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ORIGINAL PAPER

Contributions to syntheses of pyrrolo[2,1-*a*]phthalazines

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Abstract Structural elucidation of the dihydro derivatives obtained as by-products in the classic salt method synthesis of pyrrolo[2,1-*a*]phthalazines and acetylenic dipolarophiles was achieved by X-ray diffraction analysis of a representative compound. In addition, new pyrrolo[2,1-*a*]phthalazines were obtained by a one-pot three-component reaction that avoids the formation of the dihydro derivative intermediates.

Keywords Pyrrolo[2,1-*a*]phthalazine · X-ray structure determination · N-ylides · One-pot three-component reaction

Introduction

Pyrrolo[2,1-*a*]phthalazines are fused nitrogen-containing compounds which are of particular interest owing to their biological activity and optical properties [1–4]. Over time, numerous studies regarding synthesis of pyrrolo[2,1-*a*]-phthalazine derivatives have been reported [5–9]. Among the synthetic strategies, 1,3-dipolar cycloaddition of phthalazinium N-ylides with electron-deficient alkynes or alkenes is one of the most productive [10–16]. This synthesis involves a two-stage process, in the first of which the phthalazinium salts are prepared, and in the second, they react with acetylenic or olefinic dipolarophiles in the presence of a base which generates in situ the ylide affording the pyrrolo[2,1-*a*]phthalazines. In the case of symmetrical acetylenic dipolarophiles, dihydro derivative intermediates were obtained mixed with the aromatic pyrrolo[2,1-*a*]phthalazine, this outcome being of interest from a stereochemical and mechanistic viewpoint. Herein are reported the isolation and elucidation by X-ray diffraction analysis of the structure of a dihydro derivative cycloadduct obtained by the classic two-stage synthesis of pyrrolo[2,1-*a*]phthalazine, as well as the synthesis of new pyrrolo[2,1-*a*]phthalazines by a one-pot three-component procedure that avoids the formation of the dihydro derivatives, leading directly to the fully aromatic compounds. The proposed synthetic strategy benefits from concepts such as one-pot synthesis and "atom economy" in the context of sustainable chemistry, which is of great interest at present. Moreover, the hazardous chlorinated solvents used in the classical approach are avoided by using an epoxide which is more environmentally friendly.

Results and discussion

1,3-Dipolar cycloaddition of heteroaromatic N-ylides with acetylenic or olefinic dipolarophiles raises interesting stereochemical features. The reaction of the heteroaromatic N-ylides **1** with symmetrical dipolarophiles of type **2** leads to the formation of the primary cycloadducts **3**, which under the reaction conditions, rearrange to the dihydro derivatives of type **4** or **5** (Scheme 1). Intermediates of type

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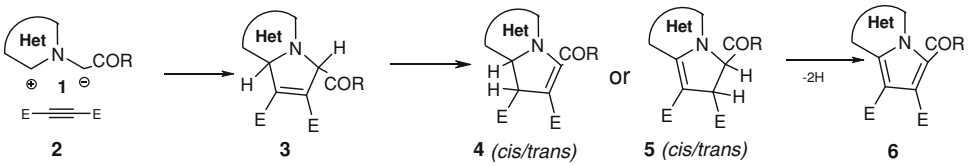
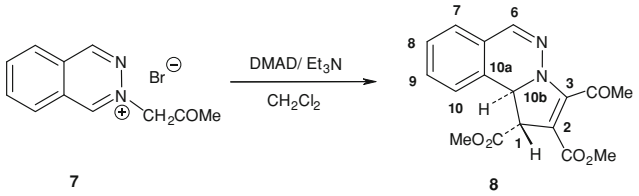
Scheme 1





Scheme 2

4 and **5** are generally unstable, leading to the fully aromatic compounds **6** by dehydrogenation [13, 14].

Isolation and characterization of hydrogenated intermediates led to investigation of their structure with the aim of elucidating the stereochemistry of the 1,3-dipolar cycloaddition [13–16]. Nuclear magnetic resonance (NMR) spectra of the dihydropyrrolophthalazines revealed a high value of the coupling constant ($J \approx 13$ Hz) between the two hydrogens in the pyrrolidine moiety. In the case of 1,10-phenanthroline (Het = 1,10-phenanthroline), a cycloadduct of type **5** [17] was isolated, where the coupling constant between pyrrolinic protons was reported as 4.8 Hz. X-ray analysis of dihydropyrrolophenanthroline of type **5** clearly indicated a *trans* stereochemistry of the two pyrrolinic protons. By comparing the NMR data of the dihydropyrrolophenanthroline of type **5** and dihydropyrrolophthalazine of type **4** the conclusion was that the magnitude of the coupling constant in the case of compounds of type **4** was sufficiently high to ascertain a *cis* [13–16] stereochemistry for the two hydrogen atoms in question. Thus, the hydrogenated intermediate **8** obtained from the corresponding phthalazinium salt **7** with dimethyl acetylenedicarboxylate (DMAD) was obtained according to Scheme 2 with the aim of performing structural studies.

The NMR data for compound **8** are in good agreement with the proposed structure. The high magnitude of the coupling constant (13.2 Hz) could predict a *cis* configuration. To establish unequivocally the configuration of the two protons from the pyrroline moiety, the representative dihydro derivative **8** was subjected to X-ray analysis, leading to elucidation of the structure of compounds of type **4**. The X-ray data showed an unexpected *trans* configuration.

The *trans* stereochemistry in **8** is evident from Fig. 1, where nonhydrogen atoms are represented as thermal ellipsoids at the 50% probability level and H atoms are drawn as spheres of arbitrary size. The relevant atoms

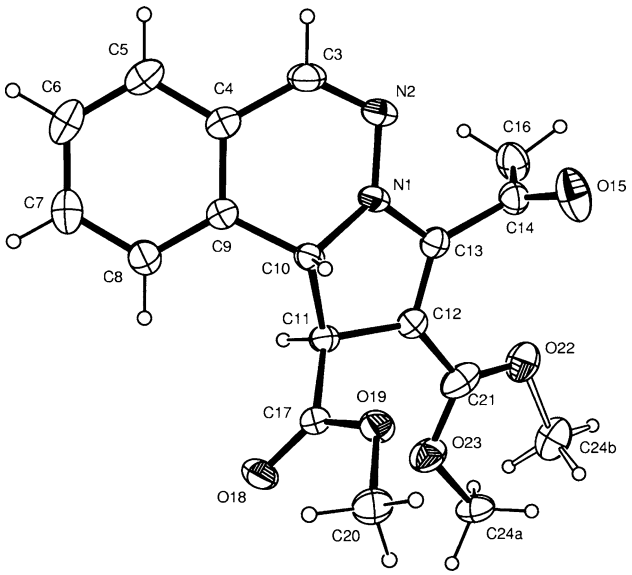
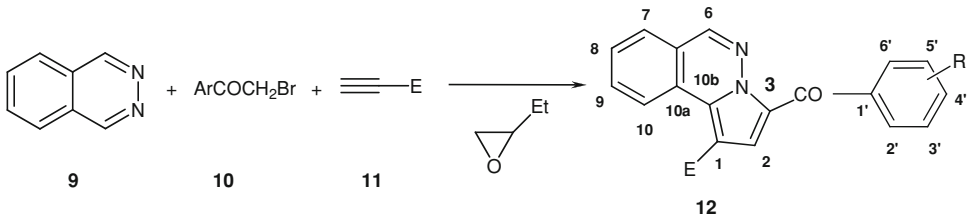


Fig. 1 Structure and conformation of **8**

(H10, H11) were located unambiguously in a difference electron density map and were added to the parent atoms in idealized positions in a riding model (final H–C–C–H torsion angle = 148.5°).

Hydrogenation of the planar phthalazinium moiety in **7** to yield the intermediate **8** (Scheme 2) induces significant bond length and conformational changes. Thus, the shortest and longest bond distances in the partially saturated phthalazine ring of **8** are N2–C3 1.292(2) Å and C9–C10 1.502(2) Å. This ring adopts an unusual conformation, which very roughly resembles a half-chair form, atoms N1, N2, C3, and C4 being roughly coplanar [dihedral angle N1–N2–C3–C4 = −5.8(2)°] and with atoms C9 and C10, respectively, below and above the plane as viewed in Fig. 1. The conformation of the dihydropyrrole ring is very close to an envelope (flap at C10), as found also in the molecule 10b-methyl-1,3-diphenyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine [18]. However, while the interatomic distances in the saturated phthalazine ring of **8** are very similar to those in the related molecule [18], the endocyclic torsion angles span the rather different respective ranges of −5.8° to 44.3° and 1.0° to −14.0°. The variability in ring conformations is attributed to the significantly different steric and electronic influences of the respective substituents on the dihydropyrrole ring in the two molecules. In molecule **8**, the methyl group of the $COOCH_3$ group

Scheme 3



9 **10** **11** **12**

attached to C12 is disordered over two positions [C24a, major component with site occupancy 0.742(4), and C24b with site occupancy 0.258(4)]. In the crystal of **8**, there are only two unique intermolecular hydrogen bonds of type C–H···O and there is no significant π-stacking.

One-pot or one-pot multicomponent reactions are of interest due to their simple procedures [19–28]. The one-pot reactions starting from azine salts or the one-pot three-component synthesis starting directly from azines proved to be efficient in the case of both symmetrical and non-symmetrical dipolarophiles [29–33]. These methods avoid formation of hydrogenated derivatives and lead directly to the aromatic compounds.

The starting materials for the one-pot three-component synthesis of pyrrolo[2,1-*a*]phthalazines **12** were phthalazine **9**, bromoacetophenones **10**, and nonsymmetrical acetylenic dipolarophiles **11**. The reaction was carried out in excess 1,2-epoxybutane with the role of generating the phthalazinium ylide in situ and as reaction medium (Scheme 3).

The one-pot three-component synthesis of pyrrolophthalazines involves in the first step the attack of the bromide ion on the oxirane ring of 1,2-epoxybutane, resulting in ring opening with formation of an alkoxide. The alkoxide abstracts one of the methylene protons in the bromide salt, generating the unstable phthalazinium N-ylide. In the next step, 1,3-dipolar cycloaddition between the N-ylide and acetylenic dipolarophile gives the primary cycloadduct of type **3**, which under the reaction conditions, rearranges to the dihydropyrrolophthalazine of type **4**, leading via dehydrogenation to the pyrrolo[2,1-*a*]phthalazines **12**.

The structures of compounds **12** were assigned by elemental analysis, infrared (IR), and NMR spectroscopy. The characteristic IR spectral features of compounds **12** are the carbonyl bands observed in the range 1,627–1,640 cm^{-1} for the carbonyl group in the benzoyl moiety, due to conjugation within the molecule. The carbonyl bands in the acetyl moiety in compounds **12a** and **12b** appear at 1,658–1,662 cm^{-1}, whereas for the carbomethoxy or carboethoxy the corresponding carbonyl bands appear in the range 1,699–1,712 cm^{-1}. The C–O vibration specific bands could be observed at $\sim$1,090 and $\sim$1,250 cm^{-1}. For compound **12e** the characteristic vibrations of the NO_2 group could be observed at 1,345 and 1,527 cm^{-1}. The regioselectivity of the cycloaddition reaction is highlighted by ^{1}H NMR spectroscopy. Thus, the hydrogen H-2 appears as a sharp singlet at 7.56–7.66 ppm. The hydrogen H-6 appears as a deshielded singlet in the range 8.69–8.89 ppm due to the vicinity of the nitrogen atom. The H-10 atom is strongly deshielded ($\delta \approx 9.80$ ppm) due to the spatial influence of the carbonyl group attached to position 1.

The ^{13}C NMR spectra show all the expected signals. The spectra of pyrrolophthalazines present the signals of the carbonyl groups at expected chemical shifts. The main signals are of carbon C-6 attached to a double C–N bond in the phthalazine moiety which appears strongly deshielded ($\delta \approx 146$ ppm) and of the C-1 in the pyrrole ring which appears shielded due to the substituent directly attached ($\delta \approx 117$ ppm for compounds **12a** and **12b** and $\sim$108 ppm for **12c**–**12k**).

In conclusion, based on the X-ray analysis, a *trans* configuration was attributed to the dihydro derivative intermediate **8** obtained by the classic two-stage synthesis of pyrrolo[2,1-*a*]phthalazine. Also, new pyrrolo[2,1-*a*]phthalazines were easily obtained by the one-pot three-component procedure, avoiding the formation of the dihydro derivatives. The proposed one-pot reaction is in line with the current trend to address issues of sustainability.

Experimental

Melting points were determined on a Boëtius hot plate apparatus. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus; their results agreed favorably with the calculated values. The IR spectra were recorded on a Fourier-transform (FT)-IR Bruker Vertex 70 spectrometer. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Supplementary evidence was given by heteronuclear correlation spectroscopy (HETCOR) and correlation spectroscopy (COSY) experiments. Phthalazine, phenacyl bromides, DMAD, methyl propiolate, triethylamine, and 1,2-epoxybutane were obtained from Aldrich and were used without further purification.

Dimethyl 3-acetyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-1,2-dicarboxylate (**8**, $C_{17}H_{16}N_2O_5$)
Into an ice-cooled mixture of 1.34 g phthalazinium salt **7** (5 mmol) and 0.79 g DMAD (5.5 mmol) in 25 cm^3 dichloromethane was added dropwise, under continuous stirring, 0.76 g triethylamine (7.5 mmol) dissolved in 5 cm^3 dichloromethane. After 20 min the reaction mixture was washed with water, and then the solvent was evaporated under vacuum. The obtained residue was triturated with cold ethanol and filtered. Yield 82%; m.p.: 135–137 °C (from 2-propanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$–7.48 (m, 1H, H-9), 7.53 (s, 1H, H-6), 7.43–7.36 (m, 2H, H-8, H-10), 7.29–7.25 (m, 1H, H-8), 5.13 (d, 1H, $J = 13.2$ Hz, H-10b), 4.35 (d, 1H, $J = 13.2$ Hz, H-1), 3.90, 3.72 (2 s, 6H, MeO), 2.59 (s, 3H, MeCO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.7$ (COMe), 173.0 (1-COO), 164.4 (2-COO), 154.9 (C-3), 142.2 (C-6), 131.8 (C-10), 130.9, 124.8 (C-6a, C-10a), 128.9, 124.8, 123.5 (C-7, C-8, C-9), 99.2 (C-2), 61.6 (C-10b), 53.0, 51.6 (2OMe), 52.2 (C-1), 30.7 (MeCO) ppm; IR (ATR): $\bar{\nu} = 1{,}687$, 1,716, 2,950, 3,048 cm^{-1}.

Procedure for pyrrolo[2,1-a]phthalazines ***12***

A mixture of 0.65 g phthalazine **9** (5 mmol), phenacyl bromide **10** (5 mmol), and nonsymmetrical acetylene **11** (7 mmol) in 20 cm^3 1,2-epoxybutane was kept under stirring at reflux temperature for 16 h. After the solvent was partly removed by evaporation, 10 cm^3 methanol was added, and the mixture was left overnight at room temperature. The solid was filtered, washed with a small quantity of cold ethanol, and crystallized from a suitable solvent.

1-Acetyl-3-(2-methoxybenzoyl)pyrrolo[2,1-a]phthalazine (**12a**, $C_{21}H_{16}N_2O_3$)
Yield 69%; m.p.: 147–149 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.75$–9.72 (m, 1H, H-10), 8.61 (s, 1H, H-6), 7.82–7.77 (m, 2H, H-7, H-9), 7.68–7.63 (m, 1H, H-8), 7.56 (s, 1H, H-2), 7.47–7.38 (m, 2H, H-4′, H-6′), 6.99 (bt, 1H, $J = 7.4$ Hz, H-5′), 6.90 (bd, 1H, $J = 7.6$ Hz, H-3′), 3.59 (s, 3H, MeO), 2.56 (s, 3H, MeCO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.8$ (COMe), 184.2 (COAr), 157.7 (C-2′), 146.5 (C-2), 132.8 (C-9), 132.1, 130.0 (C-4′, C-6′), 130.2, 129.2, 127.1, 122.3 (C-3, C-6a, C-10a, C-10b, C-1′), 130.0 (C-6′), 129.8, 127.8, 127.4 (C-7, C-8, C-10), 124.9 (C-2), 120.6, 111.6 (C-3′, C-5′), 117.5 (C-1), 55.8 (MeO), 29.5 (MeCO) ppm; IR (ATR): $\bar{\nu} = 1{,}234$, 1,627, 1,658, 2,951, 3,034 cm^{-1}.

1-Acetyl-3-(3-methoxybenzoyl)pyrrolo[2,1-a]phthalazine (**12b**, $C_{21}H_{16}N_2O_3$)
Yield 71%; m.p.: 171–173 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.87$–9.83 (m, 1H, H-10), 8.78 (s, 1H, H-6), 7.94–7.89 (m, 2H, H-7, H-9), 7.80–7.75 (m, 1H, H-8), 7.66 (1H, s, H-2), 7.52–7.50 (m, 2H, H-2′, H-6′), 7.43 (t, 1H, $J = 8.0$ Hz, H-5′), 7.18 (ddd, 1H, $J = 8.0$, 2.4, 1.1 Hz, H-4′), 3.89 (s, 3H, MeO), 2.68 (s, 3H, MeCO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.7$ (COMe), 184.5 (COAr), 159.8 (C-3′), 147.0 (C-6), 140.4 (C-1′), 133.0 (C-9), 130.2, 122.5, 119.0, 114.2 (C-2′, C-4′, C-5′, C-6′), 129.7, 127.4, 127.1, 122.4 (C-3, C-6a, C-10a, C-10b), 129.5, 127.8, 127.6 (C-7, C-8, C-10), 117.1 (C-1), 55.6 (MeO), 29.6 (MeCO) ppm; IR (ATR): $\bar{\nu} = 1{,}256$, 1,627, 1,662, 2,996, 3,038 cm^{-1}.

Methyl 3-benzoylpyrrolo[2,1-a]phthalazine-1-carboxylate (**12c**, $C_{20}H_{14}N_2O_3$)
Yield 78%; m.p.: 231–233 °C (from methanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.77$–9.74 (m, 1H, H-10), 8.69 (s, 1H, H-6), 7.89–7.86 (m, 2H, H-2′, H-6′), 7.85–7.80 (m, 2H, H-7, H-9), 7.69–7.64 (m, 1H, H-8), 7.63 (s, 1H, H-2), 7.56–7.51 (m, 1H, H-4′), 7.47–7.42 (m, 2H, H-3′, H-5′), 4.85 (s, 3H, Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 184.6$ (COAr), 164.7 (COO), 146.5 (C-6), 139.1 (C-1′), 133.0 (C-9), 132.5 (C-4′), 130.4, 127.2, 126.8, 122.2 (C-3, C-6a, C-10a, C-10b), 129.8, 127.6, 127.5 (C-7, C-8, C-10), 129.7 (C-3′, C-5′), 128.4 (C-2′, C-6′), 124.9 (C-2), 107.9 (C-1), 51.9 (MeO) ppm; IR (ATR): $\bar{\nu} = 1{,}089$, 1,265, 1,633, 1,704, 2,950, 3,025 cm^{-1}.

Methyl 3-(2-chlorobenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12d**, $C_{20}H_{13}ClN_2O_3$)
Yield 75%; m.p.: 221–222 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.81$–9.78 (m, 1H, H-10), 8.78 (s, 1H, H-6), 7.92–7.86 (m, 2H, H-7, H-9), 7.77–7.72 (m, 1H, H-8), 7.59 (s, 1H, H-2), 7.52–7.37 (m, 4H, H-3′, H-4′, H-5′, H-6′), 3.89 (s, 3H, Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 183.0$ (COAr), 164.4 (COO), 146.8 (C-6), 139.7, 131.6 (C-1′, C-2′), 133.1 (C-9), 131.6, 127.1, 122.3 (C-3, C-6a, C-10a, C-10b), 131.1, 130.1, 126.7 (C-3′, C-4′, C-5′, C-6′), 130.1, 127.7, 127.6 (C-7, C-8, C-10), 126.6 (C-2), 108.7 (C-1), 51.9 (MeO) ppm; IR (ATR): $\bar{\nu} = 1{,}091$, 1,261, 1,634, 1,711, 2,952, 3,053 cm^{-1}.

Methyl 3-(4-nitrobenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12e**, $C_{20}H_{13}N_3O_5$)
Yield 81%; m.p.: 250–252 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$ + TFA): $\delta = 9.76$–9.73 (m, 1H, H-10), 8.89 (s, 1H, H-6), 8.40 (d, 2H, $J = 8.8$ Hz, H-3′, H-5′), 7.99–8.06 (m, 4H, H-7, H-9, H-2′, H-6′), 7.91–7.86 (m, 1H, H-8), 7.58 (s, 1H, H-2), 3.98 (s, 3H, MeO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + TFA): $\delta = 184.3$ (COAr), 165.1 (COO), 150.2 (C-4′), 147.7 (C-6), 144.0 (C-1′), 134.2 (C-9), 132.9, 126.3, 125.5, 122.8 (C-3, C-6a, C-10a, C-10b), 131.4, 128.9, 128.4, 127.9 (C-2, C-6, C-7, C-8), 124.0 (C-3′, C-5′), 109.3 (C-1), 52.8 (MeO) ppm; IR (ATR): $\bar{\nu} = 1{,}096$, 1,265, 1,345, 1,527, 1,637, 1,710, 2,958, 3,029 cm^{-1}.

Methyl 3-(2-methoxybenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12f**, $C_{21}H_{16}N_2O_4$)
Yield 68%; m.p.: 181–183 °C (from acetonitrile); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.80–9.77 (m, 1H, H-10), 8.74 (s, 1H, H-6), 7.88–7.84 (m, 2H, H-7, H-9), 7.74–7.69 (m, 1H, H-8), 7.62 (s, 1H, H-2), 7.52–7.45 (m, 2H, H-4′, H-6′), 7.06 (bt, 1H, J = 7.4 Hz, H-5′), 6.99 (bd, 1H, J = 7.6 Hz, H-3′), 3.89, 3.71 (2 s, 6H, 2MeO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.2 (COAr), 164.7 (COO), 157.5 (C-2′), 146.3 (C-6), 132.9 (C-9), 131.8, 129.7, 129.6, 127.5, 127.4 (C-7, C-8, C-10, C-4′, C-6′), 130.3, 130.1, 128.6, 126.7, 122.1 (C-3, C-6a, C-10a, C-10b, C-1′), 125.6 (C-2), 120.6, 111.6 (C-3′, C-5′), 108.2 (C-1), 55.8, 51.8 (2MeO) ppm; IR (ATR): $\bar{\nu}$ = 1,092, 1,251, 1,640, 1,712, 2,947, 3,032 cm^{-1}.

Methyl 3-(3-methoxybenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12g**, $C_{21}H_{16}N_2O_4$)
Yield 77%; m.p.: 224–226 °C (from ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.79–9.76 (m, 1H, H-10), 8.76 (s, 1H, H-6), 7.88–7.82 (m, 2H, H-7, H-9), 7.72–7.66 (m, 1H, H-8), 7.66 (1H, s, H-2), 7.46–7.42 (m, 2H, H-2′, H-6′), 7.36 (t, 1H, J = 8.0 Hz, H-5′), 7.09 (ddd, 1H, J = 8.0, 2.4, 1.1 Hz, H-4′), 3.87, 3.82 (2 s, 6H, 2MeO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.5 (COAr), 164.7 (COO), 159.8 (C-3′), 146.6 (C-6), 140.5 (C-1′), 133.1 (C-9), 130.5, 127.1, 126.9, 122.3 (C-3, C-6a, C-10a, C-10b), 129.9, 122.6, 119.0, 114.3 (C-2′, C-4′, C-5′, C-6′), 129.4, 127.7, 127.6 (C-7, C-8, C-10), 108.0 (C-1), 55.6, 52.0 (2MeO) ppm; IR (ATR): $\bar{\nu}$ = 1,090, 1,259, 1,634, 1,704, 2,976, 3,037 cm^{-1}.

Methyl 3-(4-methoxybenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12h**, $C_{21}H_{16}N_2O_4$)
Yield 72%; m.p.: 190–192 °C (from ethanol);^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.79–9.76 (m, 1H, H-10), 8.70 (s, 1H, H-6), 7.97 (d, 2H, J = 8.8 Hz, H-2′, H-6′), 7.88–7.82 (m, 2H, H-7, H-9), 7.71–7.69 (m, 1H, H-8), 7.65 (s, 1H, H-2), 6.99 (d, 2H, J = 8.8 Hz, H-3′, H-5′), 3.92, 3.88 (2 s, 6H, 2MeO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.5 (COAr), 164.7 (COO), 163.4 (C-4′), 146.3 (C-6), 132.9 (C-9), 132.2 (C-2′, C-6′), 129.5, 127.6, 127.3 (C-7, C-8, C-10), 129.5, 127.6, 127.3 (C-7, C-8, C-10), 129.8, 126.8, 122.1, (C-3, C-6a, C-10a, C-10b), 123.5 (C-2), 113.7 (C-3′,C-5′), 107.5 (C-1), 55.5, 51.8 (2MeO) ppm; IR (ATR): $\bar{\nu}$ = 1,090, 1,247, 1,636, 1,702, 2,945, 3,020 cm^{-1}.

Ethyl 3-(2,4-dichlorobenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12i**, $C_{21}H_{14}Cl_2N_2O_3$)
Yield 75%; m.p.: 201–203 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.85–9.82 (m, 1H, H-10), 8.76 (s, 1H, H-6), 7.96–7.90 (m, 2H, H-7, H-9), 7.81–7.75 (m, 1H, H-8), 7.65 (s, 1H, H-2), 7.49 (d, 1H, J = 2.0 Hz, H-3′), 7.48 (d, 1H, J = 8.2 Hz, H-6′), 7.39 (dd, 1H, J = 8.2, 2.0 Hz, H-5′), 4.43 (q, 2H, J = 7.1 Hz, CH_2), 1.41 (3H, t, J = 7.1 Hz, Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.1 (COAr), 164.1 (COO), 146.8 (C-6), 138.2, 136.6, 132.8 (C-1′, C-2′, C-4′), 133.2 (C-9), 130.4, 130.2, 127.2 (C-3′, C-5′, C-6′), 131.0, 127.2, 126.8, 122.4, (C-3, C-6a, C-10a, C-10b), 130.1, 127.9, 127.7 (C-7, C-8, C-10), 126.1 (C-2), 109.5 (C-1), 61.0 (CH_2), 14.6 (Me) ppm; IR (ATR): $\bar{\nu}$ = 1,092, 1,260, 1,636, 1,704, 2,970, 3,045 cm^{-1}.

Ethyl 3-(2-methoxybenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12j**, $C_{22}H_{18}N_2O_4$)
Yield 71%; m.p.: 160–162 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.69–9.66 (m, 1H, H-10), 8.59 (s, 1H, H-6), 7.76–7.71 (m, 2H, H-7, H-9), 7.62–7.57 (m, 1H, H-8), 7.56 (s, 1H, H-1), 7.43–7.34 (m, 2H, H-4′, H-6′), 6.96 (bt, 1H, J = 7.4 Hz, H-5′), 6.88 (bd, 1H, J = 7.6 Hz, H-3′), 4.28 (q, 2H, J = 7.1 Hz, CH_2), 3.59 (s, 3H, MeO), 1.29 (t, 3H, J = 7.1 Hz, $MeCH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.2 (COAr), 164.3 (COO), 157.6 (C-2′), 146.2 (C-6), 132.8 (C-9), 131.9, 129.7, 129.6, 127.5, 127.4 (C-7, C-8, C-10, C-4′, C-6′), 130.3, 130.2, 128.6, 126.8, 122.1 (C-3, C-6a, C-10a, C-10b, C-1′), 125.2 (C-2), 120.5, 111.6 (C-3′, C-5′), 108.7 (C-1), 60.7 (CH_2), 55.8 (MeO), 14.5 ($MeCH_2$) ppm; IR (ATR): $\bar{\nu}$ = 1,089, 1,239, 1,634, 1,699, 2,937, 3,038 cm^{-1}.

Ethyl 3-(3-methoxybenzoyl)pyrrolo[2,1-a]phthalazine-1-carboxylate (**12k**, $C_{22}H_{18}N_2O_4$)
Yield 67%; m.p.: 181–183 °C (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.85–9.82 (m, 1H, H-10), 8.76 (s, 1H, H-6), 7.93–7.88 (m, 2H, H-7, H-9), 7.77–7.72 (m, 1H, H-8), 7.73 (1H, s, H-2), 7.55–7.51 (m, 2H, H-2′, H-6′), 7.43 (t, 1H, J = 8.0 Hz, H-5′), 7.17 (ddd, 1H, J = 8.0, 2.4, 1.1 Hz, H-4′), 4.42 (q, 2H, J = 7.1 Hz, CH_2), 3.89 (s, 3H, MeO), 1.42 (t, 3H, J = 7.1 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.5 (COAr), 164.3 (COO), 159.8 (C-3′), 146.5 (C-6), 140.5 (C-1′), 133.0 (C-9), 130.3, 127.2, 126.9, 122.3 (C-3, C-6a, C-10a, C-10b), 129.8, 122.6, 119.0, 114.2 (C-2′, C-4′, C-5′, C-6′), 129.4, 127.7, 127.6 (C-7, C-8, C-10), 108.4 (C-1), 60.8 (CH_2), 55.6 (MeO), 14.5 ($MeCH_2$) ppm; IR (ATR): $\bar{\nu}$ = 1,090, 1,259, 1,634, 1,704, 2,976, 3,037 cm^{-1}.

X-ray data collection

A single crystal of **8** was mounted on a Nonius Kappa CCD diffractometer and cooled in a constant stream of nitrogen vapor. Intensity data were collected with graphite-monochromated Mo K_α radiation (λ = 0.71073 Å). Data collection strategy was determined using the program COLLECT [34], and data reduction, including Lorentz-polarization corrections, was performed with DEMZO-SMN [35]. Programs SHELXS-97 and SHELXL97 were used for structure solution and full-matrix least-squares refinement [36]. In the course of refinement, an alternative

Table 1 Crystal data and refinement parameters for compound **8**

Empirical formula	$C_{17}H_{16}N_2O_5$
Formula weight (g mol^{-1})	328.32
Unit cell lengths (Å)	8.6689(4), 9.2817(3), 11.0265(6)
Unit cell angles (°)	91.899(3), 106.522(2), 112.784(2)
Cell volume (Å^3)	773.84(6)
Temperature (K)	173(2)
Calculated density (g cm^{-3})	1.409
Crystal size (mm^3)	0.09 × 0.11 × 0.16
F(000)	344
Intensity scans (°)	φ- and ω-scans of 2.00°
θ-range for data collection (°)	3.34–26.39
Range in *hkl*	−10, 10; −11, 11; −13, 13
Total no. of reflections	6,101
Independent reflections	3,157 ($R_{int} = 0.0232$)
Reflections with $I \geq 2\sigma(I)$	2,553
Data/parameters	13.6
Goodness of fit on F^2	1.036
Final R indices [$I \geq 2\sigma(I)$]	$R1 = 0.0378$
	$wR_2 = 0.0893$
R indices (all data)	$R1 = 0.0532$
	$wR_2 = 0.0967$
Largest diff. peak and hole (eÅ^{-3})	−0.26 and 0.28

position for methyl carbon atom C24A was located at 1.5 Å from carbonyl atom O22. The alternative position was modeled as C24B with the site occupancy (s.o.f.) of the two methyl groups refining as x and 1 - x. The dominant position (C24A) had a final refined s.o.f. of 0.742(4). All H atoms were located in difference Fourier syntheses and were added in idealized positions with isotropic thermal parameters 1.2–1.5 times those of their parent atoms. Non-H atoms refined anisotropically. Table 1 lists crystal data and other relevant refinement parameters. Full crystallographic data for compound **8** have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge, England (CCDC 796174).

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