

**848.** *The Reaction of Imidates with  $\alpha$ -Amino-acetals and  $\alpha$ -Amino-aldehydes.*

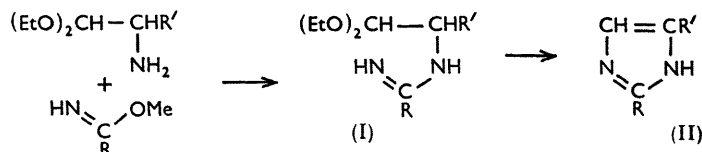
By ALEXANDER LAWSON.

$\alpha$ -Amino-aldehydes and  $\alpha$ -amino-acetals react with imidates to give the corresponding 2 : 5-disubstituted glyoxalines (II). The reaction mechanism is discussed.

2-ALKYL- and 2-aryl-substituted glyoxalines can be prepared by the oldest method<sup>1,2</sup> used for the synthesis of the glyoxaline ring, *i.e.*, reaction of the appropriate aldehyde with a dicarbonyl compound and ammonia, and this reaction has been applied with many modifications, one of which, involving the use of an  $\alpha$ -hydroxy-ketone and cupric acetate<sup>3</sup> instead of the dicarbonyl compound, has been widely used. Other methods utilise the reaction between  $\alpha$ -amino-nitriles and aldehydes<sup>4</sup> and between  $\alpha$ -halogeno-ketones and benzamidine.<sup>5</sup> Cornforth and Huang<sup>6</sup> in their investigations of oxazole syntheses showed that condensing the hydrochloride of aminoacetone or ethyl  $\alpha$ -aminoacetoacetate with imidates produced a mixture of an oxazole and a glyoxaline, the former being convertible by ammonia under pressure into a glyoxaline relatively easily when the 4-carboxylic acid

<sup>1</sup> Radziszewski, *Ber.*, 1882, **15**, 1493.<sup>2</sup> Japp and Robinson, *ibid.*, p. 1268.<sup>3</sup> Weidenhagen and Herrmann, *Ber.*, 1935, **68**, 1953.<sup>4</sup> Minovici, *Ber.*, 1896, **29**, 2097.<sup>5</sup> Kunckell, *Ber.*, 1901, **34**, 637.<sup>6</sup> Cornforth and Huang, *J.*, 1948, 1960.

group was present. The same authors reported that attempts to condense methyl benzimidate with aminoacetaldehyde hydrochloride gave a tar from which only triphenyltriazine, derived merely from the aminoacetaldehyde, could be isolated.



An examination of this reaction between a number of  $\alpha$ -amino-aldehydes and methyl or ethyl benzimidate has now shown that in all cases condensation takes place readily in aqueous ethanol at neutral pH to give the corresponding 2-phenylglyoxaline (II; R = Ph). Using the products obtainable by the Akabori reduction procedure from  $\alpha$ -amino-esters gives yields which, except for glycine and serine, are quite satisfactory; and with certain amino-acids (alanine,  $\alpha$ -phenylglycine,  $\alpha$ -*p*-hydroxyphenylglycine, phenylalanine, and tyrosine) the bulk of the product crystallises as the 2 : 4(5)-disubstituted glyoxaline hydrochloride on addition of hydrochloric acid to the reaction mixture after 3½ hours' heating. No evidence of the alternative mode of ring closure to oxazoles was obtained.

The synthesis of 4(5)-methyl-2-phenylglyoxaline, for example, accomplished by Cornforth and Huang<sup>6,7</sup> in three stages from hippuric acid by way of 4 : 5-dihydro- $\delta$ -(1-hydroxyethylidene)-2-phenyloxazol-4-one, is much more readily attained in two stages by the action of methyl benzimidate on the solution of  $\alpha$ -aminopropionaldehyde resulting from the reduction of alanine ethyl ester.

The use of aminoacetaldehyde diethyl acetal in the condensation with methyl benzimidate gives an 85% yield of 2-phenylglyoxaline and the reaction also takes place with methylaminoacetaldehyde acetal, though not quite so readily.

With imidates such as methyl hexanimidate, the reaction with  $\alpha$ -amino-aldehydes does not proceed quite so satisfactorily, owing no doubt to the instability of the imidate,

TABLE 1. 2 : 4(5)-Disubstituted glyoxalines (II).

Parent amino-acid	R	R'	Form	M. p.	Yield * (%)	Formula	Found (%)		Reqd. (%)	
							C	H	C	H
Glycine .....	Ph	H	Leaflets *	148°	18	—	—	—	—	—
Alanine .....	Ph	Me	Needles *	184	46	—	—	—	—	—
Alanine .....	C <sub>6</sub> H <sub>11</sub>	Me	Oil	—	47	C <sub>9</sub> H <sub>16</sub> N <sub>2</sub>	71.0	10.5	71.1	10.6
Aminomalonic ...	Ph	CO <sub>2</sub> Et	Needles †	174	—	C <sub>12</sub> H <sub>12</sub> O <sub>2</sub> N <sub>2</sub>	66.8	5.7	66.7	5.5
$\alpha$ -Aminobutyric	Ph	Et	Needles *	170	53	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub>	76.9	6.8	76.8	7.0
Aspartic .....	Ph	CH <sub>3</sub> ·CO <sub>2</sub> Et	Prisms *	98	37	C <sub>13</sub> H <sub>14</sub> O <sub>2</sub> N <sub>2</sub>	67.6	6.0	67.8	6.1
Glutamic .....	Ph	[CH <sub>2</sub> ] <sub>2</sub> ·CO <sub>2</sub> Et	Prisms *	123	46	C <sub>14</sub> H <sub>16</sub> O <sub>2</sub> N <sub>2</sub>	68.7	6.5	68.9	6.6
Serine .....	Ph	CH <sub>3</sub> ·OH	Leaflets †	170	10	C <sub>10</sub> H <sub>10</sub> ON <sub>2</sub>	68.9	5.6	69.0	5.7
$\alpha$ -Phenylglycine	Ph	Ph	Needles *	189	31	—	—	—	—	—
Phenylalanine ...	Ph	CH <sub>3</sub> ·Ph	Rosettes †	166	33	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub>	81.9	6.0	82.0	6.0
Tyrosine .....	Ph	CH <sub>3</sub> ·C <sub>6</sub> H <sub>4</sub> ·OH	Prisms *	245	34	C <sub>16</sub> H <sub>14</sub> ON <sub>2</sub>	76.6	5.6	76.8	5.6
$\alpha$ - <i>p</i> -Hydroxyphenylglycine	Ph	C <sub>6</sub> H <sub>4</sub> ·OH	Needles †	221	42	C <sub>15</sub> H <sub>12</sub> ON <sub>2</sub>	76.3	5.2	76.2	5.1

\* From benzene. † From EtOH. \* Based on amino-acid used.

but it was possible to isolate small yields of the 2-pentylglyoxalines (II; R = C<sub>5</sub>H<sub>11</sub>) corresponding to all the amino-aldehydes which were investigated.

Schipper and Day<sup>8</sup> offer an explanation of the ring closure of  $\alpha$ -amino-ketones with methyl benzimidate to glyoxalines based on mechanisms reported for analogous reactions.<sup>9</sup> They postulate as the first step the addition of the polarised =NH group of the imidate

<sup>7</sup> Cornforth and Cookson, *J.*, 1952, 1085.

<sup>8</sup> Schipper and Day, in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1957, Vol. V, p. 220.

<sup>9</sup> McCoy and Day, *J. Amer. Chem. Soc.*, 1943, **65**, 2159.

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to the carbonyl group, followed by the addition of the amino-group across the  $=C=N$ -bond so formed. Such a mechanism does not seem applicable to the reaction between the imidate and  $\alpha$ -amino-acetal. This reaction proceeds in two stages, the first at neutrality, in which the *N*-substituted amidine (I;  $R = Ph$ ,  $R' = H$ ), isolable as its picrolonate, is formed, and the second, under the influence of 5*N*-acid, in which presumably hydrolysis of the acetal group takes place and the amidine undergoes ring closure to give the glyoxaline (II;  $R = Ph$ ,  $R' = H$ ). A similar reaction course can presumably also take place when the amino-acetal is replaced by an amino-aldehyde. Schipper and Day's mechanism is likewise not applicable in the formation of 2-aminoglyoxalines from  $\alpha$ -amino-acetals and cyanamide,<sup>10</sup> where the acetal guanidine salt formed as an intermediate is actually isolated.

TABLE 2. Hydrochlorides of 2 : 4(5)-disubstituted glyoxalines (II).

R	R'	Form	M. p.	Formula	Found (%)		Required (%)	
					C	H	C	H
Ph	Me	Needles †	137° <sup>a</sup>	$C_{10}H_{10}N_2, HCl, H_2O$	56.2	6.1	56.4	6.1
Ph	$CH_2 \cdot CO_2Et$	Needles †	146	$C_{13}H_{14}O_2N_2, HCl$	58.3	5.6	58.5	5.6
Ph	$CH_2 \cdot CO_2H$	Needles *	202	$C_{11}H_{10}O_2N_2, HCl, H_2O$	51.4	4.9	51.4	5.1
Ph	$[CH_2]_3 \cdot CO_2Et$	Needles †	170	$C_{14}H_{16}O_2N_2, HCl$	59.8	6.2	59.8	6.1
Ph	$[CH_2]_2 \cdot CO_2H$	Needles *	144° <sup>a</sup>	$C_{12}H_{12}O_2N_2, HCl, H_2O$	53.0	5.5	53.2	5.5
$C_6H_{11}$	Ph	Prisms †	129	$C_{14}H_{18}N_2, HCl$	66.9	7.8	67.0	7.6
Ph	Ph	Needles †	273° <sup>a</sup>	—	—	—	—	—
Ph	$CH_2Ph$	Needles ‡	112	$C_{16}H_{14}N_2, HCl, H_2O$	66.1	5.7	66.4	5.9
Ph	$C_6H_4 \cdot OH$	Needles †	263	$C_{16}H_{12}ON_2, HCl$	65.8	4.9	66.1	4.8
Ph	$CH_2 \cdot C_6H_4 \cdot OH$	Needles †	252° <sup>a</sup>	$C_{16}H_{14}ON_2, HCl, H_2O$	62.6	5.6	63.0	5.6

\* From  $H_2O$ . † From  $EtOH$ . ‡ From aq. acetone-ether. <sup>a</sup> With decomp.

## EXPERIMENTAL

*Preparation of 2 : 4(5)-Disubstituted Glyoxalines from Amino-acids.*—The amino-acid (10 g.) was esterified with ethanol and reduced with sodium amalgam at pH 4 according to the Akabori procedure.<sup>11</sup> The resulting solution, after filtration, was evaporated to dryness under reduced pressure and the residue extracted with ethanol. The filtered ethanolic solution was again evaporated under reduced pressure and the residue taken up in ethanol and filtered. An aliquot part of this solution of the amino-aldehyde was mixed with methyl benzimidate or hexanimidate (1 mol.), and the pH adjusted if necessary to 7 by the addition of acetic acid. The mixture, after 1 hr. at room temperature, was heated on the steam-bath for 3–4 hr. by which time most of the ethanol had evaporated. Trituration with dilute hydrochloric acid and cooling to 0° gave, in a number of cases, crystals of the glyoxaline hydrochloride which were removed and recrystallised from the solvent mentioned in Table 2. From the aqueous solutions of the hydrochlorides the free bases were liberated by sodium hydroxide, and, if solid, purified by crystallisation. When no precipitate of the hydrochloride was obtained on addition of hydrochloric acid, the solution was made alkaline with sodium hydroxide and extracted with ether. Removal of the ether gave the free bases described in Table 1. In the cases of ethyl 2-phenyl-4-glyoxalanyl-acetate and -propionate (from aspartic and glutamic acid, respectively) it was more convenient to distil the bases at 1 mm. before crystallising them. Of the derivatives mentioned in Table 3, the picrolonates crystallised most readily.

*Preparation of Glyoxalines from  $\alpha$ -Amino-acetals.*—The acetal (0.01 mole) was heated with the imidate (0.01 mole) and glacial acetic acid (0.02 mole) on the steam-bath for 3 hr. At this stage extraction of the basic product from the dark mixture, to which water and sodium hydroxide had been added, gave, in the case of  $\alpha$ -aminoacetaldehyde diethyl acetal, an oil which formed  $\alpha$ -benzamidinoacetaldehyde diethyl acetal picrolonate, prisms (from ethanol), m. p. 139° (Found: C, 55.1; H, 5.6.  $C_{23}H_{28}O_7N_6$  requires C, 55.2; H, 5.6%). The reaction mixture (above) was heated with 5*N*-hydrochloric acid (4 ml.) for a further 0.5 hr., water was added, and the solution evaporated under reduced pressure. The residue was dissolved in water and extracted with ether to remove some benzamide in the case of benzimidate. After basification with sodium hydroxide the glyoxaline was extracted with ether and, in the case of 2-phenylglyoxaline, the residue, after evaporation of the ether, was recrystallised from benzene. The

<sup>10</sup> Lawson, J., 1956, 307.<sup>11</sup> Lawson, J., 1957, 1443.

TABLE 3. Derivatives of 2:4(5)-disubstituted glyoxalines.

Compound	Form	M. p.	Formula	Found (%)		Reqd. (%)	
				C	H	C	H
4(5)-Methyl-2-phenylglyoxaline picrate .....	Prisms †	201°	$C_{16}H_{13}O_7N_5$	49.3	3.2	49.6	3.4
4(5)-Methyl-2-pentylglyoxaline picrolonate .....	— †	190	$C_{19}H_{24}O_5N_6$	54.8	5.9	54.8	5.8
4(5)-Ethyl-2-phenylglyoxaline picrate .....	Prisms †	203	$C_{17}H_{15}O_7N_5$	50.5	4.0	50.8	3.7
4(5)-Ethyl-2-phenylglyoxaline oxalate .....	Needles *	197	$C_{13}H_{14}O_4N_2$	59.1	5.4	59.5	5.4
4(5)-Ethoxycarbonyl-2-phenylglyoxaline picrate .....	Needles *	187	$C_{18}H_{15}O_9N_5$	48.5	3.5	48.5	3.3
4(5)-Hydroxymethyl-2-phenylglyoxaline picrolonate .....	— †	230	$C_{20}H_{18}O_6N_6$	54.8	4.4	54.8	4.1
Ethyl 2-phenyl-4-glyoxalinypropionate picrate .....	Needles †	188	$C_{20}H_{19}O_9N_5$	50.5	4.3	50.7	4.0
Ethyl 2-phenyl-4-glyoxalinypropionate picrolonate .....	Needles †	186	$C_{24}H_{24}O_7N_6$	56.9	4.9	56.8	4.7
Ethyl 2-phenyl-4-glyoxalinyacetate picrate .....	Needles †	164	$C_{18}H_{17}O_9N_5$	49.8	3.7	49.7	3.7
Ethyl 2-phenyl-4-glyoxalinyacetate picrolonate .....	Needles †	212 *	$C_{23}H_{23}O_7N_6$	55.6	4.3	55.8	4.5
2-Pentyl-4(5)-phenylglyoxaline oxalate .....	Needles †	148	$C_{16}H_{20}O_4N_2 \cdot H_2O$	61.2	6.9	59.7	6.8
2-Pentyl-4(5)-phenylglyoxaline picrolonate .....	Needles †	167	$C_{24}H_{26}O_5N_6$	60.0	5.6	60.3	5.5
2:4(5)-Diphenylglyoxaline nitrate .....	Needles †	115	$C_{15}H_{13}N_3 \cdot HNO_3 \cdot H_2O$	59.7	4.8	59.8	5.0
2:4(5)-Diphenylglyoxaline picrate .....	Needles †	193	$C_{21}H_{16}O_7N_5$	55.8	3.3	56.1	3.3
4(5)-Benzyl-2-phenylglyoxaline picrate .....	Needles †	172	$C_{22}H_{17}O_7N_5$	57.0	3.7	57.0	3.7
4(5)-Benzyl-2-pentylglyoxaline oxalate .....	Prisms *	140	$C_{17}H_{22}O_4N_2$	64.5	6.7	64.2	6.9
4(5)-Benzyl-2-pentylglyoxaline picrolonate .....	Needles †	133	$C_{28}H_{28}O_5N_6$	60.9	5.8	61.0	5.7
4(5)- <i>p</i> -Hydroxyphenyl-2-phenylglyoxaline picrate .....	Needles †	222	$C_{21}H_{16}O_8N_5$	54.0	3.5	54.2	3.2
4(5)- <i>p</i> -Hydroxybenzyl-2-phenylglyoxaline picrolonate .....	Needles †	247 *	$C_{26}H_{22}O_6N_6$	60.4	4.2	60.7	4.3

\* From  $H_2O$ . † From EtOH. \* With decomp.

hydrochlorides were obtained from the bases by treatment of the ether solution with anhydrous hydrogen chloride. In this way were obtained: 2-pentylglyoxaline (75%) [picrolonate, m. p. 190° (from acetone) (Found: C, 53.4; H, 5.3. Calc. for  $C_{18}H_{22}O_5N_6$ : C, 53.7; H, 5.5%)]; 2-phenylglyoxaline (85%), leaflets (from benzene), m. p. 148° (Found: C, 74.8; H, 5.6. Calc. for  $C_9H_8N_2$ : C, 75.0; H, 5.6%) [*hydrochloride*, prisms (from ethanol), m. p. 154° (Found: C, 54.2; H, 5.3.  $C_9H_8N_2 \cdot HCl \cdot H_2O$  requires C, 54.4; H, 5.5%)]; 1-methyl-2-pentylglyoxaline (33%), an oil [*picrolonate*, needles, (from ethanol), m. p. 146° (Found: C, 54.6; H, 5.6.  $C_{19}H_{24}O_5N_6$  requires C, 54.8; H, 5.8%)]; 1-methyl-2-phenylglyoxaline (42%), an oil [*hydrochloride*, prisms (from ethanol), m. p. 178° (Found: C, 56.6; H, 6.1.  $C_{10}H_{10}N_2 \cdot HCl \cdot H_2O$  requires C, 56.5; H, 6.1%); *picrate*, needles (from ethanol), m. p. 135° (Found: C, 49.4; H, 3.3. Calc. for  $C_{16}H_{13}O_7N_5$ : C, 49.6; H, 3.4%)]]. 1-Methyl-2-pentylglyoxaline, an oil (30%) [*picrolonate*, needles, (from ethanol), m. p. 146° (Found: C, 54.5; H, 5.6.  $C_{19}H_{24}O_5N_6$  requires C, 54.8; H, 5.8%)]].

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ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,  
8 HUNTER STREET, LONDON, W.C.1.

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