SYNTHESIS OF 2-(2-ARYLAMINO-3-ALKYLOXAZOLIDYNYL-4)- AND 2-(2-ARYLAMINO-3-ALKYLTHIAZOLIDYNYL-4-N-ALKYLACETAMIDES FROM 2(5H)-FURANONE

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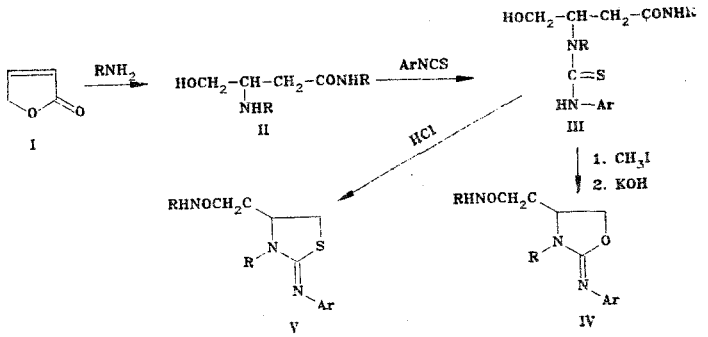
Aminolysis of 2(5H)-furanone leads to 3-alkylamino-4-hydroxy-N-alkylbutyramides which easily form hydroxy derivatives of thiourea. The latter, depending on the protonation or quaternization site, easily undergo cyclization to thiazolidine and oxazolidine derivatives.

Azolidine derivatives (oxazolidines, thiazolidines) manifest a wide spectrum of biological activity [1-4] and are used in many branches of the national economy [5].

The aim of our study is to obtain previously unknown functionally substituted amides containing azolidine rings (2-iminothiazolidines and 2-iminooxazolidines) in their structure on the basis of 2(5H)-furanone which is presently available [6].

The transformations are represented by the following scheme:



I II III V IV

IIa–Va R=C_2H_5; IIb, IIIb,c–Vb,c R=C_4H_9, IIc, IIId–Vd R=$C_{10}H_{21}$, IId, IIIe–Ve R= furfuryl; III–Va,b,d,e Ar=C_6H_5, c Ar=C_6H_4-Cl-*p*

3-Alkylamino-4-hydroxy-N-alkylbutyramides II were obtained by the interaction of 2(5H)-furanone with the corresponding primary amines at room temperature using a slight excess of the latter. The structure of aminohydroxyamides II was confirmed by their physicochemical properties (Table 1).

Interaction of butyramides II with arylisothiocyanates leads to the corresponding thioureas III — 4-hydroxy-3-(1-alkyl-3-arylthioureido)-N-alkylbutyramides. Hydroxythioureas III are unstable and decompose during storing with the formation of the starting compounds, thiazolidinethiones, and other decomposition products. The authenticity of compounds III was confirmed chromatographically and their structure was proven by the spectra (Table II); the IR spectra show absorption attributed to the amide carbonyl group at 1650-1630 cm^{-1}, and the NMR spectrum contains OH resonances at 4.33-4.08, NH groups at 3.76-3.53, and NH from the amide groups at 7.01-7.41 ppm.

The presence of the hydroxy group in the thioureas III allowed us to perform the intramolecular condensations which on the one hand, characterize the reactivity of compounds III, and, on the other hand open up a new synthetic route toward new thiazolidines and oxazolidines. On heating in hydrochloric acid, hydroxythioureas III undergo cyclization to 2-(2-arylamino-3-alkylthiazolidynyl-4-)-N-alkylacetamides V. One can assume that the protonation of

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TABLE 1. 4-Alkylamino-4-hydroxy-N-alkylbutyramides II a-d

Compound	mp, °C*	Found, %			Molecular formula	Calcd., %			Yield, %
		C	H	N		C	H	N	
IIa	83—84	51,8	10,9	17,2	$C_8H_{18}N_2O_2$	51,9	11,1	17,3	96
IIb	65—66	62,0	10,7	12,1	$C_{12}H_{26}N_2O_2$	62,1	11,3	12,2	94
IIc	72—73	72,3	12,8	7,0	$C_{24}H_{50}N_2O_2$	72,4	12,4	7,0	97
IId†	90—91	60,4	6,4	10,0	$C_{14}H_{18}N_2O_4$	60,4	6,5	10,1	90

*From ethanol by precipitation with ethyl ether.
†From a 1:10 ethanol—ether mixture.

TABLE 2. Properties of Synthesized Compounds

Compound	mp °C (from hexane)	IR spectrum, cm^{-1}	NMR spectrum, ppm				Found, %		Molecular formula	Calcd., %		Yield, %
			Ar(H)	NHCO, M	N—H, M	O—H, M	N	S(Cl)		N	S(Cl)	
IIIa	122—123	3300, 3220, 3080, 3030, 1630, 1555	6,25—6,00, m	7,06	3,73	4,08	13,2	10,7	$C_{15}H_{23}N_3O_2S$	13,6	10,4	84
IIIb*	66—67	3300, 3215, 1645, 1555	7,42—7,10, m	9.30	4,90	6,70	11,3	9,1	$C_{19}H_{31}N_3O_2S$	11,5	8,8	71
IIIc	106—107	3330, 3250, 3125, 1650, 1555	6,21, s	7,05	3,53	4,08	10,5	7,9 (9,1)	$C_{19}H_{30}ClN_3O_2S$	10,0	8,0 (8,8)	94
IIId	80—81	3400, 3370, 3180, 3090, 3030, 1620	6,22—6,20, m	7,03	3,70	4,17	7,2	5,4	$C_{31}H_{59}N_3O_2S$	7,4	5,7	76
IIIe	76—77	3310, 3180, 3060, 3030, 1635, 1540	7,54—7,03, m	7,41	3,07	3,07	9,9	7,4	$C_{21}H_{23}N_3O_4S$	10,2	7,7	91
IVa	Oil	3395, 3250, 3090, 3060, 1665, 1650, 1560	6,15—5,70, m	6,95	—	—	15,4	—	$C_{15}H_{21}N_3O_2$	15,3	—	47
IVb	Oil	3410, 3320, 3070, 1670, 1660, 1565	6,13—5,80, m	6,93	—	—	12,4	—	$C_{19}H_{29}N_3O_2$	12,7	—	41
IVc	90—91	3325, 3090, 3050, 1670, 1650, 1555	6,20,s	6,95	—	—	11,3	(9,6)	$C_{19}H_{28}ClN_3O_2$	11,0	(9,3)	38
IVe	119—120	3295, 3120, 3070, 3030, 1640, 1635, 1600, 1580	6,83,m	7,40	—	—	11,3	—	$C_{21}H_{21}N_3O_4$	11,1	—	49
Va	Oil	3380, 3240, 3080, 3040, 1630, 1560	6,22—5,62, m	6,98	—	—	14,2	11,2	$C_{15}H_{21}N_3OS$	14,4	11,0	82
Vb†	40—41	3410, 3315, 3085, 3060, 1650, 1630, 1565	7,68—6,72, m	9,10	—	—	12,3	8,9	$C_{19}H_{29}N_3OS$	12,1	9,2	73
Vc	149—150	3330, 3250, 3090, 3050, 1670, 1630, 1560	6,20, s	6,93	—	—	11,3	8,1 (9,7)	$C_{19}H_{28}ClN_3OS$	11,0	8,4 (9,3)	73

*NMR spectrum taken in $CDCl_3$ on an XL-100 instrument; internal standard TMS, the remaining spectra were taken in DMSO-d_6.
†NMR spectrum taken in CCl_4 on a XL-100 instrument; internal standard TMS.

thioureas III takes place on the hydroxy group with the subsequent cleavage of water and attack of the carbocation formed on the sulfur. An alternative variant consisting in the formation of the isothiourea cation, proposed in [7], seems to us less probable, because in

our case it is realized during the quarternization of thiourea III with methyl iodide, which causes cleavage of methyl mercaptan in the basic medium and cyclization to the oxazolidine ring, analogously to the synthesis of 1,3-oxazines [8].

The physicochemical characteristics of the synthesized iminothiazolidines V and iminooxazolidines IV are shown in Table 2. One should note that the IR, UV, and NMR spectra of compounds IV are similar to the corresponding spectra of thiazolidines V; besides the absorption characteristic of the amide carbonyl in the IR spectra, there is a strong band in the region 1620-1650 cm^{-1} attributed to the vibrations of the oxocyclic azomethine bond. The NMR spectrum does not contain any proton signals of the hydroxyl and amino groups.

Thus, we demonstrated one more aspect of the synthetic possibilities of 2(5H)-furanone which is a valuable intermediate in organic synthesis.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in paraffin oil. The NMR spectra were recorded on a Tesla BS-467 spectrometer (60 MHz, internal standard tert-butanol). The UV spectra were recorded on a Specord UV-vis instrument in ethanol. TLC was performed on Silufol in a benzene–ethanol system, 10:1.

3-Butylamino-4-hydroxy-N-butylbutyramide (IIb). To 7.3 g (100 mmole) of n-butylamine was added 1.68 g (20 mmole) of 2(5H)-furanone with stirring. The reaction mixture heated up strongly. The mixture was left overnight for 24 h. The precipitate (4.3 g) was filtered off and washed on the filter with ethyl ether. IR spectrum (film): 3390 (OH), 3325 (NH), 1635 (C-O), 1535 (NH). NMR spectrum (acetone-D_6): 0.92 (6H, m, CH_3), 1.36 (8H, m, CCH_2C), 2.14 (2H, m, CH_2CO), 2.64 (4H, m, NCH_2), 3.10 (4H, m, NCH; NH;OH), 3.32 ppm (2H, m, OCH_2).

Compounds II a, c were obtained by an analogous method (Table 1).

3-Furfurylamino-4-hydroxy-N-furfurylbutyramide (II d). A mixture of 1.94 g (20 mmole) of furfurylamine and 0.84 g (10 mmole) of 2(5H)-furanone was left at room temperature in a tightly closed flask for 3 days. The precipitated amide IId (2.5 g) was filtered off and purified by recrystallization from a mixture of ethanol–ethyl ether (1:10). IR spectrum (film): 3300 (OH, NH), 3165, 3120 (CH furan), 1635 (C=O), 1535 (NH). NMR spectrum (acetone-D_6): 2.27, (2H, m, $CH_2C=O$), 2.92 (3H, m, NCH; NH; OH), 3.45 (2H, d. of d., OCH_2, 3.75 (1H d, NCH_2-furyl), 4.28 (1H, d, NCH_2-furyl), 6.30-6.10 (4H, m, 3, 4-H-furyl), 7.35 (2H, m, 5-H-furyl).

3-(1-Butyl-3-phenylthioureido)-4-hydroxy-N-butylbutyramide (IIIb). To a suspension of 0.46 g (0.2 mmole) of butyramide IIb in 5 ml of dry ethyl 0.27 g (0.2 mmole) of phenylisothiocyanate was added dropwise. The mixture was stirred with light heating for 1 h and left for 24 h. The precipitate (0.52 g) was filtered off and purified by recrystallization from hexane. R_f = 0.3. UV spectrum (ethanol): λ_{max} 258 nm (log ε 4.37).

Thioureas IIIa, c-f were obtained by an analogous methodology.

2-(2-Phenylamino-3-butyloxazolidinyl-4)-N-butylacetamide (IVb). A mixture of 0.39 g (0.01 mmole) of compound IIb and 2 ml of methyl iodide was left for 2 h at room temperature until a clear solution was formed. The excess of methyl iodide was evaporated under vacuum, and the residue was treated with 5 ml of a saturated methanolic solution of potassium hydroxide and left for 4 h. The methanol was evaporated under vacuum and the residue was extracted with hexane. After removal of hexane 0.14 g of oxazolidine IVb was obtained. R_f = 0.65. The UV spectrum (ethanol): λ_{max} 249 nm (log ε 4,14).

Compounds IVa, c-f were obtained analogously.

2-(2-Phenylamino-3-butylthiazolidinyl-4)-N-butylacetamide (Vb). A mixture of 0.42 g (0.11 mmole) of thiourea IIb and 2 ml of concentrated hydrochloric acid was heated for 10 min on a steam bath. The acid was evaporated under vacuum and the residue was neutralized with a saturated solution of potassium carbonate. The product was extracted with ethyl ether; the extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The residual oil which solidified after 3 days was recrystallized from hexane. Yield 0.28 g. R_f 0.7. UV spectrum (ethanol): λ_{max} 252 nm, (log ε 3.79).

Thiazolidines Va, d were obtained analogously.

2-[2-(4-Chlorophenyl)imino-3-butylthiazolidinyl-4]-N-butylacetamide (Vc). A mixture of 0.6 g (0.15 mmole) of thiourea IIc and 2 ml of concentrated hydrochloric acid was heated on a steam bath. The excess of acid was evaporated under vacuum and the residue was treated with a saturated solution of potassium carbonate. The precipitate was filtered off and purified by recrystallization from hexane. Yield 0.42 g. R_f 0.45. UV spectrum (ethanol): λ_{max} 253 nm (log ε 3.78).

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