## 26. *Derivatives of 2 : 4-Dioxo-3-phenylacetamidobutanoic Acid.**

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2 : 4-Dioxo-3-phenylacetamidobutanoic acid is obtained by alkaline hydrolysis of 2-benzyl-4-oxazolylglyoxylamide (IV). The acid is shown to exist in the lactol-enol form (V). The amide (IV) undergoes ring-fission by amines to form derivatives of 4-amino-2-oxo-3-phenylacetamidobut-3-enamide (VII); these are cyclized by acid to oxopyrrolines (VIII).

2 : 4-DIOXO-3-PHENYLACETAMIDOBUTANOIC ACID * (I) or a suitable derivative was required as an intermediate in a projected synthesis of benzylpenicillinic acid. We are recording the preparation and chemical behaviour of the acid (I) and its congeners, since the chemistry is of some general interest and further development of the synthesis has for the present been set aside.

Derivatives of 2 : 4-dioxobutanoic acid were hitherto unknown. Our first idea was to make 2-benzyl-4-formyloxazole-5-carboxylic acid (II), which should readily undergo ring-fission under mildly acidic conditions,[1] but a successful synthesis eluded us, although several methods were tried. The second and more fruitful idea was based on the alkaline fission of oxazole-4-aldehydes.[2]

2-Benzyloxazole-4-carbonyl chloride (III; X = Cl) with hydrogen cyanide in pyridine–ether gave a crude acyl cyanide (III; X = CN) hydrolysable by cold concentrated hydrochloric acid to 2-benzyl-4-oxazolylglyoxylamide (IV). This substance was soluble without immediate decomposition in aqueous potassium hydroxide, but when the solution was kept a double hydrolysis took place and the product was the expected acid (I). Yields were low until provision was made for continuous removal of ammonia from the reaction mixture.

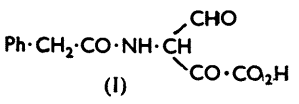
The formula (I) is the simplest conventional expression, but the possibilities of enolization and of ring-chain tautomerism are obvious, and it was soon evident that this acid was best formulated as 2 : 5-dihydro-2 : 4-dihydroxy-5-oxo-3-phenylacetamidofuran (V; R = H). Grove and Wallis[3] have studied the tautomerism of γ-oxo-acids and their

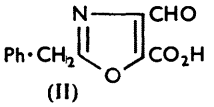
* This name is intended to include the many possible tautomeric forms of this substance.

[1] Cornforth and Cornforth, *J.*, 1953, 93.
[2] Cornforth, Fawaz, Goldsworthy, and Robinson, *J.*, 1950, 1549.
[3] Grove and Wallis, *J.*, 1951, 877.

esters; a strong absorption band in the infrared spectrum at 1750—1770 cm.$^{-1}$ is diagnostic of the lactol form. A band at 1750 cm.$^{-1}$ was found in our acid; the acyclic form (I) or its enols would not show carbonyl absorption at so high a frequency. Further proof was found in the ease with which *pseudo*-esters (V; R = Me, Et, Pr$^{i}$, Bu$^{t}$, Ph·CH$_2$) were formed by simple heating of the acid with an alcohol: even *tert.*-butyl alcohol reacted under these conditions. A *pseudo*-anilide was also obtained. All these substances showed maximal absorption at or near 1750 cm.$^{-1}$. The esters were still acidic and gave colours with ferric chloride; the continued presence of an enolic grouping was further shown by preparing methyl ethers (VI) from two of them by reaction with diazomethane.

An attempt to prepare a benzoylhydrazone from the compound (IV) led to the discovery that the oxazole ring was susceptible to fission by amines. Benzhydrazide,


(I)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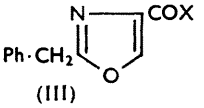
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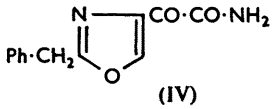
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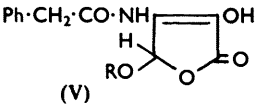
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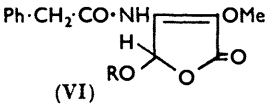
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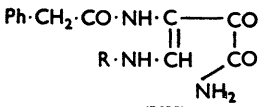
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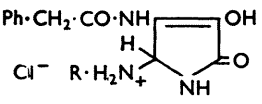
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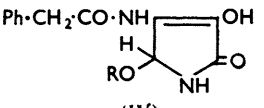
(IX)

ammonia, glycine ethyl ester, and aniline all reacted readily to give well-defined adducts formulated as the amides (VII; R = $C_6H_5$·CO·NH, H, $EtO_2C·CH_2$, Ph); indications were obtained that ring-fission occurred also with secondary and tertiary bases, but the products were less easy to isolate. The amides (VII) gave no immediate ferric chloride reaction, but on treatment with alcoholic hydrogen chloride they were converted into hydrochlorides of isomeric substances which now gave a blue ferric chloride reaction and were evidently oxopyrrolines (VIII). These hydrochlorides were unstable in hot ethanol, the ethyl ether (IX; R = Et) and an amine hydrochloride being formed. One of the hydrochlorides (VIII; R = $EtO_2C·CH_2$) on hydrolysis by hot water gave the hydroxy-analogue (IX; R = H), an unstable substance which formed the ethyl ether (IX; R = Et) in boiling ethanol.

For comparison, the action of aniline on 2-benzyloxazole-4-aldehyde was examined. The product, isolated as a hydrochloride, was evidently the dianil

PhN:CH·C(NH·CO·$CH_2$Ph):CH·NHPh.

Ultraviolet absorption spectra of some of the above-mentioned compounds are collected in the Table.

| Compound | Solvent | $\lambda_{max.}$ (m$\mu$) | $\varepsilon$ |
|---|---|---|---|
| V; R = H | EtOH | 283 | 11,000 |
| V; R = Et | EtOH | 280 | 13,200 |
| VI; R = Et | EtOH | 275 | 15,700 |
| VII; R = $EtO_2C·CH_2$ | $H_2O$ | 300 | 19,100 |
| | | 245 | 6,300 |
| VIII; R = $EtO_2C·CH_2$ | EtOH | 290 | 7,200 |
| VII; R = H | EtOH | 290 | 14,900 |
| VIII; R = H | EtOH | 285 | 11,300 |
| IX; R = Et | EtOH | 290 | 8,300 |
| Ph·$CH_2$·CO·NH·CH=C(OH)·$CO_2$H | $H_2O$ | 280 | 20,300 |

## Experimental

Infrared absorption spectra were taken in compressed potassium bromide.

The chloride of 2-benzyloxazole-4-carboxylic acid was prepared as previously reported [2]

but was recrystallized from ether–light petroleum. The *methyl ester* of this acid formed colourless prisms, m. p. 55—56°, from light petroleum (b. p. 40—60°) (Found: C, 66·4; H, 5·2; N, 6·2. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1; N, 6·5%).

*2-Benzyl-4-oxazolylglyoxylamide* (IV).—Throughout the preparation of the acyl cyanide, water was excluded. 2-Benzyloxazole-4-carbonyl chloride (9·5 g.) in ether (95 c.c.) was cooled in a freezing mixture and treated with hydrogen cyanide (5 c.c.). Pyridine (4·8 c.c.) in ether (20 c.c.) was added gradually with shaking and continuous cooling. The mixture, after being kept overnight at 0°, was diluted with ether and filtered; the ether was removed at low pressure. Addition of ether, filtration, and evaporation were then repeated. The crude acyl cyanide (7·5 g.), which was unstable in air and could not be distilled, was hydrolysed immediately by shaking it with concentrated hydrochloric acid (30 c.c.). After ¾ hr. the mixture was poured on ice and stirred. The solidified product was washed, first by trituration and then in chloroform solution, with aqueous sodium hydrogen carbonate. Crystallization from ethyl acetate then gave the *amide* (2·6 g.) as colourless plates, m. p. 146—147°. A specimen melting at 149—150° was obtained by repeating the washing and recrystallization (Found: C, 63·0; H, 4·4; N, 11·8. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·2%).

*2 : 5-Dihydro-2 : 4-dihydroxy-5-oxo-3-phenylacetamidofuran* (V; R = H).—2-Benzyl-4-oxazolylglyoxylamide (1 g.) was dissolved in aqueous 0·5N-sodium hydroxide (40 c.c.) and kept in two 3½″ dishes over dilute sulphuric acid in a partly evacuated desiccator. Next day the solution was acidified and the precipitated acid (754 mg.; m. p. 152—153°) was collected. Occasionally a deep orange colour appeared during hydrolysis and it was then best to reject the first portion of acid precipitated. Crystallization from ethyl acetate–light petroleum gave *2 : 5-dihydro-2 : 4-dihydroxy-5-oxo-3-phenylacetamidofuran* (654 mg.), m. p. 155—156° (Found: C, 57·8; H, 4·5; N, 5·7. $C_{12}H_{11}O_5N$ requires C, 57·8; H, 4·4; N, 5·6%). It gave a red colour with ferric chloride. The infrared absorption spectrum showed a strong band at 1750 cm.$^{-1}$.

*2-Alkoxy-2 : 5-dihydro-4-hydroxy-5-oxo-3-phenylacetamidofurans.*—(*a*) The acid (V; R = H) (50 mg.) was boiled under reflux in methanol (2 c.c.) for 4 hr. The product, after removal of methanol at low pressure, crystallized when rubbed with light petroleum. Recrystallization from benzene gave *2 : 5-dihydro-4-hydroxy-2-methoxy-5-oxo-3-phenylacetamidofuran* (V; R = Me) as colourless prisms, m. p. 117—118° (Found: C, 59·0; H, 5·3; N, 5·5. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 5·0; N, 5·4%). The C=O absorption was at 1745 cm.$^{-1}$. (*b*) The acid (V; R = H) (250 mg.) was boiled under reflux for 4 hr. with ethanol (10 c.c.). The solution, after treatment with charcoal, was concentrated, *2 : 5-dihydro-2-ethoxy-4-hydroxy-5-oxo-3-phenylacetamidofuran* (V; R = Et) (195 mg.) separating as colourless prisms, m. p. 175° (in bath at 170°) (Found: C, 60·5; H, 5·4; N, 5·1. $C_{14}H_{15}O_5N$ requires C, 60·6; H, 5·4; N, 5·1%). The C=O absorption was at 1750 cm.$^{-1}$. (*c*) *2 : 5-Dihydro-4-hydroxy-5-oxo-3-phenylacetamido-2-isopropoxyfuran* (V; R = Pr$^i$) was prepared in the same way as the methoxy-compound and was recrystallized from benzene–light petroleum and from ether. The colourless prisms melted at 126—128° (Found: C, 62·2; H, 6·0; N, 5·0. $C_{15}H_{17}O_5N$ requires C, 61·9; H, 5·8; N, 4·8%). (*d*) *2-tert.-Butoxy-2 : 5-dihydro-4-hydroxy-5-oxo-3-phenylacetamidofuran* (V; R = Bu$^t$) was prepared by boiling the acid (V; R = H) (50 mg.) for 3 hr. under reflux with *tert.*-butyl alcohol (2 c.c.). Evaporation at low pressure left a residue which slowly solidified when rubbed with light petroleum and was recrystallized from ether. The *pseudo*-ester (30 mg.) formed colourless needles, m. p. 135—136° raised to 136—138° by another crystallization (Found: C, 62·5; H, 6·2; N, 4·8. $C_{16}H_{19}O_5N$ requires C, 63·0; H, 6·2; N, 4·6%). The C=O absorption was at 1760 cm.$^{-1}$. (*e*) The acid (V; R = H) (602 mg.), benzyl alcohol (1·2 c.c.), and benzene (12 c.c.) were boiled for 8 hr. under reflux and filtered hot. On cooling, *2-benzyloxy-2 : 5-dihydro-4-hydroxy-5-oxo-3-phenylacetamidofuran* (V; R = Ph·CH$_2$) (743 mg.) separated in colourless prisms, m. p. 158—160° unchanged by further crystallization (Found: C, 66·8; H, 5·0; N, 4·3. $C_{19}H_{17}O_5N$ requires C, 67·2; H, 5·0; N, 4·1%).

All these *pseudo*-esters dissolved slowly in aqueous sodium hydrogen carbonate and were reprecipitated by acid. They all gave with ferric chloride the same red colour, which developed slowly in very dilute solutions.

*2 : 4-Dialkoxy-2 : 5-dihydro-5-oxo-3-phenylacetamidofurans.*—These were prepared from the ethyl (V; R = Et) and benzyl (V; R = Ph·CH$_2$) *pseudo*-esters by dissolution in chloroform and addition to ethereal diazomethane. Reaction was rapid; when it ceased, the solvents were removed at low pressure.

*2-Ethoxy-2 : 5-dihydro-4-methoxy-5-oxo-3-phenylacetamidofuran* (VI; R = Et) crystallized

from ether–light petroleum in colourless prisms, m. p. 110—111° (Found : C, 61·9; H, 6·1; N, 5·3. $C_{15}H_{17}O_5N$ requires C, 61·9; H, 5·8; N, 4·8%). The C=O absorption was at 1750 cm.$^{-1}$. 2-*Benzyloxy*-2 : 5-*dihydro*-4-*methoxy*-5-*oxo*-3-*phenylacetamidofuran* separated from benzene–light petroleum in colourless needles, m. p. 113—114° (Found : C, 68·2; H, 5·5; N, 3·8. $C_{20}H_{19}O_5N$ requires C, 68·0; H, 5·4; N, 4·0%). Neither of these compounds gave a colour with ferric chloride.

2-*Anilino*-2 : 5-*dihydro*-4-*hydroxy*-5-*oxo*-3-*phenylacetamidofuran*.—The acid (V; R = H) (50 mg.) was boiled for a few minutes with aniline (3 drops) in ethanol (2—3 c.c.). A yellow product (48 mg.) crystallized on cooling. Recrystallization from ethyl acetate and then from methanol gave 20 mg., m. p. 185° (decomp.), of the *pseudo*-anilide (Found : C, 67·1; H, 4·6; N, 8·7. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 4·9; N, 8·6%). The product gave a red colour with ferric chloride and the infrared spectrum showed a strong band at 1745 cm.$^{-1}$.

*Reaction of* 2-*Benzyl*-4-*oxazolylglyoxylamide with Amines*.—(*a*) 2-Benzyl-4-oxazolylglyoxylamide (500 mg.) was boiled under reflux for 15 min. with ethanol (20 c.c.) and ethanolic ammonia (8 c.c.; saturated at 0°). After cooling, 4-*amino*-2-*oxo*-3-*phenylacetamidobut*-3-*enamide* (VII; R = H) (437 mg.) was collected; m. p. 205—206° (decomp.; in bath at 200°). A further 23 mg. separated on concentration of the filtrate. A sample recrystallized from butanol formed pale yellow prismatic needles of the same m. p. (Found : C, 58·6; H, 5·3; N, 16·9. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%). A solution in ethanol gave no immediate colour reaction with ferric chloride but after some hours a green colour developed. (*b*) 2-Benzyl-4-oxazolylglyoxylamide (46 mg.) and benzhydrazide (27 mg.) in ethanol (2 c.c.) were boiled under reflux for 1 hr. The product (27 mg.; m. p. 185°) separated on cooling; recrystallization from ethanol gave 4-*benzoylhydrazino*-2-*oxo*-3-*phenylacetamidobut*-3-*enamide*, m. p. 193° (Found : C, 62·2; H, 4·9; N, 14·9. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·9; N, 15·3%). The product gave no colour with ferric chloride. (*c*) 2-Benzyl-4-oxazolylglyoxylamide (460 mg.) and glycine ethyl ester hydrochloride (420 mg.) were boiled for 20 min. under reflux with sodium methoxide in methanol (28 c.c. of 0·1N). The mixture was evaporated at low pressure and the residue was crystallized from benzene; 4-*ethoxycarbonylmethylamino*-2-*oxo*-3-*phenylacetamidobut*-3-*enamide* (VII; R = $EtO_2C{\cdot}CH_2$) formed faintly yellow crystals (524 mg.), m. p. 133—135° (Found : C, 57·4; H, 5·4; N, 13·0. $C_{16}H_{19}O_5N_3$ requires C, 57·7; H, 5·7; N, 12·6%). It gave a slowly developing green colour with ferric chloride in ethanol and slowly reduced Tollens's reagent. (*d*) A mixture of 2-benzyl-4-oxazolylglyoxylamide (500 mg.), aniline (0·4 c.c.), and ethanol (5 c.c.) was boiled for 10 min. The solution was diluted with benzene; on cooling, yellow needles (624 mg.; m. p. 189—191°) of 4-*anilino*-2-*oxo*-3-*phenylacetamidobut*-3-*enamide* (VII; R = Ph) separated. A further amount (80 mg.; m. p. 189°) was obtained by concentration of the filtrate. Recrystallization from ethanol did not raise the m. p. (Found : C, 67·1; H, 5·3; N, 13·1. $C_{18}H_{17}O_3N_3$ requires C, 66·9; H, 5·2; N, 13·0%).

2-*Amino*-2 : 5-*dihydro*-4-*hydroxy*-5-*oxo*-3-*phenylacetamidopyrrole Hydrochloride* (VIII; R = H).—4-Amino-2-oxo-3-phenylacetamidobutenamide (VII; R = H) (100 mg.) dissolved when rubbed with ethanolic hydrogen chloride; addition of ether precipitated the crystalline *hydrochloride* (VIII; R = H) (98 mg.) (Found : C, 50·3; H, 4·9; N, 14·6. $C_{12}H_{13}O_3N_3$,HCl requires C, 50·8; H, 4·9; N, 14·8%). A test for halogen was positive. The substance decomposed without melting in a bath at 225—230° and gave an immediate blue (or green, depending on concentration) colour with ferric chloride.

2-*Ethoxycarbonylmethylamino*-2 : 5-*dihydro*-4-*hydroxy*-5-*oxo*-3-*phenylacetamidopyrrole Hydrochloride* (VIII; R = $EtO_2C{\cdot}CH_2$).—4-Ethoxycarbonylamino-2-oxo-3-phenylacetamidobutenamide (100 mg.) was rubbed with ethanolic hydrogen chloride. Dissolution occurred and the product separated; it was collected after addition of ether. The *hydrochloride* (VIII; R = $EtO_2C{\cdot}CH_2$) (101 mg.) formed colourless crystals, m. p. 145—147°, giving an immediate blue colour with ferric chloride (Found : C, 51·9; H, 5·5; N, 11·3. $C_{16}H_{19}O_5N_3$,HCl requires C, 51·9; H, 5·4; N, 11·4%). A test for halogen was positive.

2-*Ethoxy*-2 : 5-*dihydro*-4-*hydroxy*-5-*oxo*-3-*phenylacetamidopyrrole* (IX; R = Et).—4-Anilino-2-oxo-3-phenylacetamidobutenamide (VII; R = Ph) (660 mg.) was rubbed with ethanolic hydrogen chloride (5 c.c.; saturated). The colourless solution was evaporated at low pressure and the residue was stirred with water until solid. Recrystallization of the crude product (470 mg.) from ethanol gave the *ethoxy-compound* (IX; R = Et) as colourless prisms (Found : C, 60·9; H, 5·7; N, 10·3. $C_{14}H_{16}O_4N_2$ requires C, 60·9; H, 5·8; N, 10·2%), m. p. 165° (decomp., in bath at 160°). It gave a blue colour with ferric chloride in ethanol, contained no halogen,

dissolved slowly in aqueous sodium carbonate, and could be recovered unchanged on acidification. Treatment with diazomethane gave *2-ethoxy-2 : 5-dihydro-4-methoxy-5-oxo-3-phenylacetamidopyrrole*, colourless crystals, m. p. 166—168°, after two recrystallizations from ethyl acetate (Found: C, 62·1; H, 6·5; N, 9·4. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·7%). The compound (IX; R = Et) was also obtained by boiling the hydrochlorides (VIII; R = H) and (VIII; R = $EtO_2C{\cdot}CH_2$) with ethanol.

2 : *5-Dihydro-2 : 4-dihydroxy-5-oxo-3-phenylacetamidopyrrole* (IX; R = H).—2-Ethoxycarbonylmethylamino-2 : 5-dihydro-4-hydroxy-5-oxo-3-phenylacetamidopyrrole hydrochloride (90 mg.) was boiled for 1—2 min. with water; dissolution was never complete. After cooling, the product (46 mg.) was collected and dried. It decomposed at about 205° when placed in a bath at 200°, contained no halogen, and gave a blue colour with ferric chloride (Found: C, 58·2; H, 4·7; N, 11·6. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·8; N, 11·3%). The product after being boiled for 1 hr. with ethanol gave the ethoxy-compound (IX; R = Et), m. p. and mixed m. p. 165—166°.

*Action of Aniline on 2-Benzyloxazole-4-aldehyde.*—The aldehyde was left overnight in ethanol with one equivalent of aniline; in another experiment it was boiled under reflux for 1 hr. with two equivalents of aniline. No product separated from either reaction mixture but addition of dilute hydrochloric acid precipitated solids which were recrystallized from ethanol. The product, the same from both experiments, was *N-(2-phenylacetamido-3-phenyliminopropenyl)-aniline monohydrochloride* and formed deep yellow prisms, m. p. 234° (decomp.). A test for halogen was positive (Found: C, 70·5; H, 5·6; N, 10·7. $C_{23}H_{21}ON_3,HCl$ requires C, 70·5; H, 5·6; N, 10·7%).

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