REDUCTIVE ACETYLATION OF NITROCARBOXYLIC ACIDS OF THE THIOPHENE AND FURAN SERIES OR THEIR ESTERS

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The corresponding 4-acetylamino-2-thiophenecarboxylic acids or their esters were produced by the action of reduced iron on solutions of 4-nitro-2-thiophenecarboxylic acid, its derivatives, or their esters in a mixture of acetic acid and acetic anhydride. Esters of 5-acetylamino-2-thiophenecarboxylic or 5-acetylamino-2-furancarboxylic acids are formed from esters of 5-nitro-2-thiophenecarboxylic or 5-nitro-2-furancarboxylic acids. Free 5-nitro-2-thiophenecarboxylic and 5-nitro-2-furancarboxylic acids are entirely decomposed under the conditions of reductive acetylation by iron. The ester of 5-acetylamino-3-thiophenecarboxylic acid was obtained from the methyl ester of 5-nitro-3-thiophenecarboxylic acid.

Acetylamino acids of the thiophene and furan series, as well as their derivatives, are reactive compounds, which have been used repeatedly as intermediates for the synthesis of drugs (see, for example, [1, 2]). One of the methods of production of acetylamino derivatives is the reductive acetylation of the corresponding nitro-compounds by the action of a metal reducing agent in the presence of an acetylating agent. Skeletal nickel in acetic anhydride [3, 4], zinc [5], and reduced iron in a mixture of acetic acid with acetic anhydride [6, 7] have been used for the reductive acetylation of various nitro-compounds. The methods mentioned are not free of certain limitations. For example, the method described in [3, 4] permits the production of 5-acetylamino-2-thiophenecarboxylic acid (IVa) from 5-nitro-2-thiophenecarboxylic acid (Ia) with a yield of about 50%, but when this method was used for the production of 4-acetylamino-2-thiophenecarboxylic acid (Va) the yield did not exceed 10%.

A modified variant of the method, based on the use of reduced iron [8] and permitting the production of 2- and 3-acetylaminothiophenes in good yields, appeared later. We used this variant for the production of acetylaminoketones of the thiophene series; it gave good results. In view of this, we were interested in verifying the possibilities of the method mentioned [8] for the reductive acetylation of nitrocarboxylic acids of the thiophene and furan series, as well as their esters. Insofar as we know, iron had not previously been used for this purpose. It was established in this case that 5-alkyl-4-nitro-2-thiophenecarboxylic acids and their esters form the corresponding 4-acetylamino compounds in good yields, whereas when skeletal nickel was used for reductive acetylation [3, 4] the yields did not exceed 40%. Under the action of iron under conditions of reductive acetylation on 4-nitro-5-chloro-2-thiophenecarboxylic acid (IIe), no elimination of chlorine occurred; when 4-nitro-5-bromo-2-thiophenecarboxylic acid (IIg) was used, about 10% of the bromine was split out (the debrominated compound was not isolated). The acid Ia was entirely decomposed under the action of iron, whereas under the action of skeletal nickel [3] the yield of compound IVa, as was mentioned, was ∿50%. In a comparison of these results, the idea arose of the possibility of using a difficult-to-separate mixture of nitroacids, formed in the nitration of 2-thiophenecarboxylic acid [10], for the production of compound Va. The experiment showed that under the conditions of reductive acetylation by iron, a virtually pure acid Va can be obtained from this mixture with yields of about 80%, calculated on the basis of the 4-nitro-2-thiophenecarboxylic acid (IIa) contained in the nitration products.

The methyl ester of 5-nitro-2-thiophenecarboxylic acid (Ib), in contrast to the free nitroacid, under conditions of reductive acetylation by iron, forms the methyl ester of 5-acetylamino-2-thiophenecarboxylic acid (IVb) in a good yield.

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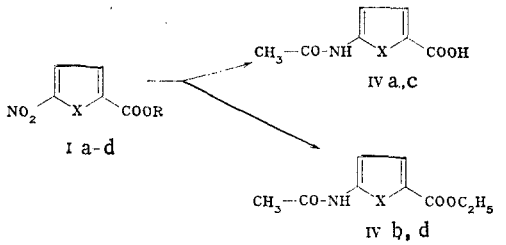
TABLE 1. Yields of Known Compounds Produced by the Proposed Method

Compound	Yield, %	Literature	Compound	Yield, %	Literature
IVa	92*	[3, 4]	Va	75	[3, 4]
IVb	78	[3, 4]	Vb	69	[4]
IVc	36*	[11, p. 166]	VIIb	82	[4]
IVd	34	[11, p. 146]			

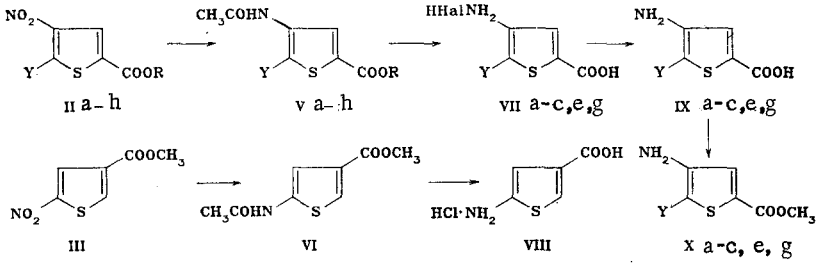
*The constants were obtained by saponification of the corresponding esters.

In the reduction acetylation of the methyl ester of 5-nitro-3-thiophenecarboxylic acid (III), the methyl ester of 5-acetylamino-3-thiophenecarboxylic acid (VI) is formed with a yield of ∿70%.

The acetylamino acids of the thiophene series obtained, with the exception of the acid IVa, form hydrochlorides of amino acids when boiled with dilute HCl. Under the action of the theoretical amount of sodium bicarbonate, the hydrochlorides are converted to the free amino acids, which melt with decomposition at high temperatures; therefore, for identification purposes the amino acids were converted to their methyl esters by the action of diazomethane. The methyl ester of 4-amino-2-thiophenecarboxylic acid was produced by the reaction of diazomethane directly with its hydrochloride.



I a X=S, R=H; b X=S, R=CH_3, c X=O, R=H, d X=O, R=C_2H_5



IIa–c,e, g R=H, d, f, h R=CH_3; a Y=H; b Y=C_2H_5; c, d Y=C_3H_7; e, f Y=Cl; g, h Y=Br

The initial nitroacids of the thiophene and furan series, as well as their esters, were produced by the method used earlier [4]. The experimental section cites an example of the production of a new 4-nitro-5-propyl-2-thiophenecarboxylic acid (IIc) by the nitration of 5-propyl-2-thiophenecarboxylic acid. The latter was synthesized by acetylation of 2-propylthiophene, followed by oxidation of the ketone formed with a solution of sodium hypochlorite.

Of the amino acids of the thiophene and furan series described previously, as well as their esters, IVa-d were produced in this work (see Table 1). The melting points of all these substances coincided with those cited in the literature.

The newly produced compounds, their yields, melting points, and the data of elementary analysis are cited in Table 2.

EXPERIMENTAL

Nitration of 5-Propyl-2-thiophenecarboxylic Acid. To a solution of 16.9 g (99 mmoles)

TABLE 2. Characteristics of the Compounds Synthesized

Compound	Y	R	Mp,* °C	Found, %					Gross formula	Calculated, %					Yield, %
				C	H	Halogen	N	S		C	H	Halogen	N	S	
Vc	C_3H_7	H	226—228	52,5	5,9		6,4	14,0	$C_{10}H_{13}NO_3S$	52,9	5,8		6,2	14,1	75
Vd	C_3H_7	CH_3	114—116	55,1	6,3		5,9	13,2	$C_{11}H_{15}NO_3S$	54,8	6,3		5,8	13,3	71
Ve	Cl	H	256—258	38,2	2,9	16,0	6,2	14,5	$C_7H_6ClNO_3S$	38,3	2,8	16,1	6,4	14,6	69
Vf	Cl	CH_3	140—141	41,1	3,6	15,2	5,9	13,7	$C_8H_8ClNO_3S$	41,1	3,5	15,2	6,0	13,7	67
Vg	Br	H	220	32,1	2,6	29,5		11,8	$C_7H_6BrNO_3S$	31,8	2,3	30,2		12,1	74
Vh	Br	CH_3	171—172	34,8	3,0	28,3	5,0	11,4	$C_8H_8BrNO_3S$	34,6	2,9	28,7	5,0	11,5	69
VI		CH_3	164—164,5	48,3	4,5		6,5	16,0	$C_8H_9NO_3S$	48,2	4,6		6,9	16,1	69
VIIa	H	H	255—258	33,5	3,4	19,1	7,8	17,3	$C_5H_5NO_2S \cdot HCl$	33,4	3,4		7,8	17,8	78
VIIc	C_3H_7	H	226—228	43,2	5,5	16,0	6,4	14,5	$C_8H_{11}NO_2S \cdot HCl$	43,3	5,5	16,0	6,3	14,5	71
VIIe	Cl	H	215	28,2	2,3	33,0		14,9	$C_5H_4ClNO_2S \cdot HCl$	28,1	2,4	33,1		15,0	75
VIIg	Br	H	256—257				4,6		$C_5H_4BrNO_2S \cdot HBr$				4,6		70
VIII	H	H	215—217	33,4	3,3	19,4	7,5	17,6	$C_5H_5NO_2S \cdot HCl$	33,4	3,4	19,7	7,8	17,9	69
IXa	H	H	264—266	42,0	3,5		9,8	22,4	$C_5H_5NO_2S$	41,9	3,5		9,8	22,4	79
IXb	C_2H_5	H	213—214	49,1	5,5		8,4	18,6	$C_7H_9NO_2S$	49,1	5,3		8,2	18,7	80
IXc	C_3H_7	H	180—182	51,7	6,0		7,8	17,3	$C_8H_{11}NO_2S$	51,9	6,0		7,6	17,3	84
IXe	Cl	H	197	33,7	2,3	19,9	7,9	18,0	$C_5H_4ClNO_2S$	33,8	2,3	20,0	7,9	18,1	89
IXg	Br	H	192—193	27,1	2,0	35,7		14,3	$C_5H_4BrNO_2S$	27,0	1,8	36,0		14,4	85
Xa	H	CH_3	82—84	45,7	4,4		8,8	20,1	$C_6H_7NO_2S$	45,8	4,5		8,9	20,4	
Xe	Cl	CH_3	87—88	37,7	3,3	18,4	7,5	16,6	$C_6H_6ClNO_2S$	37,6	3,2	18,5	7,5	16,7	36
Xc	C_3H_7	CH_3	64—66	54,3	6,9		7,0	15,8	$C_9H_{13}NO_2S$	54,3	6,6		7,0	16,1	46

*The melting point depends on the rate of heating.

5-propyl-2-thiophenecarboxylic acid in 170 ml conc. H_2SO_4 at a temperature $\leq 5°C$, 12.5 g (124 mmoles) of ground KNO_3 was gradually added, then the reaction mass was mixed for 1 h at 0°C and poured out onto ice (500 g). The precipitate was filtered off and washed with water to a neutral reaction of the wash water to Congo. The moist nitroacid, containing an admixture of 2,4-dinitro-5-propylthiophene, formed on account of the decarboxylation of part of the initial acid, was purified through the sodium salt, or the dinitro compound was steam distilled. After recrystallization, 12.5 g (59%) of the nitroacid IIc with mp 106-108°C was isolated (from toluene with heptane).

Esterification of the acid IIc with a solution of diazomethane produced the ester IId with a yield of 57%.

Reductive Acetylation of Nitroacids I-III and Their Esters. To a solution of 20 mmoles of the nitroacid or its ester in 100 ml acetic acid and 15 ml acetic anhydride we added 6 g of powdered reduced iron. The mixture, mixed energetically, was heated on a water bath to 55-60°C (until the beginning of a spontaneous temperature rise). In this case a light colored precipitate soon appeared, the reaction mass thickened, and the temperature reached 75-80°C. After the temperature began to fall, heating on the bath was resumed. Mixing at 75-80°C was continued for another 6-8 h, the mixture was cooled to 50-60°C, water was added until the precipitate dissolved, and the remaining iron and resinification products were filtered off. The filtrate was evaporated under vacuum until precipitation began; for a more complete removal of acetic acid 100 ml of water was added, and it was distilled off. The dark residue was acidified with dilute (1:1) HCl, whereupon a precipitate usually formed; the mixture was left for several hours in a refrigerator, the crystals were filtered off, washed with water, dried, and recrystallized from diluted acetic acid or alcohol.

Saponification of Acetylaminothiophenecarboxylic Acids V and VI. A mixture of 8 mmoles of the acid V or ester VI with 30 ml of conc. HCl was boiled until a yellow solution formed; it was treated with charcoal and left in a refrigerator. The crystals were filtered off, dried, recrystallized from dilute (1:1) HCl, and the hydrochlorides VII or VIII were obtained. The hydrobromide VIIg was obtained analogously by the action of hydrobromic acid on the acid Vg or its ester. The properties of the hydrohalide VII and VIII obtained are cited in Table 2. The hydrochloride of 5-amino-2-thiophenecarboxylic acid could not be produced by the action of HCl on the corresponding acetylaminoacid as a result of profound decomposition.

Isolation of Aminothiophenecarboxylic Acids IX from Their Hydrochlorides VII. A mixture of 10 mmoles of the salt VII and 9.6 mmoles of $NaHCO_3$, ground in a mortar, was gradually added to 10 ml of water, left in a refrigerator, the precipitate filtered off, washed with water, dried, and the amino acids IX obtained. The amino acids partially decomposed during recrystallization from boiling water.

Esterification of the Amino Acids IX. A solution of diazomethane in ether (prepared from 5 g nitrosomethylurea) was gradually added to a suspension of 10 mmoles of the acid IX in 25 ml of ether. The mixture was left for 3 h, the precipitate filtered off, the filtrate washed with solutions of soda and salt, dried with Na_2SO_4, evaporated, and the methyl ester of X isolated by recrystallization of the residue.

Esterification of the Hydrochloride VIIe by the Action of Diazomethane. To a suspension of 8 mmoles of the hydrochloride VII in 25 ml of ether, a solution of diazomethane in ether (prepared from 5 g nitrosomethylurea) was gradually added. After the evolution of N_2 ceased and the operations cited above were completed, the methyl ester Xe was isolated.

Hydrolysis of the Ester IVb, d. A mixture of 1.74 g (8.75 mmoles) of the ester IVb and 38 ml of a 5% aqueous solution of potash was boiled for 1 h, the yellow solution filtered off and acidified (to Congo) with dilute HCl (a precipitate formed). After standing in a refrigerator, the crystals were filtered off, washed with cold water, recrystallized from dilute alcohol, and 0.9 g (92% yield) of the acetylamino acid IVa was obtained (see [3]). The acetylamino acid IVc was produced analogously by hydrolysis of the ethyl ester Vd.

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