# *The Dehydration of Some β-Benzamido-acids with Acetic Anhydride.*

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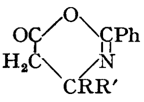
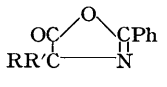
Saturated β-benzamido-acids containing quaternary β-carbon atoms are dehydrated by acetic anhydride to 5 : 6-dihydro-6-oxo-1 : 3-oxazines; other saturated β-benzamido-acids yield anhydrides. β-Benzamidocrotonic acid is dehydrated to 4-methyl-6-oxo-2-phenyl-1 : 3-oxazine which with ammonia gives the corresponding pyrimidine derivative.

THE conversion of β-benzamido*iso*valeric acid (I; R = R′ = Me) into 5 : 6-dihydro-4 : 4-dimethyl-6-oxo-2-phenyl-1 : 3-oxazine (III; R = $R_1$ = Me) by hot acetic anhydride (Baker and Ollis, *J.*, 1949, 345) appears to be the only recorded instance of this reaction. Since this 1 : 3-oxazine resembles the related oxazolones (IV) in reacting with water, ethanol, and aniline, to give the parent acid and its ethyl ester and anilide, respectively (Baker and Ollis, *loc. cit.*), it was of interest to determine if this formation of oxazines was general. The possible alternative dehydration products are the anhydrides (II) which can be readily differentiated by their lack of volatility and by the lower yields of anilide obtained with aniline at room temperature.

(I) $Ph{\cdot}CO{\cdot}NH{\cdot}CRR'{\cdot}CH_2{\cdot}CO_2H$ $(Ph{\cdot}CO{\cdot}NH{\cdot}CRR'{\cdot}CH_2{\cdot}CO)_2O$ (II)



(III)



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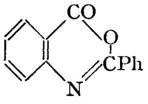

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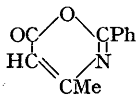
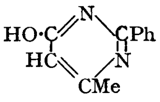


(VI)



(VII)

Dehydration of β-benzamidopropionic acid (I; R = R′ = H) gave its crystalline anhydride. Similarly β-benzamido-butyric and -β-phenylpropionic acid (I; R = H, R′ = Me and Ph respectively) gave non-crystalline anhydrides, the nature of which was proved as mentioned above. On the other hand, β-benzamido-β-phenylbutyric acid (I; R = Ph, R′ = Me) gave the oxazine (III; R = Ph, R′ = Me) which distilled at reduced pressure and gave the anilide quantitatively.

Thus, of five β-benzamido-acids examined, only those with quaternary β-carbon atoms yielded oxazines. (β-Benzamido-β : β-diphenylpropionic acid was not examined because of its inaccessibility. Cf. Posner, *Annalen*, 1912, **389**, 96.)

These results coupled with the fact that *N*-benzoylanthranilic acid may be dehydrated to an oxazine (V) (Angeli and Angelico, *Gazzetta*, 1900, **30**, II, 278) suggested that β-benzamido-crotonic acid might cyclise to an oxazine. This proved to be so. The product (VI) gave no pure product with aniline but with cold concentrated ammonia solution gave the pyrimidine (VII).

It is remarkable that heating ethyl β-benzamidopropionate with phosphoric oxide gives 6-ethoxy-2-phenyl-1 : 3-oxazine (Karrer and Miyamichi, *Helv. Chim. Acta*, 1926, **9**, 338), although only the anhydride was obtained from the acid by acetic anhydride.

The following incidental observations were made. Benzoylation of β-aminopropionic acid in aqueous alkali was much faster with benzoyl chloride prepared from benzoic acid and thionyl chloride than with " AnalaR " benzoyl chloride. This effect was observed also with other amino-acids and appears to be due to traces of benzaldehyde generally present in commercial benzoyl chloride, since addition of 0·5% of this aldehyde to the pure acid chloride also resulted in slow benzoylation. Both forms of ethyl β-benzamido-crotonate (Benary, *Ber.*, 1909, **42**, 3920) with cold ethanolic potassium hydroxide gave the same β-benzamidocrotonic acid in 5·6% yield; potassium benzoate (27%) and ethyl benzoate (47%) were also formed, the formation of the latter in an alkaline medium being noteworthy.

## EXPERIMENTAL

*β-Benzamidopropionic Acid.*—A solution of β-aminopropionic acid (10 g.), sodium hydroxide (4·5 g.), and sodium hydrogen carbonate (29 g.) in water (150 c.c.) was stirred with benzoyl chloride (prepared from benzoic acid and thionyl chloride; 25 c.c.) for 2 hr. at 5°, whereafter a sample gave no colour with boiling aqueous sodium hydrogen carbonate and ninhydrin. Acidification with hydrochloric acid in the presence of benzene (100 c.c.) yielded a syrup which solidified. By washing this with hot benzene and twice crystallising it from water, β-benzamidopropionic acid (17 g.), m. p. 133°, was obtained; Karrer and Miyamichi (*loc. cit.*) give m. p. 133°.

*β-Benzamidopropionic Anhydride.*—β-Benzamidopropionic acid (1·0 g.) in acetic anhydride (10 c.c.) was heated at 100° for 20 min. Removal of the acetic anhydride at 13 mm. and two crystallisations of the residue from absolute ethanol gave *β-benzamidopropionic anhydride* (0·4 g.) as colourless needles, m. p. 122·5—123·5° (Found : C, 66·5; H, 5·6; N, 7·8%; equiv., 184. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·5; N, 7·6%; equiv., 184). The anhydride (0·37 g.) was warmed with aniline (0·30 c.c.) in ethanol (2 c.c.), the solution acidified with dilute hydrochloric acid, and the precipitated product washed with water and then aqueous ammonia, giving *β-benzamidopropionanilide* (0·25 g.), m. p. 191°. When placed in a bath at 180° the material melted, resolidified, and remelted at 191° (Found : C, 72·2; H, 6·0; N, 10·4. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·4%). Samples of crude anhydride, obtained severally by 5, 20, 60, and 210 minutes' dehydration gave no oxazine on attempted distillation at 150°/2 mm., but gave anilide in amounts corresponding to 62, 88, 69, and 58% yields of anhydride, respectively.

*Dehydration of β-Benzamidobutyric Acid.*—Acetic anhydride (10 c.c.) and β-benzamidobutyric acid (1·00 g.; Baker and Ollis, *loc. cit.*) were kept at 100° for 20 min. Removal of acetic anhydride at 13 mm. gave a syrup which did not volatilise at 150°/2 mm. and with ethanolic aniline gave β-benzamidobutyranilide (0·60 g.), m. p. 190° (Found : N, 9·7. Calc. for $C_{17}H_{18}O_2N_2$ : N, 9·9%). Baker and Ollis (*loc. cit.*) give m. p. 190°.

*Dehydration of β-Benzamido-β-phenylpropionic Acid.*—β-Amino-β-phenylpropionic acid was obtained from cinnamic acid and hydroxylamine by Posner's method (*Ber.*, 1905, **38**, 2320); aqueous alkaline benzoylation gave the *N*-benzoyl derivative (67%), m. p. 194—196° (from acetic acid). Posner (*loc. cit.*) gives m. p. 194—196°. Dehydration of this benzamido-acid (1·0 g.) with acetic anhydride (10 c.c.) at 100° for 20 min. gave a syrup which did not distil at 150°/$10^{-2}$ mm. and with ethanolic aniline gave *β-benzamido-β-phenylpropionanilide* (0·58 g.), m. p. 235° (Found : C, 76·3; H, 5·7; N, 8·7. $C_{22}H_{20}O_2N_2$ requires C, 76·7; H, 5·9; N, 8·1%).

*Ethyl β-Benzamido-β-phenylbutyrate.*—β-Amino-β-phenylbutyric acid was prepared in 43% yield by refluxing an ethanolic solution of hydroxylamine and β-methylcinnamic acid for 240 hr. (Posner, *Annalen*, 1912, **389**, 76); β-methylcinnamic acid was recovered unchanged after 20 hours' heating with aqueous ammonia (*d* 0·88) at 150°. A suspension of the amino-acid (5·0 g.) in ethanol (50 c.c.) was saturated with hydrogen chloride at 20° and kept overnight. Ether (80 c.c.) and ice-water (200 c.c.) were added and the mixture was made alkaline with concentrated sodium hydroxide solution at $<10°$. Evaporation of the dried ($Na_2SO_4$) ethereal layer gave a crystalline residue which was dissolved in dry pyridine (30 c.c.) to which benzoyl chloride (4·5 c.c.) was then added. Next morning the mixture was warmed on a water-bath for 20 min., then poured into water, and the product extracted with ether (2 × 20 c.c.). The combined extracts were washed successively with 2N-hydrochloric acid, 2N-sodium carbonate, and then water. The syrup obtained by removing the ether from the dried ($Na_2SO_4$) extracts was then distilled at 230° (bath-temp.)/$10^{-3}$ mm., giving *ethyl β-benzamido-β-phenylbutyrate* (2·4 g.), m. p. 84° (from ether) (Found : C, 73·4; H, 6·7; N, 4·4. $C_{19}H_{21}O_3N$ requires C, 73·3; H, 6·8; N, 4·5%).

*β-Benzamido-β-phenylbutyric Acid.*—The afore-mentioned ester (1·6 g.) was stirred for 5 hr. with N-potassium hydroxide (40 c.c.) and pyridine (1·6 c.c.). Removal of unchanged ester (0·25 g.), followed by acidification of the remaining solution, gave β-benzamido-β-phenylbutyric acid as a sticky solid which was dried under vacuum to a brittle mass (1·0 g.).

5 : *6-Dihydro-4-methyl-6-oxo-2* : *4-diphenyl-1* : *3-oxazine.*—Dehydration of the foregoing acid (1·0 g.) with acetic anhydride (10 c.c.) at 100° for 4 hr., followed by the removal of the acetic anhydride and distillation of the residue, gave 5 : *6-dihydro-4-methyl-6-oxo-2* : *4-diphenyl-1* : *3-oxazine* (0·85 g.) as a viscous liquid, b. p. 170° (bath-temp.)/$10^{-3}$ mm. (Found : C, 77·2; H, 6·0; N, 5·4. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%). Ethanolic aniline converted the oxazine derivative quantitatively into *β-benzamido-β-phenylbutyranilide*, m. p. 154° (Found : C, 77·0; H, 6·2; N, 7·8. $C_{23}H_{22}O_2N_2$ requires C, 77·1; H, 6·2; N, 7·8%).

β-*Benzamidocrotonic Acid.*—Ethyl β-benzamidocrotonate (12·5 g.), m. p. 96° (cf. Benary, *loc. cit.*) was stirred for 3 hr. with ethanol (95%; 52 c.c.) containing potassium hydroxide (3·1 g.). A white solid separated, which, on acidification, gave benzoic acid (2·5 g.), m. p. and mixed m. p. 121°. The mother-liquors were poured into a solution of sodium chloride (11 g.) in water (160 c.c.), and the mixture extracted with ether. The dried ($Na_2SO_4$) extract yielded ethyl benzoate (3·8 g.), $n_D^{17}$ 1·5030, b. p. 211°. When the aqueous layer was acidified and kept at 0° for 2 hr., β-*benzamidocrotonic acid* (0·61 g.), m. p. 139° (from methanol), was obtained (Found: C, 64·1; H, 5·3; N, 7·0. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%).

4-*Methyl*-6-*oxo*-2-*phenyl*-1 : 3-*oxazine.*—Dehydration of β-benzamidocrotonic acid (0·2 g.) with acetic anhydride (2 c.c.) for 20 min. at 100°, followed by the removal of the acetic anhydride at 13 mm., gave a solid which readily sublimed at 150° (bath-temp.)/13 mm. Two crystallisations of the sublimate (0·18 g.) from ethanol gave 4-*methyl*-6-*oxo*-2-*phenyl*-1 : 3-*oxazine*, m. p. 95° (Found: C, 70·4; H, 5·1; N, 7·1. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·9; N, 7·5%). The oxazine was quantitatively converted by cold aqueous ammonia (*d* 0·88) into 6-hydroxy-4-methyl-2-phenylpyrimidine, m. p. 215° (Found: C, 70·4; H, 5·3; N, 14·6. Calc. for $C_{11}H_{10}ON_2$: C, 70·9; H, 5·4; N, 15·0%); Pinner (*Ber.*, 1885, **18**, 760) gives m. p. 216°. The acetyl derivative had m. p. 42° (Found: N, 12·2. Calc. for $C_{13}H_{12}O_2N_2$: N, 12·3%); Pinner (*ibid.*, p. 762) gives m. p. 40—41°.

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