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SYNTHESIS OF DIALKYLTETRAHYDROBENZ[f]ISO-INDOLINE, DIALKYL-4-Δ′-CYCLOHEXENYLBENZ[f]ISO-INDOLINE, AND DIMETHYL-4-ALKENYLNAPHTH[f]ISO-INDOLINE SALTS THROUGH BASE-CATALYZED INTRAMOLECULAR CYCLIZATION OF QUATERNARY AMMONIUM SALTS*

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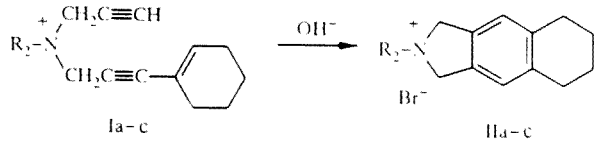
Dialkylpropargyl(3-Δ′-cyclohexenylpropargyl)ammonium salts are cyclized in the presence of a base catalyst to give dialkyltetrahydrobenz[f]iso-indoline salts in high yields. When the 3-Δ′-cyclohexenylpropargyl and 3-phenylpropargyl groups are both present in the ammonium salt molecule, cyclization proceeds in more than one direction. Salts which contain both the 3-α-naphthylpropargyl and 3-alkenylpropargyl groups are also cyclized in two possible ways.

It has been shown in previous works that in the presence of a base catalyst, salts containing β and γ-unsaturated groups, together with a 3-alkenyl- or 3-arylpropargyl group, undergo intramolecular cyclization of the diene synthesis variety [2, 3].

In the present communication we have examined the cyclization of dialkylpropargyl(3-Δ′-cyclohexenylpropargyl)-ammonium salts Ia-c and studied the behavior of dialkyl(3-phenylpropargyl)(3-Δ′-cyclohexenylpropargyl)ammonium salts IIIa-c and (3-α-naphthyl-propargyl)(3-alkenylpropargyl)ammonium salts VIa-d in aqueous alkali.

It was found that, unlike their 3-alkenyl- and 3-arylpropargyl analogues [2, 3], salts Ia-c cyclized in the presence of catalytic amounts of aqueous alkali. Moderate amounts of heat were evolved in the reaction, but heating was required for the process to go to completion. The cyclization products, namely 2,2-dialkyltetrahydro-benz[f]iso-indoline salts IIa-c, were afforded in relatively low yields (70-75%).



Ia–c IIa–c

I, II a R = Me, b R = Et, c R = $(CH_2)_5$

In previous works it was shown that when both the 3-phenyl-propargyl and 3-alkenylpropargyl (or 3-arylpropargyl) groups were present in the ammonium salt molecule, the former predominated as the potential diene fragment in the cyclization process [4-6]. In order to determine the relative capacities of the 3-phenyl-propargyl and 3-Δ′-cyclohexenylpropargyl groups, and of the 3-α-naphthylpropargyl and 3-alkenylpropargyl groups to participate in cyclization as the potential diene component when both are present in the ammonium salt molecule, we studied the behavior of dialkyl(3-phenylpropargyl)(3-Δ′-cyclohexenylpropargyl)ammonium salts IIIa-c and dialkyl(3-α-naphthylpropargyl)(3-alkenylpropargyl)ammonium salts VIa-d in aqueous alkali.

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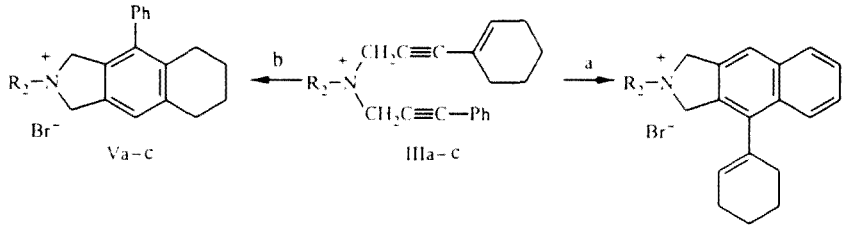
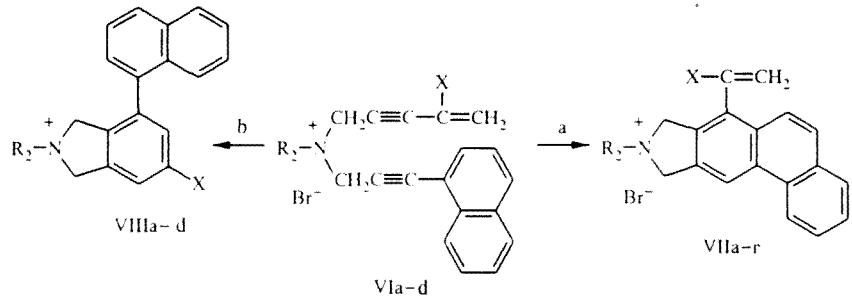
It is clear from the salt structure that cyclization may proceed via routes *a* or b, or in both directions simultaneously.



III–V a R = Me, b R = Et, c R = $(CH_2)_5$

The 3-phenylpropargyl group acts as the potential diene for cyclization via route *a* and the 3-Δ′-cyclohexenylpropargyl group for cyclization via route b. In the presence of a base catalyst the cyclization of salts IIIa-c did not proceed in one direction only and, as a result, isomeric cyclic products IVa-c and Va-c were afforded in 80-82% overall yields. 2,2-Dimethyl-4-Δ′-cyclohexenylbenz[f]iso-indoline bromide (IVa) and 2,2-penta-methylene-4-Δ′-cyclohexenylbenz[f]iso-indoline bromide (IVc) were isolated in 48 and 62% yield respectively by fractional recrystallization from aqueous solutions containing isomeric salt mixtures IVa-Va and IVc-Vc. In the case of salt IIIb it was not possible to separate any of the isomeric products in pure form from the mixture.

Salts VIa-d also cyclized in two directions in the presence of a base catalyst, isomeric cyclic products being afforded in 81-85% overall yields.



VI–VIII a X = H, R = Me; b X = Me, R = Me; c X = Me, R = Et; d X = Me, $R_2 = (CH_2)_5$

Salt mixtures VIIa-VIIIa and VIIb-VIIIb were the only solutions from which isomeric products could be isolated in pure form: 2,2-dimethyl-4-vinyl- (VIIa) and 2,2-dimethyl-4-isopropenylnaphth[f]-iso-indoline bromides (VIIb) were separated by means of fractional recrystallization in 31 and 37% yields respectively.

In the IR spectra of cyclic salts IIa-c, IVa, IVb, VIIa and VIIb, the 2220-2240 cm disubstituted C ≡ C absorption band typical of starting salts Ia-c, IIIa, IIIc, VIa and VIb were absent. Monosubstituted C ≡ C absorption bands at 2120-2140 cm^{-1} and the cyclohexenyl double bond band at 1630 cm^{-1} characteristic of salts Ia-c were also absent from the IR spectra of salts Ia-c. Absorption bands, were found for 1,2-substituted and penta-substituted benzene rings at 750-760 and 870 cm^{-1} respectively. In addition, the IR spectra of salts IIa-c and VIIa and VIIb had absorption bands corresponding to 1,2,4,5- and 1,2,3,4-substituted benzene rings at 850-870 and 810 cm^{-1}.

As could be expected [7, 8], conjugation between the cyclohexenyl double bond and the acetylene group caused the $\pi \rightarrow \pi^*$ transition bands to shift upfield (208-228 nm) and the molar absorptivity logarithms to increase (see Table 1). The presence of a cycloalkyl group in cyclic salt IIa-c molecules led to a slight upfield shift of the benzene absorption band (245-285 nm) and increased their intensity.

The combination of the triple bond and the benzene ring in salts IIIa and IIIc brought about a predictable increase in the molar absorptivity logarithms and caused an upfield shift (see Table 1) [7, 8]. In the UV spectra of cyclic salts IVa and IVc, in which the double bond in the cyclohexenyl ring is conjugated with that in the naphthalene ring, there was a bathochromic shift of the α, P, and β bands to the longer wavelength region. Despite the fact that the P band was shifted further than the α band, the latter still had the longest wavelength.

Three absorption band types, α, P, and β, were also observed in the UV spectra of starting compounds VIa and VIb and in the cyclic salts VIIa and VIIb. In the case of the two latter salts, the α-band had the longest wavelength and, as for all the phenanthrenes, the $\lambda\alpha > \lambda\rho > \lambda\beta$ relationship held true (see Table 1). The absorption bands had lower molar absorptivity logarithms than those of starting salts with comparable complexity. The combination of the phenanthrene ring and the alkenyl

TABLE 1. Physical Properties and Spectral Data for Starting Salts (Ia-c, IIIa-c, VIa-d) and Cyclic Products (IIa-c, IVa, IVc, VIIa and VIIb)

Compound	Empirical formula	mp, °C (from ethanol)	IR spectrum cm^{-1}	UV spectrum λ_{max}, nm (log ε)	Compound*	mp, °C (from abs. ethanol)	R_f †	IR spectrum cm^{-1}	UV spectrum λ_{max}, nm (log ε)	Yield %
Ia	$C_{14}H_{20}BrN$	146...147	1630, 2145, 2235	208 (4,42), 228 (4,26)	IIa	204...205	0,48	750, 760, 860, 1500, 1580, 3060	245 (2,74), 275 (2,78), 285 (2,77)	70
Ib	$C_{16}H_{24}BrN$ ‡		1635, 2140, 2240	210 (4,43), 225 (4,52)	IIb‡		0,53	750, 770, 870, 1570, 1590, 3010	242 (2,73), 273 (2,76), 285 (2,77)	72
Ic	$C_{17}H_{24}BrN$ ‡		1640, 2120, 2230	208 (4,96), 228 (4,26)	IIc	320...321	0,41	740, 750, 855, 1580, 1600, 3070	245 (2,71), 275 (2,78), 285 (2,77)	75
IIIa	$C_{20}H_{24}BrN$	141...142	630, 760, 1570, 1590, 1630, 2240	226 (4,90), 242 (4,45), 278 (3,67), 305 (2,86), 320 (2,68)	IVa	224...245	0,52	750, 870, 1510, 1600, 1630	273 (3,60), 282 (3,78), 294 (3,72)	45
IIIb	$C_{22}H_{28}BrN$ ‡		735, 770, 1590, 1600, 1630, 2235	228 (4,91), 245 (4,47), 280 (3,68), 303 (2,82), 315 (2,69)						
IIIc	$C_{24}H_{28}BrN$	145...146	690, 730, 765, 1510, 1540, 1590, 1630, 2240	208 (4,96), 232 (5,56), 272 (4,56), 283 (4,54), 295 (4,51)	IVc	325...326	0,47	760, 870, 1505, 1605, 1640	275 (3,90), 282 (3,96), 295 (3,90)	62
VIa	$C_{20}H_{20}BrN$	132...134	710, 760, 790, 905, 980, 1590, 1620, 2220	208 (4,75), 225 (4,57), 290 (3,78), 303 (3,90), 315 (3,60)	VIIa	270...272	0,41	730, 760, 810, 870, 910, 1600, 1625	222 (5,42), 253 (5,20), 302 (4,64), 310 (4,62), 345 (2,78), 353 (2,72)	31
VIb	$C_{21}H_{22}BrN$	102...103	735, 780, 890, 1310, 1580, 1620, 2230, 3010, 3070	228 (4,66), 290 (2,77), 300 (2,95), 315 (2,78)	VIIb	285	0,37	730, 760, 810, 870, 905, 1510, 1590, 1605, 1630	217 (4,83), 260 (4,98), 305 (4,28), 318 (2,62), 335 (2,69), 350 (2,63)	37
VIc	$C_{23}H_{26}BrN$	109...110	690, 760, 1590, 1630, 2240	208 (4,75), 226 (4,55), 290 (3,78), 315 (2,77)						
VId	$C_{24}H_{26}BrN$	104...105	730, 770, 880, 1500, 1625, 2220	208 (4,42), 225 (4,69), 293 (3,90), 303 (4,00), 320 (3,78)						

Compounds Ia-c, IIa-c, IIIa and IIIc, IVa and IVc, VIa and VIb, and VIIa and VIIb are isomers.
†TLC on Silufol UV-254 plates in a 8:2:2:1 n-butanol/ethanol/water/acetic acid system.
‡Hygroscopic salt.

TABLE 2. Elemental Analysis Data for Compounds Ia-c, IIa-c, IIIa-c, IVa, IVc, VIa-d, VIIa and VIIb

Compound	Empirical formula	Found, %		Calculated, %	
		N	Br	N	Br
Ia	$C_{14}H_{20}BrN$	5.17	28.62	4.96	28.37
Ib	$C_{16}H_{24}BrN$	4.78	26.11	4.52	25.81
Ic	$C_{17}H_{24}BrN$	4.17	25.03	4.35	24.84
IIa	$C_{14}H_{20}BrN$	4.75	28.93	4.96	28.37
IIb	$C_{16}H_{24}BrN$	4.28	26.45	4.52	25.81
IIc	$C_{17}H_{24}BrN$	4.53	24.49	4.35	24.84
IIIa	$C_{20}H_{24}BrN$	3.84	22.81	3.91	22.34
IIIb	$C_{22}H_{28}BrN$	3.78	20.53	3.61	20.72
IIIc	$C_{23}H_{28}BrN$	3.98	20.34	3.51	20.10
IVa	$C_{20}H_{24}BrN$	3.75	22.03	3.91	22.31
IVc	$C_{23}H_{28}BrN$	3.75	20.35	3.51	20.10
VIa	$C_{20}H_{20}BrN$	4.15	22.56	3.95	22.31
VIb	$C_{21}H_{22}BrN$	3.65	21.92	3.82	21.73
VIc	$C_{23}H_{26}BrN$	3.72	21.85	3.53	22.20
VIb	$C_{24}H_{26}BrN$	3.62	19.98	3.43	19.60
VIIa	$C_{20}H_{20}BrN$	4.11	22.55	3.95	22.31
VIId	$C_{21}H_{22}BrN$	3.68	21.95	3.82	21.73

group in salts VIIa and VIIb produced a slight increase in the molar absorptivity logarithms of the intense absorption bands (see Table 1).

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer, samples being prepared in KBr tablet form or in petroleum jelly. UV spectra were taken in ethanol using a Specord UV-vis. TLC was carried out on Silufol UV-254 plates using an n-butanol–ethanol–water–acetic acid system (8:2:3:1) with iodine vapor development.

Salts Ia-c and IIIa-c used initially were obtained by reacting dialkyl(3-Δ′-cyclohexenylpropargyl)amines [9] with propargyl chloride or 3-phenylpropargyl chloride; salts VIa-d were prepared by reacting dialkyl(3-α-naphthylpropargyl)amino [5, 10] with 3-alkenylpropargyl bromides in absolute ether, adding acetonitrile if required. Yields of the salts obtained were almost quantitative. Physicochemical properties and spectral data for starting salts Ia-c, IIIa-c and VIa-d, and cyclic compounds IIa-c, IVa, VIIa and VIIb are shown in Table 1.

Elemental analysis data for N and Br were in line with calculated values for these salts.

General Technique for Cyclizing Salts Ia-c. First, 0.8-1.5 ml of 2 N KOH solution was added to a homogeneous solution comprising 7.7-15 mmoles of the starting salt in 4-6 ml water (5:1 salt–base molar ratio), a moderate amount of heat being evolved in the reaction. When the mixture had been heated for 2 h at 70-75°C, it was acidified with hydrobromic acid and evaporated to dryness. The organic salt was extracted with absolute ethanol, salts IIa-c being precipitated from the alcoholic solution with ether (see Table 1).

General Technique for Cyclizing Salts IIIa-c. The process was similar to the previous synthesis, the difference being that 6 ml water and 1-2 ml ethanol had to be added to dissolve 6.6 mmoles of the test salt completely. When salts IIIa and IIIc were cyclized, salts IVa and IVc precipitated out on standing at room temperature and were then filtered off (see Table 1). After the usual treatment of the mother liquor, TLC analysis showed that the residue consisted of two isomeric salts, with either IVa or IVb being the predominant isomer. However, it was not possible to separate them by means of fractional recrystallization. In the case of salt IIIb it was not possible to isolate either of the isomeric salts in pure form from the isomeric mixture.

General Technique for Cyclizing Salts VIa-d. A 0.6-1.0 ml sample of 2 N KOH solution was added to a homogeneous solution of 6-10 mmoles starting salt in 5-7 ml water (5:1 salt–base molar ratio), moderate heat being evolved in the reaction. The mixture was then heated for 1 h at 70-80°C. On the following day cyclic products VIIa and VIIb were separated off by filtering the mixture (see Table 1). The mother liquors were treated in the usual way, but it was not possible to isolate any of the isomeric cyclic products in pure form from the residue using fractional recrystallization.

When salts VIc and VId were cyclized, TLC data showed that isomeric cyclic products were afforded in almost equal yields, but isolation of these compounds proved impossible.

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