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Reaction of Polynitrotoluenes with Phthalic Anhydride*

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Abstract—2,4-Dinitro- and 2,4,6-trinitrotoluenes react with phthalic anhydride in boiling *N*,*N*-dimethylaniline to give nitro group reduction products.

In the preliminary communications [1–3] we showed that 2,4,6-trinitrotoluene (**I**) is a promising intermediate product in the synthesis of previously inaccessible nitro derivatives of dibenzoxazepines, 2,1-benzisoxazoles, acridines, indoles, indazoles, 1,2-benzisothiazoles, 1,2-benzisothiazol-3-ones, 1,4-benzothiazines, and some *S*- and *N*-oxides derived therefrom which have a unique combination of functional groups. As a rule, the first stage in the synthesis of these compounds involves transformation of the methyl group in **I**; therefore, study of its possible transformation paths was of considerable interest.

According to the data of [4], reactions of 1,4,6-trinitrotoluene (**I**) and 2,4-dinitrotoluene (**II**) with phthalic anhydride in *N*,*N*-dimethylaniline give no condensation products at the methyl group (compounds **IIIa** and **IIIb**, respectively). However, such products can be used as starting compounds for the synthesis of 2-aryl-1,3-indandiones **IV** (Scheme 1) which exhibit a wide spectrum of biological activity and are used as drugs, chemical means for plant protection, and raticides. Compounds **IV** are also of interest as analytical reagents and intermediate products in the synthesis of various organic substances [5].

More recently, Clark and Fray [6] performed the reaction of dinitrotoluene **II** with phthalic anhydride under similar conditions and obtained not the expected phthalide **IIIa** but products of nitro group reduction, an isomeric mixture of *N*-(2-methyl-5-nitrophenyl)- and *N*-(4-methyl-3-nitrophenyl)phthalimides **Va** and **VI** which were identical to those synthesized by the reaction of phthalic anhydride with 2-amino-4-nitro- and 4-amino-2-nitrotoluenes [7]. Taking into account the above discrepancies in the published data, we have decided to perform a more detailed study of the reaction of 2,4,6-trinitrotoluene (**I**) and its derivatives with phthalic anhydride.

Our experiments with dinitrotoluene **II** confirmed the results reported in [6]. We have found that under analogous conditions a mixture of regioisomeric products **Va** and **VI** is formed at a molar ratio of ~2:3 (according to the ^{1}H NMR data). The isomer fractions were determined from the intensities of methyl proton signals, δ 2.63 and 2.32 ppm, respectively. We also reproduced the procedure described in [4] for trinitrotoluene **I**. In this case we isolated not the expected phthalide **IIIb** but *N*-(2-methyl-3,5-dinitrophenyl)-phthalimide (**Vb**) in 25–30% yield. The structure of **Vb** was derived from its ^{1}H NMR spectrum (see Experimental). In addition, phthalimide **Vb** was synthesized by independent method [7], by heating of 2-amino-4,6-dinitrotoluene (**VII**) with 2 equiv of phthalic anhydride in boiling glacial acetic acid (yield ~80%; Scheme 2). Amine **VII** was synthesized by a modified procedure [8]. Phthalimide **Vb** prepared by us from compound **I** was identical to the product synthesized from amine **VII** (no depression of the melting point was observed). Their ^{1}H NMR spectra were also identical. Treatment of phthalimide **Vb** with hydrazine hydrate in boiling benzene resulted in removal of the phthalimide protection, and amine **VII** was thus obtained in 60% yield.

We failed to effect condensation of phthalic anhydride at the CH_3 group of compound **I** with a view to obtain phthalide **IIIb**. Neither the procedure described in [9] (in the presence of Et_3N in Ac_2O) nor fusion with AcONa was efficient in this case. Treatment of phthalimide **Vb** with potassium carbonate in MeOH

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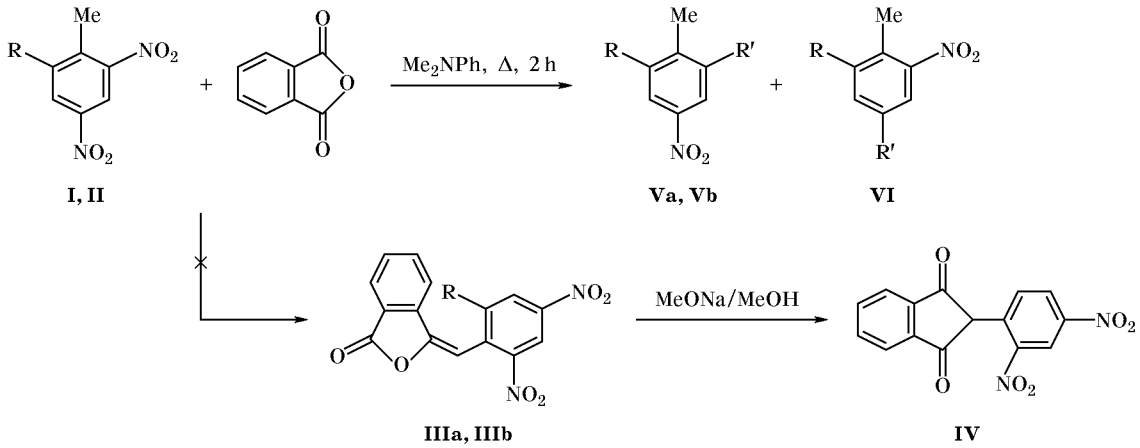
Scheme 1.



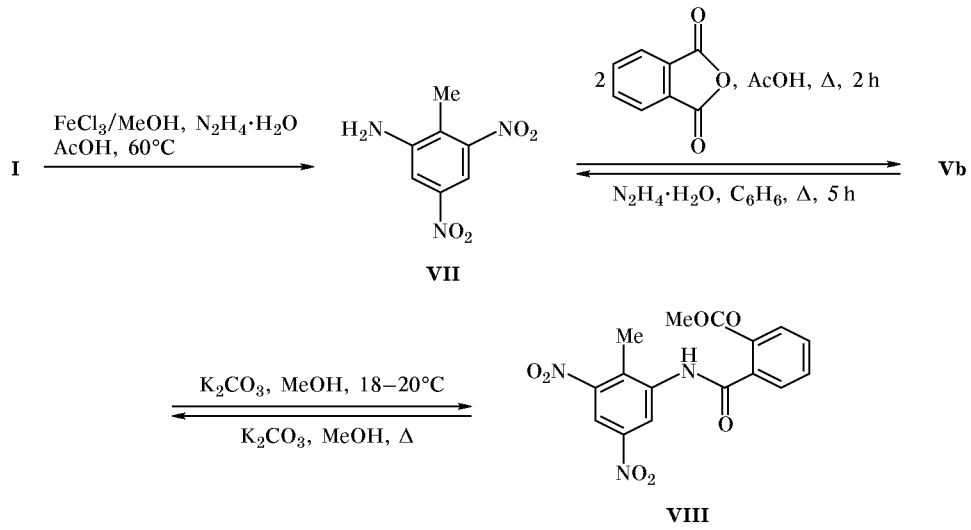
I, **IIIb**, **Vb**, R = NO_2; **II**, **IIIa**, **Va**, R = H; R′ = phthalimido.

at room temperature resulted in opening of the phthalimide ring and formation of 2-(2-methoxycarbonylbenzoylamino)-4,6-dinitrotoluene (**VIII**). Heating of the latter in methanol with simultaneos distillation of the solvent gave initial phthalimide **Vb**.

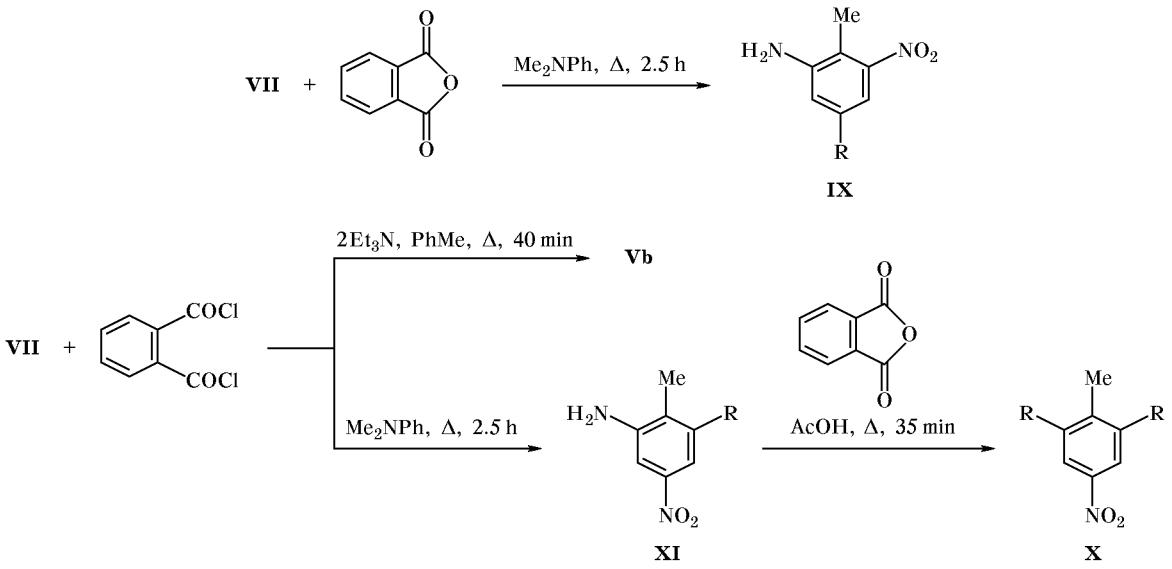
Our attempts to obtain phthalimide **Vb** by other methods, starting from amine **VII**, led to a number of unexpected results. Heating of compound **VII** with an equimolar amount of phthalic anhydride in boiling *N*,*N*-dimethylaniline afforded 6-nitro-2,4-bis(phthalimido)toluene (**IX**) (Scheme 3). The latter cannot be synthesized from compound **I** and phthalic anhydride at a molar ratio of 1:2 under similar conditions. The unsymmetrical structure of product **IX** follows from its ^{1}H NMR spectrum. It contains two signals from aromatic protons of the 6-nitrotolyl fragment at δ 8.55 and 8.56 ppm. The alternative structure of 4-nitro-2,6-bis(phthalimido)toluene (**X**) should give rise to a single signal (see below). The main factor governing the formation of bis-phthalimide **IX** is likely to be high temperature (the reaction was carried out in boiling *N*,*N*-dimethylaniline). According to Porai-Koshits and Chizhevskaya [4], the reaction of almost equimolar amounts of phthalic anhydride and amine **VII** was also performed on heating in *N*,*N*-dimethylaniline (the temperature was not given); as a result, phthalimide **Vb** was obtained.

The reaction of 2-amino-4,6-dinitrotoluene (**VII**) with an equimolar amount of phthaloyl chloride in boiling *N*,*N*-dimethylaniline involved one of the nitro groups in **VII** and afforded *N*-(3-amino-2-methyl-5-nitrophenyl)phthalimide (**XI**) instead of the expected

Scheme 2.



Scheme 3.



R = Phthalimido.

condensation product at the amino group (phthalimide **Vb**). The ^{1}H NMR spectrum of **XI** contains the following signals, δ, ppm: 1.95 s (3H, CH_3), 5.7 br.s (2H, NH_2), 7.4 s and 7.63 s (1H, 4-H, 6-H), 7.9–7.95 m (4H, H_{arom} in phthalimide). Compound **XI** gives the molecular ion peak in the mass spectrum. However, these data are equally consistent with an alternative structure, *N*-(3-amino-4-methyl-5-nitrophenyl)phthalimide (**XII**). In order to choose between the above regioisomers, the obtained product was brought into reaction with phthalic anhydride in boiling glacial acetic acid [7]. This reaction yielded 4-nitro-2,6-bis(phthalimido)toluene (**X**) which can be formed only from phthalimide **XI**. In the ^{1}H NMR spectrum of **X** we observed a characteristic singlet at δ 8.60 ppm arising from two aromatic protons of the 4-nitrotolyl fragment. These data suggest symmetric structure of molecule **X**. The ^{1}H NMR spectrum of regioisomeric unsymmetrical 6-nitrotoluene **IX** which could be formed from phthalimide **XII** is appreciably different (see above).

N-Acylation of **VII** by a standard procedure, i.e., by the action of phthaloyl chloride in an inert solvent (toluene) in the presence of triethylamine gave the expected phthalimide **Vb** (Scheme 3).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker AM-300 and Bruker WM-250 instruments operating at 300.13 and 255.13 MHz, respectively; DMSO-d_6 was used as solvent; the chemical shifts were measured relative to the residual proton signal of the solvent, δ 2.5 ppm. The IR spectra were measured in KBr on a Specord M-82M spectrometer. The mass spectra (70 eV) were obtained on a Kratos MS-30 mass spectrometer with direct sample admission into the ion source. The melting points were determined in sealed capillary using a PTP device and were not corrected. The progress of reactions was monitored by TLC on Silufol UV-254 plates using C_6H_6–AcOEt (3:1) as eluent; spots were visualized with UV light and iodine vapor. The solvents were purified by standard procedures.

***N*-(2-Methyl-3,5-dinitrophenyl)phthalimide (Vb).** *a.* A solution of 17.6 mmol of 2,4,6-trinitrotoluene (**I**) and 17.6 mmol of phthalic anhydride in 18 ml of *N*,*N*-dimethylaniline was refluxed for 1.5–2 h. The mixture was cooled to 18–20°C and acidified with dilute (1:1) hydrochloric acid to pH 1–2. The dark brown precipitate was filtered off, repeatedly washed with water, and recrystallized first from acetone–ethanol (3:1) and then from acetone. Yield 1.4–1.7 g (25–30%); pale pink crystals, mp 235–236°C. ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, Me), 7.95–8.05 m (4H, H_{arom}, phthalimide), 8.78 s and 8.86 s [2H, H_{arom}, 2-Me-3,5-$(NO_2)_2C_6H_2$]. Found, %: C 54.87; H 2.70; N 12.79. $C_{15}H_9N_3O_6$. Calculated, %: C 55.04; H 2.75; N 12.84.

b. A solution of 12.7 mmol of amine **VII** and 25.4 mmol of phthalic anhydride in 20 ml of glacial

acetic acid was refluxed for 2 h. The mixture was cooled to 20°C, and the precipitate was filtered off. The filtrate was diluted with 20 ml of distilled water to isolate an additional amount of the product. The combined precipitates were washed with 3–4 portions of water and cold (~0°C) methanol (2 × 3 ml). Yield 3.44 g (83%); slightly colored crystals, mp 235°C (from acetone); published data [4]: mp 236°C.

***N*-(2-Methyl-5-nitrophenyl)phthalimide (Va) and *N*-(4-methyl-3-nitrophenyl)phthalimide (VI)** (regioisomeric mixture; molar ratio 2 : 3) were synthesized by the procedures described in [4, 6]. ^{1}H NMR spectrum of **Va**, δ, ppm: 2.63 s (3H, Me), 7.73 s (1H, 3-H), 7.98 br.s (4H, H_{arom}, phthalimide), 8.15 s (1H, 4-H), 8.38 s (1H, 6-H). ^{1}H NMR spectrum of **VI**, δ, ppm: 2.32 s (3H, Me), 7.73 s (1H, 5-H), 7.98 br.s (4H, H_{arom}, phthalimide), 8.29 br.s (1H, 6-H), 8.38 s (1H, 2-H).

2-Amino-4,6-dinitrotoluene (VII). *a.* A solution of 1.53 mmol of phthalimide **Vb** in 50 ml of benzene containing 0.44 ml of 85% aqueous hydrazine was refluxed for 5 h. The mixture was cooled, and the precipitate was filtered off and washed with benzene. The solvent was distilled off from the filtrate under reduced pressure (water-jet pump). The dark yellow residue was dissolved in 20 ml of methanol, unreacted initial phthalimide **Vb** was filtered off, and the filtrate was heated under reflux for 15 min with charcoal. The solution was filtered, the filtrate was evaporated to a volume of ~0.5 ml, and the precipitate was filtered off. Yield 0.18 g (60%); yellow crystals, mp 170–171°C (from ethanol); published data [10]: mp 175–176°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, Me), 6.12 br.s (2H, NH_2), 7.67 s and 7.72 s (2H, 3-H, 5-H).

b. A solution of 61.6 mmol of compound **I** and 17.2 mmol of $FeCl_3$ in 120 ml of methanol was heated to 60°C, and 21 ml of a 64% aqueous solution of N_2H_4 and 70 ml of glacial acetic acid were added. The mixture was stirred for 2 h at 60°C, cooled, and diluted with water, and the precipitate was filtered off. Yield 8.6 g (71%), mp 172°C (from ethanol). IR spectrum (KBr), ν, cm^{-1}: 3420, 3350 (NH_2). Found, %: C 42.40; H 4.00; N 20.90. $C_7H_7N_3O_4$. Calculated, %: C 42.60; H 3.50; N 21.31.

Methyl 2-(2-methyl-3,5-dinitrophenylcarbamoyl)benzoate (VIII). A solution of 0.6 mmol of phthalimide **Vb** and a small amount of K_2CO_3 (on the tip of a spatula) in 30 ml of methanol was kept for 30 min at 18–20°C. The solvent was removed under reduced pressure (water-jet pump, 18–20°C), and the residue was washed with 3–4 portions of water and two 1-ml portions of methanol. Compound **VIII** was isolated as bright yellow lustrous crystals; yield 0.08 g (40%), mp 213–214.5°C (from acetone). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.60 s (3H, Me), 3.89 s (3H, COOMe), 7.65–7.75 m (4H, H_{arom}, in *o*-$MeOCOC_6H_4$), 8.56 s and 9.0 s (2H, 3-H, 5-H), 9.7 br.s (1H, NH). Found, %: C 54.26; H 3.85; N 12.59. $C_{15}H_{13}N_3O_6$. Calculated, %: C 54.38; H 3.93; N 12.69.

6-Nitro-2,4-bis(phthalimido)toluene (IX). A solution of 2.54 mmol of amine **VII** and 2.54 mmol of phthalic anhydride in 5 ml of *N*,*N*-dimethylaniline was refluxed for 2.5 h. The mixture was cooled to 18–20°C and acidified with dilute (1 : 6) hydrochloric acid to pH 1–2 (~22 ml). After 1 h, the orange precipitate was filtered off and repeatedly washed with water. Yield 0.42 g (39%, calculated on the taken amine **VII**); colorless crystals, mp >300°C (decomp.; the product was twice recrystallized from acetone). ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, Me), 7.95–8.02 m (8H, H_{arom}, phthalimide), 8.55 s and 8.56 s (2H, 3-H, 5-H). Found, %: C 64.74; H 3.16; N 9.94. $C_{23}H_{13}N_3O_6$. Calculated, %: C 64.64; H 3.07; N 9.83.

Reaction of amine VII with phthaloyl chloride. *a.* To a solution of 2.54 mmol of amine **VII** in 5 ml of *N*,*N*-dimethylaniline at 18–20°C we added dropwise an equimolar amount of phthaloyl chloride (0.37 ml), and the mixture was refluxed for 2.5 h. It was then cooled to 18–20°C, acidified with dilute (1 : 6) hydrochloric acid, and left overnight. The precipitate was filtered off and repeatedly washed with water and with two 2-ml portions of methanol. We thus isolated 0.23 g (31%) of *N*-(3-amino-2-methyl-5-nitrophenyl)phthalimide (**XI**) as bright yellow crystals with mp 270–271°C (from acetone). ^{1}H NMR spectrum, δ, ppm: 1.95 s (3H, Me), 5.7 br.s (2H, NH_2), 7.4 s and 7.63 s (2H, 4-H, 6-H), 7.9–7.95 m (4H, H_{arom} in phthalimide). $[M]^+$. 297. Found, %: C 60.67; H 3.64; N 14.05. $C_{15}H_{11}N_3O_4$. Calculated, %: C 60.61; H 3.73; N 14.14. *M* 297.

b. Amine **VII**, 2.54 mmol, was dissolved in 25 ml of boiling toluene, an equimolar amount of phthaloyl chloride (0.37 ml) was added, 5.1 mmol (0.71 ml) of triethylamine was added dropwise, and the mixture was refluxed for 40 min. It was cooled to 18–20°C, and the precipitate was filtered off and washed with toluene (2 × 3 ml). The filtrate was evaporated under reduced pressure (water-jet pump), and the residue was twice recrystallized from acetone. Yield of **Vb** 0.3 g (36%). For ^{1}H NMR spectrum of **Vb**, see above.

4-Nitro-2,6-bis(phthalimido)toluene (X). A solution of 10.4 mmol of phthalimide **XI** and 20.9 mmol of phthalic anhydride in 5 ml of glacial acetic acid was refluxed for 35 min. The mixture was cooled, and

the colorless precipitate was filtered off and washed with methanol (3 × 2 ml). Yield 0.33 g (74%); colorless crystals, mp >300°C (decomp.; the product was twice recrystallized from acetone). ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, Me), 7.94 br.c and 8.02 br.s (8H, H_{arom} in phthalimide); 8.60 s (2H, 3-H, 5-H). Found, %: C 64.76; H 3.13; N 9.91. $C_{23}H_{13}N_3O_6$. Calculated, %: C 64.64; H 3.07; N 9.83.

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