SOME 2-SUBSTITUTED DERIVATIVES OF 5-(2-AMINO-6-HYDROXY-4-OXO-3,4-DIHYDRO-5-PYRIMIDINYL)-PENTANOIC ACID*

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On condensation of 6-substituted trialkyl esters of 2-carboxy-1,7-heptanedioic acids *XIII*—*XXIII* with guanidine and subsequent saponification 2-substituted 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acids *II*—*XII* were prepared. From the pharmacological point of view some of the substances prepared had a potentiating effect on the antileukemia effect of 5-fluorouracil in mice and the antineoplastic effect manifested by a diminution of the tumours in animals with experimental tumours.

This study is a continuation of an investigation of the antimetabolites of purine and pyrimidine bases of nucleic acids. Its subject is the synthesis of 2-substituted 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acids *II*–*XII* which were prepared within the frame of the study of derivatives of 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic[1] acid (*I*, R^2 = H) (DAMVAR) which possessed an important antineoplastic effect.

Compounds *II*–*XII* were synthetized using the procedure described for the preparation of 5-substituted derivatives of barbituric acid, thiobarbituric acid and iminobarbituric acid[2–4], *i.e.* on condensation of trialkyl esters of 6-substituted 2-carboxy-1,7-heptanedioic acids *XIII*–*XXIII* with guanidine in methanol, in the presence of sodium methoxide. The alkyl esters of the acids *II*–*XII* formed were saponified with sodium hydroxide to free acids without isolation. However, in comparison with acid *I* the hydrolysis of these esters took place more slowly, probably in consequence of the steric hindrance by the alkyl group in the position 2 to the carboxyl, which is especially distinct in the cyclohexyl derivative *VII*.

Trialkyl esters of 6-substituted 2-carboxy-1,7-heptanedioic acids *XIII*–*XVII* and *XIX*–*XXII* were prepared in the described manner[5–15], *i.e.* by alkylation of diethyl ester of 1,3-propanedioic acid with 2-substituted ethyl 5-bromopentanoate in ethanol in the presence of sodium ethoxide. Ester *XVIII* was prepared by catalytic hydrogena-

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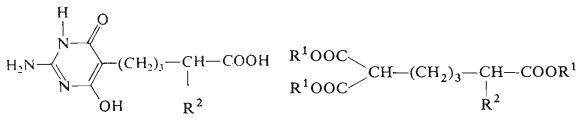

II–XII *XIII–XXIII*

II, *XIII*; R^2 = methyl
III, *XIV*; R^2 = ethyl
IV, *XV*; R^2 = propyl
V, *XVI*; R^2 = butyl
VI, *XVII*; R^2 = pentyl
VII, *XVIII*; R^2 = cyclohexyl
VIII, *XIX*; R^2 = phenyl
IX, *XX*; R^2 = 3,4-dichlorophenyl
X, *XXI*; R^2 = 1-naphthyl
XI, *XXII*; R^2 = 2-thienyl
XII; R^2 = hydroxy
XXIII; R^2 = acetoxy

R^1 = ethyl with the exception of *XXIII*, where R^1 = methyl

tion of ester *XIX*. Trimethyl ester *XXIII* was prepared on alkylation of dimethyl ester of 1,3-propanedioic acid with the methyl ester of 2-acetoxy-5-bromopentanoic acid in dimethylformamide under catalysis with sodium hydride. Among the 2-substituted alkyl 5-bromopentanoates needed methyl 2-acetoxy-5-bromopentanoate[16], ethyl 2-methyl-5-bromopentanoate[17] and ethyl 2-ethyl-5-bromopentanoate[18] are known; other esters were prepared by esterification of crude 2-substituted 5-bromopentanoic acids obtained on addition of gaseous hydrogen bromide to 2-substituted 4-pentenoic acid dissolved in hexane, in presence of dibenzoyl peroxide[17,19]. 2-Substituted 4-pentenoic acids were prepared using a procedure described in literature[20,21], *i.e.* on hydrolysis and decarboxylation of diethyl esters of 2-substituted 2-allyl-1,3-propanedioic acids. Diethyl esters of 2-(3,4-dichlorophenyl)-, 2-(1-naphthyl)- and 2-(2-thienyl)-2-allyl-1,3-propanedioic acids were prepared analogously[22] as in the preparation of diethyl 2-(3,4-dichlorophenyl)-2-ethyl-1,3-propanedioate.

The compounds of type *I* can occur in various tautomeric forms; on the basis of the similarity of the IR and the UV spectra of the compounds prepared with the spectra of *I* we assume that compounds *II–XII* have the structure of 2-substituted 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acids, while in solid state they are probably present in the form of corresponding internal salts. The results of the potentiometric titration (in 80% methylcellosolve) agree with these assumptions. The titration showed two pK_a constants for the substances titrated (one for the proton of the carboxyl group and the other for the proton of the hydroxyl group) and the substances displayed high melting points, an indication that they have the character of salts.

As regards the biological effect of the substances studied, acid *V* had a potentiating effect on the effect of 5-fluorouracil, tested on leukemia La; in a dose of 150 to 250 mg/kg *s.c.* it potentiated the effect of 5-fluorouracil (administered in a 75 mg/kg

dose) by 50%. Acid *VIII* (in a 200 mg/kg dose, *s.c.*) increased the effect by 30% and acid *II* (in a 250 mg/kg dose, *s.c.*) also by 30%. Other acids potentiated the effect of 5-fluorouracil in the dose range from 50 to 300 mg/kg, *s.c.* by 10 to 25%. During the screening of the substances for their antineoplastic effect in animals with experimental tumours, within the 100 to 200 mg/kg dose range and *p.o.* application, acids *II*–*XII* had practically the same effect on the size of the tumour S 37, Kr 2 and S 180 as substance *I*, ranging from a 10 to 40% decrease in the tumour size. The substances tested were practically non-toxic.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. The samples for analysis were dried in a vacuum at 27 Pa over P_2O_5 at a temperature elevated proportionally to their melting point. The ultraviolet spectra of the substances prepared were measured on a Unicam SP 8000 spectrophotometer at 0·001% concentration in 0·1M-HCl in 50% methanol (medium A), or 0·1M-NaOH in 50% methanol (medium B). The infrared spectra were recorded in KBr pellets using a Hilger Watts instrument. The pK_a values were determined in 80% aqueous dimethyl sulfoxide. The ^{1}H-NMR spectrum was measured on a Tesla BSC 487 (80 MHz) spectrometer at about 10% concentration in hexadeuteriodimethyl sulfoxide, using sodium 3-(trimethylsilyl) (2,2,4,4-$^2H_4$)propanoate as internal reference; the values are given in ppm, δ-scale. The purity of the substances was checked by thin-layer chromatography in chloroform–methanol–25% ammonia (2 : 2 : 1) or propanol–25% ammonia–water (7 : 1 : 2), using FP-Kieselgel F_{254} Merck, solvent front distance 15 cm. Detection was carried out in ultraviolet light or on reflexing silica gel foils with a luminescent indicator (Silufol UV_{254}, Kavalier).

Triethyl Ester of 2-Carboxy-6-cyclohexyl-1,7-heptanedioic Acid (*XVIII*)

Platinum oxide (0·1 g) according to Adams was added to a solution of 5·00 g (0·013 mol) of triethyl ester of 2-carboxy-6-phenyl-1,7-heptanedioic acid in 50 ml of acetic acid and the mixture was hydrogenated at 120°C and 15 MPa pressure for 12 h. The catalyst was filtered off and the solvent evaporated. A solution of the crude product in ether was washed with a 1M-$NaHCO_3$ solution and water, the solvent was evaporated and the remaining triester was distilled under reduced pressure. Yield 2·7 g of a liquid boiling at 135 to 138°C at 27 Pa, n_D^{20} 1·4590. UV spectrum (in methanol): λ_{max} 216·5 nm, $\log \varepsilon$ 2·8. For $C_{20}H_{34}O_6$ (370·5) calculated: 64·84% C, 9·25% H; found: 65·22% C, 9·14% H.

Trimethyl Ester of 2-Carboxy-6-acetoxy-1,7-heptanedioic Acid (*XXIII*)

Dimethyl 1,3-propanedioate (6·66 g; 0·05 mol) was added dropwise to a suspension of 1·32 g (0·055 mol) of sodium hydride in 50 ml of dimethylformamide and the mixture was stirred at room temperature for 1 h. 12·65 g (0·05 mol) of methyl 2-acetoxy-5-bromopentanoate were added dropwise to the mixture which was heated at 120°C and under stirring for 5 h. After evaporation of dimethylformamide in a vacuum water was added, the organic fraction was extracted with ether and the extract dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by vacuum distillation. The fraction boiling at 153—156°C/27 Pa was collected (*XXIII*). For $C_{13}H_{20}O_8$ (304·3) calculated: 51·31% C, 6·62% H; found: 51·51% C, 6·72% H.

TABLE I

2-Substituted 5-(2-Amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl) pentanoic Acids

Number	M.p., °C (yield, %)	Formula (mol. mass)	Calculated/Found			UV spectra max in nm (log ε) medium	
			% C	% H	% N	A	B
II[a,b,c]	285—287[d] (62)	$C_{10}H_{15}N_3O_4$ (241·2)	49·78 49·65	6·26 6·51	17·42 17·63	267·5 (4·210)	270·5 (4·124)
III[b,e,f]	270—272[d] (66)	$C_{11}H_{17}N_3O_4$ (255·2)	51·75 51·59	6·71 6·86	16·46 16·66	266·5 (4·214)	270 (4·130)
IV[b,g,h]	262—264[d] (71)	$C_{12}H_{19}N_3O_4$ (269·3)	53·52 53·41	7·11 7·45	15·60 15·88	267 (4·218)	270 (4·140)
V[b,i,j]	266—268[d] (79)	$C_{13}H_{21}N_3O_4$ (283·3)	55·11 54·88	7·47 7·59	14·83 14·94	266·5 (4·203)	269 (4·150)
VI[k,l]	265—267[m] (88)	$C_{14}H_{23}N_3O_4$ (297·3)	56·55 56·10	7·80 7·80	14·13 14·06	267 (4·180)	271 (4·154)
VII[n]	288—290[o] (80)	$C_{15}H_{23}N_3O_4$ (309·3)	58·23 58·21	7·50 7·80	13·59 13·52	265 (4·275)	268 (4·185)
VIII[b,p,q]	300—302[d] (85)	$C_{15}H_{17}N_3O_4$ (303·3)	59·40 59·13	5·66 5·85	13·85 13·80	267·5 (4·255)	278·5 (4·188)
IX[r,s]	282—284[d] (77)	$C_{15}H_{15}Cl_2N_3O_4$ (372·2)	48·40 47·95	4·06 3·91	11·29 11·29	265 (4·179) 220i (4·150)	269 (4·182) 225i (4·202)
X[t,u]	259—261[d] (93)	$C_{19}H_{19}N_3O_4$ (353·3)	64·58 64·66	5·42 5·32	11·89 11·68	269 (4·076) 224 (4·776)	272 (4·143) 225 (4·762)
XI[v,w]	290—292[d] (76)	$C_{13}H_{15}N_3O_4S$ (309·3)	50·47 50·08	4·89 4·95	13·58 13·74	271 (4·161) 238 (4·152)	269 (4·136) 238 (4·130)
XII[x,y]	255—257[z] (74)	$C_9H_{13}N_3O_5$ (243·2)	44·44 44·20	5·39 5·51	17·27 17·65	265 (4·046)	270 (4·056)

TABLE I
(*Continued*)

[a] Intermediate *XIII* was prepared analogously as in ref.[15], b.p. 190—192°C/2·5 kPa; $C_{15}H_{26}O_6$ (302·3) calculated: 58·58% C, 8·67% H; found: 59·83% C, 8·73% H. [b] IR spectrum: Similar to the spectrum of compound *I*: 3 200 (NH, OH, NH_2), 1 715 (carboxyl), 1 690 (amide carbonyl), 1 652, 1 630 or 1 580, 1 555 (—C=N—, —C=C— conjugated and keto-enol structure). [c] pK_{a1} = = 9·03, pK_{a2} = 10·28. [d] The substance was crystallized from aqueous ethanol. [e] Intermediate *XIV* was prepared analogously as in ref.[15], b.p. 130—132°C/40 Pa; $C_{16}H_{28}O_6$ (316·4) calculated: 60·73% C, 8·92% H; found: 60·52% C, 8·78% H. [f] pK_{a1} = 9·00, pK_{a2} = 10·15. [g] Intermediates: diethyl 2-propyl-2-allyl-1,3-propanedioate was prepared analogously as in ref.[20], b.p. 169—171°C/8·8 kPa; for $C_{13}H_{22}O_4$ (242·3) calculated: 64·43% C, 9·15% H; found: 64·42%C, 9·25% H. 2-Propyl-4-pentenoic acid was prepared analogously as in ref.[20] and converted, without previous purification, to ethyl 2-propyl-5-bromopentanoic acid according to ref.[17], b.p. 130 to 132°C/2·8 kPa; $C_{10}H_{19}BrO_2$ calculated: 47·82% C, 7·62% H, 31·82% Br; found: 47·56% C, 7·40% H, 32·03% Br. Triethyl ester *XV* was prepared analogously as in ref.[15], b.p. 128—130°C/ /40 Pa; $C_{17}H_{30}O_6$ (330·4) calculated: 61·79% C, 9·15% H; found: 61·96% C, 9·19% H. [h] pK_{a1} = 9·05, pK_{a2} = 10·25. [i] Intermediates: Diethyl 2-butyl-2-allyl-1,3-propanedioate, prepared analogously as in ref.[20], b.p. 138—139°C/2·7 kPa; for $C_{14}H_{24}O_4$ (256·3) calculated: 65·59% C, 9·44% H; found: 65·90% C, 9·67% H. 2-Butyl-4-pentenoic acid was prepared analogously as in ref.[20] and converted without previous purification to ethyl 2-butyl-5-bromopentanoate as in ref.[17] b.p. 105—107°C/66 Pa; $C_{11}H_{21}BrO_2$ (265·2) calculated: 49·81% C, 7·98% H, 30·14% Br; found: 49·49% C, 7·71% H, 30·37% Br. Triethyl ester *XVI* was prepared analogously as in ref.[15], m.p. 174—176°C/66 Pa; $C_{18}H_{32}O_6$ (344·4) calculated: 62·76% C, 9·37% H; found: 63·09% C, 9·74% H. [j] pK_{a1} = 9·25, pK_{a2} = 10·35. [k] IR spectrum: 1 700, 2 700 (broad band: carboxyl), 1 570 (COO^-), 1 635 (lactam), 3 170 (NH_3), 3 390 (NH). [l] Intermediates: Diethyl 2-pentyl-2-allyl-1,3-propanedioate, prepared analogously as in ref.[20], b.p. 136—138°C/1·2 kPa; analysed by gas chromatography; 2-pentyl-4-pentenoic acid was prepared as in ref.[20] and converted to ethyl 2-pentyl-5-bromopentanoate according to[17] (b.p. 113—116°C/266 Pa; for $C_{12}H_{23}BrO_2$ (279·2) calculated: 51·62% C, 8·30% H, 28·62% Br; found: 51·81% C, 8·45% H, 28·23% Br; triethyl ester *XVII* was prepared analogously as in ref.[15], b.p. 183—185°C/53 Pa; $C_{19}H_{34}O_6$ (358·4) calculated: 63·66% C, 9·56% H; found: 63·31% C, 9·75% H. [m] The substance was crystallized from ethanol. [n] IR spectrum: 1 685 (carboxyl), 1 650, 1 540 (sec. amide), 1 620 (prim. amine), 3 380, 3 080 (NH, NH_2). [o] The substance was purified by dissolution in dilute ammonia (1 : 100) and precipitation with dilute hydrochloric acid (1 : 1) at pH about 3. [p] Intermediates: Ethyl 2-phenyl-5-bromopentanoate was prepared by esterification of 2-phenyl-5-bromopentanoic acid[19], b.p. 175—180°C/2·7 kPa; for $C_{13}H_{17}BrO_2$ (285·2) calculated: 54·75% C, 6·01% H, 28·02% Br; found: 54·54% C, 6·16% H, 27·96% Br. Triethyl ester *XIX* was prepared analogously as in ref.[15], b.p. 203—207°C/53 Pa; for $C_{20}H_{28}O_6$ (364·4) calculated: 65·91% C, 7·74% H; found: 66·34% C, 8·18% H. [q] pK_{a1} = 8·50, pK_{a2} = 10·18. [r] Calculated: 19·05% Cl, found 18·92% Cl; IR spectrum: 1 700, 2 720 (broad band; carboxyl), 3 120 broad band (NH), 1 620 (lactam), 1 550 (benzene ring), 828, 880 (1,2,4-substituted benzene). [s] Intermediates: Diethyl 2-(3,4-dichlorophenyl)-2-allyl-1,3-propanedioate, prepared analogously as in ref.[22], b.p. 160 to 166°C/66 to 93 Pa; $C_{16}H_{18}Cl_2O_4$ calculated: 55·66% C, 5·26% H, 20·54% Cl; found: 55·81% C, 5·17% H, 20·64% Cl; refractive index n_D^{20} 1·5200. 2-(3,4-Dichlorophenyl)-4-pentenoic acid was prepared analogously as in ref.[21], b.p. 208—210°C/27 to 40 Pa; $C_{11}H_{10}Cl_2O_2$ (245·1) calculated: 53·90% C, 4·11% H, 28·93% Cl; found: 54·32% C, 4·32% H, 28·91% Cl; refractive index n_D^{20} 1·5571; 2-(3,4-dichlorophenyl)-5-bromopentanoic acid was prepared analogously as in ref.[19], m.p. 111—113° (cyclohexane–hexane); $C_{11}H_{11}BrCl_2O_2$ (326·0) calculated: 40·52% C,

TABLE I
(*Continued*)

3·40% H, 24·51% Br, 21·75% Cl; found: 40·57% C, 3·40% H, 24·49% Br, 21·72% Cl. Ethyl 2-(3,4-dichloro)phenyl-5-bromopentanoate was purified by column chromatography on silica gel, elution with chloroform; $C_{13}H_{15}BrCl_2O_2$ (354·1) calculated: 44·10% C, 4·27% H, 22·57% Br, 20·03% Cl; found: 44·38% C, 4·32% H, 22·35% Br, 19·89% Cl; refractive index n_D^{20} 1·5457; triethyl ester *XX* was prepared analogously as in ref.[15] in the form of an oil. It was purified by column chromatography on silica gel, elution with chloroform; for $C_{20}H_{26}Cl_2O_6$ (433·3) calculated: 55·43% C, 6·05% H, 16·36% Cl; found: 55·65% C, 6·15% H, 16·38% Cl. [t] IR spectrum: 1 710, 2 760 (broad band: carboxyl), 1 650 (lactam), 3 390, 3 200 (NH), 3 520 (OH), 1 615, 1 550 (double bonds). [u] Intermediates: Diethyl 2-(1-naphthyl)-2-allyl-1,3-propanedioate, prepared analogously as in ref.[22], b.p. 170—175°C/53 Pa; m.p. 48—50°C (hexane); $C_{20}H_{22}O_4$ (326·4) calculated: 73·60% C, 6·79% H; found: 73·50% C, 6·88% H; IR spectrum: 1 750, 1 730 (ester), 1 518, 1 580, 1 605 (naphthalene), 1 640 (C=C); UV spectrum: λ_{max} 292, 282, 271, 223, log ε 3·800, 3·938, 3·864, 4·879 (in methanol). 2-(1-Naphthyl)-4-pentenoic acid was prepared according to ref.[21], b.p. 172—177°C/27 Pa, m.p. 79—81°C (cyclohexane); $C_{15}H_{14}O_2$ (226·3) calculated: 79·62% C, 6·24% H; found: 79·38% C, 6·14% H; IR spectrum: 1 710, 2 660 (broad band: carboxyl), 1 570, 1 600 (naphthalene), 1 640 (C=C); UV spectrum: λ_{max} (log ε), medium A: 292 (3·770), 282 (3·912), 272 (3·829), 217 (4·880); medium B: 292 i (3·776), 283 (3·912), 271 (3·844), 224 (4·597). 2-(1-naphthyl)-5-bromopentanoic acid was prepared analogously as in ref.[19], m.p. 105—107°C (cyclohexane); $C_{15}H_{15}BrO_2$ (307·2) calculated: 58·65% C, 4·92% H, 26·01% Br; found: 58·69% C, 4·72% H, 26·08% Br; IR spectrum: 1 700, 2 720 (broad band; carboxyl), 1 520, 1 570, 1 600 (naphthalene), 680 (Br); UV spectrum: λ_{max} (log ε), medium A: 294 i (3·783), 284 (3·922), 273 (3·858), 225 (4·982); medium B: 295 i (3·783), 284 (3·942), 273 (3·862), 226 (3·906). Ethyl 2-(1-naphthyl)-5-bromopentanoate, oil, purified by column chromatography on silica gel, elution with chloroform; $C_{17}H_{19}BrO_2$ (335·2) calculated: 60·91% C, 5·71% H, 23·84% Br; found: 61·23% C, 5·77% H, 23·57% Br. Triethyl ester *XXI*, oil, prepared analogously as in ref.[15], purified by column chromatography on silica gel, elution with chloroform; for $C_{24}H_{30}O_6$ (414·5) calculated: 69·54% C, 7·30% H; found: 70·21% C, 7·36% H. [v] Calculated: 10·37% S; found: 10·35% S; IR spectrum: 1 690, 2 740 (broad band: carboxyl), 1 610, 1 380, 1 475 (thiophene), 1 630 (lactam), 3 340, 3 160 (NH), 1 550 (double bonds). [w] Intermediates: 2-(2-thienyl)-4-pentenoic acid was prepared analogously as in ref.[21], b.p. 170°C/1·7 kPa; $C_9H_{10}O_2S$ (182·2) calculated: 59·32% C, 5·53% H, 17·59% S; found: 59·63% C, 5·67% H, 17·26% S. 2-(2-Thienyl)-5-bromopentanoic acid was prepared as in ref.[21] and converted to ethyl 2-(2-thienyl)-5-bromopentanoate without previous purification, b.p. 188—190°C/2·7 kPa; $C_{11}H_{15}BrO_2S$ (291·2) calculated: 45·37% C, 5·19% H, 27·44% Br, 11·01% S; found: 44·68% C, 4·97% H, 27·69% Br, 10·93% S. Triethyl ester *XXII* was prepared analogously as in ref.[15], b.p. 170—180°/53 Pa; $C_{18}H_{26}O_6S$ (370·5) calculated: 58·36% C, 7·07% H, 8·66% S; found: 58·48% C, 6·79% H, 8·88% S. [x] IR spectrum: 2940, 2820 (CH_2), 3 000—2 500 broad band (COOH, OH), 1 700 (COOH), 3 600—2 500 overlapped (NH_2, NH), 1 540, 1 650 (amide bands). [y] $pK_{a1} = 7{\cdot}55$, $pK_{a2} = 10{\cdot}05$. [z] The substance was crystallized from water.

5-(2-Amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)-2-butylpentanoic Acid (*V*)

Guanidine hydrochloride (7·64 g; 0·08 mol) was added to a solution of 2·76 g (0·12 mol) of sodium in 40 ml of methanol and the suspension was stirred for 10 min. Triethyl ester of 2-carboxy-

-6-butyl-1,7-heptanedioic acid (*XVI*) (13·78 g; 0·04 mol) was added and the mixture was stirred at room temperature for 4 h. After distillation off of methanol under reduced pressure (water-pump) the residue was triturated with 80 ml of 0·5M-NaOH and stirred at room temperature for 2 h. After standing overnight and short boiling the solution was acidified with hydrochloric acid (1 : 1) to pH 2 and the product separated was filtered off under suction and purified. Yield 8·91 g of acid *V*. Using corresponding trialkyl esters acids *II*—*IV*, *VI* and *VIII*—*XII* were prepared in the same manner (Table I).

5-(2-Amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)-2-cyclohexylpentanoic Acid (*VII*)

Using the procedure described for acid *V* triethyl ester *XVIII* (2·1 g, 5·67 mmol) was reacted with guanidine hydrochloride (1·08 g; 11·34 mmol) and sodium methylate (prepared from 0·39 g, 17 mmol of sodium and 15 ml methanol) to give crude reaction product (2·17 g of a compound with 23% of solvent of crystallization, yield 95%) which was purified by dissolution in 0·5M-NaOH (22·5 ml) under heating and precipitation of the product with dilute hydrochloric acid (1 : 1) to pH 3. Yield, 1·84 g of ethyl 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)-2-cyclohexylpentanoate, containing 23% of solvent of crystallization. This could be eliminated by heating at 120°C/27 Pa, m.p. 260—262°C (under decomposition). For $C_{17}H_{27}N_3O_4$ (337·4) calculated: 60·51% C, 8·07% H, 12·45% N; found: 60·23% C, 8·13% H, 12·40% N. UV spectrum: in medium A λ_{max} 267 nm (log ε 4·259), in medium B λ_{max} 271 nm (log ε 4·204). IR spectrum (KBr pellet): 1 670, 1 560 (sec. amide), 1 620 (prim. amine), 3 150 (NH, NH_2), 1 730 (ester,) 2 700 cm^{-1} broad band, OH). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): 4·00 (2 H, m; $COOCH_2CH_3$, J = 7·0 Hz), 1·25 ppm (3 H, t; $COOCH_2CH_3$, J = 7·0 Hz).

A solution of ethyl ester free of solvent (1·15 g, 3·4 mmol) in 1M-NaOH (21 ml) was refluxed for 3 h. The mixture was acidified with hydrochloric acid (1 : 1) while hot, to pH 3, and the crude acid *VII* which separated was filtered off after cooling. The purification and the physico-chemical properties of the substances are given in Table I.

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