N-ARYL-β-AMINO ACIDS

II. 2-(N-Arylaminoethyl)benzimidazoles*

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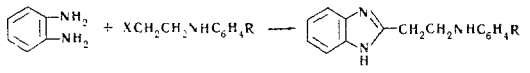
2-(N-Arylaminoethyl)benzimidazoles have been obtained by various methods. The best method is shown to be by reaction of N-aryl-β-alanine imidate ester hydrochlorides with o-phenylenediamine. It has been found that, in presence of polyphosphoric acid (PPA), N-aryl-β-alanines and their esters give 1, 2, 3, 4-tetrahydro-4-oxoquinolines.

It has previously been shown [1] that N-arylsulfonyl-N-phenyl-β-alanine imidate ester hydrochlorides are very reactive towards o-phenylenediamine, 2-(N-arylsulfonyl-N-anilinoethyl)benzimidazoles being formed.

This paper deals with the examination of various methods for the synthesis of 2-(N-arylaminoethyl)benzimidazoles (I). The starting materials used were N-aryl-β-alanines and their nitriles and imidate ester hydrochlorides, and o-phenylenediamine and its hydrochloride.



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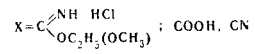

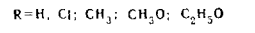

The dihydrochlorides of the methyl and ethyl N-arylalanine imidates used as starting materials (Table I) were obtained from the corresponding nitriles. The synthesis of four of these had already been described [2, 3]. The imidate ester hydrochlorides are colorless, crystalline compounds, melting with decomposition. They are hygroscopic, and are decomposed by water to the carboxylic acid esters and ammonium chloride. The melting points of the methyl imidate hydrochlorides were higher than those of the ethyl esters.

It is known that the rate of reaction of imidate esters with o-phenylenediamine, and the yields of benzimidazoles obtained, are dependent on the amount of hydrogen chloride present [4]. This was also found to hold in the case of the imidate esters of N-aryl-β-alanines. The imidate ester of N-phenyl-β-alanine, as the free base, yielded, after heating at 140° C in dry dioxane or isopentanol for 3 hr, only 55% of 2-(N-anilinoethyl)benzimidazole (II), whilst the corresponding hydrochlorides react at room temperature with evolution of heat, yields of 70–80% being obtained.

In order to confirm the structure of the benzimidazole derivatives obtained, II was prepared by reaction of 2-chloroethylbenzimidazole with aniline, and of anilinopropionitrile with o-phenylenediamine, as well as from β-anilinopropionic acid and o-phenylenediamine in 5 N HCl. The 2-(N-arylaminoethyl)benzimidazoles (I) thus prepared were colorless, crystalline compounds which are fairly stable on keeping, readily soluble in the cold in methanol and ethanol and in glacial acetic acid, and on heating in nitromethane, acetonitrile, tetrahydrofuran, dichloroethane, ethyl acetate, acetone and chloroform, and insoluble in hot ether.

It is known [5] that aromatic acids and their esters and amides afford benzimidazoles in good yield on heating with p-phenylenediamine in presence of polyphosphoric acid. We have shown that N-phenyl-β-alanine undergoes intramolecular condensation in presence of polyphosphoric acid to form small amounts of 1, 2, 3, 4-tetrahydro-4-oxoquinoline, and that it fails to react with o-phenylenediamine. In this case, the course of the reaction is apparently influenced by the presence of a four-membered side chain which is capable of participating in ring closure to give the quinoline structure. A similar cyclization product is obtained on heating N-phenyl-β-alanine methyl ester in presence of PPA.

EXPERIMENTAL

Methyl and Ethyl β-Arylaminopropionimidate Dihydrochlorides (Table 1). These were prepared by known methods [1].

2-(N-Arylaminoethyl)benzimidazoles (I, Table 2). In a three-necked flask, protected from moisture and fitted with a mechanical stirrer, reflux condenser and thermometer, there was dissolved 10.8 g (0.1 mole) of o-phenylenediamine (III) in 80 ml of absolute ethanol, followed by the finely ground crystalline methyl or ethyl β-arylaminopropionimidate dihydrochloride (0.15 mole) in one portion, with stirring. Evolution of heat was observed, the temperature of the reaction mixture rising to 25–30° C, and NH_4Cl separating. The mixture was boiled for 2 hr in order to complete the reaction, and the hot solution was neutralized with 5% sodium carbonate solution or ammonia. The oil which separated crystallized on standing, and was purified from acetonitrile. The dihydrochlorides and dipicrates were obtained in 90–93% and 62–73% yields respectively (Table 2).

2-Anilinoethylbenzimidazole (II). A) 11.53 g (0.06 mole) of ethyl β-anilinopropionimidate (free base) [2] and 5.4 g of III in 50 ml of absolute dioxane or isopentanol were heated for 3 hr at 140° C. Evolution of ammonia was observed at 119° C, the rate of evolution increasing as the temperature of the mixture increased. After removal of ethanol by distillation, the reaction mixture was poured into ice water and the dark brown precipitate filtered off, washed with acetone, and recrystallized twice from acetonitrile. Yield 6.52 g (55%).

B) A mixture of 2.1 g (0.011 mole) of ethyl β-anilinopropionimidate (free base), 0.37 g (0.01 mole) of hydrogen chloride in absolute methanol (50 ml), and 1.08 g (0.01 mole) of III were boiled for 2 hr, cooled, poured into water and basified with ammonia to give 2 g (84%) of II, mp 150.5–152° C. Found, %: N 17.3. Calculated for $C_{15}H_{15}N_3$, %: N 17.7.

*For part I, see [8].

Table 1

$RC_6H_4NHCH_2CH_2C(=NH)OR' \cdot 2HCl$

R	R'	Mp, °C* (decomp.)	Molecular formula	N, % found	N, % calculated	HCl, % found	HCl, % calculated	Yield, %
H	CH_3	127	$C_{10}H_{14}N_2O \cdot 2HCl$	11.3	11.2	29.2	29.1	98.3
H	C_2H_5	110[a]	$C_{11}H_{16}N_2O \cdot 2HCl$	10.6	10.6	27.6	27.5	88.0
4-Cl	CH_3	136	$C_{10}H_{13}ClN_2O \cdot 2HCl$	9.9	9.8	25.6	25.6	85.6
4-Cl	C_2H_5	128[b]	$C_{11}H_{15}ClN_2O \cdot 2HCl$	9.4	9.3	24.4	24.4	93.3
2-CH_3	CH_3	124	$C_{11}H_{16}N_2O \cdot 2HCl$	10.6	10.6	27.6	27.5	82.5
2-CH_3	C_2H_5	116	$C_{12}H_{18}N_2O \cdot 2HCl$	10.2	10.0	26.2	26.1	87.0
3-CH_3	CH_3	132	$C_{11}H_{16}N_2O \cdot 2HCl$	10.6	10.6	27.6	27.5	85.0
3-CH_3	C_2H_5	128	$C_{12}H_{18}N_2O \cdot 2HCl$	10.1	10.0	26.2	26.1	85.0
4-CH_3	CH_3	138	$C_{11}H_{16}N_2O \cdot 2HCl$	10.6	10.6	27.6	27.5	91.0
4-CH_3	C_2H_5	132	$C_{12}H_{18}N_2O \cdot 2HCl$	10.1	10.0	26.2	26.1	89.0
4-CH_3O	CH_3	124	$C_{11}H_{16}N_2O_2 \cdot 2HCl$	10.0	10.0	25.6	25.6	80.0
4-CH_3O	C_2H_5	112[c]	$C_{12}H_{18}N_2O_2 \cdot 2HCl$	9.7	9.5	24.8	24.7	83.0
4-C_2H_5O	CH_3	136	$C_{12}H_{18}N_2O_2 \cdot 2HCl$	9.7	9.5	24.8	24.7	84.0
4-C_2H_5O	C_2H_5	120	$C_{13}H_{20}N_2O_2 \cdot 2HCl$	9.8	9.0	23.7	23.6	77.0

*Literature values [2] [a]110° C; [b]128° C; [c]112°C.

Table 2

2-(N-Arylaminoethyl)benzimidazoles (I)

R	Mp, °C	Molecular formula	N, % found	N, % calculated	yield, %	Dihydrochlorides mp° C	Dihydrochlorides N, % found	Dihydrochlorides N, % calculated	Dipicrates mp° C	Dipicrates N, % found	Dipicrates N, % calculated
H	150.5—152	$C_{15}H_{15}N_3$	17.7	17.7	78	205—206	13.5	13.5	209—210	18.0	18.1
4-Cl	139.5—140.5	$C_{15}H_{14}ClN_3$	15.8	15.6	73	196—197	11.9	12.2	197—198	17.2	17.3
4-CH_3	105 —106	$C_{16}H_{17}N_3$	16.7	16.7	76	199—200	12.9	13.0	204—206	17.8	17.9
3-CH_3	168.5—170	$C_{16}H_{17}N_3$	16.8	16.7	75	216—217	12.9	13.0	198—199	17.8	17.9
2-CH_3	135 —136	$C_{16}H_{17}N_3$	16.7	16.7	71	185—186	13.0	13.0	177—178	17.8	17.9
4-CH_3O	174 —175	$C_{16}H_{17}N_3O$	15.6	15.7	73	207—208	12.3	12.3	217—218	17.3	17.4
4-C_2H_5O	180 —182	$C_{17}H_{19}N_3O$	14.9	14.9	72	223—224	11.8	11.9	231—232	17.7	17.0

C) 18.9 g (0.1 mole) of 2-chloroethylbenzimidazole [6] was dissolved in the threefold amount of anhydrous pyridine, and 12 g (0.12 mole) of freshly-distilled aniline added dropwise with cooling. The reaction mixture was then heated for 3 hr at 110° C, cooled, and poured into ice water to give 14 g (50%) of II.

D) 5.84 g (0.04 mole) of anilinopropionitrile and 7.24 g (0.04 mole) of the hydrochloride of III were heated in a sealed ampul for 3 hr at 150–180° C. The dark gray melt was finely ground and boiled for 1 hr with 300 ml of 5% HCl. The resulting precipitate of II dihydrochloride was isolated and converted into the free base by treatment with aqueous ammonia. Yield 4.36 g (46%).

E) 5.0 g (0.03 mole) of N-phenyl-β-alanine, 2.16 g (0.02 mole) of III and 50 ml of 5 N HCl were heated on the water bath for 10–15 hr. Yield 3.76 g (53%).

1, 2, 3, 4-Tetrahydro-4-oxoquinoline. A) A mixture of 5.0 g (0.03 mole) of N-phenyl-β-alanine, 3.24 g (0.03 mole) of III, and 50 ml of polyphosphoric acid (PPA) as a paste were heated for 10 min at 160° C, cooled to 100° C, and poured into ice water. The aqueous acid layer was basified, and the oil which separated was extracted into benzene. The benzene layer was washed with water and dried over $MgSO_4$. The viscous oil which remained after removal of the solvent in vacuo was distilled at 166–167° C (8 mm) to give 1.32 g (30%), mp 43.5–44° C [7]. Unchanged o-phenylenediamine was recovered quantitatively (3.2 g).

N-(p-Bromobenzenesulfonyl)-1, 2, 3, 4-tetrahydro-4-oxoquinoline was obtained in 78% yield by reaction of p-bromobenzenesulfonyl chloride with the 4-oxoquinoline in the presence of pyridine, mp 169.5–170° C (from aqueous alcohol) [1].

B) 17.92 g (0.1 mole) of methyl β-anilinopropionate was mixed with 180 g of freshly prepared PPA, and the paste heated for 10 min at 160° C. The cyclization product boiled at 166–167° C (8 mm). Yield 10.6%. A mixed mp with material obtained as in A) gave no depression.

REFERENCES

1. Z. F. Solomko, M. S. Malinovskii, G. A. Polinovskii, and N. M. Prikhod'ko, KhGS [Chemistry of Heterocyclic Compounds], 512, 1968.

2. A. F. Bekhli, ZhOKh, Collection 2, 1087, 1953.

3. D'Amico, C. Tung, and L. Walker, J. Am. Chem. Soc., 81, 5957, 1959.

4. F. King and R. Acheson, J. Chem. Soc., 1396, 1949.

5. D. Hein, R. Alheim, and J. Leavitt, J. Am. Chem. Soc., 79, 427, 1957.

6. F. King, R. Acheson, and P. Spensle, J. Chem. Soc., 1401, 1949.

7. W. Johnson, E. Woroch, and B. Buell, J. Am. Chem. Soc., 71, 1901, 1949.

8. Z. F. Solomko, M. S. Malinovskii, L. N. Polovina, and V. I. Gorbatenko, KhGS [Chemistry of Heterocyclic Compounds], 536, 1969.

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