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

Jiří KŘEPELKA, Jan BENEŠ, Vladimír POUZAR**, Jaroslav VACHEK and Jiří HOLUBEK

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

Received November 25th, 1981

Condensation of triethyl ester of 1,1,5-pentanetricarboxylic acid (*XXI*) with substituted guanidines *XXII*—*XXIX* gave acids *II*—*IX*, which were converted into esters *XI*—*XIX*. The acid *II* and the ester *XI* were obtained as mixtures of positional isomers. Analogously, condensation of the triester *XXI* with dicyanodiamide gave rise to acid *X*, whose nitrile group, under conditions of esterification of a carboxyl group, produced iminoether *XX*. In pharmacological tests for antineopastic activity the compounds prepared exhibited weaker efficacy than 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acid (*I*), employed as standard.

Studying antimetabolites of the pyrimidine bases of nucleic acids, we previously described synthesis and biological properties of 5-substitution derivatives of pyridimidine having an amino, hydroxy or mercapto group at the 2-position of the pyrimidine skeleton[1-5]. From the viewpoint of biological activity the most interesting compound was 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acid (*I*), which, under the name Damvar, has passed into the stage of pre-clinical and clinical tests[1]. Our preceding communications have shown that the biological activity of pyrimidine derivatives of the type of barbituric acids is very markedly dependent on the nature of substituents at the positions 2, 4, 5 and 6 (refs[1-6]), tautomerisable hydroxy or oxo groups at the 4 and 6 positions being a prerequisite for biological activity. Their replacement by other substituents, *e.g.* by amino groups, brings about loss of the activity[6]. Another prerequisite for biological activity[1,2,4] is the presence of an amino group at the 2-position and an ω-carboxyalkyl or ω-(4-carboxyphenyl)-alkyl residue at the 5-position. The presence of an amino group and a carboxyl group in the molecule transforms these substances into unnatural amino acids and profoundly modifies their physico-chemical and biological properties. Acylation of the amino group at the 2-position causes loss of biological activity[1], probably due to suppression of a basic centre in the molecule by the formation of an amide group.

* Part LXXXV in the series Substances with Antineoplastic Activity; Part LXXXIV: This Journal *48*, 299 (1983).

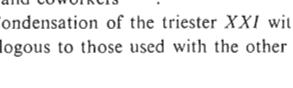
** Present address: Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6.

To get a better knowledge of the effect of substitution at the 2-position on the biological activity of pyrimidine derivatives we have now synthetized compounds with substituents attached to the amino group at the 2-position (*II*–*XX*, Table I). These were prepared either in the form of acids (*II*–*X*) or their esters (*XI*–*XX*).

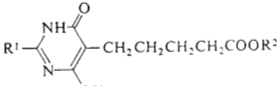
The acids *II*–*IX* were synthetized by the method described[1] for preparation of the acid *I*, *i.e.* by condensation of triethyl 1,1,5-pentantricarboxylate (*XXI*, ref.[7]) with substituted guanidines (*XXII*–*XXIX*) in methanol in the presence of sodium methoxide, followed by hydrolysis of the formed ethyl esters with aqueous sodium hydroxide.

The esters *XI*–*XIX* were obtained from the corresponding acids according to Brenner and coworkers[8–10].

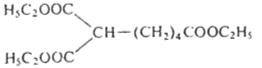
Condensation of the triester *XXI* with dicyanodiamide (*XXX*), under conditions analogous to those used with the other acids, gave the acid *X*, which was esterified



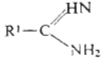
I



II–*XX*

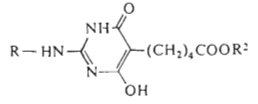


XXI

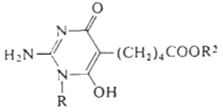


XXII: $R^1 = CH_3NH$
XXIII: $R^1 = C_2H_5NH$
XXIV: $R^1 = C_3H_7NH$
XXV: $R^1 = C_4H_9NH$
XXVI: $R^1 = CH_2{=}CHCH_2NH$

XXVII: $R^1 = C_6H_5CH_2NH$
XXVIII: $R^1 =$ 
XXIX: $R^1 = HOOCCH_2NH$
XXX: $R^1 = NC{-}NH$



A



B

TABLE I

2-Substitution derivatives of 5-(4-oxo-6-hydroxy-3,4-dihydro-5-pyrimidinyl)pentanoic acid

Compound	R^1 R^2	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found % C	% H	% N	pKa_1 pKa_2	UV spectra[a] λ_{max}, nm (log ε) 1	2	3
II[b,c]	H CH_3NH	$C_{10}H_{15}N_3O_4$ (241·2)	262—264	49·76 49·56	6·27 6·17	17·42 17·18	8·50 10·50	267 (4·080)	271 (4·070)	271 (4·088)
III[c]	H C_2H_5NH	$C_{11}H_{17}N_3O_4$ (255·3)	275—278	51·75 51·90	6·71 6·59	16·46 16·69	— —	268 (4·116) 240[d] (3·871)	275 (4·121) 241 (3·826)	275 (4·141) 241 (3·830)
IV[c]	H C_3H_7NH	$C_{12}H_{19}N_3O_4$ (269·3)	256—258	53·52 53·27	7·11 7·02	15·60 15·76	8·40 9·90	269 (4·102) 240[d] (3·864)	275 (4·116) 242 (3·814)	275 (4·126) 242 (3·824)
V[c]	H C_4H_9NH	$C_{13}H_{21}N_3O_4$ (283·3)	257—260	55·11 55·33	7·47 7·26	14·83 14·99	8·55 9·90	269 (4·114) 240[d] (3·909)	276 (4·120) 241 (3·813)	276 (4·134) 241 (3·817)
VI	H $CH_2{=}CHCH_2NH$	$C_{12}H_{17}N_3O_4$ (267·3)	255—261 (ethanol)	56·93 56·84	7·16 6·86	14·23 14·49	8·45 9·75	269 (4·120) 240[d] (3·853)	275 (4·130) 244 (3·798)	275 (4·138) 244 (3·811)
VII[c]	H $C_6H_5CH_2NH$	$C_{16}H_{19}N_3O_4$ (317·3)	234—236	60·56 60·62	6·04 6·16	13·24 13·04	8·55 9·70	270 (3·970) 228 (3·799)	275 (4·023)	275 (4·006)
VIII[c]	H 	$C_{13}H_{19}N_3O_5$ (297·3)	268—269	52·52 52·30	6·44 6·70	14·13 14·41	8·40 9·45	283 (3·998) 240 (3·964)	274 (4·052) 250[d] (3·872)	275 (4·072) 250[d] (3·868)
IX[c]	H $HOOCCH_2NH$	$C_{11}H_{15}N_3O_6$ (285·3)	225—227	46·31 46·57	5·30 5·49	14·73 14·51	— —	274 (4·030) 233 (3·828)	275 (4·083) 243 (3·726)	275 (4·118) 245[d] (3·794)
X[c]	H NCNH	$C_{10}H_{12}N_4O_4$ (252·2)	209—214	47·61 47·37	4·80 5·10	22·21 22·00	8·05 11·30	254 (4·228) 221 (4·003)	278 (4·186) 226 (4·213)	274 (4·229) 222 (4·178)

XI[b]	C_2H_5 CH_3NH	$C_{12}H_{19}N_3O_4$ (269·3)	122–124 (ethanol)	53·52 53·23	7·11 7·24	15·60 15·46	— 10·50	272 (4·118)	276 (4·116)	273 (4·229)
XII	C_2H_5 C_2H_5NH	$C_{13}H_{21}N_3O_4$ (283·3)	244–246 (ethanol)	55·11 54·82	7·47 7·48	14·83 14·89	— —	268 (4·086) 240[d] (3·864)	275 (4·122) 242 (3·818)	270 (4·212)
XIII	C_2H_5 C_3H_7NH	$C_{14}H_{23}N_3O_4$ (297·3)	252–254 (ethanol)	56·55 56·48	7·79 7·71	14·13 14·32	— —	269 (4·102) 238 (3·845)	265 (4·126) 242 (3·804)	270 (4·226)
XIV	C_2H_5 C_4H_9NH	$C_{15}H_{25}N_3O_4$ (311·4)	255–257 (ethanol)	57·86 57·98	8·09 8·29	13·50 13·65	— —	269 (4·108) 238 (3·909)	275 (4·132) 242 (3·820)	270 (4·226)
XV	C_2H_5 $CH_2{=}CHCH_2NH$	$C_{14}H_{21}N_3O_4$ (295·3)	238–239 (ethanol)	56·93 56·84	7·16 6·86	14·23 14·49	— 10·00	270 (4·084) 237 (3·879)	275 (4·120) 242 (3·830)	272 (4·180) 242[d] (3·734)
XVI	CH_3 $C_6H_5CH_2NH$	$C_{17}H_{21}N_3O_4$ (331·4)	256–257 (methanol)	61·62 61·50	6·39 6·47	12·68 12·49	— —	272 (4·102) 235 (3·978)	276 (4·147) 242 (3·884)	273 (4·174) 242 (3·883)
XVII	C_3H_7 $C_6H_5CH_2NH$	$C_{19}H_{25}N_3O_4$ (359·4)	241–242 (propanol)	63·49 63·24	7·01 6·90	11·69 11·70	— —	276 (4·126) 235 (3·808)	272 (4·072) 245[d] (3·837)	273 (4·153) 240[d] (3·877)
XVIII	CH_3 	$C_{14}H_{21}N_3O_5$ (325·4)	245–246 (methanol)	54·01 53·86	6·80 6·85	13·50 13·37	— 9·90	283 (4·092) 240 (4·066)	275 (4·094) 250[d] (3·928)	283 (4·133) 241 (4·018)
XIX	C_2H_5 $C_2H_5OCOCH_2NH$	$C_{15}H_{23}N_3O_6$ (341·3)	212–215 (ethanol)	52·78 52·38	6·79 6·79	12·31 12·37	— 9·80	275 (4·111) 232 (3·842)	274 (4·160) 243 (3·836)	275 (4·138) 233 (3·875)
XX	C_2H_5 $HN{=}C(OC_2H_5)NH$	$C_{14}H_{22}N_4O_5$ (326·4)	155–156 (ethanol)	51·52 51·50	6·79 6·71	17·16 17·26	— —	253 (4·102)	280[d] (4·102) 268 (4·128) 231 (4·128)	285 (4·136) 221[d] (3·988)

[a] 1 in 0·1M-HCl in 50% methanol, 2 in 0·1M-NaOH on 50% methanol, 3 in 50% methanol; [b] mixture of structures A and B; [c] crude product purified by re-precipitation; [d] inflexion.

to the ester *XX*. Under the conditions of this esterification the nitrile group also reacted, with the formation of an imino ether.

The guanidines *XXII*–*XXIX* were obtained by reaction of the corresponding amines with S-methylthiuronium hydrogen sulphate, in analogy to a described procedure[11–13].

As for the structures of the compounds prepared, mainly the tautomeric forms (in which they can occur in the solid state and in solutions), selected representatives were studied by their UV spectra in three media, IR spectra in KBr pellets, and ^{1}H NMR spectra. From the viewpoint of synthesis, two principal structures of the selected compounds can be considered: structure *A*, with a substituent on the amino group at $C_{(2)}$, and structure *B*, having a free amino group at $C_{(2)}$ but a substituent attached to $N_{(1)}$ of the pyrimidine ring. Analysis of the IR and ^{1}H NMR spectra has revealed that the compounds are synthetized in the form of structure *A*, excepting compounds *II* and *XI* (formed by condensation of methylguanidine with *XXI*), present as mixtures of structures *A* and *B*, in a ratio of $A : B \approx \approx 1 : 4$ (calculated from the ^{1}H NMR spectra, *viz.* from the proportion of the doublet at 2·71δ for the methyl hydrogens at $C_{(2)}$ and the singlet at 3·18δ for the methyl hydrogens at $N_{(1)}$ of the pyrimidine ring). This fact is probably due to the somewhat different reactivity of methylguanidine with 1,3-diketones, compared to non-substituted guanidine (compound *I*, ref.[1]), and to the practical absence of steric hindrance, compared to the guanidines with bulky substituents.

The IR spectrum of compound *X* revealed the presence of a nitrile group (a band at 2 200 cm^{-1}). The bands at 1 100 and 1 200 cm^{-1} of the esterification product *XX* and its ^{1}H NMR spectrum suggests the formation of an iminoether.

The titration curves of the compounds synthetized have shown that the acids *II*–*X* behave like acidic amino acids with two dissociation constants; one for the carboxyl group proton (pK_{a_1}) and the other for the hydroxyl group proton (pK_{a_2}). The basic character of the compounds, caused by the substituted amino group at the 2-position, is strongly suppressed by the inner salt formation, demonstrated in the IR spectra by a band at 1 610 cm^{-1}. The esters *XI*–*XX* behave as very weak acids, with pK_a of *c.* 10, corresponding to the hydroxyl group hydrogen. Comparison of the pK_{a_1} values of the compounds tested with the pK_{a_1} 9·37 of compound *I* (ref.[1]) reveals that substitution on the amino group at $C_{(2)}$ of the pyrimidine skeleton increases the acidity of the compounds. This is especially marked with compound *X*, where $pK_{a_1} = 8{\cdot}05$, owing to the presence of the nitrile group.

The antineoplastic effects of the compounds prepared on experimental tumours in animals were weaker than those observed with the compound *I*. Only the acid *IV*, administered *s.c.* in doses 150 and 300 mg/kg, showed an enhancing effect on the activity of 5-fluorouracil (75 mg/kg *s.c.*) in leukemia LA-VÚFB, raising it by 25%. The results of biological screening have shown that substitution on the amino group at $C_{(2)}$ of the compound *I* reduces the antineoplastic activity.

EXPERIMENTAL

The melting points, determined on the Kofler block, are not corrected. The analytical samples were dried over phosphorus pentoxide at 27 Pa and temperatures adequate to their melting points. The ultraviolet spectra ($(\lambda_{max}$, nm, $(\log \varepsilon))$ were measured employing a spectrometer Pye Unicam SP 8000 and *c.* 0·001% solution in *1*) 0·1M-HCl in 50% methanol, *2*) 0·1M-NaOH in 50% methanol and *3*) 50% aqueous methanol. The infrared spectra were recorded in KBr pellets with an apparatus Hilger–Watts. The ^{1}H NMR spectra were measured with a spectrometer Tesla BSC 487 (80 MHz), using *c.* 10% solutions in hexadeuteriodimethyl sulphoxide and tetramethylsilane as internal standard. The values of pK_a were measured in 80% aqueous dimethyl sulphoxide. The individuality of the compounds was checked by TLC in silica gel plates (DC Fertigplatten Kieselgel F_{254}, Merck), or on reflex foils Silufol UV_{254} (Kavalier) in the system 1-propanol–25% ammonia–water (7 : 1 : 2); detection with UV light, 254 nm.

Condensation of Triethyl 1,1,5-Pentanetricarboxylate (*XXI*) with Substituted Guanidines *XXII*–*XXX* (Compounds *II*–*X*)

To a stirred solution of sodium methoxide (2–3 mol equivalents) in methanol, kept at 40–45°C, was added a guanidine (*XXII*–*XXX*, 1–2 mol equivalents) in the form of hydrogen sulphate. The stirring was continued for 30 min, then the triester *XXI* (1 mol equivalent) was added. The mixture was stirred for 4 h at room temperature and left standing overnight. The methanol was distilled off *in vacuo* and the residue was dissolved in 0·5M-NaOH (1 mol equivalent). The mixture was stirred at room temperature for 2 h, then brought with dilute (1 : 1) hydrochloric acid to about pH 3. The separated compound was collected on a filter, washed with water and methanol, and purified by crystallization (see Table I) or by re-precipitation *via* an ammonium salt (*II*, *IV*, *V*, *VI* – *X*).

II: Sodium (8,65 g, 0·375 mol), 250 ml of methanol, methylguanidine hydrogen sulphate (30·5 g, 0·25 mol), triester *XXI* (36·2 g, 0·125 mol), yield 22·5 g (74·8)%. IR spectrum: 3 200 (NH_3^+), 1 610 (COO^-), 1 660 cm^{-1} (tertiary amide).

III: Sodium (8·65 g, 0·375 mol), 250 ml of methanol, ethylguanidine hydrogen sulphate (34·0 g, 0·25 mol) triester *XXI* (36·2 g, 0·125 mol), yield 23·0 g (72·2%). IR spectrum: 3 380, 3 100 (NH), 3 240 (NH_2^+), 1 610 (COO^-), 1 665 cm^{-1} (lactam). ^{1}H NMR spectrum: δ 6·30 (bt, J = 5·5 Hz, 1 H, after D_2O disappears, NH), 3·21 (m, after D_2O q, J 7·0 Hz, CH_2—N), 2·15 (bm, 4 H, Ar—CH_2, CH_2—CO), 1·39 (bm, 4 H, 2 CH_2), 1·06 (t, J = 7·0 Hz, 3 H, CH_3).

IV: Sodium (3·7 g, 0·16 mol), propylguanidine hydrogen sulphate (16·0 g, 0·106 mol), 107 ml of methanol, triester *XXI* (15·3 g, 0·053 mol), yield 6·8 g (47·6%). IR spectrum: 3 360, 3 100 (NH), 3 240 (NH_2^+), 1 665 (lactam), 1 610 cm^{-1} (COO^-).

V: Sodium (3·78 g, 0·16 mol), 75 ml of methanol, butylguanidine hydrogen sulphate (9·5 g, 0·057 mol), triester *XXI* (15·6 g, 0·054 mol), yield 6·7 g (44·0%). IR spectrum: 3 360, 3 100 (NH), 3 240 (NH_2^+), 1 660 (lactam), 1 610 cm^{-1} (COO^-).

VI: Sodium (5·5 g, 0·24 mol), 120 ml of methanol, allylguanidine hydrogen sulphate (11·89 g, 0·08 mol), triester *XXI* (22·9 g, 0·079 mol), yield 11·0 g (52·4%). IR spectrum: 3 380, 3 260 (NH), 1 735 (C=O, acid), 1 630 cm^{-1} (lactam).

VII: Sodium (8·6 g, 0·373 mol), 186 ml of methanol, benzylguanidine hydrogen sulphate (24·6 g, 0·124 mol), triester *XXI* (35·7 g, 0·124 mol), yield 17·1 g (43·8%). IR spectrum: 3 400, 3 200 (NH), 1 700 (C=O, acid), 1 630 cm^{-1} (lactam). ^{1}H NMR spectrum: δ 7·00–7·40 (m, 5 H, Ar—H), 5·10 (bs, 2 H, $ArCH_2N$), 2·15 (bm, 4 H, Ar—CH_2, CH_2—CO), 1·40 (bm, 4 H, 2 CH_2).

VIII: Sodium (4·9 g, 0·21 mol) 105 ml of methanol, morpholinylguanidine hydrogen sulphate (10·6 g, 0·06 mol), triester *XXI* (20·3 g, 0·07 mol), yield 10·5 g (50·4%). IR spectrum: 34 10, 3 060 (NH), 1 700 (C=O), acid), 1 620 cm^{-1} (lactam). ^1H NMR spectrum: δ 3·50 (bs, 8 H, morpholine), 2·15 (bm, 4 H, $ArCH_2$, CH_2—CO), 1·40 (bm, 4 H, 2 CH_2).

IX: Sodium (6·4 g, 0·278 mol), 100 ml of methanol, carboxymethylguanidine hydrogen sulphate (10·6 g, 0·07 mol), trister *XXI* (19·9 g, 0·068 mol), yield 14·0 g (72·1%). IR spectrum: 3 620 (OH), 3 440 (NH), 1 705, 1 740 (C=O, acids), 1 650 cm^{-1} (lactam).

X: Sodium (1·6 g, 0·069 mol), 50 ml of methanol, dicyanodiamide (3·2 g, 0·038 mol), triester *XXI* (10·0 g, 0·0346 mol), yield 7·1 g (74·1%). IR spectrum: 3 440 (NH), 3 120 (NH_2^+), 2 200 (CN), 1 660 (lactam), 1 610 cm^{-1} (COO^-).

Esterification of Acids *II*—*X* (Esters *XI*—*XX*)

To an alcohol pre-chilled to —10°C was added dropwise an excess of thionyl chloride; then, at the same temperature, 1 mol equivalent of an acid (*II*—*X*) and the suspension was stirred for 30 min at —5°C. The temperature was elevated to 40°C and kept at this level for 2 h. The solution was taken to dryness, the residue was stirred up in water and sodium hydrogen carbonate was added to *c.* pH 7·5. The precipitate was collected on a filter, washed with water, dried and purified by crystallization from a suitable solvent (Table I).

XI: Acid *II* (4·82 g, 0·02 mol), 30 ml of ethanol, 1·6 ml of thionyl chloride, yield 4·0 g (74·3%). IR spectrum: 3 530 (OH), 3 140 (NH), 3 420, 3 330, 1 610 $(NH)_2$, 1 730 (C=O, ester) 1 660 cm^{-1} (tertiary amide). ^1H NMR spectrum (mixture of $NHCH_3$ + $ArNHCH_3$): δ 6·90 (bs, NH_2, OH), 6·20 (q, J = 5·0 Hz, 18% H, H_3CN—H), 3·18 (s, 82% CH_3, $ArNCH_3$), 2·71 (d, J = 5·0 Hz, after D_2O-s, 18% NH—CH_3), 3·98 (q, J = 7·0 Hz, 2 H, OCH_2), 2·18 (m, 4 H, $ArCH_2$, CH_2—CO), 1·40 (m, 4 H, 2 CH_2), 1·11 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3).

XII: Acid *III* (0·5 g, 0·002 mol), 3 ml of ethanol, 0·2 ml of thionyl chloride, yield 0·35 g (61·8%). IR spectrum: 3 240, 3 120 (NH), 1 660 (lactam), 1 740 cm^{-1} (C=O, ester). ^1H NMR spectrum: δ 6·22 (bt, J = 5·0 Hz, 1 H, after D_2O disappears, NH), 4·00 (q, J = 7·0 Hz, 2 H, OCH_2), 3·20 (m — after D_2O q, J = 7·0 Hz, 2 H, NH—CH_2), 2·18 (m, 4 H, Ar—CH_2, CH_2—CO), 1·40 (m, 4 H, 2 CH_2), 1·12 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3), 1·04 (t, J = 7·0 Hz, 3 H, NCH_2—CH_3).

XIII: Acid *IV* (0·54 g, 0·002 mol), 3 ml of ethanol, 0·2 ml of thionyl chloride, yield 0·42 g (70·7%). IR spectrum: 3 380, 3 120 (NH), 1 660 (lactam), 1 740 cm^{-1} (C=O, ester). ^1H NMR spectrum: δ 6·28 (bt, J = 5·0 Hz, 1 H — after D_2O disappears, NH), 4·00 (q, J = 7·0 Hz, 2 H, OCH_2), 3·14 (m, 2 H, N—CH_2), 2·15 (m, 4 H, Ar—CH_2, CH_2—CO), 1·40 (m, 6 H, 3 CH_2), 1·11 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3), 0·81 (t, J = 7·0 Hz, 3 H, CH_2—CH_3).

XIV: Acid *V* (0·57 g, 0·002 mol), 3 ml of ethanol, 0·2 ml of thionyl chloride, yield 0·6 g (96·7%). IR spectrum: 3 370, 3 120 (NH), 1 660 (lactam), 1 740 cm^{-1} (C=O, ester). ^1H NMR spectrum: δ 6·28 (bt, J = 5·0 Hz, 1 H-after D_2O disappears, NH), 4·00 (q, J = 7·0 Hz, 2 H, OCH_2), 3·18 (m, 2 H, N—CH_2), 2·15 (m, 4 H, Ar—CH_2, CH_2—CO), 1·45 (m, 8 H, 4 CH_2), 1·12 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3), 0·86 (bt, 3 H, CH_3).

XV: Acid *VI* (4·0 g, 0·015 mol), 60 ml of ethanol, 12 ml of thionyl chloride, yield 3·1 g (70·1%). IR spectrum: 3 410, 3 140 (NH), 1 750 (C=O, ester), 1 630 cm^{-1} (lactam). ^1H NMR spectrum: δ 6·35 (bt, J = 5·0 Hz, 1 H-after D_2O disappears, NH), 5·80 (m, 1 H, =CH), 5·10 (bd, J = = 16·0 Hz, 1 H, *trans*-olefinic H), 5·05 (bd, J = 9·0 Hz, 1 H, *cis*-olefinic H), 4·00 (q, J = 7·0 Hz, 2 H, OCH_2), 3·82 (m, 2 H, N—CH_2), 2·18 (m, 4 H, Ar—CH_2, CH_2—CO), 1·40(m, 4 H, 2 CH_2), 1·15 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3).

XVI: Acid *VII* (4·0 g, 0·013 mol), 60 ml of methanol, 12 ml of thionyl chloride, yield 3·7 g (88%) IR spectrum: 3 410, 3 160 (NH), 1 750 (C=O, ester), 1 630 cm^{-1} (lactam). ^1H NMR spectrum: δ 7·40 (s, 5 H, Ar—H), 4·60 (s, 2 H, $ArCH_2N$), 3·60 (s, 3 H, OCH_3), 2·28 (m, 4 H, $ArCH_2$, CH_2—CO), 1·40 (m, 4 H, 2 CH_2).

XVII: Acid *VII* (17·1 g, 0·054 mol), 480 ml of propanol, 51·2 ml of thionyl chloride, yield 11·2 g (57·7%). IR spectrum: 3 410, 3 160 (NH), 1 740 (C=O, ester), 1 630 cm^{-1} (lactam).

XVIII: Acid *VIII* (1·85 g, 0·006 mol), 24 ml of methanol, 4·8 ml of thionyl chloride, yield 0·8 g (44·9%). IR spectrum: 3 410, 3 140 (NH), 1 760 (C=O, ester), 1 635 cm^{-1} (lactam). ^1H NMR spectrum: δ 3·58 (bs, 8 H, morpholine), 3·58 (s, 3 H, OCH_3), 2·20 (m, 4 H, Ar—CH_2, CH_2—CO), 1·40 (m, 4 H, 2 CH_2).

XIX: Acid *IX* (4·6 g, 0·016 mol), 93 ml of ethanol, 17·5 ml of thionyl chloride, yield 3·0 g (54·9%). IR spectrum: 3 380, 3 060 (NH), 1 755, 1 745 (C=O, esters), 1 630 cm^{-1} (lactam). ^1H NMR spectrum: δ 6·51 (bt, J = 5·0 Hz, 1 H after D_2O disappears, NH), 4·12 (q, J = 7·0 Hz, 2 H, OCH_2), 4·00 (q, J = 7·0 Hz, 2 H, OCH_2), 4·00 (d, J = 5·0 Hz, after D_2O s, N—CH_2), 2·18 (m, 4 H, $ArCH_2$, CH_2—CO), 1·40 (m, 4 H, 2 CH_2), 1·14 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3), 1·11 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3).

XX: Acid *X* (10·0 g, 0·04 mol), 120 ml of ethanol, 31·5 ml of thionyl chloride, yield 10·2 g (75·5%). IR spectrum: 3 370, 3 160 (NH), 1 740 (C=O, ester), 1 110, 1 200 cm^{-1} (ether). ^1H NMR spectrum: δ 4·25 (q, J = 7·0 Hz, 2 H, OCH_2), 4·03 (q, J = 7·0 Hz, 2 H, OCH_2), 2·20 (m, 4 H, Ar—CH_2, CH_2—CO), 1·40 (m, 4 H, 2 CH_2), 1·20 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3), 1·10 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3).

The analyses were carried out by Mrs J. Komancová, the dissociation constants were determined by Dr V. Velart (Analytical Department, head Dr J. Körbl). The antineoplastic effects were assessed by Mrs S. Pokorná (Pharmacological Department, head Dr J. Grimová).

REFERENCES

1. Semonský M., Černý A., Křepelka J., Kotva R., Kakáč B., Holubek J., Vachek J.: This Journal *45*, 3583 (1980).
2. Kotva R., Křepelka J., Semonský M.: This Journal, in press.
3. Kotva R., Křepelka J., Černý A., Pujman V., Semonský M.: This Journal *46*, 1397 (1981).
4. Kotva R., Křepelka J., Řežábek K., Vachek J.: This Journal *46*, 2217 (1981).
5. Kotva R., Křepelka J., Vachek J.: This Journal *47*, 2525 (1982).
6. Beran M., Černý A., Křepelka J.: Vachek J.: This Journal *48*, 292 (1983).
7. Karrer P., Keller R., Usteri E.: Helv. Chim. Acta *27*, 237 (1944).
8. Brenner M., Müller H. R., Pfister R. W.: Helv. Chim. Acta *33*, 568 (1950).
9. Brenner M., Pfister R. W.: Helv. Chim. Acta *34*, 2091 (1951).
10. Brenner M., Huber W.: Helv. Chim. Acta *36*, 1109 (1953).
11. Pant R.: Hoppe-Seyler's Z. Physiol. Chem. *335*, 272 (1964).
12. Schenck K., Kirchhof H.: Hoppe-Seyler's Z. Physiol. Chem. *158*, 97 (1926).
13. King H., Tonkin I. M.: J. Chem. Soc. *1946*, 1963.

Translated by J. Salák.