Abstract

The synthesis and crystal structures of 1-(5-methyl-1H-indol-6-yl)ethan-1-one (7), C\textsubscript{11}H\textsubscript{11}NO, and 1-{[3-[(dimethylamino)methyl]-5-methyl-1H-indol-6-yl]ethan-1-one (8), C\textsubscript{14}H\textsubscript{18}N\textsubscript{2}O, are reported. The synthesis is based on the Diels–Alder cycloaddition of a substituted 2H-pyran-2-one derivative, followed by an acid-catalyzed cyclization and concomitant deprotection (the last two steps were carried out as a one-pot domino process) yielding substituted indole 7, which was further derivatized via Mannich reaction to the gramine derivative 8. Both structures 7 and 8 were determined on the basis of IR, \(^1\)H NMR and mass spectroscopy, as well as by the elemental analysis and melting point determination. According to the single-crystal X-Ray diffraction analysis, the structure 7 has a single unique molecule in the asymmetric unit whereas the structure 8 contains four unique molecules in the asymmetric unit. Molecules 7 are linked via N–H···O hydrogen bonds between the secondary amine group and carbonyl moiety of the acetyl group of adjacent molecules, whereas molecules 8 are linked via N–H···N hydrogen bonds between the secondary and tertiary amine groups of adjacent molecules. Both structures are further stabilized by weak C–H···O, C–H···π and π···π interactions.

Keywords: Indoles, Gramines, Crystal structure, Hydrogen bonds, C–H···π interaction, π···π interaction

1. Introduction

Gramine, 3-((N,N-dimethylaminomethyl)indole, is a simple indole derivative with important functions in the plant world. The essential amino acid tryptophan and its derivatives are biosynthesized from gramine. Gramine was isolated for the first time from the giant cane (Arundo donax), has a role as an alkaloid in barley (Hordeum vulgare) and is of importance in many other plants.\(^1\)\(^,\)\(^,\)\(^2\)

Furthermore, gramine represents a valuable precursor for further derivatizations towards other targets, for example for the preparation of 1,3-disubstituted β-carboline cores by the reaction of gramines with α-(alkyldenamino) nitrites in the presence of tributylphosphine\(^3\) and for the synthesis of the 2-prenyl tryptophan core of the tryprostatins A and B.\(^4\) For the quaternary gramine derivatives it was shown that they can be used as suitable sources of the 3-methylindole fragment in various diastereoselective alkylations, as recently described by Reinfelds et al.\(^5\) Gramine has also found utility as a part of N-substituted phosphines that were used as ligands in Suzuki–Miyaura coupling reactions of aryl halogenides, conducted at room temperature in a suitable ionic liquid, thus achieving increased yields in comparison with standard ligands containing amine groups.\(^6\)

Gramine derivatives also possess various biological activities; recently it was found that a gramine derivative (i.e. N-[(1H-indol-3-yl)(pyridin-2-yl)methyl]benzo[d] thiazol-2-amine) having a pyridine and a benzothiazole moiety in its structure selectively inhibits human enterovirus 71 (EV71), a known agent of hand, foot and mouth disease in children associated with severe neurological problems, including death; on the other hand, the parent gramine does not inhibit EV71.\(^7\)

The synthetic approach used toward gramine and its derivatives is most often Mannich reaction\(^8\) of the corresponding indoles: the position 3 of the indole framework (being the most nucleophilic) attacks an intermediate formed from formaldehyde and a secondary amine. The reaction can be accelerated by the application of suitable additives, Dai \textit{et al.}\(^9\) have successfully applied zinc chloride among various other options. Such synthesis generally takes place at room temperature and is finished in a relatively short time (typically 90 min).

The scope of such reaction can be further broadened by the application of various aromatic aldehydes (instead...
of formaldehyde) and various heterocyclic compounds (instead of secondary amines) as demonstrated by Ke and co-workers. During their synthetic protocol there was no need to use any catalysts or solvents.

Analouges of gramine can be also prepared by the reaction between substituted 1,4-piperazines, 1H-indole and formaldehyde. With such an approach, Köksal Akkoç et al. were able to synthesize compounds with increased cytotoxicity against human carcinoma cells compared with the other commercially available agents, such as the standard drug 5-fluorouracil. Herein we present a straightforward approach towards a substituted gramine based on a Diels–Alder reaction between a corresponding 2H-pyran-2-one (acting as a diene) and a suitable dienophile (i.e., (Z)-1-methoxybut-1-en-3-yne) yielding a cycloadduct that is in the next step transformed into the desired indole, which is further derivatized via Mannich reaction to the substituted gramine.

2. Experimental

2.1. Materials and Measurements

Melting points were determined on a micro hot stage apparatus and are uncorrected. 1H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer at 29 °C and 300 MHz using MeSi as an internal standard. IR spectra were obtained with a Bio-Rad FTS 3000MX as KBr pellets. MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica-gel TLC-cards. All reagents and solvents were used as received from commercial suppliers.

Starting N-{5-acetyl-2-[(Z)-2-methoxyethenyl]-4-methylphenyl}benzamide (5) was prepared via Diels–Alder cycloaddition of (Z)-1-methoxybut-1-en-3-yne (4) on N-(5-acetyl-6-methyl-2-oxo-2H-pyran-3-yl)benzamide (3) as described previously. Commercially 4 is available as a 50% methanol solution and has to be distilled under vacuum prior to use; the distillation of a mixture of 7 mL of commercial 4 and 5 mL of isopentanol at 360 mbar starts at 45 °C: the first fraction is methanol, the second (distilling at 90 °C) is pure 4 (a pale yellow liquid with a characteristic odour). Purified 4 has a limited shelf life even when stored in dark at –20 °C.

Synthesis of 1-(5-Methyl-1H-indol-6-yl)ethan-1-one (7)

To a mixture of N-{5-acetyl-2-[(Z)-2-methoxyethenyl]-4-methylphenyl}benzamide (5) (0.309 g, 1 mmol) in acetonitrile (10 mL) hydrochloric acid (5%, 0.25 mL) was added. The mixture was stirred for 18 h at room temperature, thereafter neutralized with NaOH (0.113 g, 2.825 mmol dissolved in 4 mL of water). The resulting mixture was heated under reflux for 1 h, cooled to room temper-
subsequently treated as riding atoms in geometrically idealized positions, with C–H = 0.93 (aromatic), 0.97 (methylene) or 0.96 Å (CH₃), N–H = 0.86 Å and with \( U_{iso}(H) = k \cdot U_{eq}(C \text{ or N}) \), where \( k = 1.5 \) for methyl groups, which were permitted to rotate but not to tilt, and 1.2 for all other H atoms. Crystallographic data are listed in Table 1.

**Table 2.** Hydrogen bond and CH···π geometry of 7 and 8 (Å and °).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1–H1···O1</td>
<td>0.86</td>
<td>2.04</td>
<td>2.893(3)</td>
<td>174.2</td>
<td>(-x + \frac{1}{2}, y + 1, z + \frac{1}{2})</td>
</tr>
<tr>
<td>C11–H11C···O1</td>
<td>0.96</td>
<td>2.56</td>
<td>3.513(4)</td>
<td>171.2</td>
<td>(x, y + 1, z)</td>
</tr>
<tr>
<td>C9–H9A···Cg2</td>
<td>0.96</td>
<td>2.90</td>
<td>3.688(3)</td>
<td>140</td>
<td>(x, y - 1, z)</td>
</tr>
<tr>
<td><strong>8</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1–H1···N4</td>
<td>0.86</td>
<td>2.10</td>
<td>2.936(4)</td>
<td>165.1</td>
<td>(x - 1, y, z)</td>
</tr>
<tr>
<td>N3–H3···N2</td>
<td>0.86</td>
<td>2.15</td>
<td>2.983(4)</td>
<td>163.7</td>
<td>(x, y, z)</td>
</tr>
<tr>
<td>N5–H5···N8</td>
<td>0.86</td>
<td>2.11</td>
<td>2.951(4)</td>
<td>164.6</td>
<td>(x, y, z)</td>
</tr>
<tr>
<td>N7–H7A···N6</td>
<td>0.86</td>
<td>2.14</td>
<td>2.978(4)</td>
<td>164.4</td>
<td>(x + 1, y, z)</td>
</tr>
<tr>
<td>C38–H38A···O1</td>
<td>0.96</td>
<td>2.58</td>
<td>3.392(5)</td>
<td>146.2</td>
<td>(-x, y - \frac{1}{2}, -z + 1)</td>
</tr>
<tr>
<td>C42–H42A···O4</td>
<td>0.96</td>
<td>2.51</td>
<td>3.407(5)</td>
<td>154.8</td>
<td>(-x + 1, y + \frac{1}{2}, -z + 1)</td>
</tr>
<tr>
<td>C56–H56B···O1</td>
<td>0.96</td>
<td>2.51</td>
<td>3.358(6)</td>
<td>146.6</td>
<td>(-x + 1, y - \frac{1}{2}, -z + 1)</td>
</tr>
<tr>
<td>C1–H1A···Cg5</td>
<td>0.93</td>
<td>2.90</td>
<td>3.743(4)</td>
<td>151</td>
<td>(x - 1, y, z)</td>
</tr>
<tr>
<td>C15–H15···Cg2</td>
<td>0.93</td>
<td>2.88</td>
<td>3.715(4)</td>
<td>150</td>
<td>(x, y, z)</td>
</tr>
<tr>
<td>C29–H29···Cg11</td>
<td>0.93</td>
<td>2.81</td>
<td>3.668(4)</td>
<td>154</td>
<td>(x, y, z)</td>
</tr>
<tr>
<td>C43–H43···Cg8</td>
<td>0.93</td>
<td>2.82</td>
<td>3.680(4)</td>
<td>154</td>
<td>(x + 1, y, z)</td>
</tr>
</tbody>
</table>

Cg2, Cg5, Cg8 and Cg11 are C3–C8, C17–C22, C31–C36 and C45–C50 ring centroids.
3. Results and Discussion

3.1. Synthesis

The synthetic approach presented herein is based on our previous experience with Diels–Alder reactions of 2H-pyran-2-one derivatives (used as dienes) with various dienophiles. Here we applied \((\text{Z})\)-1-methoxybut-1-en-3-yne (4) as the dienophile cycloadding on 2H-pyran-2-one derivative 3 yielding a crucial intermediate 5, a substituted \(N\{2-[(\text{Z})\text{-2-methoxyethenyl}]\text{phenyl}\}\) benzamide (Scheme 1). This intermediate 5 has a strategically positioned methoxy group bound to the ethenyl fragment being in an \textit{ortho} position to the benzamido group, therefore enabling a straightforward cyclization towards the indole ring \((\text{i.e.} 6)\) already under mildly acidic conditions, as described previously. However, an indole 6 obtained in such a way still contains an \(N\)-benzoyl protection group that needs to be removed to yield the indole 7. One possibility to achieve this could be the application of aqueous NaOH in a mixture of water and acetonitrile with gentle heating.

On the other hand, our strategy was to combine both steps described above, \(\text{i.e.}\) the cyclization (5 → 6) and the removal of the \(N\)-benzoyl group (6 → 7) into a single step. Even though the first step needs acidic conditions and the second takes place in an alkaline solution, with a suitable choice of reaction parameters we were able to implement both transformations as a one-pot domino procedure. Primary cycloadduct 5, \(N\{2-[(\text{Z})\text{-2-methoxyethenyl}]\text{phenyl}\}\) benzamide derivative, was thus dissolved in acetonitrile, aqueous HCl was added and the mixture was stirred at room temperature; thereafter enough aqueous NaOH was added to neutralize the excess HCl and to increase the pH to an appropriately alkaline value (pH approx. 10) for the deprotection to occur (upon gentle heating). Such approach to 7 shortens the synthetic pathway towards 7 and increases its final yield (86% yield after a one-pot procedure 5 → 7 vs. 71% combined yield over two separate steps).

Resonances in the \(^1\text{H}\) NMR spectrum of the indole 7 are in agreement with those expected: both methyl groups were observed as singlets (at \(\delta\) 2.636 and 2.639 ppm), together with the four aromatic protons (in the range \(\delta\) 6.50–7.84 ppm) and the amino proton as a singlet at \(\delta\) 8.38 ppm. In the IR spectrum of 7 bands correspond to the NH group at 3318 cm \(^{-1}\) and carbonyl group at 1642 cm \(^{-1}\).

The starting indole 7 was thereafter derivatized under standard Mannich reaction conditions (with formaldehyde and dimethylamine in ethanol as the solvent and with zinc chloride as the additive) to form the 6-acetyl-5-methylgramine derivative 8.

For the gramine derivative 8 in the \(^1\text{H}\) NMR spectrum appropriate signals were observed: all four methyl groups as singlets (dimethylamino group at \(\delta\) 2.29 ppm and the remaining two methyl groups at \(\delta\) 2.59 and 2.62 ppm), the methylene group as a singlet at \(\delta\) 3.61 ppm, the three aromatic protons (in the range \(\delta\) 7.22–7.73 ppm) and the amino proton as a singlet at \(\delta\) 8.88 ppm. In the IR spectrum of 8 bands correspond to the NH group at 3085 cm \(^{-1}\) and carbonyl group at 1669 cm \(^{-1}\).

2H-Pyran-2-one derivatives 3, necessary for this synthetic approach, can be straightforwardly accessed via a one-pot synthesis starting from the simple commercially available precursors: a carbonyl compound 1 containing an activated CH\(_2\) group (acetylacetone), a C\(_1\)-synthon such as \(N,N\)-dimethylformamide dimethyl acetal (DMFMA) and hippuric acid (2) as an \(N\)-acylglycine derivative as previously described by Kepe and Kočevar. The synthesis takes place under heating (approx. 90 °C) in

![Scheme 1](image-url)
acetic anhydride (or in a mixture with acetic acid) as the solvent yielding desired substituted 3-benzoylamino-2H-pyran-2-ones 3.

3.2. Crystal Structures

The structure of 1-(5-methyl-1H-indol-6-yl)ethan-1-one, 7, has a single unique molecule in the asymmetric unit (Figure 1) whereas the structure of 1-[3-[(dimethylamino)methyl]-5-methyl-1H-indol-6-yl]ethan-1-one, 8, contains four unique molecules in the asymmetric unit (Figure 2). All the bond lengths of compounds 7 and 8 are within normal ranges. In both compounds 7 and 8 the central indole ring is planar. The maximum deviation from the mean plane described by the ring atoms is $+0.014(2)$ and $-0.014(2)$ Å for the C8 and C6 atoms in 7 and in the range $+0.019(4)$ to $-0.019(3)$ Å for four unique molecules in 8. These values are similar to those observed in the analogous series of benzotriazoles. The mean plane through the methylcarbonyl group (C6/C10/O1/C11) in 7 is inclined to the indole ring by 13.60(15)° while these angles in four unique molecules of 8 are 35.8(2)°, 36.3(2)°, 28.6(2)° and 32.59(19)°. Such angles in [1-methyl-2-(4-methylphenyl)-1H-indole-4,6-diyli]bis(phenylmethanone) are 22.46 and 32.54°, while in N-[2-(6-benzoyl-5-methyl-1-(methylsulfonyl)-1H-indol-2-yl]-4-methylphenyl]methanesulfonamide this angle is much larger being 48.53°. The dimethylamino group in 8 is just out of the plane of its attached indole ring as indicated by the C1–C2–C9–N2, C15–C16–C23–N4, C29–C30–C37–N6 and C43–C44–C51–N8 torsion angles of four crystallographically independent molecules in the range 95.0(4)–96.9(4)°. The indole ring is conformationally rigid, but the dimethylamino part of the molecule has conformational variation as seen from the different torsion angles of crystallographically independent molecules in the crystal structure. In N,N-dimethyl-1H-indole-3-methanamine, 1-[1-(5-bromo-1H-indol-3-yl)ethyl]azepane-2-one monohydrate, [1-(di-ri-butylphosphino)-1H-indol-3-yl]-N,N-trimethylmethanaminium iodide and N-[5-bromo-1H-indol-3-yl)methyl]-N,N-dimethylammonium...
nitrate\textsuperscript{33} equivalent torsion angles were found to be similar, with values between 92.42° and 103.70°.

In the crystal structure molecules of 7 are linked via N1–H1⋯O1(−x + ½, y + 1, z + ½) hydrogen bonding between the NH group of one molecule and carbonyl oxygen of the acetyl moiety of the adjacent molecule into an infinite zig-zag chain generating the graph set motif C(7)\textsuperscript{34} (Table 2, Figure 3). These chains are cross-linked into sheets by weak C11–H11C⋯O1(x, y + 1, z) hydrogen bonding between the hydrogen atom of the acetyl moiety of one molecule and carbonyl oxygen of the other molecule generating the graph set motif C(4). Furthermore, this 2D structure in 7 is stabilized by additional π⋯π interactions between the five membered pyrrole ring N1/C1–C3/C8 (centroid Cg1) and the six membered C3–C8 ring (centroid Cg2) of the other molecule, with a Cg1⋯Cg2(x, y + 1, z) centroid-to-centroid distance of 4.3536(16) Å, a dihedral angle between the rings of 0.91(14)°, a perpendicular distance from the centroid Cg1 to the plane of the other ring of 3.5530(12) Å and the angle between the intercentroid vector and the normal to the second ring of 35.30° (Figure 4). According to Janiak,\textsuperscript{35} this interaction can be regarded as medium-to-weak, since strong interactions exhibit rather short centroid-to-centroid contacts (Cg⋯Cg < 3.8 Å), small slip angles (< 25°) and small vertical displacements (< 1.5 Å), which translate into a sizeable overlap of the aromatic planes. In comparison, medium-to-weak interactions exhibit rather long centroid-to-centroid distances (> 4.0 Å) together with large slip angles (> 30°) and large vertical displacements (> 2.0 Å).\textsuperscript{35–37} Additional weak C–H⋯π interactions between C9–H9A⋯Cg2(x, y + 1, z) with hydrogen-to-centroid distance 3.688(3) Å also stabilize the structure.

In the crystal structure 8 four unique molecules are linked via N–H⋯N hydrogen bonding between the indole NH group of one molecule and the tertiary nitrogen atom of the dimethylamino group of the adjacent molecule into infinite zig-zag chains generating the graph set motif C(6). In each zig-zag chain two out of four unique molecules are involved. Chains are stabilized by weak C–H⋯π interactions between the CH group of the pyrrole moiety

---

Kukuljan et al.: *Synthesis and Structural Evaluation* ...
of one molecule and a six membered aromatic ring of the adjacent molecule (Table 2, Figure 5). Chains are cross-linked by weak C42–H42A···O4(−x + 1, y + ½, −z + 1) and C56–H56B···O1(−x + 1, y − ½, −z + 1) hydrogen bonding between methyl group of the acetyl moiety of one molecule and the carbonyl oxygen of the adjacent molecule together with weak C38–H38A···O1(−x, y − ½, −z + 1) hydrogen bonding between one methyl group of the dimethylamino moiety of one molecule and the carbonyl oxygen of the adjacent molecule (Table 2, Figure 6). In addition, supramolecular structure 8 is stabilized by medium strong π···π interactions between five membered pyrrole ring (Cg1, Cg4, Cg7 and Cg10) of one molecule and a six membered ring (Cg2, Cg5, Cg8 and Cg11) of the other molecule with an average centroid-to-centroid distance of 3.91 Å (Figure 7). For other data regarding π···π interactions, see Table 3.

Figure 5. Formation of two chains in 8 by four unique molecules (color code: blue, green, red, yellow) generated by N1–H1···N4, N3–H3···N2, N5–H5···N8 and N7–H7A···N6 hydrogen bonding (blue dashed lines) and C–H···π interactions (black dashed lines). Hydrogen atoms not involved in the motif shown have been omitted for clarity.

Figure 6. The arrangement of molecules of 8 formed by C42–H42A···O4, C56–H56B···O1 and C38–H38A···O1 interactions (dashed lines). Hydrogen atoms not involved in the motif shown have been omitted for clarity.

Figure 7. The formation of π···π interactions in 8 (dashed lines). Hydrogen atoms have been omitted for clarity.
CgI···CgJ, α, β and CgI-Perp are, respectively, the centroid-to-centroid distance between rings I and J (Å), the inter-ring dihedral angle (°), slip angle (°), and the perpendicular distance of CgI from ring J (Å). Ring centroids: Cg1 (N1/C1–C3/C8), Cg2 (C3–C8), Cg4 (N3/C15–C17/C22), Cg5 (C17–C22), Cg7 (N5/C29–C31/C36), Cg8 (C31–C36), Cg10 (N7/C43–C45/C50) and Cg11 (C45–C50).

### 4. Conclusion

With the Diels–Alder reaction between a substituted 2H-pyran-2-one and (Z)-1-methoxybut-1-en-3-yne as the dienophile we have prepared a cycloadduct that was in the next, one-pot domino process cyclized and deprotected into the desired 5-methyl-6-acetyl substituted indole and further derivatized via Mannich reaction to the 5-methyl-6-acetylgamine. Single-crystal X-ray diffraction analysis of both compounds provided a valuable insight into their molecular structures as well as the mode of packing and crystal architecture showing that in the indole derivative the molecules are linked via N–H···O hydrogen bonds between the secondary amine group and carbonyl moiety of the acetyl group of adjacent molecules, whereas the molecules of gamine are linked via N–H···N hydrogen bonds between the secondary and tertiary amine groups of adjacent molecules. In both structures weak C–H···O, C–H···π and π···π interactions were also observed.

### 5. Supplementary Material

Crystallographic data of 1 and 2 were deposited in the Cambridge Crystallographic Data Center under the number CCDC 1503990–1503991. CIF files containing complete information on the studied structures may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, fax +44-1223-336033; e-mail: data_request@ccdc.cam.ac.uk or from the following web site: www.ccdc.cam.ac.uk/data_request/cif.

### 6. Acknowledgement

The authors thank the Ministry of Education, Science and Sport of the Republic of Slovenia and the Slovenian Research Agency for financial support (grant Nos. P1-0230-0103 and P1-0230-0175). This work was also partially supported with infrastructure of the EN-FIST, Center of Excellence, Ljubljana, Slovenia.

### 7. References


Kukuljan et al.: Synthesis and Structural Evaluation ...
Kukuljan et al.: Synthesis and Structural Evaluation ...