SYNTHESIS OF α-AMINO-β-(1-METHYL-2-BENZIMIDAZOLYL)PROPIONIC ACID

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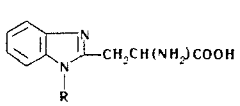
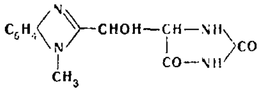
Depending on the reaction conditions, reaction of 1-methyl-2-formylbenzimidazole with hydantoin gives an aldol or crotonoid condensation product. Alkaline hydrolysis of these products gives 1,2-dimethylbenzimidazole. The dihydro derivative of the crotonoid condensation product can be hydrolyzed to α-amino-β-(1-methyl-2-benzimidazolyl)-propionic acid.

Condensation of o-phenylenediamine with asparagic acid gives α-amino-β-(benzimidazolyl-2)propionic acid (**Ia**) (23% yield), instead of the analogous β-alanine derivative and 1-amino-1, 2-di(benzimidazolyl-2')-ethane [1]. A hydantoin synthesis of the 1-methyl substituted derivative of this amino acid has been effected (**Ib**).

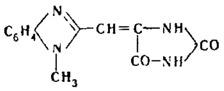


I a R=H; b R=CH_3

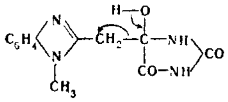
The reaction of 1-methyl-2-formylbenzimidazole (**II**) [2] with hydantoin in the presence of organic bases does not proceed further than formation of 5-(1'-methyl-2'-benzimidazolyl)hydroxymethylhydantoin (**III**). Glacial acetic acid containing sodium acetate, and dilute alkali convert this to 5-(1'-methyl-2'-benzimidazolyl)methylenehydantoin (**IV**). Thus, **II** reacts with hydantoin like cinchonine and quinaldine aldehydes[3]. Alkaline hydrolysis of **III** and **IV** gives, instead of the expected acids, a base mp 112°, which proved to be 1, 2-dimethylbenzimidazole **V**. In the reaction **III** is first converted to **IV**. Obviously hydrolysis of the latter to V, proceeds according to the general equation for splitting of a C═C bond [4, 5], via intermediate formation of **VI**.



III



IV



VI

A similar transformation with conversion of the —CH group to CH_3 has previously been observed when p-methoxy, p-chloro, and m-nitrobenzalhydantoin was heated with aqueous barium hydroxide solution [6].

Reduction of **IV** with 3% sodium amalgam gives the dihydro derivative, 5-(1'-methylbenzimidazolyl-2') methylhydantoin **VII**. The hydantoin ring in that compound is quite stable to hydrolysis. Concentrated hydrochloric acid or barium hydroxide do not cause appreciable decomposition. Only prolonged refluxing of **VII** with 10% KOH leads to its hydrolysis with formation of the amino acid **Ib**.

EXPERIMENTAL

5-(1'-Methyl-2'-benzimidazolyl)hydroxymethylhydantoin (III). A solution of 1.6 g (0.01 mole) 1-methyl-2-formylbenzimidazole, 1.5 g (0.015 mole) hydantoin, 1 ml dry pyridine, and 4–5 drops piperidine in 50 ml absolute EtOH was refluxed for 7–8 hr, the EtOH then distilled off until the volume was reduced to 25 ml, and the solid filtered off and washed with water, EtOH, and ether. Yield 2.2 g (84.5%), colorless prisms (ex MeOH), darkens about 200°, and mp 275–276° (decomp.), readily soluble in dilute alkalies and mineral acids, slightly soluble in benzene and ether. Found: C 55.08, 55.21; H 4.76, 4.75; N 21.52%, calculated for $C_{12}H_{12}N_4O_3$: C 55.38, H 4.65; N 21.53%.

5-(1'-Methyl-2'-benzimidazolyl)methylenehydantoin (IV). A mixture of 1.6 g (0.01 mole) **II**, 1 g (0.01 mole) hydantoin, 1 g (0.012 mole) fused NaOAc, and 10 ml glacial AcOH was refluxed for 4 1/2 hr. After cooling the precipitate was filtered off and washed with AcOH, water, EtOH, and ether. Yield 1.86 g (77%), yellow long needles (ex EtOH), mp 290–293°. Found: C 59.37, 59.39; H 4.05, 4.10; N 22.88, 22.93%, calculated for $C_{12}H_{10}N_4O_2$: C 59.49; H 4.16 N 23.13%

A high yield of the product is also obtained by heating the reactants together for 5–7 min on a steam bath with 10% KOH.

Alkaline hydrolysis of 5-(1'-methyl-2'-benzimidazolyl)methylenehydantoin. A suspension of 2.42 g (0.01 mole) **IV** in 50 ml 10% KOH was heated on a steam bath until the solid dissolved and evolution of ammonia ceased (4 hr). The solution became colorless, and a colorless oil separated, which, after cooling, was extracted with benzene. The extract gave 1.19 g (83%) compound as colorless needles mp 112°(after drying at 65°), identical with known 1,2-dimethylbenzimidazole (mp 112°) [2]. The same compound was obtained by heating **IV** with 10% alkali, yield 80%.

5-(1'-Methyl-2'-benzimidazolyl)methylhydantoin (VII). 102 g freshly-prepared Na-Hg amalgam was added in 4 portions to a suspension of 2.42 g (0.01 mole) **IV** in 100 ml EtOH, over a period of 2–3 hr, and the mixture boiled for about 12 hr, until the color vanished. The Hg was separated off, the EtOH distilled off, and the residue dissolved in 150 ml water. The solution was purified by boiling with charcoal, and was then made acid with acetic acid. On standing a precipitate formed, yield 2.24 g (92%), colorless prisms (ex EtOH), mp 224–225° (decomp.) Found: C 59.06, 59.02; H 5.12, 5.01%, calculated for $C_{12}H_{12}N_4O_2$: C 59.01; H 4.95%.

α-Amino-β-(1-methyl-2-benzimidazolyl)propionic acid (Ib). 2.44 g (0.01 mole) **VII** and 100 ml 10% NaOH were boiled together under reflux until evolution of ammonia ceased (~30 hr). The solution was made slightly acid with AcOH, evaporated to 35–40 ml on a water bath, and left overnight at 5°. The amino acid came down as snow white crystals. It was filtered off, washed on the filter with ice water, then with MeOH, and finally with ether. Yield 2.0 g (92%), fine long needles (ex water), mp 212–213°, slightly soluble in EtOH. Found: C 60.17, 60.11; H 5.88, 5.83; N 18.95, 19.99%, calculated for $C_{11}H_{13}N_3O_2$: C 60.26; H 5.98; N 19.16%.

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