

5-AMINOOROTIC ACID DERIVATIVES

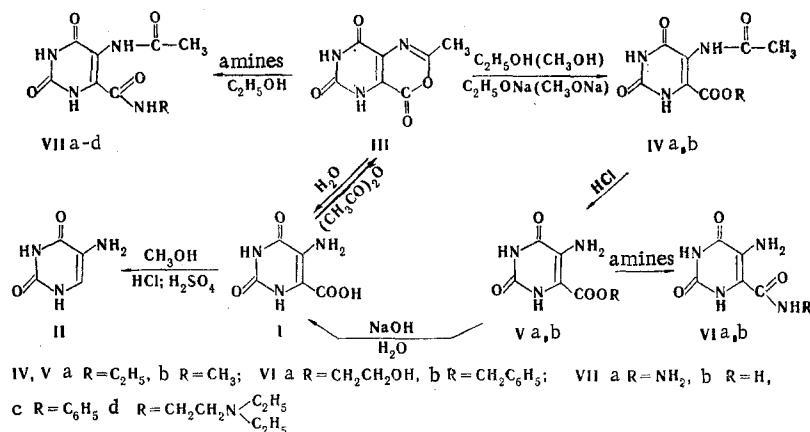
N. E. Britikova, L. A. Belova,
K. A. Chkhikvadze, and O. Yu. Magidson*

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The 2,4,8-trioxo derivative of pyrimido[5,4-d][1,3]oxazine was synthesized, and esters and amides of 5-acetamidoorotic acid were obtained from it. The acetyl group in 5-acetamidoorotic acid esters is readily hydrolyzed in acidic media to give esters of 5-aminoorotic acid, while the acetyl group in amides of 5-acetamidoorotic acid do not undergo hydrolysis.

The present paper is devoted to synthesis of esters and amides of 5-aminoorotic acid in the search for biologically active compounds. No 5-aminoorotic acid derivatives have been described in the literature. There is only an indication of the possibility of obtaining an ester of 5-aminoorotic acid in the reduction of the nitro group in an ester of 5-nitroorotic acid [1]. The usual methods for the preparations of esters of 5-aminoorotic acid did not give positive results. In an attempt to esterify 5-aminoorotic acid (I), it underwent decarboxylation to give 5-aminouracil (II). A route to the production of esters through 5-aminoorotic acid chloride is also excluded, since the carboxyl group in I proved to be unreactive under the usual conditions for the preparation of the acid chloride. In this connection, we used the method [2] employed for the production of esters of 5-aminopyrimidine-6-carboxylic acid for the synthesis of esters of 5-aminoorotic acid. The 4,6,8-trioxo derivative of pyrimido[5,4-b][1,3]oxazine (III) was obtained when I was refluxed with acetic anhydride. In the reaction of III with sodium ethoxide in alcohol, the oxazine ring was opened to give ethyl 5-acetamidoorotate (IVa). Ethyl 5-aminoorotate (Va) was isolated after treatment of IVa with hydrochloric acid in aqueous alcohol. Methyl 5-aminoorotate (Vb) was similarly obtained without isolation of the intermediate methyl 5-acetamidoorotate (IVb). The esters were readily hydrolyzed with aqueous bases, but we were able to obtain the amides (VIa,b) of 5-aminoorotic acid by heating Vb in the corresponding amine at high temperatures.

A study of the properties of III demonstrated that the oxazine opens when it is heated briefly in aqueous media, and the acetyl group is hydrolyzed to give I. The hydrazide or the corresponding amide of 5-



*Deceased.

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TABLE 1. Characteristics of the Compounds Obtained

Comp.	R	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
Va	C ₂ H ₅	284 (from water)	C ₇ H ₉ N ₃ O ₄	42,2	4,8	20,9	42,2	4,5	21,1	48
Vb	CH ₃	270 (from water)	C ₆ H ₇ N ₃ O ₄	39,1	4,0	22,2	38,8	3,8	22,7	54
VIa	(CH ₂) ₂ OH	274 (from water)	C ₇ H ₁₀ N ₄ O ₄	39,4	4,9	25,7	39,2	4,7	26,2	76,6
VIb	CH ₂ C ₆ H ₅	275 (from aqueous dimethyl-formamide)	C ₁₂ H ₁₂ N ₄ O ₃	55,1	4,8	21,3	55,4	4,6	21,5	64,5
VIIa	NH ₂	No decomp. up to 330 °C	C ₇ H ₉ N ₅ O ₄	37,4	4,1	30,2	37,0	4,0	30,7	79
VIIb	H	(from water)	C ₇ H ₈ N ₄ O ₄	39,4	3,9	26,2	39,2	3,8	26,4	83
VIIc*	C ₆ H ₅	" "	C ₁₃ H ₁₂ N ₄ O ₄ · H ₂ O	51,0	4,5	18,4	51,0	4,6	18,3	80
VIId	(CH ₂) ₂ N<C ₆ H ₅ C ₂ H ₅	232 (from alcohol)	C ₁₃ H ₂₁ N ₅ O ₄	50,4	6,8	22,8	50,2	6,7	22,5	36

* Found, %: H₂O 5.3. Calculated, %: H₂O 5.8.

acetamidoorotic acid (VIIa-d) were obtained in the reaction of III with hydrazine, ammonia, or amine. We were unable to hydrolyze the acetyl group in VII to obtain amides of 5-aminoorotic acid, since the acetyl group proved to be resistant to acid and alkaline hydrolysis; the starting VII were isolated from the reaction mixture.

EXPERIMENTAL

4,6,8-Trioxo-2-methyl-4,5,6,7,8-pentahydropyrimido[5,4-b][1,3]oxazine (III). An 8-g (0.047 mole) sample of I was refluxed in 140 ml of acetic anhydride for 4 h. The mixture was then cooled, and the crystalline precipitate of III was removed by filtration and washed with acetic acid and alcohol to give 8.3 g (91%) of a substance with mp 292° (dec.). Found, %: C 42.6; H 2.8; N 21.7. C₇H₅N₃O₄. Calculated, %: C 43.1; H 2.6; N 21.5.

Ethyl 5-Acetamidoorotate (IVa). A 1.5-g (7.7 mmole) sample of III was added at 20-25° to a solution of sodium alkoxide [from 0.35 g (0.015 mole) of sodium and 35 ml of absolute ethanol], and the reaction mixture was heated at 70° for 40 min. It was then cooled to 20-25°, and dry hydrogen chloride was then bubbled through it with stirring until it was acidic (pH 2-3). The resulting IVa was removed by filtration and washed thoroughly with alcohol to give 1.1 g (59.5%) of a substance with mp 277° (dec., from water). Found, %: C 44.8; H 4.4; N 17.3. C₉H₁₁N₃O₅. Calculated, %: C 44.8; H 4.6; N 17.4.

Ethyl and Methyl 5-Aminoorotates (Va and b). Ester Va was obtained by the method used to prepare IV; the only difference was that concentrated hydrochloric acid (17 ml of concentrated HCl from calculation for 1 g of III) was added to the reaction mass instead of bubbling gaseous hydrogen chloride through it, and the mixture was heated with stirring at 50-60° for 2 h. It was then cooled, and Va was removed by filtration. The mother liquor was evaporated in vacuo, and the residue was added to the major portion of the ester. Ester Vb was obtained via the method used to prepare Va. The physical constants and yields of Va and Vb are presented in Table 1.

Amides of 5-Aminoorotic Acid (VIa and VIb). The ethanolamide (VIa) and benzylamide (VIb) of 5-aminoorotic acid were obtained by heating ester Vb in an excess of the corresponding amine at 150° for 2.5 h. The excess amine was removed by vacuum distillation, and the residue was treated with dilute hydrochloric acid. The resulting VIa and VIb were removed by filtration and washed with water. The physical constants and yields of VIa and VIb are presented in Table 1.

Hydrazide and Amides of 5-Acetamidoorotic Acid (VIIa-d). Compounds VIIa and VIIb were obtained by reaction of III with a threefold excess of hydrazine hydrate in aqueous media or, respectively, with a threefold excess of ammonium hydroxide at 20-25° for 24 h. The reaction products were removed by filtration, treated with water, and acidified to pH 3 with hydrochloric acid. Compound VIIc was obtained by heating III with excess aniline in alcohol for 5 h. Compound VIIc was isolated in the same way as VIIa and VIIb. Compound VIId was obtained by heating III with excess diethylaminoethylamine (2.5 mole of the amine per

mole of III) in alcohol for 1.5 h. The solution was evaporated in vacuo, and the residue was dissolved in a small amount of aqueous alcohol (1:1). The solution was neutralized with hydrochloric acid, and the precipitated VIId was removed by filtration. The physical constants and yields of VIIa-d are presented in Table 1.

LITERATURE CITED

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2. Doug Han Kim and A. A. Sautilli, *J. Org. Chem.*, 35, 1680 (1970).