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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 n 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-ulser, anti-inflammatory properties [9-14], methoserpidine [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 δ 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 $CHCl_3/CH_3OH$ - 10:1, C_6H_6/CH_3OH - 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_2SO_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□-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 parametrs and charasteristics 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	*Pbca*	*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)
α (º)	90,0	90,93 (3)
β (º)	90,0	91,75 (3)
γ (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
μ (mm^{-1})	1,136	1,090
Θ range (º)	4,65-76,09	4,64-76,02
hkl range	-15 ≤ h ≤ 22 -8 ≤ k ≤ 10 -23 ≤ l ≤ 20	-10 ≤ h ≤ 7 -11 ≤ k ≤ 11 -23 ≤ l ≤ 20
Measured reflections	7170	10478
Independent reflections	2923	6151
Reflections with I >4σ(I)	1572	3564
R [F^2>4σ(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 Δρ (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_2SO_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), R_f 0.4 ($CHCl_3/CH_3OH$ -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 H_2SO_4 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), R_f 0.85 ($CHCl_3$\CH_3OH-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 H_2SO_4 (ice bath, 30 min.) and nitrating mixture, containing 2.9 g HNO_3 and 2.7 g H_2SO_4 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), R_f 0.4 (C_6H_6/CH_3OH - 25/1)

^{1}H NMR spectrum (acetone-d_6), 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 (CH_3), 1738 (O-C=O), 1574, 1545 (NO_2).

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 H_2SO_4 (ice bath) and nitrating mixture (8.96 g HNO_3 + 8.47 H_2SO_4) the corresponding compound **5** has been synthesized.

Yield: 2.0 g (48%), mp 70-72° C (ethanol), R_f 0.8 (C_6H_6/CH_3OH - 25/1)

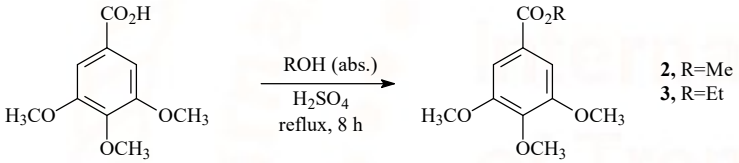
^{1}H NMR spectrum (acetone-d_6), δ, ppm, J/Hz: 4.1 (2H, q, OCH_2), 4.0 (3H, t, $OCH_2\underline{CH_3}$), 3.9 (6H, s, OMe-3,5), 3.7 (3H, s, OMe-4).

IR (KBr) cm^{-1}: 2957 (CH_3), 1734 (O-C=O), 1570, 1542 (NO_2).

RESULTS AND DISCUSSION

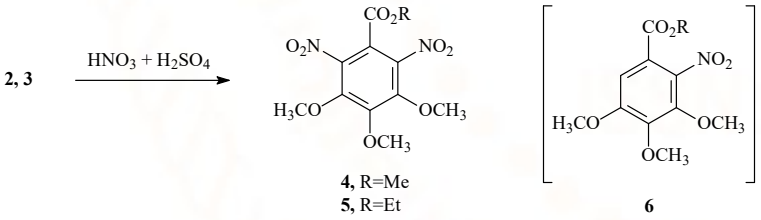
Continuing researches on the synthesis of perspective derivatives of 3,4,5-trimethoxybenzoic acid, in this work we carried out esterification of 3,4,5-trimethoxybenzoic acid and nitration of obtained methyl and ethyl 3,4,5-trimethoxybenzoates (**2**, **3**).

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:



1

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)º. Angles between the aromatic ring and nitro groups also are 64.06 (16)º (N2/O8/O9), -75.67 (15)º (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 152,11º [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)º, the angles between the nitro groups are 83.85 (15)º (N2/O8/O9), -84.37 (18)º (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)º, the angles between nitro groups are -65.55 (17)º (N2/O8/O9), 61.53 (15)º (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 155,17º [symmetry codes: *-x, -y-1, -z*]; C10B-H10F...O8A: distance C10B-H10F 0.96 Å, H10F...O8A 2,612 Å, C10B...O8A 3,501 Å, angle C10B-H10F...O8A 154,04º [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.

Table 1: Torsion angles (º) of 4 and 5 fragments

Torsion angles (º)	4	5A	5B
O3-N1-C2-C1	74,66 (42)	-95,95 (40)	118,79 (34)
O4-N1-C2-C1	-105,22 (37)	84,58 (42)	-59,81 (41)
O3-N1-C2-C3	-102,35 (37)	83,19 (41)	-64,65 (40)
O4-N1-C2-C3	77,77 (40)	-96,28 (39)	116,76 (34)
O9-N2-C6-C5	-113,80 (36)	-94,09 (35)	112,47 (34)
O8-N2-C6-C5	65,11 (43)	83,73 (37)	-66,21 (41)
O9-N2-C6-C1	62,01 (46)	84,22 (38)	-63,94 (41)
O8-N2-C6-C1	-119,09 (38)	-97,96 (36)	117,38 (35)
C2-C1-C7-O2	-141,49 (36)	-169,99 (33)	-44,51 (44)
C6-C1-C7-O2	33,87 (52)	10,24 (50)	131,92 (34)
C2-C1-C7-O1	36,66 (43)	10,68 (46)	137,43 (29)
C6-C1-C7-O1	-147,98 (31)	-169,10 (30)	-46,14 (39)

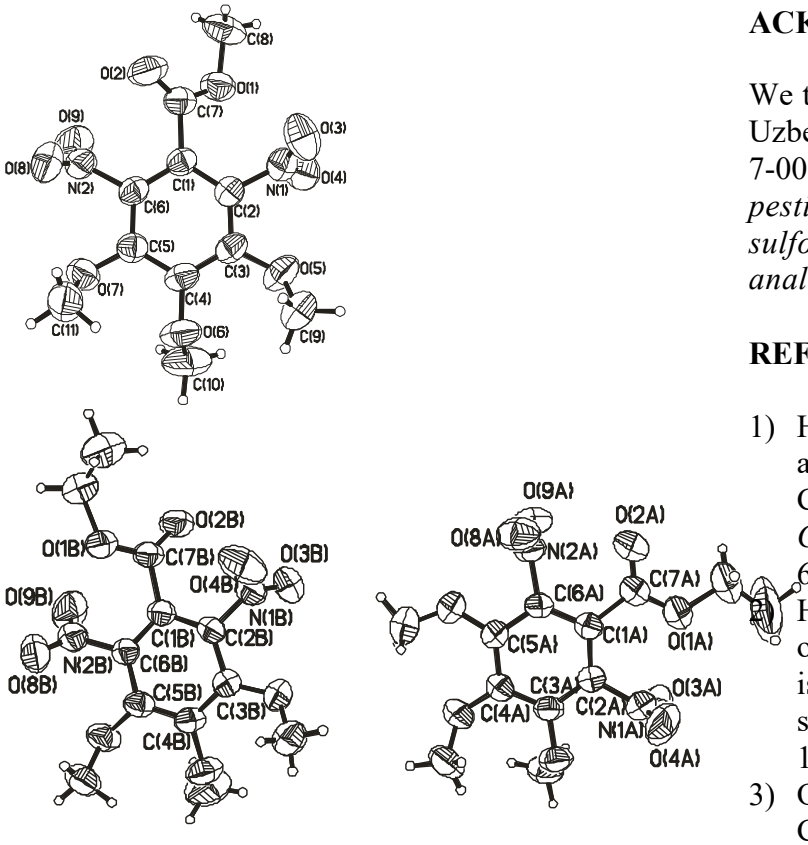


Figure 1 A representation of the molecular structure of **4** and **5** with atom labeling scheme. Ellipsoids correspond to 50 % probability level.

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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