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Dedicated to the Corresponding Member of the Russian Academy of Sciences B. V. Gidaspov on occasion of his 70th anniversary

Synthesis of γ-Polynitrocarboxylic Acids And Derivatives Thereof

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Abstract—A synthesis of new branched γ-nitrocarboxylic acids and their derivatives (nitriles, amides, trinitroethyl esters) was developed proceeding from the corresponding aldehydes obtained by nitroform or 1,1-dinitroethane addition to 2-(2,2-dinitropropyl)acrylic aldehyde according to Michael reaction.

Investigation of pharmacological activity of carboxylic acids and their derivatives (esters, amides, nitriles) demonstrated an enhanced antiphlogistic effect of butyric acid derivatives; especially prostrongly this quality manifested itself in the series of γ-nitrobutyric acids where the therapeutic activity grew with increasing number of nitro groups in the acid molecule [1].

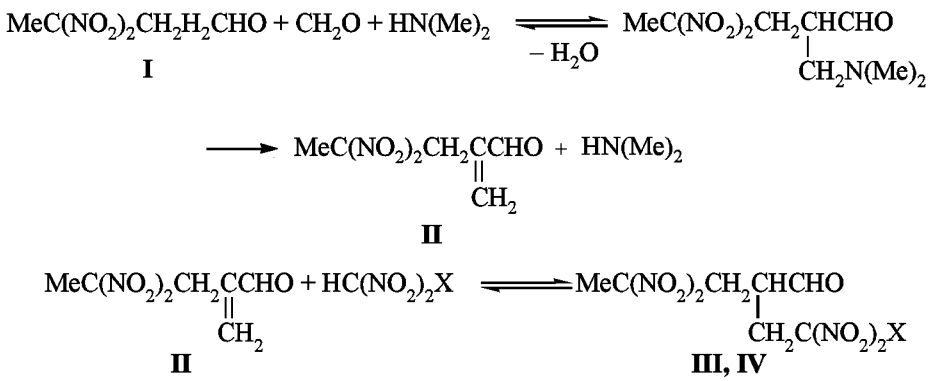
In order to extend the range of available γ-nitrocarboxylic acids for investigation of their pharmacological activity we synthesized new γ-nitrocarboxylic acids and some derivatives thereof.

γ-Nitocarboxylic acids are commonly prepared by Michael reaction α,β-unsaturated acids (or their esters, amides, and nitriles) with nitroalkanes [2]. This prcess furnished versatile mono- and dicarboxylic γ-nitroacids [3].

Another no less important procedure for preparation of γ-nitrocarboxylic acids is oxidation of γ-nitroaldehydes. It should be noted that the latter method provides wider possibilities for building up versatile desired structures, and we have used just this procedure for preparation of new γ-nitrocarboxylic acids. The synthesis of new branched γ-nitrocarboxylic acids and some their derivatives was performed proceeding from aldehydes obtained by nitroform or 1,1-dinitroethane addition to 2-(2,2-dinitropropyl)acrylic aldehyde according to Michael reaction. The γ-polynitroaldehydes are known to react with formaldehyde and dialkylamines giving the corresponding Mannich bases. For instance, 4,4-dinitrovaleraldehyde (**I**) reacted with formaldehyde and dimethylamine affording 2-dimethylaminomethyl-4-dinitrovaleraldehyde that on deamination furnished aldehyde **II** [4] (Scheme 1).

α,β-Unsaturated aldehyde **II** is capable to enter into the Michael reaction with polynitroalkanes. Treating it with 1,1-dinitroethane and trinitromethane we prepared γ-polynitroaldehydes **III** and **IV**.

Scheme 1.



X = Me (**III**), NO_2 (**IV**).

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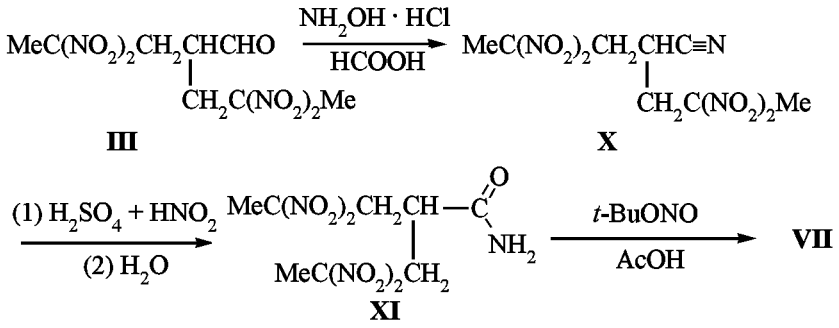
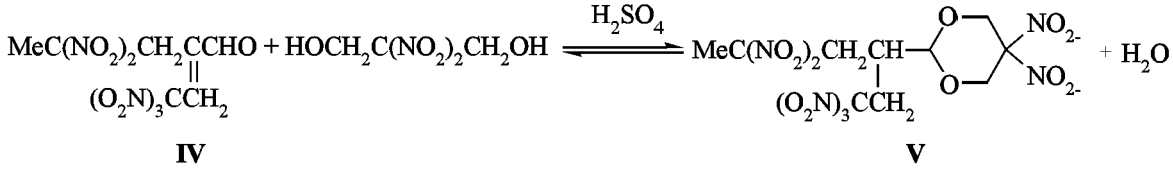
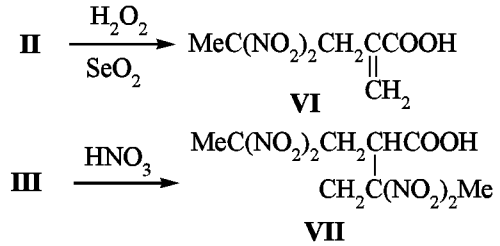
Scheme 2.



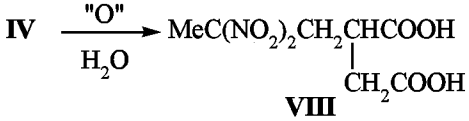
γ-Polynitroaldehydes **III, IV** are crystalline substances. The carbonyl groups in these aldehydes are considerably shielded by the bulky polynitroalkyl substituents, but this effect does not notably affect their reactivity, in particular, in acetal formation and oxidation. For instance, compound **IV** successfully reacts with 2,2-dinitro-1,3-propanediol in concn. H_2SO_4 affording a substituted 1,3-dioxane **V**.



The oxidation of carbonyl groups in γ-polynitroaldehydes into carboxy groups can be carried out both in basic and acidic medium depending on the structure of the polynitroalkyl moieties. The oxidation of 4,4-dinitrovaleric aldehyde with potassium permanganate in alkaline medium gave rise in a high yield to 4,4-dinitrovaleric acid [5]. Treating of 4,4,4-trinitrobutyric aldehyde with a mixture of hydrogen peroxide and 30% oleum provided the corresponding peroxide [6]. We showed that γ-polynitroaldehydes were oxidized with diluted nitric acid or hydrogen peroxide with selenium(IV) oxide as catalyst. Thus we carried out oxidation of compounds **II, III** into acids **VI, VII**.

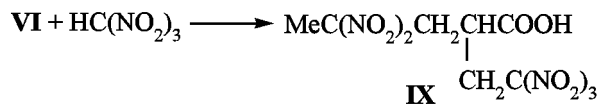


4,4-Dinitro-2-(2,2,2-trinitroethyl)pentanal (**IV**) whose trinitromethyl group is prone to oxidation into carboxy group in all cases afforded 2,2-dinitropropylsuccinic acid (**VIII**) instead of 4,4-dinitro-2-(2,2,2-trinitroethyl)valeric acid (**IX**).



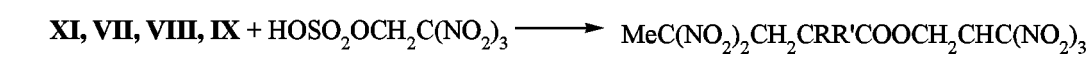
Similar examples of trinitromethyl group oxidation in polynitroaliphatic compounds to afford a carboxy group were described in the literature. For instance, at heating of water solution of 2-(2,2,2-trinitroethyl)succinic acid the oxidation of the trinitromethyl group occurs furnishing in high yield 1,2,3-propanetricarboxylic acid [7].

We succeeded in obtaining acid **IX** by condensation of 2-(2,2-dinitropropyl)acrylic acid (**VI**) with trinitromethane.



Nitriles and amides of γ-polynitrocarboxylic acids were prepared from γ-polynitroaldehydes along procedures developed for sterically hindered aldehydes [8]. First the γ-polynitroaldehyde [4,4-dinitro-2-(2,2-dinitropropyl)pentanal was taken as example] was transformed into a nitrile by reaction with hydroxylamine in a formic acid solution (Scheme 2).

Scheme 3.



XII–XIV

R, R' = CH_2 (**XII**); R = H, R' = $CH_2C(NO_2)_2Me$ (**XIII**), $CH_2C(NO_2)_3$ (**XIV**), $CH_2COOCH_2C(NO_2)_3$ (**XV**).

Then nitrile **X** was hydrolyzed into amide by treating with 100% sulfuric acid in the presence of catalytic amounts of nitric acid followed by dilution of the reaction mixture with water.

Amide **XI** was hydrolyzed into acid **VII** with *tert*-butyl nitrite in a glacial acetic acid [9].

The γ-polynitrocarboxylic acids synthesized in the highly acidic medium readily react with 2,2,2-trinitroethylsulfuric acid giving esters. Thus trinitroethyl esters of acids **VI–IX** were obtained (Scheme 3).

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from mulls in mineral oil. CHN-Analysis was carried out on an analyzer Hewlett Packard 185B. Molecular weights were measured by reversed ebullioscopy in dichloroethane. The purity of products was checked by TLC on Silufol UV-254 plates.

4,4-Dinitro-2-(2,2-dinitropropyl)pentanal (III). To a solution of 10 g (0.053 mol) of aldehyde **II** prepared by procedure from [4] in 10 ml of methanol was added at 20–25°C a solution of 6.38 g (0.053 mol) of 1,1-dinitroethane in 10 ml of methanol. The mixture was kept for 10 h and then diluted with water (50 ml). The separated oil was transferred into 5 ml of 70% nitric acid where it crystallized. The crystals were filtered off, washed, and dried for 12 h at room temperature. Yield 11.5 g (70%). On recrystallization from a mixture $CHCl_3$–CCl_4, 2 : 1, we obtained colorless crystals, mp 154–155°C. IR spectrum, ν, cm^{-1}: 1755 (C=O), 1585, 1290 (NO_2). Found, %: C 31.05; H 3.81; N 18.05. M 315. $C_8H_{12}N_4O_9$. Calculated, %: C 31.17; H 3.90; N 18.18; M 308.

4,4-Dinitro-2-(2,2,2-trinitroethyl)pentanal (IV). To a solution of 6 g (0.031 mol) of aldehyde **II** in 30 ml of ethanol at 5°C was gradually added 7 g (0.046 mol) of trinitromethane. The reaction mixture was stirred for 30 min at 5°C and then it was within 30 min heated to 70°C. On cooling the reaction mixture was poured into 200 ml of water. The separated oil quickly solidified, was filtered off and washed till colorless washings. The product was dried for 12 h at room temperature. Yield 8.5 g (79%), mp 162–163°C (decomp.) from CCl_4. IR spectrum, ν, cm^{-1}: 1760 (C=O), 1600, 1300 (NO_2). Found, %: C 24.67; H 2.50; N 20.24. M 329. $C_7H_9N_5O_{11}$. Calculated, %: C 24.78; H 2.65; N 20.65. M 339.

5,5-Dinitro-2-[3,3-dinitro-1-(2,2,2-trinitroethyl)-butyl]-1,3-dioxane (V). At 20°C 3 g (8.8 mmol) of compound **IV** was dissolved while stirring in 2,2-dinitro-1,3-propanedisulfuric acid prepared from 4 g (0.024 mol) of 2,2-dinitro-1,3-propanediol and 5.59 g (0.048 mol) of chlorosulfonic acid [10]. The reaction mixture was maintained for 4 h at 30–40°C, then it was cooled to 5°C and poured on water-ice mixture. The separated thick oil was isolated from water layer and washed with water. In the course of washing the product crystallized, it was filtered off and dried in air at 20–25°C. Yield 3.3 g (77%). On recrystallization from a mixture CCl_4–$CHCl_3$, 1 : 1, mp 155–156°C (decomp.). IR spectrum, ν, cm^{-1}: 1580, 1600, 1285, 1300 (NO_2), 1050 (C-O-C). Found, %: C 24.77; H 2.71; N 20.01. M 475. $C_{10}H_{13}N_7O_{16}$. Calculated, %: C 24.64; H 2.67; N 20.12. M 487.

2-(2,2-Dinitropropyl)acrylic acid (VI). In 26.3 g of *tert*-butanol was dissolved 6 g (0.031 mol) of aldehyde **II**, and to the solution 1.33 g (0.011 mol) of SeO_2 was added. The mixture was heated to 40°C, and within 1 h a solution of 4.35 g of 28% hydrogen peroxide in 5.75 g of *t*-BuOH was added thereto. The reaction mixture was maintained at 40°C and stirred for 20 h. Then the solvent was distilled off, and the residue was treated with 60 ml of 10% sodium bisulfite solution, then the product was extracted into ether, the extracts were dried with calcined $MgSO_4$. The ether was distilled off to leave white crystalline residue, 4.3 g (67%), mp 117°C (from CCl_4). IR spectrum, ν, cm^{-1}: 1720 (C=O), 1600 (C=C), 1585, 1285 (NO_2). Found, %: C 35.40; H 3.76; N 13.91. M 198. $C_6H_8N_2O_6$. Calculated, %: C 35.40; H 3.92; N 13.65. M 204.

4,4-Dinitro-2-(2,2-dinitropropyl)valeric acid (VII). To a solution of 6.55 g (0.055 mol) of 1,1-dinitroethane in 20 ml of ether and 1.1 ml of Radionov catalyst dissolved in alcohol was added dropwise at 20°C a solution of 10.25 g (0.55 mol) of aldehyde **II**

in 30 ml of ether within 3 h. The reaction mixture was kept at 20°C for 16 h, then washed with 2 N solution of HCl (2–25 ml). The ether solution was dried over anhydrous $MgSO_4$. The ether was evaporated, the oily residue was dissolved in 50 ml of 70% nitric acid maintaining the temperature 40°C (cooling with ice). The reaction mixture was cooled to 20°C and left standing for 12 h. The separated crystals were filtered off and dried in air at 20°C. Yield 5.5 g (31%). After double recrystallization from water mp 131–132°C. IR spectrum, ν, cm^{-1}: 1765 (C=O), 1590, 1287 (NO_2). Found, %: C 29.44; H 3.61; N 17.05. M 312. $C_8H_{12}N_4O_{10}$. Calculated, %: C 29.63; H 3.70; N 17.28. M 324.

2,2-Dinitropropylsuccinic acid (VIII). (a) In 10 ml of water was dissolved at 95°C 1.1 g (0.003 mol) of acid **IX**, and the solution was kept at this temperature for 30 min.The water solution was evaporated to dryness,the solid residue was several times washed with dichloroethane to remove traces of the initial acid **IX**. Yield 0.75 g (97%). On recrystallization from a mixture dichloroethan–ethanol, 1:1, mp 156–157°C (decomp.). IR spectrum, ν, cm^{-1}: 1755 (C=O), 1585, 1290 (NO2). Found, %: C 33.91; H 3.70; N 11.01. M 250. $C_7H_{10}N_2O_8$. Calculated, %: C 33.60; H 4.00; N 11.20. M 239.

(b) In a mixture of 90 ml of water and 30 ml of ethanol was dissolved at heating to 60°C 5.0 g (0.0245 mol) of compound **VI**, 8 g (0.053 mol) of trinitromethane was added, and the reaction mixture was stirred for 3 h at 60°C. Then the solution was evaporated to dryness The residue was recrystallized from a mixture dichloroethane–ethanol, 1:1, mp 156–157°C (decomp.). IR spectrum of the product was identical to that of sample obtained by procedure (a) Mixed sample with acid **VIII** melted without temperature depression.

(c) In 15 ml of ethanol was dissolved 1.5 g (0.004 mol) of compound **III**, 5–6 drops of 36.5% HCl (density 1.19 g cm^{-3}) and 1.4 g (0.002 mol) of hydroxylamine hydrochloride were added, and the solution obtained was boiled for 5 h. Then ethanol was removed at reduced pressure, to the residue 5 ml of concn. HCl was added, the mixture was boiled for 2 h and then evaporated. The residue was treated with dichloroethane at 60°C which resulted in crystallization. On recrystallization from a mixture dichloroethane–ethanol, 1:1, mp 156–157°C (decomp.). IR spectrum of the product was identical to those of samples obtained by procedures (a), (b). Mixed sample with acid **VIII** obtained by methods (a), (b) melted without temperature depression.

4,4-Dinitro-2-(2,2,2-trinitroethyl)valeric acid (IX). In 30 ml of methanol was dissolved 3 g (0.015 mol) of acid **VI**, 3 g (0.017 mol) of trinitromethane and 0.2 ml of water was added, and the reaction mixture was left standing at 20°C for 12 h. The solvent was evaporated at reduced pressure, the residue was washed with 3 ml of cold water, and dried. Yield 2.7 g (52%), mp 111–112°C (from CCl_4). IR spectrum, ν, cm^{-1}: 3500 (O–H), 1750 (C=O), 1600, 1300 (NO_2). Found, %: C 27.75; H 3.01; N 22.54. M 337. $C_7H_9N_5O_{12}$. Calculated, %: C 27.36; H 2.93; N 22.80. M 355.

4,4-Dinitro-2-(2,2-dinitropropyl)valeronitrile (X). In 32 ml of 18% formic acid was dissolved 6.6 g (0.021 mol) of compound **III**, 1.75 g (0.025 mol) of hydroxylamine hydrochloride and 2.16 g (0.032 mol) of sodium formate was added. The solution obtained was heated for 1 h on a boiling water bath, cooled, and diluted with 100 ml of water. The product was extracted into other (4 × 25 ml). The extract was dried over anhydrous $MgSO_4$. On evaporation of ether the oily residue was purified by recrystallization from chloroform to obtain 0.8 g (12%) of white crystalline substance, mp 110–111°C. IR spectrum, ν, cm^{-1}: 2240 (C–N), 1600, 1300 (NO_2). Found, %: C 31.22; H 3.50; N 22.60. M 298. $C_8H_{11}N_5O_8$. Calculated, %: C 31.48; H 3.61; N 22.95. M 305.

4,4-Dinitro-2-(2,2-dinitropropyl)valeramide (XI). In 12.5 ml of 100% sulfuric acid was dissolved 1.25 g (0.004 mol) of nitrile **X**, and 5–6 drops of concn. HNO_3 was added. The reaction mixture was maintained for 4 h at 70–75°C, cooled, and poured on ice. The precipitate was filtered off, washed with cold water, and dried in air. Yield 1.1 g (83%). On recrystallization first from water, and then from chloroform mp 150–151°C. IR spectrum, ν, cm^{-1}: 3350 (NH_2), 1685 (C=O), 1590, 1295 (NO_2). Found, %: C 29.60; H 4.00; N 21.44. M 318. C8H13N5O9. Calculated, %: C 29.72; H 4.02; N 21.67. M 323.

2,2,2-Trinitroethyl 2-(2,2-dinitropropyl)acrylate (XII). At 50°C 3 g (0.015 mol) of acid **VI** was dissolved in 2,2,2-trinitroethylsulfuric acid prepared from 4.5 g (0.025 mol) of 2,2,2-trinitroethanol and 2.9 g (0.029 mol) of chlorosulfonic acid [10]. The solution obtained was heated for 3 h on a boiling water bath, then cooled, and poured on ice. The separated oily substance soon crystallized. The crystals were filterd off, washed with water, and dried in air at room temperature. Yield 4.6 g (85%). After double recrystallization from carbpn tetrachloride mp 70–71°C. IR spectrum, ν, cm^{-1}: 1750 (C=O), 1600 (C=C), 1600, 1585, 1300, 1285

(NO_2). Found, %: C 26.23; H 2.67; N 19.19. M 358. $C_8H_9N_5O_{12}$. Calculated, %: C 26.16; H 2.45; N 19.07. M 367. Esters **XIII**–**XV** were similarly prepared. The following weight ratios of reagents were used for preparation of esters **XIII, XIV**: γ-polynitroacid-2,2,2-trinitroethanol-chlorosulfonic acid (1.0 : 1.5 : 1.87), for ester **XV** (1.0 : 3.0 : 3.74).

2,2,2-Trinitroethyl 4,4-dinitro-2-(2,2-dinitropropyl)pentanoate (XIII). Yield 86%, mp 102–103°C (from $CHCl_3$). IR spectrum, ν, cm^{-1}: 1755 (C=O), 1600–1590, 1300–1285 (NO_2). Found, %: C 24.81; H 2.11; N 19.98. M 475. $C_{10}H_{13}N_7O_{16}$. Calculated, %: C 24.64; H 2.37; N 20.12. M 487.

2,2,2-Trinitroethyl 4,4-dinitro-2-(2,2,2-tri-nitroethyl)pentanoate (XIV). Yield 82%, mp 111.0–111.5°C (from $CHCl_3$). IR spectrum, ν, cm^{-1}: 1760 (C=O), 1605, 1300 (NO2). Found, %: C 21.05; H 1.88; N 21.86. M 518. $C_9H_{10}N_8O_{18}$. Calculated, %: C 20.85; H 1.93; N 21.62. M 507.

Bis(2,2,2-trinitroethyl) 2-(2,2-dinitropro-pyl)-succinate (XV). Yield 72%. On recrystallization from aqueous methanol 1 : 1, mp 86.5–87.5°C. IR spectrum, ν, cm^{-1}: 1733 (C=O), 1600, 1300 (NO_2). Found, %: C 21.13; H 2.08; N 19.51. M 558. $C_{10}H_{12}N_8O_{20}$. Calculated, %: C 21.28; H 2.13; N 19.86. M 564.

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