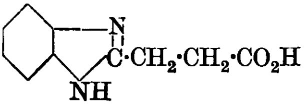
CCCC.—*Attempts to find New Anti-malarials. Part IV. β-Benziminazolylethylamine and β-5(or 6)-Ethoxybenziminazolylethylamine.*

By Bibhucharan Chatterjee.

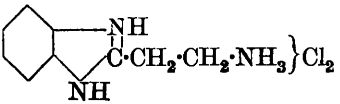
The condensation of *o*-phenylenediamine and succinic anhydride has been studied by Meyer and Lüders (*Annalen*, 1918, **415**, 37), who obtained benziminazole-2-propionic acid (I), together with succindi-*o*-aminoanilide,

$$NH_2\cdot C_6H_4\cdot NH\cdot CO\cdot[CH_2]_2\cdot CO\cdot NH\cdot C_6H_4\cdot NH_2.$$

In repeating this work, the latter substance was obtained in about 45% yield, but, when 2 mols. of the anhydride were used in xylene solution, the sole product was the succinate of (I). Attempts to apply the Curtius degradation to the hydrazide of this acid were not successful, but the amide underwent the Hofmann reaction and β-benziminazolylethylamine was isolated as the dihydrochloride (II). This base presents some points of constitutional analogy with histamine, and it is, accordingly, interesting to find that it is physiologically an inert substance. The author is greatly indebted to Dr. H. H. Dale, Sec.R.S., and Mr. J. H. Gaddum, B.A., M.R.C.S., for kindly examining the physiological properties of a specimen of the hydrochloride and they report that the substance failed to exhibit any pressor action even in relatively large dosage.



(I.)



(II.)

The 5(or 6)-ethoxy-derivatives of (I) and (II) were similarly obtained with the object suggested in the title.

EXPERIMENTAL.

Benziminazole-2-propionic Acid (I).—Succinic anhydride (83·5 g., or 96%) resulted when the acid (100 g.) was heated with pure thionyl chloride (300 c.c.) for 2 hours (compare Meyer, *Monatsh.*, 1901, **22**, 420, and McMaster and Ahmann, *J. Amer. Chem. Soc.*, 1928, **50**, 146, who reported less favourable yields in this process).

A mixture of *o*-phenylenediamine (10·8 g.), succinic anhydride (20 g.), and xylene (60 c.c.) was boiled for 3 hours, then cooled and the liquid decanted. The residue (X) was taken up in moderately concentrated, hot hydrochloric acid, and the succinic acid (9 g.), that separated on cooling, was collected, the filtrate being then saturated with sodium acetate and kept for a day. The crude, buff-coloured product was isolated (17·3 g.), and crystallised from water in silky, white needles, m. p. 228° (Found : C, 63·7; H, 5·3; N, 14·4. Calc. for $C_{10}H_{10}O_2N_2$: C, 63·2; H, 5·3; N, 14·7%). Meyer and Maier (*Annalen*, 1903, **327**, 23), who first prepared this acid, gave m. p. 226°, which Meyer and Lüders (*loc. cit.*) corrected to 236°. Many crystallisations from water failed to raise the m. p. above 228°. The acid has a very sweet taste. The *hydrochloride* crystallised from solutions in concentrated hydrochloric acid and from alcohol–ether in white, rectangular plates, m. p. 236—237° (Found : N, 12·7. $C_{10}H_{11}O_2N_2Cl$ requires N, 12·4%).

The methyl ester was prepared by passing hydrogen chloride for 3 hours through a suspension of the acid (15 g.) in methyl alcohol (150 c.c.). The isolated product (12·5 g.) crystallised from aqueous methyl alcohol in glistening white cubes, m. p. 144—145° (Found : C, 64·7; H, 6·2; N, 13·9. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·7; H, 5·9; N, 13·7%). The ethyl ester, m. p. 137°, was similarly obtained and analysed; the properties of these derivatives agree with the description of Meyer and Lüders (*loc. cit.*). These authors give the m. p. 254° for the amide, which has now been prepared in good yield by heating the methyl ester with concentrated, aqueous ammonia; it crystallised from alcohol in elongated plates, m. p. 259—260° (decomp.) (Found : C, 63·7; H, 6·1; N, 22·6. Calc. for $C_{10}H_{11}ON_3$: C, 63·5; H, 5·8; N, 22·2%).

The *hydrazide*, $C_6H_4{\cdot}N_2H{:}C{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$, was obtained by refluxing a mixture of the methyl ester (5 g.), hydrazine hydrate (20 c.c.), and methyl alcohol (25 c.c.) for an hour. The crude product (5·5 g.) crystallised from alcohol in white needles, m. p. 268° (decomp.) (Found : C, 59·1; H, 5·7; N, 27·2. $C_{10}H_{12}ON_4$ requires C, 58·8; H, 5·9; N, 27·5%). Although this is undoubtedly a true hydrazide and not the hydrazine salt of the acid, yet various attempts to prepare the azide or its transformation products led to nothing but the recovery of the original benziminazolylpropionic acid.

A sample of the above-mentioned residue (X) was crystallised from alcohol and proved to be the *succinate* of the acid. This salt had m. p. 182° (Found : N, 11·6. $C_{24}H_{26}O_8N_4$ requires N, 11·2%) and could be resolved into its components.

β-*Benziminazolylethylamine Dihydrochloride* (II).—A solution of sodium hypochlorite was prepared by dissolving chlorine (from 1·4 g. of potassium permanganate) in aqueous sodium hydroxide (5 g. in 50 c.c.) at 0° ; this was then heated to 30°, and powdered benziminazolepropionamide (5·0 g.) gradually introduced with shaking to dissolve each portion. When addition was complete, the liquid was maintained at 60—70° for 1½ hours, and then kept at room temperature for 12 hours. Potassium hydroxide (15 g.) was added, the solution heated at 60—70° for an hour, cooled, and extracted several times with ethyl acetate. The combined solutions were dried with sodium sulphate, and a *hydrochloride* precipitated by the passage of hydrogen chloride; it crystallised from alcohol in white, elongated plates, which decomposed at 270—272° (Found : C, 46·6 ; H, 5·9 ; N, 17·5 ; Cl, 30·7. $C_9H_{13}N_3Cl_2$ requires C, 46·2 ; H, 5·6 ; N, 18·0 ; Cl, 30·4%). The picrate crystallised from aqueous alcohol in yellow, rhombic plates, m. p. 193°. The free base was obtained as a viscous liquid.

2-*Nitro*-4-*ethoxysuccinanilic Acid*,

$$OEt{\cdot}C_6H_3(NO_2){\cdot}NH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H.$$

—It was thought that the reduction of this acid might constitute a convenient method of preparation of ethoxybenziminazolepropionic acid, but this did not prove to be the case. Although the reaction with, *e.g.*, tin and acetic acid, succeeded, and the required acid was isolated and identified, the yields, under a variety of conditions, were uniformly poor (some 10%).

A mixture of 3-nitro-*p*-phenetidine (18 g.), succinic anhydride (10 g.), and xylene (150 c.c.) was boiled under reflux for 3 hours. The product was purified by solution in aqueous sodium carbonate, and, after recovery, by crystallisation from aqueous alcohol in long, silky, yellow needles, m. p. 172—173° (yield, 22 g.) (Found : C, 51·2 ; H, 5·0 ; N, 10·2. $C_{12}H_{14}O_6N_2$ requires C, 51·1 ; H, 5·0 ; N, 9·9%).

5(or 6)-*Ethoxybenziminazole*-2-*propionic Acid*,

$$OEt{\cdot}C_6H_3{\cdot}N_2H{:}C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H.$$

—The methods given in the literature for the preparation of 3-amino-*p*-phenetidine are unsatisfactory. 3-Nitro-*p*-phenetidine (20 g.) was reduced by means of hydrated stannous chloride (150 g.) in concentrated hydrochloric acid (200 c.c.), and, after elimination of the tin as sulphide, the hydrochloride (17·5 g.) of the diamine was isolated. The free base, obtained by the use of concentrated, aqueous sodium hydroxide, was collected on a sintered-glass filter-plate, dried on porous tile, and worked up as quickly as possible in order to avoid oxidation.

A mixture of 3-amino-*p*-phenetidine (11 g.), succinic anhydride (15 g.), and xylene (80 c.c.) was refluxed for 3 hours, and the *acid* isolated as in the previous example (yield, 14 g.). It crystallised from water in colourless needles, m. p. 181° (Found: C, 61·2; H, 6·1; N, 11·7. $C_{12}H_{14}O_3N_2$ requires C, 61·6; H, 6·0; N, 12·0%). The product obtained by the reduction of nitroethoxysuccinanilic acid had m. p. 181° (Found: C, 61·7; H, 6·1; N, 11·7%), and a mixture of the two specimens also melted at 181°. This acid is more readily soluble in alcohol and in water than is benziminazolepropionic acid; it does not possess the sweet taste of the latter.

The *hydrochloride* crystallised from alcohol–ether in white plates, m. p. 221° (Found: N, 10·7. $C_{12}H_{15}O_3N_2Cl$ requires N, 10·4%).

The *methyl* ester was obtained like methyl benziminazolepropionate, and crystallised from ether–light petroleum in white clusters of prismatic needles, m. p. 103° (Found: C, 62·6; H, 6·1; N, 11·0. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·5; N, 11·3%).

The *amide*, obtained by heating the methyl ester (10 g.) with aqueous ammonia (50 c.c.; *d* 0·880), crystallised from ethyl acetate–light petroleum as a white powder, m. p. 189° (yield, 6·4 g.) (Found: C, 62·2; H, 6·5; N, 17·9. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·4; N, 18·0%).

β-5(or 6)-*Ethoxybenziminazolylethylamine Dihydrochloride* (R. 19). —By the method described for the preparation of β-benziminazolylethylamine, the *dihydrochloride* was isolated; it crystallised from alcohol in white plates, m. p. 251—252° (decomp.) (Found: C, 47·2; H, 5·7; N, 14·6; Cl, 25·9. $C_{11}H_{17}ON_3Cl_2$ requires C, 47·5; H, 6·1; N, 15·1; Cl, 25·6%). The free amine was a viscous liquid that did not crystallise after prolonged cooling to 0°.

The author wishes to thank Professor R. Robinson for his interest in the investigation.

THE UNIVERSITY, MANCHESTER. [*Received, November 2nd,* 1929.]