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METHOD OF OBTAINING 6-ETHOXYCARBONYLMETHYL-SULFINYL-2,3-DIHYDROXY-1,2,3,4-TETRAHYDROPYRIDINE

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Oxidation of the sulfur atom in methyl 4-(2-chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate with m-chloroperbenzoic acid in dichloromethane gave methyl 4-(2-chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfinyl-2,3-dihydroxy-2-methyl-1,2,3,4-tetrahydropyridine-3-carboxylate. The structure of the compound obtained was identified by ^{1}H NMR spectroscopy and by X-ray structural analysis.

Keywords: 6-alkylsulfanyl-1,4-dihydropyridine, 6-alkylsulfinyl-2,3-dihydroxy-1,2,3,4-tetrahydropyridine, 1,4-dihydropyridine, oxone, *m*-chloroperbenzoic acid.

It is known that 6-alkylsulfanyl-1,4-dihydropyridines show antioxidant [1, 2], antiradical [3], hepatoprotective [4], cardiovascular [5], and hypotensive [6] activity. The aim of this study was to attempt a selective oxidation of the sulfur atom in methyl 4-(2-chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**1**) because it is known that oxidation of the sulfur atom can cause a change in the biological activity of the compounds obtained. Hence, for example, the medication ampicillin (a sulfanyl derivative of penicillanic acid) is an antibiotic [7], whereas sulbactam (penicillanic acid sulfone) is an inhibitor of the β-lactamase responsible for the development of bacterial resistance to β-lactam antibiotics [8].

Different methods for the oxidation of a sulfur atom in sulfur-containing organic compounds have been reported in the literature, involving the use of *tert*-butyl peroxide, benzoyl peroxide, *m*-chloroperbenzoic acid (MCPBA) [9, 10], various peroxy acid salts [11-14], and hydrogen peroxide [15-18]. None the less, examples of the oxidation of the sulfur atom of 6-alkylsulfanyl-1,4-dihydropyridines to the corresponding sulfoxides and sulfones have not been reported in the literature.

In the development of the method for oxidizing the sulfur atom of 1,4-dihydropyridine alkylsulfanyl derivatives and for studying the features of the process we have chosen MCPBA and oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as oxidants. Methyl 4-(2-chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**1**) was chosen as model substrate. Hence MCPBA in dichloromethane gave the methyl 4-(2-chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfinyl-2,3-dihydroxy-2-methyl-1,2,3,4-tetrahydropyridine-3-carboxylate (**2**).

There apparently occurs an initial oxidation of the sulfanyl group to sulfoxide, and the 2,3-dihydroxy-1,2,3,4-tetrahydropyridine **2** is formed in the second stage. With the aim of confirming this proposal it was decided to use oxone as the oxidant, and this led to an 82% yield of the 6-ethoxycarbonylmethylsulfinyl-

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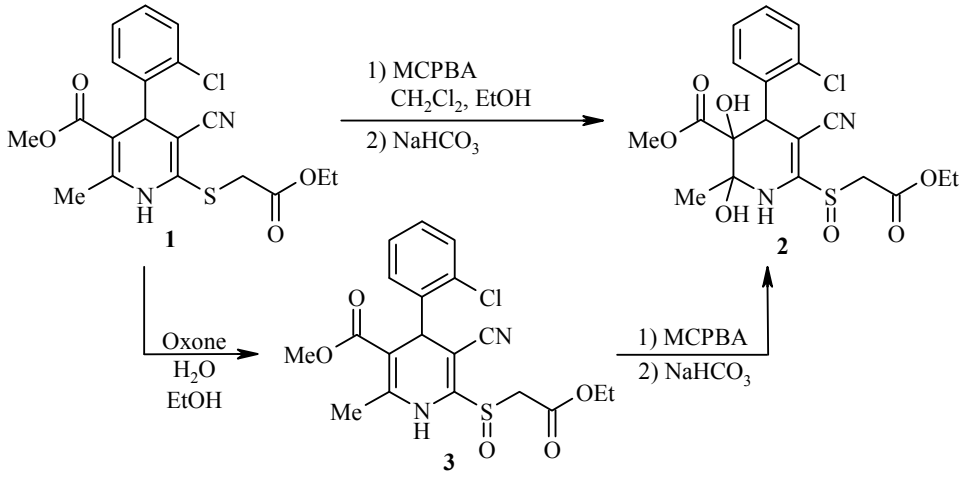
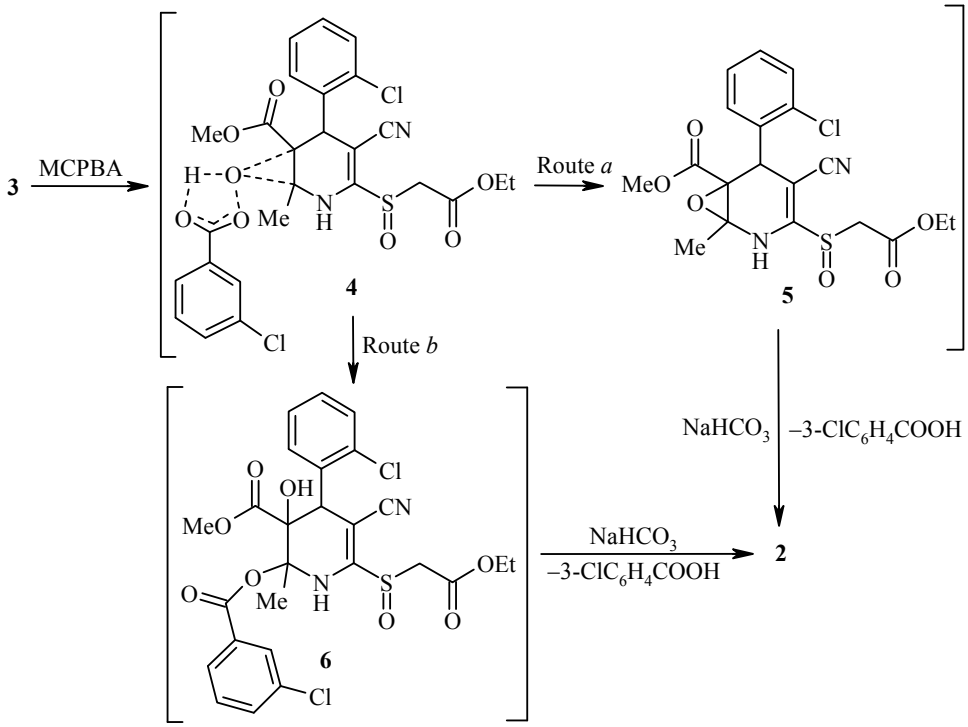
1,4-dihydropyridine **3**. Further oxidation of this compound using MCPBA gave the diol **2** in 56% yield. Oxidation of a double bond in compound **3** occurs as an electrophilic attack by the hydroperoxide group of the MCPBA on the C(2)=C(3) double bond. The reaction occurs regioselectively at only one double bond since the electron density of the C(5)=C(6) bond is lower due to the negative inductive effect of the substituents.



We have proposed two possible routes to formation of the 2,3-dihydroxy-1,2,3,4-tetrahydropyridine **2**. First, the cyclic transition state **4** can be converted to epoxide **5** which then opens under the influence of $NaHCO_3$ to give the diol **2** (route *a*). Alternatively, according to the authors of the study [19], the transition state **4** is converted to the unstable derivative **6**, which loses a *m*-chlorobenzoyl residue in the presence of $NaHCO_3$ to form compound **2** (route *b*).



Oxidation of the sulfur atom rather than the 1,4-dihydropyridine ring is indicated by the retention of the 4-CH proton signal in the ^{1}H NMR spectra of derivatives **2** and **3**, which experiences a marked shift to low fields. In addition, comparison of the spectrum of compound **1** with those of compounds **3** and **2** shows a shift of the signals of the CH_2 group protons bound to the sulfur atom from 3.50 to 3.72 and to 4.12 ppm, respectively. The ^{1}H NMR spectrum of compound **2** shows signals for the two hydroxyl groups at 4.61 and 6.28 ppm, together with hydroxyl group stretching vibrations at 3413 and 3501 cm^{-1} in the IR spectrum. Moreover, the structure of the 2,3-dihydroxy-6-ethoxycarbonylmethylsulfinyl-1,2,3,4-tetrahydropyridine **2** has been confirmed by X-ray structural analysis (Fig. 1).

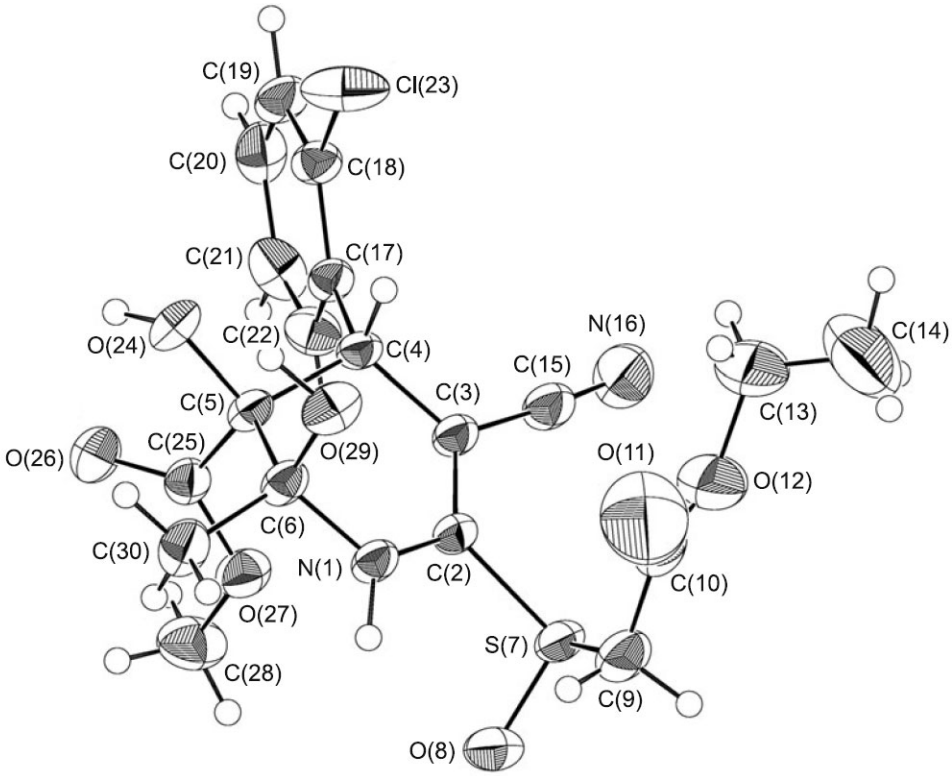


Fig. 1. Molecular structure of compound **2** with atoms represented by thermal vibration ellipsoids of 50% probability.

According to the results of the X-ray structural analysis, the heterocycle of molecule **2** has an "envelope" type conformation. The atoms N(1), C(2), C(3), C(4), and C(6) lie in a single plane within experimental error but the C(5) atom deviates from this plane by 0.679(4) Å. The dihedral angle between the planes formed by the atoms N(1), C(2), C(3), C(4), C(6) and C(4), C(5), C(6) is 131.7º. The crystal structure shows a system of OH···O and NH···O type intermolecular hydrogen bonds, through which molecules are combined as centrosymmetric associates. Through the O(24)−H···O(26) bond (distance between atoms O(24) and O(26) 2.820(3) Å, H···O(26) hydrogen bond length 1.98 Å, O(24)−H···O(26) angle 146º) the molecules are combined relative to a (0.5, 0.5, 0.5) inversion center. Through the N(1)−H···O(8) bond (distance between the N(1) and O(8) atoms 2.912(3) Å, H···O(8) hydrogen bond length 1.97 Å, N(1)−H···O(8) angle 165º) the molecules are combined relative to a (0, 0.5, 0) inversion center. The lengths of the hydrogen bonds correspond to medium strength bonds [20].

Hence we have carried out, for the first time, the oxidation of the sulfur atom of a 6-alkylsulfanyl-1,4-dihydropyridine with retention of its hydrogenated structure. Under various reaction conditions it was possible to prepare two compounds previously unreported in the literature, *viz*. 2,3-dihydroxy-1,2,3,4-tetrahydropyridine

and 6-ethoxycarbonylmethylsulfinyl-1,4-dihydropyridine. A possible mechanism is proposed for the formation of the 2,3-dihydroxy derivative obtained.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 580B spectrometer using nujol. ^{1}H NMR spectra were recorded on a Varian Mercury-200 instrument (200 MHz) using $CDCl_3$ (compounds **1** and **3**) or DMSO-d_6 (compound **2**) with HMDS as internal standard (δ 0.05 ppm). Elemental analysis was performed on a Carlo Erba 1108 analyzer. Monitoring of the reaction progress was carried out by TLC on Merck Kieselgel plates using $CHCl_3$–hexane–acetone (2:1:1) as eluent and UV visualization. Melting points were determined on a Boetius hot stage apparatus. Reagents and materials used in the experiments came from the Acros and Aldrich companies.

Methyl 4-(2-Chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate (1). Ethyl bromoacetate (0.12 ml, 1.09 mmol) was added to a solution of piperidinium 4-(2-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-methyl-1,4-dihydropyridine-6-thiolate [21] (0.40 g, 1.00 mmol) in EtOH (10 ml). The mixture obtained was heated to reflux, maintained at reflux for 2 min, and then stirred at room temperature for 30 min. The precipitate formed was filtered, washed with EtOH (3-5 ml, cooled to 0°C), and dried at 70°C. Yield 0.28 g (69%). White crystals; mp 105-107°C. IR spectrum, ν, cm^{-1}: 3225, 3180, 3080 (NH), 2200 (C≡N), 1700, 1678 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.34 (3H, s, 2-CH_3); 3.50 (3H, s, $COOCH_3$); 3.50 (2H, q, *J* = 16.0, SCH_2); 4.22 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 5.24 (1H, s, 4-CH); 6.99-7.29 (4H, m, H Ar); 8.51 (1H, s, NH). Found, %: C 55.68; H 4.71; N 6.65; S 8.11. $C_{19}H_{19}ClN_2O_4S$. Calculated, %: C 56.09; H 4.71; N 6.88; S 7.88.

Methyl 4-(2-Chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfinyl-2-methyl-1,4-dihydropyridine-3-carboxylate (3). A solution of oxone (1.84 g, 3.00 mmol) in water (150 ml) was cooled to 0°C, and a solution of the sulfanyl derivative **1** (0.40 g, 0.98 mmol) in EtOH (10 ml) was added with vigorous stirring. At the end of the process the flaky precipitated product was filtered off and recrystallized from EtOH. Yield 0.34 g (82%). White crystals; mp 128-130°C. IR spectrum, ν, cm^{-1}: 3191, 3083 (NH), 2211 (C≡N), 1739 (C=O), 1674. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.40 (3H, s, 2-CH_3); 3.51 (3H, s, $COOCH_3$); 3.72 (2H, q, *J* = 14.5, $SOCH_2$); 4.23 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 5.35 (1H, s, 4-CH); 7.11-7.25 (4H, m, H Ar); 7.30 (1H, s, NH). Found, %: C 53.59; H 4.67; N 6.23. $C_{19}H_{19}ClN_2O_5S$. Calculated, %: C 53.96; H 4.53; N 6.62.

Methyl 4-(2-Chlorophenyl)-5-cyano-6-ethoxycarbonylmethylsulfinyl-2,3-dihydroxy-2-methyl-1,2,3,4-tetrahydropyridine-3-carboxylate (2). A. A solution of the sulfanyl derivative **1** (0.81 g, 2 mmol) in EtOH (10 ml) was cooled to -5ºC. MCPBA (70%) (0.99 g, 4 mmol) in dichloromethane (25 ml) was added dropwise, so that the reaction temperature did not exceed 0ºC. At the end of the process the reaction mixture was washed with saturated $NaHCO_3$ solution and water. The organic layer was separated, evaporated, and the residue was recrystallized from EtOH. Yield 0.39 g (43%). Colorless crystals; mp 148-150ºC. IR spectrum, ν, cm^{-1}: 3501 (NH, OH), 3413, 3231, 2194 (C≡N), 1739 (C=O), 1600. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.28 (3H, s, 2-CH_3); 3.48 (3H, s, $COOCH_3$); 4.12 (2H, q, *J* = 14.9, $SOCH_2$); 4.17 (2H, q, *J* = 7.0 $C\underline{H}_2CH_3$); 4.61 (1H, s, OH); 5.07 (1H, s, 4-CH); 6.28 (1H, s, OH); 7.01-7.42 (4H, m, H Ar); 8.09 (1H, s, NH). Found, %: C 50.20; H 4.67; N 5.91; S 6.75. $C_{19}H_{21}ClN_2O_7S$. Calculated, %: C 49.95; H 4.63; N 6.13; S 7.02.

B. A solution of the sulfinyl derivative **3** (0.85 g, 2.1 mmol) in EtOH (10 ml) was cooled to -5ºC. MCPBA (70%) (0.99 g, 4.0 mmol) in dichloromethane (25 ml) was then added dropwise so that the reaction temperature did not exceed 0ºC. At the end of the process the reaction mixture was washed with saturated $NaHCO_3$ solution and water. The organic layer was separated, evaporated, and the residue was recrystallized from EtOH. Yield 0.54 g (56%). The melting point and spectroscopic data were identical to those for the product from method A.

X-ray Structural Analysis of Compound 2. Single crystals of compound **2** ($C_{19}H_{21}ClN_2O_7S$, *M* 456.91) were prepared by crystallization from EtOH and have trigonal symmetry. The unit cell parameters were: *a* 7.8845(4), *b* 10.4197(5), *c* 12.6602(5) Å, α 89.489(3), 82.023(3), γ 87.266(2)º, *V* 1028.87(8) Å^3, *F*(000) 476; μ 0.33 mm^{-1}, d_{calc} 1.475 g·cm^{-3}; *Z* 2, space group $P\bar{1}$. The intensities of 5032 independent reflections were measured on a Bruker Nonius KappaCCD diffractometer (MoKα radiation, λ 0.71073 Å, graphite monochromator) to $2\theta_{max}$ 57º at -80ºC. Reflections (3253) with I >3σ(*I*) were used in the calculation. The final probability factor *R* was 0.047. The structure was solved using the DIRDIF program. Refinement was carried out by least squares analysis in the full-matrix anisotropic approximation. The maXus program package [22] was used for the calculation. The full crystallographic information for compound **2** has been placed in the Cambridge Crystallographic Data Center as deposit CCDC 860565.

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