Targeted Intermediates of Eudesmic Acid: 
Synthesis and X-ray Investigations

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ABSTRACT

It was carried out synthesis of esters and their dinitro derivatives of 3,4,5-trimethoxybenzoic (eudesmic) acid. Esterification of eudesmic acid carried out in absolute methanol or ethanol and corresponding methyl and ethyl 3,4,5-trimethoxybenzoates (2, 3) have been synthesized in good yields. It was revealed that nitration of these esters gives only dinitro products. The structure of the synthesized compounds of the methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates (4, 5) was determined by X-ray diffraction analysis (XRD). In the asymmetric part of the crystal structures of 4, 5 one and two molecules are observed, respectively. In crystalline structures a flat nitro groups and carboxylic groups do not participate in the conjugation with aromatic rings. In the crystal structure of 4, an intermolecular C8-H...O9 hydrogen bond is observed, these H bonds link the molecules along the [010] axis. In the crystal structure of 5, intermolecular C9B-H...O4A and C10B-H...O8A hydrogen bonds form chains along the [011] axis. The formed chains are cross linked by the intermolecular C9B-H...O5A hydrogen bonds.

Keywords: synthesis; methyl and ethyl 3,4,5-trimethoxybenzoates; methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates; esterification; nitration; X-ray diffraction analysis

INTRODUCTION

Eudesmic acid is an O-methylated trihydroxybenzoic (gallic) acid (1). This natural carboxylic acid can be found in Eucalyptus spp. [1].

There is in medicine practice more than 20 drugs are successfully used, such as: trimebutine with antimuscarinic effect [2] and its maleic acid salt - recutin, polybutin [3], trimetozine (sedative activity) [4,5] is used in Europe since 1959 and has been used in the treatment of anxiety [6,7], dilazep (vasodilator) acts as an adenosine reuptake inhibition [8], troxipide is a drug used in the treatment of gastroesophageal reflux disease and it is novel systematic non-antisecretory gastric cytoprotective agent with anti-ulcer, anti-inflammatory properties [9-14], methoserpine [15] is an antihypertensive drug related to reserpine and its analogues [16] some 3,4,5-trimethoxybenzoic acid derivatives have been synthesized and studied their activity on the central nervous system [17]. Discussion of literatures shows that 3,4,5-trimethoxybenzoic acid and its derivatives are very interest and important synthons for creation of pharmacologically active drugs.

Aim of this work is developing effective methods for synthesis of 2,6-dinitro-3,4,5-trimethoxybenzoic acid, which has reactive carboxylic group and studying their
x-ray structure. We can successfully use this synthones in the synthesis of many potential bioactive substances and for introduction of pharmacophoric fragments of eudesmic acid into molecules of different natural [18] and synthetic heterocyclic compounds [19]. These investigations will be presented in our next publications.

MATERIALS AND METHODS

$^1$H NMR spectrum was recorded in acetone-$d_6$ on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxcane (HMDSO) was used as internal standard, chemical shift $\delta$ of $^1$H was recorded in ppm. Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected. IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets.

The reactionary process was monitored by TLC on Whatman UV-254 precoated aluminum plates using CHCl$_3$/CH$_3$OH - 10:1, C$_6$H$_6$/CH$_3$OH - 25:1 solvent system and developed plates were visualized under UV lamp and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na$_2$SO$_4$ and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

X-ray diffraction studies of compounds 4 and 5.

The crystals of compounds 4 and 5, suitable for X-ray diffraction, were grown by slow evaporation of solvent - EtOH at room temperature. The crystal cell parameters are determined and refined on a CCD Xcalibur Ruby (Oxford Diffraction) diffractometer using CuK$\alpha$-radiation. The correction for absorption was introduced by the Multi-scan method.

A CrysAlis Pro program package was used for the determination of cell parameters, data integration, scaling and absorption correction [21]. The structures were solved by direct methods (SHELXS-97) [22] and refined by full matrix least-square procedures on $F^2$ (SHELXL-97) [23]. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at idealized positions and refined using the riding model. A summary of the fundamental crystal and refinement data is provided in Table 2. Crystallographic data for the structural analysis was deposited with the Cambridge Crystallographic Data Centre. A copy of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44 1223 336 033, e-mail:deposit@ccdc.cam.ac.uk, or www.ccdc.cam.ac.uk.

Table 2 General crystallographic parameters and characteristics of x-ray analysis of the compounds 4 and 5

| Compounds | 4   | 5   |
|-----------|-----|-----|
| Formula   | $C_{11}H_{12}N_2O_9$ | $C_{12}H_{14}N_2O_9$ |
| Formula weight | 316,23 | 330,25 |
| Crystal system | orthorhombic | triclinic |
| Space group | $Pbc\alpha$ | $P-1$ |
| Z          | 8   | 4   |
| T (K)      | 290 (2) | 290 (2) |
| a (Å)      | 17,998 (4) | 8,5444 (17) |
| b (Å)      | 8,3932 (17) | 9,895 (2) |
| c (Å)      | 19,012 (4) | 18,785 (4) |
| $\alpha$ (º) | 90,0 | 90,93 (3) |
| $\beta$ (º) | 90,0 | 91,75 (3) |
| $\gamma$ (º) | 90,0 | 105,41 (3) |
| V (Å$^3$)  | 2872,1 (10) | 1529,9 (5) |
| Dx (g cm$^{-3}$) | 1,463 | 1,434 |
| F (000)    | 1312 | 688 |
| $\mu$ (mm$^{-1}$) | 1,136 | 1,090 |
| $\Theta$ range (º) | 4,65-76,09 | 4,64-76,02 |
| hkl range  | -15 ≤ h ≤ 22 | -10 ≤ h ≤ 7 |
|             | -8 ≤ k ≤ 10  | -11 ≤ k ≤ 11  |
|             | -23 ≤ l ≤ 20 | -23 ≤ l ≤ 20 |
| Measured reflections | 7170 | 10478 |
| Independent reflections | 2923 | 6151 |
| Reflections with $I >4\sigma(I)$ | 1572 | 3564 |
| $R[F^2>4\sigma(F^2)]$/all | 0,0586 | 0,0604 |
| $wR(F^2)$ | 0,1390 | 0,1605 |
| S all      | 0,995 | 0,991 |
| Parameters | 204 | 424 |
| Max/min $\Delta$ρ (e Å$^{-3}$) | 0,174/-0,213 | 0,293/-0,275 |
| CCDC       | 1546900 | 1546901 |

Synthesis of esters (2, 3)

Methyl 3,4,5-trimethoxybenzoate (2). 9.5 g (45 mmol) 3,4,5-trimethoxybenzoic acid was dissolved in 140 ml absolute methanol, 4.75 ml concentrated H$_2$SO$_4$ was added. Reaction mixture was refluxed for 8
h, filtered hot, and is cooled up to 5-10° C. The formed crystals were filtered off and dried.

**Yield:** 8.64 g (85%), mp 82-83°C (abs. methanol), Rf 0.4 (CHCl₃/CH₃OH -10/1).

**Ethyl 3,4,5-trimethoxybenzoate (3).** Reaction carried out analogously: 10 g (47 mmol) 3,4,5-trimethoxybenzoic acid was dissolved in 150 ml absolute ethanol, 10 ml concentrated H₂SO₄ was added. Reaction mixture was refluxed for 8 h, filtered hot, and is cooled up to 5-10° C. The formed crystals filtered off and dried.

**Yield:** 9.57 (96%) mp 50-52° C (abs. ethanol), Rf 0.85 (CHCl₃/CH₃OH-10/1)

**Synthesis of dinitroproducts (4, 5)**

**Methyl 2,6-dinitro-3,4,5-trimethoxybenzoate (4)**

1.93 g (8.5 mmol) methyl 3,4,5-trimethoxybenzoate (2) was dissolved in cooled 4 ml concentrated H₂SO₄ (ice bath, 30 min.) and nitrating mixture, containing 2.9 g HNO₃ and 2.7 g H₂SO₄ acids were added drop wise for 1 h, mixed for 30 min in ice bath and for 1 h at room temperature. Reaction mixture was decomposed with crushed ice. The formed yellow crystals were filtered off and washed with water up to pH=7 and dried.

**Yield:** 0.68 (50%), mp 106-108°C (methanol), Rf 0.4 (C₆H₆/CH₃OH - 25/1)

1H NMR spectrum (acetone-d₆), δ, ppm, J/Hz: 4.07 (3H, s, COOMe), 4.03 (6H, s, OMe-3,5), 3.78 (3H, s, OMe-4).

IR (KBr) cm⁻¹: 2961 (CH₃), 1734 (O-C=O), 1574, 1545 (NO₂).

**Ethyl 2,6-dinitro-3,4,5-trimethoxybenzoate (5).**

Reaction carried out analogously to the synthesis method of compound 4.

From 6 g (25 mmol) of ethyl 3,4,5-trimethoxybenzoate (3) in 14 ml concentrated H₂SO₄ (ice bath) and nitrating mixture (8.96 g HNO₃ + 8.47 g H₂SO₄) the corresponding compound 5 has been synthesized.

**Yield:** 2.0 g (48%), mp 70-72° C (ethanol), Rf 0.8 (C₆H₆/CH₃OH - 25/1)

1H NMR spectrum (acetone-d₆), δ, ppm, J/Hz: 4.1 (2H, q, OCH₂), 4.0 (3H, t, OCH₂CH₃), 3.9 (6H, s, OMe-3,5), 3.7 (3H, s, OMe-4).

IR (KBr) cm⁻¹: 2957 (CH₃), 1734 (O-C=O), 1570, 1542 (NO₂).

**RESULTS AND DISCUSSION**

Continuing researches on the synthesis of perspective derivatives of 3,4,5-trimethoxybenzoic acid, in this work we carried out esterification of 3,4,5-trimethoxybenzoic acid and nitration of obtained methyl and ethyl 3,4,5-trimethoxybenzoates (2, 3).

Esterification of 3,4,5-trimethoxybenzoic acid (1) was carried out in absolute methanol and ethanol in the presence of concentrated sulfuric acid in reflux for 8h:

The synthesized esters (2, 3) can react with nitrating mixture (mixture of nitric and sulfuric acids) at -2-0°C (ice bath) for 1.5-2 h and methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates (4, 5) in moderate yields:

No formation of mono-nitro product – methyl and ethyl 2-nitro-3,4,5-trimethoxybenzoates was (6) observed. Formation of mono-nitro product (6) takes place at the nitration of compound 4 by nitric acid in the medium of acetic acid [20].

Structures of synthesized methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates (4, 5) have been confirmed by physical research, including methods for the analysis of X-ray diffraction of single crystals. The XRD analysis of compound 4 shows that in an independent part of the crystal structure contains one molecule of methyl 2,6-dinitro-3,4,5-
trimethoxybenzoate. Aromatic ring is flat (C1-C6) [r.m.s. deviation 0.0135 Å], the angles between the aromatic ring and the flat carboxyl group (C7/O1/O2) are 35.69 (11)°. Angles between the aromatic ring and nitro groups also are 64.06 (16)° (N2/O8/O9), -75.67 (15)° (N1/O3/O4) (Table 1). This arrangement of carboxyl (C1) and two nitro groups (C2, C6) gives evidence that these planar fragments do not participate in the conjugation of the p-electrons of the aromatic ring. A similar picture in the arrangement of nitro groups is observed in the structure of the molecule methyl 2-nitro-3,4,5-trimethoxybenzoate [20]. In the crystal of the compound 4 is observed a weak intermolecular C8-H...O9 hydrogen bond. Parameters: C8-H8B 0.96 Å, H8B...O9 2.577 Å, C8...O9 3.454 Å, angle C8-H8B...O9 152,11° [symmetry codes: 0.5-x, 0.5+y, +z]. These H-bonds bind the molecules along the [010] axis.

The XRD results of the compound 5 show that in the independent part of the crystal structure there are two ethyl 2,6-dinitro-3,4,5-trimethoxybenzoate (5A and 5B) molecules. The arrangement of flat fragments of carboxyl groups and nitro groups is different and they do not participate in conjugation of the p-electrons of the aromatic ring. The aromatic ring (5A) is flat (C1-C6) [r.m.s. deviation 0.0101 Å], the angle between the carboxyl group (C7/O1/O2) is 10.32 (7)°, the angles between the nitro groups are 83.85 (15)° (N2/O8/O9), -84.37 (18)° (N1/O3/O4). The aromatic ring (5B) is flat (C1-C6) [r.m.s. deviation 0.0129 Å], the angle between the carboxyl group (C7/O1/O2) is 45.79 (17)°, the angles between nitro groups are -65.55 (17)° (N2/O8/O9), 61.53 (15)° (N1/O3/O4) (Table 1). In the crystal structure of 5, the formation of weak intermolecular C9B-H...O4A and C10B-H...O8A hydrogen bonds, forming the chain along the [011] axis is observed. The formed chains are cross linked by the intermolecular C9B-H...O5A hydrogen bonds.

Parameters of C9B-H9BA...O4A hydrogen bonds: distance C9B-H9BA 0.96 Å, H9BA...O4A 2.688 Å, C9B...O4A 3.582 Å, angle C9B-H9BA...O4A 155,17° [symmetry codes: -x, -y, -z]; C10B-H10F...O8A: distance C10B-H10F 0.96 Å, H10F...O8A 2.612 Å, C10B...O8A 3.501 Å, angle C10B-H10F...O8A 154,04° [symmetry codes: -x, -y, z+1]; C9B-H9BB...O5A: distance C9B-H9BB 0.96 Å, H9BB...O5A 2.593 Å, C9B...O5A 3.538 Å, angle C9B-H9BA...O5A 168.08°. The structures of the methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates (4, 5) are shown in Fig. 1.

| Torsion angles (°) | 4        | 5A       | 5B       |
|-------------------|----------|----------|----------|
| O3-N1-C2-C1       | 74.66    | -95.95   | 118.79   |
|                   | (42)     | (40)     | (34)     |
| O4-N1-C2-C1       | -105.22  | 84.58    | -59.81   |
|                   | (37)     | (42)     | (41)     |
| O3-N1-C2-C3       | -102.35  | 83.19    | -64.65   |
|                   | (37)     | (41)     | (40)     |
| O4-N1-C2-C3       | 77.77    | -96.28   | 116.76   |
|                   | (40)     | (39)     | (34)     |
| O9-N2-C6-C5       | -113.80  | -94.09   | 112.47   |
|                   | (36)     | (35)     | (34)     |
| O8-N2-C6-C5       | 65.11    | 83.73    | -66.21   |
|                   | (43)     | (37)     | (41)     |
| O9-N2-C6-C1       | 62.01    | 84.22    | -63.94   |
|                   | (46)     | (38)     | (41)     |
| O8-N2-C6-C1       | -119.09  | -97.96   | 117.38   |
|                   | (38)     | (36)     | (35)     |
| C2-C1-C7-O2       | -141.49  | -169.99  | -44.51   |
|                   | (36)     | (33)     | (44)     |
| C6-C1-C7-O2       | 33.87    | 10.24    | 131.92   |
|                   | (52)     | (50)     | (34)     |
| C2-C1-C7-O1       | 36.66    | 10.68    | 137.43   |
|                   | (43)     | (46)     | (29)     |
| C6-C1-C7-O1       | -147.98  | -169.10  | -46.14   |
|                   | (31)     | (30)     | (39)     |
CONCLUSIONS

It was carried out synthesis of dinitro derivatives of 3,4,5-trimethoxybenzoic (eudesmic) acid - methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates (4, 5), which are important synthones in the organic and bioorganic chemistry. It was found that nitration of methyl and ethyl 3,4,5-trimethoxybenzoates (2, 3) by nitrating mixture corresponding dinitro products - methyl and ethyl 2,6-dinitro-3,4,5-trimethoxybenzoates (4, 5) are synthesized and their structures were determined by X-ray diffraction analysis (XRD). No formation of mono-nitro product was (6) observed. It was revealed that in the asymmetric part of the crystal structures of 4, 5 one and two molecules are observed. It was observed that in the crystalline structures a flat nitro groups and carboxylic groups do not participate in the conjugation with aromatic rings, and in the crystal structures of 4 and 5 an intermolecular hydrogen bond are observed, which these H bonds link the molecules along the [010] and [011] axis, respectively.

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