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# Synthesis of Naturally Occurring Pyrazine and Imidazole Alkaloids from *Botryllus Leachi*[#]

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**Abstract.** The synthesis of the naturally occurring and biologically active alkaloids **1** and **2**, first isolated from the red ascidian *Botryllus leachi* by *Duran* et al. [1], is described and the structure proposed for *Botryllazine B* (**1**) is confirmed. The analytical data for 2-(*p*-hydroxybenzoyl)-4-(*p*-hydroxyphenyl)imidazole (**2**) are discussed and compared with the literature. With special emphasis of $^1$H NMR data the tautomerism of aroylimidazolemethanones is described.

**Keywords.** Pyrazine and imidazole alkaloids; Annular tautomers; *Botryllus leachi*; Biologically active compounds.

## Introduction

The pyrazine and imidazole derivatives **1** and **2**, the synthesis of which was studied in the following, belong to a class of naturally occurring alkaloids which were first isolated from the red ascidian *Botryllus leachi* by *Duran* et al. [1]. Furthermore, the authors described cytotoxicity against different human tumor cell lines. In order to obtain these alkaloids by synthesis, so getting the chance of more information on their respective pharmacological activities, *Botryllazine B* (**1**) and 2-(*p*-hydroxybenzoyl)-4-(*p*-hydroxyphenyl)imidazole (**2**) (Fig. 1) were synthesized.

[#] Dedicated to Prof. *G. Märkl* on the occasion of his 75$^{th}$ birthday

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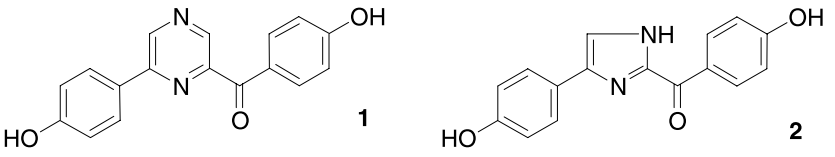
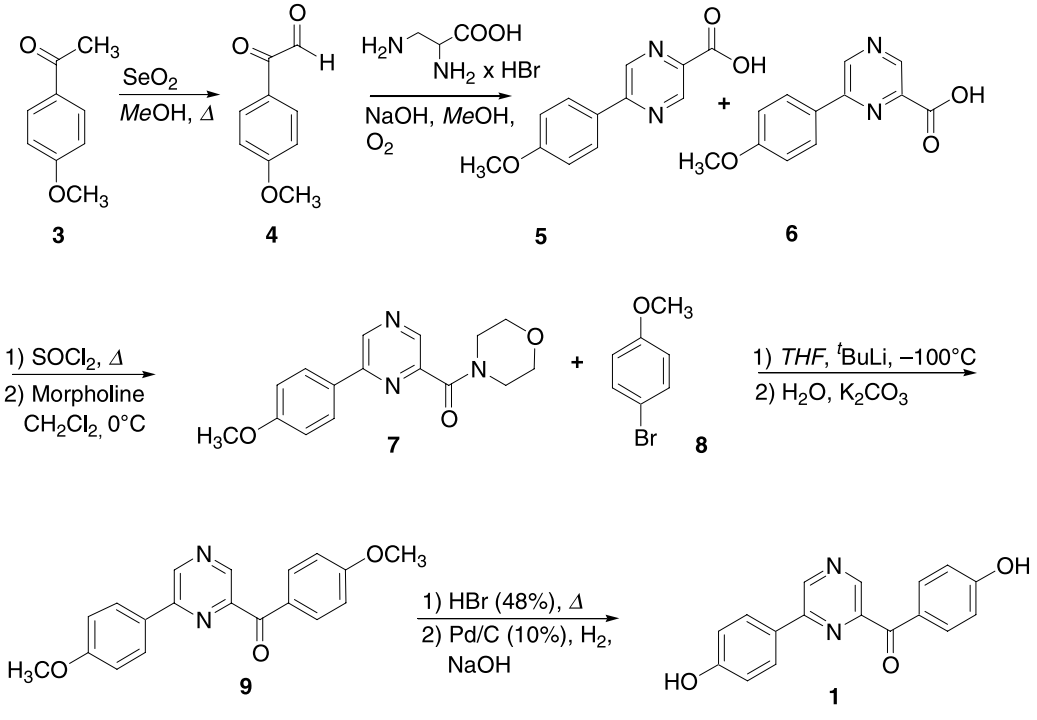



**Fig. 1.** Chemical structures of Botryllazine B (**1**) and 2-(*p*-hydroxybenzoyl)-4-(*p*-hydroxyphenyl) imidazole (**2**)

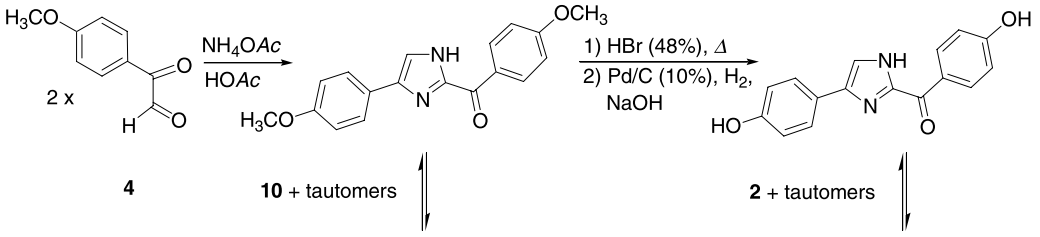
## Results and Discussion

### *Syntheses*

The pyrazine alkaloid **1** was synthesized according to Scheme 1: Oxidation of the acetophenone **3** with $SeO_2$ in methanolic solution [2] and ring closure [3] by reaction of **4** with racemic 2,3-diaminopropionic acid hydrobromide in methanolic NaOH solution [4] resulted in a mixture of the two regio-isomeric pyrazine carboxylic acids **5** and **6**, which were separated by the different solubility of their sodium salts and crystallization of the carboxylic acids. Separation of the isomers can not be recommended. Transformation of **6** to the respective morpholine derivative **7** *via* the carboxylic acid chloride [5] and condensation [6] with 4-methoxyphenyllithium, obtained from 1-bromo-4-methoxybenzene (**8**) and $^t$BuLi, yielded the alkaloid precursor **9**. The methoxy groups of **9** could be cleaved by hydrobromic acid [7]. Because brominated phenols were found as an impurity by mass




**Scheme 1.** Synthesis of Botryllazine B (**1**)




**Scheme 2.** Synthesis of 2-(*p*-hydroxybenzoyl)-4-(*p*-hydroxyphenyl)imidazole (**2**)

spectroscopy, bromine was removed from the compound by treatment of crude alkaloid **1** with hydrogen/Pd on charcoal in 1 *N* NaOH solution [8].

The substitution pattern of **1** was characterized with special emphasis to the $^4J$ and $^5J$-values [9] of the pyrazine carboxylic acids **5** and **6**. Whereas the 5-substituted compound **5** showed $^5J = 1.5$ Hz, the signals of **6** showed no coupling and only a small broadening of the respective singlets, similar to the $^1$H NMR pyrazine signals of **1** [1]. Furthermore, the identity of the synthetically obtained compound **1** and the naturally occurring alkaloid described by *Duran* et al. [1] as *Botryllazine B* was proved by comparison of the $^1$H NMR, $^{13}$C NMR, and EI MS data with those reported, although a difference in IR spectra can be observed (*cf.* Exp.).

The imidazole alkaloid **2** was synthesized according to Scheme 2 by condensation of *p*-methoxyphenylglyoxale (**4**) [2] with ammonium acetate according to *Schubert* [10], resulting in **10** [11] followed by cleavage of the methoxy groups [7] as described for alkaloid **1**. In the case of compound **2**, the analytical data reported for the natural product by *Duran* et al. [1] differ more significantly from our $^1$H NMR, $^{13}$C NMR, and IR spectroscopic data.

*Tautomerism of 2-(Aroyl)-4-arylimidazoles*

Annular tautomerism at imidazole systems is well known [12]. Also in the synthesized *2-(aroyl)-4-arylimidazoles* **10** and **2** tautomerism was well observable by $^1$H NMR spectroscopy in $CD_3OD$ solution. Additional measurements in *DMSO*-$d_6$ solution were performed, in order to obtain resonance signals for the imidazole N–H and phenolic hydrogens. The tautomeric equilibrium constants *K* were determined, respecting the integral intensities of the well separated phenolic and aromatic hydrogen atoms as shown in Fig. 2. The signals of the tautomeric structures of **10** were characterized by the coupling constants of the imidazole nucleus ($^3J_{\mathbf{A}} = 2.4$ Hz, $^4J_{\mathbf{B}} = 1.6$ Hz) and their relations in intensity, after identification of the respective N–H signals by H/D exchange in *DMSO*-$d_6$ solution. Analogously, the tautomeric equilibrium of **2** in *DMSO*-$d_6$ solution was determined (Fig. 2). In order to confirm the assignment of the tautomers, a N*O*E experiment was performed in case of **2**. The resonance signals for the imidazole N–H of tautomer **2**A exhibit a well observable N*O*E effect to the related imidazolyl hydrogen. The tautomer **2**B exclusively shows relation to the AA′ system of the phenyl hydrogens of B at 7.76 ppm. In pure $CD_3OD$ solution no duplication of the resonance signals as in *DMSO*-$d_6$ solution but very broadened signals were observed, indicating fast interconversion. Furthermore, the formation of the tautomeric equilibrium of **2** was accelerated by addition of a catalytic amount of $CF_3COOD$, resulting in a coalesc-

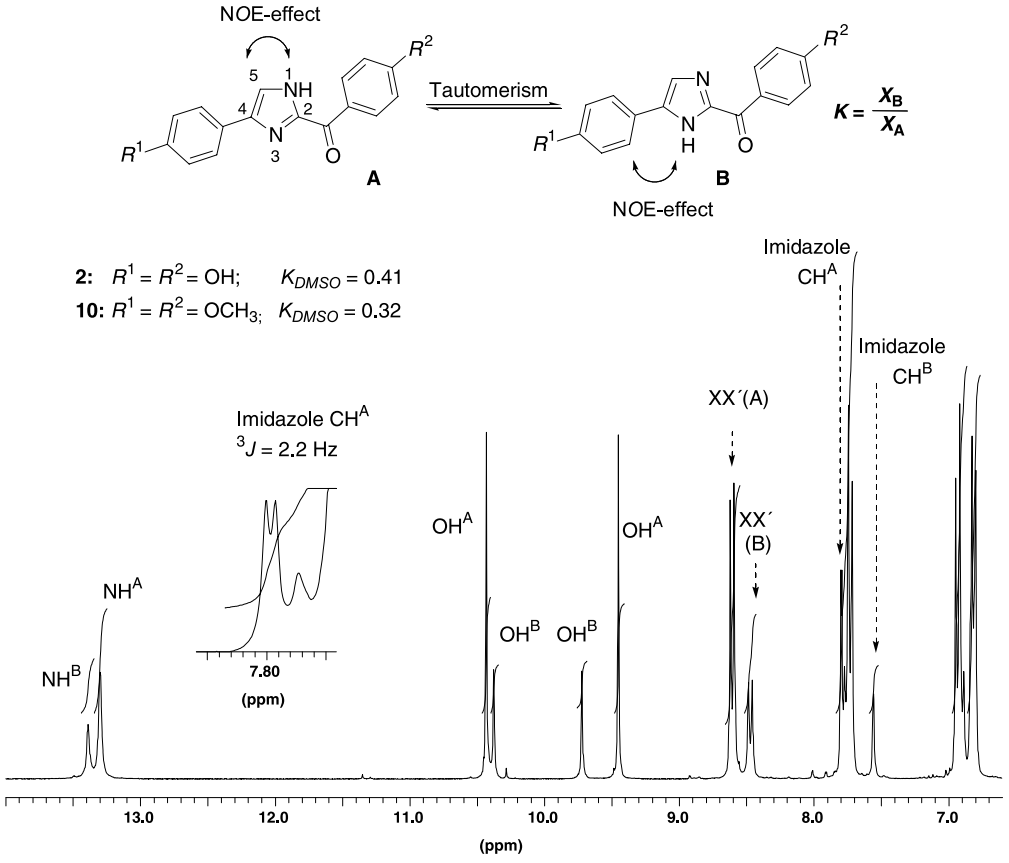



**Fig. 2.** $^1$H NMR spectrum of **2** (DMSO-$d_6$, $c = 8\,mg/cm^3$); the tautomerism constants of 2-aroyl-4-arylimidazoles **2** and **10** were determined according to the respective signal intensities in the $^1$H NMR spectra; after addition of a catalytic amount of acid the coalescence spectra are observed (not shown)

ence of the $^1$H NMR spectra, independent of the solvent used for measurement (not shown).

Surprisingly, *Duran* et al. [1] report no duplication and no broadening of $^1$H NMR signals, indicating fast interconversion of tautomers – a result we could obtain by addition of catalytic amounts of acid only.

Although the coalescence spectra we obtained, exhibit all the characteristics described by *Duran* et al. [1], aberrations of the respective chemical shifts in the $^1$H NMR as well as in the $^{13}$C NMR spectra occurred. These aberrations may be explained by different concentrations in measurement, as a strong concentration dependent shift of $^1$H NMR signals for **2** has been observed by us in $CD_3OD$ solution. A direct comparison of NMR spectral data with those of the literature was not possible, for the concentration used by *Duran* et al. [1] is not reported.

A comparison of the respective analytical data of natural **2** and of **2** obtained by synthesis is shown in Table 1.

Concerning the aberrations in the $^{13}$C NMR spectra, especially the shift of the weak resonance signals caused by the quarternary C-atoms of the imidazole nucleus at $\delta = 140.9$ (lit. 155.9, C-4) and 145.1 ppm (lit. 158.3, C-2) is surprising

**Table 1.** Analytical data of natural and synthetic **2**

| | Data from Ref. [1] | Data of synthetic **2** |
|---|---|---|
| $^1$H NMR, $\delta$ ppm | 6.84 (d, 2H), 6.89 (d, 2H), 7.59 (s, 1H), 7.71 (d, 2H), 8.38 (d, 2H) | 6.90 (AA′, 2H), 6.97 (BB′, 2H), 7.67 (AA′, 2H), 7.77 (s, 1H), 8.13 (XX′, 2H) |
| $^{13}$C NMR, $\delta$ ppm | 117.1 (d, 2C), 117.2 (d, 2C), 119.5 (s, 1C), 122.9 (d, 1C), 126.8 (s, 1C), 128.1 (d, 2C), 134.8 (d, 2C), 155.9 (s, 1C), 158.3 (s, 1C), 160.8 (s, 1C), 167.7 (s, 1C), 172.2 (s, 1C) | 116.4 (d, 2C), 116.8 (d, 2C), 120.5 (d, 1C), 122.7 (s, 1C), 128.4 (d, 2C), 128.6 (s, 1C), 134.6 (d, 2C), 140.9 (s, 1C), 145.1 (s, 1C), 159.4 (s, 1C), 164.5 (s, 1C), 180.8 (s, 1C) |
| IR, $\bar{\nu}/\mathrm{cm}^{-1}$ | 3380, 3290, 1590, 1470, 1260 $\mathrm{cm}^{-1}$ | 3388, 3251, 1617, 1602, 1440, 1273 $\mathrm{cm}^{-1}$ |
| EI-MS (70 eV) $m/z$ (%) | 281 (15) $[\mathrm{M}+1]^{+\cdot}$, 121 (100), 93 (13), 65 (14) | 281 (16) $[\mathrm{M}+1]^{+\cdot}$, 280 (100) $[\mathrm{M}]^{+\cdot}$, 252 (66), 121 (70), 93 (18), 65 (16) |

as well as the lack of a carbonyl group in the IR spectral data. Furthermore, *Duran* et al. [1] do not give a signal in the EI-MS for the molecular ion – a signal that is the most intensive of our measurements. Nevertheless, the fragmentation pattern seems to be in good correlation.

To confirm the structure of the synthetically obtained imidazole derivative **2** we decided to perform an X-ray structure analysis. On sublimation in vacuum at 0.2 Torr/200°C suitable crystals for X-ray structure analysis were obtained. The X-ray data revealed that compound **2** is indeed the described imidazole derivative, existing obviously exclusively as the 2-(*p*-hydroxybenzoyl)-5-(*p*-hydroxyphenyl) imidazole tautomer in solid state – in contrast to *DMSO*-$d_6$ solution where the 2-(*p*-hydroxybenzoyl)-4-(*p*-hydroxyphenyl)imidazole tautomer is the predominant observable tautomer (Fig. 3).

In order to exclude the possibility, that compound **2** isolated by *Duran* et al., exhibiting the analytical characteristics of a disubstituted imidazole nucleus, might be the isomeric 4-(*p*-hydroxybenzoyl)-2-(*p*-hydroxyphenyl)imidazole (**14**), this compound was synthesized and characterized in addition (Scheme 3).

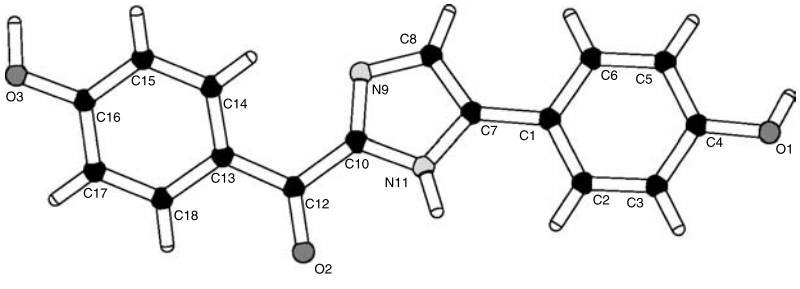
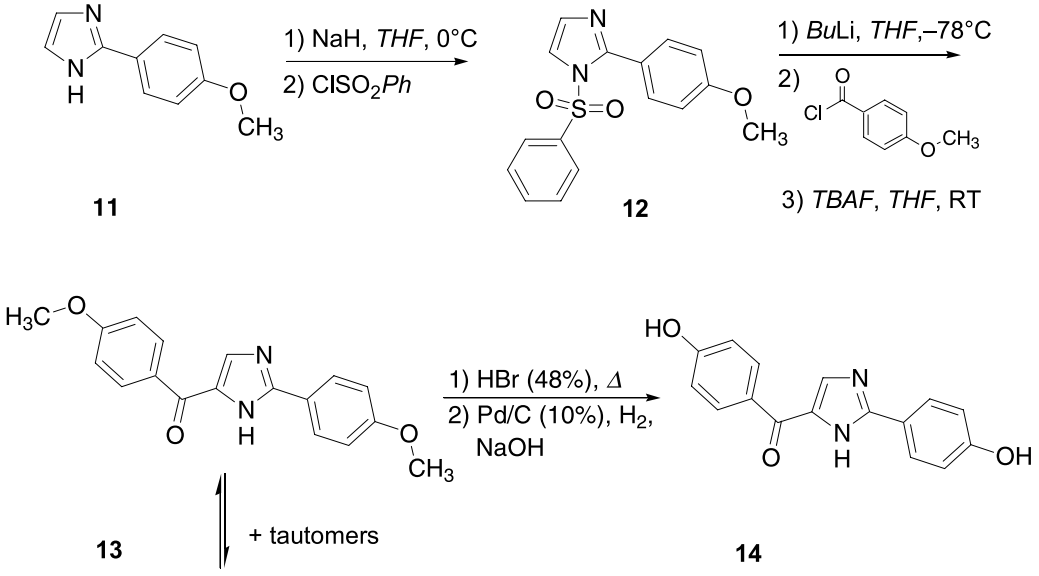



**Fig. 3.** Structure of **2** in the crystal according to X-ray structure analysis




**Scheme 3.** Synthesis of 4-(*p*-hydroxybenzoyl)-2-(*p*-hydroxyphenyl)imidazole (**14**)

The $^1$H NMR spectra of **14** exhibit two AA′BB′ systems and no observable tautomerism in *DMSO*-$d_6$ as well as in $CD_3OD$ solution as described for the sample isolated by *Duran* et al. This may be due to fast interconversion or possibly to the stabilization of the tautomeric 5-(*p*-hydroxybenzoyl)-2-(*p*-hydroxyphenyl)imidazole by an intramolecular hydrogen bond between the carbonyl group and the N–H hydrogen. Nevertheless, comparison of the respective $^1$H NMR and $^{13}$C NMR data obtained for **14** with the data given for **2**, excludes a mistake in interpretation because they differ significantly.

## Conclusion

The structure of alkaloid *Botryllazine B* (**1**) obtained from *Botryllus leachi* was confirmed by synthesis and comparison with data from the literature [1]. 2-(*p*-Hydroxybenzoyl)-4-(*p*-hydroxyphenyl)imidazole (**2**) was synthesized, the analytical data were discussed and compared with data from the literature. The possibility of an identity with the isomeric 5-(*p*-hydroxybenzoyl)-2-(*p*-hydroxyphenyl)imidazole (**14**) was excluded by synthesis and characterization of **14**. Therefore, although there are deviations of the analytical data from the natural compound and the synthetic sample, it seems reasonable that the structure proposed by *Duran* et al. [1] is in agreement with structure **2**. Compounds **2** and **10** exhibit annular tautomerism observable by $^1$H NMR spectroscopy and can be characterized by their tautomeric equilibrium constants *K*.

## Experimental

$^1$H NMR 250 MHz and $^{13}$C NMR 62.5 MHz spectra were recorded with a Bruker AC 250 F spectrometer at 300 K, using TMS as an internal standard. The $^1$H NMR signals of the tautomeric phenyl(arylimidazol-2-yl)methanones are characterized using the indices $^{A}$ or $^{B}$ according to Table 1 as far as an

exact identification was possible with respect to intensity (*cf. K* values in Table 1), N*O*E experiments, and/or coupling constants. Signals which result from both tautomers are given both indices. AA′BB′ and AA′XX′ spectra are characterized by the center of the respective AA′, BB′, or XX′ part. In order to confirm quaternary (s) and H bound carbon atoms (d), DEPT-135 experiments were performed additionally in case of $^{13}C$ NMR spectra. $^{1}H$ NMR N*O*E experiments were recorded with a Bruker BioSphere Avance 600 MHz spectrometer. – Elemental analyses were performed by the Analytical Lab. Univ. Regensburg; results were in favorable agreement with the calculated values. Melting points were determined with a *Reichert* hot-stage microscope. IR spectra (KBr) were measured with a FT Nicolet 510 spectrometer, MS spectra were measured with a Finnigan MAT 95 (EI, 70 eV).

*5- and 6-(p-Methoxyphenyl)pyrazine-2-carboxylic acid* (**5** and **6**)

To a stirred solution of 11.2 g of NaOH (280 mmol) and 13.0 g of 2,3-diaminopropionic acid hydrobromide (70.0 mmol) [5] in 0.7 $dm^3$ of *Me*OH, 11.5 g of *p*-methoxyphenylglyoxal (70.0 mmol) [2] were added at 20°C. Air was bubbled through the solution (12 h), and the solvent was removed under reduced pressure. The residue of sodium salts was extracted with 140 $cm^3$ of cold water. Acidification of the aqueous solution with conc. HCl afforded **6** which was purified by CC ($SiO_2$, *Et*OH) and crystallized (*Et*OH). The remaining sodium salt of **5** was dissolved in 560 $cm^3$ of hot water. The carboxylic acid was liberated as mentioned above and crystallized ($R_f$ of **5** < $R_f$ of **6**, butyl acetate: *Ac*OH: $H_2O$ = 40:10:2).

*5-(p-Methoxyphenyl)pyrazine-2-carboxylic acid* (**5**, $C_{12}H_{10}N_2O_3$)

Yield 3.51 g (22%) white crystals, mp 228–230°C; IR: $\bar{\nu}$ = 1692 $cm^{-1}$; $^{1}H$ NMR (*DMSO*-$d_6$): $\delta$ = 3.86 (s, 3H), 7.13 (AA′, 2H, aromat.), 8.22 (XX′, 2H, aromat.), 9.17 (d, 1H, pyrazine, $^{5}J$ = 1.4 Hz), 9.33 (d, 1H, pyrazine, $^{5}J$ = 1.4 Hz), 13.57 (s, br, 1H, exchangeable) ppm; EI-MS: *m/z* (%) = 230 (97) $[M]^{+\cdot}$, 186 (100), 133 (26), 132 (55).

*6-(p-Methoxyphenyl)pyrazine-2-carboxylic acid* (**6**, $C_{12}H_{10}N_2O_3 \cdot 1/6\ H_2O$)

Yield 3.69 g (23%) light yellowish crystals, mp 211–213°C; IR: $\bar{\nu}$ = 1732, 1611 $cm^{-1}$; $^{1}H$ NMR (*DMSO*-$d_6$): $\delta$ = 3.85 (s, 3H), 7.13 (AA′, 2H, aromat.), 8.20 (XX′, 2H, aromat.), 9.05 (s, 1H, pyrazine), 9.41 (s, 1H, pyrazine), 13.70 (s, br, 1H, exchangeable) ppm; EI-MS: *m/z* (%) = 230 (100) $[M]^{+\cdot}$, 186 (84), 133 (19), 132 (17).

*[6-(p-Methoxyphenyl)pyrazin-2-yl](morpholin-4-yl)methanon* (**7**, $C_{16}H_{17}N_3O_3$)

A solution of 3.68 g of the carboxylic acid **6** (16.0 mmol) in 50 $cm^3$ of $SOCl_2$ was refluxed for 1 h. The excess of $SOCl_2$ was removed under reduced pressure and the resulting crude product was dried in vacuo. Then it was dissolved in 50 $cm^3$ of $CH_2Cl_2$, and a solution of 4.20 $cm^3$ of morpholine (48.0 mmol) in 20 $cm^3$ of $CH_2Cl_2$ was added at 0°C. The mixture was stirred at 20°C for 12 h, 50 $cm^3$ of 2% aqueous $Na_2CO_3$ solution were added, the organic layer was separated, washed with 50 $cm^3$ of water, dried ($Na_2SO_4$), and the solvent was removed. The product was crystallized from $Et_2O$: petroleum ether (1:1) yielding 3.88 g of **6** (81%) as white crystals. Mp 105–106°C; IR: $\bar{\nu}$ = 2844, 1636, 1609 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$): $\delta$ = 3.76 (s, br, 4H), 3.86 (m, 4H), 3.89 (s, 3H), 7.04 (AA′, 2H, aromat.), 7.98 (XX′, 2H, aromat.), 8.82 (d, 1H, $^{4}J$ = 0.5 Hz, pyrazine), 9.03 (d, 1H, $^{4}J$ = 0.5 Hz, pyrazine) ppm; EI-MS: *m/z* (%) = 299 (43) $[M]^{+\cdot}$, 186 (70), 158 (16), 86 (100).

*[6-(p-Methoxyphenyl)pyrazin-2-yl](p-methoxyphenyl)methanone* (**9**, $C_{19}H_{16}N_2O_3$)

To a vigorously stirred solution of 0.66 $cm^3$ of 1-bromo-4-methoxybenzene (**8**) (5.25 mmol) in 90 $cm^3$ of dry *THF* a 1.5 *M* solution of $^t$BuLi (10.5 mmol) in *n*-pentane was added at −100°C. After 15 min a solution of 1.57 g of **7** (5.25 mmol) in 30 $cm^3$ of *THF*, pre-cooled to −78°C, was added at once, and the mixture was stirred for 1.5 h. Hydrolysis of the yellowish to red coloured solution with 100 $cm^3$ of a 2% aqueous $Na_2CO_3$ and extraction with $3 \times 50$ $cm^3$of $CH_2Cl_2$ afforded the product **9**, which was purified by CC ($SiO_2$, ethyl acetate) and crystallization (*Et*$_2$O: petroleum ether = 1:1). Yield 1.26 g (75%) white crystals, mp 120.5–121.5°C; IR: $\bar{\nu} = 2837, 1649, 1604\ cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta = 3.89$ (s, 3H), 3.92 (s, 3H), 7.01 (AA′, 2H, aromat.), 7.04 (BB′, 2H, aromat.), 8.04 (AA′, 2H, aromat.), 8.23 (BB′, 2H, aromat.), 9.04 (s, 1H, pyrazine), 9.15 (s, 1H, pyrazine) ppm.

*Botryllazine B* (**1**, $C_{17}H_{12}N_2O_3$)

A mixture of 1.10 g of **9** (3.43 mmol), 25 $cm^3$ acetic acid, and 40 $cm^3$ of 48% HBr was refluxed for 12 h. Half of the solvent was removed under reduced pressure, the mixture was cooled to room temperature, and the precipitate was filtered off. The solid was dissolved in 50 $cm^3$ of 1 *N* NaOH, a small amount of Pd/C (10%) was added, and the mixture was stirred at room temperature under hydrogen at atmospheric pressure overnight. The solution was filtered, neutralized with dil. HCl, and the product was removed. Crystallization from ethanol/water yielded 0.432 g (43%) of yellow crystals. Mp 206–208°C; IR: $\bar{\nu} = 3400, 3253, 1644, 1603\ cm^{-1}$; $^1$H NMR (*DMSO*-$d_6$): $\delta = 6.92$ (AA′, 2H, aromat.), 6.93 (BB′, 2H, aromat.), 7.98 (AA′, 2H, aromat.), 8.02 (BB′, 2H, aromat.), 8.89 (s, 1H, pyrazine), 9.35 (s, 1H, pyrazine), 9.98 (s, 1H, exchangeable), 10.57 (s, 1H, exchangeable) ppm; $^1$H NMR ($CD_3OD$): $\delta = 6.90$ (AA′, 2H, aromat.), 6.91 (BB′, 2H, aromat.), 7.98 (AA′, 2H, aromat.), 8.06 (BB′, 2H, aromat.), 8.84 (s, 1H, pyrazine), 9.16 (s, 1H, pyrazine) ppm; $^{13}$C NMR ($CD_3OD$): $\delta = 116.3$ (d, 2C), 117.1 (d, 2C), 128.1 (s, 1C), 128.7 (s, 1C), 129.8 (d, 2C), 134.9 (d, 2C), 142.8 (d, 1C), 143.5 (d, 1C), 151.4 (s, 1C), 152.4 (s, 1C), 161.3 (s, 1C), 164.4 (s, 1C), 192.4 (s, 1C) ppm; EI-MS: $m/z$ (%) = 292 (33) $[M]^+$, 121 (100), 93 (23).

*2-(p-Methoxybenzoyl)-4-(p-methoxyphenyl)imidazole* (**10**, $C_{18}H_{16}N_2O_3$)

Compound **10** was synthesized from *p*-methoxyphenylglyoxal (**4**) [2] according to Ref. [10]. The $^1$H NMR data by *Kong* et al. [11] who give only the data for the predominant tautomer are completed as follows: $^1$H NMR (*DMSO*-$d_6$), $c = 8\ mg/cm^3$): $\delta = 3.79$ (s, $3H^A$), 3.81 (s, $3H^B$), 3.88 (s, $3H^B$), 3.89 (s, $3H^A$), 6.99 (AA′, $2H^A$, aromat.), 7.02 (AA′, $2H^B$, aromat.), 7.10 (BB′, $2H^B$, aromat.), 7.14 (BB′, $2H^A$, aromat.), 7.65 (d, $1H^B$, $^4J = 1.6$ Hz), 7.85 (AA′, $2H^A$, $2H^B$, aromat.), 7.91 (d, $1H^A$, $^3J = 2.4$ Hz), 8.55 (XX′, $2H^B$, aromat.), 8.69 (XX′, $2H^A$, aromat.), 13.42 (s, $1H^A$, NH, exchangeable), 13.55 (s, $1H^B$, NH, exchangeable) ppm. The $\delta$ values of the coalescence spectra – after addition of a catalytical amount of $CF_3COOH$ – are as follows: $^1$H NMR (*DMSO*-$d_6$, $c = 8\ mg/cm^3$): $\delta = 3.81$ (s, 3H), 3.90 (s, 3H), 7.04 (AA′, 2H, aromat.), 7.17 (BB′, 2H, aromat.), 7.86 (AA′, 2H, aromat.), 8.52 (XX′, 2H, aromat.) ppm.

*2-(p-Hydroxybenzoyl)-4-(p-hydroxyphenyl)imidazole* (**2**, $C_{16}H_{12}N_2O_3$)

Synthesis by cleavage of the methoxy groups of 0.48 g of **10** (1.56 mmol) as described for Botryllazine B (**1**) without use of acetic acid as a co-solvent by heating for 4 h. Yield 0.33 g (75%) of a yellow powder, mp 295–297°C; IR: $\bar{\nu} = 3388, 3251, 1617\ cm^{-1}$; $^1$H NMR (*DMSO*-$d_6$, $c = 8\ mg/cm^3$): $\delta = 6.81$ (AA′, $2H^A$, $2H^B$, aromat.), 6.90 (BB′, $2H^B$, aromat.), 6.93 (BB′, $2H^A$, aromat.), 7.56 (s, $1H^B$), 7.73 (AA′, $2H^A$, aromat.), 7.76 (AA′, $2H^B$, aromat.), 7.80 (d, $1H^A$, $^3J = 2.2$ Hz), 8.47 (XX′, $2H^B$, aromat.), 8.60 (XX′, $2H^A$, aromat.), 9.46 (s, $1H^A$, exchangeable), 9.74 (s, $1H^B$, exchangeable),

10.38 (s, $1H^B$, exchangeable), 10.43 (s, $1H^A$, exchangeable), 13.31 (s, $1H^A$, exchangeable), 13.40 (s, $1H^B$, exchangeable) ppm. The $\delta$ values of the coalescence spectra – after addition of a catalytical amount of $CF_3COOH$ – are as follows: $^1H$ NMR ($CD_3OD$, $c = 9\,mg/cm^3$): $\delta = 6.90$ (AA′, 2H, aromat.), 6.97 (BB′, 2H, aromat.), 7.67 (AA′, 2H, aromat.), 7.77 (s, 1H), 8.13 (XX′, 2H, aromat.) ppm; $^1H$ NMR (*DMSO*-$d_6$, $8\,mg/cm^3$): $\delta = 6.87$ (AA′, 2H, aromat.), 6.97 (BB′, 2H, aromat.), 7.77 (AA′, 2H, aromat.), 7.90 (s, 1H, aromat.), 8.37 (XX′, 2H, aromat.) ppm; $^{13}C$ NMR ($CD_3OD$, $c = 18\,mg/cm^3$): $\delta = 116.4$ (d, 2C), 116.8 (d, 2C), 120.5 (d, 1C), 122.7 (s, 1C), 128.4 (d, 2C), 128.6 (s, 1C), 134.6 (d, 2C), 140.9 (s, 1C), 145.1 (s, 1C), 159.4 (s, 1C), 164.5 (s, 1C), 180.8 (s, 1C) ppm; EI-MS: $m/z$ (%) = 281 (16) $[M+1]^+$, 280 (100) $[M]^{+\cdot}$, 93 (18), 65 (16).

Crystal structure analysis of compound **2**. The data were collected on an Enraf Nonius CAD4 diffractometer, using graphite-monochromated Cu-$K_\alpha$ radiation. Data were corrected using *Lorentz*- and polarisation correction. Loss of intensity (10%) corrected with cubic spline function. The structure was solved by a SIR-92 program (direct methods), refinement performed with a SHELXL97 program (full matrix refinement) by 205 refined parameters. Weighting schema: $w = 1/[(\sigma^2(F_o) + (0.1019^*P)^2 + 0.45^*P]$ with $P = (\mathrm{Max}(F_o^2,0) + 2^*F_c^2)/3.0$. H-atoms placed at calculated positions and refined isotrop with riding motion. OHs and NH found in diff. *Fourier* maps. Non H-atoms were refined anisotropic. *R*-values $wR_2 = 0.2152$ ($R_1 = 0.0735$ for 1679 reflections with $F_o > 4\sigma(F_o)$). Goodness of fit: $S = 1.020$. *Flack* parameter $x = -0.06(68)$. Maximal deviation of parameters: $0.001^*$ e.s.d. Maximal peak height in diff. *Fourier* map 0.76, $-0.17\,eÅ^{-3}$.

*Crystal data* for $C_{16}H_{12}N_2O_3$: Weight $280.28\,gmol^{-1}$; crystal size $0.032 \times 0.096 \times 0.576$ mm yellow needle; absorption $\mu = 0.82\,mm^{-1}$; space group $Pna2_1$ (orthorhombic); lattice parameters (calculated from 25 reflections with $25° < \theta < 27°$), $a = 19.547(4)$ Å, $b = 12.237(12)$ Å, $c = 5.5049(8)$ Å; $V = 1317(1)$ Å$^3$; $z = 4$; $F(000) = 584$; temperature 295 K, density $d_X = 1.414\,g\,cm^{-3}$. Anisotropic displacement parameters and complete lists of final coordinates and equivalent displacement parameters have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. The data are available on request on quoting CCDC 215662.

*2-p-Methoxyphenyl-1-phenylsulfonyl-1H*-imidazole (**12**, $C_{16}H_{14}N_2O_3S$)

To a solution of 1.70 g of 2-*p*-methoxyphenyl-1*H*-imidazole (**11**) [7] (9.76 mmol) in $30\,cm^3$ of *THF* an equimolar amount of NaH (60% in paraffin) was added in portions at 0°C during 1 h. The mixture was allowed to reach room temperature, stirred for 1 h, and after cooling to 0°C, $1.25\,cm^3$ of benzenesulfonyl chloride (9.76 mmol) was added. After 1 h the mixture was poured into a 2% aqueous $NaCO_3$ solution and the product was extracted with $3 \times 100\,cm^3$ of methylene chloride. The combined organic layers were dried ($Na_2SO_4$) and the product was purified by CC ($SiO_2$, $CH_2Cl_2$: ethyl acetate = 1:1). Yield 2.16 g (70%) of a colourless solid, mp 79.5–80°C; $^1H$ NMR ($CDCl_3$): $\delta = 3.87$ (s, 3H), 7.33 (AA′, 2H, aromat.), 7.09 (d, 1H, $J = 1.6$ Hz), 7.30–7.43 (m, 6H, aromat.), 7.51–7.58 (m, 1H, aromat.), 7.62 (d, 1H, $J = 1.6$ Hz) ppm;. EI-MS: $m/z$ (%) = 314 (8) $[M]^{+\cdot}$, 173 (100), 158 (6), 77 (5).

*4-(p-Methoxybenzoyl)-2-(p-methoxyphenyl)-3H*-imidazole (**13**, $C_{18}H_{16}N_2O_3$)

To 1.90 g of **12** (6.05 mmol) in $30\,cm^3$ of dry *THF* 6.35 mmol of $^t$BuLi (1.5 *M* in pentane) were added at −100°C. After 5 min $0.86\,cm^3$ of a solution of *p*-methoxybenzoyl chloride (6.35 mmol) in *THF*, cooled to −78°C, was added at once. The mixture was allowed to reach room temperature over night. Tetrabutylammonium fluoride trihydrate (2.05 g, 6.50 mmol) was added, the mixture was stirred for 1 h and poured into a 2% aqueous $NaCO_3$ solution. The product was extracted with $3 \times 100\,cm^3$ of ethyl acetate. The combined organic layers were dried ($Na_2SO_4$), and the product was purified by crystallization from ethyl acetate. One-pot synthesis by use of **11** without isolation of **12** also yielded the desired product in the same amount. Yield 0.48 g (26%) of colourless crystals, mp 226°C; IR: $\bar{\nu} = 3245$, $1611\,cm^{-1}$; $^1H$ NMR (MeOD, $CF_3COOD$, sat. solution): $\delta = 3.93$ (s, 3H), 3.94 (s, 3H),

7.14 (AA′, 2H, aromat.), 7.23 (BB′, 2H, aromat.), 8.00 (AA′, 2H, aromat.), 8.05 (BB′, 2H, aromat.), 8.26 (s, 1H) ppm; EI-MS: $m/z$ (%) = 308 (100) $[M]^{+\cdot}$, 201 (7), 200 (21), 135 (15), 107 (1).

*4-(p-Hydroxybenzoyl)-2-(p-hydroxyphenyl)-3H*-imidazole (**14**, $C_{16}H_{12}N_2O_3 \bullet H_2O$)

Synthesis by cleavage of the methoxy groups of 0.69 g of **13** (2.24 mmol) as described for Botryllazine B (**1**) without use of acetic acid as a co-solvent. Yield 0.58 g (92%) of yellow crystals, mp 289–295°C; IR: $\bar{\nu}$ = 3261, 1610 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ = 6.91 (AA′, 2H, aromat.), 6.93 (BB′, 2H, aromat.), 7.72 (s, 1H, aromat.), 7.86 (AA′, 2H, aromat), 7.93 (BB′, 2H, aromat) ppm; $^1H$ NMR (*DMSO*-$d_6$): $\delta$ = 6.87 (AA′, 2H, aromat.), 6.90 (BB′, 2H, aromat.), 7.82 (s, 1H, aromat.), 7.95 (AA′, 2H, aromat.), 8.06 (BB′, 2H, aromat.), 9.84 (s, 1H, exchangeable), 10.25 (s, 1H, exchangeable), 13.24 (s, 1H, exchangeable) ppm; $^{13}C$ NMR ($CD_3OD$): $\delta$ = 116.4 (d, 2C), 116.9 (d, 2C), 121.3 (s, 1C), 129.3 (d, 2C), 130.7 (s, 1C), 132.8 (d, 2C), 133.7 (s, 1C), 135.9 (s, 1C), 151.7 (s, 1C), 160.8 (s, 1C), 163.8 (s, 1C), 186.0 (s, 1C) ppm; EI-MS: $m/z$ (%) = 280 (100) $[M]^{+\cdot}$, 251 (6), 187 (13), 186 (22), 132 (21).

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## References

[1] Duran R, Zubia E, Ortega MJ, Naranjo S, Salva J (1999) Tetrahedron **55**: 13225
[2] Sisido K, Nozaki H (1948) J Am Chem Soc **70**: 3326
[3] Felder E, Pitre D, Boveri S, Grabitz EB (1967) Chem Ber **100**: 555
[4] Krebs E (1893) Ber Dtsch Chem Ges **26**: 2264
[5] Solomons IA, Spoerri PE (1953) J Am Chem Soc **75**: 679
[6] Petitt RG, Toki B, Herald DL, Verdier-Pinard P, Boyd MR, Hamel E, Petitt RK (1998) J Med Chem **41**: 1688
[7] Jones H, Fordic MW, Greenwald RB, Hannah J, Jacobs A, Ruyle WV, Walford GL, Shen TY (1978) J Med Chem **21**: 1100
[8] Gramatica P, Giannotti MP, Speranza G, Manritto P (1986) Heterocycles **24**: 743
[9] Pretsch E, Clerc T, Seibl J, Simon W (1986) Tabellen zur Strukturaufklärung, 3rd ed. Springer, Berlin Heidelberg New York
[10] Schubert H, Hellwig A, Bleichert JL (1964) J Prakt Chem **24**: 125
[11] Kong YC, Kim K (1999) J Heterocycl Chem **36**: 911
[12] Elguero J, Martin C, Katritzky AR, Linda P (1976) The Tautomerism of Heterocycles. In: Katritzky AR, Boulton AJ (eds) Adv Heterocycl Chem, Suppl 1. Academic Press, New York, p 278

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