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INVESTIGATIONS IN THE AREA OF AMINES AND AMMONIUM COMPOUNDS. 237.* SYNTHESIS OF 2,2-DIALKYL-4-HYDROXYMETHYLBENZO-[*f*]ISOINDOLINIUM AND 2,2-DIALKYL-4-HYDROXYMETHYLISOINDOLINIUM SALTS

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The ability of the 4-hydroxy-2-butynyl group to participate as β,γ-unsaturated fragment in base-catalyzed intramolecular cyclization was established. 2,2-Dialkyl-4-hydroxymethylbenzo[f]-isoindolinium and 2,2-dialkyl-4-hydroxymethylisoindolinium salts were obtained by the cyclization of dialkyl(4-hydroxy-2-butynyl)(3-phenylpropargyl)- or dialkyl(4-hydroxy-2-butynyl)(3-alkenylpropargyl)-ammonium salts.

Keywords: alkenylpropargyl and phenylpropargyl groups, 4-hydroxy-2-butynyl group, 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium and 2,2-dialkyl-4-hydroxymethylisoindolinium salts, base catalysis, cyclization.

Under the conditions of base catalysis quaternary ammonium salts containing groups of the propargyl or allyl type together with 3-alkenyl or 3-arylpropargyl group undergo intramolecular cyclization of the diene synthesis type, forming isoindolinium and dihydroisoindolinium salts and their condensed analogs [2, 3].

In order to reveal the ability of the 4-hydroxy-2-butynyl group to participate in cyclization and in the preparation of new potentially biologically active isoindolinium salts the behavior of dialkyl(4-hydroxy-2-butynyl)(3-phenylpropargyl)ammonium bromides **1a-f** under the conditions of base catalysis was investigated. It was shown that in the presence of 0.2 mole of aqueous alkali to 1 mole of the salt they readily undergo cyclization, forming 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium bromides **2a-f** with yields of 75-80%.

Cyclization of the salts **1a-f**, in contrast to their propargyl analogs [2, 3], requires treatment of the reaction mixture at 50-55°C for 5-10 min, after which spontaneous heating is observed, and the temperature of the reaction mixture rises to 80-85°C.

* For Communication 236, see [1].

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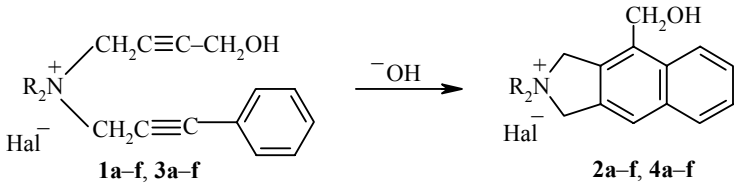


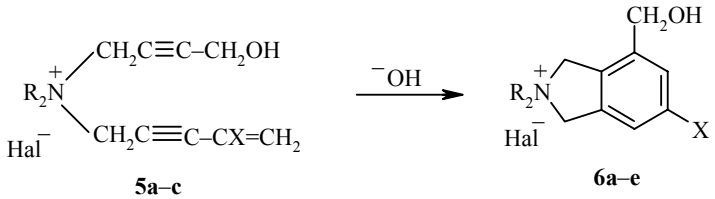
1a–f, **3a–f** **2a–f**, **4a–f**

1a, **2a** R = Et; **1b**, **2b** R = Pr; **1c**, **2c** R = Bu; **1d**, **2d** $R_2 = (CH_2)_4$; **1e**, **2e** $R_2 = (CH_2)_5$; **1f**, **2f** $R_2 = (CH_2)_2O(CH_2)_2$; **3a**, **4a** R = Me; **3b**, **4b** R = Et; **3c**, **4c** R = Pr; **3d**, **4d** R = Bu; **3e**, **4e** $R_2 = (CH_2)_5$; **3f**, **4f** $R_2 = (CH_2)_2O(CH_2)_2$; **1a-f**, **2a-f** Hal = Br; **3a-f**, **4a-f** Hal = Cl

The initial salts **1a-f** were prepared by the reaction of dialkyl-4-hydroxy-2-butynylamines [4] with 3-phenylpropargyl bromide. Dimethyl(4-hydroxy-2-butynyl)(3-phenylpropargyl)ammonium chloride **3a** was synthesized by the reaction of dimethyl-3-phenylpropargylamine with chromatographically pure 1-chloro-4-hydroxy-2-butyne, prepared by the familiar method [5]. Dialkyl(4-hydroxy-2-butynyl)(3-phenylpropargyl)-ammonium chlorides **3b-f** were synthesized in the same way. The latter, unlike their bromine analogs **1a-f**, undergo cyclization under the conditions of base catalysis under milder conditions, forming 3-hydroxymethylbenzo[*f*]isoindolinium chlorides **4a-f** with yields of 80-85%.

It is interesting in relation to the presented results to investigate further the effect of various halide ions on the physiological activity of isoindolinium salts.

As shown in the case of the salts **5a-e** the 3-alkenyl analogs of the salts **1a-e** and **3a-e** are also capable of cyclization. The cyclic products **6a-e** were obtained with yields of 70-75%.



5a–c **6a–e**

5a, **6a** R = Me, X = H, Hal = Cl; **5b**, **6b** R = Et, X = H, Hal = Cl; **5c**, **6c** R = Et, X = H, Hal = Br; **5d**, **6d** R = Et, X = Me, Hal = Cl; **5e**, **6e** $R_2 = (CH_2)_2O(CH_2)_2$; X = Me, Hal = Br

Of the products **2**, **4**, and **6** only the salts **2d-f**, **4f**, and **6e** were obtained in the crystalline form.

The IR spectra of the initial salts **1a-f**, **3a-f**, and **5a-e** contain characteristic absorption bands for the disubstituted acetylenic bond at 2220-2230 and for the hydroxyl group at 1020 and 3200-3400 cm^{-1}. In the spectra of the salts **1** and **3** containing the 3-phenylpropargyl fragment there are characteristic absorption bands of the aromatic ring at 1500, 1600, and 3060 cm^{-1} and of the monosubstituted benzene ring at 690, 720, and 750 cm^{-1}, while in the spectra of their 3-alkenylpropargyl analogs there are absorption bands for the $–CH{=}CH_2$ group at 920 and 930 cm^{-1} or $–C{=}CH_2$ group at 890 cm^{-1} and also the conjugated C=C bond at 1580-1610 cm^{-1}.

In the spectra of the cyclization products **2a-f** and **4a-f** respectively there are no absorption bands for the disubstituted C≡C bond and monosubstituted benzene ring mentioned above, while in the spectra of the cyclic salts **6a-e** there are no absorption bands for the $–CH{=}CH_2$ and $–C{=}CH_2$ fragments characteristic of the initial salts **5a-e**.

In the IR spectra of the cyclic salts **2a-f** and **4a-f** there are absorption bands for the 1,2-substituted and pentasubstituted benzene rings at 740, 750, 770, and 870 cm^{-1} respectively, while in the spectra of the salts **6a-e** there are bands for the 1,2,3- and 1,2,3,5-substituted benzene rings at 710, 720 and 850, 860, 1960 cm^{-1} respectively. The spectra of salts **2a-f**, **4a-f**, and **6a-e** also contain characteristic absorption bands for the hydroxyl group at 1050 and 3200-3500 cm^{-1}.

TABLE 1. The Characteristics of the Salts **1a-f**–**4a-f**, **5a-e**, and **6a-e**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum λ_{max}, nm (ε)	Compound*	Found, %		mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (ε)
		Hal	N					Hal	N			
1	2	3	4	5	6	7	8	9	10	11	12	13
1a	$C_{17}H_{22}BrNO$	23.50 / 23.81	4.05 / 4.17	75-76	700, 770, 1020, 1500, 3030, 3060, 3200-3500	215 (4.20)	**2a**	23.35	3.97	*[2]	730, 770, 870, 1050, 1510, 1600, 3060, 3200-3500	230 (4.51), 285 (3.87), 296 (3.65), 325 (2.70)
1b	$C_{19}H_{26}BrNO$	21.76 / 21.98	3.54 / 3.85	100-102	690, 770, 1020, 1580, 2230, 3030, 3050, 3200-3400	245 (4.25)	**2b**	22.45	3.66	*[2]	730, 760, 870, 1050, 1500, 3030, 3200-3400	233 (4.55), 275 (3.50), 325 (2.62)
1c	$C_{21}H_{30}BrNO$	20.22 / 20.41	3.30 / 3.57	120-121	700, 750, 1030, 1510, 1580, 2240, 3200-3400	245 (4.18)	**2c**	20.15	3.24	*[2]	750, 870, 1045, 1500, 3030, 3200-3450	232 (4.50), 275 (3.56), 286 (3.59), 325 (2.53)
1d	$C_{17}H_{20}BrNO$	23.73 / 23.95	4.07 / 4.19	110-112	690, 760, 1020, 1500, 1550, 1600, 2220, 3060, 3200-3300	245 (4.25)	**2d**	23.68	3.88	224-225	730, 760, 860, 1055, 1500, 1560, 1600, 3300-3400	230 (4.51), 275 (3.45), 285 (3.50), 298 (3.26), 325 (2.56)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
1e	$C_{18}H_{22}BrNO$	22.68 22.99	3.85 4.02	130-131	690, 720, 740, 1020, 1500, 2230, 3200-3400	245 (4.20)	**2e**	22.73	4.21	240-241	730, 770, 860, 1050, 1510, 1550, 1600, 3060, 3200-3400	232 (4.46), 275 (3.52), 285 (3.59), 327 (2.61)
1f	$C_{17}H_{20}BrNO_2$	22.60 22.86	3.78 4.00	168-170	690, 780, 1020, 1500, 2240, 3300-3400	245 (4.50)	**2f**	22.61	3.83	247-248	730, 770, 870, 1510, 1550, 1050, 1600, 3060, 3200-3500	232 (4.57), 275 (3.50), 287 (3.60), 297 (3.48), 322 (2.60), 327 (2.64)
3a	$C_{15}H_{18}ClNO$	13.09 13.47	5.06 5.31	*[2]	700, 770, 1020, 1510, 3060, 3200-3500	245 (4.30)	**4a**	13.22	5.12	Oil	730, 770, 860, 1050, 1510, 1600, 3030, 3200-3450	230 (4.46), 287 (3.75), 300 (3.75), 325 (2.85)
3b	$C_{17}H_{22}ClNO$	11.82 12.18	4.52 4.80	*[2]	700, 750, 1020, 1500, 1600, 2230, 3060, 3200-3500	245 (4.25)	**4b**	12.49	4.52	Oil	740, 750, 870, 1050, 1510, 1600, 3050, 3200-3500	230 (4.55), 285 (3.89), 296 (3.70), 325 (2.72)
3c	$C_{19}H_{26}ClNO$	10.88 11.11	4.07 4.38	*[2]	700, 770, 1020, 1550, 2220, 3030, 3050, 3200-3400	245 (4.32)	**4c**	10.93	4.23	Oil	730, 750, 770, 870, 1050, 1500, 3030, 3200-3350	233 (4.70), 275 (3.55), 325 (2.60)
3d	$C_{21}H_{30}ClNO$	10.38 10.22	3.96 4.03	86-87	700, 750, 770, 1020, 1500, 1560, 1600, 2230, 3060, 3170-3350	245 (4.30)	**4d**	10.42	3.87	Oil	750, 770, 870, 1045, 1510, 3030, 3200-3500	232 (4.46), 275 (3.65), 286 (3.72), 325 (2.76)
3e	$C_{18}H_{22}ClNO$	11.33 11.70	4.28 4.61	162-164	690, 750, 1020, 1500, 1550, 1600, 2220, 3060, 3200-3360	245 (4.00)	**4e**	11.47	4.42	Oil	740, 760, 870, 1050, 1500, 1550, 1600, 3030, 3200-3350	232(4.60),275 (3.62), 285(3.60), 327(2.65)

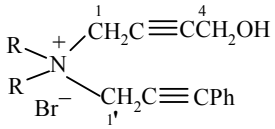
TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
3f	$C_{17}H_{20}ClNO_2$	11.30 11.62	4.23 4.58	160-161	690, 720, 770, 1020, 1500, 1590, 1600, 2220, 3250, 3300-3400	245 (4.56)	**4f**	11.33	4.36	236-237	740, 750, 770, 870, 1050, 1500, 1550, 1600, 3050, 3200-3350	232 (4.46), 275 (3.84), 287 (3.91), 297 (3.78), 327 (2.72)
5a	$C_{11}H_{16}ClNO$	16.21 16.63	6.28 6.56	*[2]	920, 990, 1020, 1580, 2240, 3200-3500	225	**6a**	16.43	6.32	Oil	710, 1050, 1590, 3045, 3250-3450	240 (2.86)
5b	$C_{13}H_{20}ClNO$	14.33 14.70	5.55 5.80	*[2]	920, 990, 1020, 1600, 2230, 3200-3500	220	**6b**	14.38	5.47	Oil	720, 1045, 1600, 3030, 3250-3500	240 (2.85)
5c	$C_{13}H_{20}BrNO$	27.66 27.97	4.58 4.90	120-122	920, 990, 1025, 1590, 2230, 3200-3400	225	**6c**	27.58	4.48	Oil	720, 1050, 1510, 1580, 3050, 3250-3500	238 (2.75)
5d	$C_{14}H_{22}ClNO$	13.49 13.89	5.18 5.48	*[2]	890, 1020, 1600, 2230, 3200-3400	222	**6d**	13.58	5.23	Oil	850, 1050, 1560, 1580, 1960, 3040, 3070, 3250-3450	240 (2.86)
5e	$C_{14}H_{20}BrNO_2$	25.13 25.48	4.14 4.46	105-106	890, 1025, 1610, 2240, 3200-3400	225	**6e**	25.15	4.15	192-193	860, 1050, 1510, 1570, 1960, 3030, 3070, 3250-3500	235 (2.95)

* The empirical formulas of the products **2**, **4**, and **6** coincide with the empirical formulas of the initial compounds **1**, **3**, and **5**.

*[2] The salt was hygroscopic.

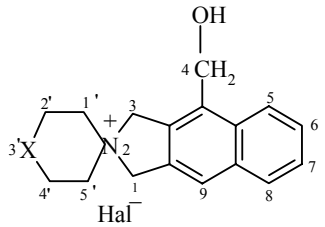
TABLE 2. The ^{1}H NMR Spectral Characteristics of the Salts **1a-f**, δ, ppm, SSCC (*J*, Hz)



Compound	1,1-H_2	4,4-H_2	1,'1'-H_2	OH, s	H_{Ph}		R
					o-, m	*m*-, *p*-, m	
1a	4.47 br. s	4.22 br. s	5.35 t, *J* = 6.0	4.63	7.61	7.48	1.36 (6H, t, *J* = 7.0, $2CH_3$); 3.55 (4H, q, *J* = 7.0, $2CH_2$)
1b	4.52 br. s	4.23 br. s	5.27 br. s	4.68	7.60	7.47	0.98 (6H, t, *J* = 6.8, $2CH_3$); 1.82 (4H, m, $2CH_2$); 3.46 (4H, m, $2CH_2N$)
1c	4.50 br. s	4.22 br. s	5.25 br. s	4.66	7.60	7.47	0.97 (6H, t, *J* = 7.0, $2CH_3$); 1.39 (4H, m, $2CH_3\underline{CH_2}$); 1.77 (4H, m, $2\underline{CH_2}CH_2N$); 3.48 (4H, t, *J* = 6.5, CH_2N)
1d	4.72 br. t, *J* = 2.0	4.19 br. s	5.26 br. s	4.91	7.58	7.40	2.28 (4H, m, $2CH_2$); 3.88 (4H, br. t, *J* = 7.2, $2CH_2N$)
1e	4.70 br. t, *J* = 2.0	4.19 br. s	5.34 br. s	4.91	7.60	7.40	1.73 (2H, m, CH_2); 1.98 (4H, m, $2\underline{CH_2}CH_2$); 3.79 (4H, m, *J* = 5.4, $2CH_2N$)
1f*	4.65 t, *J* = 2.0	4.28 t, *J* = 2.0	—	4.81	7.52	7.36	3.71 (4H, m, $2CH_2$); 4.03 (4H, m, $2CH_2O$)

* The spectrum was recorded in CD_3OD.

TABLE 3. The ^{1}H NMR Spectral Characteristics of the Salts **2e**,**f** and **4f**, δ, ppm, SSCC (*J*, Hz)



2e,**f** X = CH_2, **4f** X = O

Com-pound	1,1-H_2	3,3-H_2	4,4-H_2 br. s	5-H	6-H, m	7-H, m	8-H	9-H, s	1',1'-H_2 and 5',5'-H_2	2',2'-H_2 and 4',4'-H_2	3',3'-H_2
2e	5.39 t, *J* = 2.6	5.44 t, *J* = 2.6	4.40	8.01 q, *J* = 8.0	7.53	7.53	7.62 m	8.49	3.14 (2H) 3.44 (2H)	1.81 m (2H) 2.10 m (2H)	1.53 (1-H) 1.80 (1-H)
2f	5.22 s	5.47 s	5.04	8.14 q, *J* = 8.1	7.55	7.53	7.90 d, *J* = 8.1	7.84	4.09 (4H)	3.77 t (4H) *J* = 4.8	—
4f*	5.18 s	5.38 s	5.01	8.16 m	7.58	7.56	7.95 m	7.88	4.05 (4H)	3.71 t (4H) *J* = 4.8	—

* ^{13}C NMR spectrum for compound **4f**, δ, ppm: 58.16 ($C_{(4)}$); 58.55 ($C_{(2',4')}$); 61.35 ($C_{(1',5')}$); 65.49 ($C_{(1)}$); 66.33 ($C_{(3)}$); 121.82 ($C_{(9)}$); 123.94 ($C_{(5)}$); 126.18 and 126.44 ($C_{(6)}$ and $C_{(7)}$); 128.31 ($C_{(8)}$); 128.81; 130.41; 130.78; 133.14 and 133.33 ($C_{(3a)}$, $C_{(4)}$, $C_{(4a)}$, $C_{(8a)}$, $C_{(9a)}$).

In the UV spectra of the initial salts **1a-f** and **3a-f** there is an absorption maximum at 245 nm characteristic of the benzene ring, and for the salts **5a-e** there is absorption in the region of 220-225 nm. In the spectra of the cyclization products **2a-f** and **4a-f** the absorption maximum is shifted upfield as a result of the presence of the naphthalene ring (275, 285, 298 nm), while in the spectra of the salts **6a-e** there are absorption maxima for the benzene ring at 235-240 nm.

The structure of the salts **1a-f**, **2a**,**f**, **3a-f**, and **4f** was confirmed by ^{1}H NMR spectroscopy, and that of salt **4f** was confirmed also by ^{13}C NMR spectroscopy. The spectra of the compounds above agree well with the proposed structures.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in tablets with potassium bromide or in vaseline oil. The UV spectra were obtained on a Specord UV-Vis spectrophotometer for solutions in ethanol. The ^{1}H NMR spectra were obtained for solutions in DMSO-d_6 on a Varian Mercury-300 spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)] at 30°C (303 K) with TMS as internal standard.

The initial salts **1a-f**, **3a-f**, and **5a-e** were obtained in quantitative yields in ether–acetonitrile by reaction of dialkyl-4-hydroxy-2-butynylamines [4] with phenylpropargyl bromide **1a-f** or of the corresponding amines with chromatographically pure 4-hydroxy-1-chloro-2-butyne, obtained by the method [5] **3a-f**, **5a-e**.

The characteristics of the synthesized compounds are given in Tables 1-3.

The signals in the ^{1}H and ^{13}C NMR spectra were assigned on the basis of the COSY, NOESY, and HMQC spectra.

Cyclization of the Salts (1a-f), (3a-f), and (5a-e) (General Procedure). To solution of the salt **1**, **3**, or **5** (13-16 mmol) in water (5-6 ml) we added 2 N solution of potassium hydroxide (salt–base molar ratio 5:1) (1.3-1.6 ml). The reaction mixture was kept at 50-55°C for 5-10 min. Spontaneous heating was observed, and the temperature of the reaction mixture rose to 85-90°C. After cooling the reaction mixture was extracted with ether (2 × 30 ml) to remove the products of the side reactions. In each case 8-10% of amine of unestablished structure was detected in the extract by titration. The aqueous solution was acidified with hydrobromic acid or hydrochloric acid and evaporated to dryness. The residue was extracted with absolute ethanol. The salts **2a-c**, **4a-e**, and **6a-d** were precipitated from the extract with ether but could not be recrystallized. The salts **2d-f**, **4f**, and **6e** were precipitated from the aqueous solution, and the main part was isolated by filtration. The filtrate was treated as described above for the aqueous solution.

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