247. *2-Mercaptoglyoxalines. Part VI.* The Preparation of Mono- and Di-carbon-substituted 2-Mercaptoglyoxalines by Means of the Dakin and West Reaction.*

By R. A. F. Bullerwell and Alexander Lawson.

Several α-amino-ketones have been formed by the Dakin and West reaction and condensed with thiocyanate to give 4-mono- and 4 : 5-di-alkyl-substituted 2-mercaptoglyoxalines. An improved method for the preparation of 3-benzamido-1-benzoyl-2 : 4-diketopyrrolidine (Rügheimer, *Ber.*, 1889, **22**, 1954), and a new method for preparation of 1 : 4-dihydroxy*iso*quinoline, are described.

Except for methods of rather limited application, such as the condensation of thiourea with α-hydroxy-ketones including benzoin (Basse and Klinger, *Ber.*, 1898, **31**, 1217) and *o*-diamines, the isomerisation of 2-acylamino-5-aminothiazoles (Cook and Heilbron, *J.*, 1948, 1262), and the condensation of *S*-benzyl*iso*thiourea and phenacyl bromide followed by fission of the benzyl group (Dodson, *J. Amer. Chem. Soc.*, 1948, **70**, 2753), methods available for the preparation of 2-mercaptoglyoxalines depend on the reaction between thiocyanate with α-amino-aldehydes and -ketones. Synthesis of the last-named compounds therefore is the main problem associated with the preparation of the 2-mercaptoglyoxalines.

Dakin and West (*J. Biol. Chem.*, 1928, **78**, 91, 745, 757) showed that many α-amino-acids give acetamidomethyl ketones and carbon dioxide when heated with pyridine and acetic anhydride, though with glycine and hippuric acid low yields prohibited the useful application of the products. From the corresponding amino-ketones obtained on hydrolysis, they prepared the three 2-mercaptoglyoxalines derived from phenylalanine, tyrosine, and phenylglycine severally.

We have employed the Dakin and West reaction with acetic and propionic anhydrides to prepare six typical 4 : 5-dialkyl-substituted 2-mercaptoglyoxalines. By use of the technique adopted by Attenburrow, Elliott, and Penny (*J.*, 1948, 310) for the preparation of benzamidoacetone, acetic, propionic, butyric, and hexanoic anhydrides have been condensed with sodium hippurate to give the corresponding oxazolones from which the appropriate 4-substituted 2-mercaptoglyoxalines have been isolated after hydrolysis and treatment with thiocyanate. This method gave smaller yields than that obtainable by the Akabori reduction of amino-acid esters (Bullerwell and Lawson, *J.*, 1951, 3030). The yields diminished with increasing molecular weight of the anhydride.

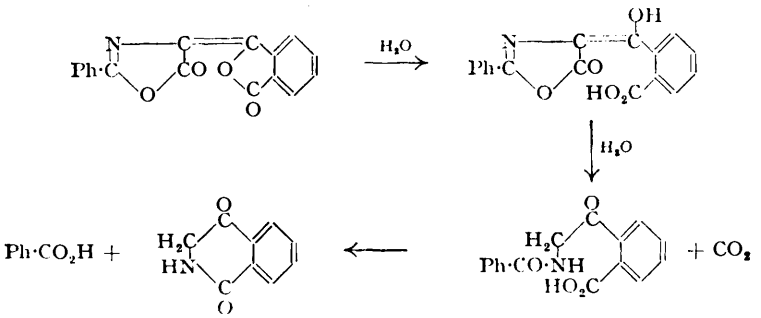
Attempts to prepare γ-keto-ornithine by the action of aspartic acid chloride azlactone on 2-phenyloxazolone were not successful. The only crystalline product isolated from the reaction was 3-benzamido-1-benzoyl-2 : 4-diketopyrrolidine, obtainable in much better yield (40%) by simply allowing 2-phenyloxazolone to stand in 2-picoline overnight. The structure of this substance, originally obtained by Rügheimer (*Ber.*, 1888, **21**, 3325; 1889, **22**, 1954), was established by Cornforth and Huang (*J.*, 1948, 1958). The formation of Rügheimer's compound may be regarded as a special case of the Dakin and West re-

* Part V, *J.*, 1951, 3030.

action in which the second oxazolone molecule behaves in a manner analogous to that of an acid anhydride.

It is possible that the compound, obtained by Attenburrow *et al.* (*loc. cit.*) from benzoyl-α-alanine and acetic anhydride, which gave analyses for $C_{20}H_{18}O_4N_2$ and for which a diketopiperazine structure was suggested, is the dimethyl homologue of Rügheimer's compound. One would expect the two molecules of 4-methyl-2-phenyloxazol-5-one to condense in the same manner as the unmethylated compound. 3-Benzamido-1-benzoyl-2 : 4-diketopyrrolidine on hydrolysis and treatment with potassium thiocyanate gave 4-aminomethyl-2-mercaptoglyoxaline, but it was not possible to develop this into a convenient preparative method for the latter substance.

Efforts to apply the Dakin and West reaction to aliphatic dibasic acid anhydrides were not successful. The only known examples of oxazolone synthesis of this kind are described by Erlenmeyer (*Annalen*, 1893, **275**, 1) who obtained 2-phenyl-4-phthalidylideneoxazol-5-one using phthalic anhydride, and by Smith and Hanna (*J. Amer. Chem. Soc.*, 1951, **73**, 2387) who used 3-nitrophthalic anhydride to make the corresponding nitro-derivative. Substituting sodium hippurate for the mixture of hippuric acid and sodium acetate, we obtained the pure oxazolone in much improved yield, in keeping with the findings of Attenburrow *et al.* (*loc. cit.*) that acetic acid had a deleterious effect on oxazolone formation. Subsequent hydrolysis of the oxazolone gave rise to 1 : 4-dihydroxy*iso*quinoline, the formation of which may be explained by the following mechanism.



Experimental

2-Phenyl-4-1′-hydroxyalkylideneoxazol-5-ones.—2-Phenyl-4-1′-hydroxyethylideneoxazol-5-one and 2-phenyl-4-1′-hydroxypropylideneoxazol-5-one were prepared by the method of Attenburrow *et al.* (*loc. cit.*) adapted for use on a small scale. Two more analogues were prepared in a similar way.

Sodium hippurate (20 g., 0·1 mole), 2-picoline (30 ml.), and butyric anhydride (48 ml., 0·3 mole) were stirred together for 3 hours in a three-necked flask fitted with a calcium chloride tube and warmed to 35°. The liquid so obtained was filtered and excess of butyric anhydride was decomposed by stirring with ethanol (17 ml.) and cooling in water. Water (170 ml.) was then added and the solution was made acid to Congo-red with 5N-hydrochloric acid (100 ml.) while stirring and cooling were continued. The solid precipitate was filtered off and dissolved in hot N-sodium hydroxide at 80°, and charcoal (1 g.) added, with stirring for 15 minutes. The filtrate was then cooled and acidified. The precipitate, of *4-1′-hydroxybutylidene-2-phenyloxazol-5-one*, after being filtered off, dried (yield, 17·5 g., 75%), and recrystallised from ethyl acetate, had m. p. 169° (Found : C, 67·5; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%).

Sodium hippurate (20 g.), 2-picoline (30 ml.), and hexanoic anhydride (70 ml.) were brought into reaction as described above. *4-1′-Hydroxyhexylidene-2-phenyloxazol-5-one*, m. p. 129° (2·6 g., 10%), was obtained (Found : C, 69·1; H, 6·4. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·6%).

Alkyl Benzamidomethyl Ketones.—By following the directions of Attenburrow *et al.*, benzamidoacetone was obtained from 4-1′-hydroxyethylidene-2-phenyloxazol-5-one by boiling water. Two more benzamidomethyl ketones were obtained in this way. It was, however, more satisfactory in the case of 4-1′-hydroxyhexylidene-2-phenyloxazol-5-one to omit the isolation of the benzamido-ketone and carry out the complete hydrolysis in one stage with dilute hydrochloric acid.

4-1′-Hydroxypropylidene-2-phenyloxazol-5-one (10 g.) was boiled in distilled water (600 ml.) for 1 hour and the yellow solution was evaporated to dryness under reduced pressure. The residue (8·0 g., 97%) was *benzamidomethyl ethyl ketone*, m. p. 68° (Found : C, 68·0; H, 6·9. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%).

4-1′-Hydroxybutylidene-2-phenyloxazol-5-one (10 g.), treated as above, gave *benzamidomethyl propyl ketone*, m. p. 63° (95%) (Found : C, 69·3; H, 7·2. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3%).

2-*Phenyloxazolone*.—Considerable difficulty was encountered in the preparation of 2-phenyloxazolone by the method of Abbot (" Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 778) but the following procedure was satisfactory.

Hippuric acid (100 g.) and acetic anhydride (300 ml.) were stirred together and heated on the steam-bath until all dissolved. The orange-coloured solution was then immediately cooled to room temperature, filtered, and evaporated to dryness *in vacuo* at 25—30°/0·1 mm. The semi-solid residue was twice ground thoroughly with cold ethanol with filtration between grindings. The solid was finally washed on the funnel with cold ethanol and dried *in vacuo* over activated alumina. The yield was 41 g. (45·5%), and the m. p. 91°.

3-*Benzamido*-1-*benzoyl*-2 : 4-*diketopyrrolidine*.—2-Phenyloxazol-5-one (20 g.) was dissolved in 2-picoline (50 ml.) and set aside for 48 hours in the refrigerator. The dark red solution was then poured on crushed ice, and, with stirring, dilute hydrochloric acid was added until the whole was just acid to Congo-red. The precipitate was filtered off and triturated with water. After draining at the pump and washing with a little cold ethanol, crude 3-benzamido-1-benzoyl-2 : 4-diketopyrrolidine (8 g., 40%) was obtained. This was recrystallised from a mixture of ethanol and water as the *hemihydrate*, m. p. 116° (Found : C, 65·5; H, 4·8; N, 8·3. $C_{18}H_{14}O_4N_2,\frac{1}{2}H_2O$ requires C, 65·3, H, 4·5; N, 8·5%). Upon losing water it solidified and melted again at 139°.

3-*Benzamido*-2 : 4-*diketopyrrolidine*.—3-Benzamido-1-benzoyl-2 : 4-diketopyrrolidine (5 g.) was dissolved in hot N-sodium hydroxide (50 ml.), and the solution was kept at 80° for ½ hour, then cooled and acidified with dilute hydrochloric acid. The precipitate of 3-benzamido-2 : 4-diketopyrrolidine obtained in 95% yield and recrystallised from ethyl acetate had m. p. 205° (Found : C, 60·5; H, 4·5; N, 12·6. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·7%).

Boiling with acetic anhydride, according to the method of Cornforth and Huang (*loc. cit.*), gave 3-acetamido-1-acetyl-2 : 4-diketopyrrolidine, m. p. 218°. Hydrolysis of this compound (see below) did not proceed smoothly enough to make it a better alternative to the benzoyl derivative for the preparation of the mercaptoglyoxaline.

Hydrolyses.—The above benzamido-ketones, 4-1′-hydroxyhexylidene-2-phenyloxazol-5-one, and 3-benzamido-2 : 4-diketopyrrolidine were hydrolysed and the amino-ketones without isolation were condensed with thiocyanate to give the corresponding mono-carbon-substituted *mercaptoglyoxalines*. One typical example is described and the results are summarised in Table 1 (crystallisation from water, except for the amyl compound from benzene–light petroleum).

Benzamidoacetone (4 g.) was refluxed for 3 hours with 20% hydrochloric acid (50 ml.). The solution was then cooled, filtered from benzoic acid, and evaporated under reduced pressure. The solid residue was washed with ether and dissolved in water (20 ml.). Ammonium thiocyanate (5 g.) was added and the solution was boiled under reflux for ½ hour. On cooling, 1·5 g. of 2-mercapto-4-methylglyoxaline (m. p. 246°) separated.

TABLE 1. 4-*Substituted* 2-*mercaptoglyoxalines*.

			Found, %					Required, %			
Substituent	Yield, % *	M. p.	C	H	N	S	Formula	C	H	N	S
Me	45	246°	—	—	—	—	$C_4H_6N_2S$	—	—	—	—
Et	40	165	47·0	6·4	—	—	$C_5H_8N_2S$	46·9	6·3	—	—
Pr	36	183	50·7	6·9	—	—	$C_6H_{10}N_2S$	50·7	7·0	—	—
C_5H_{11}	6	111	—	—	—	—	$C_8H_{14}N_2S$	—	—	—	—
$CH_2{\cdot}NH_2$,HCl	8	—	29·2	4·8	25·3	18·9	$C_4H_8N_3SCl$	29·0	4·8	25·4	19·3

* Based on sodium hippurate or phenyloxazolone.

Disubstituted 2-Mercaptoglyoxalines.—The 4 : 5-di-carbon-substituted mercaptoglyoxalines from amino-acids and acid anhydrides were prepared by Dakin and West's reaction (*loc. cit.*), *viz.* : 4-ethyl-2-mercapto-5-methylglyoxaline from DL-alanine, 4-*ethyl*-2-*mercapto*-5-*propylglyoxaline* from DL-norvaline, 4-*benzyl*-5-*ethyl*-2-*mercaptoglyoxaline* from DL-phenylalanine,

4-ethyl-5-p-hydroxybenzyl-2-mercaptoglyoxaline from L-tyrosine, and *4-(4-hydroxy-3 : 5-di-iodophenoxymethyl)-2-mercapto-5-methylglyoxaline* from DL-3 : 5-di-iodothyronine. The method is illustrated by the following example and Table 2 summarises the work.

DL-Alanine (10 g.), pyridine (25 ml.), and acetic anhydride (60 ml.) were heated together on the steam-bath until evolution of carbon dioxide had ceased. (In other cases an oil-bath at 150° was required.) Water (200 ml.) was then added and the mixture was steam-distilled until most of the pyridine was removed. After the solution had been made just alkaline with sodium carbonate, a further short steam-distillation was required to remove the remaining pyridine. The solution was then made acid to Congo-red and concentrated to 50 ml. An equal volume of concentrated hydrochloric acid was added and the solution was refluxed for ½ hour. After concentration nearly to dryness, the residue was dissolved in water, and ammonium thiocyanate (27 g.) added. The solution was boiled for 1 hour. On cooling, 7·5 g. of 2-mercapto-4 : 5-dimethylglyoxaline separated. It did not melt below 300°.

TABLE 2. 4-R-5-R′-2-*mercaptoglyoxalines.*

		Yield,			Found, %				Required, %		
R	R′	%	M. p.	Solvent	C	H	N	Formula	C	H	N
Me	Me	40	—	EtOH	47·2	6·6	—	$C_5H_8N_2S$	46·9	6·3	—
Me	Et	26	—	,,	50·9	6·7	20·0 §	$C_6H_{10}N_2S$	50·7	7·0	19·7
Pr	Et	22	297° ‡	,,	56·6	8·1	—	$C_8H_{14}N_2S$	56·5	8·2	—
CH_2Ph *	Et	27	252	,,	65·9	6·3	—	$C_{12}H_{14}N_2S$	66·0	6·4	—
p-OH·C_6H_4·CH_2 *	Et	25	282 ‡	Aq. EtOH	61·1	5·9	—	$C_{12}H_{14}ON_2S$	61·5	6·0	—
X * †	Me	21	—	Aq. AcOH	36·1	2·7	4·6	$C_{17}H_{14}O_2N_2SI_2$	36·2	2·5	5·0

X = 4-*p*-Hydroxyphenoxy-3 : 5-di-iodobenzyl.

* The corresponding acylamino-ketones could be extracted with ether, thus eliminating the steam-distillation.

† Owing to the insolubility of the amino-ketone hydrochloride, the condensation with thiocyanate was carried out in ethanol–water (1 : 1).

‡ With decomp. § Found : S, 22·5. Reqd. : S, 22·5%.

2-Phenyl-4-phthalidylideneoxazol-5-one.—Phthalic anhydride (15·7 g.), sodium hippurate (20 g.), and acetic anhydride (40 ml.) were heated together on the steam-bath for 3 hours with continual stirring. The mixture was then cooled and the solid filtered off, rubbed with ethanol (2 ml.), and drained. The solid was ground and washed with water (100 ml.) in portions. The product (20 g., 70%) had m. p. 242° (Erlenmeyer, *loc. cit.*, gives 240°). Recrystallisation was unnecessary.

1 : 4-*Dihydroxy*isoquinoline.—2-Phenyl-4-phthalidylideneoxazol-5-one (16 g.), dissolved in hot N-sodium hydroxide (250 ml.), was kept at 80° for ½ hour, then cooled and acidified with dilute hydrochloric acid. The precipitate (15·5 g.) was filtered off and refluxed for 2½ hours with 20% hydrochloric acid (200 ml.). Benzoic acid was then removed by steam-distillation. The solution was concentrated under reduced pressure and the 1 : 4-dihydroxy*iso*quinoline (5·3 g., 60%) separated. It reddened at >200° and did not melt. For identification the *4-acetate* (m. p. 207°) was prepared (Gabriel and Colman, *Ber.*, 1902, **35**, 2421) (Found : C, 64·9; H, 4·4. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4%).

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

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