SOME DERIVATIVES OF 4-[(2-AMINO-6-HYDROXY-4-OXO-3,4-DIHYDRO-5-PYRIMIDINYL)-METHYL] BENZOIC ACID*

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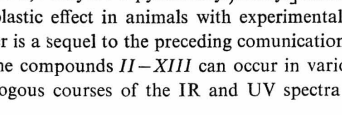
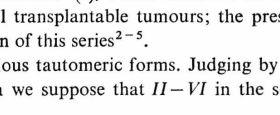
Esterification of the title acid (*I*) gave esters *II*—*VI*. Halogenation of the acid *I* afforded its 5-chloro- and 5-bromo derivatives, *VII* and *VIII*. Condensation of triesters *XIV*—*XVII* and of tetraester *XVIII* with guanidine, followed by hydrolysis, led to acids *IX*—*XIII*. Some of these compounds had a weak antineoplastic activity in animals with experimental transplantable tumours.

The paper deals with synthesis of esters of 4-[(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)methyl]benzoic acid, *II*—*VI*, and of 5-substituted 4-[(2-amino--4,6-dioxo-3,4,5,6-tetrahydro-5-pyrimidinyl)methyl]benzoic acids, *VII*—*XIII*. These esters were prepared as part of our study of derivatives of 4-[(2-amino-6-hydroxy--4-oxo-3,4-dihydro-5-pyrimidinyl)methyl]benzoic acid[1] (*I*), which exhibited an antineoplastic effect in animals with experimental transplantable tumours; the present paper is a sequel to the preceding comunication of this series[2-5].

The compounds *II*—*XIII* can occur in various tautomeric forms. Judging by the analogous courses of the IR and UV spectra we suppose that *II*—*VI* in the solid



I, $R^1 = H$
II, $R^1 = CH_3$
III, $R^1 = C_2H_5$
IV, $R^1 = C_3H_7$
V, $R^1 = C_4H_0$
VI, $R^1 = C_7H_{15}$



VII, $R^2 = Cl$
VIII, $R^2 = Br$
IX, $R^2 = C_3H_7$
X, $R^2 = CH_2—CH=CH_2$
XI, $R^2 = CH_2—C\equiv CH$
XII, $R^2 = C_6H_5$
XIII, $R^2 = (CH_2)_4—COOH$

* Part LXXXIV in the series Substances with Antineoplastic Activity, Part LXXXIII: This Journal *48*, 292 (1983).

TABLE I

Derivatives of 4-[(2-amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)methyl]benzoic acid

Number	M.p., °C (yield, %)	Formula (mol.mass)	Calculated/Found			UV spectra λ_{max}, nm (log ε)	
			% C	% H	% N	A	B
II[a]	324—326[b] (70)	$C_{13}H_{13}N_3O_4$ (275·3)	56·72 56·94	4·76 4·70	15·27 15·14	—	267 (4·24)[c] 242 (4·27)
III[d]	316—318[c] (72)	$C_{14}H_{15}N_3O_4$ (289·3)	58·12 57·89	5·23 5·12	14·53 14·50	—	267 (4·18)[c] 245 (4·30) 207 (4·47)
IV[f]	303—305[g] (80)	$C_{15}H_{17}N_3O_4$ (303·3)	59·40 58·85	5·65 5·55	13·85 13·77	—	262i (4·28)[c] 244 (4·39)
V[h]	294—297[g] (77)	$C_{16}H_{19}N_3O_4$ (317·3)	60·56 60·45	6·03 6·12	13·24 13·43	—	265 (4·24)[c] 241 (4·29)
VI[i]	291—293[g] (64)	$C_{19}H_{25}N_3O_4$ (359·4)	63·49 62·97	7·01 6·94	11·69 11·80	—	270 (4·28)[c] 247 (4·26)
VII[j,k]	< 360[g] (90)	$C_{12}H_{10}ClN_3O_4$ (295·7)	48·74 48·49	3·41 3·69	14·21 14·46	236 (4·31)	270i (3·77) 234 (4·33)
VIII[l,m]	[g,n] (98)	$C_{12}H_{10}BrN_3O_4$ (340·2)	42·37 42·19	2·96 3·32	12·35 12·29	234 (4·34)	238 (4·31)
IX[o,p]	339—341[q] (76)	$C_{15}H_{17}N_3O_4$ (303·3)	59·40 60·11	5·65 5·69	13·85 13·72	260i (3·57) 230i (4·18)	265 (4·06) 225 (4·49)
X[r,s]	335—337[q] (58)	$C_{15}H_{15}N_3O_4$ (301·3)	59·79 59·49	5·02 5·06	13·95 14·24	230i (4·09)	264 (3·82) 217 (4·60)
XI[t,u]	< 360[q] (48)	$C_{15}H_{13}N_3O_4$ (299·3)	60·20 59·96	4·38 4·23	14·04 13·80	230i (4·27)	265 (4·01) 225 (4·50)
XII[v,x]	324—327[q] (99)	$C_{18}H_{15}N_3O_4$ (337·4)	64·09 64·32	4·48 4·67	12·46 12·21	235 (4·35)	265 (3·95) 228 (4·52)
XIII[y,z]	317—319[e] (57)	$C_{17}H_{19}N_3O_6$ (261·3)	56·50 56·23	5·30 5·01	11·63 11·30	234 (4·21) 201 (4·53)	263 (3·99) 226 (4·46)

[a] IR spectrum: 1 740 (ester), 3 440, 3 200 (NH), 1 620 (lactam); [b] Crystallized from aqueous dimethylformamide; [c] In methanol; [d] IR spectrum: 1 724 (ester), 3 410, 3 390 (primary amine), 1 640 (lactam), 1 570, 1 620 (benzene ring); [e] Crystallized from aqueous ethanol; [f] IR spectrum: 1 710 (ester), 3 420, 3 320 (NH_2), 3 100 (NH), 1 550, 1 650 (secondary amide), 1 500, 810, 1 680 (disubstituted benzene ring); [g] Crystallized from a mixture dimethylformamide–methanol; [h] IR spectrum: 1 720 (ester), 3 460, 3 370 (NH), 1 650 (lactam), 1 500, 1 630 (benzene ring); [i] IR spectrum: 1 705 (ester), 3 380, 3 450 (prim. amine), 3 080 (NH), 1 610, 1 550 (sec. amide), 2 680 (OH,

state have the structure of esters of 4-[(2-amino-6-hydroxy-4-oxo-3,4-dihydro--5-pyrimidinyl) methyl]benzoic acid, whereas *VII*–*XIII* are 5-substitution derivatives of 4-[(2-amino-4,6-dioxo-3,4,5,6-tetrahydro-5-pyrimidinyl]methyl) benzoic acid.

The esters *II*–*VI* were prepared as decribed by Brenner and coworkers[6–8]. The acid *VII* (R^2 = Cl) was obtained by chlorination of the acid *I* with a mixture of dilute hydrochloric acid and 30% hydrogen peroxide, the acid *VIII* (R^2 = Br) by bromination of *I* with bromine. The compounds *IX*–*XIII* were synthetized by the procedure described for the preparation of 5-substitution derivatives of barbituric, thiobarbituric and iminobarbituric acids[9–11], *i.e.* by condensation of 2-substituted triethyl esters of 2-(4-carboxybenzyl)-1,3-propanedioic acid, *XIV*–*XVIII*, with guanidine in methanol containing sodium methoxide as condensation agent. The formed ethyl esters of *IX*–*XIII* were directly (without isolation) hydrolysed with sodium hydroxide to the free acids.

2-Substituted triethyl esters of 2-(4-carboxybenzyl)-1,3-propanedioic acid, *XIV* to *XVIII*, were prepared by a described procedure[1], *viz.* by alkylation of a 2-substituted diethyl 1,3-propanedioate with ethyl 4-bromomethylbenzoate in ethanol containing sodium ethoxide.

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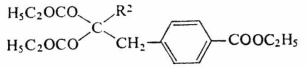
wide band); [j] IR spectrum: 3 020, 3 220 (NH, NH_2), 1 730, 2 500, 3 200 (carboxyl, wide band), 1 680 (carbonyl), 1 610 (NH_2), 1 640 (C=N), 1 490, 1 570 (benzene ring); [k] For $C_{12}H_{10}ClN_3O_4$ (295·7) calculated 11·99 Cl; found 11·26% Cl; [l] IR spectrum: 3 010, 3 190 (NH, NH_2), 1 730, 2 500, 3 200 (carboxyl, wide band), 1 680 (carbonyl), 1 610 (NH_2), 1 635 (C=N), 1 490, 1 570 (benzene ring); [m] For $C_{12}H_{10}BrN_3O_4$ (340·2) calculated: 23·49% Br; found: 22·97% Br; [n] Decomposition about 280°C without melting [o] IR spectrum: 1 730, 3 060 (carboxyl, wide band), 1 700 (carbonyl), 1 640 ((lactam), 3 400, 3 160 (NH), 1 500, 1 570, 1 620 (aromatic bands), [p] Intermediate triethyl 2-propyl-2-(4-carboxybenzyl)-1,3-propanedioate (*XIV*), prepared analogously to[1], b.p. 182–186°C/27 Pa, for $C_{20}H_{28}O_6$ (364·4) calculated: 65·91% C, 7·74% H; found: 65·56% C, 7·92% H; [q] Purified by reprecipitation from dilute solution in NaOH with HCl; [r] IR spectrum: 1 700, 2 700 (carboxyl, wide band), 1 505, 1 570 (benzene ring), 1 640 (lactam), 3 400, 3 160 (NH). [s] Intermediate triethyl 2-allyl-2-(4-carboxybenzyl)-1,3-propanedioate (*XV*), prepared analogously to[1], b.p. 174–179°C/27 Pa; for $C_{20}H_{26}O_6$ (362·4) calculated: 66·28% C, 7·23% H, found: 65·92% C, 7·26% H. [t] IR spectrum: 2 280 (C≡C), 3 370, 3 270 (NH), 1 730, 2 700 (carboxyl, wide band), 1 690 (carbonyl), 1 630 lactam; [u] Intermediate triethyl 2-propargyl--2-(4-carboxybenzyl)-1,3-propanedioate (*XVI*), prepared analogously to[1], b.p. 184–186°C/27 Pa; for $C_{20}H_{24}O_6$ (360·4) calculated: 66·65% C, 6·71% H; found: 66·27% C, 6·89% H. [v] IR spectrum: 1 625 (lactam), 1 710, 2 760 (carboxyl, wide band), 1 510, 1 575, 1 630 (benzene ring), 1 680 (carbonyl), 3 200, 3 260 (NH, NH_2). [x] Intermediate triethyl 2-phenyl-2-(4-carboxybenzyl)--1,3-propanedioate (*XVII*), prepared analogously to[1], b.p. 198–204°C/52 Pa; for $C_{23}H_{26}O_6$ (398·4) calculated: 69·33% C, 6·58% H, found: 68·97% C, 6·59% H; [y] IR spectrum: 3 410 (NH, NH_2), 3 100 (NH_3^+), 1 700, 1 730, 2 700 (carboxyls, wide band), 1 625 (lactam), 1 640 (carbonyl), 1 510, 1 580 (benzene ring), [z] Intermediate tetraethyl 2-(4-carboxybutyl)-2-(4-carboxybenzyl)--1,3-propanedioate (*XVIII*), prepared analogously to[1], b.p. 246–251°C/130 Pa, purified by column chromatography on silica gel, elution with chloroform; for $C_{24}H_{34}O_8$ (450·5) calculated: 63·98% C, 7·61% H; found: 63·46% C, 7·59% H.



XIV, $R^2 = C_3H_7$
XV, $R^2 = CH_2—CH=CH_2$
XVI, $R^2 = CH_2—C\equiv CH$

XVII, $R^2 = C_6H_5$
XVIII, $R^2 = (CH_2)_4—COOC_2H_5$

In the screening for antineoplastic activity in animals with experimental tumours the acid *VIII* exhibited a moderate effect. In a dose of 100 mg/kg administered *s.c.* to mice with tumours Sa 37 it reduced the size of the tumours by 31%, in a dose of 50 mg/kg by 25%, but did not extend the survival. The acid *X*, 100 mg/kg *s.c.*, extended the survival of mice with tumours S 180 and with Yoshida tumours by 20% and 21%, respectively. The esters *II* – *VI* exhibited no antineoplastic activity whatever. The tested compounds seemed to be non-toxic.

EXPERIMENTAL

The melting points, determined on the Kofler block, are not corrected. The analytical samples were dried at a pressure of 27 Pa over P_2O_5 at temperatures adequate to their melting points. The UV spectra of compounds *II* – *VI* were measured, employing a spectrophotometer Unicam SP 8000, in 0·1M-HCl in 50% methanol (A), or 0·1M-NaOH in 50% methanol (B) or in methanol (C). The IR spectra in KBr pellets were recorded with an apparatus Hilger–Watts. The individuality of the compounds was verified by TLC in a system chloroform–methanol–25% ammonia (2 : 2 : 1), or propanol–25% ammonia–water (7 : 1 : 2), using FP-Kieselgel F_{254} Merck, migration distance 15 cm, and detection with UV light, or reflex silica gel foils with a luminiscent indicator (Silufol UV_{254}, Kavalier).

Butyl 4-[(2-Amino-6-hydroxy-4-oxo-3,4-dihydro-5-pyrimidinyl)methyl]benzoate (*V*)

To 300 ml of butanol was added dropwise, under stirring and cooling to −35 to −40°C, 7·84 g (0·066 mol) of thionyl chloride, then 7·83 g (0·03 mol) of the acid *I* was added in portions and the suspension was stirred for 2 h at 40°C and for another 2 h at 80°C. The excess of butanol was distilled off under reduced pressure and the residue was stirred up with 400 ml of water. The suspension was neutralized with sodium hydrogen carbonate and left standing overnight. The separated product was collected on a filter and purified; yield 11·01 g of the ester *V*. Using the same procedure and the corresponding alcohols we prepared the esters *II*–*IV* and *VI* (Table I).

4-[(2-Amino-4,6-dioxo-5-chloro-3,4,5,6-tetrahydro-5-pyrimidinyl)methyl]benzoic Acid (*VII*)

7·84 g (0·03 mol) of the acid *I* was suspended in a mixture of 240 ml of 10% hydrochloric acid and 48 ml of 30% hydrogen peroxide. The mixture was left standing for a fortnight at room temperature with an occasional shaking. The product was collected on a filter and purified; yield 8·00 g of the acid *VII*.

4-[(2-Amino-4,6-dioxo-5-bromo-3,4,5,6-tetrahydro-5-pyrimidinyl]methyl)benzoic Acid (*VIII*)

5·22 g (0·02 mol) of the acid *I* was suspended in 200 ml of water and 2 ml of bromine was slowly added dropwise under stirring. The mixture was stirred for 2 h at room temperature, the product was collected on a filter and purified; yield 6·64 g of the acid *VIII*.

4-[(2-Amino-4,6-dioxo-5-allyl-3,4,5,6-tetrahydro-5-pyrimidinyl)methyl]benzoic Acid (*X*)

To a solution of 2·76 g (0·12 mol) of sodium in 40 ml of methanol was added 7·64 g (0·08 mol) of guanidine hydrochloride, the suspension was stirred for 10 min, 14·60 g (0·04 mol) of triethyl 2-allyl-2-(4-carboxybenzyl)-1,3-propanedioate (*XV*) was added and the mixture was stirred for 4 h at room temperature. Methanol was distilled off under the reduced pressure of a water pump and 80 ml of 0·5M-NaOH was added to the residue. The mixture was stirred for 2 h at room temperature and left standing overnight. Following a brief boil it was acidified with dilute (1 : 1) hydrochloric acid to pH 2 and the separated product was collected on a filter and purified; yield 6·95 g of the acid *X*.

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