2,6-DIHYDROXY-4,5-DIHYDROPYRIMIDINE DERIVATIVES

III. PREPARATION OF AMIDES AND HYDRAZIDES OF DL-DIHYDROOROTIC AND DL-UREIDOSUCCINIC ACIDS

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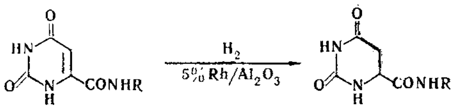
Alkylamides of DL-4,5-dihydroorotic acid were synthesized by catalytic hydrogenation (5% Rh on Al_2O_3). The reaction of the n-butyl ester of DL-4,5-dihydroorotic acid with alkylamines and hydrazine gave N,N'-dialkylamides, the dihydrazide of DL-ureidosuccinic acid, and the hydrazide of DL-4,5-dihydroorotic acid. The products of the condensation of the latter with aromatic aldehydes were obtained.

The goal of this study was the preparation and investigation of the previously undescribed amides of DL-dihydroorotic acid (IIa-f), which are of interest as potential antimetabolites of dihydroorotic acid – the precursor in the biosynthesis of pyrimidines de novo. The catalytic hydrogenation of amides of orotic acid (Ia-f) [1-4] over 5% Rh on Al_2O_3 [5] was chosen for the synthesis:



I a-f　　II a-f

I; II a R=H; b $R=CH_3$; c $R=C_2H_5$; d $R=n\text{-}C_3H_7$; e $R=n\text{-}C_4H_9$; f $R=n\text{-}C_5H_{11}$

The yields of hydrogenated amides IIa-f are low and vary as a function of radical R (see Table 1): the solubility of starting amides Ib-f increases as the size of the radical increases, as do the yields of hydrogenated products. In all cases, the reaction mixture after hydrogenation contains a small amount of the starting compounds. (The absorption maximum of low intensity at 285 nm that is characteristic for amides of orotic acid (Ia-f) is retained in the UV spectrum of an aqueous solution.) The low yields of IIa-f are due in part to the difficulties involved in the separation of amides of orotic and dihydroorotic acids, which is accomplished by repeated crystallization from water.

We proposed to accomplish the alternative synthesis of amides IIb-f from the n-butyl ester of DL-dihydroorotic acid (III) [6]. We have previously shown [6] that amide formation is not observed in the reaction of equivalent ratios of III and amines at room temperature. Transesterification of III to the ethyl and methyl esters of dihydroorotic acid occurs in ethanol and methanol.

When III is heated with excess primary amines, the 1,6 bond is cleaved to give the previously undescribed N,N'-dialkylamides of ureidosuccinic acid (IVa-e) in high yields (see Table 2). In contrast to amines, a slight excess of hydrazine hydrate readily forms the hydrazide of DL-dihydroorotic acid (V) with ester III in absolute butyl alcohol at room temperature. Cleavage of III at the 1,6 bond to form the dihydrazide of ureidosuccinic acid (IVf) is observed in the presence of a larger excess of hydrazine hydrate at higher temperatures.

The structures and purities of the compounds obtained were confirmed by paper chromatography and UV and IR spectroscopy. The ureido and dihydro derivatives do not have the absorption bands at 285-300 nm

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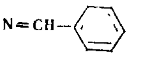
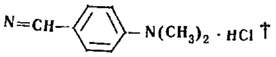
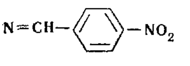
TABLE 1. Yields and Physical Constants of Amides and Hydrazides of Dihydroorotic Acid

Compound	R	Mp, °C	R_f		Empirical formula
			a	b	
IIa	H	>247 (dec.)	0,30	0,52	$C_5H_7N_3O_3$
b	CH_3	234—236	0,49	0,67	$C_6H_9N_3O_3$
c	C_2H_5	190—191	0,61	0,73	$C_7H_{11}N_3O_3$
d	n-C_3H_7	194	0,70	0,79	$C_8H_{13}N_3O_3$
e	n-C_4H_9	191—192	0,77	0,84	$C_9H_{15}N_3O_3$
f	n-C_5H_{11}	194—195	0,81	0,86	$C_{10}H_{17}N_3O_3$
V	NH_2*	196			$C_5H_8N_4O_3$
VIa		263			$C_{12}H_{12}N_4O_3$
b	 †	234			$C_{14}H_{17}N_5O_3 \cdot HCl$
c		290			$C_{12}H_{11}N_5O_5$.

(Table 1 continued)

Compound	Found, %			Calculated, %			Yield, %
	C	H	N	C	H	N	
IIa	38,32	4,41	27,38	38,22	4,49	26,74	27
b	42,11	5,84	24,53	41,72	5,42	24,56	9
c	45,12	6,06	22,59	45,23	5,96	22,55	31
d	48,48	6,67	21,09	48,26	6,58	21,10	45
e	50,77	7,37	19,36	50,70	7,09	19,71	75
f	52,67	7,43	18,20	52,83	7,54	18,48	77
V	34,81	4,89	32,80	34,90	4,69	32,56	79
VIa	55,59	4,34	21,97	55,37	4,64	21,52	96
b	49,44	5,33	20,76	49,50	5,34	20,61	85
c	47,07	3,59	23,17	47,21	3,62	22,94	82

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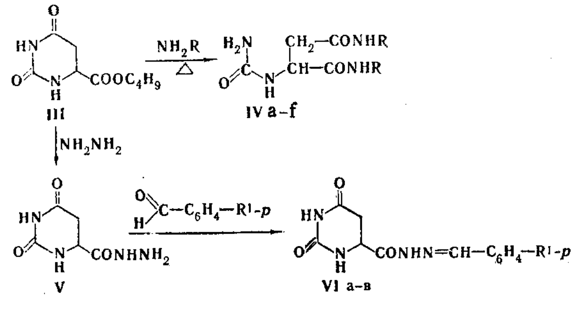
*R_f 0.69 (in solvent system c).

† Found: Cl 9.98%. Calc.: Cl 10.43%.

that are characteristic for the amides and hydrazide of orotic acid [1] and are developed on paper by means of the Erlich reagent (after treatment with 1 N NaOH in the case of the dihydro derivatives) [7]. An exception to this is the hydrazide of dihydroorotic acid V, which itself gives an orange coloration with the Erlich reagent without prior alkaline cleavage of the 1,6 bond. In this case, the amino group of the hydrazide condenses with p-dimethylaminobenzaldehyde. To confirm the structure of hydrazide V, we isolated the products of the condensation of VIa-c with aromatic aldehydes, which are formed almost quantitatively in acid media (see Table 1). To avoid the formation of side products, it is necessary to use excess aldehyde.



IV a R=CH_3; b R=C_2H_5; c R=n-C_3H_7; d R=n-C_4H_9; e R=n-C_5H_{11}; f R=NH_2;

VI a R^1=H; b R^1=$N(CH_3)_2 \cdot HCl$; c R^1=NO_2

TABLE 2. Yields and Physical Constants of N,N'-Dialkylamides and the Dihydrazide of Ureidosuccinic Acid

Compound	R	Mp, °C	R_f		Empirical formula	Found, %			Calc., %			Yield,%
			a	b		C	H	N	C	H	N	
IVa	CH_3	226—228	0,62	0,76	$C_7H_{14}N_4O_3$	41,51	7,07	27,91	41,59	6,98	27,71	66
b	C_2H_5	224—226	0,82	0,85	$C_9H_{18}N_4O_3$	47,00	7,88	24,28	46,71	8,28	24,23	74
c	n-C_3H_7	214—215	0,92	0,90	$C_{11}H_{22}N_4O_3$	51,13	8,61	21,15	50,94	8,94	21,64	65
d	n-C_4H_9	195—197	0,94	0,94	$C_{13}H_{26}N_4O_3$	54,22	9,40	19,77	54,50	9,15	19,56	71
e	n-C_5H_{11}	193—194	0,96	0,96	$C_{15}H_{30}N_4O_3$	57,32	9,86	18,01	57,10	9,91	17,76	67
f	NH_2*	184—186			$C_5H_{12}N_6O_3$	29,37	5,95	41,66	29,42	5,93	41,16	93

*R_f 0.76 (in solvent system c).

The IR spectra of the synthesized compounds are complex, and the interpretation of the individual absorption bands is extremely difficult. An intense absorption of the carbonyl groups at 1640-1730 cm^{-1} is characteristic for the amides of dihydroorotic acid (for example, IIe) and its hydrazide (V). The absorption band above 1700 cm^{-1} vanishes when the ring is opened (for example, for IVd and IVf). The band at ~1550 cm^{-1} can be assigned to secondary amide band δ_{NH}. All of the synthesized compounds have a number of absorption maxima at 3000-3500 cm^{-1}, which are related to the vibrations of both bonded and free NH groups. An additional, clearly expressed ν_{NH} maximum above 3400 cm^{-1} (for example, 3430 cm^{-1} for IVd and 3428 cm^{-1} for IVf) is characteristic for the ureido derivatives in this region.

EXPERIMENTAL

Amides Ia-f were obtained by known methods [1-4], but the methyl ester of orotic acid recommended in [2, 4] was replaced by the readily accessible n-butyl ester, which is more soluble. The yields of amides Ia and Ib are raised when the n-butyl ester is used.

The R_f values were determined by ascending chromatography on Filtrax FN-12 paper in the following solvent systems: a) butanol—acetic acid—water (2 : 1 : 1); b) isopropyl alcohol—1 N H_4OH (7 : 3); c) isopropyl alcohol—water—$(NH_4)_2SO_4$ (128 : 70 : 2). The physical constants and yields of the synthesized compounds are presented in Tables 1 and 2.

N,N'-Di-n-butyl-DL-dihydroorotamide (IIe). A 2-g (9.5 mmole) sample of N,N'-di-n-butylorotamide (Ie) [2] was suspended in 300 ml of ethanol,* 2 g of 5% Rh on Al_2O_3 was added, and the mixture was hydrogenated at atmospheric pressure and room temperature for 12 h with vigorous shaking. A total of 220 ml of hydrogen was absorbed. (The amount calculated from theory is 230 ml.) The catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The product was recrystallized from water. Alkylamides IIb, c, d, f were similarly obtained.

DL-Dihydroorotamide (IIa). A 2.8-g (16 mmole) sample of the ammonium salt of amide Ia [4] was dissolved in 550 ml of distilled water,† 1.5 g of 5% Rh on Al_2O_3 was added, and the mixture was hydrogenated for 10 h at room temperature and atmospheric pressure. A total of 380 ml of hydrogen was absorbed. (The amount calculated from theory is 385 ml.) The catalyst forms a colloid during the hydrogenation, from which it is freed by filtration of the solution through a layer of silica gel. The filtrate was vacuum evaporated to 80 ml and slowly acidified with acetic acid. The precipitate was removed by filtration and recrystallized from water.

N,N'-Di-n-butyl-DL-ureidosuccinamide (IVd). A 1-g (4.7 mmole) sample of III was suspended in 20 ml of absolute ethanol, 2 ml (20.4 mmole) of n-butylamine was added, and the mixture was refluxed for 8 h. The solution was allowed to stand overnight, and the precipitate was removed by filtration and washed with ether to give 0.46 g of a white, amorphous substance with mp 189°. The filtrate was vacuum evaporated to a volume of several millimeters, and the resulting precipitate was removed by filtration and washed with ether to give another 0.49 g of a substance with mp 188°. The product was recrystallized from water.

Alkylamides (IVc, e) were similarly obtained.

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*The use of an aqueous medium for the hydrogenation is undesirable, since the amides of dihydroorotic and orotic acids undergo steam distillation, and this complicates the isolation of the reaction products.

†An aqueous medium was used, since the ammonium salt of amide Ia does not undergo steam distillation.

N,N'-Dimethyl-DL-ureidosuccinamide (IVa). A 1-g (4.7 mmole) sample of III and 10 ml of 40% absolute methanol saturated with methylamine were sealed in an ampul, and the mixture was held at room temperature for 24 h. The precipitate was removed by filtration and recrystallized from water.

N,N'- Diethyl-DL-ureidosuccinamide (IVb) was similarly obtained from 1 g (4.7mmole) of III and 4 ml (62 mmole) of ethylamine.

DL-Dihydroorotic Acid Hydrazide (V). A 0.5-ml (10.3 mmole) sample of hydrazine hydrate was added to a suspension of 0.5 g (2.3 mmole) of III in 25 ml of absolute butyl alcohol, and the mixture was stirred at room temperature for 3 h. The mixture became homogeneous, after which a white precipitate formed. The precipitate was removed by filtration to give 0.39 g of the hydrate of V with mp 186°. Recrystallization from water and vacuum drying gave V.

DL-Ureidosuccinic Acid Dihydrazide (IVf). A 1-g (4.7 mmole) sample of III was suspended in 35 ml of absolute butyl alcohol, and 4 ml (82.4 mmole) of hydrazine hydrate was added. Compound III dissolved, and the clear solution was refluxed for 4 h until a precipitate appeared. The mixture was cooled, and the precipitate was removed by filtration to give 0.9 g of IVf. The product was crystallized from the minimum amount of water containing activated charcoal.

DL-Dihydroorotic Acid p-Dimethylaminobenzylidenehydrazide Hydrochloride (VIb). A 0.172-g (1 mmole) sample of V was suspended in a mixture of 15 ml of ethanol and 7 ml of dioxane (the latter was added to improve the solubility), and 0.21 g (1.4 mmole) of p-dimethylaminobenzaldehyde and 1 ml of 15% hydrochloric acid were added. The mixture was stirred at room temperature for 1 h and allowed to stand overnight. The orange precipitate was removed by filtration and washed with alcohol and ether to give 0.29 g of VIb.

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