SYNTHESIS AND TRANSFORMATIONS OF FURAN DERIVATIVES

VI. AMIDES OF β-(2-FURYL)- AND β-(5-NITRO-2-FURYL-α-ACYLAMIDOACRYLIC ACIDS) AND 1-SUBSTITUTED 2-PHENYL-4-(5'NITRO-2'-FURFURYLIDEN)-5-IMIDAZOLONES

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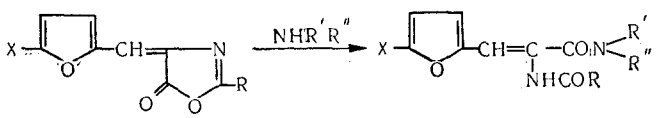
By the reactions of 2-phenyl-4-(2'-furfuryliden)-, 2-phenyl-4-(5'-nitro-2'-furfuryliden)-, and 2-methyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolones with primary and secondary amines, a series of N-mono- and N,N-disubstituted amides of the corresponding α-benzamido-β-(2-furyl)-acrylic and α-benzamido- and α-acetamido-β-(5-nitro-2-furyl)acrylic acids was synthesized. 1-Alkyl(aryl) substituted 2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-imidazolones were synthesized from the reaction of phosphorus oxychloride and the monosubstituted amides of α-benzamido-β-(5-nitro-2-furyl)acrylic acid.

In searching for new antibacterial compounds based on 2-phenyl-4-(2'-furfuryliden)-, 2-phenyl and 2-methyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolones, the synthesis of substituted amides of α-benzamido-β-(2-furyl)acrylic, α-benzamido- and α-acetamido-β-(5-nitro-2-furyl)acrylic acids, and the subsequent conversion of the monosubstituted amides of α-benzamido-β-(5-nitro-2-furyl)acrylic acid to the 1-alkyl (aryl) substituted 2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-imidazolones was carried out. The synthesis of these compounds was carried out on the basis of the literature descriptions of 2-phenyl-4-(2'-furfuryliden)-[1], 2-phenyl-4-(5'-nitro-2'-furfuryliden)-, and 2-methyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolones [2], which were obtained by the condensation of the corresponding furfurol or 5-nitrofurfurol with hippuric or aceturic acids. We obtained 2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone in an almost quantitative yield by a slightly modified procedure. The yield of the oxazolone based on 5-nitrofurfurol and aceturic acid was significantly lower (50-60%), and we could not prepare the oxazolone from furfurol and aceturic acid.

We obtained a series of substituted amides of α-benzamido-β-(2-furyl)acrylic, and α-benzamido- and α-acetamido-β-(5-nitro-2-furyl)-acrylic acids (I-XV) (Table 1) from the reaction of the oxazolones listed above with primary and secondary amines (benzylamine, isobutylamine, dimethylamine, diethylamine, dibutylamine, aniline, and morpholine).



X = H; NO_2; R = CH_3, C_6H_5; $NR'R''$ = NHC_6H_5, $NHCH_2C_6H_5$; morpholino; NHAlk; $N(Alk)_2$

It was established that the nitro group in the furan ring makes the formation of the amides possible, and the latter are even formed in the cold or upon mild heating; upon prolonged heating their yields decrease. Longer heating (1-2 h) is required to prepare amides from 2-phenyl-4-(2'-furfuryliden)-5-oxazolone. The reaction of 2-methyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone with amines is accompanied by strong tarring and only in isolated cases could we obtain amides of α-acetamido-β-(5-nitro-2-furyl)acrylic acid. Primary amines enter into reaction with oxazolones more easily than secondary. Considering all these properties, we found 3 most suitable methods of synthesis: in a medium of organic solvent with prolonged heating (method A), during a 10 min heating (method B), and with heating in an excess of amine (method C).

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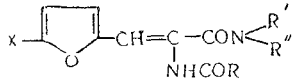
TABLE 1. Substituted Amides of Acylaminofurylacrylic Acid



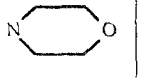
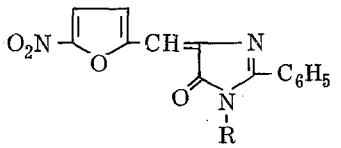
Compound	X	R	$N\langle R'_{R''}$	Method of synthesis	Yield (in %)	Melting temperature (in degrees)	Empirical formula	Found (in %)			Calculated (in %)		
								C	H	N	C	H	N
I	H	C_6H_5	$NHCH_2C_6H_5$	A	81,4	154—155	$C_{21}H_{18}N_2O_3$	72,63	5,07	8,07	72,81	5,24	8,09
II	H	C_6H_5	NHC_4H_9-*i*	A	84,6	153—154	$C_{18}H_{20}N_2O_3$	68,90	6,44	9,03	69,21	6,45	8,97
III	NO_2	C_6H_5	$NHCH_2C_6H_5$	B	89,3	195—197	$C_{21}H_{17}N_3O_5$	64,83	4,46	11,15	64,44	4,38	10,74
IV	NO_2	C_6H_5	NHC_4H_9-*i*	B	94,4	194—196	$C_{18}H_{19}N_3O_5$	60,51	5,46	12,25	60,49	5,36	11,76
V	NO_2	C_6H_5	$N(C_2H_5)_2$	B	98,0	189—190	$C_{18}H_{19}N_3O_5$	59,96	5,17	12,12	60,49	5,36	11,76
VI	NO_2	C_6H_5	$N(CH_3)_2$	B	83,3	193—194	$C_{16}H_{15}N_3O_5$	58,35	4,15	12,73	58,35	4,59	12,76
VII	NO_2	C_6H_5	$N(C_4H_9$-*i*$)_2$	A	86,6	126—128	$C_{22}H_{27}N_3O_5$	63,98	6,46	10,34	63,90	6,58	10,16
VIII	NO_2	C_6H_5	NHC_6H_5	B	99,3	203—204	$C_{20}H_{15}N_3O_5$	63,89	4,34	12,97	63,66	4,01	11,14
IX	NO_2	CH_3	$N(C_4H_9$-*i*$)_2$	A	66,9	147—149	$C_{17}H_{25}N_3O_5$	58,34	7,36	12,46	58,10	7,17	11,96
X	NO_2	CH_3	$NHCH_2C_6H_5$	B	97,6	161—163	$C_{16}H_{15}N_3O_5$	58,26	4,76	10,96	58,35	4,59	12,76
XI	H	C_6H_5	NHC_6H_5	A	73,4	201—203	$C_{20}H_{16}N_2O_3$	71,93	4,74	8,37	72,27	4,85	8,43
XII	NO_2	CH_3	$NHisoC_4H_9$	A	83,3	158—160	$C_{13}H_{17}N_3O_5$	52,86	5,80	14,09	52,87	5,80	14,23
XIII	H	C_6H_5	$N(C_2H_5)_2$	B	65,4	131—134	$C_{20}H_{18}N_2O_3$	69,08	6,13	9,13	69,21	6,45	8,97
XIV	NO_2	C_6H_5		B	96,3	195—196	$C_{15}H_{17}N_3O_5$	58,53	4,76	11,67	58,22	4,62	11,32
XV	H	C_6H_5		A	86,2	175—176	$C_{15}H_{18}N_2O_3$	66,22	5,66	8,88	66,24	5,56	8,59

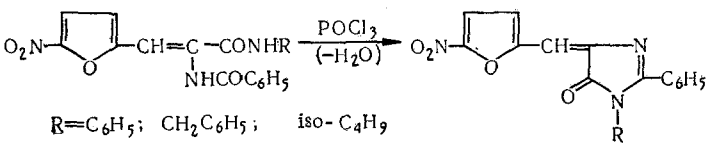
TABLE 2.



Compound	R	Yield (in %)	Melting temperature (in degrees)	Empirical formula	Found %			Calculated %		
					C	H	N	C	H	N
XVI	C_6H_5	85.0	198-200	$C_{20}H_{13}N_3O_4$	66.99	3.74	11.58	66.85	3.65	11.69
XVII	$CH_2C_6H_5$	84.2	172-174	$C_{21}H_{15}N_3O_4$	67.22	3.73	10.81	67.55	4.05	11.26
XVIII	iso-C_4H_9	88.2	196-198	$C_{18}H_{17}N_3O_4$	63.33	5.41	12.24	63.71	5.05	12.38

The synthesized amides are crystalline materials from light-yellow to orange-yellow in color, very soluble in alcohol. The substituted amides of α-acetamido-β-(5-nitro-2-furyl)acrylic acid are very soluble in water and the amides of α-benzamido-β-(2-furyl)- and α-benzamido-β-(5-nitro-2-furyl)acrylic acid are not very soluble in water.

1-Alkyl(aryl) substituted 2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-imidazolones were synthesized from the reaction of phosphorus oxychloride with the monosubstituted amides of α-benzamido-β-(5-nitro-2-furyl)acrylic acid over 2 h with heating on a water bath.



R=C_6H_5; $CH_2C_6H_5$; iso-C_4H_9

Cyclization of the amides to the imidazolones does not occur upon insufficient heating. We could not obtain the imidazolones from the monosubstituted amides of α-benzamido-β-(2-furyl)- and α-acetamido-β-(5-nitro-2-furyl)acrylic acids.

The imidazolones are crystalline materials from yellow to orange color, very soluble in alcohol and not very soluble in water.

The antibacterial activity of the initial oxazolones and of the substituted amides and imidazolones was investigated. As is shown in Table 3, in comparison with other already known derivatives of the nitrofuran series, for example, furazolidone [3, 4] and the known antitubercular agents, tubazide and streptomycin, these compounds are not very active.

EXPERIMENTAL

2-Phenyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone. 35.8 g (0.2 mole) of hippuric acid, 28.2 g (0.2 mole) of 5-nitrofurfurol, 16.4 g (0.2 mole) of anhydrous sodium acetate, and 100 ml of acetic anhydride were heated on a water bath at 60-70°C for 30 min. 330 ml of 50% alcohol was added and after cooling, the precipitated residue was filtered. The residue was washed with a small amount of ether. Yield 56.35 g (99.2%), m.p. 176-178° (from benzene).

Benzylamide of α-Benzamido-β-(2-furyl)acrylic Acid (Method A). 1.9 g (0.008 mole) of 2-phenyl-4-(2-furfuryliden)-5-oxazolone, 2.14 g (0.02 mole) of benzylamine, and 12 ml of dry benzene were heated at 70° for 2 h on a water bath and then left overnight. Upon standing a light-yellow solid precipitated. It was filtered and washed with a small amount of benzene, followed by ether. Yield 2.24 g (81.4%), m.p. 154-155° (from alcohol).

Benzylamide of α-Benzylamido-β-(5-nitro-2-furyl)acrylic Acid (Method B). 2.28 g (0.01 mole) of 2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone and 12 ml of dry benzene were heated on a water bath to 50° and 2.21 g (0.02 mole) of benzylamine was slowly added. The oxazolone dissolved and the precipitate of the amide formed immediately. The reaction mixture was heated on a water bath at 70° for 10 min. The mixture was cooled and the residue was filtered and washed with a small amount of benzene followed by ether. Yield 2.76 g (89.3%), m.p. 195-197° (from alcohol).

TABLE 3. Antibacterial Activity of Furan Derivatives

No. of compound	Compound	Minimal concentration (in micrograms/ml) arresting the growth of the microorganism*											Strain M. tuberculosis			
													medicinally sensitive		medicinally stable	
		Sh. flexneri type 2[a] No. 170	Sh. flexneri type 2[a] No. 337	Sh. sonnei No. 714	Sh. sonnei No. 5063	Salm. typhi No. 4446	Staphylococ. aur. haemolit. No. 209	Bac. mycoides	Escherichia coli No. 675	Sh. stuzerischmitzii No. 128	Salm. typhi No. 1203	Sh. boydii type 1 No. 196	H_{37} Rv	ravenel	vallee	D
I	Benzylamide of β-(2-furyl)-α-benzamidoacrylic acid	>100	66.6	>100	>100	100	111	>222			66.6		>50	33.3	>50	>50
II	Isobutylamide of β-(2-furyl)-α-benzamidoacrylic acid	166.6	111.1	>166.6	>166.6	>166	>222	>222			166.6		>50	33.3	>50	>50
III	Benzylamide of β-(5-nitro-2-furyl)-α-benzamidoacrylic acid	>100	>100	>100	>100	>100	>133	>133			>100		33.6	33.3	33.3	33.3
IV	Isobutylamide of β-(5-nitro-2-furyl)-α-benzamidoacrylic acid	>500	>500	>500	>500	>100	55	27			>100					
V	Diethylamide of β-(5-nitro-2-furyl)-α-benzamidoacrylic acid	333.3	333.3	>100	>100	>100	55	55			>100		>50	>50	>50	>50
VI	Dimethylamide of β-(5-nitro-2-furyl)-α-benzamidoacrylic acid	166.6	166.6	>100	>100	50	27	27			33.3		>50	>50	>50	>50
VII	Dibutylamide of β-(5-nitro-2-furyl)-α-benzamidoacrylic acid	>500	>500	>500	>500	>500					500		25	33.3	33.3	>50
VIII	Anilide of β-(5-nitro-2-furyl)-α-benzamidoacrylic acid	>500	>500	>500	>500	>500					>500		33.3	33.3	33.3	>50
IX	Dibutylamide of β-(5-nitro-2-furyl)-α-acetamidoacrylic acid	333.3	333.3	500	333.3	333.3					333.3		33.3	>50	>50	>50
XVI	1,2-diphenyl-4-(5'-nitro-2'-furfuryliden)-5-imidazolone	>12.5			>12.5				>12.5	>12.5						
XVII	1-Benzyl-2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-imidazolone	>12.5			>12.5				>12.5	>12.5						
XVIII	1-Isobutyl-2-phenyl-4-(5'-nitro-2'-furfuryliden)-5-imidazolone	>25			>25				>25	>25						
XIX	2-Phenyl-4-(2'-furfuryliden)-5-oxazolone	>100	>100	>100	>100	>100	666	1,333			>100					
XX	2-Phenyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone	>50	>50	>50	>50	>50	>66	>66			>50		8.3	16.7	33.3	33.3
XXI	2-Methyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone	>100	>100	>100	66.6	100	166	1,333			66.6		12.5	16.7	33.3	33.3
	Furazolidone			0.41	0.2	8.3	2	0.4			0.41		33.3	33.3	33.3	>50
	Tubazide												0.1	0.1	11.1	22.2
	Streptomycin												3.3	3.3	>50	>50

* For method of determination see [5, 6].

Diethylamide of α-Benzamido-β-(2-furyl)acrylic Acid (Method C). 1.0 g (0.0042 mole) of 2-phenyl-4-(2'-furfuryliden)-5-oxazolone and 2.9 g (0.04 mole) of diethylamine were heated at 70° for 15 min. Initially, the oxazolone dissolved in the excess amine, but after several minutes a yellow precipitate separated. The mixture was cooled, and the precipitate was filtered and washed with a small amount of benzene, followed by ether. Yield 0.85 g (65.4%), mp 131-134° (from alcohol).

1,2-Diphenyl-4-(5'-nitro-2'-furfuryliden)-5-oxazolone. 1.13 g (0.03 mole) of the anilide of α-benzamido-β-(5-nitro-2-furyl)acrylic acid and 3 ml of phosphorus oxychloride were heated on a water bath for 2 h. The hot mixture was poured into 50 ml of cold water. The mixture was left overnight. The precipitate was filtered and washed with water. Yield 0.9 g (84.2%), mp 198-200° (from alcohol).

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