DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

PREPARATIVE SYNTHESIS OF 2,4-DINITROPHENYLALKANOLS[1]

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The only representative of 2,4-dinitrophenylalkanols known before this study was 2,4-dinitrobenzyl alcohol synthesized from benzyl chloride via a multistage process [2 – 5].

In continuation of earlier work [6], we have investigated the action of concentrated sulfuric acid upon nitroesters of 4-nitrobenzyl (I) and β-(4-nitrophenyl)ethyl (II) alcohols.

It was established that these compounds, in contrast to the nitroesters of α-nitrophenylalkylcarbinols [6], exhibit the autonitration reaction at 28 – 42°C in a 93 – 96% sulfuric acid. The reaction takes place at position 2 of the benzene ring and leads to the formation of 2,4-dinitrophenylalkylsulfuric acids (C). The hydrolysis of compounds C in a dilute sulfuric acid yields 2,4-dinitrobenzyl and β-(4-dinitrophenyl)ethyl alcohols (III, IV).

The first stage in this process is apparently the hydrolysis of nitroesters I and II leading to the corresponding alcohols (A) and nitric acid.

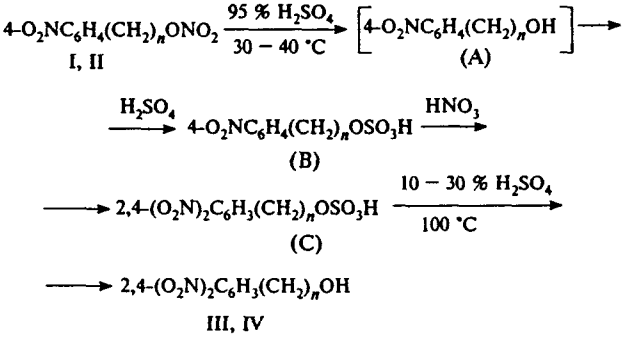
Alcohols A react with sulfuric acid to form its esters – 4-nitrophenylalkylsulfuric acids B (as is known, 4- nitrobenzylsulfuric acid forms upon dissolution of 4-nitrobenzyl alcohol in concentrated sulfuric acid [2]).

finally, the intermediate aralkylsulfuric acids B are subjected to nitration under the reaction conditions (30 – 40°C) with the formation of 2,4-dinitrophenylalkylsulfuric acids C.

As described previously [4, 5], 2,4-dinitrobenzylsulfuric acid forms upon dissolution of 2,4-dinitrobenzyl alcohol in 87 – 93% sulfuric acid.

Previously unreported β-(2,4-dinitrophenyl)ethylsulfuric acid (C, $n = 2$) was isolated in the form of ammonium salt upon completion of the autonitration process of nitroester II. The salt is readily hydrolyzed to form alcohol IV on heating in a 10% sulfuric acid.

There is no need to isolate the intermediate acids C in order to obtain 2,4-dinitrophenylalkanols III and IV. After termination of the autonitration process, the reaction mass is diluted with water, so as to provide for a 10 – 30% sulfuric acid concentration, and heated at 100°C for 3 – 4 h. Upon cooling of the reaction mass, the target alcohols are separated by filtration or extracted with an organic solvent at a yield of 70 – 87%.



$n = 1$ (I, III), 2 (II, IV).

To simplify the process, the reaction can be performed using a mixture of isomeric nitrobenzyl nitrates (VI) or α-(nitrophenyl)ethyl nitrates (VII), rather than the individual *p*-isomers.

Similarly, a mixture of α-(nitrobenzyl)ethyl nitrates (VIII) was used to obtain α-(2,4-dinitrobenzyl)ethyl alcohol (IX). The proposed structure was confirmed by the oxidation with potassium permanganate, which yielded 2,4-dinitrobenzoic acid.

It should be noted that the reaction involving mixed isomeric nitroesters leads to a mixture of 2,4-, 2.6-, and 3,5-dinitrophenylalkanols with a dominating fraction of 2,4-dinitro isomers. Fractional crystallization of these mixtures from water or aqueous ethanol (for alcohol IX – vacuum distilla-

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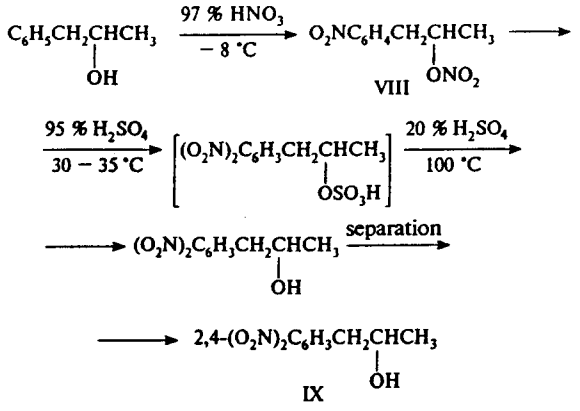
tion followed by crystallization from aqueous ethanol) gives pure 2,4-dinitrophenylalkanols (III, IV, IX) at a 20–56% yield.

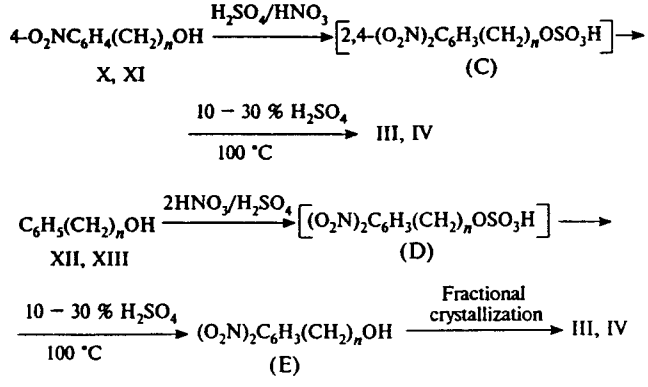


Once the sequence of stages in the transformation of nitroesters I, II into dinitrophenylalkanols III, IV was established, we proceeded to study nitration of 4-nitrobenzyl (X), β-(4- nitrophenyl)ethyl (XI), benzyl (XII), and β-phenylethyl (XIII) alcohols with mixed concentrated nitric and sulfuric acids.

In contrast to the procedures described in [7–9], we have used the following molar ratios of nitric acid to substrate: 2 : 1 for phenylalkanols (XII, XIII) and 1 : 1 for 4-nitrophenylalkanols (X, XI).

The nitration process was conducted at 4–8°C and terminated at 30–32°C. The conditions of hydrolysis of the intermediate dinitrophenylalkylsulfuric esters were the same as described above for the autonitration of nitroesters I and II.

The nitration of phenylalkanols XII, XIII leads to the mixtures of isomeric dinitrophenylalkanols (E). The fractional crystallization of compounds E yields pure alcohols III and IV.



n = 1 (X, XII); 2 (XI, XIII).

Thus, we have developed a method for the preparative synthesis of 2,4-dinitrophenylalkanols III, IV from nitrophenylakanols (yield, 70–85%) and phenylalkanols (yield, 50–53%).

EXPERIMENTAL PART

The experiments were performed with 93.6–95.6% sulfuric acid ("high-purity" grade, State Standard GOST 4204–77) and 97.5–98.6% nitric acid ("concentrated" grade, GOST 701–89).

The purity of compounds was checked by TLC on Silufol UV-254 plates; the spots were developed by exposure to iodine vapors.

The data of elemental analyses for the previously unreported compounds agree with the results of calculations according to the empirical formulas.

The initial compounds were as follows: 4-nitrobenzyl nitrate (I) [10]; a nitrobenzyl nitrate mixture (VI) [10]; 4-nitrobenzyl alcohol (X); freshly distilled benzyl alcohol (XII); β-(4-nitrophenyl)ethyl nitrate (II) [1]; a mixture of β-(nitrophenyl)ethyl nitrates (VII) [1]; β-(4-nitrophenyl)ethyl alcohol (XI); freshly distilled β-phenylethyl alcohol (XIII); and freshly distilled α-benzylethyl alcohol (XIV).

Mixed α-(nitrobenzyl)ethyl nitrates (VIII). The nitrate mixture VIII was obtained by nitrating alcohol XIV with concentrated nitric acid under the same conditions as described for the nitration of alcohol XIII [1]. Compound VIII was obtained at a 97% yield in the form of a viscous yellow liquid (not crystallized upon cooling to –5°C). The product was used in the synthesis of alcohol IX without separating the *p*-isomer.

β-(2,4-Dinitrophenyl)ethylsulfuric acid ammonium salt (V). To 192 ml of sulfuric acid heated to 39–40°C was added by small portions during 30 min with intensive stirring 36.0 g of nitroester II, so as to maintain the temperature within 40–42°C (by periodically cooling the flask with water). Then the solution was stirred at this temperature for another 30 min, cooled, and poured onto 50 g of pure crushed ice, and adjusted to pH 8 by adding 25% aqueous ammonia. The precipitate was filtered, washed with cooled water and acetone, and dried to obtain 32.0 g (61%) of compound V in the form of pale-yellow crystals; m.p., 197–201°C; upon recrystallization from ethanol m.p., 201–202°C; the crystals are soluble on heating in water and ethanol; $C_8H_{11}N_3O_8S$.

2,4-Dinitrobenzyl alcohol (III).

(a) To 12 ml of sulfuric acid was gradually added (for 8–10 min) with stirring 4.0 g of nitroester I; the temperature was maintained within 32–36°C by cooling the flask with water. Then the solution was stirred at this temperature for another 30 min, cooled, poured into 70 ml of water, and boiled for 4 h. Upon cooling, the solution was extracted with methylene chloride (4 × 40 ml). The extracts were washed with water and dried over Na_2SO_4. Finally, the solvent was distilled off to obtain 3.2 g (80%) of compound III; m.p., 108–110°C. Crystallization from water (150 ml, 2% activated charcoal) yielded 2.8 g (70%) of pure alcohol III; m.p., 114–115°C (published m.p., 114–115°C [2, 3]; 115–116°C [4, 5]).

(b) To 24 ml of sulfuric acid was added 8.0 g of mixed nitroesters of nitrobenzyl alcohols VI [10]. The reaction was conducted as described in (a), the only difference being that the technical product (5.8 g) was washed with a petroleum – methylene chloride (9 : 1) mixture and doubly recrystallized from water (in the presence of activated charcoal). Yield of alcohol III, 3.6 g (45%); m.p., 113 – 114°C.

(c) To 23 ml of sulfuric acid was added with stirring 4.6 g (0.03 mole) of alcohol X; the reaction mixture exhibited weak heating with the formation of 4-nitrobenzylsulfuric acid [2]. The reaction solution was stirred for 15 min at 30 – 32°C. Then was gradually added 1.5 ml (0.03 mole) of nitric acid and the reaction mixture was stirred for 20 min at the same temperature. The subsequent treatment, performed as described in (a), yields 4.2 g (72%) of alcohol III; m.p., 108 – 112°C; upon recrystallization from water m.p., 114 – 115°C.

(d) To a mixture of 16.2 ml sulfuric acid and 4.2 ml (99.9 mmole) nitric acid cooled to 0°C was added dropwise with intensive stirring 5.4 g (49.9 mmole) alcohol XII; the temperature was maintained within 4 – 8°C (~ 20 min). Then the reaction mixture was gradually (for 30 min) heated to 30 – 32°C, stirred for another 30 min, cooled, poured into 50 ml water, boiled for 3.5 h, and treated as described in (a) to obtain a mixture of dinitrobenzyl alcohols (7.8 g) with m.p. 90 – 100°C. The mixture was doubly recrystallized from water (in the presence of activated charcoal) to obtain 5.2 g (53%) of alcohol III; m.p., 113 – 114°C.

β-(2.4-Dinitrophenyl)ethyl alcohol (IV).

(a) To 27 ml of sulfuric acid was gradually added (for 10 min) at 40 – 42°C with stirring 9.0 g of nitroester II. Then the reaction mass was stirred at this temperature for another 30 min, cooled, poured into 150 ml of water, boiled for 4 h, and cooled. The residue was filtered, washed with water and dried to obtain 8.15 g of a product with m.p. 62 – 64°C. Extraction of the mother liquor with methylene chloride gives additionally 0.65 g of the product with m.p. 61 – 63°C. The total yield of technical-purity alcohol IV was 8.6 g (95%). Recrystallization from 16 ml of a 50% aqueous ethanol (in the presence of activated charcoal) yielded 7.85 g (87%) of pure alcohol IV; m.p., 64 – 65°C; $C_8H_8N_2O_5$.

(b) To 180 ml of sulfuric acid at 40 – 42°C was added 59.0 g of a nitroester mixture VII. The reaction was conducted as described in (a). Yield of a dinitroalcohol mixture, 50.0 g (85%); m.p., 57 – 59°C. Double recrystallization from a 50% aqueous ethanol (in the presence of activated charcoal) yielded 33.0 g (56%) of pure alcohol IV; m.p., 64 – 65°C.

(c) To 25 ml of sulfuric acid was added with stirring 5.0 g (0.03 mole) of alcohol XI, and the reaction mixture was allowed to stand for 20 min. Then was gradually added (for 10 min) 1.5 ml (0.03 mole) of nitric acid and the reaction mixture was stirred for 30 min at 32 – 35°C. The subsequent treatment was performed as described above for the synthesis of alcohol III, part (c). Yield of alcohol IV, 5.0 g (83%); m.p., 64°C (from aqueous ethanol).

(d) To a mixture of 15 ml sulfuric acid and 3.5 ml (83.0 mmole) nitric acid cooled to 0°C was gradually added (for 20 min) with stirring 5.0 g (40.9 mmole) of alcohol XIII. Then the reaction was conducted as described above for the synthesis of alcohol IV, part (a). Yield of a dinitroalcohol mixture, 8.0 g (95%); m.p., 45 – 50°C. Double recrystallization from a 50% aqueous ethanol (in the presence of activated charcoal) yielded 4.2 g (50%) of alcohol IV; m.p., 64°C.

(e) A solution of 2.0 g salt V in 7 ml of a 10% sulfuric acid was boiled for 3 h and then treated as described in (a). Yield of alcohol IV, 0.95 g (69%); m.p., 64 – 65°C.

α-(2,4-Dinitrobenzyl)ethyl alcohol (IX). To 30 ml of sulfuric acid at 30 – 35°C was gradually added 10.0 g of a nitroester mixture VIII. The reaction was conducted as described above for the synthesis of alcohol III, part (a). Yield of a mixture of α-(dinitrobenzyl)ethyl alcohols in the form of a noncrystallizing viscous oil 7.55 g (75%). The product was distilled in vacuum. The first fraction with b.p. 150 – 175°C (5 Torr), weighing 3 g, partly crystallizes on cooling. The second fraction (1.9 g; b.p., 180 – 190°C/5 Torr; m.p., 64 – 67°C) was dissolved in 10 ml ether, precipitated with petroleum ether, and recrystallized from a 50% aqueous ethanol (in the presence of activated charcoal) to obtain 1.55 g of alcohol IX; m.p., 76.5 – 77.5°C. Analogous treatment of the first fraction additionally yields 0.6 g of the same substance with m.p. 76.5 – 77.5°C. The total yield of alcohol IX, 2.15 g (21%); $C_9H_{10}N_2O_5$. The oxidation of compound IX with potassium permanganate yields 2,4-dinitrobenzoic acid hydrate; m.p.. 181 – 182°C (from water) (published m.p., 181 – 182°C [11]).

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