Chemistry of Heterocyclic Compounds, Vol. 31, No. 1, 1995

BEHAVIOR OF PROPARGYL- AND ALLYLPROPARGYL-AMMONIUM SALTS IN AQUEOUS ALKALINE MEDIUM. SYNTHESIS OF 2-METHYL-2-PHENYLBENZ[f]ISOINDOLINIUM AND 2-METHYL-2-PHENYLISOINDOLINIUM SALTS*

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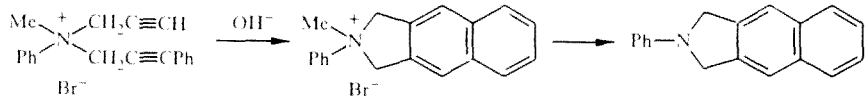
Methylphenylpropargyl-(3-phenylpropargyl)-ammonium bromide salts are cyclized almost quantitatively under base-catalysis conditions with the formation of 2-methyl-2-phenylbenz[f]isoindolinium bromide. The allyl analog is subject to rearrangement–decomposition, to a Stevens rearrangement, and to nucleophilic substitution, the cyclic product being obtained in low yield. Methylphenylpropargyl-(3-vinylpropargyl)ammonium bromide is mainly cyclized, but the 3-isopropenylpropargyl analog of this salt is subject to cyclization and subsequent decomposition under analogous conditions.

Dialkylpropargyl-(3-aryl)- or (3-alkenylpropargyl)-ammonium salts are cyclized almost quantitatively at room temperature with evolution of heat, while heat is required for the cyclization of the allyl analogs of 3-arylpropargyl salts. Rearrangement–decomposition takes place in addition to cyclization (76-84%) [2-4].

In order to obtain new data to establish the mechanism of the base-catalyzed intramolecular cyclization of ammonium salts it is expedient to clarify the influence on this reaction of the presence of an N-phenyl group. We therefore studied the ability of methylphenylpropargyl(3-phenylpropargyl)- (I), methylphenylallyl(3-phenylpropargyl), (II), methylphenylpropargyl(3-vinylpropargyl)- (III), and methylphenylpropargyl(3-isoprophenylpropargyl)- (IV) ammonium salts to undergo cyclization under base-catalysis conditions. A fortunate outcome would be the possibility of synthesizing potentially bioactive isoindolinium salts containing a phenyl group at the nitrogen atom.

It became apparent that salt (I) is cyclized almost quantitatively under base-catalysis conditions with the evolution of heat, like the dialkyl analog.



I Ia Ib

The salt (II) is almost unchanged under the conditions indicated. On gradual addition of 0.8 g-eq alkali per g-mole salt (II) with heating (90°C, 8 h) the reactions occurring were a rearrangement–decomposition (35%), a Stevens rearrangement (27%), and nucleophilic substitution (17%). Only 10% cyclization occurred.

*Part 225 of the series on "Investigations on Amines and Ammonium Compounds," see [1] for part 224.

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Institute of Organic Chemistry, Academy of Sciences of the Armenian Republic, Yerevan 375094. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 68-72, January, 1995. Original article submitted December 19, 1994.

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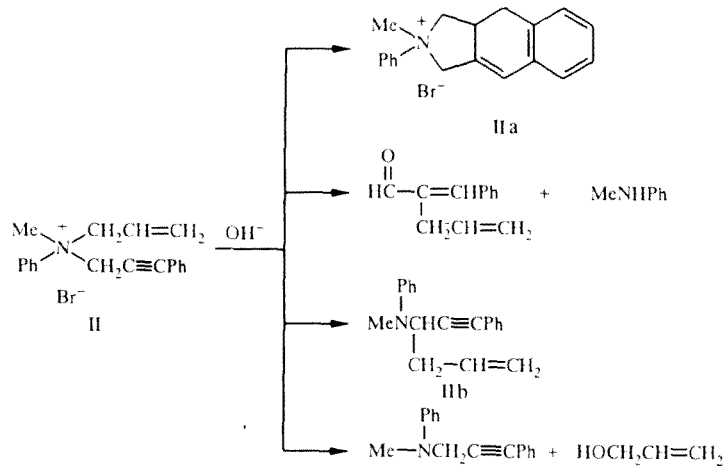
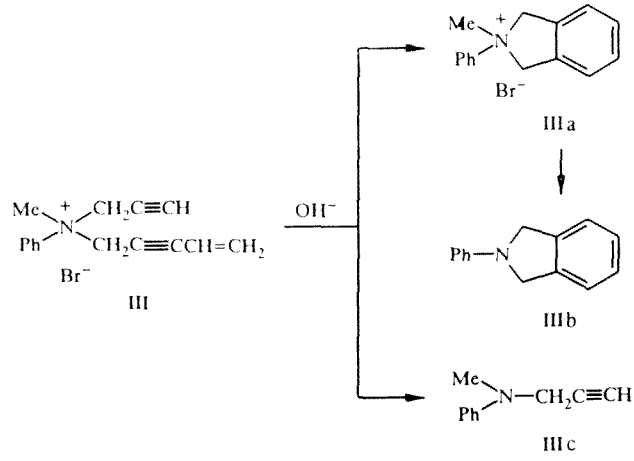
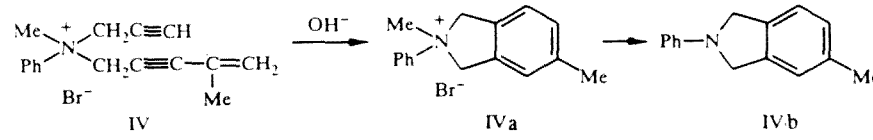


The salt (III) is cyclized at room temperature with evolution of heat, like the dialkyl analog, forming methylphenylisoindolinium bromide (IIIa) in 56% yield. In addition to the cyclic product (IIIa) a decomposition product of salt (IIIa) was obtained, viz. 2-phenylisoindoline (IIIb), in 12% yield, and the product of nucleophilic substitution of the initial salt (III), viz. methylphenylpropargylamine (IIIc), in 14% yield.

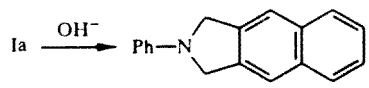


Salt (IV) rapidly undergoes cyclization–decomposition at room temperature with brisk evolution of heat and the formation of 5-methyl-2-phenylisoindoline (IVb) in 78% yield.

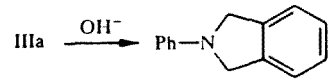


It is therefore apparent that a phenyl substitution is unfavorable for cyclization only in the case of the salt with an allyl group (II). This suggests that probably the cyclization mechanism of salts containing an allyl group as well as a 3-phenylpropargyl group is different from the cases with propargyl. These are other data in favor of this hypothesis, obtained by us previously, according to which dialkylmethallyl(3-phenylpropargyl)ammonium salts are subject only to rearrangement–decomposition under base-catalysis conditions while the propargyl analog of this salt is cyclized almost quantitatively [5].

It has been shown that, unlike the dimethyl analogs, the salts (Ia) and (IIIa) readily lose a methyl group under conditions of aqueous alkaline decomposition forming 2-phenylbenz[f]isoindoline (Ib) and 2-phenylisoindoline (IIIb) in yields of 80 and 75% respectively.



Ib



IIIb

Absorption bands for disubstituted C≡C at 2240 cm^{-1} characteristic of the initial salts (I)-(III), for monosubstituted C≡C at 1640 cm^{-1} characteristic of salt (II), and for monosubstituted C≡C at 2125 cm^{-1} characteristic of salt (I), were all absent from the IR spectra of the cyclic salts (Ia)-(IIIa). Characteristic absorption bands for a mono- and ortho-disubstituted benzene ring at 690-710 cm^{-1} were detected for salts (Ia)-(IIIa). Salt (Ia) has a characteristic absorption band for a 1,2,4,5-substituted ring a 860 cm^{-1}.

There were absorptions at 240, 245, ad 255 nm characteristic of a benzene ring in the UV spectra of salts (I)-(III). The presence of a naphthalene ring in the molecule of salt (Ia) leads to a displacement of the absorption bands to the longer wavelength region of the spectrum (270, 280, 305, 320 nm) [6]. The combination of a benzene ring with multiple bonds in the molecule of salt (IIa) leads as expected to the display in the UV spectrum of a broad absorption band at 286 nm (log ε 4.23) characterizing the overall conjugated system of the molecule [6]. The vibrational structure of the benzene absorption bands at 255-268 nm is retained in the UV spectrum of salt (IIIa). Absorption bands were also detected at 272 and 280 nm.

The structures of salts (Ia) and (IIIa) were also confirmed by PMR spectroscopy. Signals were detected in the spectra of salts (Ia) and (IIIa) for the N^+CH_3 group at 3.57 and 3.60 ppm, for the N^+CH_2 group at 5.54, 5.84, and 5.45, 5.78 ppm respectively, and signals for the aromatic protons of C_6H_5 and $C_{10}H_6$ at 7.4-8.3 ppm for (Ia) and at 7.15-8.15 ppm for (IIIa).

EXPERIMENTAL

The IR spectra were taken on a UR 20 spectrometer. Samples were prepared in KBr disks or Nujol mulls. The UV spectra were taken on a Specord UV-VIS spectrophotometer in ethanol. The PMR spectra of salts (Ia) and (IIIa) were obtained on a Perkin–Elmer R 12 instrument with an operating frequency of 60 MHz, internal standard was HMDS.

The purity of amines was established by GLC on a LMKh 72 chromatograph, the column (150 × 4 cm) was packed with Inerton Super (0.125-0.160) treated with 5% OV-1, carrier gas was helium (50 ml/min) at 180°C. The purity of salts was established by TLC on Silufol UV 254 plates in the system of n-butanol–ethanol–water–acetic acid, 8:2:3:1, visualizing with iodine vapor.

The initial N-methyl-N-propargyl- and N-methyl-N-allylanilines were obtained by the known procedures of [7, 8]. Salts (I)-(IV) were obtained by the reaction of N-methyl-N-propargyl- and N-methyl-N-allylanilines with phenylpropargyl, vinylproparyl, and isopropenylpropargyl bromides in acetonitrile. Yields were almost quantitative.

Salts (I)-(IV), (Ia)-(IIIa), N-methyl-N-(1-allyl-3-phenylpropargyl)aniline, 2-phenylisoindoline, 2-phenylisoindoline, and 2-phenyl-5-methylisoindoline are described for the first time. The physicochemical characteristics of the initial (I)-(IV) and cyclic (Ia)-(IIIa) salts for given in Tables 1 and 2.

The date of elemental analysis for Br and N for salts (I)-(IV) and (Ia)-(IIIa) for C, H, and N for amines (Ib), (IIIb), (IVb), and N-phenyl-N-(1-allyl-3-phenylpropargyl)aniline (IIb) corresponded to calculated values.

2-Methyl-2-phenylbenz[f]isoindolinium Bromide. A 1.9 N solution of KOH (2 ml) was added to a homogeneous solution of salt (I) (5.6 g) in water (22 ml) (molar ratio salt–base 5:1). The temperature of the reaction mixture rose instantly with the evolution of heat from 25 to 100°C. The isoindolinium salt (Ia) (4.9 g: 88%) was isolated by filtration.

2-Methyl-2-phenyl-3a,4-dihydrobenz[f]isoindolinium Bromide (IIa). A 1.9 N solution of KOH (89 ml) was added in portions (2 ml) to a homogeneous solution of salt (II) (5.2 g, 15 mmole) in water ((8 ml). The reaction mixture was heated at 90°C for 1.5 h and then extracted with ether (3 × 50 ml). The ether extracts were combined and the formation of amine (13.7 mmole, 78%) established by titration. The isoindolinium salt (IIa) (0.52, 10%) was isolated by filtration from the reaction mixture.

The ether extract was treated with hydrochloric acid and the acid layer separated form the ether. α-Allylcinnamic aldehyde (0.9 g, 35%) was obtained from the ether layer. The dinitrophenylhydrazone melted at 170°C and gave no depression of melting point with an authentic sample [3]. Before vacuum distillation the α-allylcinnamic aldehyde contained traces of allyl alcohol according to data of GLC and IR spectra [3200-3400 cm^{-1} (OH)]. By making the hydrochloric acid layer alkaline and

TABLE 1. Characteristics of the Initial Ammonium Salts (I)-(IV)

Compound	Empirical	Mp, °C (from abs. ethanol)	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)
I	$C_{19}H_{18}BrN$	118...120	780, 1480, 1600, 2120, 2240, 3200	208 (4,78), 245 (4,53)
II	$C_{19}H_{20}BrN$	Hygroscopic	1500, 1600, 1640, 2240	205 (4,96), 240 (4,76) 253 (4,75)
III	$C_{15}H_{16}BrN$	105...107	690, 770, 1500, 1600, 2120, 2240, 3020, 3080	225 (4,61), 238 (4,48) 208 (4,76)
IV	$C_{16}H_{18}BrN$	110...111	695, 760, 1510, 1600, 2125, 2240, 3030, 3080	208 (4,64), 245 (4,15)

TABLE 2. Characteristics of the Cyclic Salts (Ia)-(IIIa)

Compound*	Mp, °C (ethanol)	R_f*2	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum (CD_3OD), δ, ppm (J, Hz)	Yield, %
Ia	227...228	0,43	740, 770, 860, 1500, 1600, 3040, 3060	220 (4,93), 260 (4,39), 270 (4,36), 280 (4,26), 305 (3,60), 320 (3,00)	3,57 (3H, s, N^+CH_3); 5,54, 5,84 (4H, m, N^+CH_2, J = 14,5); 7,4...8,3 (11H, C_6H_5 and $C_{10}H_6$, m)	88
IIa	206	0,48	690, 740, 770, 1500, 1600	206 (4,82), 233 (5,04), 286 (4,23)		10
IIIa	182	0,50	690, 710, 770, 1500, 1590, 3040	205 (5,90), 255 (4,60), 260 (4,60), 265 (4,60), 270 (4,58), 272 (4,40), 280 (4,00)	3,60 (3H, s, N^+CH_3); 5,45, 5,78 (4H, m, N^+CH_2, J = 13,5); 7,15...8,15 (9H, C_6H_4 and C_6H_5, m)	56

*Compounds (I)-(III) and (Ia)-(IIIa) are isomers.

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

then extracting with ether (3 × 50 ml) a mixture (according to GLC) of three amines (2.1 g) was isolated. These were N-methyl-N-(1-allyl-3-phenylpropargyl)aniline (IIb) (1 g, 27%), N-methyl-N-(3-phenylpropargyl)aniline (0.54 g, 17%), and N-methylaniline (0.66 g, 35%). The initial salt (II) (0.3 g, 6%) was also obtained. The identification of the amines in the mixture was effected by chromatography with authentic samples of N-methylaniline and of (IIb) obtained under conditions of a Stevens rearrangement. The presence of N-methyl-N-(3-phenylpropargyl)aniline in the mixture of amines was established by the IR spectrum: 920, 1500, 1600, 3040, 3060 cm^{-1}.

2-Methyl-2-phenylisoindolinium Bromide (IIIa). A 2.3 N solution of KOH (1.1 ml) was added to a homogeneous solution of the initial salt (III) (3.3 g, 12.3 mmole) in water (7-8 ml) (molar ratio salt – base 5:1). The temperature of the reaction mixture rose in 5 min from 30°C to 40°C as a result of the evolution of heat and then increased instantly to 95°C. The mixture was extracted with ether (3 × 15 ml) to remove side products. Slat (IIIa) (1.85 g, 56%) was isolated by filtration. The ether extract was treated with hydrochloric acid. The amine products were isolated by making the acid solutio alkaline and extracting with ether (4 × 20 ml). 2-Phenylisoindoline (IIIb) (0.3 g, 12%) was isolated from the ether extract by filtration. IR spectrum 690, 730, 740, 750 (mono- and ortho-disubstituted benzene ring), 1510, 1600, 3030, 3070 cm^{-1} (aromatic ring). The mother liquor was dried over $MgSO_4$. Methylpropargylaniline (0.26 g, 145) was obtained after distillation of the ether. The hydrochloride melted at 142°C and gave no depression of melting point with an authentic sample [7].

2-Phenylbenz[f]isoindoline (Ib) $C_{18}H_{15}N$. A twofold molar quantity of 25% KOH solution was added to a solution of salt (Ia) (1.9 g, 5.5 mmole). Decomposition was carried out at 112-120°C with distillation for 1 h. The reaction product (Ib) crystallized as coarse yellow–green crystals in the condenser and in the aqueous distillate. Compound (Ib) (1.1 g, 80%) was separated mechanically. It charged at 240°C. IR spectrum: 690, 720, 730, 790 (mono- and ortho-disubstituted benzene ring), 870 (1,2,4,5-substituted benzene ring), 1490, 1590, 3040, 3060 (aromatic ring).

2-Phenylisoindoline (IIIb) $C_{14}H_{13}N$. A twofold molar quantity of aqueous 25% KOH solution was added to a homogeneous solution of salt (IIIa) (0.8 g, 2.8 mmole). Decomposition was effected at 110-115°C with distillation of the water for 20-30 min. The distillate and reaction residue were then extracted with dichloromethane (3 × 30 ml) and the extract dried over $MgSO_4$. After removing the solvent 2-phenylisoindoline (IIIb) (0.45 g, 75%) of mp 120°C was obtained, giving no depression of melting point with (IIIb) obtained from salt (III) under base-catalysis conditions.

5-Methyl-2-phenylisoindoline (IVb) $C_{15}H_{15}N$. A 1.9 N solution of KOH (0.8 ml) was added to a homogeneous solution of salt (IV) (2.3 g 7.5 mmole) in water (3 ml) (molar ratio salt–base 5:1). The temperature of the reaction mixture rose instantly from 25°C to 100°C with self-heating. At 80°C crystals of 2-phenyl-5-methylisoindoline (IVb) (1.2 g, 78%) of mp 121°C were precipitated. IR spectrum: 700, 780 (monosubstituted benzene ring), 875 (1,2,4-substituted benzene ring), 1510, 1590, 1600, 3040 cm^{-1} (aromatic ring).

N-Methyl-N-(1-allyl-3-phenylpropargyl)aniline (IIb) $C_{19}H_{19}$. Salt (II) (2.7 g, 7.8 mmole) was ground thoroughly with a threefold molar quantity of powdered KOH and methanol (2-3 drops) was added. Reaction occurred at room temperature with evolution of heat. The reaction mixture was extracted with ether (3 × 20 ml). The aniline (IIb) (1.5 g, 75%) was obtained by the usual processing of the ether extract and had bp 160°C (4 mm Hg), n_D^{20} 1.6020. IR spectrum: 1640 (C≡C), 2240 (C≡C), 690, 770, 1500, 1600, 3040, 3060 cm^{-1} (aromatic ring). Picrate, mp 106°C.

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