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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

8.* EFFECT OF C-SUBSTITUENTS ON THE N-METHYLATION OF 1,4-DIAZABICYCLO[2.2.2]OCTANES AND THE DEMETHYLATION OF THEIR BISQUATERNARY SALTS

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The introduction of substituents with various inductive constants in the 2 position of the diazabicyclo]2.2.2]octane ring gives rise to a change in the pK_a values and affects the ease of introduction of a methyl group in the 1 and 4 positions, as well as the rate of demethylation of the bisquaternary salts from the 1 position. When 1,4-diazabicyclo[2.2.2]octane is treated with a sufficiently strong nucleophile, the ring is opened to give a piperazine derivative.

The nucleophilicity of 1,4-diazabicyclo[2.2.2]octane (Ia) has been studied in the case of a large number of different reactions [2]. However, the literature does not contain data on the effect of C-substituents, other than alkyl groups, on the ability of this bicyclic heteroring to give quaternary salts. In addition, the previously described [3, 4] methods for the synthesis of C-substituted bicyclic system Ia lead only to bis(methylbromides), and it therefore becomes necessary to demethylate them. Taking this into account, we felt it was expedient to evaluate the effect of substituents on the N-methylation of C-substituted bicyclic system Ia and the ability of their bisquaternary salts to undergo demethylation.

Bases Ia-e react smoothly with an equimolar amount of methyl iodide in nonpolar solvents to give monoquaternary derivatives IIa-e. On the basis of the great difference in the basicities of the nitrogen atoms it can be assumed that the reaction takes place at the nitrogen atom in the 4 position. We were unable to detect an appreciable effect of the substituents on the course of the reaction (Table 1). An appreciable effect is displayed when a second N-methyl group is introduced. Bisquaternary salts IIIa-c are easily obtained, whereas an attempt to obtain a bisquaternary salt from base If by prolonged refluxing in methanol with excess methyl iodide leads only to IIf. Bisquaternary salt IIIe was obtained only after prolonged heating of ester Ie or the sodium salt of acid Ig with dimethyl sulfate. Bisquaternary

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*See [1] for communication 7.

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TABLE 1. Monomethylation of 2-Substituted 1,4-Diazabicyclo-[2.2.2]octane with Methyl Iodide

Starting base	σ_I[a]	pK_a	Reaction solvent	Reaction product	mp, °C (solvent)	R_f on paper	Yield, %	Literature data
Ia	0	8,68 3,14	Ether	IIa	286—290 methanol—ethanol	0,26	84	pK_a 8,6 and 2,95 [11] mp 289—290 [12]
Ib	0,05	8,25 3,20	Dioxane	IIb	243—245 methanol—ether	0,40	85	[5]
Ic	0,08	7,60 2,70	Dioxane	IIc[b]	139—142 methanol—ether	0,40	89	
Id	0,15	7,50 2,70	Ether	IId	262—264 methanol	0,80	93	[1]
Ie	0,31	—	Dioxane	IIe[d]	57—63 methanol—ethanol	0,38	89	
If	0,34	—	Methanol	IIe[f]	oil	0,44	96	

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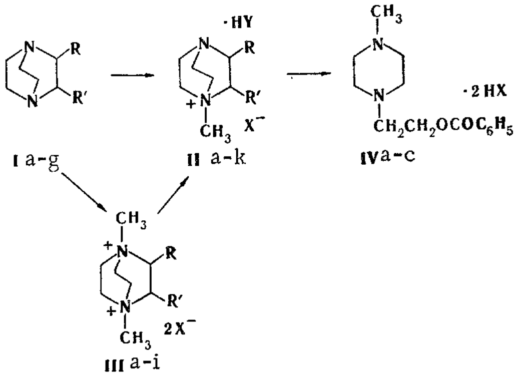
[a] The inductive constants of the substituents were taken from [14] and here and in the other tables pertain to substituent R.
[b] Found: I 41.5%. $C_8H_{16}ClIN_2$. Calculated: I 41.9%.
[c] The ester undergoes hydrolysis during determination of the pK_a value.
[d] An analytical sample was not obtained.
[e] The product was characterized after hydrolysis in the form of IIg with mp 227-229°C (48% HBr—acetone). IR spectrum: 1755 cm^{-1} (C=O). PMR spectrum (in D_2O): 3.79 (3H, s, CH_3—N_4): 4.07-4.78 ppm (10H, m, ring protons). Found: C 28.9; H 5.01; Br 48.1; N 8.18%. $C_8H_{16}Br_2N_2O_2$. Calculated: C 28.9; H 4.86; Br 48.1; N 8.44%.

salt IIId of 2,3-diphenyl-substituted Id is obtained with even greater difficulty. Data on the synthesis of the bisquaternary salts are presented in Table 2.



I a R=R′=H; b R=CH_2OH, R′=H; c R=CH_2Cl, R′=H; d R=R′=C_6H_5; e R=$COOCH_3$, R′=H; f R=$CON(CH_3)_2$, R′=H; g R=COOH, R′=H; II a R=R′=H, X=Y=Cl; b R=CH_2OH, R′=H, X=Y=Cl; c R=CH_2Cl, R′=H, X=I; d R=R′=C_6H_5, X=I; e R=$COOCH_3$, R′=H, X=I; f R=$CON(CH_3)_2$, R′=H, X=I; g R=COOH, R′=H, X=Y=Br; i R=R′=H, X=$C_6H_5COO^-$; j R=CH_2Cl, R′=H, X=Y=Br; k R=R′=C_6H_5, X=Y=Br; III a R=R′=H, X=I; b R=CH_2OH, R′=H, X=I; c R=CH_2OH, R′=H, X=I; d R=R′=C_6H_5, X=Br; e R=$COOCH_3$, R′=H, X=$CH_3SO_4^-$; f R=COOH, R′=H, X=Br; g R=R′=H, X=Br; i R=CH_2OH, R′=H, X=Br; IVa base; b X=Cl; c X = Br

One might have expected that a weaker alkylating agent, viz., methyl benzoate, would be more sensitive to the effect of the substituent in the 2 position of bicyclic system Ia. It has been shown [5] that hydroxymethyl derivative Ib reacts with methyl benzoate to give only monoquaternary salt IIb. In [5] it was found that chloromethyl derivative Ic reacts similarly, although a monoquaternary salt could not be isolated in pure form. Bicyclic ester Ie reacts with methyl benzoate with difficulty, whereas diphenyl-substituted Id does not react. In all cases the reaction is complicated by resinification, and this makes it impossible to quantitatively evaluate the effect of the substituent.

It has been noted [6] that products of methylation of base Ia with esters of some aliphatic and alicyclic acids cannot be isolated. This was explained by the instability of the monomethyl derivative of base Ia.

TABLE 2. Dimethylation of 2-Substituted 1,4-Diazabicyclo[2.2.2]-octanes

Starting base	σ_I	Methylating reagent and solvent	Product	mp, °C (methanol)	Yield, % (literature data)
Ia	0	Methyl iodide, methanol	IIIa	253—258	83 [15]
Ib	0,05	The same	IIIb	188, dec.	29 [5]
Ic	0,08	" "	IIIc[a]	180—182	32
Id	0,15	Excess dimethyl sulfate	IIId[b]	163—167 ethanol	69
Ie	0,31	The same	IIIe[c]	Deliquesces	~100
Ig[d]		" "	IIIe[c]		36

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[a] Found: C 24.5; H 4.55; N 6.07; I 56.0%. $C_9H_{19}ClIN_2$. Calculated: C 24.3; H 4.31; N 6.30; I 57.1%. [b] An analytical sample was not obtained. [c] Characterized after hydrolysis in the form of IIIf with mp 203-206°C (from 48% HBr–acetone). Found: C 31.5; H 5.43; Br 46.2; N 8.11%. $C_9H_{18}Br_2N_2O_2$. Calculated: C 31.2; H 5.24; Br 46.2; N 8.10%. The IR and PMR spectra coincide with the spectra presented in [4]. [d] In the form of the sodium salt.

When bicyclic system Ia is heated in an ampul with methyl benzoate at 100°C, the initial product is monomethyl derivative IIi according to the results of thin-layer and paper chromatography. One next observes the formation of an appreciable amount of 1-methyl-4-(2-hydroxyethyl)piperazine benzoate (IVa), which is the principal product at 160°C. Piperazine derivative IVa is evidently the product of subsequent transformation of IIi. In fact, IVa is obtained when salt IIa is heated with sodium benzoate in methyl benzoate at 130-140°C. Similar opening of the ring in bicyclic system Ia by the action of methyl-, N-methyl-N-phenylcarbamate has been previously noted [7]. It may be assumed that the complications observed in the methylation of 2-substituted bicyclic systems Ib-g with methyl benzoate are associated with similar reactions.

The data on the alkylation of Ia-g presented in Tables 1 and 2 and the results of alkylation of these compounds with methyl benzoate show that an increase in the acceptor properties of the ring substituent, which leads to a decrease in the pK_a values, does not affect the monomethylation of Ia-g with methyl iodide but does decrease their reactivity in the case of the introduction of two methyl groups and in the reaction with methyl benzoate.

It is known [8] that the quaternary salts of some cyclic amines are dealkylated by the action of nucleophiles. It is also known [9, 10] that a number of alkyl derivatives of aromatic amines are dealkylated when they are refluxed in acids, including hydrobromic acid. We therefore attempted to carry out the demethylation of bisquaternary salts IIIa-d,f in refluxing hydrobromic acid.

In fact, bisquaternary salt IIIf is converted to monoquaternary derivative IIg when it is refluxed in 48% HBr. Demethylation also occurs when the salt is heated in an ampul at 150-160°C with 10.2 N hydrochloric acid, 9 N lithium bromide, and 8 N sodium iodide. However, demethylation does not occur when the HBr concentration is decreased to 10% or in the case of simple refluxing in concentrated hydrochloric acid, nor in a solution of lithium bromide or when 77% sulfuric acid is used at 150°C. Thus demethylation is probably the result of attack by the nucleophile at the carbon atom of the methyl group.

The differences in the position of the signals of the methyl groups in the PMR spectra of bisquaternary salt IIIf and monoquaternary salt IIg (see Tables 1 and 3) made it possible to measure the rate of demethylation. Since the reaction was carried out in a large excess of HBr, it was regarded as a pseudo first-order reaction. The demethylation of bisquaternary salts IIIc,d to give the corresponding monoquaternary derivatives IIj,k was similarly studied. The kinetic data are presented in Table 4. Compounds IIIa, b are not demethylated under these conditions. With respect to their spectral characteristics and chromatographic behavior, monoquaternary derivatives IIg, j, k, which are formed by demethylation, correspond completely to the derivatives obtained from bases Ic-e and methyl iodide.

TABLE 3. PMR Spectra of Mono- and Bisquaternary Salts of 2-Substituted 1,4-Diazabicyclo[2.2.2]octanes

Compound (solvent)	CH_3—N_1 (3H)	CH_3—N_4 (3H)	C—H (1H)	Ring products	R [X]
IIa (D_2O)		3,72 s		4,24 m (12H)	
IIb (D_2O)		3,65 s		3,84—5,25 m (13H)	—^{a}
IIc (D_2O)		4,15 s		4,56—5,55 m (13H)	—^{a}
IId (d_6-DMSO)		2,59 s	5,03 d, 5,49 d	2,90—3,90 m (8H)	6,45—7,64 m (10H, C_6H_5)
IIe (D_2O)		3,44 s		3,47—4,62 m (11H)	4,08 s (3H, $COOCH_3$)
IIf (D_2O)		3,44 s		3,33—4,75 m (11H)	3,25 s (3H) and 3,44 s [3H, $CON(CH_3)_2$]^b
IIIa (48% HBr)	4,18 s (6H)			4,85 m (12H)	
IIIb (48% HBr)	3,72 s (6H)			4,07—4,56 m (13H)	—^{a}
IIIc (48% HBr)	4,20 s (6H)			4,40—5,50 m (13H)	—^{a}
IIId (48% HBr)	3,85 s (6H)		6,67 m (2H)	4,85—5,05 m (8H)	—^{c}
IIIe (D_2O)	3,88 s	3,78 s	5,20—5,55 m	4,25—4,82 m (10H)	4,33 s (3H, $COOCH_3$)
IIIf (D_2O)	3,88 s	3,78 s	—^{d}	4,07—4,77 m (10H)	[4,07 s (6H, $CH_3SO_4^-$]

^{a}The signal of the exocyclic CH_2 group coincides with the signals of the ring protons. ^{b}The CH_3—N_4 signal and one $CON(CH_3)_2$ singlet coincide and have an intensity corresponding to six protons. ^{c}The C_6H_5 signal is "hidden" by the signal of 48% HBr. ^{d}The signal of the methylidyne proton is "hidden" by the signal of water.

TABLE 4. **Demethylation** of Bisquaternary Salts of 2-Substituted 1,4-Diazabicyclo[2.2.2]octanes in Refluxing 48% HBr (125°C)

Starting salt	σ_I	Initial concn., mole/liter	$k \cdot 10^5$, sec^{-1}	$\tau_{1/2}$, h	Final product
IIIf	0,32	0,214	9,9	2,0	IIg
IIId	0,15	0,240	3,0	6,4	IIk
IIIc	0,08	0,231	2,3	8,2	IIj
IIIb	0,05	0,342	Demethylation does not take place at an appreciable rate		IIIi
IIIa	0	0,296			IIIg

It is apparent from a comparison of the PMR spectra that the signal of the methyl group attached to N_1 vanishes in the case of demethylation of salt IIIf, whereas the signal of the methyl group attached to N_4 is shifted somewhat to stronger field. Thus the results obtained confirm the assumption regarding the site of methylation of bases Ib-f and show that the demethylation of the bisquaternary salts takes place from the 1 position.

It is apparent from Table 4 that an increase in the acceptor properties of the substituent in the 2 position accelerates the demethylation of the bisquaternary salts. We were unable to remove a methyl group from the 4 position of the monoquaternary salts under these conditions. It should be noted that quaternary salts such as tetramethylammonium iodide, tetraethylammonium bromide, and tetrabutylammonium iodide, as well as dimethylaminoacetic acid methylbromide, do not undergo dealkylation when they are refluxed in 48% HBr for 6 h. The presence of an acceptor such as a secondary ammonium group evidently has a substantial effect on the course of the reaction in the case of bisquaternary salts.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian A 56/60 A spectrometer with tetramethylsilane as the external standard. Thin-layer chromatography (TLC) was carried out on Silufol in an ethanol—ammonia system (5:1) (system A) with detection of the spots by means of Dragendorf's reagent by the method in [15].* Paper chromatography was carried out on Leningrad slow paper in an ammonium hydroxide-saturated butanol—methanol system (4:1) (system B) with detection of the spots by means of Dragendorf's reagent. The pK_a values of bases Ia-e were determined by potentiometric titration with an ÉV-74 pH meter.

Monoquaternary Salts IIa-k of 2-Substituted 1,4-Diazabicyclo[2.2.2]octanes (Ia-f). A) With methyl iodide. Equimolar amounts of bases Ia-e and methyl iodide were dissolved in ether or dioxane, and the solutions were maintained at 20°C for 2 h. The solvent was removed by vacuum distillation, and the residue was either recrystallized from methanol as in the case of base Id or, as in the case of bases Ia-c,f, was reprecipitated several times from methanol by the addition of diethyl ether. For the purification of bases Ia,b methanol was saturated with hydrogen chloride. All of these salts remained at the start of Silufol in system A.

B) With methyl benzoate. A mixture of methyl benzoate and base Ib-e (the base concentrations were 2.5 moles/liter for Ib,c, 0.76 mole/liter for Id, and 0.5 mole/liter for Ie) was heated at 135-160°C until the starting compound vanished (monitoring by means of TLC); the heating times were 3 h for bases Ib,c,e, 10 h for Ic,d, and 12 h for Ie. A considerable amount of a black precipitate formed during heating in the case of bases Ic,e. The mixture was extracted with diethyl ether, and the residue was dissolved in hydrobromic or hydrochloric acid. The acid solution was clarified with OU-B charcoal, the filtrate was evaporated, and the residue was purified as described in method A. The product of methylation of base Ie was isolated after hydrolysis in the form of salt IIg in 7% yield. Base Id did not undergo the reaction and was isolated in the form of the bishydrochloride in 91% yield.

C) Demethylation of the bisquaternary salts in refluxing 48% HBr. Bisquaternary salts IIIa-d,f were refluxed in excess 48% HBr. Samples (0.3-0.5 ml) were selected, and the change in concentration was followed from the change in the integral intensities in the PMR spectra of the signals from the methyl groups of the starting compound and the final product or from the change in the ratio of the intensities of the signals of the methyl groups and the ring protons. At the end of the reaction, the monoquaternary salts were isolated from the reaction mixtures as described above.

Bisquaternary Salts IIIa-f of 2-Substituted 1,4-Diazabicyclo[2.2.2]octanes (Ia-g). Bases Ia-c were heated in refluxing methanol for 6 h with excess methyl iodide, or bases Id,e and the sodium salt of acid Ig were heated in excess dimethyl sulfate at 125-150°C until the starting compound and the monoquaternary salt vanished (monitoring by means of paper chromatography). The methanol was evaporated, and the residue was recrystallized from ethanol. The dimethyl sulfate was extracted with ether, the residue was dissolved in 48% HBr, the solution was evaporated, and the residue was again dissolved in HBr. If necessary, the solution was clarified with OU-B charcoal and evaporated, and the residue was reprecipitated from 48% HBr by the addition of acetone. All of the bisquaternary salts remained at the start on Silufol and on paper (except for salt IIId). The R_f value of IIId on paper was 0.5.

1-Methyl-4-(2-hydroxyethyl)piperazine Benzoate and Its Salts (IVa-c). A) A mixture of 0.1 g (0.895 mmole) of bicyclic system Ia and 1 ml of methyl benzoate was heated in an ampul at 100°C for 2 h. According to TLC data the mixture consisted of starting Ia (R_f 0.45) and monoquaternary salt IIi (R_f 0). After the same mixture was heated for 11 h, benzoate IVa (R_f 0.82) was formed in addiition to IIi. When the same mixture was heated at 140°C for another 3 h, it yielded IIi and IVa, which were separated in the following way. The reaction mixture was allowed to stand until layers formed. The layers were separated, and the lower layer was washed with ether. The oil that remained after washing was dissolved in methanol and was precipitated by the addition of ether saturated with hydrogen chloride. The precipitate was recrystallized from ethanol with the addition of several drops of methanol to give 0.1 g (56%) of hydrochloride IIa, which was identical to a genuine sample with respect to its properties and spectra. The ether used to wash the lower layer was combined with the upper layer, and the mixture was dissolved in methanol. The solution was treated with ether saturated with hydrogen chloride to give 0.08 g (28%) of bishydrochloride IVb with mp 237-238°C (dec., in a capillary, from ethanol—ether). IR spectrum; cm^{-1}: 3000-3100 w (aromatic C—H), 1730 s (ester C=O), 1270 s (C—O—C), and 710 m (monosubstituted aromatic ring). PMR spectrum (in D_2O): 3.33 (s, 3H, CH_3—N), 3.84-4.40 (m, 10H, protons of the piperazine ring and the hydroxyethyl group; the signal of one CH_2 group is hidden by the signal of water), and 7.67-8.50 ppm (m, 5H, C_6H_5).

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*A somewhat modified formulation for this reagent was kindly reported to us by Professor L. N. Yakhontov.

B) A 0.22-g (1.96 mmole) sample of base Ia was heated in 2.5 ml of methyl benzoate in an ampul at 160°C for 3 h, after which the mixture was dissolved in methanol and precipitated with ether saturated with hydrogen chloride. The precipitated bishydrochloride was dissolved in 48% HBr, the solution was evaporated, and the bishydrobromide was recrystallized from ethanol to give IVc (65%) with mp 225-227°C (dec., in a capillary). The IR and PMR spectra were in agreement with structure IVb. Found: C 40.1; H 5.34; Br 37.1; N 6.64%. $C_{14}H_{22}Br_2N_2O_2 \cdot 0.5H_2O$. Calculated: C 40.1; H 5.53; Br 38.1; N 6.68%. The presence of monoquaternary salt IIi in the reaction mixture was confirmed by means of TLC. We were unable to isolate it in this experiment because only very small amounts were present in the mixture.

C) A 0.09-g (0.45 mmole) sample of hydrochloride IIa was heated with an equimolar amount of sodium benzoate in 2 ml of methyl benzoate at 140°C for 4 h and at 130°C for 4 h until the starting compound vanished. The mixture was dissolved in methanol, the black precipitate was removed by filtration, and the filtrate was acidified with a solution of hydrogen chloride in ether and evaporated to dryness. The residue was extracted with ether, and the insoluble residue was recrystallized from ethanol to give 0.1 g (74%) of a compound that was completely identical to IVb with respect to its spectral and chromatographic characteristics.

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