THE AMINOMETHYLATION OF SOME FUNCTIONAL DERIVATIVES OF FURAN

L. I. Vereshchagin, R. I. Katkevich, and S. P. Korshunov

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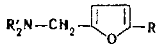
The aminomethylation of primary, secondary, and tertiary alcohols of the furan series and also of butyl pyromucate under the conditions of the Mannich reaction has given the corresponding aminomethyl-substituted compounds.

Attempts to introduce aminomethyl substituents directly into the α-position of furan or into the β-position of 2, 5-dimethylfuran have proved unsuccessful [1]. However, the analogous reaction of 2-methylfuran with formaldehyde and primary amines leads to the corresponding alkylaminomethyl derivatives. The aminomethylation of 2-(N, N-dimethylaminomethyl)-furan takes place less smoothly [2]. The possibility of aminomethylating furfuryl alcohol has also been shown [3].

Information on the application of the Mannich reaction to furan derivatives is limited to these papers. However, aminomethylfurans bearing functional substituents undoubtedly arouse considerable interest because the analogous thiophene compounds possess valuable chemotherapeutic properties [4].

We have previously carried out the aminomethylation of furfuryl alcohol with dialkylamines in piperidine [5] in order to obtain the corresponding amino aldehydes. Isonicotinoylhydrazones of dialkylaminomethylfurfurals have been described; they showed good tuberculostatic activity. In order to obtain substances possessing a similar action, we have brought about the reaction of primary, secondary, and tertiary furan alcohols with aliphatic amines and paraformaldehyde. The reaction takes place only at pH < 7, which is achieved by the use of the hydrochlorides of the corresponding amines. It is not necessary to add the crystalline salts of the amines; it is sufficient to neutralize the free bases with the calculated amount of concentrated hydrochloric acid. Aminomethylation was carried out by boiling the mixture of reactants for 12–14 hr in ethanol. This gave N, N-dialkylaminomethylfuryl carbinols, which consisted of faintly colored liquids with a characteristic amine-like odor. The primary alcohols are fairly soluble in water, which makes their isolation difficult. Consequently, the yields of the primary aminomethyl carbinols were 50–60%, and of the secondary compounds 80–90%. The introduction of unsaturated bonds into the side chain of the carbinol also led to a fall in the yields because of the resinification of the reaction products. Thus, the yield of 1-(5'-N, N-dimethylaminomethyl-2'-furyl)pent-1-en-3-ol was only 50%, and 1-(2'-furyl)-3-phenylprop-2-yn-1-ol gave only resinous reaction products. To confirm the structure of the alcohols obtained, 3-(5'-N, N-dimethylaminomethyl-2'-furyl)-1-propanol was synthesized by the Grignard reaction starting from the corresponding aminomethylfurfural. The constants of the substances obtained agreed. We have been unable to obtain acetylenic aminofuran alcohols by the Iotisich reaction with the dialkylaminomethylfurfurals.

It was interesting to investigate the possibility of the aminomethylation of furan compounds with other functional substituents. It was found that furfural and 2-furancarboxylic acid and its esters do not take part



R'₂N	R	Bp, °C (pressure, mm)	n_D^{20}	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
$(CH_3)_2N$	CH_2OH	128—133 (15)	1.4920	$C_8H_{13}NO_2$	—	—	—	—	—	—	53.0
$(C_2H_5)_2N$	CH_2OH	142—146 (15)	1.4766	$C_{10}H_{17}NO_2$	65.32	9.23	7.83	65.54	9.35	7.64	54.8
$H_{10}C_5N$	CH_2OH	145 (2)	1.5199	$C_{11}H_{17}NO_2$	67.60	8.84	7.17	67.66	8.78	7.17	73.0
$(CH_3)_2N$	$CHOHCH_3$	116—117 (6)	1.4869	$C_9H_{15}NO_2$	63.95	8 87	—	63.88	8,93	—	87.4
$(CH_3)_2N$	$CHOHC_2H_5$	92—96 (1)	1.4829	$C_{10}H_{17}NO_2$	65.65	9.04	—	65.54	9.35	—	86.2
$(CH_3)_2N$	$CHOHC_4H_9$-*n*	110 (2)	1.4780	$C_{12}H_{21}NO_2$	68.38	10.03	6.75	68.21	10.02	6.63	88.2
$(CH_3)_2N$	$(CH_2)_2CHOHC_2H_5$	114—116 (1)	1.4850	$C_{12}H_{21}NO_2$	68.11	10.19	6.39	68.21	10.02	6.63	62.5
$(CH_3)_2N$	$CH=CHCHOHC_2H_5$	120 (2)	1.5171	$C_{12}H_{19}NO_2$	69.10	9.44	6.54	68.87	9.15	6.69	50.0

in this reaction under conditions analogous to those used for the aminomethylation of the furan carbinols. At the same time, butyl furancarboxylate readily undergoes aminomethylation with free secondary amines in the presence of paraformaldehyde; this gives rise to a mixture of the butyl ester and the diethylamide of 5-(diethylaminomethyl)-2-furancarboxylic acid.

EXPERIMENTAL

Aminomethylation of furan alcohols. a) A mixture of 1 mole of an α-furyl carbinol, 1 mole of crystalline dialkylamine hydrochloride, and 1.5 mole of paraformaldehyde was boiled in ethanol for 2 hr, and then another 1 mole of paraformaldehyde was added. Boiling was continued for 10–12 hr; after this time the paraformaldehyde had dissolved completely and the mixture had acquired a dark cherry-red coloration. The ethanol was distilled off in vacuum and the residue was dissolved in water. The solution was made strongly alkaline and was then carefully extracted with ether. The ethereal extract was dried with calcined magnesium sulfate and the residue was distilled in vacuum in a current of dry nitrogen. The yields and constants of the dialkylaminomethyl carbinols obtained are given in the table.

b) With cooling, the calculated amount of concentrated hydrochloric acid was added to pyridine, and the pH was brought to 6 by the addition of a small excess of acid. An equimolar amount of furfuryl alcohol and 2.5 times the amount of paraformaldehyde were then added and the resulting mixture was then boiled for 14 hr. Distillation yielded 5-piperidinomethylfuryl alcohol with bp 155°–160° C (7 mm); n_D^{20} 1.5200. Yield 73%.

2-(Dimethylaminomethyl)-5-(but-2'-en-2'-yl) furan. 2.5 g of the reaction product obtained by the aminomethylation of 2-(α-furyl)-2-butanol [bp 92° C (6 mm), n_D^{20} 1.5030] was distilled in vacuum in the presence of catalytic amounts of iodine. The distillate was dried with magnesium sulfate and redistilled. This gave 1.6 g (70%) of dehydration product with bp 74°–76° C (1.5 mm); n_D^{20} 1.5100. Found, %: C 74.19; H 9.66; N 7.79; calculated for $C_{11}H_{17}NO$, %: C 73.70; H 9.56; N 7.81. IR spectrum: $\nu_{C=C}$ 1684 cm^{-2}.

Aminomethylation of butyl pyromucate. A mixture of 1 mole of butyl 2-furancarboxylate, 3 moles of diethylamine, and 2.5 moles of paraformaldehyde in ethanol was boiled for 3 hr in the water bath. The solvent and the excess of amine were distilled off in vacuum. The residue was a mixture of crystalline and liquid reaction products. The crystals of 5-diethylaminomethyl-2-furancarboxylic acid diethylamide were separated by filtration and recrystallized from a mixture of dimethylformamide and benzene. Yield 10%. White plates with mp 221°–222° C. Found: N 10.81%; calculated for $C_{14}H_{24}N_2O_2$, %: N 11.11.

The filtrate was distilled in vacuum. The yield of butyl 5-diethyaminomethyl-2-furancarboxylate was 50%; bp 140°–141° C (1 mm); n_D^{17} 1.4800. Found, %: C 66.08; H 9.36; N 5.93; calculated for $C_{14}H_{23}NO_3$, %: C 66.37; H 9.15; N 5.53. Literature data [6]: bp 147°–148° C (3 mm); n_D^{20} 1.4740.

1-(5'-Dimethylaminomethyl-2'-furyl)-1-propanol. In drops with stirring and ice-water cooling, an ethereal solution of 2.5 g (0.016 mole) of 5-(dimethylaminomethyl)furfural was added to an ethereal solution of the ethylmagnesium bromide prepared from 0.5 g (0.021 mole) of magnesium and 3 g (0.028 mole) of ethyl bromide. The mixture was stirred with heating in the water bath for another 2 1/2 hr. The complex was decomposed with ice water. The ethereal solution was separated off and the aqueous layer was made strongly alkaline and extracted three times with ether. The combined ethereal extracts were dried over calcined magnesium sulfate, the ether was distilled off, and the residue was distilled in vacuum. This gave 2.5 g (83%) of the carbinol with mp 92°–96° C (1 mm); n_D^{20} 1.4829. The constants of the carbinol agreed with those of the compound obtained by the aminomethylation of furyl ethyl carbinol.

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Institute of Petrochemical
and Coal-chemical Synthesis at Irkutsk State University