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SYNTHESIS OF 2-HYDROXYIMINO-1,2,3,4-TETRAHYDROPYRIMIDINES

I. V. Vozny[1], D. P. Stepanov[1], A. F. Mishnev[1], and R. Žalubovskis[1]*

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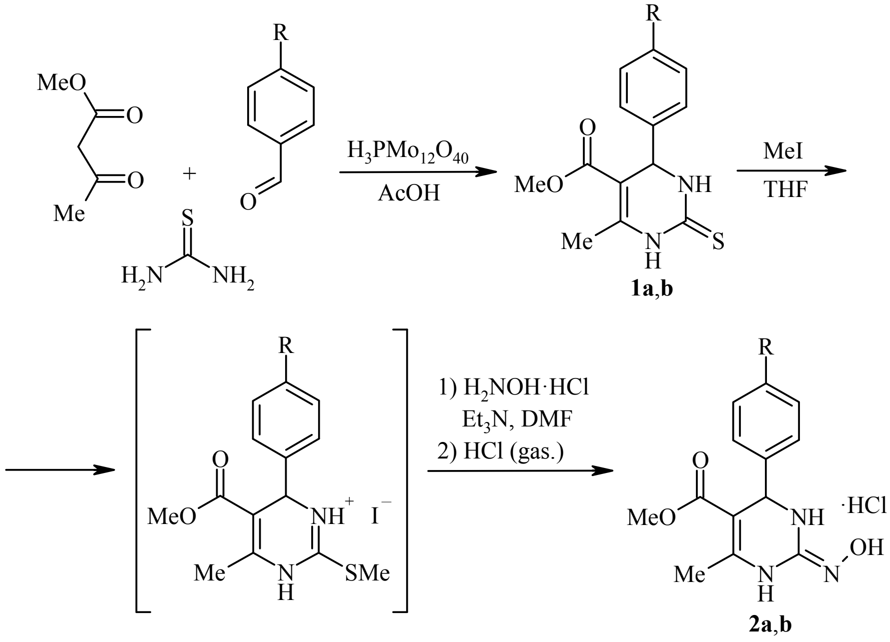
Interest in 2-imino-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid esters is mainly because they are structural subunits of a series of marine alkaloids (batzelladine B) showing a broad spectrum of biological activity [1]. Compounds of this type with a hydroxy group on an exocyclic nitrogen atom have not been reported to this time. Meanwhile, several hydroxyimino compounds of other classes are known as inhibitors of zinc-containing enzymes. Hence amidoximes are known inhibitors of histone deacetylases [2], and hydroxamic acids and their heterocyclic analogs are inhibitors of matrix metalloproteinases [3].

We propose a rather simple and convenient synthetic scheme for obtaining the 2-hydroxyimino-1,2,3,4-tetra-hydropyrimidine-5-carboxylic acid esters **2a**,**b** in reasonable yields.



a R = H, **b** R = OMe

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*To whom correspondence should be addressed, e-mail: raivis@osi.lv.

[1] Latvian Institute of Organic Synthesis, 21 Aizkraukles St., Riga LV-1006, Latvia.

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The structures of the obtained compounds **2a**,**b** were determined from ^{1}H and ^{13}C NMR and from IR spectroscopic data, from elemental analysis, and by X-ray structural analysis of compound **2b** (Fig. 1).

IR spectra were recorded on a Shimadzu FTIR IR Prestige-21 spectrometer for KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 spectrometer (400 and 100 MHz, respectively) using DMSO-d$_6$ and referenced to the solvent signals at 2.50 ppm (^{1}H nuclei) and 39.5 ppm (^{13}C nuclei). Elemental analysis was carried out on a Carlo Erba Elemental Analyzer EA 1108, and melting points were determined on an SRS OptiMelt instrument. Column chromatography was performed with silica gel (0.035-0.070 mm) from Acros.

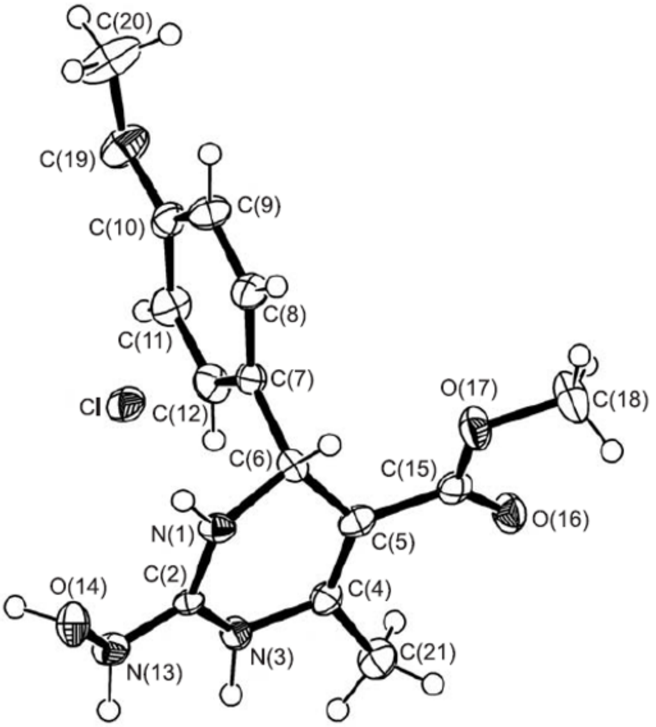

Fig. 1. Structure of the compound **2b** molecule with the atoms represented by thermal vibration ellipsoids of 50% probability.

Compounds **1a**,**b** were prepared by a three-component Biginelli condensation using phosphomolybdic acid as catalyst [4]. The physicochemical characteristics and spectroscopic data of these compounds agreed with the literature [4, 5].

(2*E*)-*N*-Hydroxy-5-methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-iminium Chloride (2a). A solution of compound **1a** (1.99 g, 7.58 mmol) and methyl iodide (1.62 g, 11.39 mmol) in absolute THF (25 ml) was stirred at room temperature for 1 day and then evaporated to dryness at reduced pressure. The residue was dissolved in anhydrous DMF (8 ml), $H_2NOH·HCl$ (2.63 g, 37.9 mmol) and Et_3N (5.36 g, 53.06 mmol) were added, and the mixture was stirred for 1 day at room temperature. The reaction mixture was poured into water (250 ml) and extracted with EtOAc (3×50 ml). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The product was isolated by column chromatography on silica gel (using CH_2Cl_2–MeOH eluent (15:1)) as the free base and immediately converted to the hydrochloride by passage of gaseous HCl through the eluate for several minutes. Evaporation of the solvent gave the product, which was recrystallized from MeOH. Yield 1.13 g (50%). Colorless prisms; mp 220-222°C (decomp.). IR spectrum, ν, cm^{-1}: 950 (N–O), 1690 (C=N), 1730 (C=O), 3450 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, 6-CH_3); 3.59 (3H, s, $COOCH_3$); 5.42 (1H, d, *J* = 2.8, 4-CH); 7.25-7.44 (5H, m, H Ph); 9.92 (1H, br. s, NH); 10.55 (1H, br. s, NH); 10.96 (1H, br. s, NH); 11.41 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 17.5

(6-CH_3); 51.5 (COO$\underline{C}H_3$); 51.7 (C-4); 102.9 (C-5); 126.5; 128.2; 128.8; 141.7; 144.7 (C-2); 151.2 (C-6); 164.9 (C=O). Found, %: C 52.46; H 5.37; N 13.98. $C_{13}H_{16}ClN_3O_3$. Calculated, %: C 52.44; H 5.42; N 14.11.

(2*E*)-*N*-Hydroxy-5-methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-iminium Chloride (2b). Prepared from compound **1b** (0.59 g, 2 mmol) similarly to compound **2a**. Yield 0.29 g (44%). Colorless prisms; mp 194-196°C (decomp.). IR spectrum, ν, cm^{-1}: 950 (N–O), 1690 (C=N), 1730 (C=O), 3450 (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, 6-CH_3); 3.58 (3H, s, $COOCH_3$); 3.73 (3H, s, ArOC$\underline{H}_3$); 5.36 (1H, d, *J* = 2.3, 4-CH); 6.79-7.01 (2H, m, H Ar); 7.09-7.32 (2H, m, H Ar); 9.85 (1H, br. s, NH); 10.51 (1H, br. s, NH); 10.91 (1H, br. s, NH); 11.35 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 17.5 (6-CH_3); 51.2 (C-4); 51.5 (COO$\underline{C}H_3$); 55.2 (C ArO$\underline{C}H_3$); 103.0 (C-5); 114.1; 127.9; 133.7 (C Ar); 144.4 (C-2); 151.2 (C-6); 159.1 (C Ar); 164.8 (C=O). Found, %: C 51.22; H 5.39; N 12.69. $C_{14}H_{18}ClN_3O_4$. Calculated, %: C 51.30; H 5.54; N 12.82.

X-ray Structural Study of Compound 2b. Single crystals of compound **2b** ($C_{14}H_{18}ClN_3O_4$, *M* 327.77) were prepared by crystallization from aqueous methanol solution. The parameters for the unit cell and intensities of 3632 independent reflections with $I > 2\sigma(I)$ were measured at a temperature of 190 K on a Bruker-Nonius Kappa CCD automatic X-ray diffractomer (MoKα radiation, λ 0.71073 Å). Crystals of compound **2b** were rhombic: *a* 8.6118(2), *b* 14.3429(4), *c* 25.133(1) Å; *V* 3104.4(2) $Å^3$; *Z* 8, d_{calc} 1.403 g/cm^3; space group $Pbc2_1$. The structure was solved by the direct method [6] and refined in full-matrix least-squares analysis using the SHELX program [7, 8]. The final difference factor values were *R* 0.064 and $wR(F^2)$ 0.160. The crystallographic parameters, atomic coordinates and their thermal parameters, bond lengths, and valence angle values in compound **2b** have been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 890695).

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