2,4-DIOXOHEXAHYDROPYRIMIDINE DERIVATIVES

V.* 5-BROMO-6-ALKOXYDIHYDROOROTIC ACIDS, AMIDES, AND ESTERS

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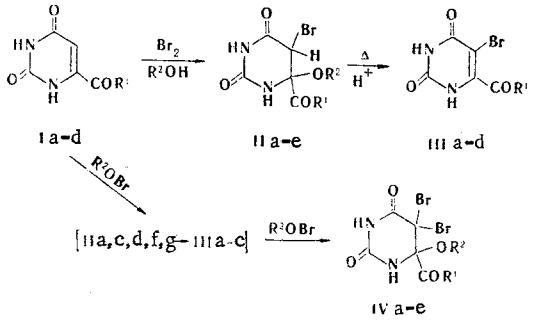
UDC 547.854.9:542.944.1

The corresponding 5-bromo-6-alkoxydihydroorotic acid derivatives were obtained by reaction of orotic acid, its methyl ester, and amide with bromine in methanol and ethanol. The reaction of methyl and butyl orotates with methyl and ethyl hypobromites gives 5,5-dibromo-6-alkoxydihydroorotic acid esters. Isoorotic acid reacts with methyl hypobromite to give 5,5-dibromo-6-methoxydihydrouracil.

Products of "mixed" addition to the 5,6 bond, among which substances with antileukemia, bactericidal, and herbicidal properties are found, are usually formed in the halogenation of uracil derivatives in hydroxyl-containing solvents. However, products of "mixed" addition were not obtained when there were carboxyl groups in the 5 or 6 position. Depending on the reaction conditions, either rapid decarboxylation of them [2-4] or the formation of unsaturated 5-halo derivatives [5, 6] was observed. 5-Bromo-6-hydroxydihydroorotic acid was isolated only in the reaction of orotic acid Ia with bromine in water [4].

We carried out the bromination of orotic acid Ia in methanol and ethanol and of its methyl and butyl esters (Ib, c) and amide Id in methanol and showed that 5-bromo-6-alkoxydihydroorotic acids IIa-e (Table 1) are practically the only reaction products at 0 to 25°C in the case of a 1:2 ratio of Ia-c and bromine (1:1 in the case of amide Id) and a reaction time of 1-2 h. As the temperature is raised, IIa-e readily



I a-d II a-e III a-d

[IIa,c,d,f,g-IIIa-c] IV a-e

I, IIIa R^1=OH; b R^1=OCH_3; c R^1=OC_4H_9; d R^1=NH_2; IIa R^1=OH, R^2=CH_3; b R^1=OH, R^2=C_2H_5; c R^1=OCH_3, R^2=CH_3; d R^1=OC_4H_9, R^2=CH_3; e R^1=NH_2, R^2=CH_3; f R^1=OC_4H_9, R^2=C_2H_5; g R^1=OCH_3, R^2=C_2H_5; IVa R^1=OH, R^2=CH_3; b R^1=OCH_3, R^2=CH_3; c R^1=OCH_3, R^2=C_2H_5; d R^1=OC_4H_9, R^2=CH_3; e R^1=OC_4H_9, R^2=C_2H_5

split out a molecule of alcohol to give 5-bromoorotic acids IIIa-d, and admixtures of the latter products were frequently detected in the isolation of products IIa-e (as a result of the effect of moisture and the workup time); for example, ester IId was not obtained in pure form because of the formation of admixed ester IIIc.

* See [1] for communication IV.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1549-1553, November, 1974. Original article submitted October 8, 1973.

TABLE 1. Derivatives of 5-Bromo(or 5,5-dibromo)-6-alkoxydihydroorotic and 5-Bromoorotic Acids

Compound	R¹	R²	mp, °C	R_f	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	Br	N	C	H	Br	N	
IIa	OH	CH_3	271—272	0,60—0,65	$C_5H_5BrN_2O_5$	26,7	3,0	29,7	10,6	27,0	2,6	29,9	10,5	56
IIb	OH	C_2H_5	273—274	0,73—0,74	$C_7H_9BrN_2O_5$	29,9	3,3	28,1	10,4	29,9	3,2	28,4	10,0	58
IIc	OCH_3	CH_3	249	0,76	$C_6H_7BrN_2O_5$	30,4	3,0	28,8	9,8	29,9	3,2	28,4	10,0	83
IIe	NH_2	CH_3	306—307	0,50	$C_6H_8BrN_3O_4$	26,8	3,0	30,5	16,2	27,1	3,0	30,0	15,8	73
IVb	OCH_3	CH_3	186—188	0,84	$C_7H_8Br_2N_2O_5$	23,0	2,3	44,1	8,2	23,3	2,2	44,4	7,8	79
IVc	OCH_3	C_2H_5	180—183	0,92	$C_8H_{10}Br_2N_2O_5$	25,7	3,0	43,2	7,8	25,7	2,7	42,7	7,5	63
IVd	OC_4H_9-n	CH_3	156—160	0,88—0,90	$C_{10}H_{14}Br_2N_2O_5$	29,7	3,8	39,5	7,3	29,9	3,5	39,7	7,0	43
IVe	OC_4H_9-n	C_2H_5	103—105	0,90—0,92	$C_{11}H_{16}Br_2N_2O_5$	31,1	3,7	38,0	7,2	31,7	3,9	38,4	6,7	36
IIIc	OC_4H_9-n	—	236	0,85	$C_9H_{11}BrN_2O_4$	36,9	3,8	27,6	9,7	37,1	3,8	27,5	9,6	62
IIId	NH_2	—	310	0,40	$C_5H_4BrN_3O_3$	25,6	1,9	34,9	17,6	25,7	1,7	34,2	18,0	75

* Compounds IIIc,d were recrystallized from water. For the remaining substances, the melting points and analytical data were determined for uncrystallized samples because of their instability.

The reaction of orotic acid derivatives Ia-c with methyl and ethyl hypobromites, obtained by the addition of Ag_2CO_3 to a solution of bromine in absolute methanol and ethanol [7], does not stop at the step involving the formation of products of the II type. Despite the fact that the HBr, which, according to the literature [8, 9], catalyzes the regeneration of a double bond, was removed from the reaction medium, complex mixtures of compounds of the II-IV type and, in the case of orotic acid, decarboxylation product VIII, were formed as the alkyl hypobromites were added. 5,5-Dibromo-6-alkoxydihydroorotic acid esters IVb-e (Table 1) were isolated and characterized only in the reaction of esters Ib,c, with a 2.5-fold to threefold excess of the alkyl hypobromites.

In a comparison of the reactivities of orotic and isoorotic acids (V) it was found that acid V reacts more readily with CH_3OBr than Ia (more rapid decolorization of the slightly yellow CH_3OBr solution). In the case of acid V, the only reaction product is 5,5-dibromo-6-methoxydihydrouracil (VIII) in the presence of a 2.3-fold to threefold excess of CH_3OBr. A mixture of V, VIII, and 5-bromouracil VII is formed in the case of an equimolar ratio of the reacting substances. The formation of product VIII was proved by alternative synthesis from 5-bromouracil and CH_3OBr; in addition to this, VIII is a known compound [10]. A spot for 5-bromo-6-methoxydihydroisoorotic acid was not detected on the chromatogram. We propose that the formation of VIII proceeds through cation VI.

V VI VII VIII

Isoorotic acid (2 : 1) reacts slowly with bromine in methanol at room temperature. After 1.5 h, 40% of acid V can be isolated from the reaction mixture, and the filtrate contains a mixture of V and VIII. Acid Ia reacts almost completely (100%) under these conditions to give acid IIa.

It is difficult to explain our qualitative results. The reasons for the greater instability of products IIa,c,d in a reaction medium containing CH_3OBr than in a bromine–methanol medium are unclear. It might be assumed that the reaction of Ia with bromine and methanol proceeds through the formation of a π complex and a bridge bromonium ion. The following facts constitute evidence in favor of this: 1) the dissolving of a suspension of acid Ia in bromine-methanol only with subsequent formation of a precipitate of acid IIa; 2) the slower reaction of bromine in methanol with isoorotic acid; 3) the stability of products of the II type in bromine–methanol (trans addition determined by the bridge brominium ion).

The UV spectra of IIa-c, e and IVb-e in aqueous or alcohol solutions do not contain the absorption maximum at 280 nm that is characteristics for orotic acid derivatives.

The IR spectra (in mineral oil) of the products of "mixed" addition at 1500-1800 cm^{-1} are shifted toward the long-frequency side as compared with orotic acid derivatives (saturation of the double bond and introduction of halogen). The C_4=O band (in boldface in Table 2) was assigned in analogy with the literature [11]. A comparison with the spectra of dihydroorotic acid derivatives [12]

TABLE 2. IR Spectra of Some Derivatives of Dihydroorotic and 5-Bromo(or 5,5-dibromo)-6-methoxydihydroorotic Acids

Compound	1800–1500 cm^{-1}
Dihydroorotic acids*	1740s †, 1725s 1662m
5-Bromo-6-methoxydihydroorotic acid (IIa)	1742sh 1730s 1669m
Methyl dihydroorotate*	1743s 1715sh 1694s
Methyl 5-bromo-6-methoxydihydroorotate (IIc)	1770s 1740s 1710s
Methyl 5,5-dibromo-6-methoxydihydroorotate (IVb)	1755sh 1705s, br
Dihydroorotic acid amide*	1720s 1690s 1645s
5-Bromo-6-methoxydihydroorotic acid amide (IIe)	1743s 1703s

* See [12].

† Abbreviations: s is strong, m is medium, sh is shoulder, and br is broad.

(Table 2) gives some idea of the spatial orientation of the halogen atoms. It follows from a comparison of the $C_4 = O$ band that the bromine atom in 5-bromo-6-methoxydihydroorotic acid IIa is oriented axially, whereas it is oriented equatorially in its ester (IIc) and amide (IIe) (the maximum at 1703 cm^{-1} in the spectrum of IIe is the result of overlapping of the ring $C_4 = O$ vibrations with the acyclic amide C = O group).

The PMR spectra of IIa,c recorded in d_6-dimethyl sulfoxide (d_6-DMSO) confirm the structure of the products of "mixed" addition. The proton attached to C_5 is split into a double doublet because of the long-range spin-spin coupling with the protons attached to the N_1 and N_3 atoms, as shown by experiments with double resonance. Consequently, the bulky bromine atom is oriented primarily axially.

EXPERIMENTAL

The UV spectra of the compounds were recorded with a Specord UV-vis automatic spectrophotometer. The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrometer. The PMR spectra of d_6-DMSO solutions were recorded with a Perkin–Elmer R-12A spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. Ascending chromatography on FILTRAK FN-1 paper was used with a butanol–acetic acid–water system (2 : 1 : 1) and development of the chromatograms of IIa-e, IVa-e, and VIII under a UV chemiscope.

5-Bromo-6-methoxydihydroorotic Acid (IIa). A 1.56-g (10 mmole) sample of acid Ia was suspended in 20 ml of absolute methanol, 1 ml (20 mmole) of Br_2 was added, and the mixture was stirred at room temperature for 1.5 h. After 20 min, acid Ia had dissolved completely, and a new precipitate appeared only after this. The precipitate was removed by filtration, washed with 8 ml of methanol and twice with 10 ml of dry ether to give 1.5 g of acid IIa. PMR spectrum, τ: 6.82 (OCH_3), 5.64 (5-H, $J_{1,5} = 1.2$ Hz; $J_{3,5} = 0.8$ Hz), 1.32 (1-H), and −0.78 (3-H) ppm.

Acid IIb was similarly obtained in 30 ml of ethanol.

Methyl 5-Bromo-6-methoxydihydroorotate (IIc). A mixture of 3.4 g (20 mmole) of ester Ib and 2 ml (40 mmole) of Br_2 in 50 ml of absolute methanol was stirred at 0 to 5° for 1 h to give 4.7 g of ester IIc with mp 249° (mixed-melting point with Ib 200-210°). PMR spectrum, τ: 6.83 (OCH_3), 6.21 ($COOCH_3$), 5.59 (5-H, $J_{1,5} = 1.2$ Hz, $J_{3,5} = 0.9$ Hz), 1.00 (1-H), and −0.83 (3-H) ppm.

5-Bromo-6-methoxydihydroorotic Acid Amide (IIe). This compound was prepared as in the case of IIa from 0.62 g (4 mmole) of amide Id and 0.2 ml (4 mmole) of Br_2 in 15 ml of absolute methanol. The reaction time was 2 h.

Solution of Methyl Hypobromite in Methanol [7]. A solution of 2.55 ml (50 mmole) and Br_2 in 150 ml of absolute methanol was cooled to 0 to 15°, and 32 g (110 mmole) of Ag_2CO_3 was added with vigorous stirring. Stirring and cooling were continued for 30 min, after which the slightly yellow solution was filtered. A solution of ethyl hypobromite was similarly obtained in ethanol. The reactions were carried out with freshly prepared solutions.*

* The amount of the alcohol solutions of alkyl hypobromites used in each reaction was varied somewhat, inasmuch as the concentrations of the alkyl hypobromites varied with each new preparation because of their volatility. The reaction was carried out until the slightly yellow color of the solution disappeared.

Methyl 5,5-Dibromo-6-methoxydihydroorotate (IVb). A 0.86-g (5 mmole) sample of ester Ib was suspended in 50 ml of absolute methanol, and 36 ml of a solution of CH_3OBr in methanol was added gradually. The mixture was stirred at room temperature for 1 h, after which it was filtered. The filtrate was evaporated to dryness at room temperature, and the dry residue was washed with 10 ml of absolute methanol and 5 ml of dry ether to give 1.43 g of ester IVb. Compound IVc was similarly obtained from 0.86 g (5 mmole) of Ib, 50 ml of ethanol, and 45 ml of C_2H_5OBr in ethanol, and IVd and IVe, respectively, were obtained from 1 g (4.7 mmole) of Ic, 100 ml of absolute methanol (or ethanol), and 40 ml of a solution of CH_3OBr in methanol (or 50 ml of a solution of C_2H_5OBr in ethanol). Splitting out of CH_3OBr or C_2H_5OBr to give derivatives of 5-bromoorotic acid was observed during attempts to recrystallize IVb-e from ethyl acetate.

5,5-Dibromo-6-methoxydihydrouracil (VIII). A total of 1.7 g (90%) of VIII was obtained (by the method used to prepare IIa) from 1 g (6.4 mmole) of acid V in 200 ml of methanol and 40 ml of CH_3OBr in methanol after a reaction time of 2 h. IR spectrum, cm^{-1}: 1732 sh, 1720 s, 1708 sh, 1495 m, 1242 m, 1199 w, 1151 w, 1087 m, 1070 sh, 3225 w, and 3064 w. The product had mp 203-205° (mp 203° [10]) and R_f 0.81-0.84. Found, %: C 19.9; H 1.9; Br 52.6; N 9.5. $C_5H_6Br_2N_2O_3$. Calculated, %: C 19.9; H 2.0; Br 52.9; N 9.3.

Compound VIII was also obtained by alternative synthesis from 1 g (5.2 mmole) of 5-bromouracil VII in 100 ml of methanol with the addition of 22 ml of a CH_3OBr solution after a reaction time of 1.5 h.

Butyl 5-Bromoorotate (IIIc). A 0.41-ml (8 mmole) sample of Br_2 was added to 1.7 g (8 mmole) of ester Ic in 35 ml of absolute methanol, and the mixture was refluxed for 2 h. The solution was cooled, and the resulting precipitate was removed by filtration and washed with ether to give 1.95 g of ester IIIc with mp 229-231°. The product was recrystallized from water. UV spectrum (ethanol): λ_{max} 292 nm (ε 5900). IR spectrum, cm^{-1}: 1738 m, 1706 s, 1660 s, 1624 sh, 1303 m, 1248 m, 1229 sh, 1196 w, 1081 m, 1064 w, 3200 sh, 3156 m, 3112 m, and 3026 s.

5-Bromoorotic Acid Amide (IIId). This compound was obtained by the method used to prepare ester IIIc. UV spectrum (water, pH 6): λ_{max} 285 nm (ε 7000). IR spectrum, cm^{-1}: 1715 s, 1680 s, 1611 w, 1289 w, 1094 w, 1042 vs, 3420 m, 3320 m, 3189 s, and 3035 s.

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