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REARRANGEMENT–CYCLIZATION OF DIALKYL(4-HYDROXYBUT-2-YNYL)METH-ALLYL- AND DIALKYLCROTYL(4-HYDROXY-BUT-2-YNYL) AMMONIUM HALIDES

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It was found that dialkyl(4-hydroxybut-2-ynyl)methallyl- and dialkylcrotyl(4-hydroxybut-2-ynyl)-ammonium halides undergo a Stevens rearrangement under the influence of aqueous alkali with transfer of the reaction center in the receiving group and inversion of the migrating group followed by cyclization to amino derivatives of furan.

Keywords: N,N-dialkyl-4-(but-1-en-3-yl)-2,5-dihydrofuran-2-ylamine, N,N-dialkyl-4-methallyl-2,5-dihydrofuran-2-ylamine, dialkyl(4-hydroxybut-2-ynyl)methallylammonium chlorides, dialkylcrotyl-(4-hydroxybut-2-ynyl)ammonium bromides, intramolecular cyclization, aqueous-alkali cleavage, Stevens rearrangement.

During the action of twice the molar amount of sodium hydroxide with heat in aqueous solution, dialkylallyl(4-hydroxybut-2-ynyl)ammonium bromides undergo a Stevens rearrangement with transfer of the reaction center and form amino alcohols containing an allene group, the intramolecular cyclization of which leads to N,N-dialkyl-4-allyl-2,5-dihydrofuran-2-ylamines [1].

In order to investigate the universality of the rearrangement–cyclization reaction and the production of new amines with a pharmacophoric hydrogenated furan ring in the present work we studied the behavior of dialkyl(4-hydroxybut-2-ynyl)methallylammonium chlorides **1a-f** and dibutylcrotyl(4-hydroxybut-2-ynyl)-ammonium (**2a**) and N-crotyl-N-(4-hydroxybut-2-ynyl)mopholinium (**2b**) bromides toward aqueous alkali (Table 1).

It was established that the salts **1a-f** and **2a**,**b** also undergo rearrangement–cyclization when heated for 2 h at 90-92°C with twice the molar amount of sodium hydroxide and form the corresponding 2-diethylamino-

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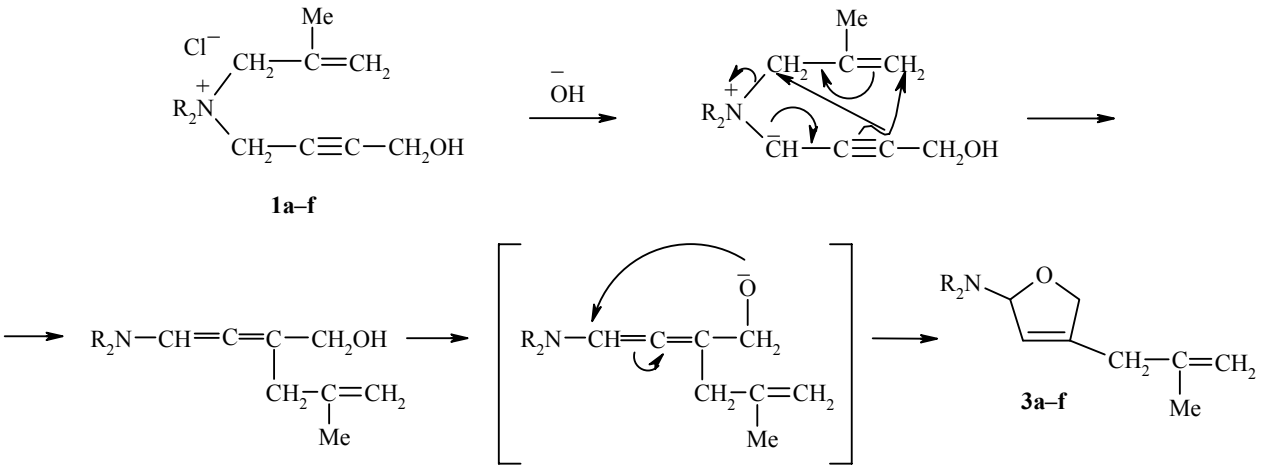
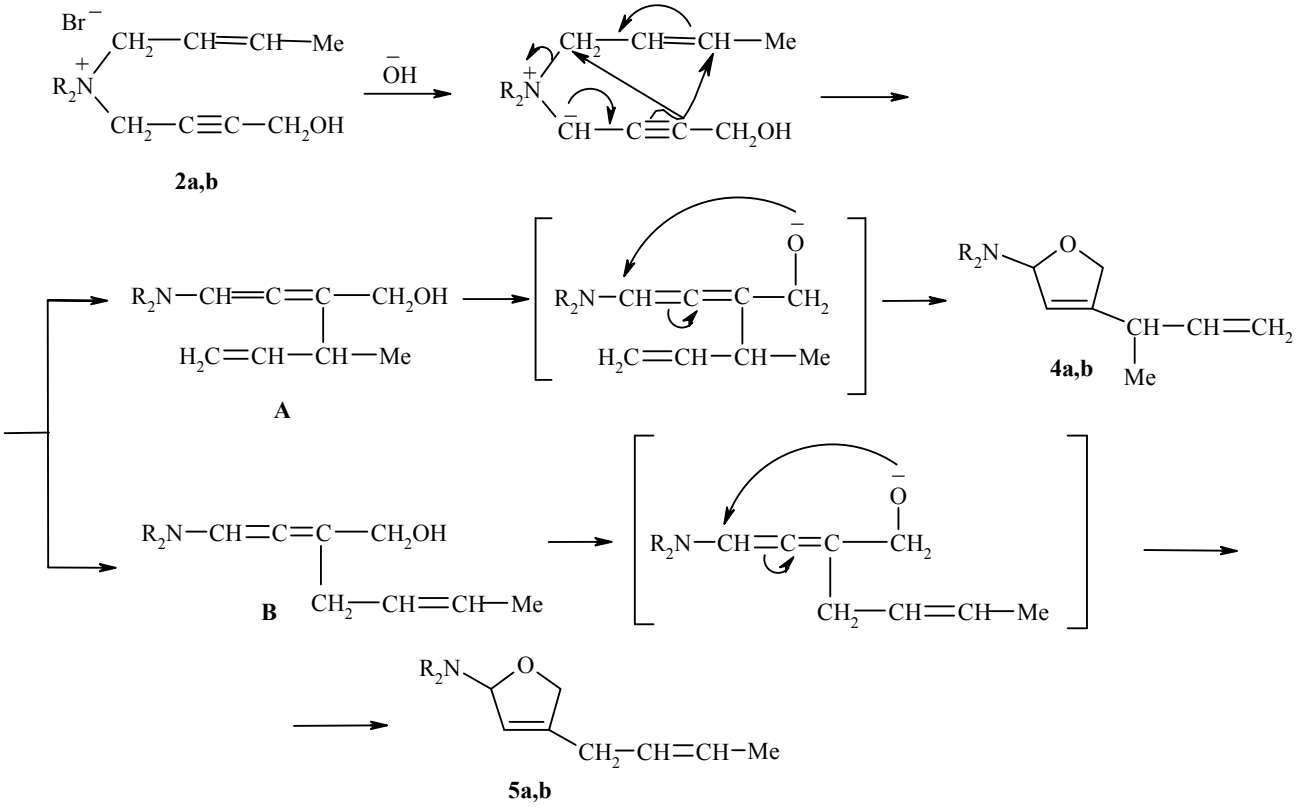
4-methallyl- (**3a**), 2-dipropylamino-4-methallyl- (**3b**), 2-dibutylamino-4-methallyl- (**3c**), 4-methallyl-2-pyrrolidino- (**3d**), and 4-methallyl-2-piperidino-2,5-dihydrofuranones (**3e**) and 2-morpholino-substituted derivatives of 4-methallyl-2,5-dihydrofuran (**3f**) with yields of 49, 29, 45, 18, 24, and 23% respectively (Tables 2-4).



1, 3 a R = Et, **b** R = Pr, **c** R = Bu, **d** $R_2 = (CH_2)_4$, **e** R = $(CH_2)_5$, **f** $R_2 = (CH_2)_2O(CH_2)_2$

The reaction includes two stages – a Stevens rearrangement with transfer of the reaction center in the receiving group and intramolecular cyclization resulting from O-alkylation. In the case of the salts **1a-f**, like the previously studied analogs [1], the structure of the migrating group does not make it possible to judge whether attack by the formed ylide occurs at the α- or at the γ-carbon atom.

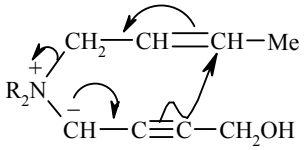


2, 4 a R = Bu, **b** $R_2 = (CH_2)_2O(CH_2)_2$

Meanwhile, in the case of the salts **2a**,**b** with a crotyl group amino alcohols with structure **A** or **B** or a mixture of two isomeric amines, intramolecular cyclization of which leads to the furan amines **4a**,**b** (Tables 2-4) or **5a**,**b** or their mixtures, can be formed depending on the point of attack.

In the IR spectra of the obtained amines, in addition to absorption in the region of 1640 and 1660 cm^{-1} characteristic of both amines **4a,b** and **5a,b**, there are also absorption bands for the vinyl group $HC=CH_2$ at 910, 990, and 3100 cm^{-1} characteristic only of the amines **4a,b**. It was established on the basis of the ^1H and ^{13}C NMR spectra that in the case of the salts **2a**,**b** mixtures of the diastereomers of 4-(1-buten-3-yl)-2-dibutylamino-2,5-dihydrofuran **(4a)** and [4-(1-buten-3-yl)-2,5-dihydrofuran-2-yl]morpholine **(4b)** are obtained with overall yields of 48 and 38% respectively. According to data from the ^1H NMR spectra the ratio of the stereoisomers in the mixture is 60:40. The formation of a mixture of two isomers in the case of the salts **2a**,**b** is due to the presence of two asymmetric carbon atoms in the molecules of the amines **4a**,**b**. The isomeric amines **5a**,**b** were not detected among the reaction products.

Thus, we have established that the Stevens rearrangement in the salts **2a**,**b** takes place both with transfer of the reaction center in the receiving group and with inversion of the migrating group according to the following scheme:



In all probability the reaction takes place similarly in the case of the salts **1a-f**.

It should be noted that the discovered effect is the only one in the field of the Stevens rearrangement. If there are alkyl substituents at the nitrogen atom in the initial salts **1a-f** and **2a**,**b** the yields of the obtained amines (with the exception of the amine **3b**) are fairly high compared with the pyrrolidine (**3d**), piperidine (**3e**), and morpholine (**3f** and **4b**) analogs.

In addition to the amines **3a-f** and **4a**,**b** diethyl-, dipropyl-, and dibutylamines, pyrrolidine, piperidine, and morpholine, identified in the form of the picrates, were also obtained with yields of 10-15%.

TABLE 1. The Physicochemical Characteristics of the Salts **1a-f** and **2a**,**b**

Compound	Empirical formula	Found, % / Calculated, %		Yield, %
		Hal	N	
1a	$C_{12}H_{22}ClNO$	14.98 / 15.33	6.27 / 6.04	97
1b	$C_{14}H_{26}ClNO$	13.99 / 13.68	5.15 / 5.39	95
1c	$C_{16}H_{30}ClNO$	12.70 / 12.35	4.68 / 4.87	98
1d	$C_{12}H_{20}ClNO$	15.12 / 15.47	6.38 / 6.10	95
1e	$C_{13}H_{22}ClNO$	14.90 / 14.58	5.50 / 5.75	96
1f	$C_{12}H_{20}ClNO_2$	14.07 / 14.46	5.91 / 5.70	96
2a	$C_{16}H_{30}BrNO$	24.55 / 24.10	4.01 / 4.22	89
2b	$C_{12}H_{20}BrNO_2$	27.96 / 27.59	4.57 / 4.83	85

* The salts **1a-f** could not be obtained in the crystalline form; mp of salt **2a** 112-113°C, salt **2b** 114-115°C.

TABLE 2. The Physicochemical Characteristics of the Amines **3a-f** and **4a**,**b**

Compound	Empirical formula	Found, % / Calculated, %			bp*, °C	n_D^{20}	Yield, %	mp of picrate,*[2] °C
		C	H	N				
3a	$C_{12}H_{21}NO$	73.41 / 73.85	10.46 / 10.77	7.47 / 7.18	81	1.4632	49	—
3b	$C_{14}H_{25}NO$	74.96 / 75.34	11.52 / 11.21	5.99 / 6.28	93	1.4660	29	128
3c	$C_{16}H_{29}NO$	76.01 / 76.49	11.87 / 11.55	5.30 / 5.58	105	1.4647	45	—
3d	$C_{12}H_{19}NO$	74.27 / 74.61	9.53 / 9.84	7.54 / 7.25	80	1.4848	18	—
3e	$C_{13}H_{21}NO$	75.02 / 75.36	10.49 / 10.14	6.37 / 6.76	95-6	1.4829	24	114-115
3f	$C_{12}H_{19}NO_2$	68.49 / 68.90	8.78 / 9.09	6.98 / 6.70	180	1.4871	23	96-97
4a	$C_{16}H_{29}NO$	76.11 / 76.49	11.88 / 11.55	5.31 / 5.58	87-93	1.4632	48	
4b	$C_{12}H_{19}NO_2$	68.53 / 68.90	9.40 / 9.09	6.53 / 6.70	90-91	1.4874	38	

* 1-2 mm Hg.

*[2] Compounds **3a**,**c**,**d** do not form picrates.

TABLE 3. The ^{1}H NMR Spectra of the Amines **3a-f** and **4a**,**b**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
3a	1.02 (6H, t, *J* = 7.2, CH_3); 1.73 (3H, t, *J* = 1.2, CH_3); 2.06 (4H, m, $N(CH_2)_2$); 2.65 (1H, m) and 2.73 (1H, d, *J* = 15.5, CH_2); 4.40 (2H, m, OCH_2); 4.72 (1H, m) and 4.77 (1H, m, $=CH_2$); 5.36 (1H, m, OCH); 5.69 (1H, sext, *J* = 1.6, =CH)
3b	0.86 (6H, t, *J* = 7.3, CH_3); 1.43 (4H, m, $C\underline{H}_2CH_3$); 1.73 (3H, t, *J* = 1.1, $=CCH_3$); 2.37-2.55 (4H, m, NCH_2); 2.66 (1H, d, *J* = 15,4) and 2.75 (1H, d, *J* = 15.4, CH_2); 4.40 (2H, m, OCH_2); 4.72 (1H, m) and 4.77 (1H, m, $=CH_2$); 5.34 (1H, ddd, *J* = 5.3, *J* = 3.0, and *J* = 1.9, OCH); 5.69 (1H, sext, *J* = 1.6, =CH)
3c	0.90 (6H, t, *J* = 7.2, CH_3); 1.18-1.45 (8H, m, $C\underline{H}_2C\underline{H}_2CH_3$); 1.72 (3H, br., CH_3); 2.48 (4H, m, NCH_2); 2.63 (1H, d, *J* = 15.4) and 2.73 (1H, d, *J* = 15.4, CH_2); 4.39 (2H, m, OCH_2); 4.70 (1H, m) and 4.77 (1H, m, $=CH_2$); 5.32 (1H, ddd, *J* = 5.3, *J* = 2.9, and *J* = 2.1, OCH); 5.68 (1H, sext, *J* = 1.6, =CH)
3d	1.72 (4H, m, $2CH_2$); 1.74 (3H, t, *J* = 1.1, CH_3); 2.66 (4H, m, $N(CH_2)_2$); 2.67 (1H, d, *J* = 15.4) and 2.76 (1H, d, *J* = 15.4, CH_2); 4.45 (2H, m, OCH_2); 4.73 (1H, m) and 4.78 (1H, m, $=CH_2$); 5.41 (1H, td, *J* = 4.2, *J* = 1.4, OCH); 5.63 (1H, sext, *J* = 1.6, =CH)
3e	1.40-1.56 (6H, m, $3CH_2$); 1.74 (3H, t, *J* = 1.1, CH_3); 2.46 (2H, m) and 2.60 (2H, m, $N(CH_2)_2$); 2.64 (1H, d, *J* = 15.4) and 2.72 (1H, d, *J* = 15.4, CH_2); 4.40 (2H, m, OCH_2); 4.73 (1H, m) and 4.78 (1H, m, $=CH_2$); 5.14 (1H, td, *J* = 4.3, *J* = 1.5, OCH); 5.69 (1H, sext, *J* = 1.6, =CH)
3f	1.75 (3H, t, *J* = 1.1, CH_3); 2.48 (2H, m) and 2.61 (4H, m, $N(CH_2)_2$); 3.56 (4H, m, $O(CH_2)_2$); 2.67 (1H, d, *J* = 15.5) and 2.75 (1H, d, *J* = 15.5, CH_2); 4.46 (2H, m, OCH_2); 4.74 (1H, m) and 4.79 (1H, m, $=CH_2$); 5.14 (1H, td, *J* = 4.2, *J* = 1.2, OCH); 5.76 (1H, sext, *J* = 1.6, =CH)
4a	0.91 (3.6H, t, *J* = 7.1) and 0.92 (2.4H, t, *J* = 7.1, CH_3); 1.11 (1.2H, d, *J* = 6.9) and 1.21 (1.8H, d, *J* = 6.9, CH_3); 1.24-1.48 (8H, m, $4CH_2$); 2.47 (2.4H, t, *J* = 7.2) and 2.50 (1.6H, t, *J* = 7.2, NCH_2); 2.84 (1H, m, $C\underline{H}CH_3$); 4.30-4.48 (2H, m, OCH_2); 4.90-5.06 (2H, m, $=CH_2$); 5.36 (0.6H, ddd, *J* = 5.1, *J* = 2.9, and *J* = 2.0) and 5.47 (0.4H, ddd, *J* = 5.1, *J* = 2.9, and *J* = 2.0, OCH); 5.60 (0.4H, m) and 5.70 (0.6H, m, CH–C$\underline{H}$=); 5.61 (0.6H, ddd, *J* = 17.1, *J* = 10.0, and *J* = 7.7) and 5.91 (0.4H, ddd, *J* = 17.1, *J* = 10.0, and *J* = 7.2, $C\underline{H}=CH_2$)
4b	1.15 (1.2H, d, *J* = 6.9) and 1.21 (1.8H, d, *J* = 6.9, CH_3); 2.48 (2H, m) and 2.60 (2H, m, $N(CH_2)_2$); 2.85 (1H, m, $C\underline{H}CH_3$); 3.55 (4H, m, $O(CH_2)_2$); 4.41-4.46 (2H, m, OCH_2); 4.90-5.06 (2H, m, $=CH_2$); 5.17 (0.6H, td, *J* = 8.0, *J* = 1.7) and 5.25 (0.4H, td, *J* = 8.0, *J* = 1.7, OCH); 5.69 (0.6H, ddd, *J* = 17.1, *J* = 10.1, and *J* = 7.5) and 5.90 (0.4H, ddd, *J* = 17.1, *J* = 10.2, *J* = 7.3, $H_2C=C\underline{H}$); 5.68 (0.4H, dt, *J* = 3.3 and *J* = 1.6) and 5.76 (0.6H, dt, *J* = 3.3, *J* = 1.6, C=CH)

TABLE 4. The ^{13}C NMR Spectra of the Amines **3a-d**,**f** and **4b**

Com-pound	Chemical shifts, δ, ppm
3a	3.3 (2C, CH_3); 21.7 (CH_3); 35.2 (CH_2); 41.2 (2C, NCH_2); 72.1 (OCH_2); 99.8 (OCH); 111.8 (=CH_2); 123.7 (=CH); 137.6 (=C); 141.6 (=C).
3b	11.4 (2C, CH_3); 21.0 (2C, CH_2); 21.8 (CH_3); 35.2 (CH_2); 49.9 (2C, NCH_2); 72.1 (OCH_2); 99.9 (OCH); 111.8 (=CH_2); 123.8 (=CH); 137.5 (=C); 141.6 (=C)
3c	13.6 (2C, CH_3); 20.0 (2C, CH_2); 21.7 (CH_3); 30.1 (2C, CH_2); 35.2 (CH_2); 47.6 (2C, NCH_2); 72.1 (OCH_2); 99.8 (OCH); 111.8 (=CH_2); 123.7 (=CH); 137.5 (=C); 141.5 (=C)
3d	21.9 (CH_3); 23.7 (2C, CH_2); 35.1 (CH_2); 45.8 (2C, NCH_2); 73.2 (OCH_2); 97.4 (OCH); 111.8 (=CH_2); 123.0 (=CH); 137.8 (=C); 141.7 (=C)
3f	21.9 (CH_3); 35.0 (CH_2); 46.7 ($N(CH_2)_2$); 66.2 ($O(CH_2)_2$); 73.2 (OCH_2); 101.2 (OCH); 112.0 (=CH_2); 124.6 (=CH); 135.8 (=C); 141.4 (=C)
4b	17.9 and 18.0 (CH_3); 35.2 (CH); 46.8 (2C, $N(CH_2)_2$); 66.2 and 66.3 (2C, $O(CH_2)_2$); 73.5 (OCH_2); 100.6 and 100.8 (OCH); 113.1 and 113.3 (=CH_2); 122.9 and 123.1 (=CH); 140.5 and 140.7 (=CH); 141.1 and 141.6 (=C)

From 15 mmol of the initial salts we also obtained 0.15-0.25 g of nonamine products, the IR spectrum of which contained characteristic absorption bands of =CH_2 at 870, 880, and 3080 cm^{-1}, the unconjugated carbonyl group at 1720 cm^{-1}, the aldehyde hydrogen at 2720 cm^{-1}, and the hydroxyl group at 3200-3500 cm^{-1}. The nonamine product gives a silver mirror reaction and decomposes during vacuum distillation, and formic acid was detected qualitatively.

The structure of the salts **1a-f** and **2a**, **b** and the amines **3a-f** and **4a**,**b** was established on the basis of the IR spectra, while the structure of the obtained amines was also confirmed by data from the ^1H and ^{13}C NMR spectra. The purity of the obtained compounds was established by elemental analysis. The IR spectra of the salts **1a-f** contain absorption bands in the regions of 870-890 (=CH_2), 2220-2240 (C≡C), and 3100-3500 cm^{-1} (O–H). In the spectra of the salts **2a**,**b** there is also absorption at 1660 cm^{-1}, characteristic of –HC=CH–. The spectra of the amines **3a-f** contain absorption bands at 880-890 and 3070-3080 cm^{-1} (=CH_2), 1640 and 1660 cm^{-1} (>C=C<), and 1020-1100 cm^{-1} (C–O–C in the ring). In the spectra of the stereoisomeric amines **4a** and **4b** there are also absorption bands in the regions of 910, 990, and 3100 cm^{-1}, characteristic of –CH=CH_2. The structure of the amines **3a-f** and **4a**,**b** was proved on the basis of the ^1H and ^{13}C NMR spectra using the two-dimensional proton–carbon correlation methods DEPT and HMQC. In particular the cyclic structure is favored by the absence of a signal for the OH group in the ^1H NMR spectrum and by the presence of two signals for the CH group in the ^{13}C NMR spectrum. Thus, the signal in the region of ~100 ppm was attributed to the asymmetric carbon atom of the O–CH–N fragment. The presence of a second asymmetric center in the side chain (compounds **4a**,**b**) leads to the formation of a mixture of two diastereomers. A more detailed discussion of the structural and spectral characteristics of the compounds of this series using two-dimensional NOE spectroscopy is presented in [1].

EXPERIMENTAL

The IR spectra were recorded in tablets with potassium bromide or in vaseline oil on a UR-20 spectrometer. The ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 VX spectrometer at 300 K (300 and 75 MHz respectively). The chemical shifts are given for solutions in 1:3 DMSO-d_6–CCl_4. The DEPT and HMQC methods were used for the assignment of the signals in the ^1H and ^{13}C NMR spectra.

The initial dialkyl(4-hydroxybut-2-ynyl)amines were obtained by the familiar method described in [2].

Synthesis of Dialkyl(4-hydroxybut-2-ynyl)methallylammonium Chlorides 1a-f and Dialkylcrotyl-(4-hydroxybut-2-ynyl) ammonium Bromides 2a,b (General Method). To a solution of the respective amine (20 mmol) in acetonitrile (15 ml), twice the molar amount of methallyl chloride or 1.5 times the molar amount of crotyl bromide was added. The reaction mixture was heated at 80-85°C for 16 h. The solvent was then distilled at reduced pressure. The salt was washed with absolute ether (2×25 ml). It was not possible to obtain the salts **1a-f** in the crystalline form even with prolonged drying over P_2O_5.

Aqueous–Alkali Cleavage of Dialkyl(4-hydroxybut-2-ynyl)methallylammonium Chlorides 1a-f and Dibutylcrotyl(4-hydroxybut-2-ynyl)ammonium (2a) and N-Crotyl-N-(4-hydroxybut-2-ynyl)morpholinium (2b) Bromides (General Method). To a solution of the salt **1a-f** (15 mmol) in water (4 ml) or salt **2a**,**b** (10 mmol) in water (3 ml), twice the molar quantity of sodium hydroxide was added. The mixture was heated at 90-92°C for 2 h and then was cooled, and extracted with ether (3×35 ml). While shaking the extract was titrated with a 0.1 N solution of sulfuric acid. In the case of the salts **1a-f** the presence of 10.4-11.0 mmol (67-73%) and in the case of the salts **2a**,**b** 6.5-6.9 mmol (65-69%) of the amine was established. By the usual treatment of the ether extract, **3a-f** and **4a**,**b** and secondary amines were obtained. The latter were identified in the form of picrates [1]. From 15 mmol of the salts we obtained 0.15-0.25 g of a compound giving a silver mirror reaction as nonamine product.

The reaction mixture was acidified with hydrochloric acid, and the solvent was partly distilled. Formic acid was qualitative detected in the distilled water by silver mirror reaction.

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