SYNTHESES IN THE SERIES OF PURINE DERIVATIVES

XXII. β-(3,7-DIMETHYLHYPOXANTHINE-2)-α-ALANINE AND AMIDES OF 3,7-DIMETHYLHYPOXANTHINE-2-ACETIC ACID

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The present communication describes the synthesis of β-(3,7-dimethylhypoxanthine-2)-α-alanine (I) isomeric to two previously obtained puryl-2-alanines [1,2]. A study of such purinyl amino acids is of theoretical interest and may be of practical importance owing to their structural similarity to naturel α-amino acids which carry proteinogenic functions and also participate in other biochemical systems. At the same time were synthesized the ether and amides of 3,7-dimethylhypoxanthine-2-acetic acid (IIa), IIb), which were not described in the literature.

The initial compound used was 3,7-dimethylhypoxanthine-2-malonic ester (III), a condensation product of an earlier described 2-chloro-3,7-dimethylhypoxanthine (IV) [3] with sodium malonic esters. Originally, the action of sulfuryl chloride converted III to 3,7-dimethylhypoxanthine-2-chloromalonic ester (V), which was to be hydrolyzed to obtain 2-chloromethyl-3,7-dimethylhypoxanthine. It was found, however, that at low pH the hydrolytic cleavage of malonic residue was accompanied by the cleavage of C_2–C bond as a result of which III was converted to theobromine (XI) in an almost quantitative yield. Hydrolysis at high pH (heating with alkali solution) leads to the formation of 2-hydroxymethyl-3,7-dimethylhypoxanthine (VI) but in a yield not over 20%.

The problem concerning the synthesis of 2-halomethyl derivative of 3,7-dimethylhypoxanthine was successfully solved by hydrolytic cleavage of III with a subsequent bromination of the finished product in the hydrolysis of 2,3,7-trimethylhypoxanthine (VII) by dioxanedibromide. The condensation of the resulting 2-bromomethyl-3,7-dimethylhypoxanthine (VIII) with acetylaminomalonic ester and subsequent hydrolysis ensured the formation of I.

TABLE 1. Derivatives of 3,7-Dimethylhypoxanthine

Compound	Melting point, °	Yield, %	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
III	160—3 (from water)	83,4	52,50	5,47	17,80	$C_{14}H_{18}N_4O_5$	52,17	5,59	17,39
VII	248—50 (from alcohol)	88,8	54,48	5,57	31,48	$C_8H_{10}N_4O$	53,93	5,62	31,46
V*	121—3 (from ethyl acetate)	75,6			15,64	$C_{14}H_{17}ClN_4O_5$			15,71
VI	250—2 (from alcohol)	13,8	49,25	5,40	29,54	$C_8H_{10}N_4O_2$	49,49	5,16	28,85
VIII†	180 (decomp., from dichloro	56,2	37,28	3,79	22,18	$C_8H_9BrN_4O$	37,35	3,50	21,77
X	221—2 (from alcohol)	61,6	52,00	5,34	17,45	$C_{17}H_{23}N_5O_6$	51,91	5,34	17,80
I	229—30 (decomp., from aqueous alcohol)	45,8	45,00	5,70	25,72	$C_{10}H_{13}N_5O_3 \cdot H_2O$	44,61	5,58	26,02
IX	190—2 (from ethyl acetate)	65	52,31	5,43	21,91	$C_{11}H_{14}N_4O_3$	52,75	5,63	21,99
II a	227—30 (from alcohol)	90	48,84	4,82	31,73	$C_9H_{11}N_5O_2$	48,86	5,01	31,66
II b	132 (from ethyl acetate)	51	55,68	7,20	26,37	$C_{15}H_{24}N_6O_2$	56,23	7,55	26,23

*Found, %: Cl 9.97. Calculated, %: Cl 9.95

†Found, %: Br 31.51. Calculated, %: Br 31.55

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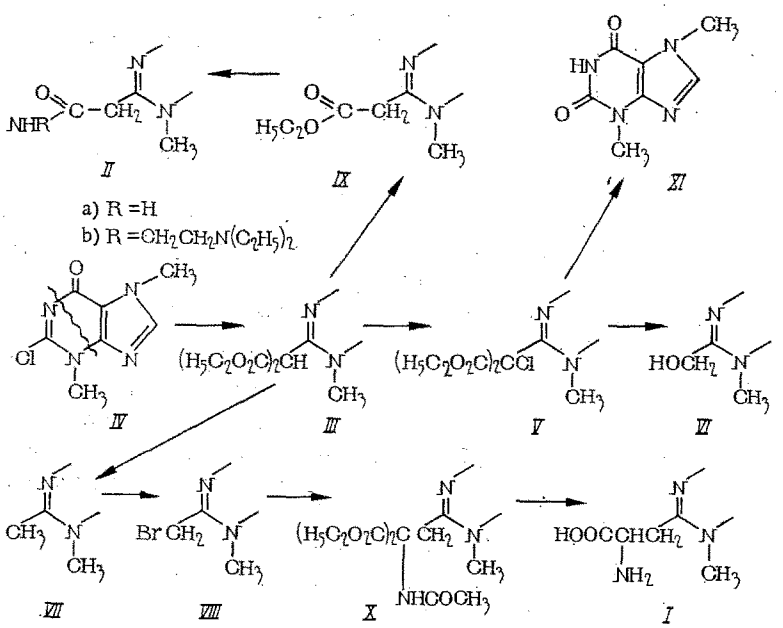
Boiling III with alcohol in the presence of catalytic amounts of hydrogen chloride gave a good yield of ethyl ester of 3,7-dimethylhypoxanthine-2-acetic acid (IX), and the latter in a reaction with ammonia or diethylaminoethylamine gave the appropriate amides IIa and IIb. We have failed to obtain free 3,7-dimethylhypoxanthine-2-acetic acid, since it readily undergoes decarboxylation independently of the pH of the medium and is converted to VII.

The data on the resulting compounds are given in Table 1. A similar hydrolytic cleavage of C_2-C bond, revealed in the example with V, is found both in the purine [4] as well as in other heterocyclic systems [5]. Such a cleavage, as well as extreme instability of 3,7-dimethylhypoxanthine-2-acetic acid, distinguishes the behavior of substituents at C_2 in 3,7-dimethylhypoxanthine derivatives from the behavior of isomeric 2-substituted derivatives of 1,7- and 1,9-dimethylhypoxanthines [1,2]. These data are in complete agreement with the information published earlier on the increased reactivity of substituents at C_2 in 3,7-dimethylhypoxanthine [3] and is supported by the quantum-chemical calculation carried out by the MO LCAO method which shows that in the transitions from 1,7-dimethylhypoxanthine to 3,7-dimethylhypoxanthine, the electron density and the free valency index of C_2 show a marked decrease.



EXPERIMENTAL

3,7-Dimethylhypoxanthine-2-malonic Ester (III). To a suspension of sodium-malonic ester in 300 ml of dry toluene (from 8 g of sodium and 80 ml of malonic ester) was added 30 g of IV; it was boiled for 1 h. To the reaction mixture was added 200-250 ml of warm water; it was stirred and the aqueous layer separated. The toluene layer was washed with water (3 × 30 ml), the wash water added to the aqueous solution, the latter acidified to pH 5.0, and the resulting precipitate filtered off and crystallized.

2,3,7-Trimethylhypoxanthine (VII). After boiling 228 g of III with 230 ml of 18% hydrochloric acid solution for 1 h, the product was evaporated to dryness, the residue dissolved in water, and the solution neutralized to pH 7.0 and again evaporated to dryness. The residue was extracted with chloroform to yield a substance which was purified by dissolving in alcohol and precipitating from an alcohol solution with ether.

3,7-Dimethylhypoxanthine-2-chloromalonic Ester (V). To 30 g of III in 300 ml of anhydrous chloroform was added 28 g of sulfuryl chloride. After 24 h the solution was washed with icy water and then with sodium bicarbonate solution, dried, and distilled off solvent; the residue was crystallized.

Hydrolysis of 3,7-Dimethylhypoxanthine-2-chloromalonic Ester. A. Acidic. After boiling 5 g of V with 50 ml of hydrochloric acid for 15 min, the solution was evaporated to dryness, the residue dissolved in water, and the solution neutralized. Yield, 1.8 g (71.4%) of theobromine, mp 342-343°.

B. Alkaline. After boiling 2 g of V with 16.8 ml of 1 N sodium hydroxide solution for 0.5 h, the product was neutralized and evaporated to dryness. The residue was extracted with 50 ml of hot alcohol and the product cooled. The substance VI, precipitated upon cooling, was crystallized.

2-Bromoethyl-3,7-dimethylhypoxanthine (VIII). After boiling 5 g of VII with a solution of dioxanedibromide (4.35 ml of bromine in 100 ml of dioxane) for 2 h, the product was cooled and the precipitate filtered off and washed with ethyl acetate in absolute alcohol. Yield, 7.5 g of VIII·HBr. The product was dissolved in a saturated solution of sodium bicarbonate and extracted with chloroform. The chloroform solution was evaporated to a small volume (15-20 ml) and the precipitate was filtered off. Yield of VIII, 3.6 g. The chloroform filtrate was evaporated to dryness and the residue crystallized from dichloroethane to yield another 0.45 g of VIII.

3,7-Dimethylhypoxanthine-2-acetylaminomalonic Ester (X). To a suspension of sodium acetylaminomalonic ester (from 1 g of sodium and 8.4 g of acetylaminomalonic ester) in 50 ml of alcohol was added 9.3 g of VIII; it was boiled for 1 h. Upon cooling, the precipitate was filtered off and crystallized.

β-(3,7-Dimethylhypoxanthine-2)-α-alanine (I). After boiling 8.9 g of X with 70 ml of 18% hydrochloric acid solution for 1 h, the product was evaporated to dryness, the residue dissolved in water and neutralized. The resulting precipitate was dissolved in water and neutralized. The precipitate formed was dissolved in water and precipitated with an equal volume of alcohol.

Ethyl Ester of 3,7-Dimethylhypoxanthine-2-acetic Acid (IX). After boiling 10 g of II with 2 ml of alcoholic hydrogen chloride in 70 ml of absolute alcohol for 8.5 h, the alcoholic solution was evaporated to dryness and the residue treated with 30 ml of water and neutralized to pH 7.0. The resulting precipitate was crystallized.

Amide of 3,7-Dimethylhypoxanthine-2-acetic Acid (IIa). After stirring 0.7 g of IX with 20 ml of 25% ammonia solution for 1 h at 20°, the solution was evaporated to dryness and the residue crystallized.

Diethylaminoethylamide of 3,7-Dimethylhypoxanthine-2-acetic Acid (IIb). After boiling 3.5 g of III with 30 ml of diethylaminoethylamine for 8 h (bath temperature, 120-140°), the excess of diethylaminoethylamine was distilled off. The substance was precipitated with ether and crystallized.

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