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Multi-Component Reactions of Aldehydes, Amines, and Ketones I. Synthesis and Crystal Structure Elucidation of a Novel Product of Condensation of Salicylaldehyde, 1-Methyl-4-piperidone, and Methylamine

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Summary. The condensation of salicylaldehyde, 1-methyl-4-piperidone, and methylamine has been studied as a model reaction. It was found that at a molar ratio of salicylaldehyde: 1-methyl-4-piperidone = 2:1 and an excess of methylamine the previously unknown heterocyclic compound 2-(3,6,13-trimethyl-1,2,3,4,4a,5,6,7-octahydro-7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocin-5-yl)-phenol was formed; its structure was elucidated by spectroscopic methods and X-ray analysis. A reaction pathway for this new multi-component condensation is suggested and discussed.

Keywords. Aldehydes; Amines; Ketones; Multi-component condensation; 1,2,3,4,4a,5,6,7-Octahydro-7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocine derivative; X-Ray structure determination.

Introduction

A main issue in modern synthetic organic chemistry dealing with the preparation of natural products, pharmaceuticals, diagnostics, agrochemicals, and other important materials is the improvement of efficiency, the avoidance of toxic reagents, the reduction of waste, and the responsible treatment of resources. One of the ways to fulfill these goals is the development and use of multi-component reactions which consist of several simultaneous bond-forming reactions and allow the highly efficient synthesis of complex molecules starting from simple substrates. Multi-component reactions, which can produce a diversity of compounds, provide one of the most efficient methods for the combinatorial synthesis of compound sortiments [1]. A general survey of the literature on multi-component reactions of aldehydes, amines, and ketones reveals that when salicylaldehyde is used, complex mixtures of products are formed the structure of which is determined to a considerable degree by the nature of the CH-active components and the reaction conditions

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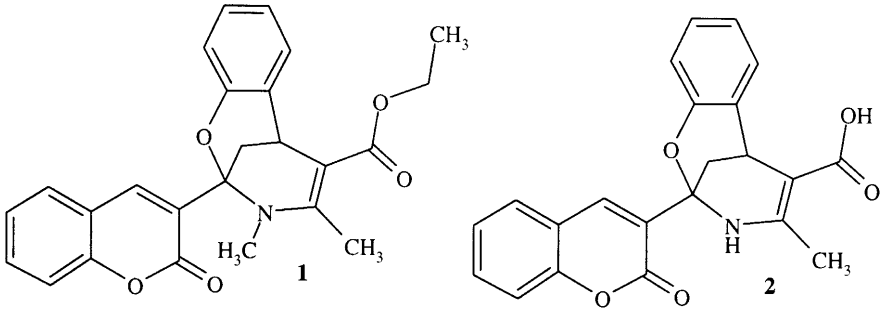
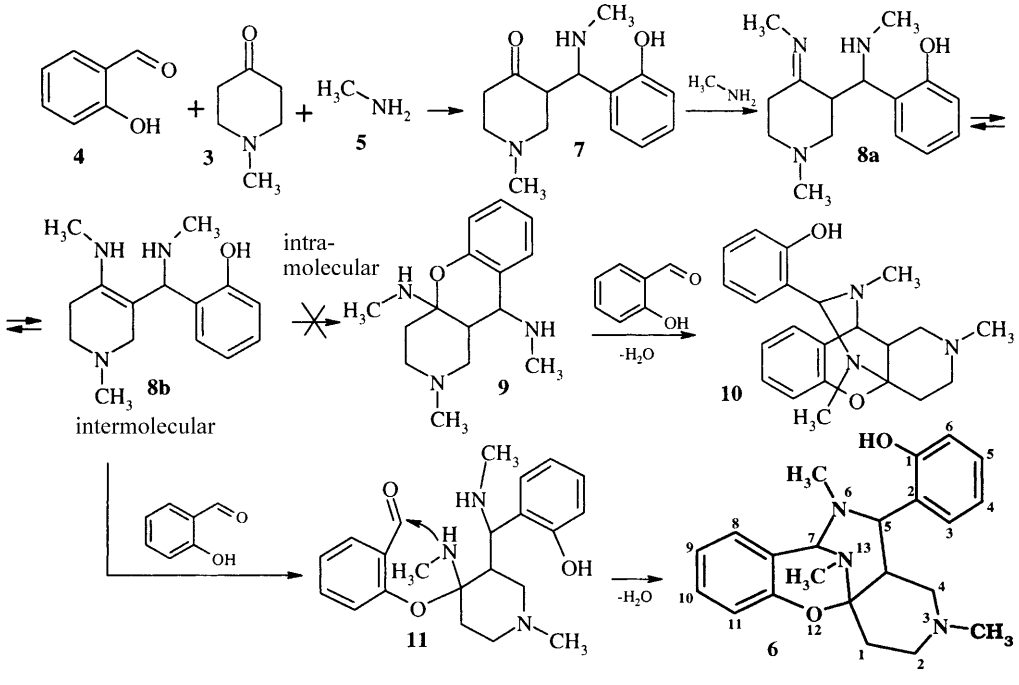


Fig. 1. Condensation products of salicylaldehyde with acetoacetic ester and methylamine (**1**) or ammonia (**2**)

[2–5]. For example, ethyl 3,4-dimethyl-2-(2-oxo-2*H*-chromen-3-yl)-3,6-dihydro-2*H*-2,6-methano-1,3-benzoxazocine-5-carboxylate (**1**, Fig. 1) was isolated as the major component (62%) from the mixture of products from the condensation of salicylaldehyde with acetoacetic ester and methylamine, and its molecular structure was established by X-ray crystallography [5]. When ammonia was used as an amine component in analogous reaction, 4-methyl-2-(2-oxo-2*H*-chromen-3-yl)-3,6-dihydro-2*H*-2,6-methano-1,3-benzoxazocine-5-carboxylic acid (**2**), structurally related to compound **1**, was isolated in only 19% yield as the major product [4].

Within our research on the multi-component synthesis of new polyheterocyclic derivatives [6, 7], our present investigation on multi-component reactions of aldehydes, amines, and ketones is focused on the possibility of utilization of salicylaldehyde (**4**), methylamine (**5**), and a cyclic saturated ketone, 1-methyl-4-piperidone



Scheme 1. Mechanistic rationalization for the formation of **6**

(**3**). The study describes the synthesis and structure determination of the new polyheterocyclic compound 2-(3,6,13-trimethyl-1,2,3,4,4a,5,6,7-octahydro-7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocin-5-yl)phenol (**6**, cf. Scheme 1) comprising the previously unknown 7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocine fragment. The following feature is noteworthy in the reaction: salicylaldehyde, methylamine, and 1-methyl-4-piperidone react regio- and chemoselectively in a 2:2:1 molar ratio, thus comprising a five-component reaction.

Results and Discussion

Synthetic aspects

It was found that manipulation of the stoichiometry of salicylaldehyde (**4**) and ketone **3** (2:1), the sequence of reagent addition, using an aqueous solution of methylamine (**5**) both as a reagent (2 equivalents) and as a co-solvent, and performing the reaction at room temperature in ethanol resulted in the formation of compound **6** containing a novel polycyclic 7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocine system.

A mechanistic rationalization as outlined in Scheme 1 may be invoked for the formation of **6**. It is conceivable that three-component *Mannich*-type reaction of **4**, **3**, and **5** leads to the formation of β-aminoketone **7** followed by its further reaction with an excess of methylamine to form intermediates **8a**/**8b**. By reacting with the second molecule of salicylaldehyde, the intermediates **8a**,**b** take an intermolecular pathway (rather than an intramolecular one; cf. Scheme 1, **8a**,**b** $\rightarrow$ **9** $\rightarrow$ **10**), thus forming intermediate **11**, which undergoes a final ring closure to give the bridged 1,2,3,4,4a,5,6,7-octahydro-7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocine product **6**.

It may be pointed out that key steps of the mechanistic postulate outlined above are reminiscent of the steps involved in the reaction of aromatic aldehydes with azomethines to yield azabicyclo[3.3.1]nonane derivatives with different heteroatoms in the polycycle [8].

Structure elucidation

The title compound **6** was fully characterized by ^{1}H and ^{13}C NMR, IR, UV/Vis, EIMS, and elemental analysis data as well as by its melting point. The IR spectrum of **6** showed eight characteristic absorption bands of strong to medium intensity in the region of 3066–2769 cm^{-1} corresponding to valence C–H vibrations and two bands at 1606 (w) and 1584 (m) cm^{-1} due to valence C=C vibrations of benzene rings as well as a strong absorption characteristic of a hydroxyl group ($\sim$ 3400 cm^{-1}). The ^{13}C NMR spectra revealed the presence of 22 carbons: three methyls attached to nitrogen atoms, three methylenes, three methines, four aromatic and one non-aromatic quaternary carbons, and eight protonated aromatic carbons. The ^{1}H NMR spectrum was characterized by the presence of overlapping signals for the protons of the ABCD systems of the aromatic fragments in the 6.60–7.21 ppm region. It also showed the appearance of three N–CH_3 singlets at 2.11 (N-3 and N-6) and 2.28 (N-13) ppm as well as the presence of six methylene protons in the 1.93–2.79 ppm region due to the piperidine ring and three methine protons: a singlet at 4.51 ppm for

the C-7 proton, a broad doublet at 2.68 ppm for the C-5 proton, and a signal at 1.77 ppm for the C-4a proton. The broad singlet at 10.38 ppm is due to an exchangeable proton, again suggesting the presence of a hydroxyl group.

Crystal structure

Analyzing the data from the Cambridge Crystallographic Data Centre, we discovered that no research has been done on compounds comprising the 1,2,3,4,4a,5,6,7-octahydro-7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocine fragment. Therefore, and for additional confirmation of the structure of **6**, the conformation of the heterocyclic fragments, and the orientation of the substituents, we undertook an X-ray crystallographic study of the polycycle.

The relevant crystallographic data and details on the structure refinement are given in the experimental part. The crystal structure together with the atom labeling scheme is depicted in Fig. 2 (the numbering of atoms does not conform to IUPAC recommendations).

6 may be visualized consisting of the following fragments (Fig. 2): a saturated bicycle with fused chairs conformation (atoms N_1, N_2, N_3, C_1, C_2, C_9, C_{10}, C_{17}, C_{18}, C_{19}; weighted root mean square (*RMS*) deviation of non-H atoms from least-squares plane: 0.24 Å; P_1), two aromatic rings (P_2; atoms O_1, C_3, C_4, C_5, C_6, C_7, C_8; *RMS* deviation: 0.02 Å), and P_3 (atoms C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}; *RMS* deviation: 0.006 Å). The angles between these fragments are as follows: $(P_1, P_2) = 87.7(2)^\circ$, $(P_1, P_3) = 76.3(1)^\circ$. The aromatic rings are firmly set relative to a saturated bicyclic fragment because the P_2 fragment is condensed with the 3,4-dihydro-2*H*-1,3-oxazine portion of the molecule and the P_3 fragment is additionally stabilized by an intramolecular hydrogen bond linking the hydroxyl group to an opposing nitrogen ($H_2 \cdots N_2$: 1.99(1) Å, $O_2 \cdots N_2$: 2.679(2) Å, O_3–H_2–N_2 angle: 141(2)°). Comparison of the structure of compound **6** with benzoxazocinecarboxylate (**1**, [5]) shows

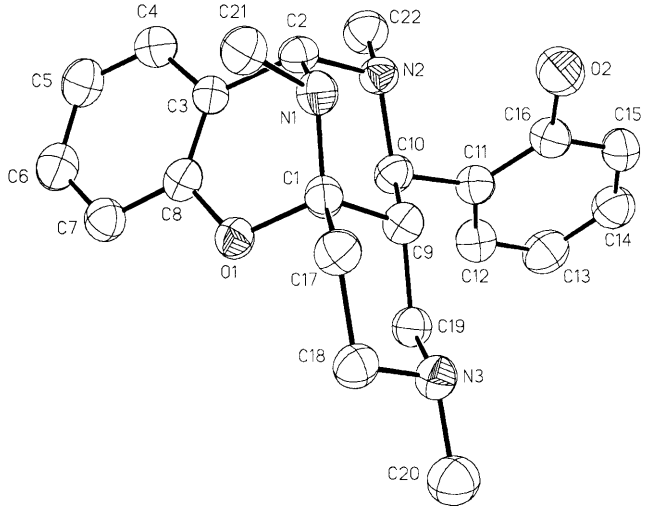


Fig. 2. Crystal structure of **6** showing non-hydrogen atoms and atom labeling scheme; thermal ellipsoids are drawn at 50% probability level

the most important differences: all nitrogen atoms in **6** are in tetrahedral conformation with unshared electron pairs, and all C–N–C angles are in an 109–117° interval. It is notable that the maximum value of C–N–C angle is found for the N_1 atom, which is bridging the 2-oxa-6,9-diazabicyclo[3.3.1]non-3-ene fragment.

Moreover, in compound **6** three pairs of electrons on nitrogen atoms are forming a highly specific three-dimensional cavity, thus opening the possibility for the compound to be selectively bound to receptors or to serve as a host molecule to remove one specific molecule or ion from a mixture.

In conclusion, the multi-component reaction described herein provides a simple and direct entry with minimal synthetic efforts into an interesting novel 1,2,3,4,4a,5,6,7-octahydro-7,12a-epiminopyrido[4,3-*b*][1,5]benzoxazocine polyheterocyclic derivative that may be of value in medicinal chemistry. The present studies might open a new avenue for the synthesis a variety of heterocyclic systems of biological significance. Further work to explore the scope and mechanistic implications of the reaction is in progress.

Experimental

X-Ray analysis

Data were collected using a Siemens P3/PC four-circle autodiffractometer (MoK_α radiation, $\lambda = 0.71073$ Å, graphite monochromator). Orthorhombic crystals of **6** were obtained from EtOH; $C_{22}H_{27}N_3O_2$, $M_r = 364.47$, space group *Fdd*2, $a = 30.803(13)$, $b = 37.024(13)$, $c = 6.454(2)$ Å, $V = 7360(5)$ Å^3, $Z = 16$, $D_c = 1.319\,g \cdot cm^{-3}$, $F_{000} = 3136$, $\mu(MoK_\alpha) = 0.086\,mm^{-1}$; $2\theta/\theta$-scans within $5° \leq 2\theta \leq 60°$, reflections collected: 2793, independent reflections: 2679 ($R_{int} = 0.0233$), observed reflections with $I > 2\sigma(I)$: 1339. The structure was solved and refined using the SHELX-97 program package [9]. The SHELXTL PLUS program was used for graphics purposes. Final *R* indices (observed data): $R = 0.0316$, $wR_2 = 0.0452$; *R* indices (all data): $R = 0.0453$, $wR_2 = 0.0462$.

Crystallographic data, including atomic coordinates, equivalent isotropic displacement parameters, bond lengths, and bond angles of **6** have been deposited at the Cambridge Crystallographic Data Centre (CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; www: http://www.ccdc.cam.ac.uk; e-mail: deposit@ccdc.cam.ac.uk) under No. CCDC 162339; copies of the data can be obtained on application to CCDC.

Synthesis

The melting point was measured with a Büchi melting point apparatus and is uncorrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). Elemental analysis of **6** afforded results which were within ±0.3% of the theoretical value. ^{1}H and ^{13}C NMR spectra were recorded on a Varian WXR-400 spectrometer in $CDCl_3$ or *DMSO*-d_6 + CCl_4 using *TMS* as an internal standard. The mass spectrum was obtained with a Finnigan MAT-4615B spectrometer at an ionization potential of 70 eV. The infrared spectrum was recorded in KBr pellets on a computer-controlled Specord M-80 spectrometer. The UV/Vis spectrum was registered in EtOH on a computer-controlled Specord M-40 instrument.

3,6,13-Trimethyl-1,2,3,4,4a,5,6,7-octahydro-7-12a-epiminopyrido[4,3-b][1,5] benzoxazocin-5-yl)-phenol (**6**; $C_{22}H_{27}N_3O_2$)

To a solution of salicylaldehyde (**4**; 1.22 g, 10 mmol) in 10 cm^3 of EtOH, 1-methyl-4-piperidone (**3**; 1.13 g, 10 mmol) and methylamine (**5**; 8 cm^3, 25% aqueous solution) were added dropwise. After the

mixture was shaken for 24 h at ambient temperature, the second equivalent of salicylaldehyde (1.22 g, 10 mmol) was added, and shaking was continued for *ca*. 2 days. The precipitate formed (colorless needles) was filtered off, washed several times with cold EtOH, and recrystallized from EtOH to yield 1.66 g (45%) of **6**.

M.p.: 197.5–199°C (dec.); IR (KBr): $\nu = 3400$ (br, OH), 3066–2769 (C–H), 1606 (C=C), 1584 (C=C) cm^{-1}; UV/Vis (EtOH): λ_{max} ($\log\varepsilon$) = 203 (4.46), 276 (3.72), 283 (3.68) nm; MS (EI): $m/z = 365$ ($M^{+\cdot}$); ^{1}H NMR (400 MHz, *DMSO*-d_6 + CCl_4): $\delta = 10.38$ (br s, 1H, OH), 7.21 (ddd, $J = 8.1$, 8.1, 1.5 Hz, 1H, H-10), 7.06 (m, 1H, H-5′), 7.03 (dd, $J = 7.3$, 1.5 Hz, 1H, H-8), 6.83 (dd, $J = 8.1$, 7.3 Hz, 1H, H-9), 6.81 (d, $J = 8.1$ Hz, 1H, H-3′), 6.69 (d, $J = 8.1$ Hz, 1H, H-11), 6.60 (d, $J = 4.5$ Hz, 2H, H-4′ and H-6′), 4.51 (s, 1H, H-7), 2.79 (d, $J = 11.8$ Hz, 1H, H-4), 2.68 (br d, $J \approx 11.0$ Hz, 1H, H-5), 2.44 (ddd, $J = 11.8$, 11.8, 1.5 Hz, 1H, H-2), 2.28 (s, 3H, N–CH_3), 2.28 (m, 1H, H-2), 2.11 (2s, 6H, 2 N–CH_3), 2.03–1.93 (m, 3H, H-4, 2 H-1), 1.77 (ddd, $J = 12.5$, 12.5, 4.4 Hz, 1H, H-4a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.84$ (CH_2), 34.70 (N–CH_3), 38.80 (CH), 45.82 (N–CH_3), 46.51 (N–CH_3), 50.96 (CH_2), 53.72 (CH_2), 62.54 (CH), 76.37 (CH), 87.26 (C), 113.46 (C), 115.05 (CH), 116.78 (CH), 118.48 (CH), 118.98 (CH), 122.48 (CH), 128.81 (CH), 129.60 (CH), 129.70 (CH), 129.72 (CH), 154.65 (C), 156.76 (C–OH) ppm.

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