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

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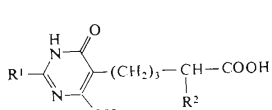
Received October 26th, 1981

Condensation of trialkyl esters of 6-substituted 2-carboxy-1,7-heptanedioic acids *XII*—*XVII* with urea or thiourea and subsequent saponification gave 2-substituted 5-(2,6-dihydroxy-4-oxo--3,4-dihydro-5-pyrimidinyl)pentanoic acids *II*—*VI* or 5-(2-mercapto-6-hydroxy-4-oxo-3,4-dihydro-6-pyrimidinyl)pentanoic acids *VII*—*XI*, respectively. Compounds *II*, *VII* and *X* had a weak antineoplastic effect in animals with experimental transplantable tumours.

The paper is a continuation of a study of antimetabolites of purine and pyrimidine bases of nucleic acids. It describes the synthesis of 2-substituted 5-(2,6-dihydroxy--4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acids *II*—*VI* and 5-(2-mercapto-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acids *VII*—*XI* which were prepared in connection with the study of derivatives of 5-(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acid[1] (*I*; $R^1 = NH_2$, $R_2 = H$) (DAMVAR) which displayed some positive properties utilisable for the modulation of biological responses of other drugs administered together with it[2-5].



I—*XI*

The meaning of substituents R^1 and R^2 see Table I.

On the basis of the analogous form of their IR and UV spectra, we assume that substances *II*—*VI* have in solid state the structure of 2-substituted 5-(2,4,6-trioxo-hexahydro-5-pyrimidinyl)pentanoic acids and substances *VII*—*X* the structure of 2-substituted 5-(2-thioxo-6-hydroxy-4-oxo-1,2,3,4-tetrahydro-5-pyrimidinyl)penta-

* Part LXXXI in the series Substances with Antineoplastic Activity; Part LXXX: This Journal *47*, 1867 (1982).

TABLE I

2-Substituted 5-(4-oxo-3,4-dihydro-5-pyrimidinyl)pentanoic acids

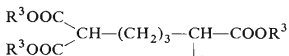
Number	R^1 R^2	M.p., °C yield (%)	Formula (mol.weight)	Calculated/Found				UV spectra, λ_{max}, nm (log ε) medium	
				% C	% H	% N	% S	A	B
II	OH[a]	207–209[b]	$C_{10}H_{14}N_2O_5$	49·58	5·83	11·57	—	264 (3·18)	270 (4·31)
	CH_3	(67)	(242·2)	49·33	5·73	11·12	—	213 (3·83)	230 (3·81)
III	OH[c]	163–164[b]	$C_{11}H_{16}N_2O_5$	51·56	6·29	10·93	—	262 (3·17)	269 (4·21)
	C_2H_5	(69)	(256·3)	51·80	6·59	10·70	—	211 (3·86)	231 (3·71)
IV	OH[d]	137–138[b]	$C_{12}H_{18}N_2O_5$	53·33	6·71	10·36	—	263 (3·37)	269 (4·22)
	C_3H_7	(55)	(270·3)	53·36	6·70	10·53	—	213 (3·87)	232 (3·83)
V	OH[e]	132–134[b]	$C_{13}H_{20}N_2O_5$	54·92	7·09	9·85	—	263 (3·39)	269 (4·31)
	C_4H_9	(69)	(284·3)	54·40	7·01	9·53	—	209i (3·99)	
VI	OH[f]	144–145[b]	$C_{14}H_{22}N_2O_5$	56·36	7·43	9·39	—	262 (3·25)	268 (4·30)
	C_5H_{11}	(63)	(298·3)	56·41	7·42	9·61	—	210i (3·92)	232 (3·73)
VII	SH[g]	193–194[b]	$C_{10}H_{14}N_2O_4S$	46·50	5·46	10·85	12·41	286 (4·28)	290 (4·08)
	CH_3	(77)	(258·3)	45·90	5·48	11·32	12·54	235i (3·82)	238 (4·22)
VIII	SH[h]	70–72[i]	$C_{12}H_{18}N_2O_4S$	50·33	6·34	9·78	11·20	285 (4·26)	290 (4·06)
	C_3H_7	(80)	(286·3)	50·50	6·29	9·56	11·13	234i (3·38)	270i (3·98)
								209 (3·83)	236 (4·18)

IX	SH[j]	165–167[i]	$C_{13}H_{20}N_2O_4S$	51·98	6·71	9·33	10·67	285 (4·27)	288 (4·09)
	C_4H_9	(93)	(300·4)	52·11	6·82	9·56	10·94	232i (3·80)	272i (4·04)
								208 (3·93)	236 (4·15)
X	SH[k]	75–76[i]	$C_{14}H_{22}N_2O_4S$	53·48	7·05	8·91	10·20	285 (4·28)	287 (4·08)
	C_5H_{11}	(94)	(314·4)	53·44	6·93	8·72	10·07	209 (3·99)	235 (4·20)
XI	SH[l,m]	238–250[b]	$C_9H_{12}N_2O_5S.H_2O$	38·84	5·07	10·07	11·52	286 (4·30)	289 (4·10)
	OH	(68)	(278·3)	38·39	4·51	10·29	11·49	225i (3·90)	266i (4·03)
								210 (4·05)	237 (4·23)

[a] IR spectrum: 1 720 (carboxyl), 1 680 (carbonyls), 3 040, 3 110 (NH); [b] The substance was crystallized from water; [c] IR spectrum: 1 750 (carboxyl), 1 700 (carbonyls), 3 180, 3 070, (NH); [d] IR spectrum: 1 730, 2 700 (carboxyl, broad band), 1 700 (carbonyls), 3 200, 3 065 (NH); [e] IR spectrum: 1 740 (carboxyl), 1 700 (carbonyls), 3 170, 3 060 (NH), 1 570 (secondary amide); [f] IR spectrum: 1 750, 2 700 (carboxyl, broad band), 1 710 (carbonyls), 3 230, 3 120 (NH), [g] IR spectrum: 1 690 (carboxyl), 3 420 (OH), 3 080 (NH), 1 630 1 572 (secondary amide), 1 460 (N—C=S); [h] IR spectrum: 1 690 (carboxyl), 3 400 (OH), 3 100 (NH), 1 630, 1 575 (secondary amide), 1 620 (C=C), 1 460 (N—C=S); [i] The substance was crystallized from aqueous ethanol; [j] IR spectrum: 1 680 (carboxyl), 3 500 (OH), 3 140, 3 060 (NH), 1 630, 1 570 (secondary amide), 1 650 (C=C), 1 475 (N—C=S); [k] IR spectrum: 1 700, 2 500 (carboxyl, broad band), 3 510 (NH), 1 640 (lactam), 3 380 (NH), 1 570 (N—C=S); [l] IR spectrum: 1 700 (carboxyl), 1 600, 1 560 (double bonds), 3 320, 3 200, 3 140 (OH), 2 600 (the band is indistinct); [m] The substance crystallized with one molecule of crystal water. For $C_9H_{12}N_2O_5S.H_2O$ calculated: 6·47% water, found: 5·84% water.

noic acids and compound *XI* the structure of 5-(2-mercapto-4,6-dihydroxy-5-pyrimidinyl)-2-hydroxypentanoic acid.

Compounds *II*–*XI* were synthetized by the method used for the preparation of 5-substituted barbituric acid and thiobarbituric acid derivatives (refs[6-8]), *i.e.* by condensation of trialkyl esters of 6-substituted 2-carboxy-1,7-heptanedioic acids *XII*–*XVII* with urea or thiourea in methanol, in the presence of sodium methoxide. The alkyl esters of acids *II*–*XI* were saponified to free acids without isolation, using a sodium hydroxide solution.



XII; $R^2 = CH_3$, $R^3 = C_2H_5$ — *XV*; $R^2 = C_4H_9$, $R^3 = C_2H_5$
XIII; $R^2 = C_2H_5$ $R^3 = C_2H_5$ — *XVI*; $R^2 = C_5H_{11}$, $R^3 = C_2H_5$
XIV; $R^2 = C_3H_7$, $R^3 = C_2H_5$ — *XVII*; $R^2 = CH_3COO$, $R^3 = CH_3$

Trialkyl esters of 6-substituted 2-carboxy-1,7-heptanedioic acids *XII*–*XVII* have been described in a previous paper of this series[9].

In a test on antineoplastic effect on animals with experimental tumours acid *X* showed a mild antineoplastic effect. In a 100 mg/kg dose, applied subcutaneously to mice with the tumour Kr 2, it decreased the size of the tumour by 22%. Acid *VII* prolonged the survival time of animals with the tumour Kr 2 by 21%, when the administered dose was 50 mg/kg c.s. Acid *II* prolonged the survival of animals with an ascitic form of Yoshida's tumour, in a 100 mg/kg *s.c.* dose, by 27%. The substances tested were non-toxic.

EXPERIMENTAL

The melting points of the substances were determined on a Kofler block and they are not corrected. Samples for analysis were dried in a 27 Pa vacuum over P_2O_5 at a temperature elevated proportionally to their melting point. The ultraviolet spectra of the prepared substances were measured on a Unicam SP 8000 spectrophotometer at a 0·001% concentration, in 0·1M-HCl in 50% methanol (A), or 0·1M-NaOH in 50% methanol (B). The infrared spectra were recorded in KBr pellets on a Hilger Watts instrument. The purity of the substances was evaluated by thin-layer chromatography, using chloroform–methanol–25% ammonia (2 : 2 : 1) or propanol–25% ammonia–water (7 : 1 : 2) as solvent and FP-Kieselgel F_{254} Merck as adsorbent. Length of development was 15 cm and the detection was carried out by inspection under an ultraviolet lamp or using reflecting silica gel foils with luminescent indicator (Silufol UV_{254}, Kavalier).

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

Thiourea (91·35 g; 1·20 mol) was added to a solution of 27·6 g (1·20 mol) of sodium in 400 ml of methanol, followed by triethyl ester of 2-butyl-6-carboxy-1,7-heptanedioic acid (137·78 g;

0·40 mol), at 40 to 50°C and under stirring. The stirring was continued for 4 h at room temperature and the mixture was then allowed to stand overnight. Methanol was distilled off under reduced pressure and the residue was allowed to stand with 800 ml of 0·5M-NaOH at 20 to 25°C for 2 h. After filtration the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 3. The precipitated substance was filtered off after cooling, washed with water and dried. The substance obtained was purified by crystallization from 50% of aqueous ethanol. In the same manner acids *II*—*VIII* and *X*—*XI* (Table I) were prepared from corresponding trialkyl esters.

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Translated by Ž. Procházka.