THE SYNTHESIS OF N-SUBSTITUTED 5-AMINOFURFURALS

Z. N. Nazarova and V. S. Pustovarov

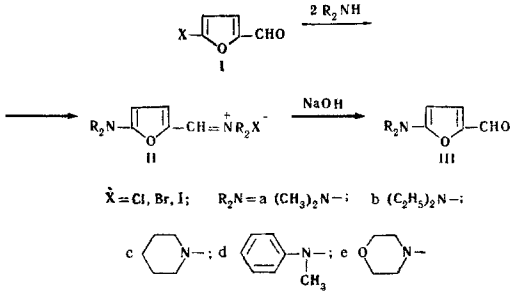
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 4, pp. 586–590, 1969

UDC 547.724'.1.722.6.07

A simple method for the synthesis of N-substituted 5-aminofurfurals based on the reaction of 5-halogenofurfurals with secondary amines has been developed. The reaction takes place through the formation of quaternary salts of N-substituted 5-aminofurfurals. 5-(Diethylamino)-, 5-(N-methyl-N-phenylamino)-, and 5-piperidinofurfurals have been obtained for the first time.

It has been established previously [1] that the reaction of 5-halogenofurfurylideneanilines with dimethylamine and morpholine gives, as the final products of the reaction, quaternary salts which, on neutralization with alkali, are converted into 5-dimethylaminofurfural (IIIa) and 5-morpholinofurfural (IIIe), respectively. However, the isolation of other aminoaldehydes from the reaction mixtures proved to be difficult.

In the course of a further investigation of nucleophilic substitution in the furan series, we have studied the reaction of the 5-halogenofurfurals **I** with secondary amines giving quantitative yields of the quaternary salts **IIa–IIe**.



The structure of these salts was confirmed by the presence in their spectra of a strong band in the visible region at 395–405 nm and also by the presence in the IR spectrum of bands in the 1644–1678 cm^{-1} region which we ascribe to the stretching vibrations of the $C{=}\overset{+}{N}{<}$ group [2] (see Table 1). The treatment of the salts **II** with alkali gave good yields of the corresponding N-substituted 5-aminofurfurals **IIIa–IIIe** (see Table 2).

In individual cases, the salts **IIb** and **IIc** form substances which are difficult to crystallize and deliquesce in the air and the isolation of which in the crystalline state is difficult, and the preparation of the aminoaldehydes is preferably carried out without the isolation of the salts by the addition of alkali to the reaction mixture after the amine. In the case of amines possessing a limited solubility in water (methylaniline, morpholine), the aminoaldehydes are freed from the initial amine by binding it with phthalic anhydride.

The IR spectra of the aldehydes **IIIa–IIIe** obtained exhibit a band in the 1637–1656 cm^{-1} region which we have ascribed to the stretching vibrations of the aldehyde group [2]. Bands characteristic for a furan ring are also observed. In the UV spectra there is a strong band at 365 nm which agrees with the structure proposed for **III**. This structure is also confirmed by qualitative reactions for an aldehyde group (formation of a silver mirror) and also by condensation with compounds having mobile hydrogen atoms.

EXPERIMENTAL

5-Dimethylaminofurfural (IIIa). A solution of 17.5 g (0.01 mole) of 5-bromofurfural in 20 ml of ethanol was heated to 40° C, and 60 ml of 33% aqueous dimethylamine was added in three or four portions. The addition was complete after 25–30 min. During this time the temperature of the mixture was kept strictly between 40 and 45° C. A rise in the temperature may lead to a vigorous decomposition of the reaction mixture. After the end of the reaction, the mixture was heated to 70° C and was then cooled to 0° C and treated with 40% NaOH until it separated into two layers (~60 ml). The upper layer was separated off and was left in a Petri dish in an exhaust hood for 2 hr with periodic stirring. The precipitate that deposited was filtered off, dried in a desiccator, and recrystallized from benzene. Yield 12.1 g (87%). A mixture with authentic 5-dimethylaminofurfural [1] gave no depression of the melting point.

Dimethyl(5-dimethylaminofurfurylidene)ammonium bromide (IIa, X = Br). A solution prepared by heating 1.75 g (0.01 mole) of 5-bromofurfural and 4 ml of ethanol to 35° C was treated with 4 ml of 50% ethanolic dimethylamine in portions. The mixture was kept at 35° C until the exothermic reaction began (as shown by the vigorous heating of the reaction mixture) and was then cooled. The precipitate that deposited was separated off, washed with ethanol, and recrystallized from ethanol. The yield was quantitative. A mixture of the salt obtained with an authentic sample [1] gave no depression of the melting point.

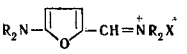
The following were obtained similarly: dimethyl(5-dimethylaminofurfurylidene)ammonium iodide and chloride (IIa, X = I and Cl).

5-Diethylaminofurfural (IIIb). A mixture of 17.5 g (0.1 mole) of 5-bromofurfural, 20 ml of ethanol, and 30 ml of diethylamine was heated at 50° C under reflux for 1 hr; after the cooling of the reaction mixture, the diethylamine was distilled off and the solution was cooled again and treated with a 40% solution of NaOH. The upper layer was separated off, the ethanol was driven off, and the residue was distilled in vacuum. The **IIIb** distilled over in the form of a light yellow oil. Yield 15 g (90%). On cooling, the oil crystallized.

Diethylamino(5-diethylaminofurfurylidene)ammonium iodide (IIb, X = I). A mixture of 11.1 g (0.05 mole) of 5-iodofurfural, 15 ml of diethylamine and 15 ml of ethanol was heated at 50° C for 1 hr; after the end of the reaction, the excess of diethylamine and the ethanol were distilled off and the crystals that had deposited were separated off. and washed with ethanol. The yield was quantitative. The treatment of **IIb** with a 40% solution of alkali gave **IIIb**.

5-Piperidinofurfural (IIIc). A mixture of 17.5 g (0.1 mole) of 5-bromofurfural and 20 ml of ethanol was heated to 35° C, and 17 g of piperidine was added in portions. After the formation of a precipitate the temperature of the mixture was raised to 45° C and kept there for 30 min, and it was then heated to 60° C, cooled, and treated with a 40% solution of alkali, after which the upper layer was separated off and distilled in vacuum. Light yellow oil crystallizing on standing. Yield 13.2 g (74%).

Table 1



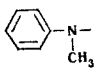
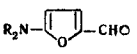
Compound	R_2N—	X	Mp, °C	Color of the crystals	λ_{max}, nm	log ε	ν C=O, cm^{-1}	Empirical formula	Found, %			Calculated, %		
									C	H	N	C	H	N
IIa	$(CH_3)_2N$—	Br	190—191	Bright yellow	396	4.70	1678	$C_9H_{15}BrN_2O$	43.62	6.16	11.36	43.74	6.12	11.33
		I	193—194	Light green	398	4.73	1678	$C_9H_{15}IN_2O$	36.59	5.31	9.57	36.75	5.14	9.42
		Cl	182—183	Pale yellow	396	4.74	1677	$C_9H_{15}ClN_2O$	53.67	7.28	13.71	53.43	7.42	13.85
IIb	$(C_2H_5)_2N$—	I	129—130	Light yellow	400	4.32	1666	$C_{13}H_{23}IN_2O$	44.32	6.74	7.89	44.57	6.57	7.99
IIc		I	160.5—161	Yellow	405	4.38	1668	$C_{15}H_{23}IN_2O$	48.05	6.31	7.62	48.17	6.15	7.94
IId		I	147.5—148.5	Green	400	3.64		$C_{19}H_{19}IN_2O$	54.52	4.71	6.64	54.69	4.59	6.71
			148—148.5	Yellow	400	2.93	1644	$C_{19}H_{19}IN_2O$	54.47	4.75	6.67	54.69	4.59	6.71
IIe		Br	Decomposes above 300° C	Yellow-green	393	4.42	1644	$C_{13}H_{19}BrN_2O_3$	47.04	5.92	8.53	47.14	5.78	8.45

Table 2



Compound	R_2N—	Mp, °C	Bp, °C (pressure, mm)	Color	λ_{max}, nm	log ε	ν C=O, cm^{-1}	Empirical formula	Calculated, %			Found, %		
									C	H	N	C	H	N
IIIa	$(CH_3)_2N$—	74—75		Colorless	364	4.52	1653	$C_7H_9NO_2$	60.24	6.64	9.87	60.40	6.52	10.06
IIIb	$(C_2H_5)_2N$—	35—36	161 (5)	Cream	365	4.55	1656	$C_9H_{13}NO_2$	64.49	7.99	8.56	64.65	7.84	8.38
IIIc		50.5—51.5	204 (30)	White	365	4.51	1646	$C_{10}H_{13}NO_2$	67.28	7.18	7.98	67.02	7.31	7.81
IIId		76—77		Pale yellow	365	4.45	1637	$C_{12}H_{11}NO_2$	71.49	5.61	7.08	71.65	5.47	6.96
IIIe		50—50.5	190 (10)	White	356	4.18	1642	$C_9H_{11}NO_3$	59.62	6.11	7.92	59.68	5.92	7.78

N-(5-Piperidinofurfurylidene)piperidinium iodide (IIc, X = I). A mixture of 11.1 g (0.05 mole) of 5-iodofurfural, 8 g of piperidine, and 20 ml of ethanol was heated at 30° C until a white precipitate had formed, and then the temperature of the mixture was raised to 45–50° C and heating was continued at this temperature for 30 min. After this, the solution was heated to 65° C, cooled, and treated with 20 ml of ethanol. When the ethanol was evaporated off, the reaction product crystallized. The crystals that had deposited were separated off, washed with ethanol, and recrystallized from ethanol. The yield qas quantitative. The treatment of **IIc** with a 40% solution of NaOH yielded **IIIc.**

5-(N-Methyl-N-phenylamino)furfural (IIId). A solution of 50 ml of methylaniline in 50 ml of ethanol was added in portions to a solution of 33.3 g (0.15 mole) of 5-iodofurfural in 60 ml of ethanol; the temperature of the mixture was kept at about 50° C. After the addition of the whole of the methylaniline, the solution was heated to 65° C and kept at this temperature for 25 min, and then it was heated to 80° C and was cooled. After this it was treated with a 40% solution of NaOH and the reaction product was extracted five times with benzene. The benzene extracts were combined and dried with potassium carbonate and were then treated with 100 g of powdered phthalic anhydride, with stirring. After 1.5 hr, the phthalamic acid was extracted from the solution with 500 ml of a 20% solution of NaOH with vigorous shaking for 30 min. Then the benzene layer was separated off, dried with potassium carbonate, and treated again with 60 g of phthalic anhydride. After a day, the phthalamic acid was extracted with alkali solution, the benzene solution was dried with potassium carbonate, the benzene was distilled off, and the resulting oil was left in the refrigerator. After 5–7 days the oil crystallized. Yield 12.6 g (42%).

Methyl[5-(methylphenylamino)furfurylidene]phenylammonium iodide (IId, X = I). A solution of 11 ml of methylaniline in 10 ml of ethanol was added in portions to a solution of 11.1 g (0.05 mole) of 5-iodofurfural in 20 ml of ethanol at 30° C. After the addition of the whole of the methylaniline, the temperature of the mixture was raised to 60° C and was kept at this level for 30 min, then it was raised to 75° C, after which the solution was cooled and treated with 30 ml of ethanol, the ethanol was evaporated off, and the crystals that deposited were separated off. The yield was quantitative. The precipitate was separated by repeated crystallization into two isomers: dark green crystals crystallizing in the form of spherical nodules and yellow crystals (see Table 1). The treatment of **IId** with a 40% solution of NaOH gave **IIId.**

N-(5-Morpholinofurfurylidene)morpholinium bromide (IIe, X = Br). A mixture of 17.5 g (0.1 mole) of 5-bromofurfural, 30 ml of ethanol, and 18 g (0.02 mole) of morpholine was heated at 45–50° C until a precipitate formed, after which the temperature of the mixture was raised to 65° C and heating was continued at this temperature for 40 min. The subsequent treatment was similar to that for **IIc.** The yield was quantitative.

5-Morpholinofurfural (IIIe). To obtain a purer morpholinofurfural, the salt **IIe** (X = Br) was purified by recrystallization from ethanol, after which it was treated with a 40% solution of NaOH. The reaction product was extracted with benzene and the benzene extracts were washed with water (3 × 10 ml) and were treated with phthalic anhydride as described above. The yield was 13.8 g (50%). A mixture of the aldehyde obtained with 5-morpholinofurfural [1] gave no depression of the melting point.

IIIe can also be obtained without the isolation of the salt in a similar manner to **IIId.**

REFERENCES

1. Z. N. Nazarova, V. N. Novikov, and V. S. Pustovarov, ZhOrKh, 2, 162, 1966.

2. K. Nakanishi, Absorption Spectroscopy, Practical [Russian translation], Moscow, 1965.

8 February 1967

Rostov-on-Don State University