346. *Attempts to find New Antimalarials. Part VI. Preparation of β-6 : 7-Dimethoxyquinaldyl(4)-ethylamine Dihydrochloride.*

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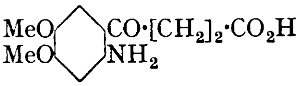
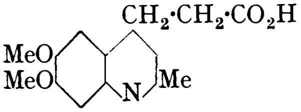
The issue of this Journal dated August 1933 (p. 1087) contains a communication by Haq, Kapur, and Rây which at some points touches work which we carried out in 1930 and we now submit an account of this investigation, the duplication of experimental detail not being extensive.

Our ultimate objective was the synthesis of bases analogous both to plasmoquine and to quinine, that is, bases containing aminoalkylamino-side chains but with at least two nitrogen atoms in the relative positions which they occupy in the quinine molecule. To this end we synthesised the substance named in the title and it remains to introduce an aminopropylamino-group by the method described in Part III (Baldwin, J., 1929, 2959).

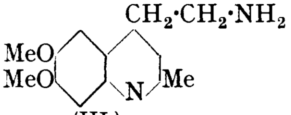
β-2-Amino-4 : 5-dimethoxybenzoylpropionic acid (I) condenses with acetone to β-6 : 7-*dimethoxyquinaldyl*(4)-*propionic acid* (II), which by the stages of the Curtius reactions furnishes β-6 : 7-*dimethoxyquinaldyl*(4)-*ethylamine* (III). The interrupted work in this field has now been resumed.



(I.)



(II.)



(III.)

The acid (III) has m. p. 249°; yet Haq, Kapur, and Rây (*loc. cit.*) describe its lower homologue, β-6 : 7-dimethoxyquinolyl(4)-propionic acid, as having m. p. 120°, or 141° after drying. A recent repetition of the experiment showed that, as suspected, the substance which they isolated must have been unchanged aminoveratroylpropionic acid, the acetaldehyde employed having been rapidly destroyed in the hot alkaline solution.

Experimental.

Succinic Anhydride.—A convenient method of preparation is the following. Powdered, dried succinic acid (100 g.) and phosphoryl chloride (70 g.) were heated (oil-bath at 120°) under reflux for 4 hours with occasional stirring. The excess of phosphoryl chloride was distilled and the residue extracted with hot chloroform, affording pure succinic anhydride on cooling (yield, 81 g. or 94%).

In the preparation of β-veratroylpropionic acid we employed carbon disulphide as solvent : the method of the Indian authors (*loc. cit.*) using nitrobenzene is apparently to be preferred.

β-2-*Nitro*-4 : 5-*dimethoxybenzoylpropionic Acid.*—Powdered β-veratroylpropionic acid (30 g.) was added with stirring to a mixture of nitric acid (250 c.c., *d* 1·42) and acetic acid (30 c.c.) cooled in ice and salt. After 2 hours, water was added and the nitro-acid collected (29·4 g.); it crystallised from alcohol or acetic acid in long, pale yellow needles (Found : C, 51·1; H, 4 6; N, 5·0. Calc. for $C_{12}H_{13}O_7N$: C, 50·9; H, 4·6; N, 4·9%). In agreement with Haq, Kapur, and Rây, who estimated the nitrogen content only, the m. p. found was 212°. The constitution of the acid was proved by heating it (0·5 g.) with nitric acid (18 c.c., *d* 1·42) on the steam-bath for 1 hour, followed by evaporation of the nitric acid at 100°; the residue crystallised from alcohol in yellow needles, m. p. 127·5°, which did not depress the m. p. (127°) of authentic 4 : 5-dinitroveratrole.

β-2-*Amino*-4 : 5-*dimethoxybenzoylpropionic Acid* (I).—The nitro-acid (5 g.) was reduced by means of seven times its weight of hydrated ferrous sulphate and excess of ammonia in boiling aqueous solution and isolated by rendering the filtered liquid faintly acid with acetic acid. After one recrystallisation from hot water the yield was 4 g., m. p. 141·5°. Five recrystallisations failed to remove the pale brownish tint of the long needles, m. p. 141—142·5° after drying in a vacuum (Found : C, 57·1; H, 6·0; N, 5·6. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 5·9; N, 5·5%). For this compound, Haq, Kapur, and Rây (*loc. cit.*) record the m. p. 118°, but as they did not carry out an estimation of carbon and hydrogen their product may have been hydrated. Addition of ferric chloride to a dilute aqueous solution of this substance causes the slow development of a blue and then an intense violet coloration.

β-6 : 7-*Dimethoxyquinaldyl*(4)-*propionic Acid* (II).—An attempt to condense the above amino-acid with acetone in boiling aqueous sodium hydroxide failed and the original material was recovered even though the reaction was prolonged for 25 hours. The condensation occurred, however, in alcoholic solution. A mixture of aminoveratroylpropionic acid (5·7 g.), sodium hydroxide (4·7 g.), acetone (25 c.c.), and alcohol (150 c.c. of 96%) was refluxed for 12 hours or longer and then (A) cooled and neutralised with hydrochloric acid; the precipitate was collected and washed with alcohol and water (yield, 4·1 g., m. p. 245°). The quinaldine derivative crystallised from 50% alcohol in minute, woolly, colourless needles, m. p. 249° after sintering at 247°, readily soluble in hot water, but separating as a gel on cooling (Found in material dried at 110° : C, 65·3; H, 6·4; N, 5·0. $C_{15}H_{17}O_4N$ requires C, 65·4; H, 6·2; N, 5·1%).

Haq, Kapur, and Rây (*loc. cit.*) condensed aminoveratroylpropionic acid with acetylacetone and isolated a product, m. p. 245°. Similarly the quinolines from aminoveratroylpropionic acid and acetophenone and dibenzoylmethane had m. p.'s 231—232° and 229° respectively. Carbon and hydrogen estimations are required in order to confirm the view taken of the constitution of the products from acetylacetone and dibenzoylmethane, because the possibility of loss of an acyl residue exists and has not been experimentally disproved.

As a convenient alternative (B) the reaction mixture obtained as above may be evaporated in a vacuum, the residue taken up in dilute hydrochloric acid, and the solution washed with ether and again evaporated; the dry residue is then extracted with boiling alcohol and after concentration of the extracts, the *hydrochloride* of the dimethoxyquinaldylpropionic acid separates. The salt crystallises from alcohol in white needles, m. p. 216° (decomp.) after sintering at 214° (Found : C, 57·9; H, 5·9; N, 4·8; Cl, 11·0. $C_{15}H_{17}O_4N,HCl$ requires C, 57·8; H, 5·8; N, 4·5; Cl, 11·4%).

The *methyl* ester was prepared in 90% yield by refluxing the acid or its hydrochloride with methyl-alcoholic hydrogen chloride, evaporating the solution to dryness, and adding aqueous sodium carbonate to the residue, The ester, collected by means of chloroform, crystallised from chloroform–light petroleum in long white needles, m. p. 101·5—102° (Found : C, 66·8; H, 6·5; N, 5·1. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6; N, 4·8%).

The *hydrazide* (II with $CO{\cdot}NH{\cdot}NH_2$ for CO_2H) was obtained by refluxing a mixture of the methyl ester (4 g.), hydrazine hydrate (1·8 g.), and alcohol (5 c.c.) for 30 minutes. The solution was evaporated to dryness, and the residue washed with ether and chloroform. The hydrazide in this condition (yield, 3·5 g.) could be used for the preparation of the azide; it crystallised from alcohol–ether at 0° in long white needles, m. p. 188·5° after sintering at 186° (Found : C, 58·4; H, 6·7; N, 13·7. $C_{15}H_{21}O_4N_3,H_2O$ requires C, 58·6; H, 6·8; N, 13·7%). The formation of the azide proves that this substance is not the hydrazine salt of the acid.

A solution of sodium nitrite (0·9 g.) in water (3 c.c.) was added to one of the hydrazide (1 g.) in acetic acid (10 c.c. of 40%) cooled in a freezing mixture. After 1 hour, sodium carbonate was added, liberating the *azide* (II with CON_3 for CO_2H),which was collected, washed with water, and dried in a vacuum (yield, 0·85 g., decomposing at 94—95° with evolution of nitrogen) (Found : N, 18·3. $C_{15}H_{16}O_3N_4$ requires N, 18·7%).

β-6 : 7-*Dimethoxyquinaldyl*(4)-*ethylurethane* (III with $NH{\cdot}CO_2Et$ for NH_2).—The acid azide (0·85 g.) was heated with alcohol (20 c.c.) on the steam-bath until evolution of nitrogen ceased. The product (0·68 g.) crystallised from 30% alcohol in colourless woolly needles, m. p. 154° (Found : C, 64·1; H, 7·0; N, 8·8. $C_{17}H_{22}O_4N_2$ requires C, 64·1; H, 6·9; N, 8·8%).

β-6 : 7-*Dimethoxyquinaldyl*(4)-*ethylamine* (III).—The urethane is difficult to hydrolyse and this is a case to which the ingenious device of Manske (*J. Amer. Chem. Soc.*, 1929, **51**, 1202) has recently been found to be applicable. The urethane is converted into a substituted phthalimide by heating with phthalic anhydride and the phthalimino-derivative is then hydrolysed in the known manner by means of hydrazine. The details will be submitted later, as this base is the starting point of a current investigation.

Before the introduction of Manske's method we operated as follows : A mixture of the urethane (0·5 g.) and hydrochloric acid (10 c.c., *d* 1·16) was heated in a sealed tube at 130° for 5 hours. The resulting solution was evaporated in a vacuum, the residue extracted with ethyl alcohol, and the *dihydrochloride* precipitated by the addition of ether (yield, 0·4 g.). The salt, recrystallised from alcohol–ether, formed white microscopic prisms which became brown at 270° without melting (Found : Cl, 20·9; loss at 110° in a high vacuum, 5·5. $C_{14}H_{18}O_2N_2,2HCl,H_2O$ requires Cl, 21·1; H_2O, 5·4%. Found in anhydrous material : C, 52·4; H, 6·4; Cl, 22·1. $C_{14}H_{18}O_2N_2,2HCl$ requires C, 52·7; H, 6·3; Cl, 22·2%).

Autocondensation of Aminoveratroylpropionic Acid.—A solution of the amino-acid (1 g.) and sodium hydroxide (2 g.) in alcohol (40 c.c.) was refluxed for 30 hours. The product was isolated after neutralisation with hydrochloric acid and crystallised from alcohol in white woolly needles, m. p. 271—272° (decomp.) with slight previous decomposition (Found: C, 65·9; H, 6·2; N, 9·9. $C_{15}H_{16}O_3N_2$ requires C, 66·2; H, 5·9; N, 10·3. $C_{24}H_{25}O_5N_3$ requires C, 65·9; H, 6·2; N, 9·6%). The *substance* is sparingly soluble in water and alcohol but readily soluble in dilute hydrochloric acid or in warm aqueous sodium hydroxide. It develops only a brownish-yellow coloration on the addition of ferric chloride to an acid solution and no evidence of a primary aromatic amine group could be obtained on attempted diazotisation and coupling with β-naphthol. In alcoholic solution the ferric reaction is orange-brown. The substance is being further investigated.

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[*Received, October 5th,* 1933.]