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SHORT COMMUNICATIONS

Guanidine Alkylation

I.A. Larionova[a], A.V. Golounin[b], and V.A. Sokolenko[b]

[a]*State University of Nonferrous Metals and Gold, Krasnoyarsk, 660025 Russia*
[b]*Institute of Chemistry and Chemical Engineering, Siberian Division, Russian Academy of Science, Krasnoyarsk, Russia*

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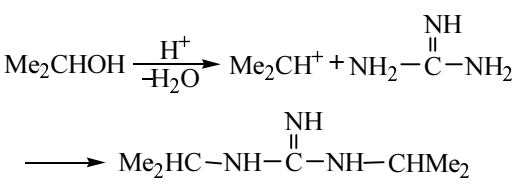
Although the guanidine alkyl derivatives are already known for a long time, they are still difficultly available reagents for their synthesis involves the application of hazardous substances: cyanamide, cyanogens bromide and chloride, thus presenting certain processing problems [1, 2].

Another way of alkylguanidines preparation consists in treating the guanidine carbonate with secondary alcohols in the presence of concn. sulfuric acid [3, 4]. This procedure is more convenient, but in the course of the synthesis tarring occurs due to oxidation under the action of the sulfuric acid. Besides the obtained mixture of mono- and dialkyl derivatives resists separation. Inasmuch as often pure dialkylguanidines are required the optimization of the alkylation process for preparation mainly dialkylguanidines appeared expedient.

Assuming that guanidine alkylation occurs under the action of carbocations arising by dehydration of the protonated alcohol the ions generation should be performed with the use of acid and superacid systems. It is known that to this end mineral acids are applied, like sulfuric and phosphoric acids [5].



The use of orthophosphoric acid instead of sulfuric acid did not increase the yield of alkylation products, and therefore we decided to test as a catalyst of guanidine alkylation a mixture of concn. sulfuric and phosphoric acids. The acids mixture is a weaker oxidant at 80–100°C than the concn. sulfuric acid.

The general procedure of the synthesis is described below. To a mixture of 30 ml of concn. H_2SO_4 and 50 ml of anhydrous orthophosphoric acid was added 0.1 mol of guanidine carbonate. After the end of CO_2 liberation 0.3 mol of alcohol was added, and the mixture was heated for 24 h at 80–100°C. On cooling the reaction mixture was diluted with cold water and extracted with benzene. The extract containing the tar was removed. The acid solution was poured on ice, neutralized with 10% alkali and alkalinized to pH 13. Then the product was extracted into 2-propanol, the extract was dried with calcined $MgSO_4$, and evaporated on a boiling water bath under reduced pressure. The oily thick residue crystallized at long storage. To obtain pure compounds the product was recrystallized from ethanol or a benzene–ethyl acetate mixture.

In contrast to aliphatic alcohols the guanidine reaction with benzyl alcohol was completed at 80°C within 20–30 min. On the surface of the acids separated a thick light organic layer; the workup of the latter provided *N*-benzylguanidine.

***N,N'*-Diisopropylguanidine**, yield 99%, mp 163–164°C [4]. ***N,N'*-diisobutylguanidine,** yield 99%, mp 173–174°C [4]. ***N,N'*-Dicyclohexylguanidine,** yield 60%, mp 157–158°C [4]. ***N*-Benzylguanidine,** yield 93%, mp 68–69°C [6]. IR spectra of compounds synthesized contain characteristic bands of >N–H, =N–H, and >C=N in the region 3300–3500 and 1620–1660 cm^{-1} [7]. In the ^{13}C NMR spectra of the alkylguanidines the carbon signal of the fragment >C=NH appears at 153–155 ppm. The ^1H NMR spectra of compounds synthesized permit an unambiguous interpretation (see the table). The assignment was confirmed by registering for comparison the ^1H NMR spectrum of *N,N'*-dioctylguanidine

^{1}H NMR spectra of *N,N'*-dialkylguanidines $(R_2CHNH)_2C{=}NH$ (DMSO-d_6)

R	CH	N–CH_2	CH_2	CH_3	NH
i-Pr	3.55–3.8, 4.2–4.4 m			1.1 q	7.0, 9.0 two s
i-Bu	3.53–3.56 d		1.7–1.9 m	0.84–1.13 d	7.05 s
cyclo-C_6H_{11}	3.31 s	1.1–1.8 m	1.02–1.05 m		5.84 s
C_8H_{17}		2.93–2.96 br.s	1.2–1.6 br.s	0.87 unresolved t	5.4 s, 6.1s (2:1)

synthesized by reaction of cyanogen bromide with octylamine [2]. The ^{1}H NMR spectrum of *N*-benzylguanidine contained signals at 3.85 (CH_2), 7.1 (Ph), and 7.2 ppm (NH).

It is worth mentioning that in the ^{1}H NMR spectrum of *N,N'*-diisopropylguanidine the methine hydrogen atoms are nonequivalent presumably due to the presence of several conformers.

In the ^{1}H NMR spectrum of *N,N'*-diisobutylguanidine there is a singke peak of hydrogen atoms attached to nitrogen at 7.0 ppm suggesting the existence of the 1-3-sigmatropic shift of the hydrogen in the =N–H bond which results in the equivalence of the amino groups protons. This shift lacks in the *N,N'*-dioctylguanidine due to steric reasons, and in the spectrum of the latter appear two NH signals at 5.4 and 6.1 ppm at a ratio 2:1. Besides in the *N,N'*-diisobutylguanidine a free rotation is possible around the C–N bond, and the conformers can be mutually converted.

IR spectra were recorded from KBr pellets on a spectrophotometer Specord 75IR. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance 200, internal reference TMS, solvent DMSO-d_6 or $CDCl_3$.

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