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Alcoholysis of 2,2-Dichloropropyl Derivatives of Carbazole, Phenothiazine, and Phenoxazine[*]

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Abstract—Reactions of 9-(2,2-dichlorocyclopropyl)carbazole, 10-(2,2-dichlorocyclopropyl)phenothiazine, and 10-(2,2-dichlorocyclopropyl)phenoxazine with alcohols in the system *t*-BuOK–DMSO yield the corresponding *N*-(1-alkoxy-2-propynyl) derivatives. Hydrolysis of 9-(1-methoxy-2-propynyl)carbazole and 10-(1-methoxy-2-propynyl)phenothiazine in 60% aqueous dioxane in the presence of sulfuric acid gives the corresponding heterocyclic amine and 2-propynal.

We recently synthesized 2,2-dichlorocyclopropyl derivatives of heterocyclic amines: 9-(2,2-dichlorocyclopropyl)carbazole (**I**), 10-(2,2-dichlorocyclopropyl)phenothiazine (**II**), and 10-(2,2-dichlorocyclopropyl)phenoxazine (**III**) [1]. Chemical properties of geminal dichlorocyclopropanes having a heteroatom substituent as donor of electron pair, especially of those possessing a nitrogen-containing group, have been studied relatively poorly. We have found that, by analogy with 2,2-dichloropropyl derivatives of *N*-nitroamines [2, 3], N-substituted heterocyclic compounds **I**–**III** are weakly sensitive to alkalies and strong acids. Attempts to reduce them using Zn/HCl, K/CH₃OH, Na/CH₃OH, and SnCl₂/HCl were unsuccessful. The goal of the present work was to study transformations of 2,2-dichlorocyclopropyl derivatives **I**–**III** under more severe conditions, in the system *t*-BuOK–alcohol–DMSO. Alcoholysis of 2,2-dichlorocyclopropylamines in this system was not reported previously.

It is known [4] that electron-donor substituents weaken C−C bonds in three-membered ring and that reactions of such compounds are generally accompanied by opening of the three-membered ring. Therefore, we expected formation of two open-chain alcoholysis products, α-alkoxy-β-chloroallylamine and α-alkoxy-2-propynylamine (Scheme 1). Experi-

ments showed that alcoholysis of compounds **I**–**III** occurs with opening of the three-membered ring even at room temperature. The products were hitherto unknown 1-alkoxy-2-propynylamines **IV**–**VII**. No intermediate 1-alkoxy-2-chloroallylamines were detected in the reaction mixtures. The reaction conditions and yields of products **IV**–**VII** are given in Table 1.
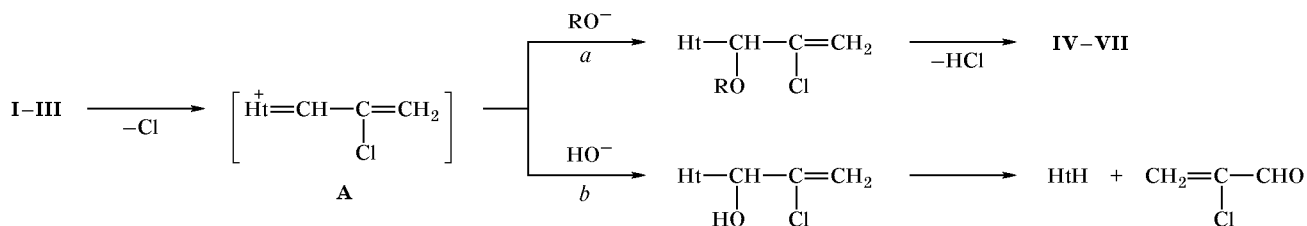
Scheme 1.
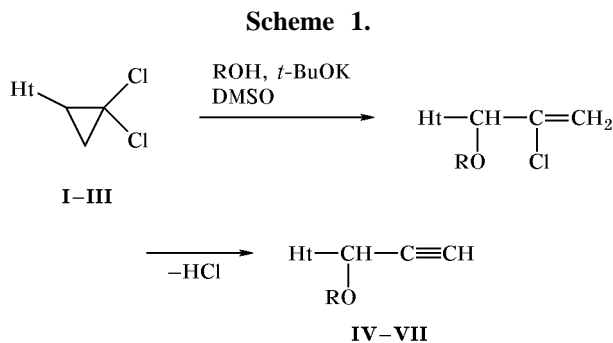
I, IV, V, Ht = 9-carbazolyl; II, VI, Ht = 10-phenothiazinyl;
III, VII, Ht = 10-phenoxazinyl; IV, VI, VII, R = CH₃;
V, R = *iso*-C₃H₇.

The reaction time was 3–7 h; it strongly depends on the reactant ratio. The solvent (DMSO) was taken in an amount of 10–15 ml per gram of initial cyclopropane. The optimal ratio **I**–**III** : alcohol was 1 : 10. Its variation almost did not affect the product yield, but the reaction time increased as the amount of alcohol was reduced (Table 1). The required amount

Scheme 2.

$$\text{I–III} \xrightarrow[-\text{Cl}]{} \left[\overset{+}{\text{Ht}}=\text{CH}-\underset{\underset{\text{Cl}}{|}}{\text{C}}=\text{CH}_2 \right] \longrightarrow$$

$$\overset{a}{\xrightarrow{\text{RO}^-}} \quad \text{Ht}-\underset{\underset{\text{RO}}{|}}{\text{CH}}-\underset{\underset{\text{Cl}}{|}}{\text{C}}=\text{CH}_2 \xrightarrow{-\text{HCl}} \text{IV–VII}$$

$$\overset{b}{\xrightarrow{\text{HO}^-}} \quad \text{Ht}-\underset{\underset{\text{HO}}{|}}{\text{CH}}-\underset{\underset{\text{Cl}}{|}}{\text{C}}=\text{CH}_2 \longrightarrow \text{HtH} + \text{CH}_2=\underset{\underset{\text{Cl}}{|}}{\text{C}}-\text{CHO}$$

A

Ht = 9-carbazolyl, 10-phenoxazinyl, 10-phenothiazinyl; R = CH$_3$, *iso*-C$_3$H$_7$.

of potassium *tert*-butoxide depends on the reactivity of the substrate and alcohol nature. In the reactions of carbazole derivative **I**, the optimal molar ratio **I**:*t*-BuOK was 1:2.2 for methanol and 1:3.0 for isopropyl alcohol. A solution of *t*-BuOK in *t*-BuOH was dropwise added to the reaction mixture over a period of 2–2.5 h. Fast mixing of the reactants resulted in formation of a complex mixture of products, the corresponding heterocyclic amine being the major product (TLC). The yields of alkoxypropynyl derivatives **IV**–**VII** were 56–96%. The products were fairly sensitive to temperature and acids. Product **VII** was especially unstable; it was isolated as a mixture with phenoxazine (about 30%, according to the ^{1}H NMR data).
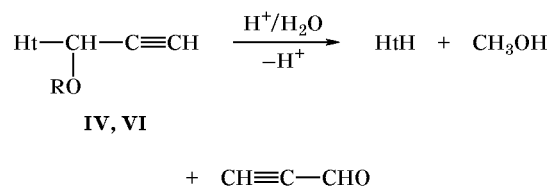
The structure of compounds **IV**–**VII** was proved by the IR and ^{1}H and ^{13}C NMR spectra and elemental analyses. The NMR data are presented in Table 2 and in Experimental. The IR spectra of **IV**–**VII** contained a broad absorption band at 3250–3300 cm^{-1} and a weak band at 2120–2160 cm^{-1}, which were assigned to stretching vibrations of acetylenic C−H and C≡C bonds, respectively. The absorption at 950–1250 cm^{-1} belongs to stretching vibrations of the ether moiety.

Presumably, alcoholysis of 2,2-dichlorocyclopropyl derivatives **I**–**III** involves cleavage of the C^1−C^3 bond which is located opposite to the CCl$_2$ fragment. It is known [4, 5] that π-donor substituents (in our case, heterocyclic groups) induce lengthening and hence weakening of all cyclopropane C−C bonds, the effect on the contiguous bond is the strongest. By contrast, σ-acceptor substituents (such as chlorine atoms) cause shortening of the contiguous C−C bonds which become stronger. Assuming that the effects of different substituents are additive [4], the C^1−C^3 bond in the three-membered ring of **I**–**III** should be weakened to the greatest extent. Then, the reaction mechanism is similar to that found for alcoholysis of 2,2-dichlorocyclopropyl ethers [6]: in alkaline medium cyclopropyl–allyl rearrangement occurs with formation of allyl cation **A** (Scheme 2).

Nucleophilic attack on cation **A** and subsequent elimination of HCl molecule lead to formation of 1-alkoxy-2-propynyl derivatives **IV**–**VII** (path *a*). We detected no products of nucleophilic attack by *tert*-butoxide ion on cation **A**, presumably because of its lower nucleophilicity compared to methoxide or isopropoxide ion [6, 7]. Moreover, the concentration of *tert*-butoxide ions should be very small since the dissociation constant of the conjugate acid (*t*-BuOH) is low. Hydroxide ions present in the reaction mixture are also capable of reacting with cation **A**; the resulting adduct is unstable [8], and it decomposes into heterocyclic amine (which was detected by TLC) and 2-chloroacrolein (path *b*).

Like alkoxyalkylcarbazoles [9, 10], alkoxypropynyl derivatives **IV**–**VII** are sensitive to acids. Hydrolysis of compounds **IV** and **VI** in 60% aqueous dioxane in the presence of sulfuric acid gave the corresponding heterocyclic amine and 2-propynal (Scheme 3).

Scheme 3.

$$\text{Ht}-\underset{\underset{\text{RO}}{|}}{\text{CH}}-\text{C}\equiv\text{CH} \xrightarrow[-\text{H}^+]{\text{H}^+/\text{H}_2\text{O}} \text{HtH} + \text{CH}_3\text{OH}$$

IV, VI

$$+ \quad \text{CH}\equiv\text{C}-\text{CHO}$$

The reaction was complete in 19 h for compound **IV** and in 5 min for **VI** (room temperature, initial substrate concentration 6×10^{-2} M, H$_2$SO$_4$ concentration 1.5×10^{-2} M; TLC data). The products, carbazole and phenothiazine were isolated in quantitative yield; 2-propynal was identified as the corresponding 2,4-dinitrophenylhydrazone [11].

Thus base-catalyzed alcoholysis of *N*-(2,2-dichlorocyclopropyl)-substituted heterocyclic amines gave a series of new compounds, *N*-(1-alkoxy-2-propynyl)-derivatives of carbazole, phenothiazine, and phenoxazine. It should be noted that previous attempts to

Table 1. Alcoholysis of 9-(2,2-dichlorocyclopropyl)-carbazole (**I**), 10-(2,2-dichlorocyclopropyl)phenothiazine (**II**), and 10-(2,2-dichlorocyclopropyl)phenoxazine (**III**)

Substrate (mmol)	Alcohol (mmol)	*t*-BuOK, mmol	DMSO, ml	Time, h	Yield, %
I (12.7)	MeOH (125)	27.9	35	3	96
I (11.0)	MeOH (75)	24.5	30	5	92
I (12.7)	*i*-PrOH (125)	37.5	35	4	56
II (10.7)	MeOH (100)	29.5	35	3.5	90
III (11.3)	MeOH (100)	35.8	30	7	84[a]

[a] Product **VII** was isolated in a mixture with phenoxazine.

Table 2. ^{1}H NMR spectra of *N*-(1-alkoxy-2-propynyl) derivatives **IV**–**VII** in CDCl$_3$

Comp. no.	Chemical shifts δ, ppm
IV	2.54 d (1H, ≡CH, *J* = 1 Hz), 3.15 s (3H, CH$_3$) 6.28 d (1H, NCH, *J* = 1 Hz), 7.1–8.1 m (H$_{arom}$)
V	0.88 d (3H, CH$_3$, *J* = 7 Hz), 1.15 d (3H, CH$_3$, *J* = 7 Hz), 2.46 d (1H, ≡CH, *J* = 1 Hz), 3.5 m (1H, CH), 6.46 d (1H, NCH, *J* = 1 Hz), 7.0–8.0 m (H$_{arom}$)
VI[a]	1.87 d (1H, ≡CH, *J* = 1 Hz), 2.98 s (3H, CH$_3$), 5.18 d (1H, NCH, *J* = 1 Hz), 6.5–7.4 m (H$_{arom}$)
VII	2.5 d (1H, ≡CH, *J* = 1 Hz), 3.46 s (3H, CH$_3$), 5.5 d (1H, NCH, *J* = 1 Hz), 6.6–7.1 m (H$_{arom}$)

[a] In C$_6$D$_6$.

synthesize α-alkoxyalkyl derivatives by reactions of phenoxazine and phenothiazine with aldehydes and alcohols (which readily occur with carbazole [9, 10, 12–14]) resulted in preparation of only alkoxymethyl-phenothiazines [15]; α-alkoxyalkyl-substituted phenoxazines were not reported. The results of our study of alcoholysis of 2,2-dichlorocyclopropyl derivatives **I**–**III** show that these compounds are very promising for synthesis of various *N*-substituted carbazoles, phenothiazines, and phenoxazines.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS-497C spectrometer (100 MHz) from 10% solutions in CDCl$_3$ or C$_6$D$_6$. The ^{13}C NMR spectra were obtained on a Tesla BS-567A instrument (25.14 MHz) with complete decoupling from protons; C$_6$D$_6$ was used as solvent (10% solutions), and HMDS, as internal reference. The progress of reactions was monitored by TLC on Silufol plates using hexane–diethyl ether (6 : 1) as eluent. When studying alcoholysis of compounds **II** and **III** and hydrolysis of methoxypropynyl derivative **VI**, chromatographic plates were preliminarily impregnated twice with a saturated solution of sodium hydroxide in methanol and were dried in air. The chromatograms were developed with nitrogen oxide vapor.

9-(1-Methoxy-2-propynyl)carbazole (IV). A 0.82 N solution of potassium *tert*-butoxide in *tert*-butyl alcohol, 34 ml (27.9 mmol), was added dropwise over a period of 2 h to a mixture of 3.5 g (12.7 mol) of compound **I**, 35 ml of DMSO, and 5 ml (125 mmol) of methanol, continuously stirred at room temperature. The mixture was stirred for an additional 1 h, diluted with 200 ml of water, and extracted with pentane (4 × 50 ml). The combined extracts were washed with water (3 × 500 ml) and dried over solid NaOH. Removal of the solvent under reduced pressure and subsequent evacuation for 1 h (21 hPa, 30°C) gave 2.86 g (96%) of product **IV**, mp 88°C (from ethanol). ^{13}C NMR spectra, δ$_C$, ppm: 108.98 (C^1), 124.18 (C^2), 118.68 (C^3, C^4), 122.39 (C^{4a}), 137.81 (C^{9a}), 76.50 (HtCH), 73.44 (C≡), 72.94 (HC≡), 52.88 (CH$_3$O). Found, %: C 81.05; H 5.88; N 6.25. C$_{16}$H$_{13}$NO. Calculated, %: C 81.67; H 5.58; N 5.95.

9-(1-Isopropoxy-2-propynyl)carbazole (V). A 1.5 N solution of potassium *tert*-butoxide in *tert*-butyl alcohol, 25 ml (37.5 mmol), was added dropwise over a period of 2.5 h to a mixture of 3.5 g (12.7 mol) of compound **I**, 35 ml of DMSO, and 9.5 ml (125 mmol) of isopropyl alcohol, continuously stirred at room temperature. The mixture was stirred for an additional 1.5 h, diluted with 200 ml of water, and extracted with pentane (4 × 50 ml). The combined extracts were washed with a 5% solution of KCl (3 × 500 ml) and dried over solid NaOH. Removal of the solvent and subsequent evacuation for 1 h (21 hPa, 30°C) gave 1.85 g (56%) of compound **V**, mp 76°C (from ethanol). Found, %: C 81.83; H 7.29; N 5.09. C$_{18}$H$_{17}$NO. Calculated, %: C 82.09; H 6.52; N 5.32.

10-(1-Methoxy-2-propynyl)phenothiazine (VI). A 0.82 N solution of potassium *tert*-butoxide in *tert*-butyl alcohol, 36 ml (29.5 mmol), was added

dropwise over a period of 2 h to a mixture of 3.3 g (10.7 mol) of compound **II**, 35 ml of DMSO, and 4 ml (100 mmol) of methanol, continuously stirred at room temperature. The mixture was stirred for an additional 1.5 h, and the product was isolated as described above for compound **IV**. Yield 2.57 g (90%), mp 73–74°C (from methanol). ^{13}C NMR spectrum, δ_C, ppm: 116.83 (C^1), 125.32 (C^2), 126.04 (C^3), 125.10 (C^4), 141.52 (C^{10a}), 80.29 (HtCH), 76.50 ($C\equiv$), 73.86 (HC$\equiv$), 51.95 (CH_3O). Found, %: C 71.79; H 4.32; N 5.23. $C_{16}H_{13}NOS$. Calculated, %: C 71.87; H 4.91; N 5.24.

9-(1-Methoxy-2-propynyl)phenoxazine (VII). A 1.12 N solution of potassium *tert*-butoxide in *tert*-butyl alcohol, 32 ml (35.8 mmol), was added dropwise over a period of 2.5 h to a mixture of 3.3 g (11.3 mol) of compound **III**, 30 ml of DMSO, and 4 ml (100 mmol) of methanol, continuously stirred at room temperature. The mixture was stirred for an additional 4.5 h, and the product was isolated as described above for compound **V**. Yield 2.38 g. Analysis of the product by TLC showed the presence of phenoxazine (30 mol %, according to the ^1H NMR data).

Hydrolysis of 9-(1-methoxy-2-propynyl)carbazole (IV) and 10-(1-methoxy-2-propynyl)phenothiazine (VI). A 0.249-g (1.06-mmol) portion of compound **IV** was dissolved in 10 ml of dioxane, and 5 ml of 0.05 M H_2SO_4 and 1.7 ml of water were added. In a similar way, a solution of 0.267 g (1 mmol) of compound **VI** was prepared. The reaction was carried out in dioxane–water (3:2, by volume), the initial concentration of compounds **IV** and **VI** was 6×10^{-2} M, and the sulfuric acid concentration was 1.5×10^{-2} M. The mixture was stirred at 18°C, and the progress of the reaction was monitored by TLC until the initial compound disappeared completely. The mixture was then diluted with 150 ml of water, and the precipitate of carbazole, 0.148 g (84%), or phenothiazine, 0.189 g (95%), was filtered off. 2-Propynal was determined by the procedure reported in [11]. In the hydrolysis of **IV** and **VI** we isolated, respectively, 0.208 g (84%) and 0.215 g (92%) of 2-propynal 2,4-dinitrophenylhydrazone whose structure was confirmed by the ^1H NMR spectrum (C_6D_6), δ, ppm: 4.07 s (1H, $\equiv$CH), 7.00 s (1H, CH), 7.30 s (1H, NH), 7.9–9.0 (3H, H_{arom}).

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