894. *The Reaction of Cyanoacetamide with 1 : 2-Diketones.*

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Cyanoacetamide reacts with benzil yielding the pyrrolinone (I; R = CN). Further reaction gives a substituted pyrrolidone (III; R = Ph), analogues of which are isolated when cyanoacetamide reacts with aliphatic 1 : 2-diketones.

These pyrrolidones are easily hydrolysed to the dilactones of β-acyl-β-alkyl(or phenyl)glutaric acids (VI).

Derivatives of some of these compounds are described.

Although cyanoacetamide condenses with 1 : 3-diketones in the presence of piperidine to yield 4 : 6-dialkyl-3-cyanopyridones,[1] the same reaction with 1 : 2-diketones does not lead to the corresponding dialkyl*iso*pyrrolones.

One molecule of benzil first condenses with one of cyanoacetamide to give a hydrate which is converted by aqueous pyridine into an anhydrous product also formed from ammonia and ethyl 3-benzoyl-2-cyanocinnamate.[2] Unlike the latter, neither of the two compounds shows the light-absorption at 6·05 μ corresponding to a ketone and no ketonic derivatives could be prepared. Moreover, the compounds dissolve in aqueous alkali from which in both cases the hydrate is precipitated on acidification.

An absorption peak at 295 mμ (or 300 mμ for the hydrate) is consistent with the presence of a cinnamoyl grouping. The anhydrous compound forms stable *O*-alkyl derivatives, a diacetate, an *N*-methyl derivative (acidic), and an *ON*-dimethyl derivative (non-acidic).

These data indicate the pyrrolinone structure (I; R = CN) in which the acid properties are due to an allylic hydroxyl group.

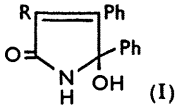
Another example of ring formation by an αβ-unsaturated γ-oxo-amide has been reported

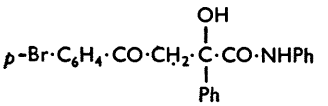
[1] Bardhan, *J.*, 1929, 2223; Weiburg and Wagtendonk, *Rec. Trav. chim.*, 1942, **61**, 728.
[2] Bacher, *J. prakt. Chem.*, 1929, **120**, 331.

by Lutz and Hill,[3] and Bashour and Lindwall [4] have described the cyclisation of the amide (II) to the corresponding pyrrolinone with hydrogen chloride.

The cyanide group of the pyrrolinone (I; R = CN) is eliminated by alkali.

Cyanoacetamide also reacts readily with diacetyl, dipropionyl, and dibutyryl, but in these cases, two molecules of amide combine with one of diketone with loss of one of water; an analogous product is obtained from the pyrrolinone (I; R = CN) by further reaction with cyanoacetamide. These substances are non-ketonic and show no ethylenic or αβ-unsaturation. They are therefore assigned the hydroxypyrrolidone structures (III; R = Me, Et, Pr, or Ph).


(I)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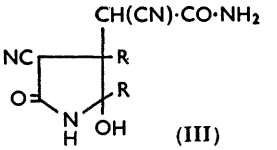
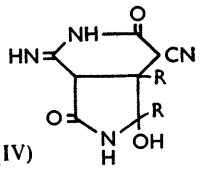

(III)

Since ammonia is not evolved from these hydroxypyrrolidones with water at 100° the cyanoacetamide residue is *trans* to the cyanide group, for if these groups were *cis*, interaction would occur [5] leading to an easily hydrolysed imino-imide (IV).[6]

Cold 90% sulphuric acid converts (III; R = Me or Et), by addition of two molecules of water and loss of one of ammonia, into a non-ketonic acid, probably (V; R = Me or Et, R′ or R″ = CN, R″ or R′ = $CO{\cdot}NH_2$). Carbon dioxide is lost spontaneously during the attempted formation of the phenyl compound (III; R = Ph) giving a non-acidic product; the other acids are readily decarboxylated at their melting points.

When boiled with 80% sulphuric acid these acids or the amides (III) are converted into the dilactones (VI; R′ = H), a reaction which proceeds in over 90% yield for the aliphatic and in 10% yield for the phenyl compound. The aliphatic dilactones form 2 : 4-dinitrophenylhydrazones (see Emery [7]).

Fittig and Salomon [8] have prepared the dilactone (VI; R = R′ = Me) in 3% yield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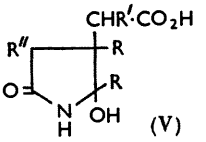
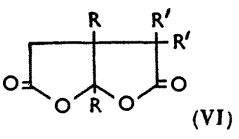

(V)


(VI)

from 1 : 1 : 2-trimethyltricarballylic (camphoronic) acid and acetic anhydride. We have failed to isolate (VI; R = Me, R′ = H) from the corresponding reaction with β-methyltricarballylic acid.

Experimental

Melting points are corrected.

4-Cyano-2-hydroxy-5-oxo-2 : 3-diphenyl-Δ³-pyrroline (I; R = CN).—Piperidine (22 g.) was added dropwise, during 15 min., to a stirred mixture of cyanoacetamide (16·7 g.), benzil (41·9 g.), and ethanol (700 ml.), and the resulting solution refluxed for ½ hr. After removal of solvent, the residue was washed with water and crystallised from aqueous ethanol yielding the *hydrate* (31·7 g.), m. p. 170°, of (I; R = CN) (Found: C, 69·9; H, 4·7; N, 9·4. $C_{17}H_{12}O_2N_2,H_2O$ requires C, 69·4; H, 4·8; N, 9·5%). Light absorption, $\lambda_{max.}$ 300 mμ (ε 6800) in ethanol.

Recrystallisation of the hydrate from aqueous pyridine gave the anhydrous *product*, m. p.

[3] Lutz and Hill, *J. Org. Chem.*, 1941, **6**, 175.
[4] Bashour and Lindwall, *J. Amer. Chem. Soc.*, 1935, **57**, 178.
[5] Thorpe and Kon, *J.*, 1919, **115**, 686.
[6] Curtis, Day, and Kimmins, *J.*, 1923, **123**, 3131.
[7] Emery, *Annalen*, 1897, **295**, 123.
[8] Fittig and Salomon, *ibid.*, 1901, **314**, 92.

186° (Found: C, 73·6; H, 4·7; N, 9·9. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·4; N, 10·1%). Light absorption, $\lambda_{max.}$ 295 mμ (ε 11,000) in ethanol. Both compounds show a peak at 5·85 μ (in Nujol) (ethyl 3-benzoyl-2-cyanocinnamate shows peaks at 5·85 and 6·05 μ).

(ii) Ethyl 3-benzoyl-2-cyanocinnamate (1 g.), ethanol (30 ml.), and ammonia (*d* 0·88; 7 ml.) were kept for 4 hr. at 70° and then concentrated; the anhydrous product crystallised and had m. p. 186° undepressed on admixture with a specimen prepared as above.

The hydrate was refluxed with (i) methanol and (ii) ethanol, both containing 10% of hydrogen chloride; after evaporation of the solvent and crystallisation of the residue from ethanol, there were obtained (i) the O-*methyl* derivative, m. p. 194° (Found: C, 74·3; H, 5·0; N, 9·2. $C_{18}H_{14}O_2N_2$ requires C, 74·5; N, 4·8; N, 9·7%), and (ii) the O-*ethyl* derivative, m. p. 184° (Found: C, 74·7; H, 5·3; N, 9·0. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3; N, 9·2%).

4-Cyano-2-hydroxy- and 4-Cyano-2-methoxy-1-methyl-5-oxo-2 : 3-diphenyl-Δ³-pyrroline.—Prepared from aqueous sodium hydroxide (1·32 g. in 20 ml.), the hydrate of (I; R = CN) (2·9 g.), and dimethyl sulphate (7·6 g.) at room temperature the precipitated *2-methoxy-pyrrolinone* formed needles (2·1 g.), m. p. 158° (from 60% aqueous ethanol) (Found: C, 75·0; H, 5·4; N, 8·9; OMe, 12·9. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3; N, 9·2; OMe, 10·2%). On acidification of the combined filtrate and washings with 10% sulphuric acid, the *2-hydroxy-pyrrolinone* was precipitated; it formed needles (0·8 g.), m. p. 222° (from 60% aqueous ethanol) (Found: C, 74·0; H, 4·6; N, 9·5; OMe, 2·8. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·8; N, 9·7; OMe, nil %).

2-Acetoxy-1-acetyl-4-cyano-5-oxo-2 : 3-diphenyl-Δ³-pyrroline. The hydrate of (I; R = CN) (2·0 g.) was refluxed for 10 min. with acetic anhydride (6·0 g.) in pyridine (20 ml.). After concentration at 100°/10 mm., the residue was dissolved in 70% acetone; the *product* (1·5 g.) had m. p. 159° (from 70% acetone) (Found: C, 70·2; H, 4·4; N, 7·8. $C_{21}H_{16}O_4N_2$ requires C, 70·0; H, 4·4; N, 7·8%).

2-Hydroxy-5-oxo-2 : 3-diphenyl-Δ³-pyrroline (I; R = H). The hydrate of (I; R = CN) (1 g.) was refluxed for 2 hr. with 15% sodium hydroxide solution (20 ml.), and the mixture then cooled and acidified with dilute hydrochloric acid. The *product* was isolated by ether; it slowly solidified and was crystallised from 50% aqueous ethanol forming plates (0·7 g.), m. p. 141° (Found: C, 76·3; H, 5·4; N, 5·2. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

2 : 3-Disubstituted 4-Cyano-3-cyanoacetamido-2-hydroxy-5-oxopyrrolidines (III).—To a stirred solution of cyanoacetamide (20 g.) in ethanol (150 ml.) at 55—60°, the diketone (0·125 mole) was added during ½ hr., stirring continued for a further 2 hr., and the mixture left for 12 hr. The precipitate was collected, washed with ethanol, and recrystallised as indicated. The following derivatives were prepared: 2 : 3-*dimethyl* (90%) (from water), m. p. 289° (Found: C, 50·8; H, 5·3; N, 24·0. $C_{10}H_{12}O_3N_4$ requires C, 50·8; H, 5·1; N, 23·8%); 2 : 3-*diethyl* (49%) (from glycol), m. p. 325—326° (Found: C, 54·3; H, 6·0; N, 21·0. $C_{12}H_{16}O_3N_4$ requires C, 54·6; H, 6·1; N, 21·2%); 2 : 3-*dipropyl* (8·5%) (prepared by using water not ethanol as solvent; crystallised from glycol), m. p. 343° (Found: C, 57·8; H, 7·0; N, 19·1. $C_{14}H_{20}O_3N_4$ requires C, 57·5; H, 6·8; N, 19·1%).

The 2 : 3-*diphenyl* derivative (5·3%), obtained by substituting the hydrate of (I; R = CN) (0·25 mole) for a diketone and refluxing the reaction mixture for 80 hr., was purified by successive washings with boiling ether, acetone, ethanol, and water; it had m. p. 426° (Found: C, 66·7; H, 4·5; N, 15·1. $C_{20}H_{16}O_3N_4$ requires C, 66·7; H, 4·4; N, 15·5%).

2 : 3-Disubstituted 3-Carboxyacetamido(or carboxycyanomethyl)-4-cyano(or amido)-2-hydroxy-5-oxopyrrolidines (V; R′ = CN or CO·NH₂, R″ = $CONH_2$ or CN).—The amide (III; R = Me or Et) (1 g.) in 90% sulphuric acid (11·5 ml.) was kept for 24 hr., then diluted with ice–water (30 ml.) and left for a further 36 hr. The deposited crystals were collected; the following were thus prepared: 2 : 3-dimethyl derivative (75%), m. p. 334° (from water) (Found: C, 47·1; H, 5·4; N, 16·6. Calc. for $C_{10}H_{13}O_5N_3$: C, 47·1; H, 5·1; N, 16·5%); and 2 : 3-diethyl derivative (25%), m. p. 337—338° (from aqueous glycol) (Found: C, 51·0; H, 6·0; N, 14·6. Calc. for $C_{12}H_{17}O_5N_3$: C, 50·9; H, 6·0; N, 14·8%).

By this method the diphenylpyrrolidone (III; R = Ph) gave 3-acetamido(or cyanomethyl)-4-cyano(or amido)-2-hydroxy-5-oxo-2 : 3-diphenylpyrrolidine (51%), m. p. 338° (from glycol) (Found: C, 68·1; H, 5·1; N, 12·4. Calc. for $C_{19}H_{17}O_3N_3$: C, 68·1; H, 5·1; N, 12·5%).

Dilactones of β-Acyl-β-alkyl(or phenyl)glutaric Acids.—The corresponding pyrrolidone (III) was refluxed for 24 hr. with 8N-sulphuric acid (20 ml.). On cooling, the product separated and was crystallised from water. Thus were prepared the *dilactones* of: β-acetyl-β-methylglutaric

acid (95%), m. p. 148° (Found: C, 56·5; H, 5·8. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%) [2 : 4-*dinitrophenylhydrazone*, m. p. 256° (Found: C, 48·0; H, 3·8; N, 15·7. $C_{14}H_{14}O_7N_4$ requires C, 48·0; H, 4·0; N, 16·0%)]; β-*ethyl*-β-*propionylglutaric acid* (95%), m. p. 100° (Found: C, 60·5; H, 7·3. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%); β-*butyryl*-β-*propylglutaric acid* (90%), m. p. 88—89° (Found: C, 63·9; H, 7·8. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%) [2 : 4-*dinitrophenylhydrazone*, m. p. 235—238° (Found: C, 52·8; H, 5·4; N, 14·3. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%]; and β-*benzoyl*-β-*phenylglutaric acid* (10%), m. p. 203—204° (Found: C, 73·3; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·4; H, 4·8%).

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