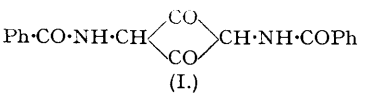
397. "*Dibenzamidodioxytetrol.*"

By J. W. Cornforth and H. T. Huang.

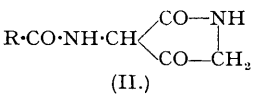
The structure (III; R = Ph) for a product obtainable from various hippuric acid derivatives is confirmed.

An acidic substance $C_{18}H_{14}O_4N_2$, first obtained (Rügheimer, *Ber.*, 1888, **21**, 3325; 1889, **22**, 1954) from ethyl hippurate with sodium or sodium ethoxide, has since been obtained in many other ways, though not always recognised by the workers concerned. Rügheimer named it "dibenzamidodioxytetrol", for its reactions led him to conclude that it was an enolised form of 2 : 4-diketo-**1** : 3-dibenzamido*cyclo*butane (I). Hydrolysis or alcoholysis leads to the loss on one benzoyl group and the product, $C_{11}H_{10}O_3N_2$, was formulated by Rügheimer as 3-benzamido-2 : 4-diketopyrrolidine (II; R = Ph) as the alternative amino*cyclo*butanedione structure was not in accord with the properties; the formation of (II; R = Ph) from (I) was held to be a hydrolytic ring-fission followed by lactam formation.

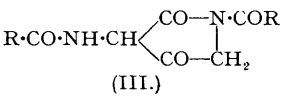
The evidence relating to these two substances has been discussed by one of us ("The Chemistry of Penicillin," Chap. XXI) and it was concluded that the substance $C_{18}H_{14}O_4N_2$ was probably 3-benzamido-2 : 4-diketo-1-benzoylpyrrolidine (III; R = Ph).



(I.)

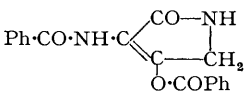


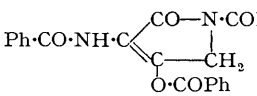
(II.)



(III.)

(IV.)





(V.)

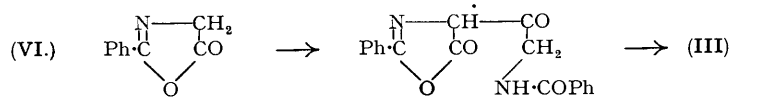
Benzoylation of (II; R = Ph) with benzoyl chloride and pyridine has now been found to give a new substance which, from the absence of acidity and negative ferric chloride test, was 3-*benzamido*-2-*keto*-4-*benzoyloxy*-Δ^3-*pyrroline* * (IV). With benzoic anhydride, however, two benzoyl groups were introduced and the *product*, evidently (V), was identical with a substance obtained from Rügheimer's $C_{18}H_{14}O_4N_2$ compound with benzoyl chloride and pyridine. It is

* This substance was prepared independently by Dr. A. H. Cook (personal communication).

thereby confirmed that the substances $C_{18}H_{14}O_4N_2$ and $C_{11}H_{10}O_3N_2$ have the same nucleus, and the structure (III; R = Ph) for the former is no longer in doubt.

Catalytic hydrogenation of (II; R = Ph) led to 3-*hexahydrobenzamido*-2 : 4-*diketopyrrolidine* (II; R = C_6H_{11}); the resistance of the pyrrolidione ring to reduction is noteworthy. Boiling acetic anhydride displaced a benzoyl group from (II; R = Ph) and the product was apparently identical with the 3-acetamido-2 : 4-diketo-1-acetylpyrrolidine (III; R = Me) obtained by Brodrick and Peak ("The Chemistry of Penicillin," Chap. XXI) from 3-hexamido-2 : 4-diketopyrrolidine (II; R = C_5H_{11}) and acetic anhydride.

The formation of (III; R = Ph) from ethyl hippurate and sodium ethoxide doubtless proceeds by lactam formation from the intermediate ethyl α-hippurylhippurate. The formation from 2-phenyloxazolone (VI), induced by various reagents (Cook, Elvidge, Heilbron, and Levy, "The Chemistry of Penicillin," Chap. XXI; Bailey, Baker, and Bradley, *ibid.*), may proceed as follows:



The formation of (III; R = Ph) from hippurazide and alkali (Curtius and Lenhard, *J. pr. Chem.*, **1904**, **70**, 240) and from hippuryl chloride in various ways (Scheiber and Reckleben, *Ber.*, **1913**, **46**, 2413; Karrer and Itschner, *Helv. Chim. Acta*, **1932**, **15**, 420) may well involve the oxazolone (VI) as intermediate.

Experimental.

Preparation of Materials.—The compound $C_{18}H_{14}O_4N_2$ was prepared by the methods of Rügheimer and of Karrer and Itschner (*locc. cit.*). The hemihydrate separated from ethanol in slender needles, m. p. 116° (Found: C, 65·4; H, 4·6. Calc. for $C_{18}H_{14}O_4N_2,0{\cdot}5H_2O$: C, 65·3; H, 4·5%). The hydrolysis product $C_{11}H_{10}O_3N_2$ was recrystallised from ethanol; white plates, m. p. 205° (Found: C, 60·2; H, 4·6. Calc. for $C_{11}H_{10}O_3N_2$: C, 60·6; H, 4·6%). On shaking the latter product with 2 : 4-dinitrophenylhydrazine in 5N-hydrochloric acid for 2 days, a 2 : 4-*dinitrophenylhydrazone* was obtained; dull red prisms from pyridine, m. p. above 310° (Found: N, 21·3. $C_{17}H_{14}O_6N_6$ requires N, 21·1%).

Benzoylation of (II) *and* (III; R = Ph).—(*a*) Benzoyl chloride (0·2 c.c.) was added dropwise to a cooled solution of 3-benzamido-2 : 4-diketopyrrolidine (0·3 g.) in pyridine (3 c.c.). After ½ hour ether (10 c.c.) was added, and the product collected, dried (0·3 g.), and recrystallised twice from ethanol–acetic acid, giving 3-*benzamido*-2-*keto*-4-*benzoyloxy*-Δ^3-*pyrroline*: slender silky needles, m. p. 230°, insoluble in aqueous sodium carbonate and giving no colour with ferric chloride in alcohol (Found: C, 66·7; H, 4·4; N, 8·6. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·4; N, 8·7%). The substance (50 mg.) was warmed with sodium hydroxide (1 c.c. of N) until solution was complete; acidification then gave 3-benzamido-2 : 4-diketopyrrolidine (II; R = Ph), m. p. and mixed m. p. 205° after recrystallisation.

(*b*) 3-Benzamido-2 : 4-diketopyrrolidine (0·2 g.) was refluxed gently with benzoic anhydride (1 g.) for 5 hours. After being cooled and washed with ether, the insoluble residue (200 mg.) was collected and recrystallised from ethanol–acetic acid, giving 3-*benzamido*-2-*keto*-4-*benzoyloxy*-1-*benzoyl*-Δ^3-*pyrroline* (V), fine needles m. p. 185—186° (Found: C, 70·7; H, 4·3. $C_{25}H_{18}O_5N_2$ requires C, 70·4; H, 4·3%). The substance was neutral and gave no colour with alcoholic ferric chloride.

(*c*) 3-Benzamido-2 : 4-diketo-1-benzoylpyrrolidine (III; R = Ph; 170 mg.) in pyridine (1·5 c.c.) was chilled and treated with benzoyl chloride (0·1 c.c.). After one hour ether (10 c.c.) was added, and the crystalline product (150 mg.) collected. Recrystallisation from ethanol–acetic acid gave the benzoyl derivative (V); m. p. and mixed m. p. 185—186°.

3-*Acetamido*-2 : 4-*diketo*-1-*acetylpyrrolidine* (III; R = Me).—The diketopyrrolidine (II; R = Ph; 200 mg.) was refluxed with acetic anhydride (3 c.c.) for 4 hours. Water (10 c.c.) was then added, and the mixture when homogeneous was evaporated at low pressure. Five recrystallisations of the residue from ethanol gave the diketopyrrolidine (III; R = Me); platelets (100 mg.), m. p. 218° (Brodrick and Peak, *loc. cit.*, gave m. p. 218°), soluble in aqueous sodium hydrogen carbonate and giving a violet colour with ethanolic ferric chloride (Found: C, 48·5; H, 5·1; N, 14·4. Calc. for $C_8H_{10}O_4N_2$: C, 48·5; H, 5·1; N, 14·1%).

Hydrogenation of (II; R = Ph).—The diketopyrrolidine (697 mg.) and platinum oxide (100 mg.) suspended in methanol (15 c.c.) were hydrogenated at 15°/1 atm.; reduction was still proceeding slowly after 18 hours, when the hydrogen consumed was equivalent to 4 atoms per molecule of (II; R = Ph). The mixture was warmed, and the catalyst and solvent removed. The solid residue dissolved completely in N-sodium hydroxide. Saturation of this solution with carbon dioxide precipitated (incompletely) 3-*hexahydrobenzamido*-2 : 4-*diketopyrrolidine* (II; R = C_6H_{11}); most of the product remained in solution along with unreduced material. The hydrogenation product crystallised from methanol in needles, m. p. 203—204° depressed by (II; R = Ph) to 180—190° (Found: C, 59·2; H, 7·1; N, 11·9. $C_{11}H_{16}O_3N_2$ requires C, 58·9; H, 7·2; N, 12·5%). With alcoholic ferric chloride it gave a deep blue colour.

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