OXIDATIVE TRANSFORMATIONS OF SOME PYRIMIDINE DERIVATIVES INTO OXAZOLIDINE DERIVATIVES*

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The action of dilute hydrogen peroxide in aqueous alkaline solutions on compounds *I*—*VI* and *XX* produced derivatives of 2-iminooxazolidine-4-one, *VII*—*XI* and *XXI*. Their structures were demonstrated by spectral comparison with hydantoin derivatives *XXII*, *XXIV* and *XXV*, which were prepared from 2-aminoalkanedioic acids *XXVIII*, *XXX* and *XXXI* by reaction with potassium cyanate, followed by ring closure induced by a mineral acid. The structure of compound *X* was revealed by basic hydrolysis to 2-hydroxy-1,7-heptanedioic acid (*XXVII*) and by conversion of the latter, in an acid medium, into a derivative of oxazolidine-2,4-dione, *XXIX*. To elucidate the probable mechanism of the oxidative transformation, compound *IV* was converted by oxidation in an acid medium into the 5-hydroxy derivative *XXXII*. Exposure of the latter to an alkaline medium gave compound *X*. Bromination of acid *IV* with bromine, or with a mixture of potassium bromide and bromate in an acid solution, afforded the 5-bromo derivative *XXXIV*. Analogously, reaction of the acid *IV* with a mixture of hydrogen peroxide and hydrochloric acid gave the 5-chloro derivative *XXXV*. Boiling the compound *XXXIV* in aqueous sodium hydroxide led to the acid *IV* and a smaller amount of compound *X*. Reaction of the compound *X* with morpholine yielded the morpholine analogue *XXXVI*.

In the screening for antineoplastic activity, compounds *XXXII* and *XXXVI* showed weak antitumorous effects with some types of experimental tumours. Compound *X* was quite ineffective in the general pharmacological screening.

In studying the antineoplastic activity of ω-(2-amino-4-oxo-6-hydroxy-3,4-dihydropyrimidine-5-yl)alkane acids *I*—*V* we observed[1] that 5-(2-amino-4-oxo-6-hydroxy-3,4-dihydropyrimidine-5-yl)pentanoic acid (*IV*), called Damvar, had a power to modulate the biological responses to other drugs, administered in combination with it[2–4]. The acid *IV* is rather stable when in solid state, but in the form of alkaline salts in aqueous solutions it readily undergoes oxidation and decomposition[5].

The present paper deals with the mechanism of the oxidative transformation reaction, characterization of the products, syntheses of compounds needed for elucidat-

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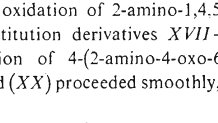
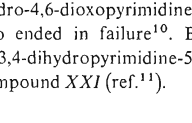
ing the mechanism of the oxidation transformation, and spectral corroboration of the assumed structures of the products. The biological activity of selected compounds has also been investigated.

The course of the oxidative transformation was first studied[1] with the acids *I*–*V* and the ester *VI*, and on the basis of the findings obtained we chose reaction conditions for other derivatives of pyrimidine (*XIII*–*XX*). The compound *I*–*VI* were taken into aqueous solutions by the action of dilute ammonium hydroxide and were then treated with 2–3% hydrogen peroxide for 1 to 2 weeks at room temperature. After acidification of the reaction mixtures with hydrochloric acid we isolated compounds *VII*–*XI* (Table I), which were identified, on the basis of spectral analysis, as 5-substitution derivatives of 2-iminooxazolidine-4-one.

The course of the oxidative transformation was studied in greater detail on the compound *IV*. We have found that the corresponding oxazolidine derivative *X* can also be obtained by bubbling oxygen or air through a solution of the compound *IV* in aqueous ammonia or alkali hydroxide. The formation of compound *X* from ester *VI* is in accordance with the ready hydrolysis of the ester group in the medium used[1]. The compound *X* was also characterized in the form of the ethyl ester *XII* (Table I), prepared by reaction of the compound *X* with the addition product of thionyl chloride and ethanol, in analogy with refs[6–8]. To ascertain whether the oxidative transformation occurs with other derivatives of pyrimidine we applied hydrogen peroxide in aqueous ammonia to other 2-substitution derivatives and analogues of the compound *IV*, *i.e.* compounds with a mercapto (*XIII*, ref.[1]), hydroxy (*XIV*, ref.[1]) or benzylamino group (*XV*, ref.[9]) at the 2-position. The oxidative transformation did not occur. Attempted oxidation of 2-amino-1,4,5,6-tetrahydro-4,6-dioxopyrimidine (*XVI*) and its 5,5-substitution derivatives *XVII*–*XIX* also ended in failure[10]. By contrast, the oxidation of 4-(2-amino-4-oxo-6-hydroxy-3,4-dihydropyrimidine-5-yl)-methylbenzoic acid (*XX*) proceeded smoothly, giving compound *XXI* (ref.[11]).





I: $R^1 = H$, $R^2 = NH_2$, $n = 1$
II: $R^1 = H$, $R^2 = NH_2$, $n = 2$
III: $R^1 = H$, $R^2 = NH_2$, $n = 3$
IV: $R^1 = H$, $R^2 = NH_2$, $n = 4$
V: $R^1 = H$, $R^2 = NH_2$, $n = 5$
VI: $R^1 = CH_3$, $R^2 = NH_2$, $n = 4$
XIII: $R^1 = H$, $R^2 = SH$, $n = 4$
XIV: $R^1 = H$, $R^2 = OH$, $n = 4$
XV: $R^1 = H$, $R^2 = NHCH_2C_6H_5$, $n = 4$

VII: $R^1 = H$, X = NH, $n = 1$
VIII: $R^1 = H$, X = NH, $n = 2$
IX: $R^1 = H$, X = NH, $n = 3$
X: $R^1 = H$, X = NH, $n = 4$
XI: $R^1 = H$, X = NH, $n = 5$
XII: $R^1 = C_2H_5$, X = NH, $n = 4$
XXIX: $R^1 = H$, X = O, $n = 4$

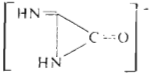
The elemental analyses, IR spectra, NMR spectra and mass spectra of the oxidation products did not allow us to decide unequivocally on their structures, since, in analogy to reported data[12-17] on conversions of substituted barbituric acids, both the 5-substitution derivatives of hydantoin (*XXII*–*XXVI*) and derivatives of oxazolidine-4-one (*VII*–*XI*) were possible. As the literature gives no fundamental spectral data for comparing the two types of compounds, we chose other approaches to the problem. Compound *X* was hydrolysed by the action of barium hydroxide in an autoclave at 160°C and the isolated and spectrally corroborated product was 2-hydroxy-1,7-heptanedioic acid (*XXVII*), instead of 2-amino-1,7-heptanedioic acid (*XXVIII*), which would have resulted from hydrolysis of the hydantoin derivative *XXV*. In another test compound *X* was hydrolysed with 10% sulphuric acid, the product being 5-(4-carboxybutyl)oxazolidine-2,4-dione (*XXIXa*) (Table I), whose solid state, as the IR spectrum suggests, seems to be the enol form *XXIXb*.

TABLE I
Some 5-substitution derivatives of oxazolidine 4-one

Compound *n*	X R	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found % C	% H	% N
VII	NH	$C_5H_6N_2O_4$	229–231	37·98	3·83	17·72
1	H	(158·1)	(methanol–water)	37·79	3·72	17·76
VIII	NH	$C_6H_8N_2O_4$	225–226	41·86	4·68	16·28
2	H	(172·1)	(methanol–water)	42·10	4·81	16·26
IX	NH	$C_7H_{10}N_2O_4$	213–215	45·16	5·41	15·05
3	H	(186·2)	(methanol–water)	44·93	5·59	15·33
X	NH	$C_8H_{12}N_2O_4$	207–209	47·97	6·04	14·00
4	H	(200·1)	(methanol–water)	48·04	6·31	14·25
XI	NH	$C_9H_{14}N_2O_4$	196–198	50·46	6·59	13·08
5	H	(214·2)	(methanol)	50·40	6·55	13·22
XII	NH	$C_{10}H_{16}N_2O_4$	157–158	52·56	7·07	12·33
4	C_2H_5	(227·2)	(ethanol)	52·62	7·07	12·27
XXIX	O	$C_8H_{11}NO_5$	110–111	47·76	5·51	—
4	H	(201·2)	(water)	47·80	5·60	—
XXI	—	$C_{11}H_{10}N_2O_4$	305–308	56·41	4·30	11·96
		(234·2)	(dimethylformamide–water)	56·35	4·36	12·03

To verify and compare the results of spectral analysis of the oxazolidine derivatives and to rule out any coincidence in the interpretation of the spectra we synthetized hydantoin derivatives having ω-(carboxy)alkyl residues at the 5-position (*XXII*, *XXIV*, *XXV*). The procedure was analogous[18] to that described for the compound *XXII*, consisting in the reaction of the corresponding 2-aminoalkanedioic acid (*XXVIII*, *XXX*, *XXXI*) with potassium cyanate in an aqueous alkaline medium, followed by ring closure by hydrochloric acid at an elevated temperature.

The mass spectra of the hydantoin type compounds *XXII*, *XXIV* and *XXV* differ from those of *VII*–*XI* in several fundamental features. In the first place it is the formation, from the compounds *VII*–*XI*, of ions $C_2H_2N_2O^+$ (m/z 70) which give rise to very intense spectral peaks, mainly the principal ones. These ions are the product of rather a simple cleavage of the fundamental oxazolidine-4-one skeleton and can be ascribed structure *A*



A

With the hydantoin compounds the peaks m/z 70 are much less apparent and are produced by ions of different elemental compositions ($C_3H_4NO^{+\bullet}$, $C_4H_6O^{+\bullet}$, $C_4H_8N^{+\bullet}$, $C_5H_{10}^{+\bullet}$), which cannot originate from the oxazolidine structure. Ions of type *A* cannot be generated by a simple mechanism from hydantoin-like compounds. The differences in stability of molecular ions are of great importance. The hydantoin type compounds produce molecular ions which liberate water much more readily. This difference was especially significant with compounds *VII* and *XXII* (where $n = 1$). The molecular peak m/z 158 is intense in the case of the stable molecular ions of compound *VII*, but the molecular ion of compound *XXII* very readily releases water, as a result of close vicinity of carboxyl and an amide hydrogen, in contrast to compounds *VII*–*XI*, *XXIV* and *XXV* (Table II).

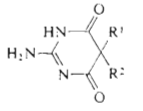
The foregoing results allow us to draw the conclusion that 5-substitution derivatives of oxazolidine-4-one arise from such pyrimidine derivatives as have an amino group at the 2-position, an ω-carboxyalkyl or carboxyaralkyl group at the 5-position and a tautomerisable hydroxy group at the 6-position. Transformation of such derivatives of pyrimidine is probably a complex one, and proceeds *via* intermediates which in the given reaction conditions are too labile to be isolated. In view of the ready oxidation of compound *IV* (ref.[2]) in an acid medium, even practically useful for analytical determination of the compound[19], we employed this reaction to elucidate the mechanism of the reaction; a suspension of the compound *IV* was oxidized by potassium dichromate in sulphuric acid and the 5-hydroxy derivative obtained (*XXXII*) was

TABLE II

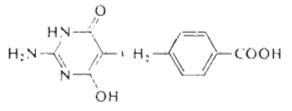
Mass spectra of the compounds prepared

Compound	$M^{+\cdot}$	$(M+1)^{+\cdot}$	*m/z* (rel. int. %)							
VII	158 (13)		70 (100)	44 (85)	42 (81)	71 (71)	43 (65)	113 (28)	69 (15)	87 (15)
VIII	172 (2)		70 (100)	42 (63)	85 (61)	71 (49)	43 (38)	44 (36)	113 (34)	100 (26)
IX	186 (0·5)		70 (100)	71 (70)	100 (60)	42 (57)	43 (45)	99 (33)	44 (25)	55 (20)
X	200 (0·3)		100 (100)	70 (91)	71 (56)	113 (47)	42 (47)	43 (37)	41 (28)	55 (20)
XI	214 (0·3)		100 (100)	70 (76)	71 (56)	42 (43)	43 (40)	87 (31)	41 (31)	55 (30)
XII	228 (2)		113 (100)	100 (91)	70 (54)	67 (50)	71 (45)	55 (38)	69 (25)	95 (20)
XXI	231 (16)		70 (100)	135 (89)	42 (76)	190 (74)	103 (38)	191 (38)	77 (38)	165 (37)
XXII	158 (0·6)		60 (100)	112 (77)	42 (61)	43 (31)	44 (30)	41 (29)	40 (17)	45 (15)
XXIV		187 (0·3)	43 (100)	168 (92)	60 (84)	112 (73)	42 (71)	100 (64)	41 (58)	99 (50)
XXV		201 (0·1)	43 (100)	100 (95)	55 (65)	138 (59)	41 (40)	126 (37)	56 (37)	73 (36)
XXVII		177 (0·1)	113 (100)	67 (66)	41 (38)	43 (33)	55 (30)	57 (23)	95 (22)	85 (20)
XXIX		202 (0·1)	55 (100)	101 (75)	83 (49)	41 (43)	43 (35)	44 (33)	42 (29)	39 (27)
XXXIII	271 (0·2)		86 (100)	55 (39)	101 (28)	143 (20)	114 (15)	73 (14)	83 (12)	59 (10)
XXXVI	270 (2)		170 (100)	112 (85)	42 (55)	113 (55)	70 (28)	55 (22)	41 (19)	183 (19)

also characterized in the ester form (*XXXIII*). Compound *XXXII* in the solid state proved very stable and practically insoluble in most solvents. However, in an aqueous alkaline medium it went into solution and was gradually converted into com-



XVI: $R^1, R^2 = H$
XVII: $R^1 = H$, $R^2 = C_2H_5$
XVIII: $R^1 = C_2H_5$, $R^2 = (CH_2)_4COOH$
XIX: $R^1, R^2 = (CH_2)_4COOH$



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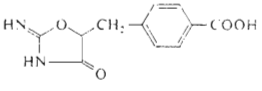
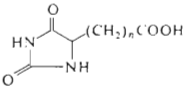
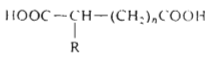


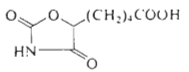
XXI



XXII: $n = 1$
XXIII: $n = 2$
XXIV: $n = 3$
XXV: $n = 4$
XXVI: $n = 5$



XXVII: R = OH, $n = 4$
XXVIII: $R = NH_2$, $n = 1$
XXX: $R = NH_2$, $n = 3$
XXXI: $R = NH_2$, $n = 4$



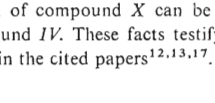
XXIXa *XXIXb*

pound *X*, in agreement with refs[12,13]. This fact accounts for the impossibility to isolate compound *XXXII* under alkaline conditions of the conversion. On the basis of these findings we assume that in both acid and alkaline solutions compound *IV* is hydroxylated by the action of the oxidizing medium. Compound *XXXII*, *i.e.* the primary oxidation product, can be isolated from an acid solution only. In alkaline media the process goes on, probably giving rise to enolate of the 5-hydroxy derivative. This derivative, in consistence with the assumptions in the literature[20], attacks the 2-position of the pyrimidine ring, thus producing an oxazolidine derivative. The action of an acid medium on the compound during its isolation splits off a residue from the pyrimidine skeleton and the oxidation product separates from the solution. Since the yields of the oxidation products were always about 60% we assume that the

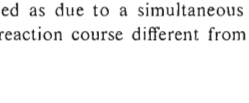
oxidation process was accompanied by side reactions whose products we failed to isolate.

The fact that compound *X* was formed from acid *IV* either by direct oxidation in the alkaline medium or indicretly by primary oxidation in the acid medium to the 5-hydroxy derivative *XXXII*, followed by basic hydrolysis of the latter, suggests the rule that the oxidative transformation is possible with such derivatives of pyrimidine as can form a 5-substituted 2-amino-4,6-dioxo-5-hydroxypyrimidine, *i.e.* compounds that can be hydroxylated at the 5-position.

The literature describes transformation of 5-bromobarbituric acids and its derivatives by the action of an alkaline medium on a mixture of oxazolidine-4-one and hydantoin derivatives[12,13,17]. To get a better insight into the course of the reaction we synthetized 5-bromo derivative *XXXIV* from compound *IV* by the action of bromine or a mixture of potassium bromide and bromate, and its 5-chloro analogue *XXXV* by the action of hydrogen peroxide in hydrochloric acid. The compound *XXXIV* was heated in aqueous sodium hydroxide, giving compound *IV* as the main product. TLC of the mother liquor detected compound *X*. This suggests that the replacement of the bromine atom at the 5-position by a hydroxyl group in the alkaline medium is not followed by transformation into a derivative of oxazolidine. The formation of compound *X* can be explained as due to a simultaneous oxidation of compound *IV*. These facts testify to a reaction course different from that propounded in the cited papers[12,13,17].



XXXII: $R^1 = H$, $R^2 = OH$
XXXIII: $R^1 = C_2H_5$, $R^2 = OH$
XXXIV: $R^1 = H$, $R^2 = Br$
XXXV: $R^1 = H$, $R^2 = Cl$



XXXVI

In the literature, derivatives of oxazolidine are regarded as drugs affecting the central nervous system, anticonvulsive or psychoenergetic. In analogy to a described procedure[21] we modified compound *X* by the action of morpholine in ethanol to the morpholine derivative *XXXVI*, and both compounds were tested *in vivo* for the expected biological activity. However, none whatever was observed. Analogously, in assessing the antineoplastic activity in animals with transplanted tumours compounds *VII*–*XI* and *XXI* proved ineffective, whereas *XXXVI*, administered *s.c.* in a dose of 100 mg/kg, extended survival of rats with Yoshida tumours by 28% and of mice with Crocker tumours S 180 by 60%, the reduction of tumour size being

not significant. Antineoplastic screening of compound *XXXII* gave results similar to those obtained with compound *IV* (ref.[1]). Compounds *XXXIV* and *XXXV* exhibited no activity.

EXPERIMENTAL

The melting points, determined on the Kofler stage, are not corrected. The analytical samples were dried over phosphorus pentoxide at a pressure of 27 Pa and temperatures proportional to their melting points. The IR spectra were recorded employing the KBr technique and 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 mass spectra were measured with an apparatus MS-9. Purity of the compounds was tested by TLC on silica gel plates (DC-Fertigplatten Kieselgel F_{254}, Merck) or on reflex foils Silufol UV_{254} (Kavalier) in systems 1-propanol–ammonia–water (7 : 1 : 2) or chloroform–methanol–ammonia (2 : 2 : 1). The spots were detected by UV light (254 nm) or by chlorination.

5-Substitution Derivatives of 2-Iminooxazolidine-4-one (*VII*–*XI*, *XXI*)

To a suspension of 10 mmol of compound *I*–*VI* or *XX* in 50 ml of water was added dropwise concentrated ammonium hydroxide until the solution had clarified (pH 8–9), then 6 ml of 30% hydrogen peroxide was added. The mixture was left standing at room temperature until no starting compound could be detected by TLC (1–2 weeks), acidified with dilute hydrochloric acid (1 : 1) to pH 3 and left standing overnight at 5°C. The separated crystals were collected on a filter, washed with cold water and purified by recrystallization. The mass spectra are given in Table II.

VII: Acid *I* (2·0 g), reaction time 1 week, yield 0·9 g (58%). ^{1}H NMR spectrum: δ 8·35 (bs, 2 H, NH), 4·96 (dd, J = 3·0; 8·5 Hz, 1 H, OCH), 2·65 (m, 2 H, CH_2COOH).

VIII: Acid *II* (2·0 g), reaction time 2 weeks, yield 0·9 g (52%). ^{1}H NMR spectrum: δ 8·30 (bs, 2 H, NH), 4·70 (dd, J = 3·0; 8·5 Hz, 1 H, OCH), 1·60–2·60 (m, 4 H, aliphatic CH_2).

IX: Acid *III* (2·1 g), reaction time 1 week, yield 1·1 g (60%).

X: *a*) Acid *IV* (2·3 g), reaction time 2 weeks, yield 1·3 (65%); *b*) ester *VI* (2·4 g), reaction time 1 week, yield 1·2 g (60%). ^{1}H NMR spectrum: δ 8·22 (bs, 1 H, CONH), 4·58 (t, 1 H, NCH), 2·12 (bt, 2 H, CH_2COOH), 1·00–1·90 (m, 6 H, aliphatic CH_2). IR spectrum: 3 240 (NH), 1 690, 1 290 (COOH), 1 670, 1 560 cm^{-1} (sec-amide).

XI: Acid *V* (2·4 g), reaction time 2 weeks, yield 1·5 g (62%). ^{1}H NMR spectrum: δ 8·25 (bs, 2 H, NH), 4·65 (bt, 1 H, OCH), 2·18 (bt, 2 H, CH_2COOH), 1·10–1·90 (m, 8 H, aliphatic CH_2).

XXI: Acid *XX* (2·6 g), reaction time 2 weeks, yields 1·2 g (51%). ^{1}H NMR spectrum: δ c. 8·50 (bs, 1 H, NH), 8·30 (bs, 1 H, CONH), 7·89 (d, J = 8·5 Hz, 2 H, *p*-substituted Ar-α C=O), 7·45 (d, J = 8·5 Hz, 2 H, *p*-substituted Arα-CH_2), 5·00 (dd, J = 8·0; 4·0 Hz, 1 H, OCH), 3·10 (m, 2 H, CH_2Ar). IR spectrum: 3 265 (NH), 1 680 (COOH), 1 660, 1 550 (sec-amide), 1 610, 1 575 cm^{-1} (Ar).

Ethyl 5-(2-Amino-4-oxooxazolidine-5-yl)pentanoate (*XII*)

To 20 ml of ethanol at −70°C was added dropwise under stirring 0·87 ml (1·4 g, 12 mmol) of thionyl chloride, then 2·0 g (10 mmol) of 5-(2-imino-4-oxooxazolidine-5-yl)pentanoic acid (*X*) was added

and the stirring was continued for 15 min. The mixture was allowed to attain room temperature, then it was warmed to 40°C and stirred for 2 more hours. The volatile components were removed *in vacuo* (water jet pump), the residue was stirred up in 50 ml of water, cautiously alkalinized with sodium hydrogen carbonate to pH 7·5, and the suspended solid was collected on a filter, washed with water and dried; yield 1·4 g (61·4%). ^{1}H NMR spectrum: δ 8·40 (bs, 2 H, NH), 4·68 (bt, 1 H, OCH), 4·05 (q, J = 7·0 Hz, 2 H, OCH_2), 2·28 (bt, 2 H, CH_2CO), 1·30—1·80 (m, 6 H, aliphatic CH_2), 1·18 (t, J = 7·0 Hz, 3 H, $OCH-CH_3$).

5-(Carboxymethyl)hydantoin (*XXII*)

The compound was prepared from aspartic acid in analogy to the procedure described[18]; m.p. 215—217°C (water), reported[18] m.p. 214—216°C.

5-(3-Carboxypropyl)hydantoin (*XXIV*)

To a suspension of 7·8 g (48·5 mmol) of 2-amino-1,6-hexanedioic acid (*XXX*) in 50 ml of 1M aqueous potassium hydroxide was added 4·0 g (50 mmol) of potassium cyanate; the mixture was stirred for 1 h and left standing overnight. The undissolved portion was removed by filtration and the filtrate was acidified with dilute (1 : 1) hydrochloric acid to pH 2. The mixture was taken to dryness in a vacuum evaporator and the residue was stirred up in 100 ml of ethanol. The undissolved component (KCl) was filtered off, the filtrate was concentrated and 12 ml of dilute (1 : 1) hydrochloric acid was added. The mixture was boiled under a reflux condenser for 2 h, then concentrated to half the volume. The substance that separated after cooling was collected on a filter (2·3 g, 25·5%) and purified by crystallization from water; m.p. 167—168°C. For $C_7H_{10}N_2O_4$ (186·2) calculated: 45·16% C, 5·41% H, 15·05% N; found: 44·93% C, 5·32% H, 15·24% N. ^{1}H NMR spectrum: δ 11·65 (bs, 1 H, CONHCO), 7·98 (bs, 1 H, CONH), 4·00 (bm, 1 H, NCH), 2·20 (bt, 2 H, CH_2COOH), 1·60 (bm, 4 H, aliphatic CH_2).

5-(4-Carboxybutyl)hydantoin (*XXV*)

To a solution of 3·0 g (17 mmol) of 2-amino-1,7-heptanedioic acid (*XXXI*) in 18 ml of 1M-KOH was added 1·7 g (20 mmol) of potassium cyanate. The mixture was left standing overnight, brought to pH 2 with dilute hydrochloric acid, and taken to dryness. The residue was stirred up in 50 ml of ethanol, the insoluble inorganic salt was filtered off, the filtrate was concentrated and boiled with dilute (1 : 1) hydrochloric acid. The volatile portions were distilled off and the residue was crystallized from water; yield 0·9 g (26%) of the product, m.p. 150—151°C. For $C_8H_{12}N_2O_4$ (200·2) calculated: 48·00% C, 6·04% H, 13·99% N; found: 48·25% C, 6·15% H, 13·82% N. ^{1}H NMR spectrum: δ 11·60 (bs, 1 H, CONHCO), 7·90 (bs, 1 H, CONH), 4·00 (bm, 1 H, NCH), 2·18 (bt, 2 H, CH_2COOH), 1·50 (bm, 6 H, aliphatic CH_2).

Hydrolysis of Compound *X* to 2-Hydroxy-1,7-heptanedioic Acid (*XXVII*)

A steel autoclave, volume 100 ml, was charged with 6·5 g (20 mmol) of barium hydroxide octahydrate, dissolved in 50 ml of water, and 2·0 g (10 mmol) of compound *X*. The mixture was heated to 170°C with occasional stirring. After cooling, a 2% solution of ammonium carbonate (50 ml) was added, the precipitate was filtered off and the filtrate was taken to dryness. The residue, dissolved in 25 ml of water, was applied to a column of 50 g of Dowex 80 W in the H-form. After elution with water and crystallization of the combined fractions from water there was obtained 0·9 g (45·9%) of the product, m.p. 93—94°C; reported[22] m.p. 89·5—90·5°C. ^{1}H NMR spectrum: δ 3·88 (t, 1 H, CHOH), 2·15 (bt, 2 H, CH_2CO), 1·40 (m, 6 H, 3 CH_2). IR spectrum: 1 700, 1 260 cm^{-1} (COOH).

5-(4-Carboxybutyl)oxazolidine-2,4-dione (*XXIX*)

A suspension of 5·0 g (25 mmol) of compound *X* in 100 ml of 10% sulphuric acid was boiled under a reflux condenser for 30 min. The solution thus formed was cooled down and allowed to crystallize in a refrigerator. The separated substance was collected on a filter and purified by crystallization from water; yield 3·2 g (64%) of compound *XXIX*, m.p. 110–111°C. ^{1}H NMR spectrum: δ 11·90 (bs, 1 H, CONHCO), 4·98 (t, J = 6·0 Hz, 1 H, OCH), 2·19 (bt, 2 H, CH_2.COOH), 1·10–2·00 (m, 6 H, aliphatic CH_2). IR spectrum: 1 785 (lactone), 1 730 cm^{-1} (COOH).

5-(2-Amino-4,6-dioxo-5-hydroxy-1,4,5,6-tetrahydropyrimidine-5-yl)pentanoic Acid (*XXXII*)

To a suspension of 10 g (44 mmol) of compound *IV* in 100 ml of water was added 10 g of potassium dichromate and 20 ml of 5M sulphuric acid. The mixture was stirred at 20 to 25°C for 1 h. The suspension was collected on a filter, washed with water and ethanol, taken in 30 ml of water and stirred for another 15 min, collected on a filter, washed with water and ethanol, and dried; yield 7·2 g (67%) of the product, m.p. 243–249°C. For $C_9H_{13}N_3O_5$ (243·2) calculated: 44·44% C, 5·39% H, 17·28% N; found: 44·09% C, 5·61% H, 17·42% N.

Ethyl 5-(2-Amino-4,6-dioxo-5-hydroxy-1,4,5,6-tetrahydropyrimidine-5-yl)pentanoate) (*XXXIII*)

To 20 ml of ethanol at −70°C was added dropwise under stirring 0·87 ml (12 mmol, 1·4 g) of thionyl chloride, then 2·43 g (10 mmol) of acid *XXXII* was added. The mixture was stirred for 15 min, warmed to 40°C and kept at this temperature for 2 h, then it was boiled under a reflux condenser until a clear solution had formed (2 h). The solution was taken to dryness, the residue was stirred up in 50 ml of water and the solution was brought to pH 7·5 with sodium carbonate. The separated solid was collected on a filter, washed with water, dried and crystallized from ethanol; yield 1·8 g (66%) of the product, m.p. 238–240°C. For $C_{11}H_{17}N_3O_5$ (271·3) calculated: 48·70% C, 6·32% H, 15·49% N; found: 48·81% C, 6·26% H, 15·58% N. For mass spectrum see Table II.

5-(2-Amino-5-bromo-4,6-dioxo-1,4,5,6-tetrahydropyrimidine-5-yl)pentanoic Acid (*XXXIV*)

a) To a suspension of 5 g (22 mmol) of compound *IV* in a mixture of 100 ml of acetic acid, 20 ml of 20% aqueous potassium bromide and 20 ml of 20% hydrochloric acid was added dropwise under stirring 40 ml of 1M potassium bromate. The mixture was stirred at room temperature for 1 h, concentrated to half the volume and left standing in a refrigerator to crystallize. The product was collected on a filter, washed with water and ethanol, and dried, m.p. 193–197°C.

b) To a suspension of 6·8 g (30 mmol) of compound *IV* in 300 ml of water was added dropwise at 20–25°C 4·8 g (60 mmol) of bromine and the mixture was stirred for 2 h. The suspension was collected on a filter, washed with water and dried; m.p. 193–195°C. For $C_9H_{12}BrN_3O_4$ (305·1) calculated: 35·31% C, 3·95% H, 26·11% Br, 13·73% N; found: 35·50% C, 3·98% H, 26·24% Br, 13·66% N.

5-(2-Amino-5-chloro-4,6-dioxo-1,4,5,6-tetrahydropyrimidine-5-yl)pentanoic Acid (*XXXV*)

To a suspension of 4·5 g (20 mmol) of compound *IV* in 160 ml of dilute (1 : 2) hydrochloric acid at 20–25°C was added under stirring 30 ml of 30% hydrogen peroxide and the mixture was left standing at this temperatur for a week. The suspension was collected on a filter, washed with hot water and dried; m.p. 214–216°C (decomposition). For $C_9H_{12}ClN_3O_4$ (261·6) calculated: 41·29% C, 4·62% H, 13·55% Cl, 16·06% N; found: 41·38% C, 4·60% H, 13·42% Cl, 16·23% N.

Conversion of Acid XXXII into Compound *X*

A solution of 486 mg (2 mmol) of the acid *XXXII* in 10 ml of 5% aqueous ammonium hydroxide was left standing overnight at room temperature. After concentration to half the volume the mixture was brought to pH 3 with hydrochloric acid and left standing to crystallize. The crop was collected on a filter, washed with cold water and dried; yield 298 mg (74·5%) of compound *X*, m.p. 208—209°C.

Conversion of Acid *XXXIV* into *IV*

A solution of 612 mg (2 mmol) of the acid *XXXIV* in 20 ml of 10% sodium hydroxide was boiled under a reflux condenser for 4 h. After cooling the solution was brought to pH 3 with dilute (1 : 1) hydrochloric acid. The precipitate was collected on a filter, washed with water and dried; yield 0·3 g (66%) of acid *IV*, m.p. 312—316°C (ref.[1]).

5-(4-Carboxybutyl)-2-(4-morpholinyl)oxazolidine-4-one (*XXXVI*)

A solution of 2·0 g (10 mmol) of compound *X* in 100 ml of ethanol, and 1·74 g (20 mmol) of morpholine was boiled under a reflux condenser for 11 h. The volatile components were removed by distillation and the residue was crystallized from 2-propanol; yield 2·4 g (88%), m.p. 120 to 122°C. For $C_{12}H_{19}N_2O_5$ (271·3) calculated: 53·13% C, 7·06% H, 10·33% N; found: 53·30% C, 6·86% H, 10·31% N. ^{1}H NMR spectrum (deuteriochloroform): δ 10·50 (bs, 1 H, COOH), 4·70 (bt, 1 H, OCH), c. 3·70 (m, 8 H, cycl. CH_2), 2·30 (bt, 2 H, CHCOOH), 1·30—2·10 (m, 6 H, aliphatic CH_2). IR spectrum: 1 725 (COOH), 1 700 cm^{-1} (amide).

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