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The Synthesis of Some Optically Active 5,6-Dihydrouracils

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From L-β-amino-δ-methyl-hexanoic acid (L-β-homoleucine, Ia) some in 6-position optically active 5,6-dihydrouracils (IVa—e) were prepared *via* the corresponding β-ureido esters (IIIa—e). Several methods were tried and the preferable conditions for the retention of optical activity studied. By two ways it was shown that no loss of optical activity during reaction stages I—IV occured: *a)* alkaline hydrolysis performed on IVa—c gave β-ureido acids (Va—e) which could be converted in dihydrouracils having the same optical activity; *b)* acid hydrolysis of IVa yielded the optically unchanged β-homoleucine (Ia).

Several methods have been reported in literature dealing with the cyclization of β-ureido acids, or their esters into the corresponding 5,6-dihydrouracils. In most cases the ring closure was performed with aqueous or concentrated hydrochloric acid[1,2], but sulphuric acid[3], acetyl chloride[4], acetic anhydride[5] and even application of heat[6] were also used. In spite of the fact that some compounds of this type had been prepared at the end of 19th century, only a small number of β-ureido acids had been subjected to this cyclization before Rodionov and his collaborators[7] synthesized several new β-ureido acids and converted them into 5,6-dihydrouracils. Birkofer[8] also obtained 5,6-dihydrouracils by melting α, β-unsaturated acids with urea.

The factors influencing cyclization of β-ureido acids to the corresponding dihydrouracils have been studied by several authors, but a uniform rule has not been given yet. Johnson and Livak [9] found that a great influence in ring closure had to be ascribed to the relative positivity or negativity of the group attached to the external nitrogen of the β-ureido acid, and also that sometimes sterical reasons might prevent cyclization. So for example the failure of some (3-phenyl)- and (3-α-naphthyl)-β-ureido acids to undergo cyclization was explained by sterical hindrance[9,10].

5,6-dihydrouracils were found to be labile compounds, hydrolyzing with alkali solutions under mild reaction conditions to β-ureido acids[11,12] and decomposing completely when heated with barium hydroxide solution in a sealed tube at 150° [11].

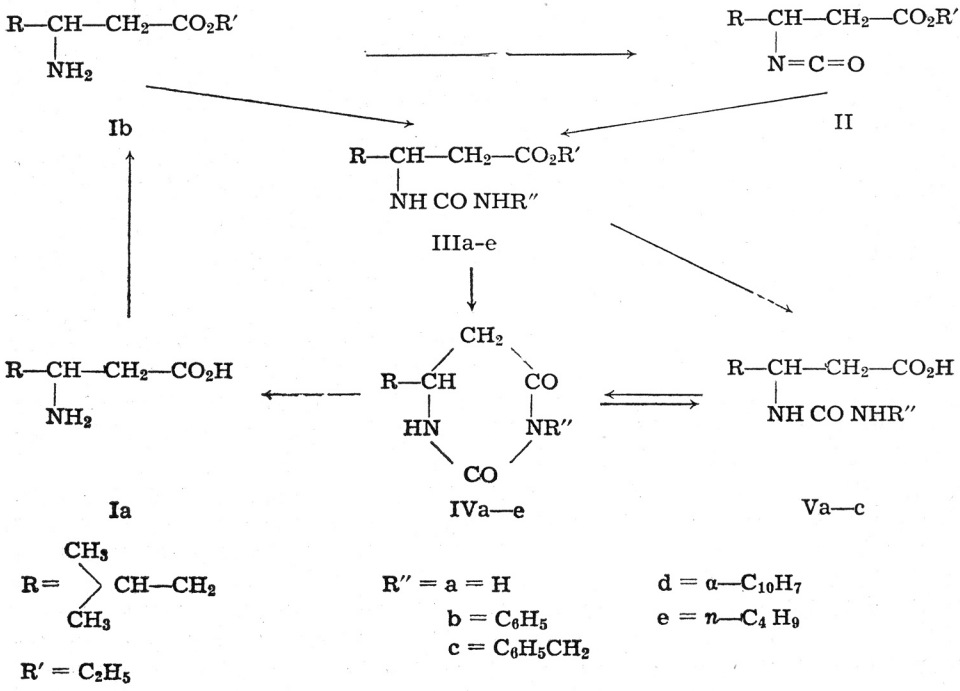
In principle carbon atoms 5 and 6 in dihydrouracils could fulfil the conditions for optical activity. Since the carbon atom in 6-position originates from the β-C atom of a β-ureido acid, optically active β-amino acids can serve as the starting material for dihydrouracils, which are optically active in the 6-position. Optically active β-amino acids can be conveniently synthesized from L- or D-α-amino acids by a general method given by Balenović[13].

Rodionov reported two syntheses of 5,6-dihydrouracils where the β-amino acids, used as the starting material, had two asymmetrical carbon atoms. In the first case[14], the β-amino acid, being asymmetrical at the positions α and β, was resolved by fractional crystallization into diastereoisomeric pairs, converted into ureido derivatives and cyclisized; in the second case[15], the β-amino acid, being asymmetrical at the positions β and γ, was prepared from the optically active aldehyde, and then by fractional crystallization resolved into the two diastereoisomers. However, no optical rotation of either β-ureido acids or dihydrouracils obtained were given, only melting points being cited. Thus, to our knowledge, no conditions under which optically active 5,6-dihydrouracils are formed have been studied, and no optical rotation data for this type of compounds have been recorded.

The purpose of this work was to prepare from the optically active β-amino-δ-methyl-hexanoic acid (β-homoleucine, Ia)[16] the corresponding dihydrouracils and to find out which conditions were preferable for the retention of the optical activity.

In general, three methods have been described in the literature for the preparation of β-ureido acids and/or their esters: *a)* interaction of an β-amino acid with urea[17,18], *b)* reaction of the β-amino acid or its ester with potassium cyanate[14,19], alkyl or aryl isocyanate[2] and *c)* addition of an amine to the ester of a β-*N*-carbonyl amino acid[10].

In our experiments all three methods were tried.



Method *a)*, giving products, more than 50% racemized in a low yield proved to be inadequate. Method *b)*, when applied to the acid Ia failed; potas-

sium cyanate and Ia gave an oily product that could not be brought to crystallization; when cyclized to dihydrouracil, it showed to be only 50% optically pure. From phenyl isocyanate and Ia in alkaline solution, the only identified product obtained was diphenylurea. However, excellent results were achieved when instead of the free acid, the ester Ib and aryl isocyanate[2] were used. Method *c)*, performed with ethyl β-*N*-carbonyl-δ-methyl hexanoate (II) also proved to be very successful. With respect to the optical activity of the final products both methods *b)* (only using ester and substituted isocyanate) as well as *c)* proved to be of equal value. However, as observed in the two cases (IIIb, d) the reaction proceeded more smoothly and the purity of products obtained was much higher when method *b)* applied to Ib was used. This could be explained by the fact that the groups to which the NCO moiety was attached (phenyl, naphthyl) increased the reactivity of isocyanate towards nucleophilic attack[21] in a higher degree than the aliphatic group to which NCO was bound in the ester II.

Cyclization of β-ureido esters (IIIa—e), carried out in diluted hydrochloric acid gave high yields of the corresponding dihydrouracils (IVa—e). This fact shows the absence of any appreciable sterical hindrance, even when phenyl respectively naphthyl substituted ureido esters were used. That could also be shown by Stuart models.

Cyclization by sodium ethylate, performed only once (IIIa) resulted in a rather low yield of IVa, but with respect to the optical activity, the method is equally good as the cyclization in hydrochloric acid. The optical rotation data of dihydrouracils obtained are summarized in Table I.

TABLE I

Optical rotation data for dihydrouracils IVa—e

$[\alpha]_D^{22}$

Compound	THF*	Ethanol	Benzene
IVa	—12.3° c, 0.73	insoluble	insoluble
IVb	—15.5° c, 1.49	insoluble	insoluble
IVc	—17.7° c, 1.02	—21.4° c, 1.82	—17.9° c, 1.05
IVd	—12.2° c, 1.03	insoluble	—12.8° c, 0.86
IVe	—11.8° c, 1.28	—24.8° c, 0.56	—2.2° c, 0.89

* tetrahydrofuran

IVa decomposed rapidly in *N* alkaline solution and the rate of its decomposition was followed by the change of optical rotation. From Fig. 1 it could be seen that at room temperature the hydrolysis had been completed within 30 minutes. The optical value obtained after this period was identical

with that of pure β-ureido acid Va and did not change even after allowing the solution to stand for four weeks.

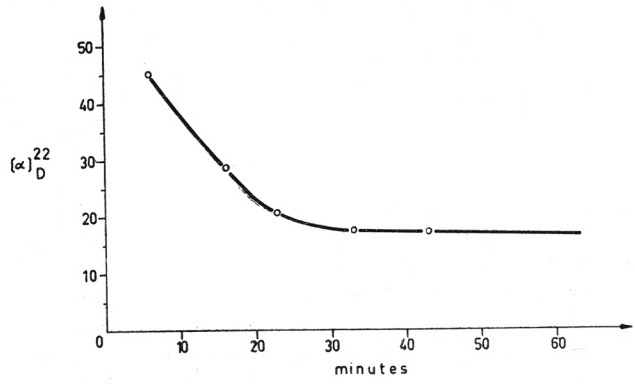


Fig. 1. The rate of hydrolysis of IVa in *N* NaOH at room temperature.

In order to establish whether the ring closure respectively the ring opening had proceeded without loss of optical activity, alkaline and acid hydrolyses were tried. Dihydrouracil IVa when subjected to alkaline hydrolysis gave crystallized β-ureido acid Va, which proved to be optically identical with the acid prepared by hydrolysis of the ester IIIa. When boiled with hydrochloric acid, Va reverted to IVa of unchanged optical rotation. The hydrolysis of IVb and IVc as well as IIIb and IIIc yielded viscous oils. All attempts to bring them to crystallization failed, whereas distillation even at high vacuum, resulted in decomposition. However, when boiled with hydrochloric acid, those oils reverted to IVb respectively IVc without loss of optical activity. Prolonged boiling of IVa in strong hydrochloric acid[22] resulted in partial decomposition of the ring; β-homoleucine (Ia) isolated from the solution proved to be of the same optical activity as the starting Ia. As the configuration of L-β-homoleucine has been already established[23,24], it can be assumed that dihydrouracils IVa—e have also the same configuration.

TABLE II

Infrared absorption band (cm^{-1}) assignment

Compound	N—H stretching frequencies		C=O stretching frequencies		O—H stretching frequencies	
IVa	3200	3120	1695	1740		
IVc	3280	3120	1650	1725		
IVd	3250	3150	1680	1725		
IVe	3270	3118	1650	1730		
Va	3500	3400	1670	1560	1950	2480

The assignments of infrared absorption bands of dihydrouracil derivatives as well as β-ureido acid Va, are given in Table II, and a representative spectrum of each type is shown in Fig. 2. The spectra of all compounds show a peak in the 1650—1695 cm^{-1} region, which has been ascribed to the ureido carbonyl group in the 2-position of the ring, respectively carbonyl group in the β-ureido moiety of the acid. Urea exhibits a C=O stretching band at 1660 cm^{-1} and value for

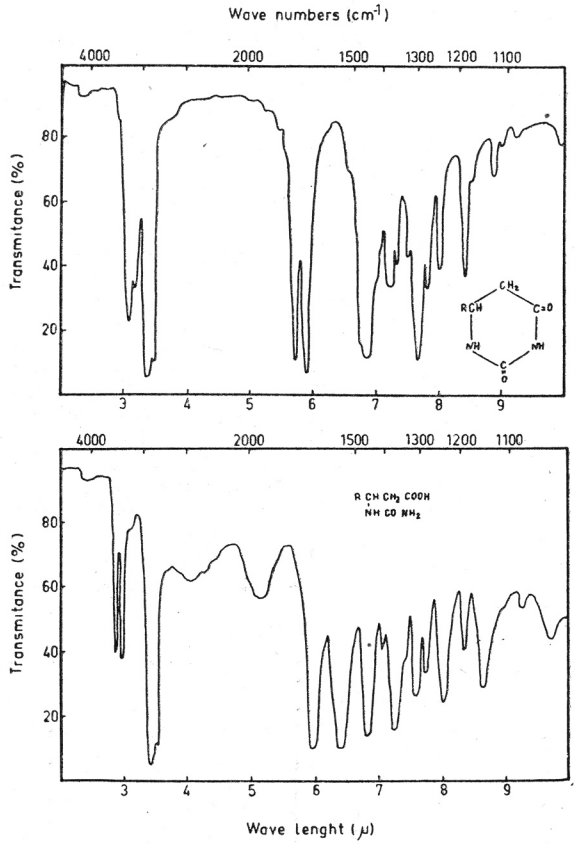


Fig. 2. Infrared absorption spectra in Nujol (Perkin-Elmer Mod. 21 spectrophotometer, NaCl prisms).

dihydrouracil, and dihydrothymine[12] have been reported 1680 cm^{-1} and 1720 cm^{-1}. The peak in the 1722—1750 cm^{-1} region, detectable only in dihydrouracils has been attributed to amide carbonyl in 4-position. The value is somewhat higher than the usual C=O stretching frequency of cyclic secondary amides, but agrees well with the absorption bands reported for dihydrouracil and dihydrothymine[12]. The shift of the second carbonyl band to 1560 cm^{-1} in Va, as well as the appearance of the bands near 2500 cm^{-1} and 1900 cm^{-1} may be considered characteristic of the carboxyl free acetylated amino acids, the simplest representative of which is acetylglycine[25,26].

EXPERIMENTAL

All melting points are uncorrected

Ethyl β-amino-δ-methyl hexanoate (Ib)

In an ice-cooled suspension of L-β-amino-δ-methyl hexanoic acid, (L-β-homoleucine, Ia, 9.5 g., 65.5 mMoles, $[\alpha]_D^{20} + 28^0$, in water) in absolute ethanol (120 ml.) dry hydrogen chloride was introduced for one hour. After standing overnight at room temperature the mixture was evaporated *in vacuo* and the residue dissolved in chloroform (100 ml.). The solution was cooled to 0° and dry ammonia bubbled in. Ammonium chloride was filtered off, chloroform removed and the remaining liquid distilled *in vacuo*. 10.25 g (90.5%) of Ib was obtained as a colourless liquid (b. p. 95—98°/18 mm.) and showed $[\alpha]_D^{22} + 14.7^0 \pm 1$ (c, 4.11 in ethanol). The analytical sample was redistilled at 97—98°/18 mm.

Anal. 11.211 mg. subst.: 25.572 mg. CO_2, 11.157 mg. H_2O
$C_9H_{19}O_2N$ (173.25) calc'd.: C 62.39; H 11.05%
found : C 62.24; H 11.14%

Ethyl β-N-carbonyl-δ-methyl hexanoate (II)

The reaction was performed in a three-necked flask fitted with an air-tight stirrer, a gas inlet tube, and a reflux condenser capped with a $CaCl_2$ tube connected to an empty safety flask and a flask containing toluene to remove any phosgene. 3.77 g. (46 mMoles) of Ib ($[\alpha]_D^{22} + 14.7^0$ in ethanol) was dissolved in absolute toluene (25 ml.) and dry hydrogen chloride passed over the surface of the stirred solution, which was cooled by ice. After half an hour the introduction of hydrogen chloride was interrupted, the flask immersed into an oil bath heated at 130—135° and phosgene dried over conc. sulphuric acid was introduced as a steady stream.[20] The reaction was finished when the evolution of hydrogen chloride ceased (about one hour). Toluene was removed under reduced pressure and the residue distilled *in vacuo*. 3.65 g. (84%) of II as a colourless liquid (b. p. 110—112°/18 mm.) was obtained. $[\alpha]_D^{22} - 6.5^0 \pm 1$ (c, 4.77 in carbontetrachloride) $[\alpha]_D^{23} - 5.9^0 \pm 1$ (c, 2.31 in benzene). For analysis it was redistilled twice (b. p. 112—113°/18 mm.).

Anal. 6.844 mg. subst.: 15.109 mg. CO_2, 5.139 mg. H_2O
$C_{10}H_{17}O_3N$ (199.24) calc'd.: C 60.28; H 8.60%
found : C 60.24; H 8.40%

Ethyl-β-ureido-δ-methyl hexanoate (IIIa)

Into an ice-cooled solution of 778 mg. (3.5 mMoles $[\alpha]_D^{22} - 6.5^0$, in CCl_4) of II in chloroform (10 ml.), dry ammonia was introduced for fifteen minutes. The mixture was evaporated to about one third of its volume and petroleum-ether (b. p. 60—80°) added till turbidity persisted. A viscous oil separated, which crystallized after scratching and cooling at 0° as white needles. Yield: 634 mg. (75%). For analysis it was recrystallized from chloroform-petroleum ether (b. p. 60—80°). M. p. 60.5—63°, $[\alpha]_D^{22} - 32.0^0 \pm 0.5$ (c, 2.06 in ethanol).

Anal. 6.198 mg. subst.: 12.584 mg. CO_2, 5.194 mg. H_2O
$C_{10}H_{20}O_3N_2$ (216.28) calc'd.: C 55.53; H 9.32%
found : C 55.41; H 9.38%

Preparation of substituted β-ureido esters (IIIb—e)

The following general procedure was used: isocyanate (10 mMoles) dissolved in absolute ether (5 ml.) was added dropwise under stirring to an ice-cooled solution of amine (10 mMoles) in absolute ether (5 ml.). After keeping for two hours at room temperature, the solvent was evaporated to about half its volume and petroleum-ether (b. p. 60—80°) added till turbidity persisted. The products were crystallized from chloroform-petroleum ether.

Ethyl β-[3-*(phenyl)-ureido*]-δ-*methyl hexanoate* (IIIb)

From Ib and phenylisocyanate. Yield: 97%, m. p. 87—89°, $[\alpha]_D^{22}$ — 27.3° ± 1 (c, 0.86 in ethanol).

Anal. 6.038 mg. subst.: 14.530 mg. CO_2, 4.429 H_2O
$C_{16}H_{24}O_3N_2$ (292.37) calc'd.: C 65.72; H 8.27%
found : C 65.67; H 8.21%

The same compound, showing $[\alpha]_D^{23}$ — 26.7° ± 1.5 (c, 2.58 in ethanol) was obtained from II and aniline in 88% yield.

Ethyl β-[3-*(benzyl)-ureido*]-δ-*methyl hexanoate* (IIIc)

From II and benzylamine. Yield: 86%, m. p. 50.5—52.5°, $[\alpha]_D^{22}$ — 17.5° ± 1.5 (c, 1.02 in ethanol).

Anal. 6.908 mg. subst.: 16.943 mg. CO_2, 5.419 mg. H_2O
$C_{17}H_{26}O_3N_2$ (306.39) calc'd.: C 66.64; H 8.55%
found : C 66.93; H 8.78%

Ethyl β-[3-(α-*naphthyl)-ureido*]-δ-*methyl hexanoate* (IIId)

From Ib and α-naphthylisocyanate. Yield: 83%, m. p. 84—87.5°, $[\alpha]_D^{22}$ — 20.6° ± 1 (c, 1.69 in ethanol).

Anal. 5.843 mg. subst.: 15.075 mg. CO_2, 4.130 mg. H_2O
$C_{20}H_{26}O_3N_2$ (342.42) calc'd.: C 70.15; H 7.65%
found : C 70.41; H 7.91%

The same compound, showing $[\alpha]_D^{21}$ — 19.1° ± 1.5 (c, 1.42 in ethanol) was obtained from II and α-naphthylamine in 61% yield.

Ethyl β-[3-(n-*butyl)-ureido*]-δ-*methyl hexanoate* (IIIe)

Obtained as a colourless viscous oil from II and *n*-butylamine. Yield: 94%, b. p. 152—155°/0.004 mm., $[\alpha]_D^{22}$ — 24.9° ± 1 (c, 0.88 in ethanol).

Anal. 6.584 mg. subst.: 14.923 mg. CO_2, 5.969 mg. H_2O
$C_{14}H_{28}O_3N_2$ (272.38) calc'd.: C 61.73; H 10.36%
found : C 61.85; H 10.14%

Cyclization of β-*ureido esters into the corresponding 5,6-dihydrouracils*

A. By diluted hydrochloric acid. — The following general procedure was used: β-ureido ester (2—3 mMoles) and hydrochloric acid (1:1, by vol.) were boiled for two hours. During this time, excepting in the case of IVa, crystals of dihydrouracils began to separate. The cooled mixture was filtered and the precipitate washed with cold water. For analysis IVa was recrystallized from water and IVb—e from ethanol-water (1:1, by vol.).

6-iso-*butyl-5,6-dihydrouracil* (IVa)

The solution was evaporated to dryness and the residue treated as described above.

Yield: 64%, m. p. 215—217°.

Anal. 7.225 mg. subst.: 15.008 mg. CO_2, 5.389 mg. H_2O
4.211 mg. subst.: 0.615 ml. N_2 (20°, 751 mm.)
$C_8H_{14}N_2O_2$ (170.21) calc'd.: C 56.45; H 8.29; N 16.46%
found : C 56.68; H 8.35; N 16.48%

*3-phenyl-6-*iso-*butyl-5,6-dihydrouracil* (IVb)

Yield: 79%, m. p. 205—207°.

Anal. 6.433 mg. subst.: 16.146 mg. CO_2, 4.274 mg. H_2O
$C_{14}H_{18}N_2O_2$ (246.30) calc'd.: C 68.27; H 7.36%
found : C 68.49; H 7.43%

3-benzyl-6-iso-butyl-5,6-dihydrouracil (IVc)

Yield: 81%, m. p. 113—114°

Anal. 6.510 mg. subst.: 16.572 mg. CO_2, 4.523 mg. H_2O
4.301 mg. subst.: 0.420 ml. N_2 (23°, 760 mm.)
$C_{15}H_{20}N_2O_2$ (260.33) calc'd.: C 69.20; H 7.74; N 10.76%
found: C 69.47; H 7.78; N 11.02%

3-(α-naphthyl)-6-iso-butyl-5,6-dihydrouracil (IVd)

Yield: 55%, m. p. 185—187°

Anal. 7.411 mg. subst.: 19.864 mg. CO_2, 4.648 mg. H_2O
4.770 mg. subst.: 0.410 ml. N_2 (21°, 750 mm.)
$C_{18}H_{22}N_2O_2$ (296.36) calc'd.: C 72.95; H 6.80; N 9.45%
found: C 73.14; H 7.02; N 9.66%

3-(n-butyl)-6-iso-butyl-5,6-dihydrouracil (IVe)

Yield: 83%, m. p. 119—121°.

Anal. 6.577 mg. subst.: 15.421 mg. CO_2, 5.740 mg. H_2O
$C_{12}H_{22}N_2O_2$ (226.31) calc'd.: C 63.68; H 9.80%
found: C 63.98; H 9.77%

B. By sodium ethylate. — Sodium (50 mg.) was refluxed with absolute ethanol (2 ml.) and after all the metal had reacted, IIIa (322 mg., 1.5 mMoles) dissolved in absolute ethanol (2 ml.) was added. The mixture was maintained at 80° for eight hours, and then allowed to stand overnight at room temperature. The mixture was saturated with carbon dioxide, ethanol evaporated *in vacuo*, and ice-cooled water (10 ml.) added to the residue. The suspension was boiled, treated with charcoal and filtered. 89 mg (35%) of IVa as white needles separated, m. p. 213—217°. Mixed m. p. and optical rotation value, $[\alpha]_D^{21} = -11.9° \pm 1.5$ (c, 0.72 in THF), showed the substance to be identical with the compound obtained from IIIa and hydrochloric acid as the condensation agent.

β-ureido-δ-methyl hexanoic acid (Va)

A. By alkaline hydrolysis of IVa. — 400 mg. (2.4 mMoles) of IVa was suspended in water (10 ml.) and *N* sodium hydroxide (4 ml.) added whereupon the compound dissolved completely in a few minutes. The solution was allowed to stand at room temperature for four hours and then was passed through a column (25×1 cm) of Dowex 50—X8. The column was washed with water (50 ml.) and the combined effluents evaporated to dryness *in vacuo:* 367 mg. (83%) of Va was obtained. For analysis it was recrystallized twice from aceton-chloroform, m. p. 125—127°; $[\alpha]_D^{23} = -35.0° \pm 2$ (c, 1.80 in water), $[\alpha]_D^{23} = -16.0° \pm 1$ (c, 0.91 in *N* NaOH). Descending paper chromatography carried out on Whatman No 1. filter paper, with *n*-butanol-acetic acid-water (4:1:5) as solvent system gave a red-brown spot with *p*-benzoquinone, and a yellow spot with *p*-dimethylaminobenzaldehyde, having $R_f = 0.82$.

Anal. 9.165 mg. subst.: 17.120 mg. CO_2, 6.991 mg. H_2O
$C_8H_{16}N_2O_3$ (188.22) calc'd.: C 51.05; H 8.57%
found: C 50.97; H 8.54%

B. By alkaline hydrolysis of IIIa. — From IIIa (500 mg., 2.3 mMoles, $[\alpha]_D^{22} = -30.4°$ in ethanol) treated as described for IVa, 169 mg. (39%) of the free acid was obtained, which proved by its m. p., R_f value and optical rotation data, $[\alpha]_D^{24} = -35.3° \pm 1.5$ (c, 1.80 in water), to be identical with Va.

Ring closure of Va

The β-ureido acid Va (100 mg., 5.3 mMoles) was boiled in hydrochloric acid (1:1 by vol., 5 ml.) for one hour. The solvent was evaporated to dryness and the residue crystallized from water. 52 mg. (58%) of white needles separated m. p. 214—217°, showing no depression with original IVa, $[\alpha]_D^{22} = -12.7° \pm 1$ (c, 0.74 in THF).

Alkaline hydrolysis and recyclization of IVb and IVc

The same procedures as described for hydrolysis of IVa were followed. IVb and IVc are water and alkaline insoluble, but after shaking in *N* NaOH for several hours the compounds dissolved, yielding the corresponding β-ureido acids (Vb, Vc). Recyclization of Vb yielded IVb showing $[\alpha]_D^{22}$ $-16.0^0 \pm 1$ (c, 0.78 in THF) and Vc yielded IVc with $[\alpha]_D^{22}$ $-20.9^0 \pm 1$ (c, 1.53 in ethanol).

Acid hydrolysis of IVa

150 mg. (0.79 mMoles) of IVa ($[\alpha]_D^{22}$ -12^0, in THF) was boiled in hydrochloric acid (1:1, 5 ml.) for 48 hours. After cooling, crystals of unchanged IVa were filtered off, and the mother liquor passed through a column of Amberlite IR 4-B. The effluent was evaporated to dryness *in vacuo* and the residue recrystallized from ethanol-ether. 23 mg. (20%) of white crystals giving no depression with L-β-homoleucine (Ia) were obtained. $[\alpha]_D^{23}$ $+ 26.2^0 \pm 1.5$ (c, 0.62 in water).

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IZVOD

Sinteza nekih optički aktivnih 5,6-dihidrouracila

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U položaju 6 optički aktivni 5,6-dihidrouracili (IVa—e) priređeni su iz L-β-amino-δ-metil heksanske kiseline (L-β-homoleucin, Ia) preko odgovarajućih ureido estera (IIIa—e). Kako bi bili pronađeni najbolji uvjeti za zadržavanje optičkog aktiviteta, ispitivano je nekoliko načina priređivanja tih spojeva. Optička čistoća dobivenih dihidrouracila dokazana je na dva načina: a) alkalnom hidrolizom prevedeni su IVa—c u β-ureido kiseline Va—c, koje su zatim ciklizacijom dale dihidrouracile s nepromijenjenim skretanjem; b) kiselom hidrolizom IVa dobiven je β-homoleucin (Ia) nepromijenjenog skretanja.

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ZAGREB

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