DERIVATIVES OF 2,6-DIHYDROXY-4,5-DIHYDROPYRIMIDINES

I. DL-4,5-Dihydroorotic Acid and Its Methyl Derivatives and Salts

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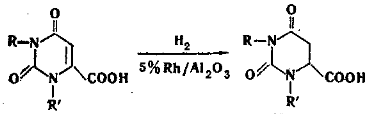
By the catalytic hydrogenation (5% of Rh on Al_2O_3) of orotic acid and its derivatives, DL-4,5-dihydroorotic and DL-1-methyl- and DL-1,3-dimethyldihydroorotic acids have been obtained. A number of salts of DL-4,5-dihydroorotic acid with amines have been synthesized.

Dihydroorotic acids have been obtained by the cyclization of L-, D-, and DL-N^{α}-ethoxycarbonylasparagines [1], and also by the reduction of orotic acid (Ia) in the presence of Adams catalyst at elevated pressure and temperature [2], or with 3% sodium amalgam [3]. In the last method, the reaction is carried out in an ammoniacal medium, and during the reaction the mixture becomes more alkaline and the risk arises of decomposition of the dihydroorotic acid at the 1,6- bond with the formation of ureidosuccinic acid.



Ia-в IIa-в

a $R=R'=H$; b $R=CH_3$, $R'=H$; c $R=R'=CH_3$

In order to obtain DL-4,5-dihydroorotic acid (IIa) we have developed a method for the catalytic hydrogenation of orotic acid over 5% Rh on Al_2O_3, which selectively hydrogenates the 4,5- double bond of 2,6-dihydropyrimidines at atmospheric pressure and room temperature [4]. Because of the poor solubility of Ia, its salt with n-butylamine was used as the starting material. After the reaction, the IIa was isolated by acidification with HCl. 1-Methyldihydroorotic acid (IIb) was obtained similarly. 1,3-Dimethyldihydroorotic acid (IIc) was obtained by the direct hydrogenation of Ic.

Table 1. Salts of DL-Dihydroorotic Acid with Amines

Compound	Amine	Method	Mp, °C	Empirical formula	Found, %			Calculated, %		
					C	H	N	C	H	N
IIIa	n-Propylamine	A	183—185[a]	$C_5H_6N_2O_4 \cdot C_3H_9N$	44,64	7,11	19,71	44,24	6,96	19,34
IIIb	n-Butylamine	A	184—186[b]	$C_5H_6N_2O_4 \cdot C_4H_{11}N$	46,58	7,26	18,58	46,73	7,41	18,17
IIIc	Diethylamine	A	195—196[c]	$C_5H_6N_2O_4 \cdot C_4H_{11}N$	46,29	7,09	17,93	46,73	7,41	18,17
IIId	Di-n-propylamine	A	189—193[d]	$C_5H_6N_2O_4 \cdot C_6H_{15}N$	51,47	8,14	16,70	50,94	8,16	16,20
IIIe	Di-n-butylamine	A	181—186[a]	$C_5H_6N_2O_4 \cdot C_8H_{19}N$	54,14	8,90	14,96	54,31	8,77	14,62
IIIf	Morpholine	A B	225[e]	$C_5H_6N_2O_4 \cdot C_4H_9NO$	44,02	6,44	16,97	44,08	6,16	17,13
IIIg	L-Arginine	B	247[e]	$C_5H_6N_2O_4 \cdot C_6H_{14}N_4O_2$	39,65	6,17	25,29	39,64	6,31	25,26
IIIh	Methyl ester of DL-methionine	B	151—154[c]	$C_5H_6N_2O_4 \cdot C_6H_9NO_2S$	41,38	5,99	13,40	41,11	5,96	13,08
IIIi	DL-methionine Methyl ester of DL-β-phenyl-α-alanine	B	188[b]	$C_5H_6N_2O_4 \cdot C_{10}H_{13}NO_2$	53,60	5,62	12,55	53,39	5,68	12,46
IIIj	Allylamine	B	183—185[b]	$C_5H_6N_2O_4 \cdot C_3H_7N$	44,65	6,15	19,54	44,66	6,09	19,53

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[a] From methanol. [b] From ethanol. [c] From a mixture of ethanol and ether. [d] From a mixture of ethanol and ether. [e] From aqueous ethanol.

In order to study their physiological activity, we have synthesized a number of salts of DL-dihydroorotic acid with amines (IIIa-j) (see Table 1). Some of the salts were obtained by hydrogenating the corresponding salts of the acid Ia (method A), and others were synthesized by the reaction of the acid IIa with amines in water (method B).

EXPERIMENTAL

The 5% Rh on Al_2O_3 catalyst [5] and the 1-methyl- and 1,3-dimethylorotic acids (Ib, c) [6] were obtained by published methods. The saturation of the double bond was determined by the disappearance of the absorption maximum at 278 nm (pH 7) which is characteristic for orotic acid and its methyl derivatives, and by ascending paper chromatography on FILTRAK FN-1 paper in the following systems: $n\text{-}C_4H_9OH-CH_3COOH-H_2O$ (2 : 1 : 1) (system 1) and $i\text{-}C_3H_7OH-1N$ NH_4OH (7 : 3) (system 2). In system 1 and 2 the R_f values of IIa were identical with the R_f values of IIIa-j (yellow spots after treatment with 1 N NaOH and Ehrlich's reagent [7]). Compounds IIb and c did not give a color with Ehrlich's reagent and therefore their R_f values were not determined.

DL-4,5-Dihydroorotic acid (IIa). A suspension of 4 g of Ia in 250 ml of water was treated with 2.5 ml of n-butylamine and was then heated until the Ia had dissolved, after which the solution was cooled to room temperature and 2 g of 5% Rh on Al_2O_3 was added. With vigorous shaking, hydrogenation was carried out at room temperature and atmospheric pressure for 8 hr. The amount of hydrogen absorbed was 665 ml (calculated theoretically 620 ml). The catalyst was filtered off, and the solution was evaporated in vacuum to a volume of 85 ml and was slowly, dropwise, acidified with HCl until the formation of a precipitate was filtered off to give 3.95 g of IIa. It was recrystallized from water. The yield of the monohydrate of IIa was 3.4 g (75%). It was dried in vacuum over P_2O_5 at 70°C. Mp 260°C (according to the literature [1], mp 259°C); R_f 0.42 (system 1) (according to the literature [7], R_f 0.43); R_f 0.55 (system 2). Found %: C 38.04; H 3.77; N 17.48. $C_5H_6N_2O_4$. Calculated %: C 37.98; H 3.80; N 17.72.

DL-1-Methyl-4,5-dihydroorotic acid (IIb). In a similar manner to the synthesis of IIa, from 1.09 g of Ib and 0.63 ml of n-butylamine in 100 ml of water in the presence of 1 g of 5% Rh on Al_2O_3 was obtained 0.9 g (81%) of IIb. Mp 217-218°C. After crystallization from ethanol, it was dried in vacuum over P_2O_5. Mp 227-228°C. Found %: C 42.10; H 4.75; N 15.98. $C_6H_8N_2O_4$. Calculated %: C 41.85; N 4.68; N 16.28.

DL-1,3-Dimethyl-4,5-dihydroorotic acid (IIc). A solution of 2.5 g of Ic in 100 ml of water was treated with 2 g of 5% Rh on Al_2O_3 and hydrogenation was carried out with vigorous shaking for 8 hr. The catalyst was filtered off and the solution was evaporated in vacuum at 40°C to dryness. The residue was dissolved in 20 ml of absolute methanol, and the solution was again evaporated to dryness with the formation of an oily residue which partially crystallized on standing for two days in the refrigerator. The crystals were separated off and washed with ether and were then dried in vacuum over P_2O_5. This gave 0.9 g (35%) of IIc. Mp 115-117°C. Found %: C 44.86; H 5.69; N 15.12. $C_7H_{10}N_2O_4$. Calculated %: C 45.15; H 5.79; N 15.05.

Salt of DL-4,5-dihydroorotic acid with morpholine (IIIf). A) A mixture of 1 g (6.4 mM) of Ia and 0.50 ml (6.4 mM) of morpholine in 100 ml of water was hydrogenated in the presence of 1 g of 5% Rh on Al_2O_3 for 8-10 hr. Then the mixture was filtered and evaporated under vacuum to the minimum volume, after which ethanol precipitated 1.2 g (77%) of IIIf. Mp 225°C (decomp.).

B) A suspension of 0.72 g (4.1 mM) of the monohydrate of IIa in 30 ml of water was treated with 0.32 ml (4.1 mM) of morpholine and shaken until the solid matter dissolved, and then it was filtered, evaporated to the minimum volume, and precipitated with ethanol. Yield 0.77 g (71%). Mp 225°C (decomp.).

REFERENCES

1. C. S. Miller, E. L. Engelhardt and J. T. Gordon US patent no. 2273872, 1956; C. A., 51, 2886, 1957.
2. R. D. Batt, J. K. Martin, J. Mc. T. Ploeser, and J. Murray, J. Am. Chem. Soc., 76, 3663, 1954.
3. K. Tsuji, Japanese patent no. 13932, 1964; C. A., 62, 574, 1965.
4. M. Green and S. S. Cohen, J. Biol. Chem., 225, 397, 1957.
5. N. K. Kochetkov, E. I. Budovskii, V. N. Shibaev, and G. M. Eliseeva, DAN 159, 605, 1964.
6. W. V. Curran and R. B. Angier, J. Org. Chem., 31, 201, 1966.
7. R. M. Fink, Anal. Chem., 28, 4, 1956.

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