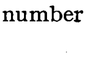
21. *Use of γ-Lactones in the Synthesis of Amino-acids.*

By G. B. BARLOW and A. J. MACLEOD.

The reaction of benzenediazonium chloride with α-acetyl-γ-lactones, followed by hydrolysis and reduction, has been used to synthesise a number of α-amino-acids.

ADAMS and VANDERWERF have shown that the reaction between an epoxide  and the sodio-derivative of acetoacetic ester gives a γ-lactone with the substituent R in the γ-position.[1]

The reaction of α-acyl-lactones with ethyl nitrite [2] or with benzenediazonium chloride (the Japp–Klingermann reaction [3]), followed by hydrolysis and reduction, can be used as described below to give α-amino-γ-hydroxybutyric acids. Hydrolysis of the lactone phenylhydrazones to the keto-acid phenylhydrazones is accompanied by a hypsochromic shift in the ultraviolet spectrum.

---

[1] Adams and VanderWerf, *J. Amer. Chem. Soc.*, 1950, **72**, 4368.

[2] Snyder, Andreen, Cannon, and Peters, *J. Amer. Chem. Soc.*, 1942, **64**, 2082.

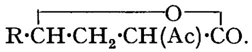
[3] Phillips, "Organic Reactions," ed. R. Adams, Wiley, New York, 1959, Vol. X, p. 143.

At a dose of 0·5 mg./g., DL-2-amino-4-hydroxy-5-isopropoxypentanoic acid showed marked antimitotic properties (as measured by the interruption of pregnancy in mice). Our other amino-acids were inactive.

EXPERIMENTAL

α-Acetyl-γ-butyrolactone.—This was prepared by the method of Snyder *et al.*[2] in 54% yield, had b. p. 90°/1 mm., and gave a semicarbazone, m. p. 164° (lit.,[4] m. p. 166—167°). Other *lactones* prepared similarly are given in Table 1.

TABLE 1.



Lactones, $R{\cdot}CH{\cdot}CH_2{\cdot}CH(Ac){\cdot}CO$.

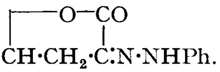
	R	B. p./ 1 mm.	Yield (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
1	H	90°	54	56·4	6·7	$C_6H_8O_3$	56·3	6·3
2	Me	95 ‡	35	59·4	7·5	$C_7H_{10}O_3$	59·2	7·0
3	Et	110	49	61·6	7·9	$C_8H_{12}O_3$	61·5	7·7
4	$Pr^iO{\cdot}CH_2$	135	59	59·7	8·6	$C_{10}H_{16}O_4$	60·0	8·0
5	$Bu^nO{\cdot}CH_2$	147	44	61·3	8·3	$C_{11}H_{18}O_4$	61·7	8·4
6	$CH_2{:}CH{\cdot}CH_2{\cdot}O{\cdot}CH_2$	124	38	60·5	8·2	$C_{10}H_{14}O_4$	60·6	7·1
7	Ph	158 *	57			$C_{12}H_{12}O_3$		
8	$PhO{\cdot}CH_2$	212 †	32	66·4	6·1	$C_{13}H_{14}O_4$	66·7	6·0
9	o-$Me{\cdot}C_6H_4{\cdot}O{\cdot}CH_2$	210	52			$C_{14}H_{16}O_4$		
10	p-$MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2$	224	38			$C_{14}H_{16}O_5$		

Semicarbazones.

	M. p.	Found (%) N	Required (%) N	$\varepsilon_{max.}$ at 222 mμ	$\varepsilon_{max.}$ at 274 mμ
1	163—164°	22·7	22·7	11,800	5700
2	147	20·9	21·1	11,700	5400
3	145—146	19·8	19·7	11,500	5600
4	137	16·6	16·3	11,400	5200
5	137	15·9	15·5	11,400	5300
6	132	16·5	16·5	11,600	5400
7	181—182	16·1	16·1	17,300	5200
8	142	14·2	14·4	17,200	7000
9	163—164	14·1	13·8	17,400	6600
10	161—162	13·0	13·1	22,700	6700

* M. p. 49° (lit.,[1] a liquid); α 0. † M. p. 75°. ‡ Lit.,[1] b. p. 88—90°/2 mm.

TABLE 2.



Lactone phenylhydrazones, $R{\cdot}CH{\cdot}CH_2{\cdot}C{:}N{\cdot}NHPh$.

R	M. p.	Yield (%)	Found (%) N	Formula	Reqd. (%) N	$\varepsilon_{max.}$ at 233 mμ	$\varepsilon_{max.}$ at 294·5 mμ	$\varepsilon_{max.}$ at 333 mμ
H	227°	82	14·6	$C_{10}H_{10}N_2O_2$	14·7	14,900	9500	30,800
Me	200	63	13·6	$C_{11}H_{12}N_2O_2$	13·7	14,600	9500	31,500
Et	222	64	12·9	$C_{12}H_{14}N_2O_2$	12·8	14,700	9300	31,600
$Pr^iO{\cdot}CH_2$	143	48	10·4	$C_{14}H_{18}N_2O_3$	10·7	14,300	9900	31,600
$Bu^nO{\cdot}CH_2$	122	35	10·4	$C_{15}H_{20}N_2O_3$	10·1	14,900	9300	22,200
$CH_2{:}CH{\cdot}CH_2{\cdot}O{\cdot}CH_2$	98	62	10·8	$C_{14}H_{16}N_2O_3$	10·8	11,900	8200	22,500
Ph	201	77	10·5	$C_{16}H_{14}N_2O_2$	10·5	18,400	9600	31,500
$PhO{\cdot}CH_2$...............	215	88	9·5	$C_{17}H_{16}N_2O_3$	9·5	18,000	9600	31,000
o-$Me{\cdot}C_6H_4{\cdot}O{\cdot}CH_2$ ...	176	43	9·0	$C_{18}H_{18}N_2O_3$	9·0	—	8400	24,400
p-$MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2$	166	8	8·6	$C_{18}H_{18}N_2O_4$	8·6	—	10,300	24,500

α-Phenylhydrazono-γ-butyrolactone.—α-Acetyl-γ-butyrolactone (5·0 g.) was dissolved in 2·5% aqueous sodium hydroxide (155 ml.) at 0°. Freshly prepared benzenediazonium chloride (from aniline, 4 ml.) was added slowly, with stirring. The orange-red precipitate recrystallised

---

[4] Feofilaktov and Onishchenko, *Zhur. obshchei Khim.*, 1939, **9**, 304 (*Chem. Abs.*, 1940, **34**, 378.)

from ethyl acetate–ethyl alcohol as a yellow solid, m. p. 227° (82%). Harradence and Lions[5] report m. p. 220°. Table 2 lists the *phenylhydrazones* of other lactones prepared in a similar manner.

γ-Hydroxy-α-phenylhydrazonobutyric Acid.—The preceding lactone hydrazone (20 g.) was refluxed with 10% sodium hydroxide solution (80 ml.) for 20 min., then cooled to 0°, and neutralised with hydrochloric acid. The precipitate, recrystallised rapidly from aqueous alcohol (91% yield), had m. p. 158° (lit.,[6] m. p. 156°). The *acid phenylhydrazones* listed in Table 3 were prepared similarly.

TABLE 3.

Butyric acid phenylhydrazones, $\mathrm{R{\cdot}CH(OH){\cdot}CH_2{\cdot}C(CO_2H){:}N{\cdot}NHPh}$.

		Yield	Found (%)			Reqd. (%)		$\varepsilon_{\text{max.}}$ at	
R	M. p.	(%)	N	M.W.	Formula	N	M.W.	292·5 mμ	317 mμ
H	158°	91	13·0	204	$C_{10}H_{12}N_2O_3$	13·4	208	15,200	17,000
Me	121	85	12·6	218	$C_{11}H_{14}N_2O_3$	12·6	222	14,400	17,100
Et	128	93	11·9	236	$C_{12}H_{16}N_2O_3$	11·9	236	15,000	17,100
$\mathrm{Pr^iO{\cdot}CH_2}$	101	94	10·2	285	$C_{14}H_{20}N_2O_4$	10·0	280	15,000	17,200
$\mathrm{Bu^nO{\cdot}CH_2}$	67	97	9·1	292	$C_{15}H_{22}N_2O_4$	9·5	294	15,000	17,200
$\mathrm{CH_2{:}CH{\cdot}CH_2{\cdot}O{\cdot}CH_2}$	85	98	9·5	274	$C_{14}H_{18}N_2O_4$	10·1	278	15,000	17,200
Ph	157	87	10·0	285	$C_{16}H_{16}N_2O_3$	9·9	284	15,000	18,600
$\mathrm{PhO{\cdot}CH_2}$	149	98	9·1	315	$C_{17}H_{18}N_2O_4$	8·9	314	15,000	18,800
o-$\mathrm{Me{\cdot}C_6H_4{\cdot}O{\cdot}CH_2}$	103	78	8·7	330	$C_{18}H_{20}N_2O_4$	8·5	328	15,500	18,200
p-$\mathrm{MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2}$	160	99	8·2	343	$C_{18}H_{20}N_2O_5$	8·1	344	18,300	18,300

TABLE 4.

DL-α-Amino-acids, $\mathrm{R{\cdot}CH(OH){\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H}$.

	M. p.	Yield	Found (%)					Required (%)			
R	(decomp.)	(%)	C	H	N	M.W.	Formula	C	H	N	M.W.
H	189°	59	40·2	7·6	11·7	121	$C_4H_8NO_3$	40·3	7·6	11·8	119
Me	205 *	58	45·1	8·5	10·7	133	$C_5H_{10}NO_3$	45·1	8·3	10·5	133
Et	219—220	54	49·3	9·2	9·6	149	$C_6H_{12}NO_3$	49·0	8·8	9·5	147
$\mathrm{Pr^iO{\cdot}CH_2}$	204—205	42	50·6	9·2	7·5	194	$C_8H_{17}NO_4$	50·3	8·9	7·3	191
$\mathrm{Bu^nO{\cdot}CH_2}$	200	63	52·8	9·2	6·9	204	$C_9H_{19}NO_4$	52·7	9·3	6·8	205
$\mathrm{CH_2{:}CH{\cdot}CH_2{\cdot}O{\cdot}CH_2}$	198—199	61	51·0	7·8	7·0	185	$C_8H_{15}NO_4$	50·8	7·9	7·4	189
Ph	216—218 †	63	61·8	6·8	6·8	199	$C_{10}H_{13}NO_3$	61·5	6·7	7·2	195
$\mathrm{PhO{\cdot}CH_2}$	216—217	60	58·9	6·8	6·5	225	$C_{11}H_{15}NO_4$	58·7	6·7	6·2	225
o-$\mathrm{Me{\cdot}C_6H_4{\cdot}O{\cdot}CH_2}$	215—216	47	60·1	7·0	5·7	243	$C_{12}H_{17}NO_4$	60·2	7·1	5·9	239
p-$\mathrm{MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2}$	224—225	43	56·5	7·0	5·8	258	$C_{12}H_{17}NO_5$	56·5	6·7	5·5	255

* Gaudry (*Canad. J. Chem.*, 1951, **29**, 544) gives 215°. † Fraser and Raphael (*J.*, 1950, 2245) give 219° (decomp.).

DL-*Homoserine.*—γ-Hydroxy-α-phenylhydrazonobutyric acid (20 g.) was hydrogenated in aqueous ethyl alcohol over 10% palladium–charcoal at 100 atm. Homoserine was precipitated with acetone and, recrystallised from water–ethyl alcohol, had m. p. 189° (59%) (Armstrong[7] records 186°). Table 4 gives properties of *α-amino-acids* prepared by this method.

Biological Properties.—These were examined by Mrs. S. Keene.

We thank S. Garcia and C. Jenkins for technical assistance, Professor J. Yudkin for his interest, and the London Research Foundation for financing the work.

DEPARTMENT OF NUTRITION, QUEEN ELIZABETH COLLEGE,
CAMPDEN HILL, LONDON W.8.

[*Received, May 2nd*, 1963.]

---

[5] Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, 1938, **72**, 221.

[6] Duffin and Kendall, *J.*, 1955, 3470.

[7] Armstrong, *J. Amer. Chem. Soc.*, 1949, **71**, 3399.