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

II*. ESTERS OF DL-DIHYDROOROTIC ACID

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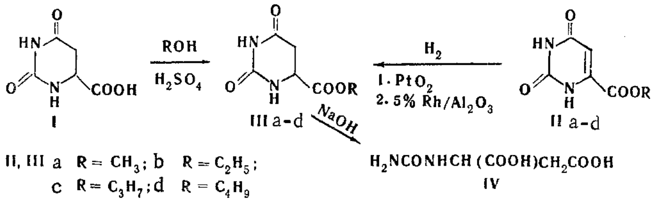
Esters of DL-dihydroorotic acid have been obtained by catalytic hydrogenation of esters of orotic acid (using PtO_2 and 5% Rh on Al_2O_3 as catalysts), and by esterifying DL-dihydroorotic acid. Transesterification is observed with butyl dihydroorotate in the presence of secondary amines, and this ester is hydrolyzed in acid and alkaline media to dihydroorotic and ureidosuccinic acid, respectively.

We have described in a previous communication [1] a new synthesis of DL-dihydroorotic acid (I). We now describe the synthesis and examination of the hitherto unknown esters of DL-dihydroorotic acid (IIIa-d). We have obtained these esters by esterifying DL-dihydroorotic acid, by catalytic hydrogenation of the esters of orotic acid (IIa-d), and by transesterification of butyl dihydroorotate (IIId).



II, III a $R = CH_3$; b $R = C_2H_5$; c $R = C_3H_7$; d $R = C_4H_9$

As a result of the poor solubility of orotic acid in methanol and ethanol, the preparation of IIa and b is attended with considerable difficulty [2]. This method is suitable for the preparation of n-propyl and n-butyl orotates [3, 4] (IIc and d). IIa and b were obtained from orotyl chloride [4, 5]. Apparently as a result of the higher solubility of dihydroorotic acid in alcohols, its velocity of esterification is much higher than that of orotic acid. On boiling I in alcoholic solution in the presence of concentrated sulfuric acid (method A, see Table 1), reaction was complete in one h.

The catalysts used in the preparation of IIIa-d from IIa-d by hydrogenation were PtO_2 (method B, see Table 1), and 5% rhodium on aluminum oxide [6] (method C) [7]. The results showed that, firstly, the yields in the saturation of the 4-5 bond with hydrogen in presence of PtO_2 were lower than when rhodium was used, and secondly, that the yields of hydrogenation products increased with increasing size of R. The latter effect is probably due to the increased solubilities of esters of orotic and dihydroorotic acid with increasing size of the alkyl group.

It is interesting that when ethanolic and methanolic solutions of IIId were treated with primary or secondary amines (morpholine or n-amylamine), instead of the expected amides, transesterification occurred rapidly to give the methyl and ethyl esters, IIIa and b, in very high yields (method D).

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*For Part I, see [1].

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TABLE 1. Esters of Dihydroorotic Acid

Compound	R	Mp, °C	R_f		Molecular formula	Found, %			Calculated, %			Yield, % *			
			1†	2		C	H	N	C	H	N	A	B[a]	C[a]	D
IIIa	CH_3	202— —203	0,64	0,49	$C_6H_8N_2O_4$	42,0	4,7	16,4	41,8	4,6	16,2	81	9	40	78
IIIb	C_2H_5	177	0,74	0,52	$C_7H_{10}N_2O_4$	45,5	5,4	15,0	45,2	5,4	15,0	79	10	40	71
IIIc	n-C_3H_7	141	0,81	0,55	$C_8H_{12}N_2O_4$	48,1	6,0	14,1	48,0	6,0	14,0	—	15	55	—
IIId	n-C_4H_9	141— —142	0,84	0,59	$C_9H_{14}N_2O_4$	50,1	6,4	13,3	50,5	6,6	13,1	76,5	30	70	—

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*Methods of synthesis: A) Esterification of dihydroorotic acid; B) Hydrogenation with PtO_2; C) Hydrogenation with 5% rhodium on Al_2O_3; D) Transesterification of IIId (a – yield after recrystallization from water).

† 1 and 2 are the systems described in the Experimental.

We have examined the hydrolytic stability of IIId in acid and alkaline media. The literature records [8] that dihydroorotic acid is degraded in acid media to ureidosuccinic acid. We have carried out the hydrolysis of IIId in ~0.6 N HCl by boiling for 3 h, when the main product was dihydroorotic acid, with only traces of ureidosuccinic acid (IV), detected by chromatography. This is in agreement with literature results [9] on the acid hydrolysis of the dihydrouracil ring, in which the equilibrium between the open-chain and ring forms is shifted in the direction of the open-chain form in 5 N HCl (and stronger acid). Alkaline hydrolysis of IIId results in rapid fission of the 1-6 bond to give ureidosuccinic acid.

EXPERIMENTAL

Saturation of the double bond was determined by disappearance of the absorption maximum (λ_{max} 284 nm, pH 7) characteristic of esters of dihydroorotic acid, and by ascending paper chromatography in systems 1 (CH_3COOH : n-C_4H_9OH : H_2O, 1 : 2 : 1); 2 (i-C_3H_7OH : 1 N NH_4OH, 7 : 3); 3 (CH_3COOH : n-C_4H_9OH : H_2O, 1 : 4 : 1). The paper used was FILTRAK FN-12, and the spots of IIIa-d, IV, and I were developed with Erlich's reagent [10].

Elementary analyses were obtained on IIIa-d obtained by catalytic hydrogenation over 5% Rh on Al_2O_3. The identity of the esters obtained by the other methods were established by the absence of depression of their mp's, and by paper chromatography.

n-Butyl Dihydroorotate (IIId). A) A portion of I monohydrate 0.42 g [(2.4 mmole)] was suspended in 25 ml of n-butanol, 0.1 ml of conc. H_2SO_4 was added, and the mixture was boiled for 0.5 h. The mixture was cooled and filtered to give 0.29 g of IIId. Addition of ether to the mother liquors precipitated a further 0.1 g of IIId. Overall yield 0.39 g (76.5%), mp 141° (from water).

B). A portion of IId [0.5 g (2.4 mmole)] and 0.5 g of PtO_2 were suspended in 100 ml of water, and hydrogen was introduced at atmospheric temperature and pressure until no more hydrogen was taken up. The catalyst was filtered off, and the residue after evaporation to dryness was crystallized twice from the minimum amount of water (the solid should preferably not be dissolved completely in the water, since IId remains in the residue on account of its low solubility) to give 0.15 g of IIId.

C) A portion of IIId [0.5 g (2.4 mmole)] and 0.2 g of 5% Rh on Al_2O_3 were suspended in 100 ml of water, and hydrogenated at 20° and 778 mm pressure until absorption of hydrogen was complete (76 ml after 15 h). The catalyst was filtered off, and the filtrate was evaporated to dryness in vacuo. Recrystallization from water gave 0.35 g of IIId.

Methyl Dihydroorotate (IIIa). To a suspension of 1.07 g (5 mmole) of IIId in 25 ml of methanol was added 0.82 ml (~10 mmole) of morpholine, and the mixture was stirred for 2 h. While stirring, IIId dissolved, and a new precipitate separated. This was filtered off and washed with ether to give 0.67 g of IIIa.

Hydrolysis of IIId. A) A portion of IIId [0.3 g (1.4 mmole)] was suspended in 20 ml of water, 1 ml of conc. HCl was added, and the mixture was boiled for 3 h. The solution was evaporated in vacuo to 7 ml, and cooled. The solid was filtered off to give 0.13 g (59%) of I, mp 258° [8], R_f 0.42 (system 1); R_f 0.22 (system 3). Ureidosuccinic acid, R_f 0.45 (system 3) was detected in the filtrate [11].

B) An amount of NaOH [0.16 g (4 mmole)] was dissolved in 20 ml of water, 0.4 g (~2 mmole) of IIId was added, and the mixture was boiled for 3 h. After keeping overnight, it was acidified to pH 2, concentrated to 5 ml, and cooled. The solid was filtered off, washed with 5 ml of water, and recrystallized from water to give 0.1 g (30%) of ureidosuccinic acid, mp 180° [12], R_f 0.45 (system 3) [11].

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