43. The Transmission of Polar Effects
Polar Effects. Part II

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Summary

The pK_a^* values for nine acyclic, mono- and bicyclic α-, β- and γ-(trimethyl)ammonio acids, **1**(α-γ), **2**(α-γ) and **3**(α-γ), respectively, have been measured in 50% aqueous ethanol. The comparison of these values with those for the nine homomorphous α-, β- and γ-acids, **4**(α-γ), **5**(α-γ) and **6**(α-γ), respectively, permits an evaluation of the steric effect of the (trimethyl)ammonio groups which is superimposed on their polar effect in the former acids. The pK_a^* values, corrected for the steric effect, correlate very well with the reciprocal distance between the positive nitrogen atom and the dissociable proton. This confirms our earlier conclusion that the strength of these acids is determined by the field effect of the (trimethyl)ammonio groups only, the inductive model failing to account for the results. The distinction between two different transmission mechanisms for the polar effect therefore becomes unnecessary, the inductive model appearing as an atomistic description of the field effect.

One of the prominent effects which determine the reactivity of organic molecules can be traced to the presence of charged or polar substituents. It is, therefore, of electrostatic origin and referred to as the polar effect. Two modes of transmission of this effect are usually distinguished, namely through the intervening bonds and atoms and directly through space or solvent [1]. According to the former inductive model the substituent effect is propagated by successive polarization of bonds, the magnitude of the effect depending on the length and number of chains. The direct or field effect, however, is dependent on the distance and orientation of the substituent with respect to the reaction center. This dichotomy of transmission mechanisms for the polar effect appears to stem from the notion, clearly stated by *Ingold* [1], that the inductive effect is transmitted internally, *i.e.* through the molecule and that the field effect is transmitted externally, *i.e.* through the space immediately enveloping the molecule. In practice it is extremely difficult to distinguish between these two modes of transmission, the relative importance of which is still under dispute¹).

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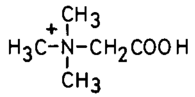
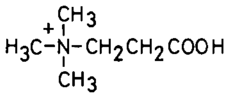
¹) For reviews see [2].



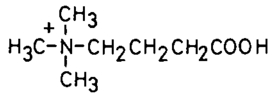
$H_3C-\overset{+\,CH_3}{\underset{CH_3}{N}}-CH_2COOH$

1-α



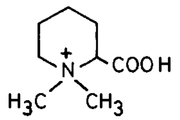
$H_3C-\overset{+\,CH_3}{\underset{CH_3}{N}}-CH_2CH_2COOH$

1-β

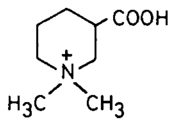


$H_3C-\overset{+\,CH_3}{\underset{CH_3}{N}}-CH_2CH_2CH_2COOH$

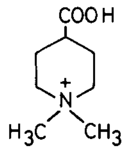
1-γ



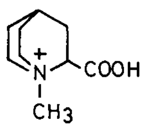
2-α



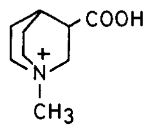
2-β



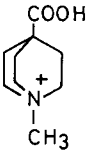
2-γ



3-α



3-β



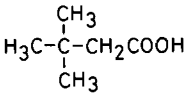
3-γ

In 1955 we reported an attempt to determine the relative importance of the two modes of transmission by measuring the pK_a values of the three classes of α-, β- and γ-(trimethyl)ammonio carboxylic acids **1**(**α**-**γ**), **2**(**α**-**γ**) and **3**(**α**-**γ**), respectively [3]. Whereas the shortest chains connecting the positive charged nitrogen atom (N^+) and the dissociable proton are of equal length in the α-, β- and γ-series, respectively, the distances between N^+ and the proton differ markedly in the γ-series for conformational reasons. The differences are strongly reflected in the pK_a values and a plot of pK_a against the corresponding reciprocal distances showed the linear relationship expected on the basis of the *Bjerrum*-type [4] equation (1):

$$\ln(K/K_0) = e^2/k\,T\,r\,D_E \qquad (1)$$

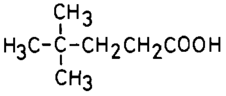
where K and K_0 denote the dissociation constants for sterically comparable acids with and without a positive charge and k, T, r and D_E are *Boltzmann*'s constant, absolute temperature, direct distance and the effective dielectric constant, respectively. Hence, it was concluded that the field effect is the decisive factor which determines acid strength and that it is no longer meaningful to distinguish between two physically different transmission mechanisms. On this basis, the polar effect is a function of the distance between electrostatically interacting groups and the dielectric constant (D_E) of the intervening medium, *i.e.* a chain of atoms, solvent or, in gases, empty space according to the structure of the molecules. These conclusions are supported by the extensive experimental studies of *Stock* [5], *Wilcox* [6], *Liotta* [7], *Grubbs* [8] and others [2a], who employed polar substituted carboxylic acids.

Our preliminary study [3] was incomplete in that the effect of steric factors on acidity was not taken into account. Specifically, steric hindrance to solvation of the carboxylate groups, which is noticeable in molecular models of the α-acids **1-α**, **2-α** and **3-α**, should counteract the polar effect and tend to be acid-weakening [9]. The importance of this steric effect can be evaluated by comparing the pK_a of corresponding acyclic, monocyclic and bicyclic acids without ammonio groups, such as the homomorphous α-, β- and γ-acids **4**(**α**-**γ**), **5**(**α**-**γ**) and **6**(**α**-**γ**), respectively.



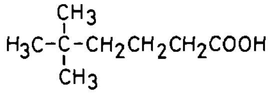
$H_3C-C(CH_3)_2-CH_2COOH$

4-α



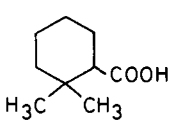
$H_3C-C(CH_3)_2-CH_2CH_2COOH$

4-β

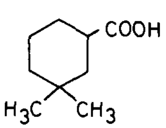


$H_3C-C(CH_3)_2-CH_2CH_2CH_2COOH$

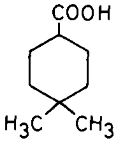
4-γ



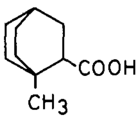
5-α



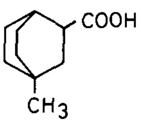
5-β



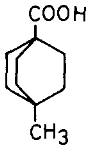
5-γ



6-α



6-β



6-γ

These acids were not available at the time and have now been prepared[2]. Furthermore, their apparent pK_a^* have been measured in 50% aqueous ethanol along with the pK_a^* for the α-, β- and γ-(trimethyl)ammonio acids **1**(**α**-**γ**), **2**(**α**-**γ**) and **3**(**α**-**γ**). Hence, the latter can be corrected for the steric effect and a more accurate measure is obtained for the polar effect of N^+ in the nine ammonio carboxylic acids. In this paper the mode of transmission of the polar effect in the nine α-, β- and γ-(trimethyl)ammonio acids **1**(**α**-**γ**), **2**(**α**-**γ**) and **3**(**α**-**γ**) is discussed in the light of these revised measurements.

Results. - The α-, β- and γ-(trimethyl)ammonio carboxylic acids of the classes **1**, **2** and **3** were prepared following known procedures[3] and isolated as perchlorates. The thermodynamic pK_a values for the nine acids (Table 1) were determined in 0.025 M aqueous solution at 25.0° and an ionic strength of 0.03-0.06 as described

[2] This is described in the following paper [10].

[3] See experimental section.

in Part I [11]. Apparent pK_a^* values were measured in 50% (*W/W*) aqueous ethanol at a constant ionic strength of 0.2 [12]. In Table 1 these values are compared with those for the homomorphous acids of the classes **4**, **5** and **6**. The differences between corresponding *α*-, *β*- and *γ*-acids (ΔpK_a^* in Table 1) are a measure of the polar effect of the ammonio substituents.

As shown, the pK_a^* for the *β*- and *γ*-isomers of each class of homomorphous acids **4**, **5** and **6** are practically the same, whereas those for the *α*-isomers are considerably higher; *i.e.* the latter are less acidic by 0.25, 0.41 and 0.25 pK_a^* units, respectively. These differences reflect the acid-weakening steric effect of the various substituents in the *β*-acids which is discussed in the subsequent paper [10]. Since this effect is superimposed on the polar effect in the *α*-(trimethyl)ammonio carboxylic acids **1**-*α*, **2**-*α* and **3**-*α*, respectively, subtraction of the pK_a^*-differences of the homomorphous *α*- and *β*-acids from the pK_a^* of these ammonio acids leads to the corrected values listed in brackets in Table 1.

Table 1. *Thermodynamic* pK_a *values in water and apparent* pK_a^* *values in 50% ethanol* (± 0.01–0.02) *at 25.0°*. Values corrected for steric effect in brackets

	pK_a water[a]	pK_a^* 50% ethanol[b]		pK_a^* 50% ethanol[b]	ΔpK_a^*
1-α	1.72	2.93 (2.68)	**4-α**	6.37	3.44
1-β	3.27	4.16	**4-β**	6.12	1.96
1-γ	3.96	4.96	**4-γ**	6.13	1.17
2-α	1.72	2.96 (2.55)	**5-α**	6.71	3.75
2-β	3.18	4.22 (4.18)	**5-β**	6.30	2.08
2-γ	3.62	4.69	**5-γ**	6.26	1.57
3-α	1.66	2.97 (2.72)	**6-α**	6.86	3.89
3-β	3.27	4.35	**6-β**	6.61	2.26
3-γ	3.32	4.57	**6-γ**	6.60	2.03

[a] Initial concentration 0.025 M; ionic strength 0.03–0.06;
[b] Initial concentration 0.05 M; ionic strength 0.2.

In Fig. 1, 2 and 3 pK_a^* values (corrected for the steric effect where necessary) are plotted against the reciprocal distance 1/r between N^+ and the dissociable proton. The distances r were measured directly with *Dreiding* models assuming the following conformations: a) Fully staggered conformations for the acyclic acids **1**, b) the chair conformation and an equatorial carboxyl group for the piperidine derivatives **2** and c) the conformation of the carboxyl group leading to the greatest distance between N^+ and the dissociable proton[4]. The r-values thus obtained were rounded off to the next tenth of 1 Å and are listed in Table 2.

Table 2. *Distances r and reciprocal distances 1/r in Å*

	1-α	**1-β**	**1-γ**	**2-α**	**2-β**	**2-γ**	**3-α**	**3-β**	**3-γ**
r	4.5	5.8	7.0	4.5	5.8	6.3	4.5	5.6	5.8
1/r	0.22	0.172	0.143	0.22	0.172	0.158	0.22	0.179	0.172

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[4] This choice is based on the reasonable assumption that the proton leaves and returns to a position as far removed from N^+ as possible.

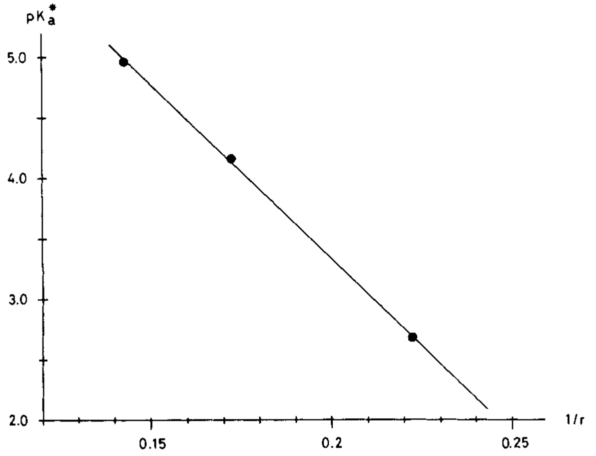


Fig. 1. *Plot of* pK_a^* *for* **1-α**, **1-β** *and* **1-γ** *against* $1/r$ (correlation coefficient 0.9997)

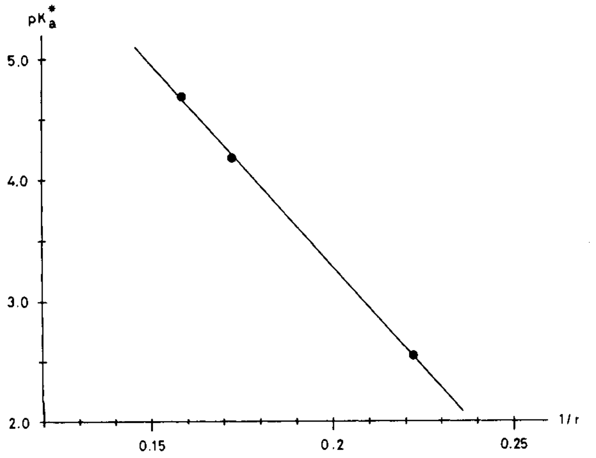


Fig. 2. *Plot of* pK_a^* *for* **2-α**, **2-β** *and* **2-γ** *against* $1/r$ (correlation coefficient 0.9997)

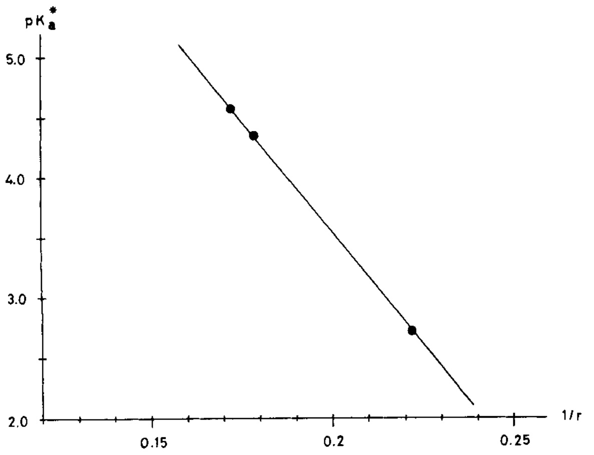
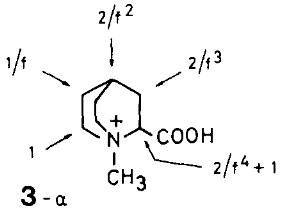


Fig. 3. *Plot of* pK_a^* *for* **3-α**, **3-β** *and* **3-γ** *against* $1/r$ (correlation coefficient 0.9999)

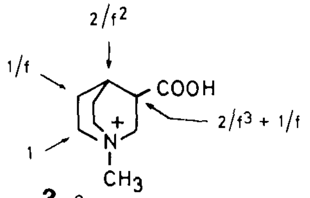
Discussion. - The corrected pK_a^* values in Table 1 reveal that the β-isomers are approximately 60% less acidic (in pK_a units) than the corresponding α-isomer in all three classes **1**, **2** and **3**, respectively. On the other hand the γ-isomers are 19%, 12% and 5% less acidic than the β-isomers in the case of **1**, **2** and **3**, respectively. Clearly, the geometry of these ammonio acids is the decisive factor and not the chain length. In fact, the corrected pK_a^* values correlate very well with reciprocal distance (Fig. 1, 2 and 3) as expected on the basis of the field model. From the slopes of the regression lines the effective dielectric constants (D_E) for the three types of ammonio acids can be calculated with the aid of equation (1), namely 8.6, 7.4 and 6.6 for **1**, **2** and **3**, respectively. These values are not directly related to macroscopic dielectric constants, which are defined and measured in a different way. It seems significant, however, that the values of D_E fall in the order $\mathbf{1} > \mathbf{2} > \mathbf{3}$, *i. e.* as the bulk of the model compounds increases and the contribution of the solvent dielectric constant (49.4 at 25° for 50% ethanol) to D_E decreases. This is supported by the ΔpK_a^* values (Table 1) which are a measure of the polar substituent effect and which increase in the order $\mathbf{1} < \mathbf{2} < \mathbf{3}$, *i. e.* as the bulk of the molecules increases.

Table 1 includes thermodynamic pK_a values of all nine (trimethyl)ammonio acids in water. In these cases a correction for the steric effect, which is present in the hindered α-acids **1**, **2** and **3**, is not possible since the homomorphous acids were measured in 50% ethanol. A plot of pK_a against $1/r$ is therefore less satisfactory than for pK_a^* as shown by the correlation coefficients of 0.9974, 0.9998 and 0.9962, respectively. It is, however, informative to compare the pK_a values for the β- and γ-acids in the three classes of compounds where steric effects are negligible. Thus, the differences between the pK_a for the γ- and β-acids, *i. e.* $pK_a(\gamma) - pK_a(\beta)$, for **1**, **2** and **3** decrease from 0.69 to 0.44 to 0.05, respectively, as do the direct distances r and as predicted by the field model.

It remains to be discussed how well the data fit the inductive model. According to the latter the substituent effect should decrease at each consecutive atom in the chain by a constant fall-off factor f, account being taken of the number of transmission paths [2a] [2b] [6] [7][5]. According to this model the polar effect at C(3) and C(2) of 3-carboxy-1-methyl-quinuclidinium ion **3-β** and its 2-isomer **3-α** are $2/f^3 + 1/f$ and $2/f^4 + 1$, respectively.



3-α



3-β

The ratio of the corrected pK_a^* for **3-β** and **3-α** can be calculated by equation (2)

$$\frac{pK^*_{3\text{-}\beta} - pK^*_{6\text{-}\beta}}{pK^*_{3\text{-}\alpha} - pK^*_{6\text{-}\alpha}} = \frac{2/f^3 + 1/f}{2/f^4 + 1} \qquad (2)$$

[5] The fall-off factor f is the reciprocal of the transmission coefficient ε.

which leads to a fall-off factor $f_{\alpha/\beta}$ of 2.23. The same type of calculation with **3-γ** and **3-β** leads to $f_{\beta/\gamma} = 2.56$[6]. Calculated f values for the acid classes **1**, **2** and **3** are listed in Table 3. Evidently, these are different for each intervening σ-bond within the same class of compound **1**, **2** or **3**. The differences are even greater for corresponding bonds in the different classes of compounds, ranging from 1.68 to 2.56. In contrast to the inductive model fall-off factors are far from constant for the same type of bond.

Table 3. *Calculated fall-off factors f for α-, β- and γ-(trimethyl)ammonio acids.*

(trimethyl)ammonio acids	$f_{\alpha/\beta}$	$f_{\beta/\gamma}$
1	1.76	1.68
2	2.10	2.19
3	2.23	2.56

This fact is also borne out by a comparison of the dissociation constants K_a for the three γ-acids **1-γ**, **2-γ** and **3-γ**, respectively, in water. These are not modified by steric factors and are therefore a true measure of the polar effect. According to the inductive model the K_a values should increase in the ratio $1/f^2 : 2/f^2 : 3/f^2$, *i.e.* as 1:2:3, since the effect is transmitted to the γ-position by one, two and three chains, respectively. The observed K_a values (from pK_a in Table 1) are 1.10×10^{-4} for **1-γ**, 2.40×10^{-4} for **2-γ** and 4.79×10^{-4} for **3-γ**; *i.e.* they increase in the ratio 1:2.18:4.35. The mono- and, particularly, the bicyclic acid is therefore considerably stronger than predicted by the inductive model.

In *conclusion*, the acid-strengthening polar effect of the (trimethyl)ammonio group in the α-, β- and γ-acid classes **1**, **2** and **3** is best described by the field model, as previously proposed [3]. The polar effect is thus a function of the direct distance between substituent and reaction center and of the dielectric constant of the intervening medium. Depending on the shape of the molecule this will be part of the molecule itself, solvent or, in gases, empty space[7]. On this basis the distinction between two physically different modes of transmission becomes unnecessary, the inductive model being an atomistic description of the role of the dielectric in the field model. Furthermore, there is then no need to abandon the term inductive substituent constant which was used in Part I [11] for the quantitative evaluation of polar substituent effects.

We thank PD. Dr. *H. Seiler* for his assistance with the pK_a measurements. This work was financed by the *'Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung'*, grant Nr.2.164.74.

Experimental Part

Melting points (m.p.) were determined on a *Kofler*-Block and are corrected.

Syntheses. - *Carboxymethyl-trimethylammonium* (**1-α**) *perchlorate*. To 1.15 g (7.52 mmol) of the corresponding chloride *(Fluka)* in 5 ml of water 0.1N aqueous $AgClO_4$ was added until the precipitation

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[6] Fall-off factors of 2 to 3.3 are cited in [2a] [6] [7].

[7] To our knowledge *G. Schwarzenbach et al.* [13] were among the first to stress the importance of structure in determining the effective dielectric constant and hence the magnitude of polar substituent effects.

of AgCl was complete. Filtration through a sintered glass filter and evaporation in a vacuum rotary evaporator (VRE) yielded **1-*a*** perchlorate. From ethanol 1.5 g (92%), m.p. > 300°.

$C_5H_{12}ClNO_6$ (217.609) Calc. C 27.60 H 5.56 N 6.44% Found C 27.74 H 5.41 N 6.59%

(2-Carboxyethyl)-trimethylammonium (**1-β**) *perchlorate.* The corresponding chloride was prepared from β-propiolactone and trimethylamine as described [14], m.p. 208–210°, and converted to the perchlorate as described above. From ethanol m.p. 147–148.5°.

$C_6H_{14}ClNO_6$ (231.636) Calc. C 31.11 H 6.09 N 6.05% Found C 31.31 H 6.30 N 6.25%

(3-Carboxypropyl)-trimethylammonium (**1-γ**) *perchlorate* was prepared from the chloride [15] as described above. From ethanol m.p. 111–113°.

$C_7H_{16}ClNO_6$ (245.667) Calc. C 34.23 H 6.57 N 5.70% Found C 34.40 H 6.74 N 5.95%

The three *piperidine derivatives* **2-α**, **2-β** and **2-γ** were prepared from the known esters of the corresponding 1-methyl piperidine carboxylic acids [16] by treatment with methyliodide and subsequent hydrolysis with 20% aqueous hydrochloric acid. Treatment of the chlorides with $AgClO_4$ yielded the perchlorates.

2-Carboxy-1,1-dimethylpiperidinium(**2-α**)*perchlorate* was obtained from the chloride [17]. From ethanol/ether m.p. 156–157°.

$C_8H_{16}ClNO_6$ (257.675) Calc. C 37.29 H 6.26 N 5.44% Found C 37.54 H 6.22 N 5.60%

3-Carboxy-1,1-dimethylpiperidinium(**2-β**)*perchlorate* was obtained from the chloride [17]. From ethanol m.p. 142–143.5.

$C_8H_{16}ClNO_6$ (257.675) Calc. C 37.29 H 6.26 N 5.44% Found C 37.32 H 6.21 N 5.67%

4-Carboxy-1,1-dimethylpiperidinium(**2-γ**)*perchlorate* was obtained from the chloride with $AgClO_4$. From ethanol m.p. 175–176°.

$C_8H_{16}ClNO_6$ (257.675) Calc. C 37.29 H 6.26 N 5.44% Found C 37.18 H 6.38 N 5.21%

The three quinuclidine derivatives **3-α**, **3-β** and **3-γ** were prepared from esters of the corresponding quinuclidine carboxylic acids by methylation with methyl iodide and subsequent hydrolysis.

2-Carboxy-1-methylquinuclidinium(**3-γ**)*perchlorate.* A solution of 3.0 g (16.37 mmol) of 2-ethoxycarbonyl-quinuclidine [18] and 4.64 g (32.74 mmol) methyl iodide in 30 ml acetone was left at 25° for 12 h. Addition of ether precipitated 4.90 g (92%) of the methiodide, m.p. 86.5–88°. This salt was heated under reflux with 50 ml of 20% hydrochloric acid for 24 h. Evaporation in VRE. and recrystallization of the residue from acetone/CCl_4 yielded 3.80 g of a mixture of **3-α** chloride and iodide, which was dissolved in bidistilled water. 0.1 N $AgClO_4$ solution was then added until precipitation of halide ions was complete. After filtration through a sintered glass filter the aqueous solution was evaporated to dryness in a VRE. The residue was crystallized from 2-propanol/pentane to yield 3.50 g (91.5%) **3-α** perchlorate, m.p. 185–187°.

$C_9H_{16}ClNO_6$ (269.686) Calc. C 40.08 H 5.98 N 5.19% Found C 40.06 H 5.87 N 5.46%

3-Carboxy-1-methylquinuclidinium(**3-β**)*perchlorate.* 1.70 g (10 mmol) 3-methoxycarbonyl-quinuclidine [19] were converted to the methiodide with 1.70 g (12 mmol) methyl iodide in 5 ml acetone. The salt was precipitated by addition to ether. From methanol/ether 2.83 g (91%), m.p. 159–160°. 2.34 g (7.5 mmol) of the methiodide were hydrolysed as described above and the mixture of **3-β** chloride and iodide converted to the perchlorate. The latter was recrystallized from acetone/pentane. Yield 1.81 g (90%) of **3-β** perchlorate, m.p. 98–98.5°.

$C_9H_{16}ClNO_6$ (269.686) Calc. C 40.08 H 5.98 N 5.19% Found C 40.24 H 6.10 N 5.07%

4-Carboxyl-1-methylquinuclidinium(**3-γ**)*perchlorate.* 1.83 g (10 mmol) 4-ethoxycarbonyl-quinuclidine [20] were converted to the methiodide with 1.70 g (12 mmol) methyl iodide in 5 ml acetone. The salt was precipitated with ether. From acetone/ether 2.95 g (91%), m.p. 209–210.5°. 2.44 g (7.5 mmol) of the methiodide was hydrolysed as described for **3-α** and the mixture of **3-γ** chloride and iodide converted to the perchlorate. The latter was crystallized from ethanol to yield 1.68 g (83%) **3-γ** perchlorate, m.p. 247–250°.

$C_9H_{16}ClNO_6$ (269.686) Calc. C 40.08 H 5.98 N 5.19% Found C 40.03 H 6.21 N 5.41%

pK_a-Measurements. - These were carried out in a thermostated titration flask *(Metrohm)* at 25.0° (± 0.02°). pH values were registered on a precision compensator (*Metrohm* E388) using a glass electrode (*Metrohm* EA 109/UX) and a calomel reference electrode (*Metrohm* EA404) and a micro piston burette (*Metrohm* E457). These were calibrated with a potassium tetraoxalate buffer (pH (25°) = 1.679) and a potassium hydrogen phtalate buffer (pH (25°) = 4.008) following known procedures [12].

0.25 mmol perchlorate were dissolved in 10 ml bidistilled water and titrated in 100 µl portions with 0.1N NaOH with magnetic stirring in a N_2 atmosphere. The ionic strength varied from 0.03 to 0.06. For measurements in 50% *(W/W)* ethanol 0.05 mmol of acid were dissolved in 10 ml of a 0.2M solution of LiCl in 50% *(W/W)* ethanol. This solution was titrated in 20 µl portions with 0.1N NaOH in 50% *(W/W)* ethanol with magnetic stirring in a N_2-atmosphere. The apparatus was calibrated with a potassium hydrogen phtalate buffer (pH (25°) = 4.008) and a phosphate buffer (pH 25° = 6.865). pK_a values were computed from the titration curves as described [11] [12].

Microanalyses were carried out by *Mr. E. Thommen.*

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