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BRIEF COMMUNICATIONS

Synthesis of 1-Alkoxy-3-*N*-succinimido-2-propanols

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Abstract—Procedures for preparing 1-alkoxy-3-chloro-2-propanols, with their subsequent transformation to 1-alkoxy-*N*-succinimido-2-propanols, were developed.

N-Substituted succinimides show a wide spectrum of pharmacological properties [1, 2]. They are effective against convulsions caused by Metrazole and electric shocks; some of them have also proved to be effective against epilepsy. Many *N*-aryl-substituted succinimides have been tested for activity and toxicity; among these compounds, *N*-*p*-xylylsuccinimide is the most promising as anticonvulsant [1–3]. 2-Ethyl-3-methyl-3-phenylsuccinimide exhibits sedative, anticonvulsive, and tetragenic properties [4]. Other nontoxic highly active anticonvlusants for treating apoplectic shocks are *N*-methyl-2-phenyl-2-ethylsuccinimide and *N*-methyl-2-phenyl-3-methylsuccinimide [5]. *N*-Methyl-2-phenylsuccinimide (Milontin) is an antiepileptic drug and is used as a reference for comparing the anticonvulsive activities [6].

In this context, synthesis of *N*-substituted succinimides by the reaction of sodium succinimide with 1-alkoxy-3-chloro-2-propanols is a topical problem. The first step is to prepare sodium succinimide **III** by the reaction of sodium isopropylate **I** with succinimide **II**:

$$\underset{\mathbf{I}}{(CH_3)_2CHONa} + \underset{\mathbf{II}}{\begin{matrix}CH_2—CO\\|\\CH_2—CO\end{matrix}>NH} \xrightarrow{-(CH_3)_2CHOH} \underset{\mathbf{III}}{\begin{matrix}CH_2—CO\\|\\CH_2—CO\end{matrix}>NNa.}$$

Reactions of sodium succinimide with 1-alkoxy-3-chloro-2-propanols **IV**–**IX** are carried out at 70–75°C in the course of 3 h and yield the corresponding *N*-substituted succinimides **X**–**XV** (see table):

$$\underset{}{\begin{matrix}CH_2—CO\\|\\CH_2—CO\end{matrix}>NNa} + \underset{\mathbf{IV}–\mathbf{IX}}{ClCH_2CH(OH)CH_2OR} \xrightarrow{-NaCl} \underset{\mathbf{X}–\mathbf{XV}}{\begin{matrix}CH_2—CO\\|\\CH_2—CO\end{matrix}>NCH_2CH(OH)CH_2OR,}$$

where R = CH_3 (**IV**, **X**); C_2H_5 (**V**, **XI**); C_3H_7 (**VI**, **XII**); C_4H_9 (**VII**, **XIII**); C_5H_{11} (**VIII**, **XIV**); C_6H_{13} (**IX**, **XV**).

Yields, boiling points, refractive indices, and elemental analyses of substituted succinimides **X**–**XV**

Compound	Yield %	bp, °C (P, mm Hg)	n_D^{20}	Found, %/Calculated, %			Formula
				C	H	N	
X	60	149–150 (0.7)	1.4922	51.15/51.33	7.03/7.00	7.73/7.48	$C_8H_{13}NO_4$
XI	55	154–155 (0.6)	1.4894	53.65/53.72	8.07/7.51	6.93/6.96	$C_9H_{15}NO_4$
XII	53	168 (1.0)	1.4847	55.39/55.80	8.13/7.96	6.52/6.51	$C_{10}H_{17}NO_4$
XIII	50	160 (0.6)	1.4836	57.12/57.62	8.79/8.35	6.47/6.11	$C_{11}H_{19}NO_4$
XIV	48	176 (1.0)	1.4825	58.78/59.24	8.62/8.70	5.94/5.76	$C_{12}H_{21}NO_4$
XV	49	179–180 (0.7)	1.4060	60.95/60.68	9.28/9.01	5.16/5.44	$C_{13}H_{23}NO_4$

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The starting 1-alkoxy-3-chloro-2-propanols **IV**–**IX** were prepared by reactions of epichlorohydrin with aliphatic alcohols in the presence of $ZnCl_2$ (yield 80–90%). It should be noted that alternative procedures are also known [7, 8]. In particular, Floress Gallardo and Pollard [7] reacted epichlorohydrin with aliphatic alcohols in the presence of H_2SO_4; the yield of the target products did not exceed 55%. With $BF_3 \cdot OEt_2$ used as acid catalyst [8], the yield of the target products did not exceed 55%, either.

In both the studies cited, the yield of the target product was relatively low, and one of the reactants was taken in a large excess (threefold or sixfold excess of aliphatic alcohol, or sixfold excess of epichlorohydrin). Furthermore, $BF_3 \cdot OEt_2$ used in [8] is expensive and toxic.

We tested as acid catalysts in the reactions of epichlorohydrin with aliphatic alcohols both Brønsted (H_2SO_4, $HClO_4$) and aprotic Lewis acids ($AlCl_3$, $SnCl_4$, $ZnCl_2$). The best result was obtained with $ZnCl_2$. When the reaction was performed at the equimolar ratio of the alcohol and epichlorohydrin in the presence of 1.2 wt % $ZnCl_2$ (relative to the sum of the reactants) at the boiling point of the alcohol for 2.5–3 h, the yield of 1-alkoxy-3-chloro-2-propanols **IV**–**IX** reached 80–90%. Thus, the procedure is improved by eliminating the excess of one of the components, using a cheaper catalyst, and making shorter the reaction time.

The reaction course and the accumulation of 1-alkoxy-3-chloro-2-propanols were monitored by gas–liquid chromatography on a Tsvet-104 device (flame ionization detector; 200×0.03-cm column packed with 5% polyethylene glycol adipate on Porapak; sample volume 0.1 μl; P_{He} 0.8 kg cm^{-2}; paper feed velocity 240 mm h^{-1}; column temperature 140°C; vaporizer temperature 200°C).

The composition and structure of substituted succinimides **X**–**XV** were confirmed by elemental analysis, IR and NMR (^{1}H, ^{13}C) spectroscopy, and TLC.

The IR spectra of substituted succinimides **X**–**XV** contain bands at 3604–3598 (free OH groups), 3537–3532 (intramolecular hydrogen bond), and 1715–1705 cm^{-1} (C=O).

The highest-field signal in the ^{1}H NMR spectra of **X**–**XV** is the triplet of the terminal methyl group (3H) at 0.9–1.0 ppm. The OCH_2 protons give a multiplet at about 2.9 ppm. A broad singlet centered at 4.15–4.20 ppm belongs to the hydroxyl proton. The methine proton appears as a multiplet at about 3.71 ppm. Two methylene groups of the succinimide ring give a singlet at 4.8–5.7 ppm. In the ^{13}C NMR spectrum, the C=O signals are observed at 178–237 ppm.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Bruker spectrometer operating at 300 MHz, and the IR spectra, on a Specord 75-IR spectrophotometer (thin films).

The purity of the products and the reaction progress were monitored by TLC on Silufol UV-254 plates, with isopropyl alcohol–heptane (1 : 5) as eluent.

1-Propoxy-3-chloro-2-propanol. A three-necked flask was charged with 6 g of 1-propanol, 9.3 g of epichlorohydrin, and 0.2 g of $ZnCl_2$. The mixture was heated at 90–95°C for 3 h, after which the product was cooled and vacuum-distilled. Yield 13 g (85%), bp 95–96°C (20 mm Hg), n_D^{20} 1.4391. Published data [7]: bp 97–98°C (20 mm Hg), n_D^{20} 1.4378.

Other 1-alkoxy-3-chloro-2-propanols **IV**–**IX** were prepared similarly; their constants agree with published data [7, 8].

1-Propoxy-3-*N*-succinimido-2-propanol XII. A three-necked flask equipped with a reflux condenser, dropping funnel, thermometer, and stirrer was charged with 50 ml of 2 propanol, after which 4.6 g of finely divided sodium metal was added with vigorous stirring. When the whole amount of sodium dissolved, the mixture was cooled, 19.8 g of succinimide was added, and the mixture was stirred on a water bath at 70–75°C for 1 h. After that, 1-propoxy-3-chloro-2-propanol was added dropwise over a period of 20 min. The resulting mixture was heated on a water bath at 90°C for 3 h and then cooled; the NaCl precipitate was filtered off. The 2-propanol was distilled off in a water-jet-pump vacuum, and the product was vacuum-distilled. Yield of the substituted succinimide 23 g (53%), bp 168°C (20 mm Hg), n_D^{20} 1.4847.

Found, %: C 55.39, H 8.13, N 6.52.
$C_{10}H_{17}NO_4$.
Calculated, %: C 55.80, H 7.96, N 6.51.

N-Substituted succinimides **X**–**XV** were prepared similarly.

CONCLUSIONS

(1) The optimal conditions of the reaction of epichlorohydrin with aliphatic alcohols in the presence of

$ZnCl_2$ were found, and 1-alkoxy-3-chloro-2-propanols were obtained in 80–90% yields.

(2) A procedure was developed for preparing 1-alkoxy-3-*N*-succinimido-2-propanols in 48–60% yield from 1-alkoxy-3-chloro-2-propanols and sodium succinimide.

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