Three-component condensation of diethyl 2,4,6-trioxoheptanedicarboxylate with salicylaldehyde and ammonium acetate as a new method for the synthesis of the [1]benzopyrano[4,3-*b*]pyridine system

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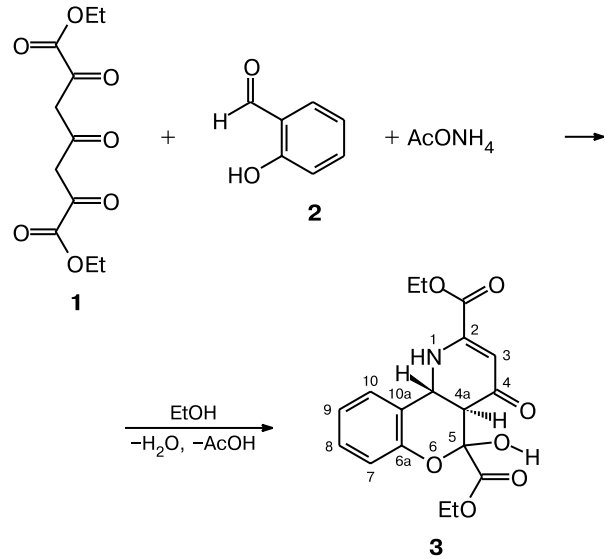
Three-component condensation of diethyl 2,4,6-trioxoheptanedicarboxylate with salicylaldehyde and ammonium acetate in EtOH affords 2,5-diethoxycarbonyl-5-hydroxy-4-oxo-4,4a,5,10b-tetrahydro-1*H*-[1]benzopyrano[4,3-*b*]pyridine.

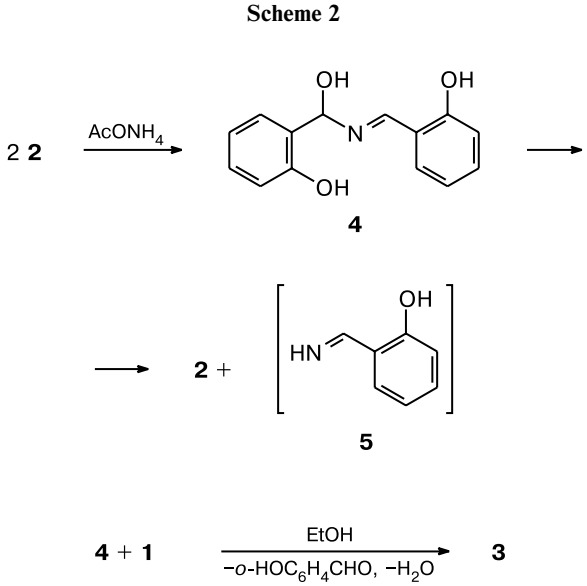
Key words: three-component condensation, salicylaldehyde, salicylaldimine, [1]benzopyrano[4,3-*b*]pyridine, X-ray diffraction study.

The symmetrical structure of diethyl 2,4,6-trioxoheptanedicarboxylate (**1**),[1] which contains two ethoxalyl residues attached at positions 1 and 3 of the acetone fragment, attracts attention as the starting compound in the synthesis of various functionalized heterocyclic systems. However, the synthetic potential of compound **1**, which was synthesized for the first time as early as 1891, was not fully realized because the synthesis of compound **1** is a complex procedure and, in most cases, this compound is unstable in a medium, in which the reaction occurs.

Scheme 1



Scheme 2



We found that the reaction of diethyl 2,4,6-trioxoheptanedicarboxylate (**1**)[1] with salicylaldehyde (**2**) in EtOH in the presence of ammonium acetate afforded an aza analog of the heterocyclic system of cannabinol,[2] *viz.*, 2,5-diethoxycarbonyl-5-hydroxy-4-oxo-4,4a,5,10b-tetrahydro-1*H*-[1]benzopyrano[4,3-*b*]pyridine (**3**) (Scheme 1), which includes the C(2)C(3)C(4)C(4a)C(5) fragment from compound **1**.

We found that the reaction of α,2-dihydroxy-*N*-(2-hydroxybenzylidene)benzylamine (**4**), which is easily prepared by condensation of two salicylaldehyde mol-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1494—1496, June, 2005.

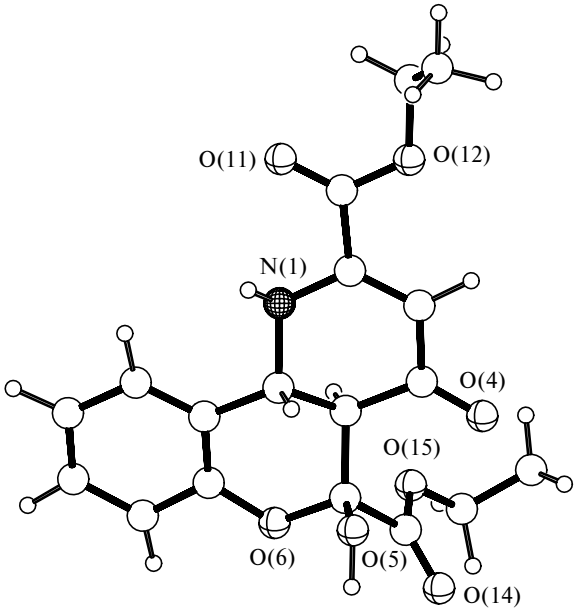


Fig. 1. Molecular structure of compound **3** in the crystal.

ecules with ammonium acetate, with diethoxalylacetone **1** also produces tricyclic system **3** (Scheme 2). Hence, we believe that the reaction proceeds through intermediate unstable salicylaldimine (**5**). Evidently, imine **4** decomposes under the reaction conditions and serves as a source of salicylaldimine (**5**).

The structure of compound **3** was established by ^{1}H and ^{13}C NMR and IR spectroscopy and X-ray diffraction (Fig. 1). Since the crystal of compound **3** is centrosymmetric, the relative configurations of the chiral centers in molecule **3** are as follows: (*S*)-C(4a), (*R*)-C(5), (*R*)-C(10a). The extension of this new reaction of diethoxalylacetone **1** to other salicylaldehyde derivatives and the detailed study of the reaction mechanism will be published elsewhere.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer (400.13 MHz for ^{1}H and 100.6 MHz for ^{13}C) at 25 °C. The IR spectra were measured on a Bruker Vector-22 instrument in the 400—3600 cm^{-1} frequency region in Nujol mulls. The progress of the reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates (diethyl ether—petroleum ether—methanol, 2 : 1 : 0.1, as the eluent). The melting points were determined on a Boetius hot-stage microscope.

2,5-Diethoxycarbonyl-5-hydroxy-4-oxo-4,4a,5,10b-tetrahydro-1*H*-[1]benzopyrano[4,3-*b*]pyridine (3). A solution of salicylaldehyde (0.24 g, 2 mmol) in EtOH (5 mL) was added with stirring to a solution of ammonium acetate (0.092 g, 1.2 mmol) in EtOH (10 mL). The reaction mixture was stirred for 10 min. Then a solution of diethoxalylacetone **1** (0.26 g, 1 mmol) in EtOH (10 mL) was added dropwise, and the mixture was stirred at 50—55 °C for 16 h. The white crystals that precipitated were filtered off, washed with cold EtOH (2×15 mL), dried in air, and recrystallized from Pr^{i}OH. Compound **3** was obtained in a yield of 0.25 g (70%), R_f 0.45, m.p. 178—179 °C. Found (%): C, 59.83; H, 5.07; N, 3.72. $C_{18}H_{19}NO_7$. Calculated (%): C, 59.88; H, 5.26; N, 3.88. IR, ν/cm^{-1}: 743, 767, 778, 823, 835, 862, 935, 1014, 1046, 1077, 1099, 1119, 1166, 1200, 1222, 1235, 1267, 1304, 1353, 1393, 1454, 1482, 1507, 1602, 1659, 1715, 1737, 3369, 3457. ^{1}H NMR ($CDCl_3$), δ: 1.33 and 1.38 (both t, 3 H each, 2 $OCH_2C\underline{H}_3$, J = 7.0 Hz); 3.27 (d, 1 H, H(4a), J = 16.2 Hz); 4.32—4.48 (m, 4 H, 2 $OC\underline{H}_2CH_3$); 4.92 (br.s, 1 H, OH); 5.00 (d, 1 H, H(10b), J = 16.2 Hz); 5.90 (s, 1 H, H(3)); 6.21 (br.s, 1 H, NH); 6.94—7.30 (m, 4 H, H(7), H(8), H(9), H(10)). ^{13}C NMR ($CDCl_3$), δ: 14.28 (qt, $\underline{C}H_3CH_2O$, J = 149.94 Hz, J = 5.31 Hz); 14.45 (qt, $\underline{C}H_3CH_2O$, J = 153.92 Hz, J = 5.31 Hz); 48.63 (dm, C(4a) or C(10b), $J \approx$ 133.60 Hz); 49.90 (dm, C(10b) or C(4a), $J \approx$ 139.30 Hz); 63.48 (tq, $CH_3\underline{C}H_2O$, J = 149.94 Hz, J = 5.31 Hz); 63.84 (tq, $CH_3\underline{C}H_2O$, J = 153.92 Hz, J = 5.31 Hz); 93.94 (split.s, C(5)); 103.43 (dd, C(3), J = 171.16 Hz, J = 3.98 Hz); 118.50 (dd, C(7) or C(10), J = 161.88 Hz, J = 7.40 Hz); 119.66 (split.s, C(2)); 122.50 (split.d, C(8) or C(9), $J \approx$ 155.24 Hz); 124.06 (split.d, C(9) or C(8), $J \approx$ 153.91 Hz); 130.19 (dd, C(10) or C(7), J = 163.21 Hz, J = 7.96 Hz); 148.15 (s, C(6a)); 151.33 (br.s, C(10a)); 163.51 (m, C=O); 169.37 (m, C=O); 190.70 (s, C=O).

α,2-Dihydroxy-*N*-(2-hydroxybenzylidene)benzylamine (4). A solution of salicylaldehyde (0.49 g, 4 mmol) in ethanol (5 mL) was added to a solution of ammonium acetate (0.184 g, 2.4 mmol) in ethanol (20 mL). The reaction mixture was stirred for 6 h and concentrated under reduced pressure to 1/5 of the initial volume. The pale-yellow precipitate was separated and twice washed with ethanol. The yield was 0.36 g (73%), m.p. 257—259 °C. Found (%): C, 69.02; H, 5.41; N, 5.63. $C_{14}H_{13}NO_3$. Calculated (%): C, 69.15; H, 5.35; N, 5.76. IR, ν/cm^{-1}: 754, 797, 903, 992, 1019, 1043, 1150, 1239, 1275, 1392, 1492, 1592, 1628, 3048, 3253 (br.). ^{1}H NMR (acetone-d_6), δ: 6.49 (s, 1 H, C$\underline{H}$OH); 6.76—7.50 (m, 10 H, 2 C_6H_4 + 2 OH); 8.84 (s, 1 H, CH=N); 13.19 (br.s, 1 H, CHO$\underline{H}$).

Synthesis of tetrahydrobenzopyrano[4,3-*b*]pyridine (3) from imine 4. A solution of diethoxalylacetone **1** (0.26 g, 1 mmol) in ethanol (10 mL) was added to a solution of imine **4** (0.24 g, 1 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 3 h. After vacuum distillation of the major portion of the solvent, the white crystals that formed were filtered off, washed with cold ethanol (2×15 mL), dried in air, and recrystallized from Pr^{i}OH. Compound **3** was obtained in a yield of 0.15 g (42%). The melting point, R_f, and the spectroscopic characteristics of compound **3** are identical to those of the compound prepared according to the above-described procedure.

X-ray diffraction study of compound 3 was performed on an automated four-circle Enraf-Nonius CAD-4 diffractometer. Crystals of **3**, $C_{18}H_{19}NO_7$, are monoclinic. At 20 °C, a = 10.491(2) Å, b = 14.007(3) Å, c = 11.981(2) Å, β = 104.92(2)°, V = 1701(3) Å^3, Z = 4, d_{calc} = 1.41 g cm^{-3}, space group $P2_1/c$. The unit cell parameters and intensities of 7430 reflections, 1655 of which were with $I \geq 3\sigma$, were measured at 20 °C (λ(Mo-Kα) = 0.7107 Å, graphite monochromator, ω/2θ scanning technique, $\theta \leq 22.73°$). The intensities of three check reflections showed no decrease in the course of X-ray data collection. The absorption correction was ignored (μ(Mo) = 1.10 cm^{-1}). The structure was solved by direct methods using

the SIR program[3] and refined first isotropically and then anisotropically. Subsequently, the positions of all hydrogen atoms were revealed from difference electron density maps. The contributions of the hydrogen atoms to the structure amplitudes were taken into account with fixed positional and thermal parameters in the final steps of the least-squares refinement. The final reliability factors were as follows: $R = 0.048$, $R_w = 0.048$ using 1655 independent reflections with $F^2 \geq 3\sigma$. All calculations were carried out using the MolEN program package[4] on an AlphaStation 200. The molecular structure was drawn using the PLATON program.[5]

This study was financially supported by the Russian Foundation for Basic Research (Project Nos 03-03-32865 and 02-03-32280), the Charity Foundation for Support of Russian Science, and the Council on Grants of the President of the Russian Federation (Program for Support of Leading Scientific Schools of the Russian Federation, Grant NSh 2030.2003.3).

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Received May 26, 2004;
in revised form November 17, 2004