A STUDY OF FURAN COMPOUNDS

XXXV. Synthesis of Certain Ureides of Furanmonocarboxylic Acids*

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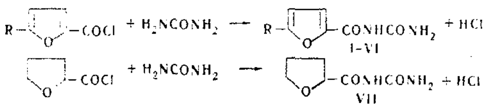
[N-(2-Furoyl)-, N-(5-methyl-2-furoyl)-, N-(5-chloro-2-furoyl)-, N-(5-bromo-2-furoyl)-, N-(5-iodo-2-furoyl)-, N-(5-nitro-2-furoyl)-, and N-(tetrahydro-2-furoyl) ureas were obtained by acylation of urea with the corresponding acid chlorides.

Among the large number of different urea derivatives including physiologically active compounds, with the exception of N-(5-nitro-2-furoyl2) urea [1], the N-(5-R-furoyl-2)ureas have not been studied until recently. However neither the method of synthesis nor the properties (outside of antimicrobial activity) of N-(5-nitrofuroyl-2)urea have been described.

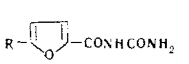
Compounds of this type and also N-tetrahydrofuroylurea are of interest for two reasons. First, a number of structural characteristics indicate the possibility of interesting transformations of these compounds (including intramolecular transformations) which will be the subject of subsequent communications. Secondly, as ureides and as derivatives of the amide of pyromucic acids, they must possess physiological properties [2].

Various methods for synthesizing ureides and their nitrogen substituted forms are described in the literature [3–10]. Attempts to obtain N-(2-furoyl-2) urea by fusing the ethyl ester of furan-2-carboxylic acid with urea and also by interaction of these reagents in the presence or absence of sodium ethoxide have not been successful.

Synthesis of ureides I–VII (see table) was achieved by means of the reaction between urea and furoyl chloride [11], 5-methylfuroyl chloride [12], 5-chlorofuroyl chloride [13], 5-bromofuroyl chloride [14], 5-iodofuroyl chloride [15], 5-nitrofuroyl chloride [16] and tetrahydrofuroyl chloride [22], respectively in a medium of anhydrous benzene with equimolecular ratio of the reagents and at the boiling point of the mixture. The quantity of benzene employed was equivalent to 10–25 ml/g urea.



In this reaction the furoyl chlorides react as electrophilic reagents, and thus their comparative activity is determined by the electronic density of the carbon atom in the carboxylic group. The ionization constants of the corresponding furancarboxylic acids are dependent on the value of the latter. The 5-nitrofuran-2-carboxylic acid ($K_a = 38.1 \cdot 10^{-5}$) and 5-methylfuran-2-carboxylic acid ($K_a = 870.1 \cdot 10^{-5}$) are the strongest and weakest acids respectively in the series of 2-furancarboxylic acids examined. The 5-chloro-, 5-bromo-, 5-iodo-, and unsubstituted 2-furnacarboxylic acids have a K_a value of $147.4 \cdot 10^{-5}$, $144.3 \cdot 10^{-5}$, $116.0 \cdot 10^{-5}$ and $75.2 \cdot 10^{-5}$ respectively [17]. Tetrahydrofuran-2-carboxylic acid has a K_a value of $1.4 \cdot 10^{-4}$ [18]. It was found that 5-nitro-2-furoyl chloride and tetrahydrofuroyl chloride reacted most readily, and that 5-methyl-2-furoyl chloride reacted most weakly with urea, which was apparent in the yields of the products. These observations are clearly qualitatively correlated with the presented K_a values.



Compound	R	Mp, ° C * (solvent for crystallization)	Empirical formula	Found,%			Calculated,%			Yield,%
				C	H	N	C	H	N	
I	H	223.5—225 (decomp., water)	$C_6H_6N_2O_3$	47.00 47.12	4.02 4.29	18.20 18.24	46.76	3.92	18.18	68.0
II	CH_3	192.5—193 (water)	$C_7H_8N_2O_3$	49.56 49.64	4.95 4.65	16.39 16.77	50.00	4.79	16.66	12.0
III	Cl	224.5—225 (dioxane)	$C_6H_5ClN_2O_3$	38.32 38.36	2.61 2.87	15.28 15.41	38.21	2.67	14.85	79.4
IV	Br	213.5—214 (ethanol)	$C_6H_5BrN_2O_3$	30.99 30.89	2.28 2.39	12.05 11.75	30.92	2.16	12.02	44.9
V	I	211—211.5 (methanol)	$C_6H_5JN_2O_3$	25.93 25.94	2.09 2.17	10.09 10.15	25.73	1.79	10.00	71.6
VI	NO_2	237—237.5 (decomp., water)	$C_6H_5N_3O_5$	35.92 35.92	2.65 2.78	21.04 21.47	36.19	2.53	21.11	83.5
VII	**	116—116.5 (water)	$C_6H_{10}N_2O_3$	45.84 45.72	6.52 6.40	17.93 17.79	45.56	6.37	17.72	60.0

*The mp was determined in an aluminum block. Samples which decompose on melting were transferred into the block at 15° C up to the mp and the temperature was subsequently increased at a rate of 5° C per minute.

**Tetrahydrofuroylurea.

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*For part XXXIV, see [23].

Claylike precipitates formed during furoylurea reaction are often in the reaction mixture. These precipitates, by coating the crystals of urea, hinder access of furoyl chloride to the latter even during vigorous agitation. Acylation ceases prematurely and a portion of the furoyl chloride remains unutilized. In order to increase the yield of the specific ureides, after subsidence of the reaction the residue was removed, urea was added to the mother liquor and the mixture was stirred under experimental conditions. It was thus possible to obtain an additional amount of furoylureas.

Ureides are crystalline compounds, stable in air, poorly soluble in water (aqueous solutions are neutral) and in organic solvents (except VII), and are soluble in aqueous solutions of sodium hydroxide.

A. A. Stolyarchuk et al. [19] (Department of Pharmacology, Institute of Medicine, Vinnitsa) found that compounds I–VII have a diuretic activity.

The most important data concerning the synthesized compounds are presented in the table. The authors thank V. G. Frolova for his participation in the Experimental.

EXPERIMENTAL

5-Chlorofuroyl chloride. A 14.65 g (0.1 mole) quantity of 5-chloro-2-furancarboxylic acid [20] and 12.1 g (0.11 mole) of $SOCl_2$ were boiled in 100 ml absolute benzene. The carboxylic acid which did not enter into the reaction was removed by passing the mixture through a Shott No. 2 filter. Benzene and SOCl were removed from the filter by distillation under reduced pressure. The brown residue was poured rapidly into a flask with a herring-bone fractionating column (8–10 cm) and distilled under vacuum. The fraction with a mp of 91–93° C (20 mm) was collected. The product was crystallized; yield, 10 g (60%).

Tetrahydrofuroyl chloride. a) A 17.4 g (0.5 mole) quantity of tetrahydrofuran-2-carboxylic acid was added to 20.8 g (0.175 mole) $SOCl_2$. Effervescence of the mixture was observed during this procedure. The mixture was then heated for 3 hr in a water bath (at 85–95° C) and left for 12–14 hr. The yield after vacuum distillation was 8.3 g (47%), mp 82–85°C (30 mm), n_D^{25} 1.4593.

b) An 11.6 g (0.1 mole) quantity of tetrahydrofurancarboxylic acid was added to 22.9 g (0.11 mole) PCl_5 over the course of 8–10 min. There was an increase in temperature of the mixture. The contents of the flask were then heated in a water bath (85–90° C) for 2 hr and distilled under vacuum. The fraction with a bp of 81–84° C (30 mm) and n_D^{20} 1.4625 was collected, yield, 30.9 g (76.5%). According to data in the literature, bp 80–81° C (30 mm), n_D^{25}, 1.4592 [22].

N-(2-Furoyl)urea (1). A 14 g (0.23 mole) quantity of urea, 300 ml dry benzene, and 26.1 g (0.2 mole) furoyl chloride were introduced into a flask provided with a mechanical shaker with a shut-of device, a reflux condenser, and a calcium chloride tube. The agitated mixture was boiled in a water bath for 20 hr. The product was washed first with benzene and then with water. It was then recrystallized from water. Fine white needles (yield, 21.9 g).

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