

SYNTHESIS OF CONDENSED ANALOGS OF DIHYDROISOINDOLINIUM COMPOUNDS
BY THE BASE-CATALYZED INTRAMOLECULAR DIENE CYCLIZATION OF DIALKYL-
2-ALKENYL-(3- α -NAPHTHYLPROPARGYL)AMMONIUM SALTS*

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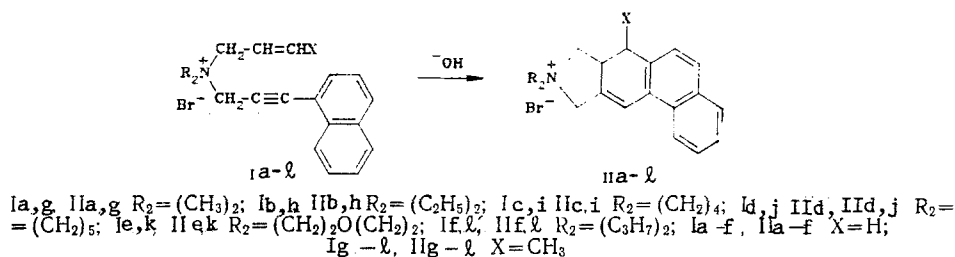
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Quaternary ammonium salts containing a 3- α -naphthylpropargyl group together with an allyl-type group undergo base-catalyzed intramolecular diene cyclization to give 2,2-dialkyl-naphtho[f]-3a,4-dihydroisoindolinium salts. Cleavage of the latter with aqueous alkali gives dialkylaminomethylphenanthrenes.

It has previously been shown that quaternary ammonium salts containing, in addition to a β,γ -unsaturated group, 3-alkenyl(aryl)propargyl group undergo base-catalyzed intramolecular cyclization to give isoindolinium compounds [2-4].

In order to obtain condensed isoindolinium analogs similar in structure to steroids, the cyclization of quaternary ammonium salts containing both an allyl-type group and a 3- α -naphthylpropargyl group as the potential diene fragment has been examined.

It has been found that dialkylallyl- ((Ia-e) and dialkyl-2-butenyl- (Ih-k))-(3- α -naphthylpropargyl)ammonium bromides, on heating (90-92°C, 2 h) in the presence of 0.2 mole of aqueous alkali undergo exclusively cyclization to 2,2-dialkyl- (IIa-e) and 2,2-dialkyl-4-methyl- (IIh-k)-naphtho[f]-3a,4-dihydroisoindolinium salts in high yields, in contrast to their 3-phenylpropargyl analogs. In the case of (If) and (Il), in addition to the cyclization products (75%), by-products were also formed (Table 2).



Under these conditions, the salts (Ig) gives the cyclization product (IIg) in a yield of only 51%, part of the starting material (34%) remaining unchanged. Under more severe conditions (0.4 mole of alkali, 90-92°C, 4-5 h), (IIg) was obtained in 74% yield.

The structures of the products were confirmed by their IR and UV spectra. The IR spectra of the cyclic salts (IIa-l) showed no absorption for disubstituted $C=C$ at 2230-2235 cm^{-1} , or for unsubstituted or monosubstituted $C=C$ at 930-960, 1640, or 1660 cm^{-1} , characteristic of the starting salts (Ia-l), but absorption was seen for the 1,2,3,4-substituted benzene ring at 800-820 cm^{-1} .

The UV spectra of the starting salts (Ia-l) showed characteristic absorption maxima for the naphthalene ring at 220, 275, 297, and 310 nm, whereas the spectra of the cyclic salts (IIa-l) showed a shift in these maxima towards longer wavelengths as a result of the presence of the dihydroisoindolinium ring.

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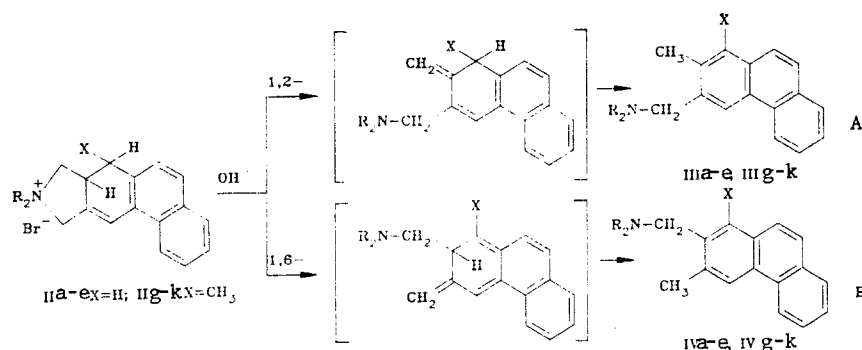
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TABLE 1. Properties of Dialkyl-3- α -naphthylpropargylamines (Vc-f)

Compd	Empirical formula	mp, °C (p, mm)	n_D^{20}	IR spectrum, cm^{-1}	Yield, %	mp of picrate, °C (from ethanol)
Vc	$\text{C}_{17}\text{H}_{17}\text{N}$	175 (3)	1.6255	700, 740, 780, 1510, 1540, 1590, 2220, 3015, 3060, 3090	70	155
Vd	$\text{C}_{18}\text{H}_{19}\text{N}$	197 (5)	1.6265	740, 780, 1510, 1580, 1865, 1920, 2230, 3010, 3060, 3095	66	174
Ve	$\text{C}_{17}\text{H}_{17}\text{NO}$	191...192 (4)	1.6230	705, 740, 1500, 1580, 1910, 1940, 2230, 3005, 3060, 3090	70	174...175
Vf	$\text{C}_{19}\text{H}_{23}\text{N}$	188...189 (4)	1.5840	780, 1500, 1560, 1600, 2240, 3060	65	138...140

The cleavage of 2,2-dialkyl-3- α -naphthyl-4-dihydroisondolinium (IIa-e) and 2,2-dialkyl-4-methylnaphthyl-3- α -4-dihydroisondolinium (IIa-l) salts with aqueous alkali has been examined (Tables 3 and 4). The cleavage of these salts may occur by the 1,2- or 1,6-pathways to give the two isomeric amines A or B [5].

Cleavage of these salts with aqueous alkali gives basically a single isomer. IR, UV, and PMR (60 MHz) spectroscopy failed to establish the mutual arrangement of the substituents in the nucleus. In all likelihood, those reaction products predominate which arise by the short 1,2-cleavage, i.e., amines of structure A. With the salts (IIh), (IIi), and (IIk), mixtures of the two isomeric amines A and B are obtained in overall yields of 77, 74, and 75% respectively. In the case of (IIk), recrystallization of the mixture from ether gave only one isomer, in a yield of 44%.



The IR spectra of IIIa-e, (IVa-e) and IIIg-k, (IVg-k) showed absorption for the 1,2-, 1,2,3,4-, and 1,2,4,5- or pentasubstituted benzene ring at 735-770, 810-850, and 870-880 cm^{-1} respectively (Tables 3 and 4).

The UV spectra of these amines showed maxima characteristic of the phenanthrene ring at 350-375 nm ($\log \epsilon$ 2.53-2.84). The PMR spectra gave little information. For example, the PMR spectrum of IIIj (IVj) was as follows: 1.43 (6H, br., piperidine ring CH_2), 2.41 (4H, br., piperidine ring N-CH_2), 2.63 (3H, s, CH_3), 2.72 (3H, s, CH_3), 3.56 (2H, s, N-CH_3), and 7.3-8.6 ppm (7H, m, =CH).

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer. Samples were prepared as KBr disks or in Vaseline grease. UV spectra were obtained in ethanol on a Specord UV-VIS. The PMR spectra of (IIIj) (IVj) was obtained in $\text{CCl}_4\text{-CD}_3\text{OD}$ (5:1) on a Perkin-Elmer R-12B, operating frequency 60 MHz. Chemical shifts are given on the δ scale relative to TMS. TLC was carried out on Silufol UV-254 plates in the system n-butanol-ethanol-water-acetic acid (8:2:3:1) and on alumina plates (Brockman grade II activity) in benzene in the system benzene-ether (1:1), visualized with iodine vapor.

The starting salts (Ia-l) were obtained by the reaction between the dialkyl-3- α -naphthyl-propargylamines and allyl bromide or 2-butenyl bromide in dry ether or a mixture of dry ether

TABLE 2. Properties of Starting (Ia-l) and Cyclic (IIg-l) Salts

Com- pound	Empirical formula	mp, °C (from ethanol)	IR spectrum, cm ⁻¹	UV spectrum, λ _{max} , nm	Com- pound*	mp, °C (from water) yield, %	n _D ²⁰	IR spectrum, cm ⁻¹	UV spectrum, λ _{max} , nm	Yield, %
Ia	C ₁₈ H ₂₀ BrN	61 ... 62	780, 940, 970, 1500, 1590, 1640, 2230, 3020	225, 235, 300	IIa	237 ... 238	0.45	770, 810, 1515, 1540, 1595, 1630, 3020	255, 263, 280, 305, 320, 332	93
Ib	C ₂₀ H ₂₄ BrN	139 ... 140	800, 950, 1500, 1640, 2230, 3000, 3030	227, 300, 312	IIb	274 ... 275	0.47	750, 770, 810, 1500, 1600, 1630	230, 270, 280, 310, 330	88
Ic	C ₂₀ H ₂₂ BrN	169	930, 960, 1500, 1600, 1640, 2230, 3030, 3060, 3090	220, 260, 280, 300, 348	IIc	300 ... 302	0.51	750, 780, 820, 1505, 1590, 1615, 3030, 3060	255, 280, 305, 320, 332	86
Id	C ₂₁ H ₂₄ BrN	170	750, 785, 940, 1510, 1590, 1640, 2235, 3060, 3090	225, 285, 300, 312	IId	311	0.46	730, 810, 1500, 1590, 3020, 3060	225, 260, 275, 285, 295, 315, 330	80
Ie	C ₂₀ H ₂₂ BrNO	158 ... 160	750, 970, 1510, 1590, 1640, 2230, 3050, 3070	225, 290, 305, 315	IIe	268 ... 269	0.48	750, 780, 1515, 1590, 1625, 3070	238, 320, 335	98
If	C ₂₂ H ₂₆ BrN	152 ... 153	930, 960, 1500, 1600, 1640, 2230, 3030, 3060, 3090	220, 260, 280	II f	232 ... 233	0.50	750, 780, 820, 1500, 1570, 3030, 3060	250, 280, 320, 330	75
Ig	C ₁₈ H ₂₂ BrN	113	740, 780, 1510, 1590, 1660, 2230	225, 285, 300, 312	IIg	263 ... 265	0.41	760, 810, 1500, 1530, 1580, 1610	240, 305, 320, 335	51 #
Ih	C ₂₁ H ₂₆ BrN	98 ... 100	760, 780, 1590, 1660, 2230	225, 290, 300, 312	IIh	225	0.43	760, 810, 1500, 1600, 1610	230, 280, 320, 340	91
Ii	C ₂₁ H ₂₄ BrN	138 ... 139	760, 785, 1660, 2230	227, 288, 300, 315	IIi	270	0.46	760, 810, 1500, 1600, 1610	230, 260, 272, 292, 300, 340	97
Ij	C ₂₀ H ₂₂ BrN	165	770, 1500, 1600, 1660, 2240	228, 300	II j	308 ... 309	0.48	730, 760, 810, 1510, 1610	230, 275, 310, 330	84
Ik	C ₂₁ H ₂₄ BrNO	163	735, 770, 790, 1500, 1580, 1660, 3050	228, 288, 298, 308	IIk	285 ... 287	0.50	730, 770, 800, 1500, 1600	230, 260, 280, 295, 305, 342	97
Il	C ₂₃ H ₃₀ BrN	149 ... 150	760, 1500, 1660, 2235	227, 300, 310	IIl	232 ... 234	0.44	730, 760, 825, 1500, 1600	228, 255, 265, 280, 290, 300, 340	75

*Compounds (Ia-l) and (IIa-l) are isomers.

†TLC was carried out on Silufol UV-254 plates in the system n- butanol-ethanol-water-acetic acid (8:2:3:1).

#In the presence of 0.4 equiv, of aqueous alkali and on heating for 45 h at 90-92°C, the product (IIg) was obtained in 74% yield.

TABLE 3. Properties of 2(3)-Methyl-3(2)-dialkylaminomethyl-phenanthrenes IIIa-e (IVa-e)

Compound	Empirical formula	bp, °C (p, mm)	IR spectrum, cm ⁻¹	UV spectrum, λ_{\max} , nm (log ϵ)	Yield, %	mp of picrate, °C (from ethanol)
IIIa (IVa)	C ₁₈ H ₁₉ N	160 (0,3)	740, 810, 855, 1500, 3040	255 (5,01), 300 (3,08), 350 (2,53)	83	176...177
IIIb (IVb)	C ₂₀ H ₂₃ N	175 (2)	750, 775, 810, 870, 1500, 1620, 3010, 3020, 3030	215 (3,57), 223 (3,36), 332 (2,85), 380 (2,56)	85	134...136
IIIc (IVc)	C ₂₀ H ₂₁ N	130 (0,1)	760, 815, 870, 1520, 1600, 3040, 3060	252 (5,04), 292 (4,11), 312 (2,89), 328 (2,81), 345 (2,59)	79	152...153
IIId (IVd)	C ₂₁ H ₂₃ N	180 (0,1)	760, 770, 810, 850, 1500, 1600	218 (4,62), 260 (4,85), 280 (4,28), 300 (4,06), 332 (2,85), 350 (2,52)	75	194
IIIe (IVe)	C ₂₀ H ₂₁ NO	185 (0,1)	750, 770, 810, 870, 1500, 1600	215 (4,75), 255 (4,96), 295 (4,30), 330 (2,70), 345 (2,48)	73	203...205

TABLE 4. Properties of 1.2(3)-Dimethyl-3(2)-dialkylaminomethylphenanthrenes IIIg, j, k (IVg, j, k)

Compound	Empirical formula	mp, °C (from ether)	R _f *	IR spectrum, cm ⁻¹	UV spectrum, λ_{\max} , nm (log ϵ)	Yield, %	mp of picrate, °C (from ethanol)
IIIg (IVg)	C ₁₉ H ₂₁ N	55	0,52	820, 870, 1600	218 (4,52), 260 (4,80), 298 (3,85), 350 (2,69)	94	153...155
IIIj (IVj)	C ₂₂ H ₂₅ N	112	0,79	750, 770, 810, 880, 1510, 1590	252 (4,77), 260 (4,97), 290 (4,03), 300 (4,11), 350 (2,67)	87	210
IIIk (IVk)	C ₂₁ H ₂₃ NO	122	0,58	730, 760, 870, 1590	217 (4,43), 253 (4,42), 260 (4,55), 280 (3,86), 300 (3,76), 355 (2,84)	44†	194...195

*TLC was carried out on alumina plates using benzene-ether (1:1) for IIIg (IVg) and IIIk (IVk), and benzene for IIIj (IVj).

†The yields given are for the amount of pure amine isolated from the mixture.

and acetonitrile. The synthesis of the required dimethyl- (Va) and diethyl- (Vb) 3- α -naphthylpropargylamines has been described [6]. 3- α -Naphthylpropargylpyrrolidine (Vc), 3- α -naphthylpropargylpiperidine (Vd), 3- α -naphthylpropargylmorpholine (Ve), and dipropyl-3- α -naphthylpropargylamine (Vf) were obtained similarly (Table 1). The physico-chemical characteristics of the starting amines, the starting and cyclic salts, and the cleavage products are given in Tables 1-4. The elemental analyses of (I) and (II) for Br and N, and of (III-V) for C, H, and N were in agreement with the calculated values.

General Method of Cyclization of Dialkylallyl- (Ia-f) and Dialkyl-2-butenyl- (Ig-l) -(3- α -naphthylpropargyl)ammonium Bromides. To a homogeneous solution of 5-10 mmole of the salt in 5-10 ml of water was added 0.5-1.0 ml of 2 N KOH (molar ratio of salt to base, 5:1). No evolution of heat was noted. The mixture was heated for 2 h at 90-92°C. After 1-2 days, crystals of the cyclic salt separated out. To remove possible by-products, the mixture was extracted with ether (2 \times 10 ml). Filtration gave the cyclization product.

Cleavage of Salts (IIa-e) and (IIg-k) with Aqueous Alkali. To an aqueous solution of 3-5 mmole of the salt in 5-10 ml of water was added a threefold molar amount of 25% aqueous KOH. Cleavage was carried out at 120-130°C, the product being distilled with water, more water (30-40 ml) being added from time to time to ensure completion of the cleavage. Heating was continued for 2-3 h, the temperature being raised over the last 5-10 min to 150-160°C. The distillate and the residue were then extracted with ether (3 \times 25 ml), and the ether extract treated with hydrochloric acid. Basification of the hydrochloric acid solution and extraction

with ether (3 × 30 ml) gave the amine products. The ether layer was washed with water (2 × 10 ml), and dried over magnesium sulfate.

In the case of amines IIIa-e (IVa-e), the ether was removed, and the residue distilled in vacuo. In preparing the amines IIIg-k (IVg-k), the ether extract was partially evaporated, and the crystals which separated were filtered off and recrystallized from ether.

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SYNTHESIS AND PROPERTIES OF 2,7-DIAZABICYCLO[2.2.2]OCTANE-3,8-DIONES AND -3,8-DITHIONES

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In an alkaline medium, 3,4-dihydropyridin-2(1H)-ones form 2,7-diazabicyclo[2.2.2]-octane-3,8-diones, which are thiolated to the corresponding dithiones. The alkylation of the last proceeds at the sulfur atoms with the formation of 2,7-diazabicyclo[2.2.2]octa-2,7-dienes.

The formation of bicycles in the series of 1,4-dihydropyridines is known when they are alkylated with dibromopropane [1], as a result of the reaction of ortho substituents in 4-aryl-substituted 1,4-dihydropyridines with the dihydropyridine ring [2], as well as in the cycloaddition of styrene or allyl-trimethylsilane to dihydropyridines [3].

We investigated the formation of 2,7-diazabicyclo[2.2.2]-octane-3,8-diones based on 3-amido-substituted 3,4-dihydropyridin-2(1H)-ones.

It was found that 3-carbamoyl-4,6-diphenyl-3,4-dihydropyridin-2(1H)-one (I) and 3-carbamoyl-4,6-diphenyl-6-hydroxy-3,4-dihydropyridin-2(1H)-one (IA) undergo intramolecular cyclization in an alkaline medium with the formation of 2,7-diaza-1,5-diphenylbicyclo[2.2.2]-octane-3,8-dione (IIa).

It was shown that the bicycle (IIa) is identical to the product obtained by the condensation of benzylidenacetophenone and malonic diamide, for which the structure of 3,4-dihydropyridin-2(5H)-one (III) was proposed on the basis of the ^1H NMR spectrum [4, 5].

