Products from dehydration of dicarboxylic acids derived from anthranilic acid

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Treatment of *N*-(carboxymethyl)-anthranilic acids **1** with several dehydrating agents, gave the cyclic ortho amides **6**, or the 7-membered anhydrides **7**. After reaction of *N*-(carboxymethyl)-anthranilic acid (**1a**) with acetic anhydride, a diacetylated fused diketopiperazine indole dimer (**18**) could be isolated. Dehydrations of 2,2′-iminobis-benzoic acid led to the corresponding cyclic ortho amides **23**. The dynamic behaviour of some of these compounds, and their precursors, was studied.

Introduction

Several workers have treated *N*-(carboxymethyl)-anthranilic acids with various dehydrating agents, not least during the classical era of indigo synthesis.[1] In 1890 Heumann prepared indigo by air oxidation of indoxylic acid which was in turn prepared by dehydration of *N*-(carboxymethyl)anthranilic acid (**1a**) in an alkali melt (Scheme 1).[2] Ullman and Kopetschni[3] and Friedländer and coworkers[4] respectively used in principle the same method to prepare various symmetric bromo and methyl derivatives of indigo in the early years of the twentieth century. In the latter two instances the dehydration to the indoxylic acid was performed using acetate in acetic anhydride.


Scheme 1 Indigo synthesis.
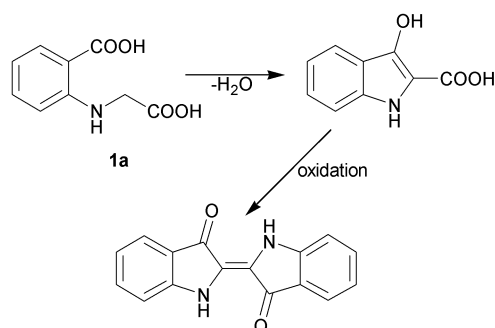
In more recent times it has been reported that treatment of the diacid **1a** with hot acetic anhydride (Ac₂O) can give rather unexpected products, as exemplified by the benzoxazinone **2** (Chart 1),[5] initially incorrectly reported as the fused zwitterionic quinoline derivative **3**.[6]

1a R=H
b R=Me
c R=Et
**d** R=COCF₃

Chart 1
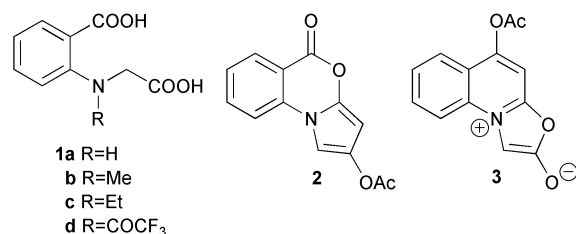
Herein we present a modern study, with reference to older work, on dehydration reactions of some dicarboxylic acids derived from anthranilic acid, in particular *N*-(carboxymethyl)anthranilic acids.

Results and discussion

It has recently been shown that when *N*-(phenylacetyl)anthranilic acid (**4**) is treated with oxalyl chloride in acetonitrile, the cyclic ortho amide derivative **5** is formed (Chart 2).[7] There is an extensive series of articles covering synthesis and reactions of ortho amides, in which the two first articles describe their properties in general terms.[8,9] More recently a review has been published.[10]

Chart 2
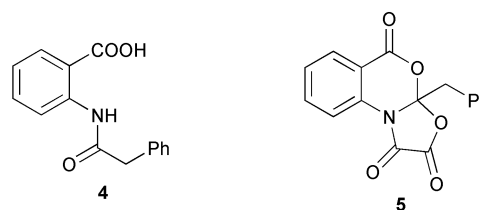
In analogy with the facile formation of **5** from **4** we anticipated that **1a**, when treated with trifluoroacetic anhydride (TFAA), should give rise to the cyclic orthoamide **6a** (Scheme 2), which also proved to be the case. The product has previously

Scheme 2
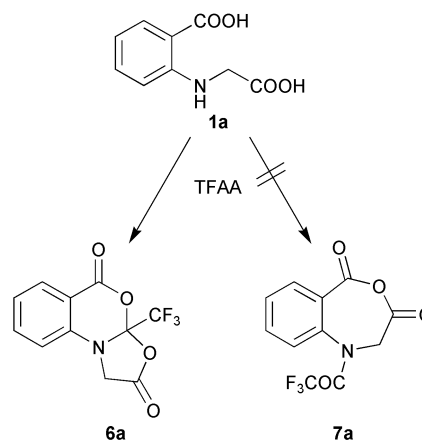
been reported as having the 7-membered anhydride structure **7a**,[6] but this structure is not consistent with the spectral data. The diastereotopic protons of the methylene group resonated at 4.26 and 4.56 ppm respectively in CDCl₃. In the ¹³C-NMR spectrum the signal from the non-carbonyl quaternary aliphatic carbon atom appeared as a quartet at 105.7 ppm ($^2J_{CF}$ = 39 Hz).

Treatment of the diacid **1a** with pentafluoropropionic anhydride similarly yielded the cyclic orthoamide **6b** (Fig. 1), which formed large regular crystals (racemic) and the structure could be solved by X-ray crystallography (Fig. 1) proving the structures of type **6**.
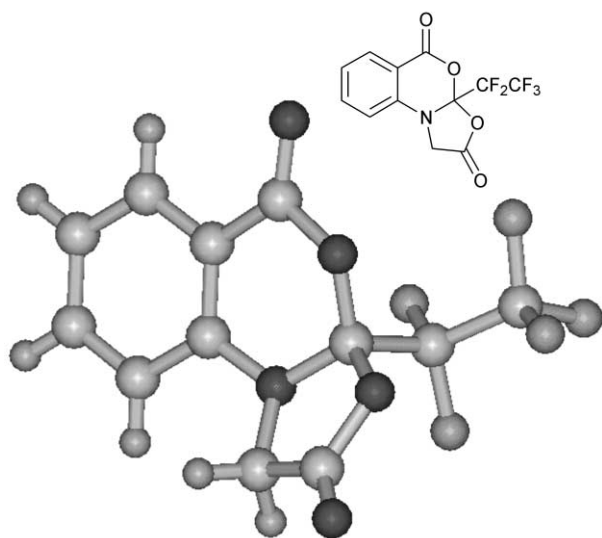

Fig. 1 X-Ray crystal structure of **6b** (*S*-enantiomer shown), showing the skewed middle ring.

The precursor of **6a**, *i.e.* the open diacid **1d**, could easily be cyclised to **6a** when heated for a short period of time in Ac$_2$O. No NMR evidence for the coexistence of **1d** with either of its ring tautomers **8a** or **8b** could be obtained (Scheme 3). The same is true for the known parent compound *N*-trifluoro-acetylphenylglycine.[11] When **6a** was dissolved in wet DMSO-d_6 and NMR spectra were obtained over a period of time, two sets of signals appeared, one matching **6a** and one matching **1d**. After one week only signals from **1d** could be detected. Thus, **6a** must be in equilibrium with its half-open forms and water in DMSO solution. In fact, formation of **6a** must go through this equilibrium.
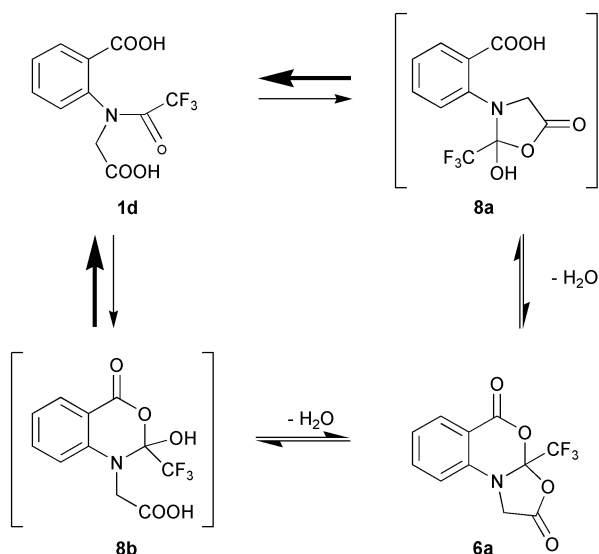
Scheme 3 Formation of the cyclic orthoamide **6a**.

Related ring-chain tautomerisms have been investigated by Bowden and Byrne.[12] By means of ^{1}H-NMR and pK_a-measurements it was concluded that molecules of the general structure **9** (Scheme 4) also reside mainly in their chain forms. However, ^{13}C-NMR data (in CDCl$_3$) did, in some cases, show additional
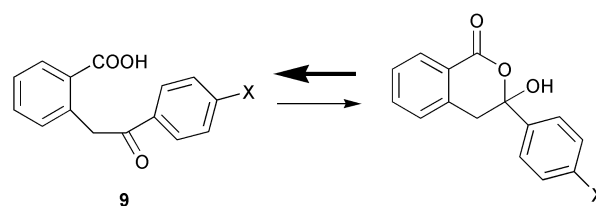
Scheme 4

ester carbonyl and lactol carbon signals, a clear indication of the presence of small amounts of the cyclic forms.

Very recently a study of the dynamic ring-chain behaviour of the bislactam *N*-(2-aminoacetyl)-2-pyrrolidone has been published, in which cyclol forms are discussed.[13]

A compound with a structure related to **6a**, namely compound **10** (Chart 3), has previously been prepared from the acid **11**[14] (deprotection with TFA, followed by treatment of the resulting *N*-trifluoroacetamide derivative with base).[15] The reported spectroscopic data for compound **10** are strikingly similar to that of the compounds **6**: IR v_{max}/cm^{-1} 1830, 1720, 1630; δ_H (DMSO-d_6): 4.00 (2 H, d, no *J* given, CH$_2$); δ_C (DMSO-d_6): 54.0 (CH$_2$), 112.9 (bridging quaternary carbon). Similarly, for the peptide cyclols **12** (X-ray structure was given)[16] and **13**[17] the authors have argued for the assigned structure based on the fact that one ^{13}C-NMR carbonyl signal disappears on ring-closure, and reappears as a singlet (at 96.4 and 94.1 ppm respectively in CDCl$_3$) of the bridging carbon.
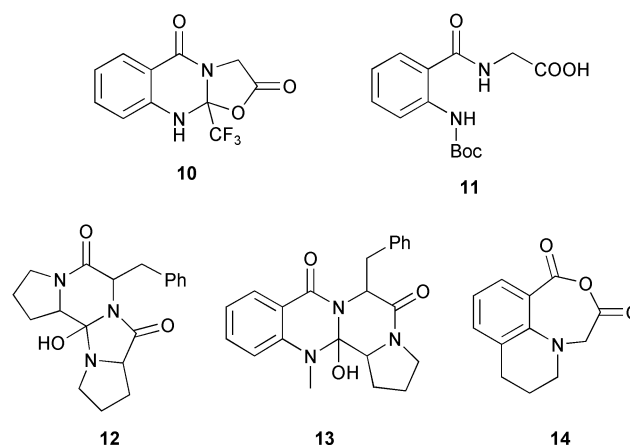

Chart 3

Although the seven-membered anhydride **7a** seems still to elude preparation, it was discovered that the N-alkylated diacids **1b** and **1c** could easily be converted to the corresponding cyclic anhydrides **7b** and **7c** respectively, when heated in Ac$_2$O (Chart 4).
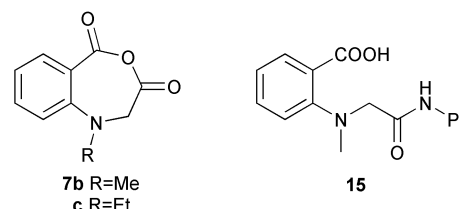
Chart 4

This cyclisation could also be effected by DCC. Compound **7b** exhibited IR carbonyl absorptions at 1784 and 1719 cm^{-1}, typical of deactivated cyclic anhydrides and indeed close to the absorptions reported for the tricyclic compound **14** (1775, 1710 cm^{-1}) (Chart 3).[18] Surprisingly the methylene ^{1}H-NMR signals of the anhydrides **7** appeared as singlets (integratating for 2 H) at room temperature, but it was discovered that on cooling

they formed AB-type patterns (Fig. 2) and the free energy of coalescence for **7b** could be calculated to 59 kJ mol^{-1}, using a modified Eyring equation for the coalescence temperature -5 °C.[19] This energy must correspond to a ring inversion. Although no similar structures are known, the result is in good agreement with ring inversion energies for other 7-membered rings with torsional restraints.[20] The relatively high barrier to ring inversion is likely to be a result of the torsional restraints of the benzene ring combined with the repulsive forces of the lone pair electrons of the four hetero atoms. A series of cyclic 7-membered oxamide derivatives (also with four heteroatoms) show inversion barriers in the range 46–97 kJ mol^{-1}.[21]
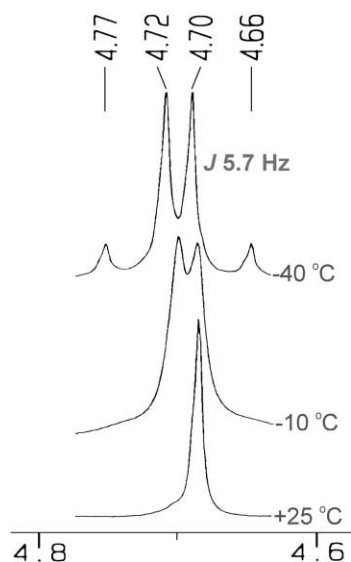

Fig. 2 Dynamic ^{1}H-NMR of the methylene group in the cyclic anhydride **7b** in CDCl$_3$.

Treatment of the anhydride **7b** with aniline, afforded the ring-opened amide-acid **15** (Chart 4), the structure of which was confirmed by an HMBC NMR spectrum which showed a ^3J-coupling between the NH and the methylene carbon (which would not be present had the ring-opening occurred in the other direction).

Experiments involving heating of the diacid **1a** with a large excess Ac$_2$O (without base present) has been reported to yield two structurally very different products. Virtually the same conditions have been claimed to lead to the monomeric compound **2** (Chart 1),[5] or the dimeric compound **17a** (Scheme 5).[22] We have had great difficulties reproducing these results. When **1a** was treated in this fashion, complex tarry mixtures resulted. Even at lower temperatures a multitude of inseparable polar compounds were formed. After treatment of **1a** with lesser amounts of Ac$_2$O in refluxing MeCN until dissolution (about 30 min), a solid could be isolated which resembled the described characteristics for compound **17a**, but it could not be purified satisfactory for NMR analysis. However, when the same experiment was carried out with a slight excess Ac$_2$O at reflux for 14 h, a low yield of an insoluble compound could be obtained. It was identified as the diacetylated compound **18** by parallel synthesis from compound **19** (by heating in Ac$_2$O). This fused diketopiperazine indole dimer can be prepared in two steps from the diacid **17b**,[23] which intriguingly is the chain–chain tautomer of the alleged compound **17a**. Compound **19** can also be prepared by high temperature treatment of the methyl ester of indoxylic acid.[24] According to the spectral data, **19** shall be represented as its dihydroxy tautomer. The synthetic procedure to the diacid **17b** from 2-iodobenzoic acid was improved, and it was found that treatment of **17b** with hot acetic anhydride gave a yellow insoluble compound, having the same elemental composition as **19**, but the NMR-data clearly showed an unsymmetrical molecule with only one methylene group. Hence structure **20** was proposed. The dehydration could also be accomplished in high yield at room temperature with Boc$_2$O (di-*tert*-butyl dicarbonate) in pyridine. Interestingly, **20** can easily be transformed into the bis-trifluoro-acetylated compound **21** (Scheme 6) in high yield *via* a ring-contraction induced by TFAA. This tetracyclic compound could subsequently be hydrolysed to **19**, providing a new synthesis of this compound in a 69% overall yield from 2-iodobenzoic acid. In fact, this hydrolysis also came about when the compound **21** was stored in air for a few days. Imine–enamine tautomerisms lie at the heart of the he proposed mechanisms for formation of **21**, *via* **19** and **20** from **17b** (Scheme 6).

In both cases the formation of the product is driven by the low solubilities in the media. Indeed, compounds **18**–**21** were all very insoluble, and acquisition of good NMR data for **18** and **21** was impossible as they decomposed at high temperature. Compound **20** proved to be soluble in deuterated TFA (possibly in a protonated form).
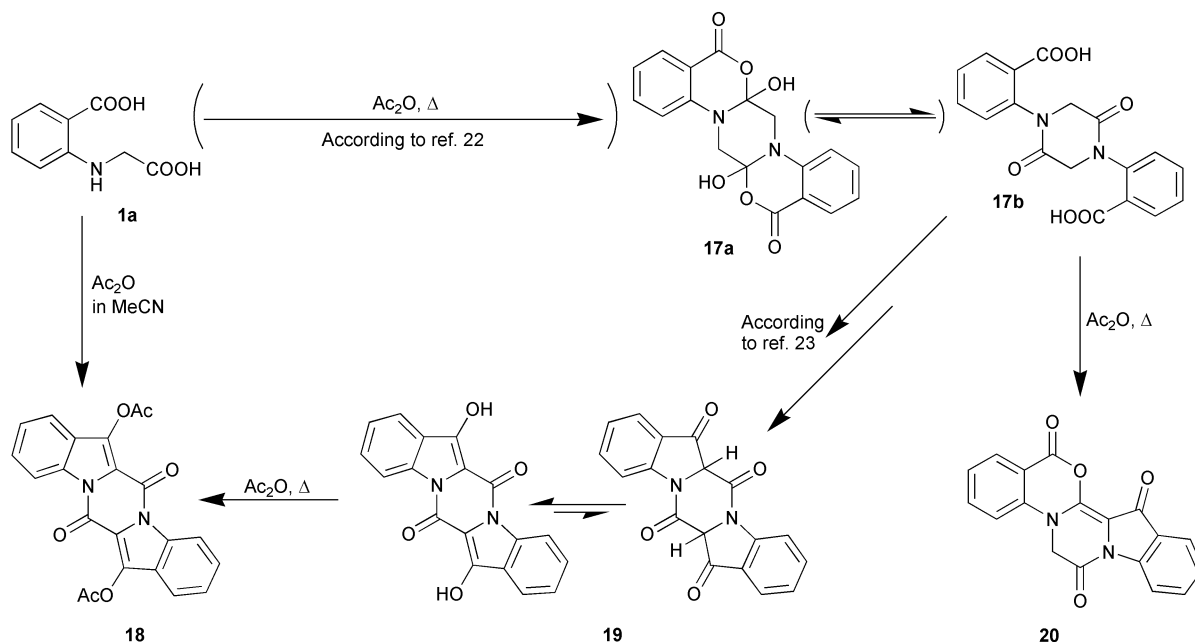
Scheme 5 Diketopiperazine indole dimers.
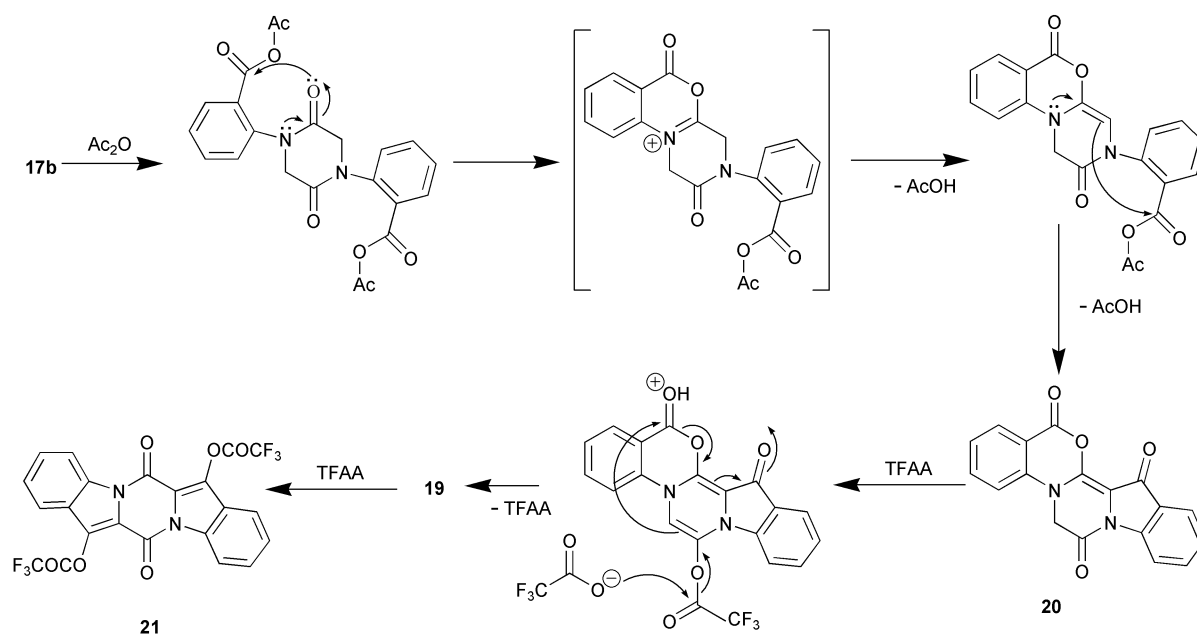
Scheme 6

Treatment of 2,2′-iminobis-benzoic acid with hot Ac₂O has been reported to yield the anhydride **22** (Chart 5).[25] In light of the discoveries reported above, this structural interpretation was questioned, and the ¹³C-NMR spectrum of this product revealed three quaternary signals (110.5, 142.7, 159.1 ppm in CDCl₃), and a single carbonyl signal (159.8 ppm). The structure must therefore be **23a**. Compound **23b** could also be prepared, but in this case accompanied by formation of the known[26,27] acridone-4-carboxylic acid. Compound **24**, with a related structure, has been reported by Aversa and coworkers who obtained it by heating *N*-(2-hydroxybenzyl)-anthranilic acid with TFAA.[28] The structure was confirmed by X-ray crystallography. Another molecule, **25**, with an interesting structural relationship with the compounds **23**, has been reported by Katritzky *et al.*,[29] and a discussion of the bisamide equivalent to **23a** has also appeared.[30]
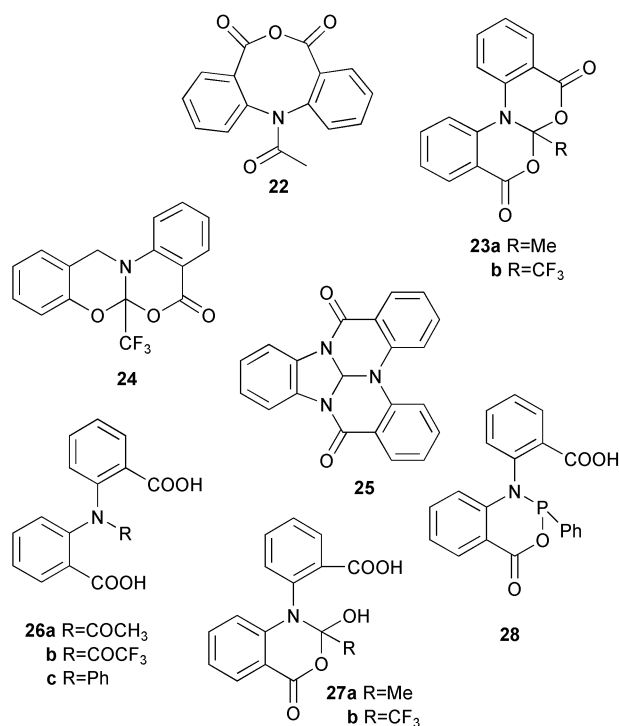
Treatment of 2,2′-iminobis-benzoic acid with Ac₂O for a shorter period of time (2–5 min at 105 °C), gave a good yield of a compound that featured three non-aromatic quaternary signals (167.3, 167.6, 169.8 ppm in DMSO-*d₆*) and eight aromatic CH signals in the ¹³C-NMR spectrum at 25 °C. However, when the sample was heated the ¹H-spectrum gradually simplified in the temperature range 60–85 °C, and at the higher end of this range the ¹³C-NMR spectrum showed only two carbonyl carbons. Since the process of heating and then cooling the sample could be repeated several times without any spectral change, the dynamic behaviour indicated hindered rotation in a symmetric molecule. The structure was therefore determined to be the amide **26a**. In direct parallel to the relationship between **1d** and **6a** (Scheme 2), the presence of the ring tautomer of **26a**, *i.e.* **27a**, could thus not be detected. The solvent dependant equilibria of the tautomeric forms of the corresponding phosphorous compound **28** has previously been studied.[31] Compound **26b** could also be prepared, and it too displayed hindered rotation (a time averaged symmetric ¹³C-NMR appeared at 95 °C). Both **26a** and **26b** could be ring closed to the compounds **23a** and **23b** respectively by treatment with Ac₂O In this context it is worth mentioning that the asymmetric hydrogen bonded solid state conformation of compound **26c** has very recently been investigated.[32]

There is yet another dehydration of an anthranilic acid derivative which has figured in the literature since the 1800s. It has been claimed that the condensation product obtained from the reaction of anthranilic acid and phthalic anhydride should be the cyclol **29a** (Chart 6).[33–35] We have reacted the two substrates in a melt according to Gabriel,[36] in refluxing tetraline using a Dean–Stark trap according to Balasubramaniyan and Argade,[35] and in refluxing acetic acid. The products were spectroscopically identical, but the product from the reaction in acetic acid was by far the purest. In light of the ¹³C-NMR spectrum of this compound (two carbonyl signals and three aromatic singlets), structure **29a** can unequivocally be refuted and the structure established as the phthalimide **30**.

In the literature several derivatives of **29a** have been reported, among them the acetylated molecule **29b** has been reported to be the product after refluxing **29a** (*i.e.* **30**) in Ac₂O with sodium acetate.[35] We found this experiment to give a low yield of a compound that we could also prepare in a better yield by omitting the sodium acetate (and thus the need for aqueous work up). The product was identified as the anhydride of the starting material, *i.e.* compound **31** (Scheme 7). The same
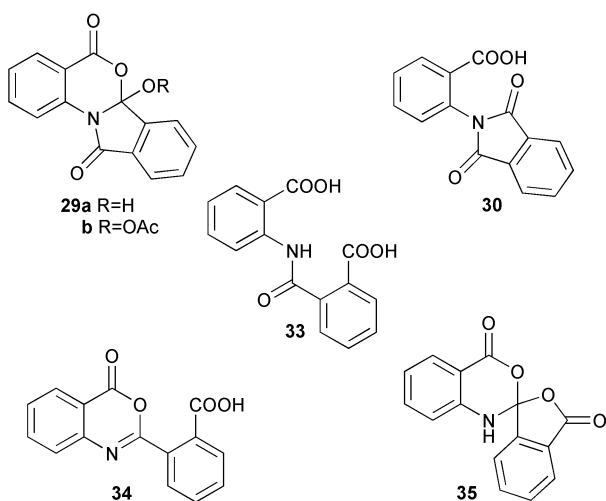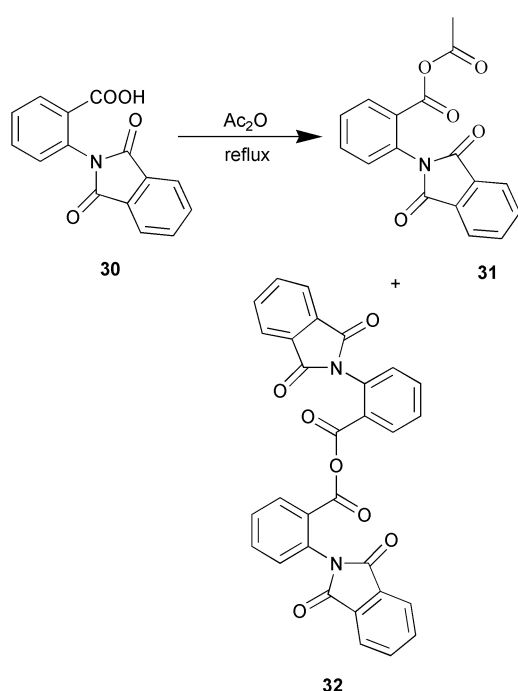

Chart 5

Chart 6 Compounds derived from anthranilic acid and phthalic acid.

Scheme 7

reaction also yielded a much less soluble compound also having the high carbonyl IR absorption typical of anhydrides. The IR-data exactly matched those reported for the dimeric anhydride **32**,[37] and the acquired NMR-data also supports this structural assignment.

It has also been claimed that the open diacid **33** (Chart 6) can be prepared directly from anthranilic acid and phthalic anhydride in refluxing benzene.[33] We have not been able to reproduce this experiment in any solvent. However, this compound can easily be prepared in quantitative yield by hydrolysis of **30**. Several different formal dehydration products of the diacid **33** have appeared in the literature, among them compound **34**[37] which has been mistaken for compound **35** at least twice.[38,39] Compound **34** can be prepared from anthranilic acid and phthalic dichloride,[37,38] and can in fact be transformed into the true **29b**.[37]

Experimental

NMR spectra were recorded on a Bruker DPX ([1]H 300 MHz, [13]C 75 MHz) or a JEOL Eclipse ([1]H 500 MHz, [13]C 125 MHz) at 25 °C unless otherwise stated. Chemical shifts (δ) are given relative to the solvent residual proton signals and solvent [13]C-

signals.[40] Coupling constants (J) are given in Hz. Multiplicities (connectivity) of ^{13}C-signals due to proton coupling were determined with DEPT, APT or PENDANT pulse sequences. IR spectra were recorded on a Perkin Elmer 1600 FT-IR on KBr tablets. Elemental analyses were performed by H. Kolbe, Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Single-crystal X-ray diffraction analysis was performed by Birgitta Stensland (AstraZeneca PAR&D/SBBG, Solid State Analysis, Södertälje, Sweden). Melting points were determined on a Leica Kofler hot stage, or a Büchi B-545 capillary melting point apparatus.

2-[Carboxymethyl-(2,2,2-trifluoroacetyl)amino]benzoic acid (1d)

N-(Carboxymethyl)-anthranilic acid(1.95 g, 10.0 mmol) acid dispersed in 20 mL MeCN was stirred with TFAA (5.0 mL) for 2 h. The reaction mixture was filtered into water (50 mL). After 24 h the mixture was filtered and extracted with 2 × 40 mL Et$_2$O. The combined organic layers were dried (Na$_2$SO$_4$) and thoroughly evaporated to yield a semi-solid material (1.58 g) which was dissolved in 20 mL Et$_2$O. After addition of 20 mL cyclohexane, the solution was filtered and heated until a solid formed. This yielded 0.84 g (29%) slightly yellow powder, mp 148 °C. Satisfactory elemental analysis could not be obtained, probably due to ring-closure to **5a**. IR ν_{max}/cm^{-1}; 3032, 2656, 2558, 1725, 1698, 1687, 1292, 1253, 1165, 1142, 1101, 1009, 900, 782, 761, 706, 686, 626. δ_H (300 MHz; DMSO-d_6): 4.01 (1 H, d, J 17), 4.63 (1 H, d, J 17), 7.58–7.63 (2 H, m), 7.73 (1 H, t, J 7.5), 8.04 (1 H, d, J 7.8), 13.24 (1 H, br s); δ_C (75 MHz; DMSO-d_6): 53.1 (t), 116.0 (s, q$_{CF}$, J 387), 128.7 (s), 130.3 (d), 130.5 (d), 131.7 (d), 133.4 (d), 138.9 (s), 155.4 (s, q$_{CF}$, J 35), 165.7 (s), 169.0 (s).

3a-Trifluoromethyl-3,4-dioxa-9b-azabenz[*e*]indene-2,5-dione (6a)

N-(Carboxymethyl)anthranilic acid (1.95 g, 10.0 mmol) was treated with TFAA (3.0 mL, 21 mmol), and stirred for 20 h. Evaporation *in vacuo* yielded an oil which was extracted with 30 mL hot hexane–chloroform 2 : 1. On cooling of the extract, a crystalline material formed. This material was recrystallised from hexane–chloroform to afford 1.40 g (51%) white fine needles, mp 110 °C (lit.[6] mp 100–102 °C). When compound **1d** was heated in Ac$_2$O, cooled and the excess Ac$_2$O evaporated *in vacuo*, the same compound resulted; IR ν_{max}/cm^{-1}: 1852, 1841, 1764, 1610, 1496, 1473, 1446, 1377, 1302, 1261, 1205, 1182, 1096, 1042, 1011, 914, 840, 752, 732; δ_H (500 MHz; CDCl$_3$): 4.22 (1 H, d, J 16.0), 4.54 (1 H, d, J 16.0), 6.88 (1 H, d, J 7.8), 7.21 (1 H, dt, J 0.92 and 7.8), 7.67 (1 H, dt, J 1.8 and 7.9), 8.04 (1 H, dd, J 1.3 and 7.9); δ_C (75 MHz; CDCl$_3$): 49.6 (t), 105.7 (s, q$_{CF}$, J_{CF} 39), 111.4 (s), 116.8 (d), 120.0 (s, q$_{CF}$, J_{CF} 288), 123.7 (d), 130.9 (d), 137.2 (d), 142.2 (s), 156.6 (s), 164.4 (s).

3a-Pentafluoroethyl-3,4-dioxa-9b-azabenz[*e*]indene-2,5-dione (6b)

N-(Carboxymethyl)anthranilic acid (1.95 g, 10.0 mmol) was treated with pentafluoropropionic anhydride (6.51 g, 21 mmol), and stirred for 24 h. Evaporation gave an oil which was dissolved in a small volume Et$_2$O. After addition of a larger volume of hexane, crystals slowly formed. After 12 h the liquid was decanted off and the crystalline material recrystallised from hexane to give 1.35 g (42%) large crystals, mp 99 °C (Found C, 44.72; H, 1.85; N, 4.41. C$_{12}$H$_6$F$_5$NO$_4$ requires C, 44.60; H, 1.87; N, 4.33%); IR ν_{max}/cm^{-1}: 1849, 1762, 1610, 1446, 1372, 1310, 1226, 1171, 1100, 1086, 972, 881, 742; δ_H (500 MHz; CDCl$_3$): 4.23 (1 H, d, J 16.0), 4.53 (1 H, d, J 16.0), 6.90 (1 H, d, J 7.8), 7.20 (1 H, t, J 7.8), 7.67 (1 H, dt, J 1.4 and 7.8), 8.00 (1 H, dd, J 1.4 and 7.8); δ_C (125 MHz; CDCl$_3$): 49.5 (s), 107.0 (s, t$_{CF}$, J_{CF} 30), 110.4 (s, tq$_{CF}$, J_{CF} 37 and 294), 111.5 (s), 117.0 (d), 117.8 (s, qt$_{CF}$, J_{CF} 35 and 288), 123.8 (d), 130.8 (d), 137.3 (d), 142.4 (s), 156.3 (s), 164.2 (s).

Crystal structure determination †. : A colourless crystal (0.11 × 0.14 × 0.23 mm) was selected for the single-crystal diffraction analysis. The diffracted intensities were collected at rt with monochromatized MoKα radiation (λ = 0.71073 Å) on a KappaCCD single crystal X-ray diffractometer, with a κ-axis goniometer and a CCD area detector. 139 Frames were collected with increments of 2.0° with 20 s exposure per frame. Raw data was processed within the *Denzo-SMN* software and the structure was solved with direct methods. The structure was refined with full-matrix least-squares calculations within the *MaXus* program system[41]. All *non*-H atoms were refined with anisotropic thermal parameters. The H-atom positions, verified from subsequent Fourier electron density maps were placed in geometrical relevant positions at a distance 0.96 Å from the parent atom and supplied with isotropic thermal displacement factors, U(iso) = 0.05 Å^2. No absorption correction was done. *Crystal data*: $C_{12}H_6OF_5O_4N$, M = 323.18, monoclinic, a = 10.323(1), b = 8.328(1), c = 15.665(1) Å, β = 108.30(1)°, U = 1278.6(2) Å^3, T = 298 K, space group: $P2_1/c$, Z = 4, D_c = 1.679(1) g cm^{-3}, μ = 1.72 cm^{-1}, 2851 reflections measured. A total of 1148 unique reflections [$F^2 > 4\sigma(F^2)$] refined on F were used to give R = 0.0499, R_w = 0.060 for 200 parameters (w = 1/ $\sigma^2 F_o^2$ + 0.0300F_o^2). $(\Delta/\sigma)_{max}$ = 0.0001, $\Delta\rho_{max}$ = 0.40 e Å^{-1}, $\Delta\rho_{min}$ = −0.31e Å^{-1} and $\Delta\rho_{mean}$ = 0.05 e Å^{-1}. S = 1.554.

1,2-Dihydro-1-methyl-4,1-benzoxazepine-3,5-dione (7b)

N-(Carboxymethyl)-*N*-methylanthranilic acid[42–44] (2.09 g, 10.0 mmol) was refluxed in 12 mL Ac$_2$O for 30 min. On cooling large crystals of the title anhydride formed and were separated off to yield 1.48 g (78%), mp 144–145 °C (Found C, 62.78, H, 4.73, N, 7.30. $C_{10}H_9NO_3$ requires C, 62.82, H, 4.75, N, 7.33%); IR v_{max}/cm^{-1}: 1782, 1715, 1606, 1557, 1508, 1439, 1331, 1299, 1261, 1203, 1177, 1103, 1000, 747, 708; δ_H (300 MHz; DMSO-d_6): 3.24 (3 H, s), 4.13 (2 H, s), 6.95 (1 H, dt, J 0.9 and 6.1), 7.16 (1 H, d, J 8.2), 7.56 (1 H, dt, J 1.6 and 6.1), 7.89 (1 H, dd, J 1.6 and 8.2); δ_C (75 MHz, DMSO-d_6): 39.7 (q), 112.4 (s), 115.7 (d), 118.4 (d), 134.1 (d), 135.0 (d), 149.5 (s), 162.3 (s), 162.7 (s).

1,2-Dihydro-1-ethyl-4,1-benzoxazepine-3,5-dione (7c)

N-(Carboxymethyl)-*N*-ethyl-anthranilic acid[42,44] (2.23 g, 10.0 mmol) was treated as above (see **7b**) to yield 1.68 g (82%) solid material, mp 107–108 °C (Found C, 64.16; H, 5.32, N, 6.69. $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.83%); IR v_{max}/cm^{-1}: 1784, 1719, 1605, 1501, 1448, 1284, 1250, 1171, 1004, 979, 747; δ_H (500 MHz; DMSO-d_6): 1.16 (3 H, t, J 6.9), 3.67 (2 H, q, J 6.9), 4.13 (2 H, s), 6.92 (1 H, t, J 7.0), 7.21 (1 H, d, J 8.3), 7.54 (1 H, t, J 8.3), 7.88 (1 H, d, J 7.0); δ_C (125 MHz; DMSO-d_6): 12.8 (q), 47.1 (t), 55.3 (t), 113.0 (s), 116.2 (d), 118.8 (d), 134.9 (d), 135.7 (d), 149.1 (s), 162.9 (s), 164.0 (s).

2-{Methyl[2-oxo-2-(phenylamino)ethyl]amino}benzoic acid (15)

Compound **7b** (0.38 g, 2.0 mmol) was refluxed in 5 mL dioxane with aniline (0.23 mL, 2.5 mmol) for 30 min. The reaction mixture was poured on 20 mL water. After a few minutes the pure product was filtered off and let dry. This yielded 0.40 g (70%) of a white granular solid, mp 163 °C (lit.[45] mp 155–158 °C); IR v_{max}/cm^{-1}: 3259, 3198, 3039, 1691, 1599, 1558, 1499, 1487, 1458, 1446, 1361, 1315, 835, 755; δ_H (300 MHz; DMSO-d_6): 2.81 (3 H, s), 4.00 (2 H, s), 7.05 (1 H, t, J 7.5); 7.22 (1 H, dt, J 1.1 and 7.2), 7.31 (2 H, m), 7.46 (1 H, d, J 7.9), 7.55 (1 H, dd, J 1.5 and 7.2), 7.59–7.62 (2 H, m), 7.88 (1 H, dd, J 1.5 and 7.9); δ_C (75 MHz; DMSO-d_6): 44.0 (q), 58.7 (t), 119.0 (d), 121.9 (d), 123.5 (d), 124.0 (d), 124.3 (s), 128.8 (d), 130.0 (d), 133.2 (d), 138.6 (s), 151.2 (s), 167.5 (s), 168.0 (s).

2,2′-(2,5-Dioxo-1,4-piperazinediyl)bis-benzoic acid (17b)

2,5-Piperazinedione (1.14 g, 10.0 mmol) and 2-iodobenzoic acid (5.0 g, 20.2 mmol) was refluxed for 2 h in 40 mL DMF with 0.5 g copper powder and K$_2$CO$_3$ (3.0 g, 22 mmol) under a nitrogen atmosphere. The reaction mixture was cooled to rt and the excess copper powder filtered off. The filtrate was poured on 250 mL ice–water. After several hours the product could be filtered off and washed with water. After letting the material dry, this yielded 3.10 g (88%) beige powder, mp *ca.* 270 °C. For analytical purposes this material could be recrystallised from EtOH to yield a white solid, mp 282–284 °C (dec.) (lit.[23] mp 279–281 °C); IR v_{max}/cm^{-1}: 3496, 2926, 2627, 1708, 1637, 1600, 1492, 1474, 1335, 1260, 1243, 759; δ_H (300 MHz; DMSO-d_6): 4.35 (4 H, s), 7.39–7.53 (4 H, m), 7.70 (2 H, t, J 7.5), 7.93 (2 H, d, J 7.5), 13.13 (2 H, br s); δ_C (75 MHz; DMSO-d_6): 53.6 (t), 128.3 (d), 129.0 (d), 129.1 (s), 131.0 (d), 133.5 (d), 139.9 (s), 164.6 (s), 166.6 (s).

7,14-Diacetoxy-6H,13H-pyrazino[1,2-a:4,5-a′]diindole-6,13-dione (18)

Method 1. : *N*-(Carboxymethyl)anthranilic acid (1.95 g, 10.0 mmol) was refluxed in 20 mL MeCN with 3.0 mL Ac$_2$O for 14 h. The mixture was poured on 100 mL water. The solid was filtered off and was washed with water. When dry, this material was washed with portions of hot EtOAc until the washings were colourless. This gave 0.22 g (5.5%) off white solid.

Method 2. : Compound **19** (0.32 g, 1.0 mmol) was refluxed in 3.0 mL Ac$_2$O for 18 h. The mixture was cooled to rt. The formed solid was filtered off, washed with Et$_2$O and triturated with hot AcOH to yield 0.36 g (89%) of the title compound as a solid material, mp 285 °C. For analytical purposes the material could be recrystallised from *N,N*-dimethylacetamide, which gave a yellowish material, mp 296–299 °C (Found C, 65.74; H, 3.61; N, 6.99. $C_{22}H_{14}N_2O_6$ requires C, 65.67; H, 3.51; N, 6.96%); IR v_{max}/cm^{-1}: 1783, 1704, 1593, 1573, 1453, 1402, 1357, 1238, 1186, 1162, 1110, 1021, 1007, 863, 765, 752, 738, 542; The compound was too insoluble for NMR analysis.

7,14-Dihydroxy-6H,13H-pyrazino[1,2-a:4,5-a′]diindole-6,13-dione (19)

Compound **21** (0.26 g, 0.50 mmol) was hydrolysed with NaOH (0.20 g) in 10 mL dioxane–1.5 mL water at reflux for 16 h. The mixture containing the red dianion of the product was poured into 30 mL 2 M HCl, after which time the yellow coloured product could be filtered off. After drying, this gave 0.15 g (94%) of compound **19**, mp 394 °C (lit.[23] mp >320 °C); IR v_{max}/cm^{-1}: 3358, 1688, 1667, 1618, 1596, 1574, 1453, 1411, 1277, 1238, 1167, 1019, 994, 751, 738; δ_H (300 MHz; DMSO-d_6); 7.39 (2 H, t, J 7.8), 7.61 (2 H, t, J 7.5), 7.91 (2 H, d, J 7.5), 8.52 (2 H, d, J 7.8); δ_C (125 MHz; 85 °C, DMSO-d_6): 109.4 (s), 116.6 (d), 121.1 (d), 123.3 (s), 124.6 (d), 130.2 (d), 133.9 (s), 150.0 (s), 154.2 (s). The spectral properties were identical to those of the products from literature procedures.[23,24]

12-Oxa-4b,6a-diazaindeno[2,1-a]phenanthrene-6,11,13-trione (20)

Method 1. : The diacid **17b** (1.06 g, 3.0 mmol) was refluxed in 12 mL Ac$_2$O for 15 min. The flask was cooled to rt, and the solid filtered off and washed with Et$_2$O. This gave 0.72 g (75%) intensely yellow fine powder.

Method 2. : The diacid **17b** (1.06 g, 3.0 mmol) was stirred in 7.5 mL pyridine with di-*tert*-butyl dicarbonate (Boc$_2$O, 1.35 g, 6.2 mmol) for 1 h. During the first minutes gas evolved. 40 mL Et$_2$O was added and the solid was filtered off to yield 0.81 g (84%) intensely yellow fine powder, mp 308–310 °C (dec.) (Found C, 67.78; H, 3.11; N, 8.89. $C_{18}H_{10}N_2O_4$ requires C,

67.92; H, 3.17; N, 8.80%); IR v_{max}/cm^{-1}: 1766, 1696, 1679, 1602, 1564, 1481, 1466, 1422, 1396, 1309, 1219, 914, 748; δ_H (300 MHz; 75 °C, DMSO-d_6): 4.86 (2 H, s), 7.42 (2 H, m), 7.52 (1 H, d, J 8.4), 7.71 (1 H, t, J and 8.4), 7.80 (1 H, d, J 7.7), 7.90 (1 H, t, J 7.3), 8.07 (1 H, d, J 7.3); δ_H (500 MHz; CF$_3$OOD): 5.44 (2 H, s), 7.64 (1 H, t, J 8), 7.73 (1 H, d, J 8), 7.82 (1 H, t, J 8), 7.94 (1 H, t, J 8), 8.11 (1 H, d, J 8), 8.16 (1 H, t, J 8), 8.44 (1 H, d, J 8), 8.51 (1 H, d, J 8) [Coupling constants could not be matched with higher accuracy]; δ_C (125 MHz; CF$_3$OOD): 52.3 (t), 103.8 (s), 114.6 (s), 118.0 (s), 119.5 (d), 124.5 (s), 125.1 (d), 130.4 (d), 133.1 (d), 134.4 (d), 139.1 (d), 139.5 (s), 140.1 (s), 142.4 (d), 154.5 (s), 156.5 (s), 160.4 (s).

7,14-Bis(trifluoroacetoxy)-6*H*,13*H*-pyrazino[1,2-a:4,5-a′]di-indole-6,13-dione (21)

Compound **20** (0.63 g, 2.0 mmol) was stirred with 3.0 mL TFAA in 15 mL MeCN at 50 °C for 1 h. The reaction mixture was poured on 50 mL water, after which the product was filtered off and washed with water. This gave 0.67 g (66%) yellow powder, mp 385 °C (dec.); IR v_{max}/cm^{-1}: 1813, 1707, 1596, 1575, 1453, 1398, 1366, 1338, 1242, 1175, 1098, 755; When left standing in air, the compound was hydrolysed to compound **19**, and the performed elemental analysis also match this compound (Found C, 68.10; H, 3.21; N, 8.72%). Compound **21** itself proved to be very insoluble in DMSO-d_6 (and in CDCl$_3$ and acetone-d_6) and the spectra acquired at high temperature exactly matched those of compound **19** (hydrolysis *in situ*).

6a-Methyl-6,7-dioxa-12b-azabenzo[*c*]phenanthrene-5,8-dione (23a)

2,2′-Iminobis-benzoic acid (2.57 g, 10.0 mmol) was refluxed in 25 mL Ac$_2$O for 30 min. The crystalline material which formed on cooling of the reaction mixture was collected and dried to yield 2.65 g (95%) of **23a**, mp 280–283 °C [lit.[25] mp 280–287 °C (dec.)]; IR v_{max}/cm^{-1}: 1751, 1606, 1485, 1392, 1297, 1020, 962, 898, 774, 696, 523; δ_H (300 MHz; CDCl$_3$): 1.94 (3 H, s), 7.16 (2 H, d, J 8.1), 7.35 (2H, dt, J 0.85 and 8.1), 7.64 (2H, dt, J 1.6 and 7.7), 8.13 (2 H, dd, J 1.6 and 7.7); δ_C (75 MHz; CDCl$_3$): 26.8 (q), 110.5 (s), 117.5 (s), 121.4 (d), 125.8 (d), 131.0 (d), 135.6 (d), 142.7 (s), 159.8 (s).

6a-Trifluoromethyl-6,7-dioxa-12b-azabenzo[*c*]phenanthrene-5,8-dione (23b)

Compound **23b** (0.70 g, 2.0 mmol) was refluxed in 5 mL Ac$_2$O for 5 min. On cooling crystals of the product formed and were collected to yield 0.59 g (88%) solid material which on heating (200–250 °C) formed acridone-4-carboxylic acid (Found: C, 57.79; H, 2.51; N, 4.21. C$_{16}$H$_8$F$_3$NO$_4$ requires C, 57.32; H, 2.41; N, 4.18%); IR v_{max}/cm^{-1}: 1765, 1608, 1586, 1484, 1457, 1308, 1268, 1217, 1175, 1102, 954, 772, 751; δ_H (300 MHz; DMSO-d_6): 7.50–7.55 (4 H, m), 7.89 (2 H, dt, J 1.2 and 7.4), 8.09 (2 H, dd, J 1.2 and 8.1); δ_C (75 MHz; DMSO-d_6): 103.1 (s, q$_{CF}$, J_{CF} 35), 115.0 (s), 119.5 (s, q$_{CF}$, J_{CF} 291), 121.4 (d), 126.7 (d), 130.4 (d), 137.3 (d), 139.9 (s), 156.4 (s).

2,2′-(Acetylimino)bis-benzoic acid (26a)

2,2′-Iminobis-benzoic acid (2.57 g, 10.0 mmol) was heated in 25 mL Ac$_2$O for 2 min at 105 °C. The hot mixture was filtered (by suction) and, on rapid cooling of the filtrate, crystals of the product formed. This yielded 1.51 g (50%) of white solid, mp 220 °C (dec.) (Found: C, 64.52; H, 4.28; N, 4.72. C$_{16}$H$_{13}$NO$_5$ requires C, 64.21; H, 4.38; N, 4.68%); IR v_{max}/cm^{-1}: 3072, 3000, 2896, 2825, 1720, 1691, 1638, 1598, 1574, 1491, 1374, 1348, 1303, 1272, 1234, 1092, 770; δ_H (300 MHz; DMSO-d_6): 1.79 (3 H, s), 7.05 (1 H, dd, J 0.8 and 8.0), 7.28 (1 H, dt, J 1.1 and 7.5), 7.43–7.62 (4 H, m), 7.79 (1 H, dd, J 1.4 and 7.7), 8.00 (1 H, dd, J 1.1 and 7.5), 13.15 (2 H, br s); δ_C (75 MHz; DMSO-d_6):

22.9 (q), 126.2 (d), 127.9 (d), 128.1 (d), 129.7 (s), 129.8 (d), 130.0 (d), 130.3 (s), 131.2 (d), 132.4 (d),133.6 (d), 141.7 (s), 142.8 (s), 167. 3 (s), 167.6 (s), 169.8 (s); δ_C (75 MHz; 85 °C, DMSO-d_6): 22.7, 125.6, 127.5, 129.5, 130.4, 131.6, 132.7, 166.8, 169.2.

2,2′-(Trifluoroacetylimino)bis-benzoic acid (26b)

2,2′-Iminobis-benzoic acid (2.57 g, 10.0 mmol) was refluxed in 20 mL MeCN with 5 mL TFAA for 10 min. On cooling a crop of 1.20 g (50%) acridone-4-carboxylic acid, mp 322 °C (lit.[27] mp 324–325 °C) precipitated out of solution and was removed by filtration. The filtrate was concentrated *in vacuo* and diluted with methyl acetate, resulting in precipitation of the title compound. Filtration gave 1.65 g (47%) light yellow material of **26b** which on heating (200–250 °C) formed acridone-4-carboxylic acid (Found: C, 54.08; H, 2.72; N, 3.82. C$_{16}$H$_{10}$F$_3$NO$_5$ requires C, 54.40; H, 2.85; N, 3.97%); IR v_{max}/cm^{-1}: 3084, 3050, 2905, 2648, 2543, 1698, 1680, 1599, 1572, 1454, 1402, 1274, 1225, 1152, 757, 736; δ_H (300 MHz; DMSO-d_6): 7.17 (1 H, dd, J 0.8 and 7.7), 7.42 (1 H, dt, J 0.8 and 7.7), 7.54–7.66 (4 H, m), 7.94 (1 H, dd, J 1.5 and 7.7), 8.12 (1 H, dd, J 1.4 and 7.7), 13.81 (2 H, very br s); δ_C (75 MHz; DMSO-d_6): 116.0 (s, q$_{CF}$, J_{CF} 287), 127.8 (d), 127.9 (d), 128.1 (s), 129.1 (s), 129.3 (d), 130.0 (s), 130.9 (d), 131.6 (d), 133.3 (d), 134.0 (d), 139.7 (s), 140.5 (s), 156.2 (s, q$_{CF}$, J_{CF} 35), 166.3 (s), 166.7 (s).

2-Phthalimidobenzoic acid (30)

Phthalic anhydride (16.0 g, 0.11 mol) and anthranilic acid (13.7 g, 100 mmol) were refluxed for 3 h in 50 mL AcOH. The hot solution was poured on 100 mL water and the solid which formed was filtered off, washed with water and let dry. This yielded 21.7 g (81%) white granular powder, mp 212 °C (lit.[36] mp 217 °C from aq. EtOH); IR v_{max}/cm^{-1}: 3071 (br, w), 2668 (w), 2553 (w), 1708, 1686, 1600, 1492, 1380, 1287, 1273, 1219, 1111, 1073, 892, 756, 720; δ_H (300 MHz; DMSO-d_6): 7.55 (1 H, dd, J 1.1 and 7.9), 7.63 (1 H, dt, J 1.1 and 7.5), 7.77 (1 H, dt, J 1.5 and 7.5), 7.91–7.94 (2 H, m), 7.96–8.00 (2 H, m), 8.05 (1 H, dd, J 1.5 and 7.9), 13.12 (1 H, br s); δ_C (75 MHz; DMSO-d_6): 123.5 (d), 129.2 (d), 129.2 (s), 130.6 (d), 131.0 (d), 131.4 (s), 131.7 (s), 133.0 (d), 134.8 (d), 166.1 (s), 167.1 (s).

Acetyl-(2-phthalimido)benzoyl anhydride (31) and 2-phthalimido-benzoic acid anhydride (32)

Compound **30** (1.34 g, 5.00 mmol) was refluxed in 7.5 mL Ac$_2$O for 15 h. After cooling and evaporation *in vacuo*, an oil remained. This material was extracted with 3 × 20 mL boiling diisopropylether from which the product precipitated on cooling. This gave 0.58 g white needles of compound **31** (38%), mp 135 °C (lit.[33] mp 125 °C); IR v_{max}/cm^{-1}: 1800, 1719, 1382, 1175, 1003, 716, 703; δ_H (300 MHz; CDCl$_3$): 2.22 (3 H, s), 7.45 (1 H, dd, J 1.3 and 7.8), 7.58 (1 H, dt, 1.3 and 7.8), 7.77–7.83 (3 H, m), 7.93–7.98 (2 H, m), 8.14 (1 H, dd, J 1.5 and 7.8); δ_C (75 MHz; CDCl$_3$): 22.5 (q), 124.0 (d), 126.7 (s), 129.4 (d), 130.9 (d), 132.2 (s), 132.2 (d), 132.7 (s), 134.6 (d), 134.7 (d), 160.3 (s), 165.7 (s), 167.3 (s). The remaining residue was found to be 0.81 g of compound **32** (62%). It could be triturated with chloroform to yield a white solid, mp 295 °C (dec.) (lit.[37] mp 287–288 °C); IR v_{max}/cm^{-1}: 1791, 1717, 1383, 1208, 1016, 721, 709; δ_H (300 MHz, 45 °C, CDCl$_3$): 7.44 (2 H, dd, J 1.0 and 7.8), 7.55 (2 H, dt, J 1.3 and 7.8), 7.70–7.78, (6 H, m), 7.87–7.96 (4 H, m), 8.17 (2 H, dd, J 1.3 and 7.8); δ_C (75 MHz; 45 °C,CDCl$_3$): 124.0 (d), 124.1 (d), 126.8 (s), 129.4 (d), 131.0 (d), 132.4 (d), 132.4 (s), 133.3 (s), 134.4 (d), 134.4 (d), 159.6 (s), 167.2 (s).

N-(2-Carboxybenzoyl)anthranilic acid (33)

2-Phthalimidobenzoic acid (**30**) (2.67 g, 10.0 mmol) was stirred in 50 mL water with 0.40 g NaOH for 15 h. The reaction mixture was filtered and acidified with 3 mL conc. HCl. The

precipitated product was filtered off, washed with water and dried. This gave 2.70 g (100%) of **33** as a white solid, mp 183 °C (lit.[33] mp 171–172 °C); IR v_{max}/cm^{-1}: 3040 (br), 2637 (w), 2692 (w), 1715, 1688, 1636, 1608, 1589, 1533, 1452, 1366, 1326, 1227, 1152, 754, 727; δ_H (300 MHz; DMSO-d_6): 7.20 (1 H, dt, J 0.88 and 7.1), 7.59–7.72 (4 H, m), 7.87 (1 H, d, J 7.4), 8.02 (1 H, dd, J 1.5 and 7.9), 8.61 (1 H, d, J 8.3), 11.53 (1 H, s), 13.35 (1 H, br s); δ_C (75 MHz; DMSO-d_6): 116.5 (s), 119.9 (d), 123.0 (d), 127.3 (d), 129.7 (d), 130.2 (d), 130.5 (s), 131.2 (d), 131.9 (d), 134.2 (d), 138.1 (s), 141.1 (s), 167.0 (s), 167.6 (s), 169.2 (s).

References

1 C. Hollins, *The Synthesis of Nitrogen Ring Compounds Containing a Single Hetero-Atom (Nitrogen)*, Ernest-Benn Ltd., London, 1924.
2 K. Heumann, *Ber.*, 1890, **23**, 3431–3435.
3 F. Ullman and E. Kopetschni, *Ber.*, 1911, **44**, 425–431.
4 P. Friedländer, S. Bruckner and G. Deutsch, *Justus Liebigs Ann. Chem.*, 1912, **388**, 23–49.
5 E. Tighineanu, D. Raileanu, Y. Simonov and P. Bouros, *Tetrahedron*, 1996, **52**, 12475–12482.
6 E. Tighineanu, F. Chiraleu and D. Raileanu, *Tetrahedron*, 1980, **36**, 1385–1397.
7 J. Bergman and C. Stålhandske, *Tetrahedron*, 1996, **52**, 753–770.
8 H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann and P. Grieshaber, *Chem. Ber.*, 1968, **101**, 41–50.
9 G. Simchen, H. Hoffmann and H. Bredereck, *Chem. Ber.*, 1968, **101**, 51–57.
10 U. Pindur, The chemistry of acid derivatives, part 2, *The chemistry of functional groups; Supplement B*, ed. S. Patai, Wiley Chichester, UK, 1992, 967–1030.
11 B. C. Nicholson and T. M. Spotswood, *Aust. J. Chem.*, 1973, **26**, 135–145.
12 K. Bowden and J. M. Byrne, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1921–1924.
13 T. Guedez, A. Nunez, E. Tineo and O. Nunez, *J. Chem. Soc., Perkin Trans. 2*, 2002, 2078–2082.
14 M. Feigel and G. Lugert, *Liebigs Ann. Chem.*, 1989, 1089–1092.
15 G. Lugert, Thiophen und Anthranilsäure als Ringbestandteil von Cyclopeptiden: Synthese und Analyse von Peptidkonformationen, Ph.D. thesis, Universität Erlangen-Nürnberg, 1989.
16 G. Lucente, F. Pinnen, G. Zanotti, S. Cerrini, W. Fedeli and E. Gavuzzo, *Tetrahedron Lett.*, 1981, **22**, 3671–3674.
17 F. Pinnen, G. Zanotti and G. Lucente, *Tetrahedron Lett.*, 1984, **25**, 5201–5204.
18 T. Kappe, G. Baxevanidis and E. Ziegler, *Monatsh. Chem.*, 1970, **101**, 932–940.
19 J. Sandström, Dynamic NMR Spectroscopy, Academic Press, London, 1983.
20 R. S. Glass, Conformational Analysis of Medium-Sized Heterocycles, VCH, New York, 1988.
21 R. Isaksson and T. Liljefors, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1815–1821.
22 B. Abdel-Fattah, *Pharmazie*, 1982, **37**, 637–639.
23 D. L. Coffen, D. A. Katonak, N. R. Nelson and F. D. Sancilio, *J. Org. Chem.*, 1977, **42**, 948–952.
24 M. Conrad and H. Reinbach, *Ber.*, 1902, **35**, 511–525.
25 G. Ege, E. Beisiegel and P. Arnold, *Chem. Ber.*, 1972, **105**, 2898–2912.
26 F. Ullman and R. Maag, *Ber.*, 1907, **40**, 2515–2524.
27 G. W. Rewcastle and W. A. Denny, *Synthesis*, 1985, 217–230.
28 M. C. Aversa, P. Giannetto and G. Bruno, *J. Heterocycl. Chem.*, 1988, **25**, 297–299.
29 A. Banerji, J. C. Cass and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1162–1166.
30 K. Ozaki, Y. Yamada and T. Oine, *J. Org. Chem.*, 1981, **46**, 1571–1575.
31 L. Munoz Lamande and A. Munoz, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1993, **75**, 241.
32 J. E. Field and D. Venkataraman, *Chem. Commun.*, 2002, 306–307.
33 E. Abramowitz and M. Lamchen, *J. Chem. Soc.*, 1965, 2165–2173.
34 V. Balasubramaniyan and N. P. Argade, *J. Prakt. Chem.*, 1988, **330**, 626–628.
35 V. Balasubramaniyan and N. P. Argade, *Tetrahedron*, 1989, **45**, 835–842.
36 S. Gabriel, *Ber.*, 1878, **11**, 2260–2262.
37 I. Butula and W. Otting, *Monatsh.Chem.*, 1968, **99**, 1320–1335.
38 H. P. Kaufmann, A. Seher and P. Hagedorn, *Justus Liebigs Ann. Chem.*, 1954, **587**, 226–230.
39 P. Langer, M. Döring and H. Görls, *Eur. J. Org. Chem.*, 2001, 1511–1517.
40 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512–7515.
41 S. Mackay, C. Edwards, A. Henderson, C. Gilmore, N. Stewart and K. Shanklands, *MaXus Program Package*. A state of the art computer program for solving, refining and publishing crystal structures from X-ray diffraction data. Chemistry Department, The University of Glasgow, 1999.
42 D. Vorländer and E. Mumme, *Ber.*, 1902, **35**, 1699–1701.
43 G. G. Guilbault, J. E. Hieserman and M. H. Sadar, *Anal. Lett.*, 1969, **2**, 185–196.
44 M. L. Thominet, USP 3573325/1971; FR 1503908/1967 (*Chem. Abstr.*, 1967, **70**, 37651).
45 K. Görlitzer and E. Engler, *Arch. Pharm.*, 1980, **313**, 405–416.