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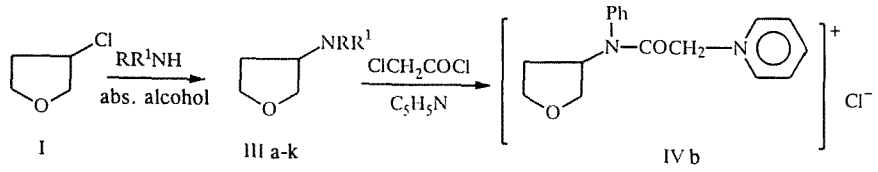
SYNTHESIS OF AMINES OF THE TETRAHYDRO-3-FURYL SERIES

R. F. Talipov, Kh. F. Sagitdinova, A. M. Gaisin, D. V. Petrov, and M. G. Safarov

From β-tetrachlorotetrahydrofuran a series of aromatic and aliphatic amines has been synthesized, the members of which are of interest as biologically active compounds. It is shown to be possible to convert them to water-soluble salts by sequential treatment with chloroacetyl chloride and pyridine.

The practical interest in amines of the tetrahydrofuryl series is due to their pronounced neurophysiological [1, 2], anticholinergic, and local anesthetizing [3] activity. At the present time, however, these compounds do not find wide use because of the lack of convenient methods of synthesis (a consequence of the relatively low reactivity of the chlorine atom in the β-position on the tetrahydrofuran ring [4]) as well as the difficulty in obtaining the starting material.

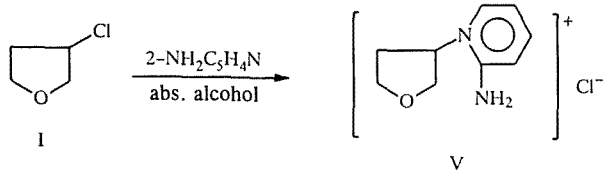
This paper deals with the synthesis of a series of amines of the tetrahydro-3-furyl series which are of interest as biologically active compounds. We accomplished the conversion starting from β-tetrachlorotetrahydrofuran (I) obtained by a known procedure [5] from tetrahydrofuran-3-ol (II). Synthesis of the latter was carried out as described in [6].



I III a-k IV b

III a R = H, R^1 = CH_2Ph, b R = H, R^1 = Ph, c R = H, R^1 = $C_6H_4CH_3$-*o*, d R = H, R^1 = $C_6H_4CH_3$-*p*, e R = H, R^1 = $C_6H_4CH_3$-*m*, f R = H, R^1 = $C_6H_4OCH_3$-*o*, g R = H, R^1 = $C_6H_4OCH_3$-*p*, h R = H, R^1 = C_6H_4Cl-*o*, i R = C_2H_5, R^1 = Ph, j R + R^1 = $(CH_2)_5$, k R + R^1 = $(CH_2)_6$

In the presence of strong bases, triethylamine for example, or when heated above 140°C, dehydrochlorination products become appreciable. The yield of amines IIIa-k is also determined by the basicity of the starting amine (see Table 1). This is confirmed sufficiently graphically by the participation of 2-aminopyridine in the reaction with chloride I.



I V

Here, the main reaction product was identified as 1-(3-tetrahydrofuryl)-2-aminopyridine (V). No product from the reaction of the less basic, primary amine group was found.

The possibility of converting synthesized amines IIIa-k to water-soluble salts by sequential treatment with chloroacetyl chloride and pyridine in dry ether was shown with compound IIIb as an example. The yield of the desired N-pyridinoacetyl-N-(3-tetrahydrofuryl)aniline chloride (IVb) was 54%.

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TABLE 1. Physicochemical Characteristics of Synthesized Compounds IIIa-k, IVb

Compound	T_{bp}, °C/mm, Hg	n_D^{20}	PMR spectrum, δ, ppm*			Yield, %
			4-H, m	2-, 3-, 5-H, m	NH*2 (hd.s.)	
IIIa	130...131/16	1,5349	1,6...2,3	3,3...4,0	1,5...1,6	31
IIIb	63...67/3	1,5783	1,8...2,4	3,6...4,3		36
IIIc	115...118/3	1,5661	1,6...2,4	3,5...4,2		27
IIId	121...123/3	1,5658	2,0...2,7	3,8...4,4		23
IIIe	120...121/3	1,5690	2,2...2,8	3,8...4,4	4,5...4,7	44
IIIf	129...130/3	1,5702	2,0...2,6	3,8...4,4	4,5...4,7	28
IIIg	141...143/3	1,5685	2,0...2,5	3,8...4,3		29
IIIh		1,5834	1,8...2,6	3,7...4,8		1
IIIi	118...120/16	1,5570	1,8...2,3	3,6...4,5		13
IIIj	223/760	1,4860	1,8...2,1	2,7...3,1 (3-H) 3,5...4,1 (2-, 5-H)		64
IIIk	108...110/16	1,4916	1,4...2,2	3,2...4,2		54
IVb	*3		2,2...2,6	3,4...4,1		54

*Solvent $CDCl_3$ or $(CD_3)_2SO$ (in case IV).

*2 Protons of NH groups identified by addition of trifluoroacetic acid.

*3 T_{mp} 217°C.

EXPERIMENTAL

PMR spectra were taken on a Tesla BS-487C (80 MHz) instrument, HMDS internal standard. The GLC analyses were done on an LKhM-8MD chromatograph with DIP on 3500 × 3 mm stainless steel columns with 15% SE-30 on chromatone N-AW-HMDS. Carrier gas was nitrogen (20 ml/min).

Elementary analyses of the synthesized compounds corresponded to the calculated values.

Amines of the Tetrahydro-3-furyl Series (IIIa-k). A mixture of 17 mmoles of chloride I, 34 mmoles of starting amine, and 2 ml of abs. alcohol were held in a sealed ampule at 125-130°C for 25-35 h. The contents of the ampule were cooled, the alcohol distilled off, and the residue thinned with ether and filtered off. The filtrate was concentrated and distilled under reduced pressure to isolate the desired product. Compounds IIIh-j were purified by column chromatography on silica gel. Eluent, 4:1 benzene:acetone (IIIh, R_f 0.71), 3:1 hexane:ethyl acetate (IIIi, R_f 0.68), 2:1 hexane:acetone (IIIj, R_f 0.52).

1-(3-Tetrahydrofuryl)-2-aminopyridinium Chloride (V). A mixture of 9 mmoles of I, 9 mmoles of 2-aminopyridine, and 1 ml of abs. alcohol was treated as described above. After removal of the alcohol the residue was washed with ether and then acetone, and 0.9 g (50%) of a viscous, water-soluble oil was obtained. PMR spectrum (δ, ppm, $(CD_3)_2SO$): 2.7-3.1:(2H, m, CH_2); 3.8-4.4 (5H, m, CH_2OCH_2CH); 5.5-6.0 (2H, br.s, NH_2); 6.6-8.2 (4H, m, C_5H_4N).

N-Pyridinoacetyl-N-(3-tetrahydrofurylaniline) Chloride (IVb). To a cooled suspension of 4.9 mmoles of amine IIIb and 14.7 mmoles of potash in 20 ml of dry ether was added 5.2 mmoles of chloroacetyl chloride. The reaction mixture was heated and stirred on a water bath for 8 h. The residue was then filtered off, and 4.9 mmoles of pyridine added to the filtrate, which was then heated for another 8 h. The ether was removed, the residue cooled with ice, and the precipitated product washed with acetone. Yield of salt IVb was 0.84 g.

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