SYNTHESIS OF ω-SUBSTITUTED 3-ALKYLOROTIC ACIDS

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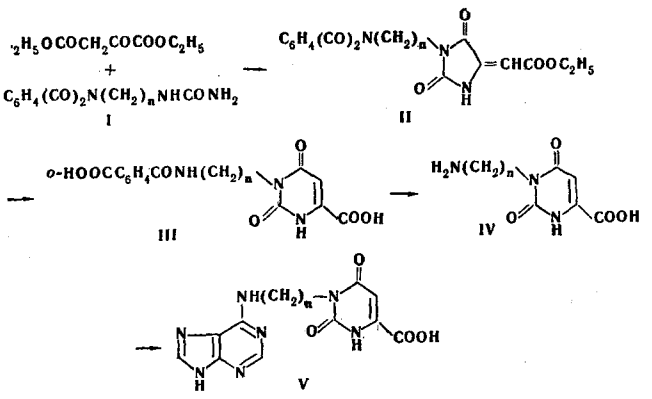
3-(ω-Phthalimidoalkyl)-5-carbethoxymethylenehydantoins were synthesized by the reaction of ω-phthalimidoalkylureas with ethyl oxalacetate and then converted to 3-(ω-aminoalkyl)-orotic acids. Condensation of the latter with 6-chloropurine yielded 3-[ω-(6-purinylamino)-alkyl]orotic acids.

In the development of investigations of the synthesis of covalently bonded nucleic bases [1] it was of interest to obtain 3-alkylorotic acids (V) which contain an adenine residue in the ω-position of the alkyl radical.



3-(ω-Phthalimidoalkyl)-5-carbethoxymethylenehydantoins (II, Table 1) were synthesized as a result of condensation of ω-phthalimidoalkylureas (I) [2] with diethyl oxalacetate [3, 4]. The structures of the substituted hydantoins were confirmed by the IR spectra, which have a characteristic maximum at 1790-1800 cm^{-1} (ν 4-CO) [5, 6].

Opening of the phthalimide ring occurs along with rearrangement of the hydantoin ring to a pyrimidine ring [7] when solutions of hydantoins IIb-d in 1 N potassium hydroxide are heated to 65°. The corresponding phthalamic acids (III) precipitate after acidification of the reaction medium; they were isolated and, without additional purification,* were refluxed with water, during which 3-(ω-aminoalkyl)orotic acids (IV, Table 2) formed with splitting out of phthalic acid.

In the case of hydantoin IIa, in which the amino groups of the phthalimide and hydantoin rings are separated by only one methylene link, the indicated treatment led to the isolation of orotic acid, which formed as the result of the facile splitting out of an aminomethyl residue.

The presence of an aminoalkyl group attached to the nitrogen atom in the 3-position in the substituted orotic acids (IV) is confirmed by the bathochromic shift of the absorption maximum in the UV region from 280 to 300 nm on passing from a neutral to an alkaline medium [8, 9].

*One of the phthalamic acids (III) – 3-[β-(o-carboxybenzoylamino)ethyl]orotic acid – was purified for analysis (see the experimental section).

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TABLE 1. 3-(ω-Phthalimidoalkyl)-5-carbethoxymethylenehydantoins

Compound	n	Mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IIa	1	199—200	$C_{16}H_{13}N_3O_6$	56,2	3,9	12,2	56,0	3,7	12,2	15
IIb	2	184—185	$C_{17}H_{15}N_3O_6$	57,3	4,4	11,9	57,1	4,2	11,8	40
IIc	3	159—160	$C_{18}H_{17}N_3O_6$	58,3	4,6	11,2	58,2	4,6	11,3	50
IId	5	138—139	$C_{20}H_{21}N_3O_6$	59,9	5,3	10,6	60,1	5,3	10,5	50

TABLE 2. 3-(ω-Aminoalkyl)orotic Acids

Compound	n	Mp, °C (decomp.)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IVa	2	287—288	$C_7H_9N_3O_4$	42,2	4,8	21,0	42,2	4,6	21,1	80
IVb	3	296—297	$C_8H_{11}N_3O_4$	44,9	5,3	19,3	45,1	5,2	19,7	78
IVc	5	322—323	$C_{10}H_{15}N_3O_4$	49,6	6,2	16,8	49,8	6,3	17,4	75

TABLE 3. 3-[ω-(6-Purinylamino)alkyl]orotic Acids

Compound	n	Mp, °C (decomp.)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
Va	2	330—331	$C_{12}H_{11}N_7O_4 \cdot H_2O$*	43,0	3,9	29,4	43,0	3,9	29,2	52
Vb	3	326—327	$C_{13}H_{13}N_7O_4$	47,2	4,1	30,5	47,1	4,0	29,6	63
Vc	5	303—305	$C_{15}H_{17}N_7O_4$	49,8	5,1	27,3	50,1	4,8	27,3	50

* Found %: H_2O 5.15. Calculated %: H_2O 5.37.

The condensation of the aminoalkylorotic acids (IV) with 6-chloropurine was accomplished by refluxing in water in the presence of alkali. The purinylaminoalkylorotic acids thus obtained (V, Table 3) are readily soluble in glucosamine solutions.

EXPERIMENTAL

3-(ω-Phthalimidoalkyl)-5-carbethoxymethylenehydantoins [(IIa-d), Table 1]. A strong stream of dry HCl was passed for 1 h with stirring at 106° (bath temperature) into a mixture of 0.02 mole of ω-phthalimidoalkylurea (I), 7.52 g (0.04 mole) of diethyl oxalacetate, and 3 ml of glacial acetic acid. The reaction mixture was allowed to stand for several days. The resulting viscous, colorless paste was ground with water, and the crystalline product was separated, washed with water and alcohol, and recrystallized from alcohol to give fine needles of IIa-d.

3-(ω-Aminoalkyl)orotic Acids (IVa-c, Table 2). A solution of 0.01 mole of IIb-d in 50 ml of 1 N KOH was heated for 2 h at 65° with stirring, cooled, and acidified with concentrated HCl until it gave a strongly acid reaction to Congo. The resulting precipitate was separated and refluxed for 3 h with 200 ml of water; the IVa-c which precipitated on cooling were separated and recrystallized from water. Similar treatment of IIa yielded orotic acid, which was identified by comparison with an authentic sample.

3-[β-(o-Carboxybenzoylamino)ethyl]orotic Acid. Compound IIIb was treated as described above, and the precipitate after acidification of the solution was separated and purified by reprecipitation from alkaline solution to give an almost quantitative yield of colorless crystals with mp 113-115°. Found %: C 49.6; H 4.3; N 11.6; H_2O (Fischer method) 4.2. $C_{15}H_{13}N_3O_7 \cdot H_2O$. Calculated %: C 49.3; H 4.1; N 11.5; H_2O 4.9.

3-[ω-(6-Purinylamino)alkyl]orotic acids [(Va-c), Table 3]. A solution of 0.01 mole of IVa-c, 1.6 g (0.01 mole) of 6-chloropurine, and 1.2 g (about 0.02 mole) of potassium hydroxide in 50 ml of water was refluxed with stirring for 3 h, cooled, and acidified with dilute hydrochloric acid. The resulting precipitate was separated and crystallized from water.

The IR spectra of mineral oil suspensions were obtained with a UR-10 spectrophotometer.

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