AZABICYCLO COMPOUNDS. XII.*

4-SUBSTITUTED QUINUCLIDINES AS MODEL COMPOUNDS FOR THE STUDY OF POLAR EFFECTS TRANSFER

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Constants pK_a of 4-substituted quinuclidines *I* in 5% ethanol-water (v/v), 50% ethanol–water (w/w), and 80% Methyl Cellosolve–water (w/w), as well as the rate constants of their reactions with methyl iodide in methanol were measured. The results were analysed using a Hammett type equation. Excellent correlations were obtained when σ_I constants were used. Reaction constants for ionisation reactions are almost independent of the medium. When *F* constants were applied a good correlation was obtained but appreciable deviations were observed in the case of some substituents. Further, the polar effect of the methyl group and the deuterium is discussed. The syntheses of several as yet underscribed 4-substituted quinuclidines *I* are also described.

One of the most frequent approaches to the understanding of the effect of substituents on the reaction center is based on the utilization of the linear relationship of free energies, expressed by a Hammett-type equation[1]. In the case of saturated compounds two models are taken into consideration for the transfer of polar effects of the substituent: the transfer caused by subsequent polarisation of the σ-bonds (inductive effect), and direct electrostatic effect through space (field effect)[2,3]. The questions of relative importance of both effects has been much studied. In some instances[4–6] good agreement was found between experimental and calculated values by means of the Kirkwood–Westheimer theory and recently by means of the CNDO/2 method[7] which proves the transfer through space (field effect). However, papers exist[8–10] which demonstrate that the inductive effect is decisive. Ehrenson[11], after adjusting the factors for the transfer of the polar effects *via* the bonds, came to the conclusion that both models predict similar results. From quantum chemical studies[12,13] based on the EHT method it may be judged that the decisive effect on the ratio of single transfer types is due to the arrangement of orbitals in the direction of the transfer.

The effect of the transfer of unconjugative polar effects of the substituent on the reaction center was studied in a series of cyclic and bicyclic compounds with carboxyl groups[4–7,14–18]. Presently the most suitable models having a rigid structure without a steric interaction were 4-substituted bicyclo[2,2,2]octanoic acids *II*, studied by Roberts and Moreland[14] and later by other authors[5,7,17,18]. In this group of substances π-electrons of the carboxyl group also take part in the transfer of polar effects of substituents to the reaction center.

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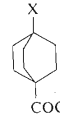


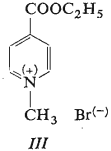
II

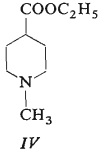
Ia, X = H, *Ig*, X = CH_2OOCCH_3, *Im*, X = OH,
Ib, X = D, *Ih*, X = CH_2Cl, *In*, X = $OOCCH_3$,
Ic, X = CH_3, *Ii*, X = CH_2Br, *Io*, X = Cl,
Id, X = CD_3, *Ij*, X = $CON(CH_3)_2$, *Ip*, X = Br,
Ie, X = CH_2OH, *Ik*, X = $CONH_2$, *Iq*, X = CN,
If, X = CD_2OH, *Il*, X = $COOC_2H_5$, *Ir*, X = CD_2Br.

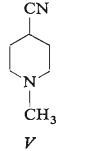
We found that 4-substituted quinuclidines *I* are suitable model substances for the study of the transfer of polar effects of the substituent[19]. The rigid structure of the quinuclidine nucleus causes the polar group oriented in the axis with the reaction center in the skeleton to be distant from it by approx. 2·7 Å. The absence of π-electrons excludes the possible effect of the π-interaction considered in the case of carboxylic acids *II*, and hence the transfer of the polar effects of substituents is affected only by σ-electrons. These facts are evident from the sensitivity of the reaction center on the changes of the substituent *X*. Substitution of hydrogen for a nitrile group causes an approximately 900-fold increase of the dissociation constant.

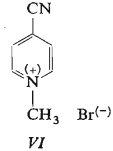
The starting compound for the series of 4-substituted quinuclidines *I* is cyano derivative[20] *Iq*; the key intermediate for its synthesis is 1-methyl-4-cyanopiperidine (*V*). On the basis of our experience[21] that on hydrogenation of methobromides of pyridine bases on Adams catalyst corresponding saturated derivatives are formed in almost quantitative yield we chose two pathways for the synthesis of nitrile *V*: in the first case methobromide *III* was hydrogenated on platinum oxide giving rise to 1-methyl-4-ethoxycarbonylpiperidine (*IV*) which was transformed to cyano derivative *V*. In the second 1-methyl-4-cyanopyridinium bromide (*VI*) was hydrogenated under the same conditions as above, and the crude product was column chromatographed affording a small amount of compound *V*.

Azeotropic esterification of the crude acid, prepared by alkaline hydrolysis[20] of nitrile *Iq*, gave 4-ethoxycarbonylquinuclidine *Il*. When the synthesis of amide *Ik*


III

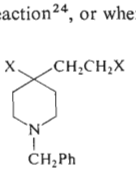

IV


V

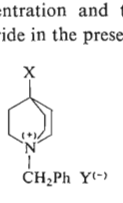

VI

was carried out according to literature[22] the pure product could be obtained only after chromatographic purification of the sublimated product on an alumina column. N,N-Dimethylcarbamoyl derivative *Ij* was prepared in two ways; in the first case ethyl ester *Il* was heated with excess dimethylamine at 100–120°C. However, even after prolonged reaction time we isolated from the reaction mixture chromatographically in addition to the required product *Ij* mainly unreacted compound *Il*. In the second the required derivative *Ij* was obtained after reaction of the hydrochloride of 4-quinuclidinecarboxylic acid chloride (prepared from the crude acid by reaction with thionyl chloride in the presence of dimethylformamide) with dimethylamine in chloroform.

Reduction of 4-ethoxycarbonylquinuclidine *Il* with lithium aluminium hydride or deuteride gave 4-hydroxymethyl[20]- (*Ie*) or 4-hydroxydeuteriomethylquinuclidine (*If*). 4-Chloromethylquinuclidine (*Ih*) obtained earlier in a low yield[25] only in the form of picrate was prepared from hydroxy derivative *Ie* on reaction with thionyl chloride under catalysis with dimethylformamide. Only after repeated heating of alcohol *Ie* with approx. 75% hydrobromic acid we isolated bromide *Ii*. On a single long-lasting heating to 150–160°C we isolated from the reaction product by column chromatography on alumina in addition to the required product *Ii* also the starting compound *Ie*. 4-Bromomethylquinuclidine (*Ii*) was reduced with zinc in acetic acid to the known 4-methyl derivative *Ic*. By an analogous reaction sequence we prepared from the 4-hydroxydideuteriomethyl derivative *If* the bromo derivative *Ir*, and from it 4-trideuteriomethylquinuclidine (*Id*). Esterification of hydroxymethyl derivative *Ie* with acetic anhydride gave acetate *Ig*. In this case too esterification had to be repeated at least twice in order to eliminate the starting compound *Ie* from the reaction product. The low reactivity of 4-hydroxymethylquinuclidine (*Ie*) in substitution reactions may be explained by the fact that it is a neopentyl type compound. 4-Acetoxyquinuclidine (*In*) was prepared on reaction of the known tosylate *Im* with acetic anhydride[23]. After hydrogenolytic elimination of the benzyl group from the quaternary salt *IX* prepared from aminodiol *VII via* dibromide *VIII* we isolated the known[23] bromo derivative *Ip* of higher melting point. On increasing hydrogen chloride concentration and temperature during the reaction[24], or when reacting with thionyl chloride in the presence of pyri-



VII, X = OH
VIII, X = Br
X, X = Cl



IX, X = Y = Br
XI, X = Y = Cl

dine we prepared hydrochloride *X* in high yield from substance *VII*. From this substance we prepared by the usual sequence $X \rightarrow XI \rightarrow Io$ chloro derivative *Io*.

Other 4-substituted derivatives *I* were prepared by procedures described by Grob and coworkers[20,22–25]. Infrared and mass spectra of substances *Ia–Iq* are in agreement with their structure. Methoiodides of 4-substituted quinuclidines *I* were prepared from corresponding bases on reaction with methyl iodide in ether or ethanol solution; their physical and chemical constants are listed in Table I.

EXPERIMENTAL

Temperature data are not corrected. The melting points were determined on a Boetius block. Samples for analysis were dried over phosphorus pentoxide at 2—4 Torr for 10 h. For chromatography alumina of activity III according to Brockmann was employed and for detection of thin-layer chromatograms iodine vapours were used. The infrared spectra were measured on a Perkin Elmer 325 apparatus, in chloroform. The mass spectra were recorded on a LKB 9000 apparatus (combined gas chromatograph-mass spectrometer) at 12 eV and 70 eV, ionising current 60 mA. The samples were introduced either directly or *via* the glc inlet. Quinuclidine (Ia) was prepared by combination of the described procedures[26–29] in a total yield of 12·4%. The solvents and chemicals used were purified by the described procedures: methanol, ethanol and dimethylformamide[33], Methyl Cellosolve[34].

1-Methyl-4-ethoxycarbonylpyridinium Bromide (*III*)

To a methanolic solution of methyl bromide (1 000 ml; content 492 g, *i.e.* 5·18 mol of methyl bromide) ethyl nicotinate (381·0 g; 2·52 mol) was added in several portions under cooling with water and ice and stirring. After five days standing at room temperature the solvents were distilled off *in vacuo* and the product (the yield of which was almost quantitative) crystallized for analysis from ethanol–benzene mixture, m.p. 142—143°C (sealed capillary). For $C_9H_{12}BrNO_2$ (246·1) calculated: 43·92% C, 4·92% H, 32·47% Br; found: 44·05% C, 5·15% H, 32·81% Br.

1-Methyl-4-ethoxycarbonylpiperidine (*IV*)

To methobromide *III* (612 g; 2·49 mol) in 2 000 ml of ethanol 3 g of platinum oxide were added and the mixture hydrogenated at 835 Torr and 25°C. After 20 h 142 l of hydrogen were consumed (theoretical consumption is 166 l), the catalyst was filtered off and ethanol evaporated *in vacuo*. Almost the theoretical amount of methobromide *IV* was obtained, which (a 10 g portion) after crystallization from ethanol–ethyl acetate mixture melted at 131—132° C. For $C_9H_{18}BrNO_2$ (252·1) calculated: 42·86H C, 7·20% H, 31·69% Br, 5·56% N; found: 42·82% C, 7·43% H, 31·51% Br, 5·50% N. The crude methobromide *IV* was dissolved in 150 ml of water, 300 ml of ether were added, the mixture alkalized with 40% sodium hydroxide solution to pH 12—14 and the organic layer separated. The aqueous layer was then extracted four times with 400 ml of ether. The combined extracts were dried over a mixture of potassium carbonate and potassium hydroxide, the solvents evaporated, and the residue distilled, affording 322·5 g (75·8%) of product, b.p. 112 to 114°C/35 Torr. For $C_9H_{17}NO_2$ (171·2) calculated: 63·13% C, 10·01% H, 8·18% N; found: 63·40% C, 10·07% H, 8·46% N.

1-Methyl-4-cyanopyridinium Bromide (*VI*)

To a solution of 3·3 g (31·7 mmol) of 4-cyanopyridine (prepared[30] from ethyl isonicotinate) in 15 ml of methanol 6 g (63·2 mmol) of methyl bromide in 40 ml benzene were added. After 10 days standing at room temperature the separated crystals were filtered off under suction and

TABLE I

Methoiodides of 4-Substituted Quinuclidines *I*

Compound	M.p., °C solvent[a]	Formula (m.w.)	Calculated/Found			
			% C	% H	% N	% I
Id CD_3	275—276 A	$C_9H_{15}D_3IN$ (270·6)	39·95 39·82	7·97[b] 7·63[b]	5·18 5·27	46·90 46·53
Ie CH_2OH	248—250[c] B	$C_9H_{18}INO$ (283·2)	38·17 38·50	6·41 6·23	4·95 4·82	44·82 44·56
If CD_2OH	253—254 B	$C_9H_{16}D_2INO$ (285·2)	37·95 37·83	7·07[b] 7·29[b]	4·91 4·53	44·50 44·78
Ig CH_2OOCCH_3	154—156 B	$C_{11}H_{20}INO_2$ (325·3)	40·63 40·75	6·20 6·34	— —	39·02 38·85
Ih CH_2Cl	151—153 C	$C_9H_{17}ClIN$ (301·6)	35·84 35·67	5·68 5·56	4·64 4·75	42·08 42·51
Ii CH_2Br	144—145 C	$C_9H_{17}BrIN$ (346·1)	31·23 31·80	4·95 5·21	4·05 4·08	36·67 36·74
Ij $CON(CH_3)_2$	193—195 A	$C_{11}H_{21}IN_2O$ (324·2)	40·75 40·82	6·52 6·75	8·64 8·97	39·14 38·79
Ik $CONH_2$	305—306 A	$C_9H_{17}IN_2O$ (296·2)	36·50 36·96	5·79 6·05	9·46 9·77	42·85 42·30
Il $COOC_2H_5$	210—211 A	$C_{11}H_{20}INO_2$ (325·2)	40·63 40·93	6·20 6·12	4·31 4·25	— —
Im OH	329—331 B	$C_8H_{16}INO$ (269·1)	35·70 35·88	5·99 6·16	— —	47·15 47·00
In $OOCCH_3$	254—256 C	$C_{10}H_{18}INO_2$ (311·2)	38·59 38·34	5·83 6·25	4·50 4·19	40·78 40·11
Io Cl	256—258 A	$C_8H_{15}ClIN$ (287·6)	33·41 33·96	5·26 5·55	4·87 4·87	44·13 44·25
Ip Br	290—291 C	$C_8H_{15}BrIN$ (332·0)	28·92 29·06	4·55 4·77	4·22 4·14	38·22 38·45
Iq CN	331—332[d] A	$C_9H_{15}IN_2$ (278·1)	38·86 38·54	5·44 5·32	10·07 10·21	45·63 45·78

[a] A ethanol, B ethanol–light petroleum, C ethanol–ether; [b] the value corresponds to the sum H + D; [c] lit.[25] gives 247—248°C, without analysis; [d] lit.[20] says that it does not melt up to 310°C, without analysis.

the mother liquors concentrated, affording another crop of crystals. Crystallisation from methanol–benzene (1 : 2) gave 6·1 g (96·7%) of product, m.p. 234—235°C. For $C_7H_7BrN_2$ (199·1) calculated: 42·24% C, 3·54% H, 40·15% Br, 14·07% N; found: 42·35% C, 3·72% H, 40·25% Br, 13·84% N.

1-Methyl-4-cyanopiperidine (*V*)

To methobromide *VI* (5·65 g) in 20 ml methanol Adams catalyst (130 mg) was added and the mixture hydrogenated at room temperature and 845 Torr pressure until 1 900 ml of hydrogen were consumed (theoretical amount for three double bonds is 1 810 ml). The catalyst was filtered off and the solvents evaporated. Distillation residue (5·4 g) was chromatographed on alumina, affording 0·7 g of product, b.p. 84—87°C/12 Torr (Hickmann flask). Literature[31] gives b.p. 84—86°C/11 Torr.

4-Ethoxycarbonylquinuclidine (*II*)

A mixture of 8·0 g (58·8 mmol) of nitrile *Iq* (ref.[20]) and 124 ml of 5% sodium hydroxide was heated at 140—160°C for 18 h and then evaporated *in vacuo*. The residue was triturated with 20 ml of ethanol and 50 ml of benzene, evaporated and esterified azeotropically with a mixture of 80 ml ethanol, 200 ml benzene, and 14 ml conc. H_2SO_4. After 10 h boiling the aqueous phase stopped separating and the solvents were evaporated. The oily residue was dissolved in 20 ml of ice-cold water, additioned with 30 ml of ether, and alkalized under external cooling with ice and water with a saturated potassium carbonate solution. The organic phase was separated and the aqueous extracted four times with 50 ml portions of ether. The combined extracts were dried over potassium carbonate and evaporated, leaving 8·47 g (81·4%) of product, b.p. 120—121°C/13 Torr. For $C_{10}H_{17}NO_2$ (183·2) calculated: 65·54% C, 9·35% H, 7·64% N; found: 65·32% C, 9·40% H, 7·81% N.

4-Hydroxydideuteriomethylquinuclidine (*If*)

To a suspension of 512 mg of lithium aluminium deuteride in 20 ml of ether 1·82 g of ester *II* in 10 ml of ether were added and the reaction mixture boiled for 5 h. After decomposition with 2 ml of a 4% sodium hydroxide solution and working up in the standard manner the product was sublimated (bath temperature 120—130°C) at 14 Torr, affording 1·24 g of substance, m.p. 139—140°C. For $C_8H_{13}D_2NO$ (143·2) calculated: 67·09% C, 11·96% H + D, 9·78% N; found: 67·27% C, 11·92% H + D, 9·95% N.

4-Acetoxymethylquinuclidine (*Ig*)

A mixture of 848 mg (6 mmol) of hydroxy derivative[20] *Ie* and 5·1 ml (5·5 g; 54 mmol) of acetic anhydride was refluxed for 10 h and evaporated *in vacuo* to dryness. After addition of the same amount of acetic anhydride the procedure was repeated. The distillation residue was dissolved in 3 ml of ice water, 5 ml of ether were added and the mixture alkalized with a saturated potassium carbonate solution to pH 12—13. After the usual working up 650 mg of product were obtained (59·1%), b.p. 70—72°C/1 Torr (Hickmann flask, bath temperature 110—120°C), m.p. 32—35°C. For $C_{10}H_{17}NO_2$ (183·2) calculated: 65·54% C, 9·35% H, 7·64% N; found: 65·65% C, 9·40% H, 7·86% N.

4-Bromomethylquinuclidine (*Ii*)

A mixture of 1·5 g (10·6 mmol) of substance *Ie* and 35 ml of approx. 75% hydrobromic acid was heated at 120—130°C in a pressure tube for 6 h. After distilling off the hydrobromic acid *in vacuo* the operation was repeated with the same amount of acid and the distillation residue was crystallised twice from ethanol–ethyl acetate (charcoal) affording 2·48 g (82·1%) of hydrobromide *Ii*, m.p. 260—261°C. For $C_8H_{15}Br_2N$ (285·0) calculated: 33·71% C, 5·30% H, 4·91% N, 56·07% Br; found: 34·01% C, 5·59% H, 4·83% N, 56·25% Br. A part of hydrobromide *Ii* (2·0 g, 7 mmol) was dissolved in 5 ml of water, 10 ml of ether were added, and the base liberated with saturated potassium carbonate solution. After the conventional working up 1·15 g (80·0%) of product was obtained, b.p. 65—68°C/1 Torr (Hickmann flask, bath temperature 100—110°C). For $C_8H_{14}BrN$ (204·1) calculated: 47·07% C, 6·91% H, 6·86% N, 39·15% Br; found: 46·84% C, 7·14% H, 6·58%N, 39·99% Br.

4-Bromodideuteriomethylquinuclidine (*Ir*)

Taking 620 mg of alcohol *If* and applying the same working up as in the case of 4-bromomethyl derivative *Ii*, 727 mg (81·6%) of product of b.p. 66—68°C/2 Torr (Hickmann flask, bath temperature 80—90°C) were obtained. For $C_8H_{12}D_2BrN$ (206·1) calculated: 46·61% C, 7·83% H + D, 38·77% Br, 6·08% N; found: 46·32% C, 7·51% H + D, 39·05% Br, 6·54% N.

4-Methylquinuclidine (*Ic*)

Crude hydrobromide of bromo derivative *Ii* (2·39 g) prepared from 1·1 g (7·8 mmol) of hydroxy derivative *Ie* was dissolved in 20 ml of glacial acetic acid and zinc dust added to it (7 g in four portions, over 20 min) under stirring and refluxing for 5 h. After cooling and alkalization with 40% sodium hydroxide solution the bases were steam-distilled and the distillate neutralized with dilute hydrochloric acid and evaporated *in vacuo*. The base set free from the crude hydrochloride was extracted with ether (50 ml) and worked up in the usual manner, affording 670 mg of substance (68·8% calculated per starting hydroxy derivative *Ie*), b.p. 154—156°C (Hickmann flask, bath temperature 170—175°C). Literature[32] gives 158—160°C/738 Torr.

Picrate: m.p. 295—296°C (ethanol). Literature[20,32] gives 292—294°C and 291°C (ethanol).

4-Trideuteriomethylquinuclidine (*Id*)

To 654 mg of bromo derivative *Ir* in O-deuterioacetic acid (prepared from 10 ml of acetic anhydride and 2·1 ml of deuterium oxide) 3·5 g of zinc dust (freed from occluded water) were added in three portions and the mixture refluxed for 4 h. After the conventional working up of the reaction mixture 272 mg (62·5%) of product were obtained, b.p. 156—158°C/746 Torr (Hickmann flask, bath temp. 165—175°C), m.p. 48—50°C (sealed capillary). For $C_8H_{12}D_3N$ (128·2) calculated: 74·93% C, 14·14% H + D, 10·92% N; found: 74·57% C, 13·93% H + D, 10·88% N.

Picrate: m.p. 304—305°C (ethanol–water). For $C_{14}H_{15}D_3N_4O_7$ (357·3) calculated: 47·06% C, 5·92% H + D, 15·68% N; found: 46·91% C, 5·83% H + D, 15·79% N.

4-Chloromethylquinuclidine (*Ih*)

To 800 mg (5·67 mmol) of hydroxymethyl derivative *Ie* in 2 ml of ethanol 3 ml of 6M ethanolic hydrogen chloride solution were added, the mixture was allowed to stand for 10 min and then ethanol was evaporated to dryness. To hydrochloride *Ie* 0·3 ml of dimethylformamide and 10 ml

thionyl chloride were added and the mixture was heated for 4 h. After standing at room temperature overnight excess thionyl chloride was distilled off *in vacuo*. The crude product was dissolved in 7 ml of water, alkalized with potassium carbonate and worked up in the usual manner, affording 600 mg (66·2%) of product, b.p. 93—95°C/12 Torr. For $C_8H_{14}ClN$ (159·7) calculated: 60·18% C, 8·84% H, 8·77% N, 22·21% Cl; found: 60·46% C, 8·91% H, 8·62% N, 22·31% Cl.

Picrate: m.p. 246—248°C (methanol). Literature[25] gave 244—246°C.

4-Carbamoylquinuclidine (*Ik*)

It was prepared from 1·0 g of nitrile *Ie* according to literature[22]. The obtained product (830 mg) melted at 229—235°C (literature[22] gives 222—224°C). On chromatography on alumina (120 g, act. III, 4% ethanol in chloroform as eluant) 710 mg of product were obtained which was sublimated (bath temperature 160—170°C at 1—1·5 Torr), m.p. 236—237°C (sealed capillary). For $C_8H_{14}N_2O$ (154·2) calculated: 62·30% C, 9·15% H, 18·17% N; found: 62·59% C, 9·47% H, 18·31% N.

4-(N,N-Dimethylcarbamoyl)quinuclidine (*Ij*)

Hydrochloride of 4-quinuclidinecarboxylic acid, prepared from 0·7 g of cyano derivative *Iq*, was refluxed with 0·6 ml of dimethylformamide and 16 ml of thionyl chloride for 3 h. Excess thionyl chloride was distilled off in a vacuum and the distillation residue dissolved in 25 ml of chloroform (freed from stabilizer). The solution was externally cooled with ice and water and additioned over 10 min under stirring with 1·51 ml (1·03 g) of dimethylamine dissolved in 5 ml of the same solvent. After one hour stirring at this temperature the reaction mixture was slowly heated to 20—25°C and stirred for another 3 hours. It was then washed with 5 ml of 20% sodium hydroxide and the chloroform solution dried over potassium carbonate and evaporated. The crude product (720 mg) was chromatographed on a column of alumina (70 g, column height 35 cm, 4% ethanol in chloroform as eluent). The product (515 mg; 54·9%) was sublimated (bath temperature 140—150°C/12 Torr), m.p. 91—92°C (sealed capillary). For $C_{10}H_{18}N_2O$ (182·3) calculated: 65·89% C, 9·96% H, 15·37% N; found: 65·45% C, 9·97% H, 15·41% N.

Picrate: m.p. 249—251°C (ethanol). For $C_{16}H_{21}N_5O_8$ (411·4) calculated: 46·72% C, 5·15% H, 17·03% N; found: 46·58% C, 5·38% H, 17·52% N.

4-Acetoxyquinuclidine (*In*)

From a mixture of 1947 mg of tosylate *Im* (prepared according to literature[23]) and 16 ml of acetic anhydride excess anhydride was distilled off *in vacuo* after 7 h refluxing. Fresh acetic anhydride (16 ml) was added to the distillation residue and the operation repeated. The distillation residue was dissolved in 10 ml of water, the same amount of ether was added and the mixture alkalized with saturated potassium carbonate solution. The ethereal layer was separated and the aqueous layer extracted five times with 20 ml of the same solvent. After the conventional work-up the product was sublimated (bath temperature 110—120°C/10 Torr) affording 750 mg of product, m.p. 77—79°C (sealed capillary). For $C_9H_{15}NO_2$ (169·2) calculated: 63·88% C, 8·93% H, 8·28% N; found: 64·12% C, 9·18% H, 8·20% N.

Hydrobromide of 1-Benzyl-4-bromo-4-(2-bromoethyl)piperidine (*VIII*)

A mixture of 10 g (42·5 mmol) of aminodiol *VII* and 150 ml of approx. 75% hydrobromic acid was heated in a pressure tube at 90—100°C for 8 hours. The reaction mixture was diluted with

water, filtered with charcoal, and concentrated to a small volume. After cooling the separated crystals were filtered off under suction and crystallized from water, affording 17·7 g (94·2%) of hydrobromide *VIII*, m.p. 162—163°C. Literature[23] gives an identical melting point.

4-Bromoquinuclidine (*Ip*)

From 17·7 g of hydrobromide *VIII* 8·0 g (56·2%) of hydrobromide *Ip* were prepared in the described manner[23]. From 1 g of this product 630 mg (90·9%) of base were liberated which melted after sublimation (90—95°C bath temperature) at 105—107°C (sealed capillary). Literature[23] gives 89—89·5°C. For $C_7H_{12}BrN$ (190·1) calculated: 44·23% C, 6·36% H, 7·37% N, 42·04% Br; found: 44·51% C, 6·28% H, 7·11% N, 42·37% Br.

Hydrochloride of 1-Benzyl-4-chloro-4-(2-chloroethyl)piperidine (*X*)

A) 4 g (17 mmol) of aminodiol *VII* were dissolved in 100 ml of chloroform and the solution saturated with gaseous hydrogen chloride at −60 to −50°C. After 16 h heating of this mixture in a pressure tube (bath temperature 120—130°C) the solvents were evaporated and the residue crystallised from water (charcoal). Yield 4·5 g (85·8%) of product, m.p. 177—179°C. Literature[24] gives 168—172°C. For $C_{14}H_{20}Cl_3N$ (308·7) calculated: 54·47% C, 6·53% H, 34·46% Cl, 4·54% N; found: 54·48% C, 6·37% H, 34·69% Cl, 4·88% N.

B) To a mixture of hydrochloride of aminodiol *VII* (prepared from 1·59 g of aminodiol *VII*), 0·25 ml of pyridine, and 15 ml of chloroform 2·41 g of thionyl chloride in 10 ml of chloroform were added under stirring and cooling, over 15 min. After 30 min stirring and cooling and 7 hours refluxing the mixture was evaporated in a vacuum. Crystallisation of the residue from water (charcoal) gave 1·7 g (82·1%) of product, m.p. 175—177°C.

4-Chloroquinuclidine (*Io*)

From 3·6 g (11·6 mmol) of hydrochloride *X* 1·54 g (88·5%) of hydrochloride *Io* was obtained in a similar manner[24]. From this substance the base was liberated which was extracted with ether. The extract was dried shortly over potassium carbonate and the solvents evaporated. The residue at 120—130°C (bath temperature) was sublimated to give 1·07 g (87·0%) of product melting at 102—104°C (sealed capillary). For $C_7H_{12}ClN$ (145·6) calculated: 57·72% C, 8·31% H, 24·35% Cl, 9·62% N; found: 57·93% C, 8·44% H, 23·88% Cl, 9·75% N.

Picrate: m.p. 248—249°C (ethanol). For $C_{13}H_{15}ClN_4O_7$ (374·7) calculated: 41·67% C, 4·03% H, 9·46% Cl, 14·95% N; found: 42·01% C, 4·14% H, 9·39% Cl, 15·19% N.

Measurement of Dissociation Constants

The pK_a values were measured in 5% aqueous ethanol (v/v), 50% ethanol (*w*/*w*), and 80% Methyl Cellosolve–water (w/w) at 25 ± 0·1°C on Potentiograph AG Herisau (Switzerland). The measurements were carried out using a glass electrode EA 109 X and a saturated calomel electrode EA 404. In view of the fact that the titration was carried out in 0·1M perchloric acid the saturated potassium chloride solution in the calomel electrode was substituted by a saturated sodium chloride solution. The pH-meter used was calibrated before each measurement and after it, using an aqueous solution of potassium hydrogen phthalate (pH 4·01 at 25°C). The given pK_a values represent the averages of at least two measurements which did not differ for more than ±0·03 units. In all instances fresh solutions were prepared (approximate concentration 0·01 to 0·015M)

and the titration carried out in thermostated vessels under nitrogen with 0·1M perchloric acid in corresponding solvent.

Measurement of Rate Constants

A 0·01M solution of quinuclidine derivative was prepared at 25 ± 0·1°C containing a 10-fold amount of methyl iodide in methanol. Aliquot samples (2 ml) were withdrawn from the solution at definite time intervals (the time of addition of methyl iodide represented the zero point) and added to a mixture of 4 ml of dimethylformamide and 4 ml of acetate buffer of pH 4·7. The content of iodide anions was determined polarographically on a LP 60 apparatus connected with an EZ 2 recorder, making use of thermostated Kalousek vessel with separate saturated mercury-(I)-sulfate electrode. The reaction course was followed up to at least 50% reaction of the corresponding quinuclidine derivative. When the rate constants of 4-substituted quinuclidines *I* were measured calibration was always carried out with methoiodide under the same conditions. The results were worked up by the described procedure[35].

Competitive Reactions

To a mixture of quinuclidine (*Ia*) and 4-deuterioquinuclidine (*Ib*) (0·90 mmol, 1 : 1 ratio) in 1 ml of ether a solution of methyl iodide (0·45 mmol) in 0·1 ml of ether was added. After half-an-hour standing at 25 ± 1°C the precipitated salts were separated by filtration under suction. The relative ratio of substances *Ia* and *Ib* in the starting and after reaction mixture (mother liquors) was determined from the relative heights of the molecular ionic species *m/e* 111 and *m/e* 112, measured twice. In the initial mixture of substances *Ia* and *Ib* the relative ratio of the mentioned ionic species was 1·63 and after reaction it was 1·64. Analogously the reaction was carried out with a mixture of 4-methyl-(*Ic*) and 4-trideuteriomethylquinuclidine (*Id*). The determined relative ratio of molecular ionic species *m/e* 125 and *m/e* 128 was 1·33 before the reaction and 1·29 after it.

DISCUSSION

The effect of the substituent X in quinuclidine derivatives *I* was determined in the case of protonation on one hand, and in the case of quaternization on the other, by reaction with methyl iodide. In the first case dissociation constants of the bases in three solvent systems were measured: 5% of ethanol in water (v/v), 50% of ethanol in water (w/w), and 80% of Methyl Cellosolve in water (w/w) at 25°C. Due to the limited solubility of some derivatives water could not be used for the measurement of the dissociation constants and therefore we chose 5% ethanolic solution. The dissociation constants measured in this solvent did not practically differ from those determined in water. For quinuclidine (*Ia*) and bromo derivative *Ip* we determined pK_a values 11·0 and 8·46 which is in good agreement with the values determined in water: 10·95 (ref.[36]) and 8·60 ± 0·1 (ref.[37]). In the second case the rate constants of the reaction of 4-substituted quinuclidines (*I*) with methyl iodide in methanol at 25°C were measured polarographically by the method described by Sicher and coworkers[35]. Experimental results are listed in Table II.

From Table II it is evident that the changes of the substituent X have a substantial effect on the reactivity of the compounds studied. The effect of the substituent X on the changes of the pK_a values is parallel with the effect observed in substituted acetic acids (Fig. 1) and 4-substituted bicyclo[2,2,2]octanoic acids (*II*). As is evident from Fig. 3 and Table III our model is also justified by the correlation of the measured

TABLE II

Experimental Values of pK_a and log (K/K_H) of 4-Substituted Quinuclidines *I* in various solvents, Rate Constants and log (k/k_H) of the Reaction with Methyl Iodide in Methanol at 25°C, and the σ_I-Constants Used

Compound X	σ_I	A[a] pK_a (log (K/K_H))	B[a] pK_a (log K/K_H))	C[a] pK_a (log (K/K_H))	$k \cdot 10^3$ l/mol s (log (k/k_H))
Ia	0·00[+]	11·00	9·98	8·88	10·35[b]
H		(0·00)	(0·00)	(0·00)	(0·000)
Ib	0·004	10·98	9·91	—	10·35
D		(0·02)	(0·07)	—	(0·000)
Ic	0·014	10·92	9·77	—	10·00
CH_3		(0·08)	(0·21)	—	(−0·015)
Id	0·02	10·89	9·70)	—	—
CD_3		(0·11)	(0·28)	—	—
Ie	0·05[+]	10·42	9·57	8·83	7·56
CH_2OH		(0·58)	(0·41)	(0·05)	(−0·136)
If	0·10	10·43	9·52	—	—
CD_2OH		(0·57)	(0·46)	—	—
Ig	0·16	10·10	8·94	—	6·80
CH_2OOCCH_3		(0·90)	(1·04)	—	(−0·183)
Ih	0·16	10·08	8·84	—	—
CH_2Cl		(0·92)	(1·14)	—	—
Ii	0·18[+]	10·00	8·75	8·08	6·55
CH_2Br		(1·00)	(1·23)	(0·80)	(−0·199)
Ij	0·28	9·51	8·61	—	7·00
$CON(CH_3)_2$		(1·49)	(1·37)	—	(−0·170)
Ik	0·28	9·40	8·46	—	6·85
$CONH_2$		(1·60)	(1·52)	—	(−0·179)
Il	0·32[+]	9·47	8·27	7·55	5·17
$COOC_2H_5$		(1·53)	(1·71)	(1·33)	(−0·302)
Im	0·25[+]	9·35	8·65	8·05	6·80
OH		(1·65)	(1·33)	(0·83)	(−0·183)
In	0·37	8·95	7·82	—	4·93
$OOCCH_3$		(2·05)	(2·16)	—	(−0·322)
Io	0·47[+]	8·57	7·49	—	3·70
Cl		(2·43)	(2·49)	—	(−0·477)
Ip	0·45[+]	8·46	7·37	6·73	3·67
Br		(2·54)	(2·61)	(2·11)	(−0·450)
Iq	0·59[+]	8·05	7·02	6·46	2·73
CN		(2·95)	(2·96)	(2·42)	(−0·579)

[a] A 5% ethanol–water (v/v), B 50% ethanol–water (w/w), C 80% Methyl Cellosolve–water (w/w); [b] lit.[35] gives the value 10·1 in 98% methanol.

dissociation constants and reaction rates. Our data permit the computation of the constants σ_I of the inductive effect independently of the earlier experiments. However, in order to preserve the scale of the accepted σ_I constants, we calculated ϱ_I for formula[39,40] $\log(K/K_H) = \varrho_I \sigma_I$ as the corresponding normalizing factor[38]. For this we used 8 substituents (in Table II indicated by +) the constants σ_I of which are considered reliable. Using the value of the reaction constant $\varrho_I = 4{\cdot}85$ ($r = 0{\cdot}9858$, $s = 0{\cdot}1859$) we calculated σ_I based on our dissociation constants measurements in 5 vol. % of ethanol in water (Table II) even for substituents marked with a cross. In view of the high ϱ_I value these σ_I values may be more precise than the earlier ones, but in principle they agree, as is also shown by the correlations with the substituted acetic acids (Fig. 1) and derivatives of bicyclooctane *II* (Fig. 2). Eventually we calculated the reaction constants ϱ_I for all our measurements (Table III) on the basis of our values for σ_I constants. From Table III and Fig. 4 it is evident that the quality of the correlations confirms the reliability of σ_I constants when used as the measure of the polar effects of substituents on the reaction center.

Among the σ_I values found three cases deserve more detailed discussion. For the methyl group we calculated the value of the σ_I constant, 0·014, which differs from the commonly given value $-0{\cdot}05$[40] and $-0{\cdot}08$[9]. Much attention was paid recently to the electronic effect of the methyl group[41]. The view that the alkyl groups are donors of electrons when compared with hydrogen found much support[41–43]. However, it appears that this is valid only for alkyl groups bound to sp and sp^2 hybridized carbon atoms. The finding that the methyl group retards the addition of 2,4-dinitrobenzenesulfenyl chlorides to cyclohexene[44], the acetolysis of 4-substi-

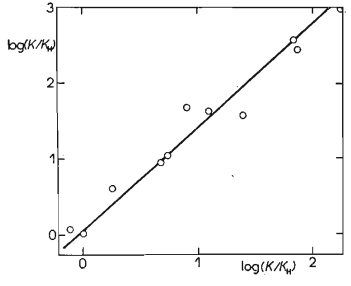


FIG. 1

Dependence of $\log(K/K_H)$ of Substituted Acetic Acids in Water on $\log(K/K_H)$ of 4-Substituted Quinuclidines *I* in 5% Ethanol–Water (v/v) at 25°C

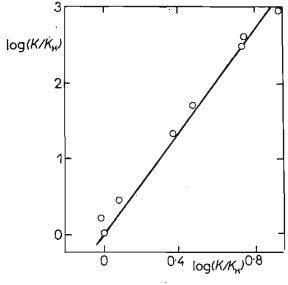


FIG. 2

Dependence of $\log(K/K_H)$ of 4-Substituted Quinuclidines *I* on $\log(K/K_H)$ of 4-Substituted Bicyclo[2,2,2]octanecarboxylic Acids in 50% Ethanol–Water (w/w) at 25°C

tuted cyclohexyl tosylates[45], the hydrolysis of 3-methyl-1-bromoadamantanes[46], and accelerates the S_N2 reactions of 4-substituted bicyclo[2,2,2]octylmethyl tosylates[10] suggested that the polar effect of the methyl group depends on the hybridization of the carbon atom to which it is attached. On the basis of measurements the mentioned authors[44–46] came to the conclusion that the methyl group bound to the sp^3 hybridized carbon atom is an electron acceptor in relation to hydrogen.* The same results, *i.e.* that the methyl group in the CH_3—Csp^3 grouping draws the electrons, were also obtained by Laurie and Muenter[47] during the measurement of the Stark effect in the microwave region of methylacetylene, propane, and their deuterio-analogues. These views are in agreement with the finding of Brown[48] that the bonds between the carbon atoms of different hybridization are polar.

The value $\sigma_I^{CH_3}$ 0·014 calculated by us also differs from the value 0·03 given by Kwart and coworkers[45]. This small difference may be explained both from the differences of measurements (solvents and reaction type) and from the structural differences of the investigated compounds. Mislow[49] found that the structural differences influence the hybridization of carbon atoms, which is then reflected in the bond polarization and, hence, also in the effect of the methyl group.

Deuterium as a substituent of the benzene nucleus is characterized as a weak electron donor in relation to hydrogen[50,51]. During the measurement of the dissociations constants of 4-substituted quinuclidines *I* we found only negligible pK_a

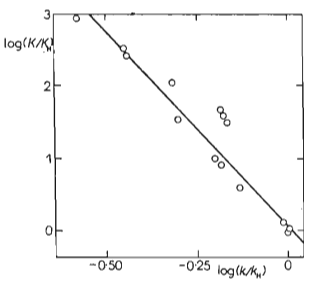


FIG. 3

Dependence of log (K/K_H) in 5% Ethanol–Water (v/v) on log (k/k_H) in 100% Methanol of 4-Substituted Quinuclidines *I* at 25°C

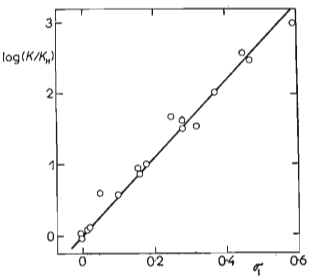


FIG. 4

Dependence of log (K/K_H) in 5% Ethanol–Water (v/v) of 4-Substituted Quinuclidines *I* at 25°C on σ_I-Constants

* Similar conclusions on the polar effect of the methyl group in 4-methylquinuclidine were also drawn by Grob and coworkers (private communication, see Grob C. A., Simon W., Treffert D.: Angew. Chemie, in press).

differences between deuterated and non-deuterated derivatives (Table II). In order to have a better idea we give the measured differences $\Delta pK_a = pK_a^H - pK_a^D$ for derivatives *Ia* – *Ib* = 0·02 vol. (5% of ethanol in water), 0·07 (50 weight % ethanol–water), *Ic* – *Id* = 0·03 and 0·07 and for *Ie* – *If* = 0·01 and 0·05. For substances *Ia* and *Ib* the same value (Table II) was determined during the measurement of the rate of quaternization with methyl iodide. In order to check these measurements we carried out a 50% quaternization with methyl iodide (competitive reaction) of equimolar amounts of the non-deuterated and deuterated compound in the mixture. The ratio of these substances was determined mass spectrometrically from the intensities of molecular ionic species before and after the reaction. These measurements are in agreement with the results obtained in the determination of pK_a and the reaction rates of quaternization with methyl iodide. From our measurements it follows that deuterium as a substituent displays a negligible polar effect. In contrast to the findings of Streitwieser and coworkers[51] it behaves as a very weak electron acceptor in comparison with hydrogen. This fact indicates that analogous relations exist in electronic shifts caused by the CH_3—Csp^2 or CH_3—Csp^3, and D—Csp^2 or D—Csp^3.

The substantial difference in the values of σ_I constants for CH_2OH group, *i.e.* the introduced value 0·05 and calculated from the equation, 0·1, shows that the primary value is to a certain extent inaccurate. It is known[38,40] that between the hydroxy groups and the solvent a specific interaction takes place under formation of solvates; therefore the results should always be worked up with a certain precaution. Nevertheless we suppose that the effect of this group is better expressed by the value $\sigma_I = 0{\cdot}07$ computed from the relation $\sigma_I = \log(K/K_H)/3{\cdot}95$, where K and K_H mean ionisation constants of the substituted and unsubstituted acetic acid[52,55]. Though we are aware that regardless of the value we are using, *i.e.* 0·05 or 0·07, it has no substantial effect on the accuracy of correlation.

Swain and Lupton[53] returned to the idea of a practical differentiation of the "field effect F and the resonance effect R", including the inductive effect in the "field effect". For the calculation of constants F they derived the following relationship

$$F = (2{\cdot}18 \pm 0{\cdot}03)\sigma_m - (0{\cdot}58 \pm 0{\cdot}02)\sigma_p$$

The constants F calculated from this equation were correlated with $\log(K/K_H$ of 4-substituted quinuclidine I measured in 5% ethanol–water (v/v). The correlation is generally good (Table III), but there are appreciable deviations from the regression line for some substituents (chloromethyl, bromomethyl, carbamoyl, ethoxycarbonyl). The view seems correct[54] that efforts to estimate the polar effect of the substituents using σ_m and σ_p constants simplify the given problem appreciably and probably will not be successful (see also the above discussion of the effect of carbon hybridization) in the series of saturated compounds. Nevertheless, this approach might be useful in the calculation of the σ constants for systems similar to benzene.

The high values of the reaction constants for ionisation reaction indicate a high sensitivity of the reaction center toward polar effects of the substituent. In Table IV a comparison with substituted acetic acids[55], 4-substituted bicyclo[2,2,2]octane-carboxylic acids[5], and 10-substituted triptycene-9-carboxylic acids[56] is presented. The measure of sensitivity was chosen according to literature[56] $\Phi = (\varrho_I$ studied

TABLE III

Reaction Constants ϱ_I

Type of correlation	ϱ_I	l^a	r^a	s^a	n^a
$\log (K/K_H)_I$ on $\log (K/K_H)$ of substituted acetic acids, (Fig. 1)	1·21	0·17	0·9834	0·187	11
$\log (K/K_H)_I$ on $\log (K/K_H)$ of 4-substituted →bicyclo[2,2,2]octanecarboxylic acids[b], (Fig. 2)	3·07	0·20	0·9889	0·183	8
$\log (K/K_H)_I$ on $\log (k/k_H)_I$, (Fig. 3)	−5·18	0·17	0·9519	0·306	14[c]
	−5·30	0·17	0·9690	0·248	14[d]
$\log (K/K_H)$ on σ_I, (Fig. 4)	5·11	0·09	0·9904	0·133	17[c]
	5·09	0·13	0·9908	0·133	17[d]
	4·41	−0·08	0·9894	0·150	7[e]
$\log (K/K_H)_I$ on F constants	3·08	0·23	0·9779	0·211	11
$\log (k/k_H)_I$ on σ_I	−0·91	−0·005	0·9626	0·049	14

[a] l is section on y axis, r is correlation coefficient, s is standard deviation, n is the number of the substituents studied; [b] the values from literature[5]; [c] correlation of values in 5% ethanol–water (v/v); [d] correlation of values in 50% ethanol–water (w/w); [e] correlation of values in 80% Methyl Cellosolve–water (w/w).

TABLE IV

Comparison of Reaction Constants ϱ_I and (Φ) for the Ionisation at 25°C

Medium	Acetic acids[a]	I		Triptycene acids[b]		Octane carboxylic acids[c]	
Water	3·95	5·11[d]	(1·29)	—		—	
50% ethanol (w/w)	4·18	5·09	(1·22)	1·10	(0·26)	1·65	(0·39)
80% Methyl Cellosolve	4·04	4·41	(1·09)	1·11	(0·27)	—	

[a] Substituted acetic acids[55]; [b] 10-substituted triptycene-9-carboxylic acids[56]; [c] 4-substituted bicyclo[2,2,2]octanecarboxylic acids[5]; [d] measured in 5% ethanol–water (v/v).

system)/(ϱ_I acetic acids). From Table IV it is evident that 4-substituted quinuclidines *I* are more sensitive to the transfer of polar effects of substituents than are corresponding acetic acids. Another remarkable property of the reaction constants ϱ_I of the investigated substances during ionisation reactions is the insensitivity to the changes in the polarity of the medium, as is evident from Table IV comparable with substituted acetic acids. Bowden and coworkers[55] ascribe this insensitivity of the reaction constants to the polarity of the medium to the transfer of the polar effects of the substituent through the hollow (*i.e.* to the direct electrostatic effect) without the participation of the solvent caused by the short distance ~2·8 Å of the dipole-reaction center. Hoffmann and coworkers[12] proved, on the contrary, by means of EHT calculation, that the direct electrostatic connection through space is of short range, negligible when the distances are close to ~2·5 Å. The propagation of the substituent's polar effects through σ-bonds often has a longer range than expected[13] in consequence of a suitable geometrical arrangement of these bonds. When studying diazabicycloalkanes with nitrogens at branching points the EHT calculations[12] gave the following results (in agreement with experimental results): each of two-carbon bridges of 1,4-diazabicyclo[2,2,2]octane (*XII*) has its optimum orientation for the connection of free electron pairs in nitrogen along the bonds. Only when these bridges are substituted by one-carbon ones, *i.e.* in 1,3-diazabicyclo[1,1,1]pentane (*XIII*) a transfer predominantly through space takes place. Derivatives of quinuclidine *I* are isosteric with diazaoctane *XII*. Therefore we may suppose that the polarized C—X bond of the same orientation as the electron pair will be connected with the

XII

XIII

free electron pair on the nitrogen atom in an analogous manner. From this idea the conclusion follows that the effect of the substituent on the reaction center is transmitted predominantly through σ-bonds, *i.e.*, that the inductive effect predominates.

The presented data show clearly that 4-substituted quinuclidines *I* are a sensitive model for the study of the transmission of the polar effects of substituents onto the reaction center. On the basis of high values of the reaction constants ϱ_I it may be justly supposed that this model will be suitable for a more precise determination of σ_I-constants, mainly in the case of alkyl groups bound to a sp^3 hybridized carbon.

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