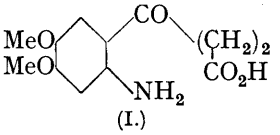
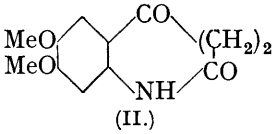
288. *Quinoline Derivatives. Part III. β-2-Amino-4 : 5-dimethoxybenzoylpropionic Acid and its Derivatives.*

By M. Abdul Haq, Jnanendra N. Rây, and M. Tuffail-Malkana.

Haq, Kapur, and Rây (J., 1933, 1087) obtained a β-2-amino-4 : 5-dimethoxybenzoylpropionic acid (I) of m. p. 118°, whereas Miki and Robinson (*ibid.*, 1467) found this acid to melt at 141° and suggested that the former specimen was hydrated. This has now been verified, for the acid of m. p. 118° is a *monohydrate*, and after drying at 100° it melts indefinitely at 141°. On being heated more strongly, it is converted into the lactam (II), the constitution of which is based on the absence of a diazotisable amino-group.



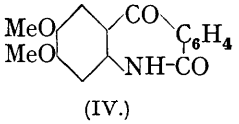
(I.)



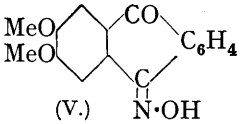
(II.)

$C_6H_2(OMe)_2(NH_2)\cdot CO\cdot C_6H_4\cdot CO_2H$

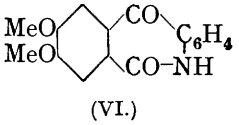
(III.)



(IV.)



(V.)



(VI.)

The ease with which such a seven-membered ring is formed is illustrated by the fact that 2-amino-4 : 5-dimethoxybenzoylbenzoic acid (III) cannot be isolated in the free state,

* The numbers R 55, etc., identify specimens submitted for biological tests.

passing readily into the *lactam* (IV). A lactam of this type has been prepared by Beckmann (*Ber.*, 1923, **56**, 16) by the transformation of anthraquinone-monoxime. Therefore, histazarin dimethyl ether *monoxime* (V) was prepared, and submitted to the Beckmann change, but the product (probably VI) was different from (IV). Irradiation with ultra-violet light converted the *trans*-oxime into a mixture (cf. Kailan, *Z. physikal. Chem.*, 1914, **87**, 33; *Monatsh.*, 1925, **38**, 13) in which the *cis*-form predominated. Treatment with phosphorus pentachloride in acetyl chloride converted it into a mixture of isomeric lactams, (IV) and (VI), in which (IV) predominated and was separated by fractional crystallisation.

The condensation of β-2-amino-4 : 5-dimethoxybenzoylpropionic acid with acetylacetone (Haq, Kapur, and Rây, *loc. cit.*), having given a compound of m. p. close to that of the compound similarly obtained from acetone by Miki and Robinson (*loc. cit.*), the possibility of an extrusion of the acyl group was examined, but the original constitution was confirmed.

We have also repeated the condensation of the amino-acid with acetaldehyde; further analytical data confirm that condensation took place, but the product is contaminated; moreover, it melts at 241° (with previous shrinking) instead of 141° as wrongly stated previously (*loc. cit.*).

Experimental.

β-2-Amino-4 : 5-dimethoxybenzoylpropionic acid, prepared according to Haq *et al.* (*loc. cit.*), was dried in air and in a vacuum over calcium chloride for 24 hrs., and obtained as a *monohydrate*, m. p. 118° (Found : C, 52·89; H, 6·28; N, 5·5. $C_{12}H_{15}O_5N,H_2O$ requires C, 53·13; H, 6·27; N, 5·2%). When it (1 g.) was heated at 110° for ¼ hr., 145° for ¼ hr., and then at 160—170° for ½ hr., it afforded the *lactam* (II), which crystallised from benzene, m. p. 183° (decomp.); it was insoluble in alkali solution, and did not give a ferric chloride or diazo-reaction (Found : C, 60·6; H, 6·0; N, 6·0. $C_{12}H_{13}O_4N$ requires C, 61·2; H, 5·6; N, 6·0%).

6 : 7-Dimethoxy-3-acetyl-2-methylquinoline-4-propionic acid, prepared as described by Haq *et al.*, was reanalysed (Found : C, 64·0; H, 6·0; N, 4·5. Calc. for $C_{17}H_{19}O_5N$: C, 64·35; H, 6·0; N, 4·4%). Its *piperonylidene* derivative crystallised from benzene–ethyl acetate, m. p. 240° (decomp., shrinking earlier) (Found : N, 3·0. $C_{25}H_{23}O_7N$ requires N, 3·1%).

The possibility of extrusion of the benzoyl group in the similar condensation with dibenzoylmethane (*loc. cit.*) was also negatived by repeating the process with zinc chloride as condensing agent. The 6 : 7-dimethoxy-3-benzoyl-2-phenylquinoline-4-propionic acid had m. p. 229—230° (decomp.) (Found : C, 72·8; H, 5·19; N, 3·4. Calc. for $C_{27}H_{23}O_5N$: C, 73·4; H, 5·2; N, 3·2%); in admixture with 6 : 7-dimethoxy-2-phenylquinoline-4-propionic acid, it had m. p. 171—197°.

3 : 4-*Dimethoxybenzoylbenzoic Acid.*—This acid was prepared in 25% yield by Lagodzinski (*Ber.*, 1895, **28**, 118; *Annalen*, 1905, **342**, 96), but the following method gives a much better yield. To a cold solution of anhydrous aluminium chloride (13·5 g.) in nitrobenzene (25 c.c.), a solution of phthalic anhydride (7·5 g.) and veratrole (7·0 g.) in the same solvent (25 c.c.) was added; the whole was kept at 0—5° for 24 hrs., with occasional shaking, and then at 40° for ¼ hr. Ice and hydrochloric acid were added, the solvent removed in steam, and the residue dissolved in alkali, whence the acid (m. p. 236—237°, from acetic acid) was isolated; yield 8—9 g.

2-*Nitro*-4 : 5-*dimethoxybenzoylbenzoic Acid.*—A solution of the above acid (1·0 g.) in acetic acid (25 c.c.) was mixed with nitric acid (*d* 1·42; 5 c.c.) and warmed at 75° for 2 mins.; it was cooled, sulphuric acid (0·5 c.c.) added, and the mixture kept at 0° for ¼ hr. Water was added till the solution became turbid, and the *nitro-acid* (1 g.) slowly separated; crystallised from ethyl alcohol, it had m. p. 165° (Found : N, 4·36. $C_{16}H_{13}O_7N$ requires N, 4·2%).

The *lactam* of 2-*amino*-4 : 5-*dimethoxybenzoylbenzoic acid* (IV) was prepared by reducing a solution of the nitro-acid (1·0 g.) in ammonia (*d* 0·88; 10 c.c.) and water (7 c.c.) at 100° with a solution of hydrated ferrous sulphate (10 g.) for 1 hr. The mixture was filtered, the residue washed with hot water, and the combined filtrate and washings cooled to 0°, acidified with acetic acid, and extracted with ethyl acetate. Removal of the solvent left a yellowish mass, which crystallised from dilute alcohol in canary-yellow leaflets, m. p. 256° (after drying at 100°) (Found : C, 68·3; H, 4·9; N, 5·0. $C_{16}H_{13}O_4N$ requires C, 67·9; H, 4·6; N, 4·9%). The substance is insoluble in sodium carbonate solution and does not give a diazo-reaction.

Histazarin Dimethyl Ether.—3 : 4-Dimethoxybenzoylbenzoic acid (1 g.), dissolved in sulphuric acid (*d* 1·84; 10 c.c.), was heated at 40—60° for 1 hr. The product isolated after pouring the reaction mixture on ice was washed with sodium carbonate solution, and crystallised from dilute acetic acid; deep yellow, silky needles, m. p. 235—236° (Lagodzinski, *loc. cit.*, gives 237°); yield theoretical.

A mixture of this ether (0·2 g.), pyridine (5 c.c.), and hydroxylamine hydrochloride (0·1 g.) in water (4 c.c.) was gently boiled for 5 hrs. under reflux, and then poured into potassium hydroxide solution (10 c.c. of 5%). The clear deep red filtrate was acidified with acetic acid, and the resulting yellowish precipitate crystallised from dilute alcohol in glistening leaflets, m. p. 210—212° (decomp.) (Found : N, 4·8. $C_{16}H_{13}O_4N$ requires N, 4·94%). The method enabled anthraquinone-monoxime to be more readily prepared than by earlier methods; m. p. 217° from alcohol (Found : N, 6·3. Calc. for $C_{14}H_9O_2N$: N, 6·3%) (Schunk and Marchlewski, *Ber.*, 1894, **27**, 2125, give m. p. 224°).

A mixture of the monoxime (V) (0·5 g.), acetyl chloride (5 g.), and phosphorus pentachloride (1 g.) was kept at 0° for 12 hrs. After the removal of volatile products on the steam-bath, the residue was decomposed with ice; the yellowish mass which separated crystallised from dilute acetic acid in yellow needles, m. p. 235° (decomp.), mixed m. p. with (IV), 186—195° (Found : N, 5·1. $C_{16}H_{13}O_4N$ requires N, 4·9%).

Hydrogen chloride was passed into a solution of the monoxime (V) in ether at 0°, and the yellowish-orange precipitate was dried, well powdered, and exposed to ultra-violet light from a mercury-vapour lamp for 40 minutes with stirring; it was then introduced into a mixture of acetyl chloride (10 g.) and phosphorus pentachloride (5 g.) and kept for 12 hrs. The product was worked up as previously described, and after crystallisation from alcohol had m. p. 256°, not lowered by admixture of the lactam (IV) prepared as described above.

In view of the use of acridine derivatives as antimalarials, β-2-amino-4 : 5-dimethoxybenzoylpropionic acid (1 g.) was condensed with *cyclo*hexanone (0·5 c.c.) by ½ hour's heating at 110—120°; powdered zinc chloride (2 g.) was then introduced and heating continued for 10 hrs. The product was washed with tepid water, dissolved in dilute hydrochloric acid, and filtered. The filtrate was basified with ammonia in presence of ammonium chloride, then made slightly acidic with acetic acid; a crystalline *substance* was formed, and recrystallised from hot methanol, it had m. p. 262° (Found : N, 4·4. $C_{18}H_{21}O_4N$ requires N, 4·4%).

3 : 4-*Dimethoxyphenylphthalide.*—3 : 4-Dimethoxybenzoylbenzoic acid (1·1 g.) was reduced with sodium amalgam (3%; 15 g.); the solution was filtered, and boiled with dilute hydrochloric acid; the resulting crystalline precipitate was recrystallised from hot acetic acid; m. p. 144° (Found : C, 70·6; H, 4·8. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·1%).

2-*Nitro*-4 : 5-*dimethoxyphenylphthalide.*—The above phthalide (0·8 g.) in acetic acid (5 c.c.) was nitrated with nitric acid (*d* 1·42; 2·8 c.c.). Water precipitated a yellow substance which crystallised in bright yellow, silky needles from dilute acetic acid, m. p. 224° (Found : N, 4·2. $C_{16}H_{13}O_6N$ requires N, 4·4%).

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