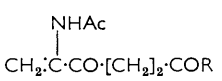
73. *The Synthesis of Primocarcin and Analogues.**

By R. E. Bowman, M. D. Closier, and P. J. Islip.

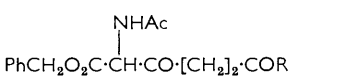
The synthesis of primocarcin, 5-acetamido-4-oxohex-5-enamide, and a number of analogues is described.

This Paper describes the synthesis of primocarcin (I; R = NH_2), an antitumour antibiotic isolated from *Nocardia fukayae*.[1] Reduction of 1-benzyl 6-ethyl 2-hydroxyimino-3-oxohexane-1,6-dioate [2] with zinc–acetic acid–acetic anhydride afforded, in high yield, 1-benzyl 6-ethyl 2-acetamido-3-oxohexane-1,6-dioate (II; R = OEt). Attempts to prepare the amide (II; R = NH_2) from this ester and ammonia failed. The ester (II; R = OEt) with alkaline formaldehyde solution gave the hydroxymethyl derivative (III; R = OEt), which, on catalytic hydrogenation over 10% palladised strontium carbonate followed by dehydration with pyridine,[3] gave an oil [$\lambda_{max.}$ 256 mμ (ε 2350)] (I; R = OEt). Treatment with ammonia gave a gum, which from infrared and ultraviolet measurements was not the required amide (I; R = NH_2).

The hydroxymethyl ester (III; R = OEt) with aminomagnesium bromide [4] furnished the ester (II; R = OEt) in good yield. Hydrolysis of the ester (II; R = OEt) with



(I)



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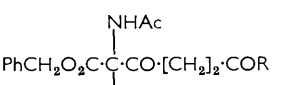


(III)

concentrated hydrochloric acid at 0° gave 1-benzyl hydrogen 2-acetamido-3-oxohexane-1,6-dioate (II; R = OH). Neuberger and his co-workers [2] reported the synthesis of this acid, in low yield, from 1-benzyl 6-ethyl 2-hydroxyimino-3-oxohexane-1,6-dioate. The above method affords the acid (II; R = OH) in 65% overall yield from the oxime.

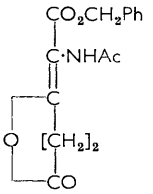
Treatment of the acid (II; R = OH) with triethylamine and ethyl chloroformate at 0° gave the enol lactone (IV) [$\nu_{max.}$ 1826 cm.$^{-1}$ (lactone C=O) and $\lambda_{max.}$ 235 mμ (ε 11,900)].

* Preliminary communication, Bowman, Closier, and Islip, *Tetrahedron Letters*, 1964, 1897.

[1] (*a*) Isono and Suzuki, *J. Antibiotics* (*Tokyo*), *Ser. A*, 1962, **15**, 77; (*b*) Isono, *ibid.*, p. 80.
[2] Laver, Neuberger, and Scott, *J.*, 1959, 1474.
[3] Cf. Alberti, Bernardi, Camerino, Cattapan, Larini, and Vercellone, *Gazzetta*, 1954, **84**, 512.
[4] Cf. Oddo and Calderaro, *Gazzetta*, 1923, **53**, 64.

With ethanol, the lactone gave the ester (II; R = OEt), and with ammonia in dioxan, the amide (II; R = NH_2) in high yield.

Hydroxymethylation of the foregoing amide with formaldehyde and sodium hydrogen carbonate [5] afforded the hydroxymethyl amide (III; R = NH_2). Hydrogenation of this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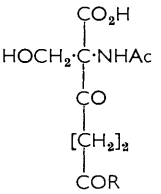
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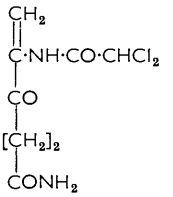
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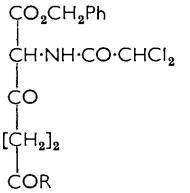
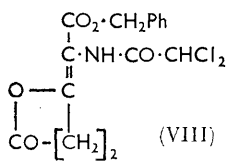

(VII)

amide over 10% palladised strontium carbonate afforded primocarcin (I; R = NH_2), m. p. and mixed m. p. 127—128°, $\lambda_{max.}$ 253 mμ (ε 3600) [lit.,[1a] m. p. 130—131°, $\lambda_{max.}$ 253 mμ (ε 3420)] whose infrared spectrum was identical with that of an authentic sample. The intermediate β-keto-acid (V; R = NH_2) appeared to be relatively stable, and decarboxylation (followed by dehydration) occurred only on evaporation of the hydrogenation mixture.

In a similar manner, hydrogenation of the amides (III; R = NHMe, NMe_2, and NHPh) [prepared from the lactone (IV) and the appropriate amine, followed by hydroxymethylation] afforded the primocarcin analogues (I; R = NHMe, NMe_2, and NHPh).

Hydroxymethylation of the acid (II; R = OH) gave the acid (III; R = OH), which was also hydrogenated to 5-acetamido-4-oxohex-5-enoic acid (I; R = OH). Decarboxylation (and subsequent dehydration) of the intermediate α-acetamido-β-keto-acids (V; R = OH and NHPh) was slow (*ca.* 20 min.) and did not start until the evaporated hydrogenation mixture had been triturated with ethanol, and scratched.

In an attempt to prepare the dichloro-analogue (VI) of primocarcin, 1-benzyl 6-ethyl 2-hydroxyimino-3-oxohexane-1,6-dioate was reduced with zinc–acetic acid and the product treated with dichloroacetyl chloride. The resulting ester was hydrolysed with cold concentrated hydrochloric acid to the acid (VII; R = OH), which with triethylamine and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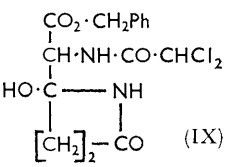
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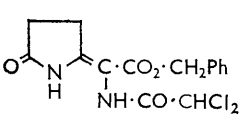
(X)

ethyl chloroformate gave the lactone (VIII). The amide, from the lactone and ammonia, was found to exist in the cyclic form (IX) rather than the straight-chain form (VII; R = NH_2) [$\nu_{max.}$ ($CHCl_3$) 3640 $cm.^{-1}$ (OH)]. It readily dehydrated to the pyrrolidone (X) [$\lambda_{max.}$ 266 mμ (ε 21,000)], and all attempts to hydroxymethylate it failed.

Experimental

Unless otherwise stated, all evaporations were carried out *in vacuo* with a bath temperature of less than 30°.

Zinc–Acetic Acid Reductions of 1-Benzyl 6-Ethyl 2-Hydroxyimino-3-oxohexane-1,6-dioate.—(*a*) *With acetic anhydride.* Zinc dust (80 g.) was added to a stirred, cooled solution of the oxime [2] (35 g.) in acetic acid (125 c.c.) and acetic anhydride (75 c.c.) at such a rate that the internal temperature remained below 45°. After 2 hr. the zinc was collected, washed with

[5] Long and Troutman, *J. Amer. Chem. Soc.*, 1949, **71**, 2473.

ether, and the combined filtrates evaporated (100°) to give a gum (34·7 g.) which crystallised on trituration with ether. Recrystallisation from ether afforded needles of 1-*benzyl* 6-*ethyl* 2-*acetamido*-3-*oxohexane*-1,6-*dioate*, m. p. 69—70° (Found: C, 61·2; H, 6·4; N, 4·5. $C_{17}H_{21}NO_6$ requires C, 60·9; H, 6·3; N, 4·2%).

(*b*) *With propionic anhydride.* In a similar manner the oxime (7·0 g.) in acetic acid (15 c.c.) was reduced with zinc dust (16 g.). After 2 hr. the zinc was filtered off, and the filtrate treated with propionic anhydride. Evaporation (100°) and recrystallisation of the residue from ether furnished the 2-*propionamido-analogue* (3·4 g.) as needles, m. p. 70·5—71·5° (Found: C, 62·1; H, 6·8; N, 4·2. $C_{18}H_{23}NO_6$ requires C, 61·9; H, 6·6; N, 4·0%). Mixed m. p. with the acetamido-compound was 58—63°.

(*c*) *With dichloroacetyl chloride.* The oxime (12·9 g.) in acetic acid (46 c.c.) was reduced with zinc dust (29·5 g.). After removal of the zinc, the solution was treated with dichloroacetyl chloride (10 c.c.) (with cooling) and left for 1½ hr. Evaporation (100°), and isolation of the neutral material with ether gave 1-*benzyl* 6-*ethyl* 2-*dichloroacetamido*-3-*oxohexane*-1,6-*dioate* (8·0 g.) as prisms, m. p. 66—67° (from aqueous ethanol) (Found: C, 50·4; H, 4·8; N, 3·7. $C_{17}H_{19}Cl_2NO_6$ requires C, 50·5; H, 4·7; N, 3·5%).

1-*Benzyl Hydrogen* 2-*Acetamido*-3-*oxohexane*-1,6-*dioate*.—1-Benzyl 6-ethyl 2-acetamido-3-oxohexane-1,6-dioate (50 g.) was dissolved in concentrated hydrochloric acid (250 c.c.) and the solution left overnight at 0°. Solid was filtered off, pressed dry, ground up with water, and collected (33 g.), needles, m. p. 99—100° (lit.,[2] 105·5—106° or 130—131·5°) (Found: C, 58·6; H, 5·7; N, 4·4. Calc. for $C_{15}H_{17}NO_6$: C, 58·6; H, 5·6; N, 4·6%).

1-*Benzyl Hydrogen* 2-*Dichloroacetamido*-3-*oxohexane*-1,6-*dioate*.—The dichloro-ester (17·1 g.) was suspended in concentrated hydrochloric acid (196 c.c.) and enough ether was added until solid just dissolved without the formation of two layers; the solution was then left overnight at 0°. Ether was removed, the solid collected, washed with water, and recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) to give the *acid* as clusters of needles, m. p. 120—121° (Found· C, 47·9; H, 4·0; N, 3·9. $C_{15}H_{15}Cl_2NO_6$ requires C, 47·9; H, 4·0; N, 3·7%).

γ-(*Acetamidobenzyloxycarbonylmethylene*)-γ-*butyrolactone* (IV).—A solution of 1-benzyl hydrogen 2-acetamido-3-oxohexane-1,6-dioate (4·54 g.) and triethylamine (2·06 c.c.) in chloroform (15 c.c.) at 0° was treated dropwise with ethyl chloroformate (1·42 c.c.). After the gas evolution ceased, the solution was stirred for ½ hr. and the neutral material isolated with chloroform (counter-extraction with ethyl acetate). The *lactone* (2·75 g.) separated from ethyl acetate as needles, m. p. 119—120° (Found: C, 62·4; H, 5·2; N, 5·0. $C_{15}H_{15}NO_5$ requires C, 62·3; H, 5·2; N, 4·8%), $\nu_{max.}$ (Nujol) 1826 cm.$^{-1}$ (lactone C=O), $\lambda_{max.}$ (EtOH) 235 mμ (ε 11,900).

The lactone (0·2 g.) in ethanol (5 c.c.) with 2N-hydrochloric acid (0·1 c.c.) was heated on a steam-bath for 2 hr. Solvent was removed, and the residue crystallised from ether to give needles of 1-benzyl 6-ethyl 2-acetamido-3-oxohexane-1,6-dioate, m. p. and mixed m. p. 68—69°.

γ-(*Dichloroacetamidobenzyloxycarbonylmethylene*)-γ-*butyrolactone* (VIII).—In a similar manner the dichloro-acid (1·86 g.) with triethylamine (0·69 c.c.) and ethyl chloroformate (0·48 c.c.) in chloroform (10 c.c.) afforded the *dichloroacetamido-lactone* (0·66 g.) as clusters of needles, m. p. 154—155° (from ethyl acetate) (Found: C, 49·9; H, 3·3; Cl, 19·7. $C_{15}H_{13}Cl_2NO_5$ requires C, 50·3; H, 3·7; Cl, 19·8%), $\nu_{max.}$ (Nujol) 1821 cm.$^{-1}$ (lactone C=O).

Reaction of the Lactone (IV) *with Amines*.—The lactone was treated with a solution of the appropriate amine in dioxan (5 mol.), and the resulting solution left overnight. Solvent was removed, and the *product* (Table 1) recrystallised from ethyl acetate.

TABLE 1.

Benzyl 2-acetamido-3-oxo-5-(*N*-substituted carbamoyl)pentanoates (II).

			Found (%)				Required (%)		
R	M. p.	Yield (%)	C	H	N	Formula	C	H	N
NH_2	143—144°	80	59·0	6·0	9·1	$C_{15}H_{18}N_2O_5$	58·8	5·9	9·2
NHMe	131—132	78	60·1	6·7	9·0	$C_{16}H_{20}N_2O_5$	60·0	6·3	8·8
NMe_2	108—109	84	60·7	6·6	8·8	$C_{17}H_{22}N_2O_5$	61·1	6·6	8·4
NHPh	144—145	79	66·3	6·0	7·1	$C_{21}H_{22}N_2O_5$	66·0	5·8	7·3

Benzyl 5-*Carbamoyl*-2-*dichloroacetamido*-3-*oxopentanoate*.—The dichloro-lactone (0·93 g.) with 0·47M-ammonia in dioxan (15 c.c.) furnished the *amide* as prisms, m. p. 198—199° (decomp.)

(half-melts at 124—128° then resolidifies) [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 48·2; H, 4·7; N, 7·7. $C_{15}H_{16}Cl_2N_2O_5$ requires C, 48·0; H, 4·3; N, 7·5%). On heating at 150° for ½ hr. the last-mentioned amide afforded 5-(*dichloroacetamidobenzyloxycarbonyl methylene*)-2-*pyrrolidone* as needles, m. p. 200—201° (decomp.) (from ethyl acetate) (Found: C, 50·0; H, 3·8; N, 8·0. $C_{15}H_{14}Cl_2N_2O_4$ requires C, 50·4; H, 3·9; N, 7·8%).

Hydroxymethylation Experiments.—An excess of formaldehyde solution (40%) was added to (i) a suspension of the compound (*ca.* 10 g.) in ethanol and N-sodium hydroxide solution (0·5 c.c.) (method A), (ii) a solution of the compound in 1 equivalent of sodium hydrogen carbonate solution containing N-sodium hydroxide solution (0·5 c.c.) (method B), or (iii) a suspension of the compound in ethanol with sodium hydrogen carbonate (0·13 mol.) at 35° (method C). After the solid had dissolved, the solution was cooled, just acidified with glacial acetic acid, and the *product* (Table 2) collected by filtration, or isolated with ethyl acetate after dilution with water.

TABLE 2.

Hydroxymethyl compounds (III).

R	Method	M. p.	Yield (%)	Recryst. from	Found (%) C	H	N	Formula	Required (%) C	H	N
OEt	A	108—109°	83	Benzene	58·9	6·2	4·0	$C_{18}H_{23}NO_7$	59·2	6·3	3·8
OH	B	148—149	82	Water	57·3	5·8	4·0	$C_{16}H_{19}NO_7$	57·0	5·7	4·2
NH_2	C	122—123·5	60	Ethyl acetate	57·1	6·2	7·9	$C_{16}H_{20}N_2O_6$	57·1	6·0	8·3
NHMe	C	101—102	64	Ethyl acetate	57·9	6·4	7·7	$C_{17}H_{22}N_2O_6$	58·3	6·3	8·0
NMe_2	C	98—99	60	Ethyl acetate	59·6	6·8	7·9	$C_{18}H_{24}N_2O_6$	59·3	6·6	7·7
NHPh	C	139—140	50	Ethyl acetate	64·5	6·1	7·2	$C_{22}H_{24}N_2O_6$	64·1	5·9	6·8

1-*Benzyl* 6-*Ethyl* 2-*Acetamido*-2-*acetoxymethyl*-3-*oxohexane*-1,6-*dioate*.—The 2-hydroxymethyl ester (1·5 g.) in benzene (10 c.c.) was treated with acetyl chloride (3 c.c.) at 20°. After 2 hr. solvent was removed, and the *acetate* (1·3 g.) recrystallised from benzene–light petroleum (b. p. 60—80°) as prisms, m. p. 89—90° (Found: C, 58·6; H, 5·8; N, 3·3. $C_{20}H_{25}NO_8$ requires C, 59·0; H, 6·2; N, 3·4%).

Hydrogenation Experiments.—The hydroxymethyl derivative (*ca.* 3·0 g.) in ethanol (150 c.c.) was hydrogenated over 10% palladised strontium carbonate (1·0 g.) with as rapid shaking as possible. When 1·1 mol. of hydrogen had been taken up, the rate of absorption dropped from *ca.* 135 to 5 c.c./min.

The filtered solution was evaporated to small volume, and either the solid was collected, or the gummy residue triturated with ethanol and scratched until precipitation (accompanied by decarboxylation and dehydration) was complete. The *product* (Table 3) was recrystallised from 96% ethanol.

TABLE 3.

Hydrogenation products (I).

R	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
OH	134—135°	46	51·8	6·2	7·2	$C_8H_{11}NO_4$	51·9	6·0	7·6
NH_2	127—128 *	35	52·4	6·9	15·5	$C_8H_{12}N_2O_3$	52·2	6·6	15·2
NHMe	110—112	26	54·6	7·4	14·4	$C_9H_{14}N_2O_3$	54·5	7·1	14·1
NMe_2	75—76	25	56·6	7·7	13·6	$C_{10}H_{16}N_2O_3$	56·6	7·6	13·2
NHPh	116—118	44	64·9	6·4	11·1	$C_{14}H_{16}N_2O_3$	64·6	6·2	10·8

* From methanol (lit.,[1a] m. p. 130—131°).

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