HYDROXYLAMINE DERIVATIVES

III. Synthesis and Some Reactions of Hydroxylamine Derivatives of 2-Methylbenzimidazole*

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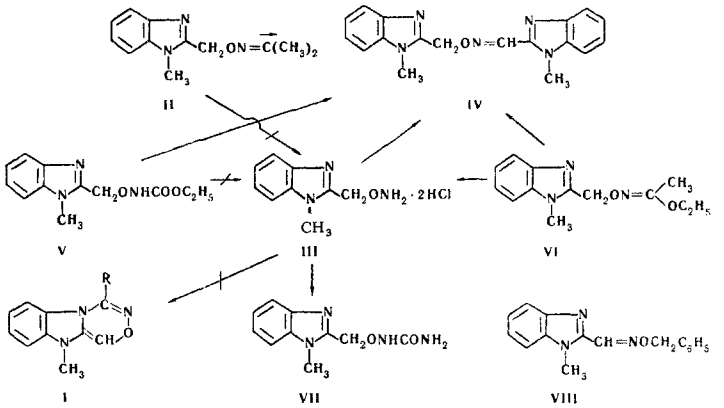
The condensation of urethane and ethyl acetohydroximate with 2-chloromethyl-1-methylbenzimidazole has given, respectively, N-ethoxycarbonyl-O-(1-methylbenzimidazol-2-ylmethyl)hydroxylamine and ethyl N-(1-methylbenzimidazol-2-ylmethoxy)acetimidate. Acid hydrolysis of the latter has given O-(1-methylbenzimidazol-2-ylmethyl)hydroxylamine. The reactions of its derivatives with HCl have been studied, and it has been shown that 1-methylbenzimidazole-2-aldehyde O-(1-methylbenzimidazole-2-methyl)oxime is formed. The structure of the latter has been shown by an analysis of its PMR spectra.

Continuing our search for biologically active compounds among hydroxylamine derivatives [1], we have attempted to synthesize substance I, which contains a potential hydroxylamine grouping in a six-membered ring linked with benzimidazole.



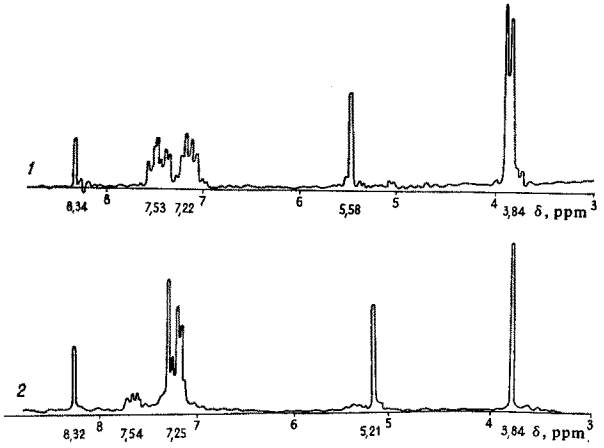
The condensation of 2-chloromethyl-1-methylbenzimidazole with acetone oxime and hydrolysis of the acetoxy derivative II was carried out as described previously [2]. However, when compound II was hydrolyzed instead of the hydrochloride of O-(1-methylbenzimidazol-2-ylmethyl)hydroxylamine (III) reported by Schumann et al. [2], a substance was obtained whose elementary analysis corresponded to the formula $C_{18}H_{17}N_5O \cdot 2HCl \cdot 2H_2O$ which, when treated with alkali, gave the base IV. It was also impossible to obtain III via N-ethoxycarbonyl-O-methylbenzimidazol-2-ylmethyl)hydroxylamine (V), synthesized from 2-chloromethyl-1-methylbenzimidazole and urethane. Under the action of caustic potash in 75% ethanol both at room temperature and with heating for 5 hr, substance V was not hydrolyzed but only converted into its potassium salt. However, attempts to hydrolyze substance V by boiling it with 20% HCl led to the formation of the dihydrochloride of IV.

The synthesis of III was effected by the condensation of 2-chloromethyl-1-methylbenzimidazole with ethyl acetohydroximate in an ethanolic solution of sodium methoxide and subsequent acid hydrolysis under mild conditions of ethyl N-(1-methylbenzimidazol-2-ylmethoxy)acetimidate (VI) which formed. When VI was boiled with 20% hydrochloric acid, hydrolysis led, as in II and V, to formation of the dihydrochloride of IV. In the preparation of VI, 2-ethoxymethyl-1-methylbenzimidazole was also formed, its structure being confirmed by synthesis from 2-chloromethyl-1-methylbenzimidazole and sodium ethoxide.

The substance III obtained by hydrolysis crystallized from 95% ethanol in the form of a monohydrate. On prolonged drying in vacuum over P_2O_5 it was converted into the anhydrous compound. In this process its decomposition

*For part II, see [1].

temperature gradually rose from 128° C (monohydrate) to 165° C (anhydrous). The structure of III was confirmed by preparing (1-methylbenzimidazol-2-ylmethoxy)urea (VII) from it and sodium cyanate. Compound III is stable only at normal temperature. When it was heated with 20% HCl it was converted into the dihydrochloride of IV, and under the action of caustic alkali, sodium carbonate, or sodium acetate it yielded IV as the free base. Attempts to obtain a formyl derivative from III by the action of formic acid and sodium acetate also led to IV.



PMR spectra (JNM 4H-100 instrument): 1) 1-methylbenzimidazole-2-aldehyde O-(1-methylbenzimidazol-2-ylmethyl)oxime (IV) in dimethyl sulfoxide, 2) 1-methyl-benzimidazole-2-aldehyde O-benzyloxime (VIII) in $CHCl_3$.

On the basis of its elementary analysis and PMR spectrum,* compound IV can apparently be assigned the structure of 1-methylbenzimidazole-2-aldehyde O-(1-methylbenzimidazol-2-ylmethyl)oxime. The PMR spectrum of compound IV has the following signals: split peak at 3.84 ppm corresponding to the protons of two methyl groups attached to nitrogen; singlet of CH_2 protons at 5.58 ppm, and singlet of a CH=N proton at 8.34 ppm. In addition, the spectrum has a complex multiplet at 7.22–7.53 ppm relating to the aromatic protons of the benzimidazole ring. We confirmed this assignment of the protons by comparing the PMR spectra of the oximes IV and VIII (figure) obtained from 1-methylbenzimidazole-2-carbaldehyde and O-benzylhydroxylamine. In the spectrum of VIII, the peak corresponding to the protons of the methyl group attached to the nitrogen is not split, since in this compound there is only one methyl group.

The formation of compound IV can be explained in the following manner. When II, V, or VI is hydrolyzed under comparatively severe conditions, the III which forms is cleaved with the liberation of ammonia and the formation of 1-methylbenzimidazole-2-carbaldehyde. The latter reacts with an unchanged molecule of III to form the oxime IV. A similar transformation of the hydrochlorides of some O-alkylhydroxylamines has been described in the literature [3]. The formation of oximes from carbonyl derivatives and O-alkylhydroxylamine hydrochlorides is also known [4].

EXPERIMENTAL

N-Ethoxycarbonyl-O-(1-methylbenzimidazo-2-ylmethyl)hydroxylamine (V). Urethane, 5.8 g (56 mM), was added to the alkoxide derived from 1.1 g (48 mM) of sodium in 60 ml of absolute ethanol, and the mixture was stirred for 30 min and then treated with 9 g (48 mM) of 2-chloromethyl-1-methylbenzimidazole. After 6 hr stirring at 20° C, the precipitate was separated off and washed with ethanol, water, and ethanol again. The yield of V was 8.6 g (78.4%), decomp 170–171° C. It is soluble in hot ethanol and insoluble in ether, benzene, and water. With an ethanolic solution of KOH it gives an easily-hydrolyzed potassium salt. Found, %: C 57.7; H 5.9; N 16.4. Calculated for $C_{12}H_{15}N_3O_3$, %: C 57.8; H 6.1; N 16.9.

Ethyl N-(1-methylbenzimidazol-2-ylmethoxy)acetimidate (VI) and 2-ethoxymethyl-1-methylbenzimidazole. Ethyl acetohydroximate, 6 g (58 mM), was added to the alkoxide derived from 1.33 g (58 mM) of sodium in 40 ml of absolute ethanol, the mixture was stirred for 20 min, and 10.5 g (58 mM) of 2-chloromethyl-1-methylbenzimidazole in 40 ml of

*The PMR spectra were taken by G. P. Syrova.

absolute ethanol was added. After 5 hr stirring, the reaction mixture was poured into water, the oil was extracted with ether, the ether was driven off, and the residue was distilled in vacuo. The yield of **2-ethoxymethyl-1-methylbenzimidazole** was 5 g (45.4%), bp 127–131° C (0.5 mm). After three distillations the substance crystallized, mp 40° C (from ether and petroleum ether). Found, %: C 69.1; H 7.3; N 14.7. Calculated for $C_{11}H_{14}N_2O$, %: C 69.4; H 7.4; N 14.9. From the second fraction, boiling at 142–153° C (0.5 mm), substance **VI** crystallized on standing. Yield 5 g (34.6%), mp 47--49° C (petroleum ether). Found, %: C 62.8; H 6.8; N 17.0. Calculated for $C_{13}H_{17}N_3O_2$, %: C 63.1; H 6.9; N 17.0.

2-Ethoxymethyl-1-methylbenzimidazole. With stirring, 3.1 g (17 mM) of 2-chloromethyl-1-methylbenzimidazole in 10 ml of ethanol was added to the alkoxide derived from 0.4 g (17 mM) of sodium in 10 ml of absolute ethanol, the mixture was stirred for 1 hr, then filtered, and the filtrate was evaporated in vacuo. The residue was treated with ether, the ethereal solution was filtered, then the ether was evaporated, and the residue was distilled in vacuo. Yield 2.4 g (75%), bp 132--135° C (0.5 mm), mp 40–42° C. The compound was identical with that described above.

Dihydrochloride of O-(1-methylbenzimidazol-2-ylmethyl)hydroxylamine (III). A solution of 7 g (28 mM) of **VI** in 25 ml of absolute ether was treated with 0.5 g (28 mM) of water and 40 ml of 8% ethereal HCl until the substance precipitated completely. The oily residue crystallized after trituration, and was washed with ether. The yield of **III** was 4.5 g (60%), decomp. p. 128° C. Found, %: C 40.5; H 5.8; N 15.2; Cl 26.0; H_2O 7.0. Calculated for $C_9H_{11}N_3O \cdot 2HCl \cdot H_2O$, %: C 40.3; H 5.6; N 15.7; Cl 26.4; H_2O 6.7. The same substance was obtained at 20° C from 4.7 g (19 mM) of **VI** and 0.34 g (19 mM) of water in 30 ml of 10% ethanolic HCl. The yield of **III** was 3.2 g (62.7%). After drying for 2 weeks in a desiccator over P_2O_5, mp 165° C (decomp). Found, %: C 43.2; H 4.9; N 16.9. Calculated for $C_9H_{11}N_3O \cdot 2HCl$, %: C 43.2; H 5.2; N 16.8. The **picrate** was obtained from **III** and picric acid with the addition of an equimolecular amount of ethanolic alkali, decomp. p. 217° C. Found, %: C 44.9; H 3.7; N 20.5. Calculated for $C_9H_{11}N_3O \cdot C_6H_3N_3O_7$, %: C 44.3; H 3.5; N 20.7.

(1-Methylbenzimidazol-2-ylmethoxy)urea (VII). A mixture of 0.4 g (1.6 mM) of **III**, 0.2 g (4 mM) of sodium cynate, and 3 ml of water was heated at 80° C for 1 hr. The precipitate was filtered off and washed with water. The yield of **VII** was 0.2 g (57.1%), decomp. p. 173° C (ethanol). Found, %: C 54.2; H 5.4; N 25.2. Calculated for $C_{10}H_{12}N_4O_2$, %: C 54.5; H 5.5; N 25.4.

1-Methylbenzimidazole-2-aldehyde O-(1-methylbenzimidazol-2-ylmethyl)oxime (IV). A) A mixture of 1 g (4 mM) of **VI** and 3 ml of 20% HCl was heated at 100° C for 6 hr. The precipitate that deposited on cooling was separated off, crystallized from 25% HCl, washed with ethanol and ether, and dried in a vacuum desiccator. The yield of the **dihydrochloride of IV** was 0.3 g (17%), decomp. p. 156° C. Found, %: C 50.3; H 5.2; N 16.4; Cl 17.0. Calculated for $C_{18}H_{17}N_5O \cdot 2HCl \cdot 2H_2O$, %: C 50.5; H 5.4; N 16.3; Cl 16.6. The free base **IV** had decomp. p. 198–200° C. Found, %: C 67.5; H 5.5; N 22.0. Calculated for $C_{18}H_{17}N_5O$, %: C 67.7; H 5.4; N 21.9. **Picrate of IV**, decomp. p. 232° C. Found, %: C 46.1; H 3.0; N 20.3. Calculated for $C_{18}H_{17}N_5O \cdot 2C_6H_3N_3O_7$, %: C 46.3; H 3.0; N 19.8.

B) A mixture of 0.5 g (2 mM) of **V** and 3 ml of 20% HCl was boiled for 4 hr and evaporated in vacuo, and the solid residue was dissolved in water and treated with bicarbonate. The yield of **IV** was 0.15 g (23.5%), decomp. p. 198–200° C.

C) A mixture of 0.5 g (2 mM) of **III**, 20 ml of ethanol, and 2 ml of HCl was boiled for 6 hr. Then 0.2 g (31.3%) of **IV** was isolated by the method described above.

D) A mixture of 3.4 g (15 mM) of **II** and 22 ml of 6 N HCl was treated with steam for 2 hr. The solution was evaporated and the residue was washed with ether. The yield of the dihydrochloride of **IV** was 3.7 g (55.2%), decomp. p. 156° C (ethanol). It yielded the free base **IV** with decomp. p. 198–200° C.

E) An aqueous solution of 3.8 g of the dihydrochloride of **IV** was neutralized with bicarbonate, saturated with sodium chloride solution, and extracted several times with dichloroethane and benzene. The combined extracts were evaporated in vacuo. The semisolid residue of **IV** (1.5 g), after the removal by vacuum distillation of a small amount of a substance boiling at 179–181° C (0.9 mm), solidified to a product with decomp. p. 200° C (ethanol).

F. A mixture of 1.5 g (6 mM) of **III**, 1.5 g of sodium acetate, 15 ml of 80% formic acid, and 10 ml of water was heated in a boiling water bath for 3 hr. The excess acid was distilled off and the residue was poured into water and neutralized with bicarbonate to pH 7. The precipitate was filtered off, washed with water, and dried in a vacuum desiccator. The yield of **IV** was 1 g (53.4%).

1-Methylbenzimidazole-2-aldehyde O-benzyloxime (VIII). A mixture of 0.8 g (5 mM) of 1-methylbenzimidazole-2-carbaldehyde [5], 5 ml of ethanol, and 0.6 g (mM) of O-benzylhydroxylamine was boiled with stirring for 1 hr 30 min and then poured into water. The oily deposit, which solidified upon trituration, was filtered off; mp 94° C (ethanol). Found, %: C 72.1; H 5.2; N 15.5. Calculated for $C_{16}H_{15}N_3O$, %: C 72.4; H 5.7; N 15.8.

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