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Synthesis of Methyl 5(6)-(4-Aminophenoxy)- and 5(6)-(2-Aminophenoxy)-2-benzimidazolyl Carbamates and Their Biological Properties

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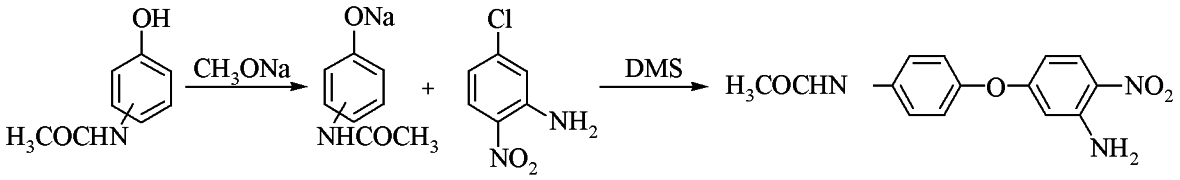
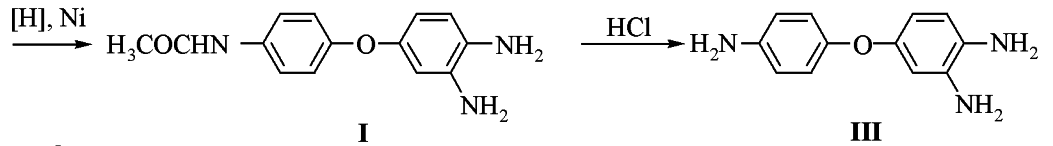
Abstract—A procedure was developed for preparation of methyl 5(6)-(4-aminophenoxy)- and 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamates by reaction of 3,4,4‘-triaminodiphenyl or 3,4,2‘-triaminodiphenyl ethers respectively with methyl cyanocarbamate in water solution in the presence of 7–10 molar excess of acetic acid. The helminthicidal properties, embryotoxicity, and overall toxicity of compounds obtained were estimated.

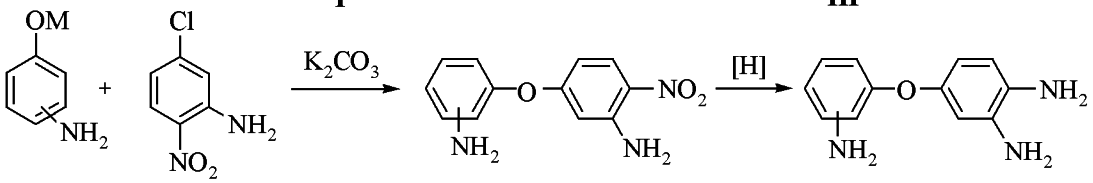
It is known [1] that 4'-acetylamino-3,4-diaminodiphenyl ether (**I**) and 2'-acetylamino-3,4-diaminodiphenyl ether (**II**), semiproducts at production of 3,4,4'-triaminodiphenyl (**III**) or 3,4,2'-triaminodiphenyl (**IV**) ethers and helminthicidal preparations based thereon are obtained from sodium 4-acetylamino-(**V**) or 2-acetylamino-(**VI**)phenolates by condensation with 2-nitro-5-chloroaniline in DMSO (DMF) in the presence of anhydrous potassium carbonate at heating. The synthesis of triaminodiphenyl ethers **III** and **IV** can be described by Schemes 1 and 2.



V, VI



I **III** (1)



III, IV (2)

In keeping with Scheme 1 diphenyl ether **III** is obtained from a solution of 4-acetylamino-3,4-diaminodiphenyl ether **I** by boiling for 1–2 h in 5% water solution of hydrochloric acid under a nitrogen atmosphere.

Along the Scheme 2 were prepared both isomers of triaminodiphenyl ethers **III** and **IV** [3].

We developed a preparation procedure for triaminodiphenyl ethers **III** and **IV** by reaction of

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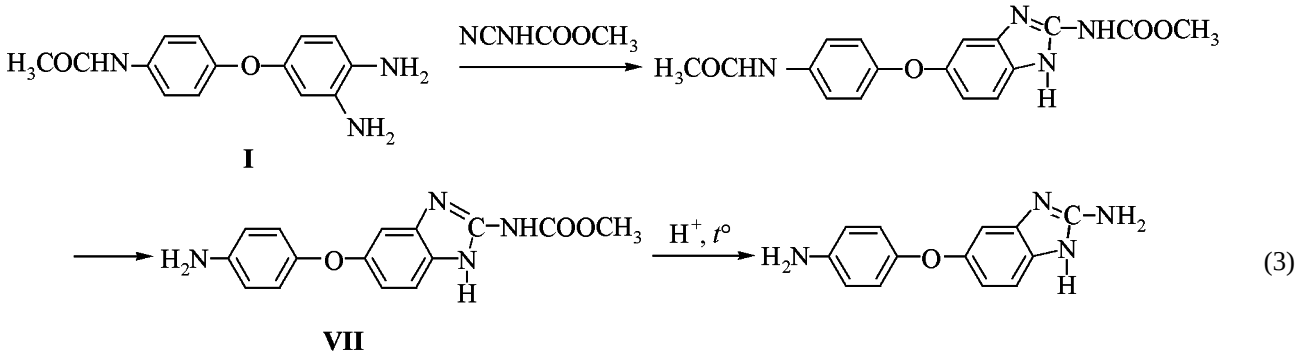
acetylaminophenol (**V**) with more accessible 4-nitro and 2-nitochlorobenzenes respectively. The reaction is carried out in DMF in the presence of anhydrous potassium carbonate and furnishes 4-acetylamino-4'-nitro- and 4-acetylamino-2'-nitrodiphenyl ethers respectively. The 4-acetylamino-4'-nitro- and 4-acetylamino-2'-nitrodiphenyl ethers obtained then undergo nitration with the concn. HNO_3 in chloroform or acetic acid respectively, and the formed 4-acetylamino-3,4'-dinitro-(**I**) and 4-acetylamino-3,2'-dinitrodiphenyl ethers are hydrolyzed by alkaline solution in 2-propanol. The isolated 4-amino-3,4'-dinitro- and 4-amino-3,2'-dinitrodiphenyl ethers are reduced with hydrazine hydrate in the presence of iron(III) chloride and activated carbon in a mixture of ethylene glycol and dioxane or in butanol affording triaminodiphenyl ethers **III** and **IV** [4, 5].

The preparation procedures of methyl 5(6)-(4-aminophenoxy)-2-benzimidazolyl carbamate (**VII**) and methyl 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamate (**VIII**) and their acetyl derivatives were published in [1, 6], their high helminthicidal efficiency was shown but no data were mentioned concerning the embryotropic activity and the theurapeutic index.

It is known [7, 8] that preparation of derivatives at the nitrogen atom in position *1* of the benzimidazole ring provides a possibility to modify certain characteristics of benzimidazolyl carbamates (solubility, activity, biological availability etc.).

The presence of a free amino group in methyl 2-benzimidazolyl carbamates **VII** and **VIII** gives additional opportunities for modifying these characteristics by introducing various substituents to the amino group.

Besides the procedures are known for replacement an amino group on aromatic compounds by a hydrogen [9–11]. However this conversion can be feasible only if a cheaper method would be developed for production of methyl 2-benzimidazolyl carbamates **VII** and **VIII** than the known procedures [1, 6]. These procedures were based on selective hydrolysis at high temperature of methyl 5(6)-(4-acetylaminophenoxy)- and 5(6)-(2-acetylaminophenoxy)-2-benzimidazolyl carbamates in the presence of strong mineral acids (hydrochloric, sulfuric or phosphoric acids). The course of reaction here is not unambiguous for the urethane group partially suffers hydrolysis (Scheme 3).

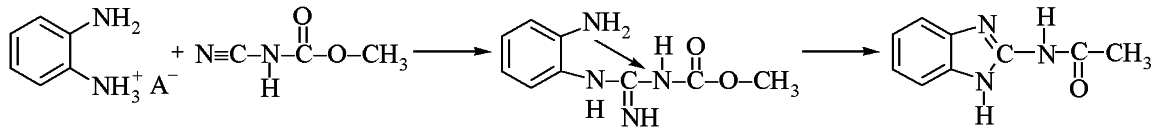


(3)

Apparently in [1, 6] the synthesis of methyl 2-benzimidazolyl carbamates **VII** and **VIII** was purposefully performed from triaminodiphenyl ethers **III** and **IV**. The basicity of aniline is known [12] to exceed that of 1,2-phenylenediamine, and therefore the closure of the benzimidazole ring may compete with addition to the amino group of the aniline fragment of the molecule (in positions *4* and *2*) of the methyl cyanocarbamate. Therefore the amino group requires preliminary protection. However the synthesis of initial monoacylated triaminodiphenyl ethers **I** and **II** has significant drawbacks as compared to our method of preparation of nonacylated triaminodiphenyl ethers **III** and **IV**. Therefore the development of procedures for synthesis of methyl 2-benzimidazolyl carbamates **VII** and **VIII** with the use as initial compounds more easily available triaminodiphenyl ethers **III** and **IV** is very urgent.

The reaction of 1,2-phenylenediamine with methyl cyanocarbamate (a product obtained from calcium cyanoamide and methyl chloroformate) resulting in formation of the benzimidazole ring proceeds in acid medium. The acid medium is necessary for conversion of the calcium salt of methyl cyanocarbamate into the active form. On the other hand, 1,2-phenylenediamine in acid medium can be present in monoprotonated or diprotonated form depending on the pH.

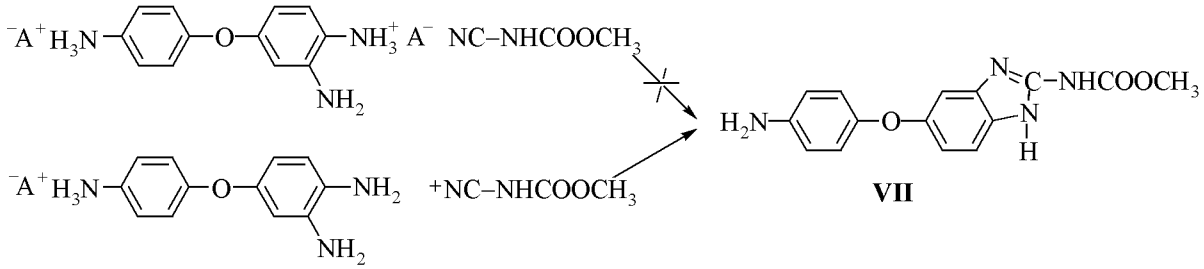
Therefore the medium should be moderately acidic (pH 3.5–4.5) for the methyl cyanocarbamate should be nonionized, and 1,2-phenylenediamine should not lose all its nucleophilicity (Scheme 4).



(4)

In the molecules of triaminodiphenyl ethers **III** and **IV** in contrast to 1,2-phenylenediamine three nucleophilic sites are present: the nitrogen of the aniline fragment and the nitrogens of the 1,2-phenylenediamine fragment. The selective preparation of methyl 2-benzimidazolyl carbamates **VII** and **VIII** requires deactivation of the most basic nitrogen in the aniline fragment.

We suggested that just in the acid medium the strongest nucleophilic site could be completely blocked providing it would be totally protonated. Same as in the case of 1,2-phenylenediamine, the triaminodiphenyl ethers **III** and **IV** can conserve sufficient reactivity toward the methyl cyanocarbamate only if their molecules are monoprotonated (Scheme 5).

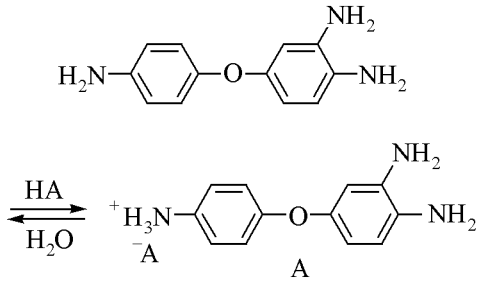


(5)

VII

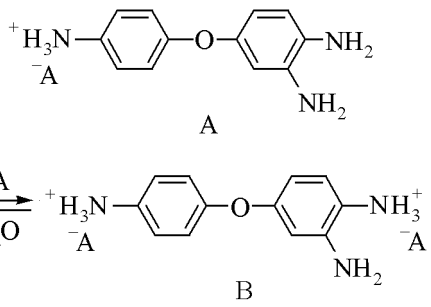
It should be taken into account that the cyclization of triaminodiphenyl ethers **III** and **IV** in the presence of methyl cyanocarbamate occurs with ammonia liberation; the latter can bind the acid necessary for blocking the aniline nitrogen. Therefore it is necessary to add acid into the reaction mixture during the course of the process to maintain the optimum pH.

Triaminodiphenyl ethers **III** and **IV** are relatively weak bases, and since the synthesis is carried out in diluted acid water solutions the following equilibria may exist between the different protonated forms of the ethers (Schemes 6 and 7).



(6)

A



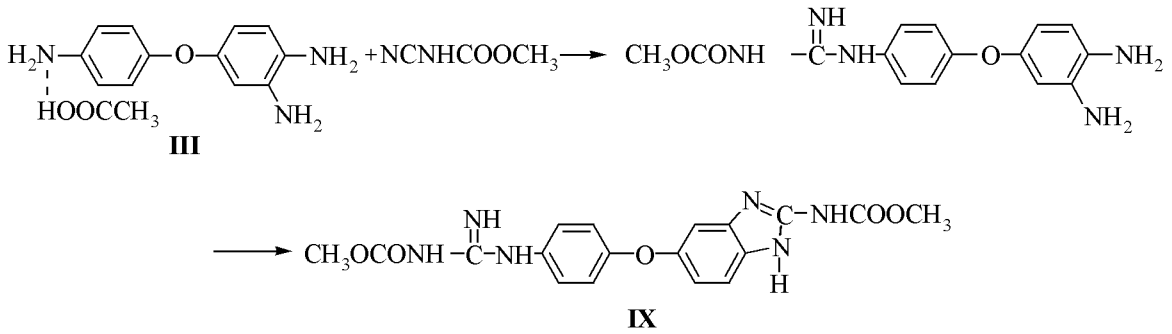
(7)

A

B

The equilibrium position depends not only on dilution but also on the strength of the acid used for protonation. At the use of a strong acid, e.g., of hydrochloric acid, at equimolar ratio of triaminodiphenyl ether–acid the ethers would exist prevailingly in form A; at the ratio 1 : 2 the form B would dominate.

At the use of weak acids, e.g., of acetic acid, the reaction mixture would contain a lot of nonprotonated forms of triaminodiphenyl ether (Scheme 6). At the use of excess acetic acid the equilibrium almost would not shift to B formation.



III

IX

(8)

Thus the preparation of methyl 2-benzimidazolyl carbamates **VII** and **VIII** from the corresponding triaminodiphenyl ethers **III** and **IV** requires the application of weak acids, for instance, of acetic acid. But the acid should be used in a large excess to avoid the formation of a considerable amount of a side product **IX** (Scheme 8).

Actually we failed to find optimal preparation conditions for methyl 2-benzimidazolyl carbamates **VII** and **VIII** of good quality and in a high yield when using hydrochloric acid. For instance, at excess hydrochloric acid the rate of the reaction was low; on the contrary, at small amount of the acid the conversion of the initial ethers **III** or **IV** was fast but the products contained many impurities. The side product **IX** we succeeded to convert into the target compound by prolonged boiling with hydrochloric acid, but the process was accompanied by hydrolysis of the urethane group in the benzimidazole part of the molecule.

At the 3–5 molar excess of acetic acid with respect to triaminodiphenyl ether **III** or **IV** the synthesis was accompanied with formation of the side product **IX**. Only at application of 7–10 molar excess of acetic acid we succeeded in preparation of the target methyl esters **VII** and **VIII** in high yield (80–85%) and with trace impurities.

In patent [1] where the preparation method is described for methyl esters **VII** and **VIII** the methyl 5(6)-(4-aminophenoxy)-2-benzimidazolyl carbamate (**VII**) is shown to be highly efficient helminthicide, no worse than the most well-known preparation of Hoehst Co. (Phenbendazole, Panakur). No data is presented on the helminthicidal activity of methyl 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamate (**VIII**), and the data on toxicity and embryotropic properties of both benzimidazolyl carbamates **VII** and **VIII** are also lacking.

The obtained by us methyl 2-benzimidazolyl carbamates **VII** and **VIII** were tested for helminthicidal activity and embryotropic properties at the laboratory of cattle therapy of the Skryabin Russian Central Helminthology Institute. The tests confirmed the high helminthicidal efficiency of benzimidazolyl carbamate **VII**: It showed 100% efficiency at a dose 10mg kg^{-1}, whereas benzimidazolyl carbamate **VIII** at a dose 20 mg kg^{-1} was only to 70% efficient against gastroenteric strongyloidosis of sheep. However benzimidazolyl carbamate **VII** possesses strong embryotoxic properties at the therapeutic dose 10 mg kg^{-1}; embryotoxic properties of methyl ester **VIII** are weakly pronounced. Besides benzimidazolyl carbamate **VII** possesses also a general toxicity, but benzimidazolyl carbamate **VIII** was nontoxic.

The tests demonstrated that the presence of a free amino group in methyl 5(6)-(4-aminophenoxy)-(**VII**) and 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamates (**VIII**) supplies them with unwanted biological properties that should be removed either by deamination or by preparation of derivatives at the amino group possessing necessary biological activity.

EXPERIMENTAL

Synthesis of 4-acetylamino-4′(2′)-nitrodiphenyl ether. To 1.2 l of DMF at vigorous stirring was added 339.2 g (2.24 mol) of 4-acetylaminophenol, 321.4 g (2.04 mol) of 4-nitrochlorobenzene or 2-nitrochlorobenzene, and 345 g (2.45 mol) of anhydrous potassium carbonate. The reaction mixture was heated to 145–150°C and was vigorously stirred at this temperature for 8–10 h. The completion of reaction was monitored by disappearance of nitrochlorobenzene. If a residue of nitrochlorobenzene remained in the reaction mixture, a small amount of 44% water solution of sodium hydroxide was added thereto, and the mixture was stirred for 1 h. After complete con-

sumption of nitrochlorobenzene the reaction mixture was poured into water, cooled to room temperature, the precipitated 4-acetylamino-4'-nitrodiphenyl ether or 4-acetylamino-2'-nitrodiphenyl ether was filtered off, washed with 0.5 N alkali solution, with water, and dried. 4-Acetylamino-4'-nitrodiphenyl ether and 4-acetylamino-2'-nitrodiphenyl ether were obtained in 93 and 95.6% yield respectively (518.1 and 533.4 g). 4-Acetylamino-2'-nitrodiphenyl ether: mp 128–129°C, R_f 0.30 (eluent benzene–ethanol, 10:2). Found, %: C 61.80; H 4.42; N 10.31. 4-Acetylamino-4'-nitrodiphenyl ether: mp 153–154°C, R_f 0.36 (eluent benzene–hexane, 3:7). Found, %: C 61.78; H 4.45; N 10.22. $C_{14}H_{12}N_2O_4$. Calculated, %: C 61.76; H 4.44; N 10.29.

Synthesis of 4-acetylamino-2',3-dinitrodiphenyl ether. In 350 ml of acetic acid was added at stirring 163.2 g (0.60 mol) of 4-acetylamino-2'-nitrodiphenyl ether. To the mixture was added 66 ml (0.70 mol) of acetic anhydride, and then at vigorous stirring while cooling with brine of temperature between +10 and +15°C into the reactor was added dropwise within 40–50 min 77 ml (1.8 mol) of nitric acid (*d* 1.5 g ml^{-1}, 90%). After addition the reaction mixture was stirred for 20–25 min at 20–25°C, then heated to 40–45°C and vigorously stirred at this temperature for 4–6 h more. The reaction progress was monitored by TLC.

On disappearance from the reaction mixture of the initial compound the content of the reactor was poured into cold water, the precipitate of 4-acetylamino-2',3-dinitrodiphenyl ether was filtered off, thoroughly washed on the filter with water, and dried. Yield of dinitrodiphenyl ether 92% (175.1 g), mp 98–99°C, R_f 0.56, of initial compound 0.30 (system benzene–ethanol, 10:2). Found, %: C 53.05; H 3.52; N 13.28. $C_{14}H_{11}N_3O_6$. Calculated, %: C 53.00; H 3.49; N 13.24.

Synthesis of 4-acetylamino-3,4'-dinitrodiphenyl ether. To a suspension of 188.7 g (0.69 mol) of 4-acetylamino-4'-nitrodiphenyl ether in 950 ml of chloroform was added 66 ml (0.7 mol) of acetic anhydride and dropwise at 45–50°C 90 ml (2.1 mol) of nitric acid (*d* 1.5 g ml^{-1}). The reaction mixture was stirred at the same temperature for 6 h. Then 500 ml of water was added, and the precipitate formed was filtered off. We obtained 213 g (97%) of 4-acetylamino-3,4'-dinitrodiphenyl ether, mp 121–123°C. R_f 0.7, of initial compound 0.36 (system benzene–ethanol, 10:2). Found, %: C 52.98; H 3.46; N 13.30. $C_{14}H_{11}N_3O_6$. Calculated, %: C 53.00; H 3.49; N 13.24.

Synthesis of 4-amino-3,4'-dinitro- and 4-amino-2',3-dinitrodiphenyl ethers. To 600 ml of 2-propanol was added 123.9 g (0.39 ml) of 4-acetylamino-3,4'-dinitrodiphenyl ether or 4-acetylamino-2',3-dinitrodiphenyl ether. The mixture was vigorously stirred at 25–30°C, and gradually a solution of 16.5 g (0.40 mol, 97%) of sodium hydroxide in 66 ml of water was added thereto. Then the reaction mixture was heated to 70–75°C, and it was vigorously stirred at this temperature for 1.5–3.0 h. Then the reaction mixture was poured into cold water, the separated precipitate of 4-amino-3,4'-dinitrodiphenyl ether or 4-amino-2',3-dinitrodiphenyl ether was filtered off, washed with water on the filter, and dried. 4-Amino-2',3-dinitrodiphenyl ether (101,5 g) and 4-amino-3,4'-dinitrodiphenyl ether (102.9 g) were obtained in 95 and 96.3% yield respectively. 4-Amino-3,4'-dinitrodiphenyl ether: mp 179–181°C, R_f 0.78 (eluent benzene–ethanol, 10:2). Found, %: C 52.30; H 3.21; N 15.20. 4-Amino-2',3-dinitrodiphenyl ether: mp 162–163°C, R_f 0.53 (eluent benzene–ethanol, 10:2). Found, %: C 52.42; H 3.32; N 15.47. Calculated, %: C 52.36; H 3.29; N 15.27.

Synthesis of 3,4,4'-triamino- and 2',3,4-triaminodiphenyl ethers. The reduction of 4-amino-2',3-dinitrodiphenyl and 4-amino-3,4'-dinitrodiphenyl ethers was carried out in a glass four-neck reactor of 1 l capacity equipped with a stirrer, a thermometer, a dropping funnel, and a reflux condenser connected to a Dean-Stark trap. The trap was used when the reaction was carried out in butanol. The required temperature was maintained in the reactor by supplying into the reactor jacket a heat carrier from an ultrathermostat.

When the reaction was carried out in butanol the water formed was removed from the reaction mixture as an azeotrope with butanol and was collected in the Dean-Stark trap where separation into a water and butanol layers occurred. Together with water and butanol hydrazine was also partially carried away and in the trap it was distributed between the water and organic layer. The water solution was removed into a special receiver, and the alcoholic layer was continuously returned into the reaction zone. The hydrazine fraction lost with water is relatively small and amounts to several percent.

When the reduction was performed with hydrazine hydrate to a solution of 63 g (0.216 mol) of 4-amino-3,4'-dinitrodiphenyl ether in 210 ml of butanol was added about 1.2 g (0.0045 mol) of $FeCl_3$–$6H_2O$ ground with 7.5 g of activated carbon. The mixture was heated to 95–105°C (to boiling) for 30 min at

passing through the reactor of a weak flow of nitrogen. Then at the same temperature within 4–6 h was added dropwise 75 ml (1.5 mol) of hydrazine hydrate. Thereafter the reaction mixture was heated at weak reflux without stirring for 6–10 h till completion of the reduction.

After completion of the reduction from the reaction mixture was distilled in a vacuum in a nitrogen flow the major part of butanol and the remnants of hydrazine. The residue was poured out from the reactor into a cooled boiled water. After stirring from the butanol–water mixture slowly crystallized the triaminodiphenyl ether which was washed with cold water on the filter and then dried.

The following reagents ratio are optimum for reduction in butanol: molar ratio of 4-amino-3,4'(2',3)-dinitrodiphenyl ether to hydrazine (64–67%) is 1.0 : (6.0–7.0), weight ratio of 4-amino-3,4'(2',3)-dinitrodiphenyl ether to butanol is 1.0:(2.7–2.8). At these conditions the yield of crude 3,4,4'-triamino- or 2',3,4-triaminodiphenyl ethers was 87 and 84% respectively at content of the main product no less than 95%.

3,4,4'-Triaminodiphenyl ether: mp 162–163°C, R_f 0.14, of initial compound 0.78 (system benzene–ethanol, 10 : 1). Found, %: C 66.85; H 6.24; N 19.44. $C_{12}H_{13}N_3O$. Calculated, %: C 66.95; H 6.09; N 19.52. 2',3,4-Triaminodiphenyl ether: mp 147–148°C, R_f 0,23, of initial compound 0.53. Found, %: C 66.81; H 5.91; N 19.53.

Synthesis of methyl 5(6)-(4-aminophenoxy)- and 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamates. To a suspension of 54 g (0.51 mol) of 77% calcium cyanamide in 450 ml of distilled water at 38–41°C was added dropwise 49.9 g (40 ml, 0.52 mol) of methyl chloroformate, the mixture was stirred for 1 h at this temperature, then filtered, and the residue on the filter was washed with 60 ml of water. To a solution of 58.1 g (0.27 mol) of 3,4,4'-triamino- or 2'-3,4-triaminodiphenyl ether in 200 ml of 2-propanol and 110 ml of acetic acid was poured the above obtained filtrate, and the mixture was boiled for 6 h. We obtained 66.78 g (83%) of methyl 5(6)-(4-aminophenoxy)-2-benzimidazolyl carbamate. The yield of methyl 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamate was 67.59 g (84%).

Methyl 5(6)-(4-aminophenoxy)-2-benzimidazolyl carbamate: mp 289–291°C (publ. mp 292°C, with a flash [1]). Methyl 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamate: mp 272–274°C (publ. mp 276°C, with a flash [1]).

The analysis of mixtures of acetylaminophenol (or aminophenol), nitrochlorobenzene, acetylaminonitrodiphenyl ether, acetylaminodinitrodiphenyl ether, and triaminodiphenyl ether was performed by HPLC on a column with a reversed phase Rsil or Ultraspher ODS in eluent system 65 vol% of methanol and 35 vol% of water; to 1 l of this eluent was added 25 ml of 10% solution of 18-crown-6 in methanol. The calculation of chromatograms was performed by internal normalization of peaks areas.

The analysis of crude methyl 5(6)-(4-aminophenoxy)- and 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamates was carried out on liquid chromatograph of Altex Co equipped with a pump of model 110, a UV detector of model 153, a loop feeder of model 210 of 20 μl volume, Hamilton microsyringes of SNR type of 30, 50, and 100 μl capacity, a stainless-steel column 0.25 m long of internal diameter 4.6 mm.

The analysis of methyl 5(6)-(4-aminophenoxy)- or 5(6)-(2-aminophenoxy)-2-benzimidazolyl carbamates in the reaction mixture was performed by TLC on Silufol plates, visualization of spots by diazotization and azocoupling with α-naphthol. The other products do not hamper the analysis.

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