3, 7.28 (dd, 9, 4.4); CH_3-butyl 1.4 (s).

Quinaldines **10–18**

10–18 were synthesized by a modified *Doebner-Miller* procedure[15]. Compounds **10**[12], **11**[12], **12**[16], **13**[16], **14**[17], **15**[12], **16**[18], and **17**[19] have been previously described. Melting points or melting points of picrates are given below if the data were not accessible.

12: Picrate, m.p. 165.5–166.5° (ethanol).

13: M.p. 25°.

16: Picrate, m.p. 154–155.5° (ethanol).

18: From *o*-trifluoromethylaniline (EMKA-Chemie) and acetaldehyde[15] in 20% yield. M.p. 52–54° (ethanol). ^{1}H-NMR ($CDCl_3$) δ (*J*): H-4, 8.13 (d, 9); H-5, H-6, H-7, 8.2–7.5; H-3, 7.50 (d, 9); CH_3-2, 2.81 (s).

Hydrogenations in CF_3COOH

These were carried out with the apparatus and reagents, and by the procedure previously reported[2b]. The product composition was determined by GC following total distillation in a Kugelrohr apparatus at reduced pressure. The 5,6,7,8-*THP*'s were isolated after acetylation of secondary amines, and purified by distillation and (where applicable) recrystallization. The 1,2,3,4-tetrahydroproducts were prepared by hydrogenation of the parent quinolines or quinaldines in methanol over platinum[2b] if needed for comparison purposes.

5,6,7,8-Tetrahydroproducts

The compounds derived from **1**, **2**, **4—10**, **15** and **17** have been characterized before [2,19]. The synthesis of 5,6,7,8-tetrahydro-7-methylquinoline has also been reported[20]. The ^{1}H-NMR spectra and the melting points of the remaining compounds (or m.p.'s of picrates) are listed below.

7-*tert.* Butyl-5,6,7,8-tetrahydroquinoline. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-2, 8.43 (dd, 4.8, 1.8); H-4, 7.40 (dd, 8, 1.8); H-3, 6.08 (dd, 8, 4.8); H-5, 6,7, 8, 3.4–1.2; CH_3-*tert.* butyl, 0.93 (s). Picrate, m.p. 150–152° (ethanol).

5,6,7,8-Tetrahydro-2,6-dimethylquinoline. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-4, 7.17 (d, 8); H-3 6.80 (d, 8); H-5,6,7,8, 3.2–1.3; CH_3-2, 2.45 (s); CH_3-6, 1.03 (d, 5.2). M.p. 28–29°. Picrate, m.p. 150–151.5° (ethanol).

5,6,7,8-Tetrahydro-6-isopropyl-2-methylquinoline. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-4, 7.27 (d, 8); H-3, 6.88 (d, 8); H-5,6,7,8 and CH-isopropyl, 3.1–1.2; CH_3-2, 2.50 (s); CH_3-isopropyl, 0.97 (d, 5.4). Picrate, m.p. 95–97° (ethanol).

6-*tert.* Butyl-5,6,7,8-tetrahydro-2-methylquinoline. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-4, 7.23 (d, 8); H-3 6.83 (d, 8); H-5,6,7,8, 3.1–1.1; CH_3-2, 2.45 (s); CH_3-*tert.* butyl, 0.90 (s). M.p. 48–50° (petroleum ether).

6-Trifluoromethyl-5,6,7,8-tetrahydro-2-methylquinoline. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-4, 7.27 (d, 8); H-3, 6.90 (d, 8); H-5,6,7,8, 3.5–1.3; CH_3-2, 2.50 (s). M.p. 73–75° (petroleum ether).

5,6,7,8-Tetrahydro-8-isopropyl-2-methylquinoline. ^{1}H-NMR ($CDCl_3$ δ (*J*): H-4, 7.16 (d, 8); H-3, 6.76 (d, 8); H-5,6,7,8 and CH-isopropyl, 3.1–1.1; CH_3-2, 2.47 (s); CH_3-isopropyl (diastereotopic), 1.00 (d, 6) and 0.57 (d, 6). Picrate, m.p. 101–102° (ethanol).

8-Trifluoromethyl-5,6,7,8-tetrahydro-2-methylquinoline. ^{1}H-NMR ($CDCl_3$) δ (*J*): H-4, 7.33 (d, 8); H-3, 7.00 (d, 8); H-8, 3.67 (m); H-5,6,7, 3.1–1.3; CH_3-2, 2.51 (s).

Potentiometric Titrations and pKa-Values

Acetic anhydride (p. A., Fluka or Merck) was distilled under dry, oxygen-free N_2. Perchloric acid (0.10 *N* in acetic acid) (Merck) was used as purchased.

The compounds used as standards (see Table 2) were either prepared for hydrogenation (**1**, **2**, **6**, **10**, **11**, **15**), synthesized by literature procedures or obtained

Table 2. *Titration of standards in acetic anhydride*

Compound	*HNP* (mV)	*pKa*			ΔpKa[c]
		Lit.	(Ref.)	Calc.	
N,N-Dimethylbenzylamine	185	8.91	(21)	8.44	−0.47
2,3,5,6-Tetramethylpyridine	247	7.85[a]	(22)	7.20	−0.65
2,4,6-Trimethylpyridine	255	7.43	(3a)	7.04	−0.39
4-Methoxypyridine	268	6.47	(23)	6.78	+0.31
11	315	5.46	(24)	5.84	+0.39
10	319	5.78[a]	(25)	5.76	−0.02
N,N-Diethylaniline	323.5	6.58[a]	(26)	5.67	−0.91
15	325	4.11[b]	(24)	5.64	+1.54[b]
Isoquinoline	328.5	5.37[a]	(27)	5.57	−0.20
Pyridine	336.5	5.22	(28)	5.41	+0.19
2	346	5.22	(25)	5.22	0
1	355	4.81	(29)	5.04	+0.24
6	366	5.00[a]	(25)	4.82	−0.18
8-Fluoroquinoline	437	3.34	(30)	3.40	+0.16
Methylurea	570	0.9	(31)	0.74	−0.16
Urea	592.5	0.5	(32)	0.29	−0.21
Phenylurea	629.5	−0.3	(31)	−0.45	−0.15

[a] Corrected to 25° by the equation $dpKa/dT = -0.011\,°C$[3c].

[b] This literature value is obviously erroneous; it is smaller than the value for **6**, although the 2-CH_3-group invariably increases the basicity.

[c] *pKa* (calc.) − *pKa* (lit.).

commercially from various sources. Purity in each case was tested by chromatography and/or NMR spectroscopy. The compounds were either recrystallized and dried, or distilled in a Kugelrohr apparatus and kept under N_2, or purified by preparative GC, prior to weighing and dissolving 1 mmol in 100 ml acetic anhydride in a volumetric flask. Titrations were carried out after pipetting 25 ml of these solutions and diluting with 75 ml acetic anhydride in a cell kept at 25 °C, under a nitrogen atmosphere. The cell cover had ground glass openings for glass electrode, nitrogen inlet and outlet, burette and thermometer. The solutions were stirred magnetically during titrations.

A digital Orion Model 701-00 mV/*pH*-Meter was used. At first attempts were made with combined glass-Ag/AgCl/KCl-electrodes (Ingold, type 104023144), equilibrated in acetic anhydride; however, these became unusable after few

titrations. A combined glass-Ag/AgCl/LiCl/CH_3COOH electrode (Ingold, type 104053605) was then used throughout the experiments.

Titration end points and *HNP*'s were determined graphically. All runs were carried out at least in duplicate; if differences of more than 10 mV between values were observed, additional titrations were performed and stray values rejected. Values in Table 2 are averages.

A plot of *HNP*'s (acetic anhydride) vs. *pKa*'s (H_2O) taken from the literature (data considered most reliable by Ref.[4] were used) provided a linear relationship $y = kx + d$, with $y = pKa$ (H_2O) and $x = HNP$'s observed. From the data of the 17 standards listed in Table 2, $k = -0.02$ and $d = 12.14$ was obtained by linear regression analysis ($r = 0.978$). The values for the compounds in Table 1 were then calculated from their average *HNP*'s. Standard deviation for ΔpKa is 0.24 (neglecting the value for **15**; see footnote b, Table 2), which is not unsatisfactory considering the different methods and sources for the literature *pKa*-values.

To have some control for the *pKa*'s not found in the literature, calculations using the *Hammett*-relationship were carried out for the 6- and 7-substituted compounds. The necessary substituent constants were taken from the ionization of substituted benzoic acids[33]. Various forms[34] of the *Hammett* approach were tried, and agreement between the values obtained by titration and calculation was $\leqslant 0.1$ *pK*-units.

References

[1] Preceding paper in this series: *Hönel M., Vierhapper, F. W.*, J. Chem. Soc. Perkin I **1982**, 2607.

[2] (a) *Vierhapper F. W., Eliel E. L.*, J. Org. Chem. **40**, 2729 (1975); b) *Hönel M., Vierhapper F. W.*, J. Chem. Soc. Perkin I **1980**, 1933.

[3] (a) *Gero A., Markham J. J.*, J. Org. Chem. **16**, 1835 (1951); (b) *Brown H. C., Mihm X. R.*, J. Amer. Chem. Soc. **77**, 1723 (1955); (c) *Katritzky A. R., Leahy D. E., Maquestiau A., Flammang R.*, J. Chem. Soc. Perkin II **1983**, 15.

[4] *Perrin D. D.*, "Dissociation Constants of Organic Bases in Aqueous Solution", IUPAC, Analytical Chemistry Division. London: Butterworths. 1965.

[5] *Streuli C. A.*, Anal. Chem. **30**, 997 (1958).

[6] *Markgraf J. H., Katt R. J.*, J. Org. Chem. **37**, 717 (1972); *Thummel R. P., Kohli D. K.*, ibid. **43**, 4882 (1978); *Markgraf J. H., Antin J. H., Walker F. J., Blatchly R. A.*, ibid. **44**, 3261 (1979).

[7] *Skomoroski R. M., Schriesheim A.*, J. Phys. Chem. **65**, 1340 (1961).

[8] *Arnett E. M., Chawla B.*, J. Amer. Chem. Soc. **100**, 217 (1978).

[9] (a) *Knight S. B., Wallick R. H., Bowen J.*, J. Amer. Chem. Soc. **76**, 3780 (1954); (b) *Knight S. B., Wallick R. H., Balch C.*, ibid. **77**, 2577 (1955).

[10] (a) *Brown H. C., Kanner B.*, J. Amer. Chem. Soc. **88**, 986 (1966); (b) *Arnett E. M., Chawla B.*, ibid. **101**, 7141 (1979); (c) *Aue D. H., Webb H. M., Bowers M. T., Liotta C. L., Alexander C. J., Hopkins H. P.*, ibid. **98**, 854 (1976).

[11] *Lachowicz A., Mazonski F.*, Roczn. Chem. **40**, 609 (1966).

[12] *Manske R. H. F., Marion L., Leger F.*, Can. J. Res. 20 B, 133 (1942).

[13] *Jantzen*, Dechema-Monographie Nr. 48, Berlin 1932.

[14] *Biekart H. J. B., Dessens H. B., Verkade P. E., Wepster B. M.*, Rec. Trav. Chim. Pays-Bas **71**, 321 (1952).

[15] *Mills W. H., Harris J. E. G., Lambourne H.*, J. Chem. Soc. **119**, 1294 (1921).

[16] *Angelo M. M., Capps D. B., Culbertson T. P.*, US-Patent 4 207 320 (CA 93: P 20465 w).

[17] *Foye W. O., Kauffman J. M.*, J. Pharm. Sci. **68**, 336 (1979).
[18] *Deeming A. J., Rothwell I. P., Hursthouse M. B., Malik K. H. A.*, J. Chem. Soc. Dalton **1979**, 1899.
[19] *Vierhapper F. W., Eliel E. L., Zuniga G.*, J. Org. Chem. **45**, 4844 (1980).
[20] *Irie H., Katayama I., Mizumo Y., Koyama J., Suzuta Y.*, Heterocycles **12**, 771 (1979).
[21] *Goldschmidt H., Salcher R. M.*, Z. phys. Chem. **29**, 89 (1899).
[22] *Essery J. M., Schofield K.*, J. Chem. Soc. 1961, 3939.
[23] *Murmann R. K., Basolo F.*, J. Amer. Chem. Soc. **77**, 3484 (1955).
[24] *Felsing W. A., Biggs B. S.*, J. Amer. Chem. Soc. **55**, 3624 (1933).
[25] *Riccardi R., Bresesti M.*, Ann. Chim. (Roma) **48**, 826 (1958); **49**, 1891 (1959).
[26] *Hall N. F., Sprinkle M. R.*, J. Amer. Chem. Soc. **54**, 3469 (1932).
[27] *Albert A., Phillips J. N.*, J. Chem. Soc. **1956**, 1294.
[28] *Andon R. J. L., Cox J. D., Herington E. F. G.*, Trans. Faraday Soc. **50**, 918 (1954).
[29] *Baciocchi E., Illuminati G.*, Gazz. Chim. Ital. **87**, 981 (1957).
[30] *Miller W. K., Knight S. B., Roe A.*, J. Amer. Soc. **72**, 4763 (1950).
[31] *Hall N. F.*, J. Amer. Chem. Soc. **52**, 5115 (1930).
[32] *Lemaire H., Lucas H. J.*, J. Amer. Chem. Soc. **73**, 5198 (1951).
[33] *McDaniel D. H., Brown H. C.*, J. Org. Chem. **23**, 420 (1958).
[34] *Perrin D. D., Dempsey B., Serjeant E. P., PKa* Prediction for organic acids and bases. London: Chapman and Hall. 1981; and literature cited therein.