Product diversity in cyclisations of maleamic acids: the imide–isoimide dichotomy

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Cyclisation of maleamic acids with acetic anhydride in dimethylacetamide (DMA) at *ca.* 75 °C, with or without added cobalt naphthenate, gives predominantly maleimides when the parent maleic anhydride is unsubstituted. However, when the maleic anhydride has either one or two methyl substituents, the products are ≥95% maleisoimides (5-imino-2,5-dihydrofuran-2-ones). In contrast all maleamic acids investigated, regardless of the extent of substitution, give exclusively maleimides when heated in acetic acid under reflux. Isoimide formation in the Ac_2O–DMA–cobalt naphthenate procedure appears to arise from kinetic control, since the isoimide preference was reduced at higher reaction temperature. The preferred *Z*-stereochemistry of the isoimide 3 is confirmed by X-ray crystallography.

Introduction

One of us described recently a series of fluorescent reagents designed for specific labelling of cysteine side chains of proteins.[1] All but one of these compounds contained as the site for conjugation with proteins an *N*-alkyl substituted maleimide, which was constructed by reaction of an aliphatic amine with maleic anhydride in dimethylacetamide (DMA), followed by addition of a catalytic amount of cobalt naphthenate, together with acetic anhydride to effect cyclisation. This procedure was adapted from work by Kiefer and Haug[2] who investigated the effect of a variety of metal salts on the yield of *N*-alkylmaleimides. In our earlier paper it was shown that the effectiveness of the reaction could be improved by reducing the amount of metal salt added, but that omitting it altogether reduced the reaction yield.[1]

In seeking further to extend the range of fluorescent labelling reagents, we were interested in preparing derivatives of methylmaleimide, and began by examining the reaction of benzylamine with methylmaleic (citraconic) anhydride. This reaction had been described by Kiefer and Haug[2] to give a product (mp 57–58.5 °C) which was reported to be 'according to MS and NMR spectrum, with certainty *N*-benzylcitracone amide' (*sic*). Metha *et al.*[3] have previously described preparation of *N*-benzylcitraconimide (1-benzyl-3-methyl-2,5-dihydropyrrole-2,5-dione) **1** by cyclisation of mixed isomers of *N*-benzylcitraconamic acid with acetic anhydride–sodium acetate and reported a product with mp 29 °C. To resolve these conflicting data we have reinvestigated these products and those from related reactions.

Results and discussion

The reaction of benzylamine with citraconic anhydride was repeated as described by Kiefer and Haug[2] but with a reduced amount of cobalt naphthenate (see Experimental section) and the crude material which crystallised upon dilution of the reaction mixture with water was shown by ^{1}H NMR spectroscopy to contain three products in the ratio *ca.* 1:5:14. The least abundant product was shown to be *N*-benzylcitraconimide **1** by comparison with the ^{1}H NMR spectrum of an authentic sample, prepared by heating benzylamine and citraconic anhydride under reflux in acetic acid (*cf.* Gill *et al.*[4]). The two more prominent products, which were separated by chromatography, were crystalline solids with melting points of 83–84 and 110–111 °C, and elemental analysis showed that both had the same empirical formula as *N*-benzylcitraconimide. We concluded that the two compounds were isomeric isoimides and this was confirmed by the presence of strong IR bands at 1790 and 1695 cm^{-1} for each.[5]

Table 1 ^{13}C NMR Chemical shift differences for anhydrides and isoimides

Anhydride	Isoimide	$\Delta\delta_\alpha$[a]	$\Delta\delta_\beta$[a]
Maleic[b]	*N*-Phenylisomaleimide[c] (*Z*-isomer)	−9.5	+5.7
Citraconic[b]	**3**	−10.9	+5.3
	4	−7.2	+3.7
Dimethylmaleic[b]	**16**	−8.5	+5.3

[a] α- and β-carbons are specified relative to the carbonyl group of the isoimide. [b] Data from ref. 8. [c] Data from ref. 7.

Provisional structural assignments for these compounds as the lower melting, less abundant isomer **3**, and the higher melting, more abundant isomer **4** were made by comparison with published ^{1}H and ^{13}C NMR spectra[6] of the isomeric iminopyrrolones **7** and **8**. For example, in the ^{1}H spectra of the four compounds the olefinic proton resonated at lower field for compounds **3** and **7**, in which it is β to the carbonyl group, than it did in the respective isomers **4** and **8**, in which it is α to the carbonyl. The methyl group was at higher field in compounds **3** and **7** than in **4** and **8**. Corresponding trends were consistently present in the ^{13}C NMR spectra. Further support can be gained from comparison of the ^{13}C spectra of isoimides and their parent anhydrides (see Table 1). The data reveal a consistent upfield shift for the olefinic carbon α to the carbonyl and a downfield shift for the β-carbon. Such effects have been discussed previously for unsaturated isoimides on the basis of deshielding in preferred resonance contributions.[7] Confirmation of the structural assignment was obtained when the isomerically pure citraconamic acid **9** (prepared as previously described[9]) was cyclised under the same conditions and gave solely the lower melting isomer **3** together with a little *N*-benzylcitraconimide **1** (ratio *ca.* 20:1). Finally, the structure of isomer **3** was also determined by single crystal X-ray diffraction which confirmed the *Z*-stereochemistry (see below).

The formation under these conditions of the isoimides **3** and **4** in almost complete preference to the imide **1** was unexpected in view of the previous results with synthesis of maleimides[1,2] and the claimed[2] synthesis of the imide **1**. Isoimides as a class of compounds are of some interest as monomers for polymerisation[10] or as polyisoimides,[11] as co-reactants in [2 + 2]

cycloadditions,[12] and as *N*-acylation reagents[13] either to attach chromophores, *etc.* to amino side chains of proteins[14a] or for derivatisation of low molecular weight amines.[14b] Most known isoimides are *N*-aryl substituted and a mild method giving access to *N*-alkylisoimides in reasonable yield may be of value. Of the known reagents for synthesis of maleisoimides by cyclisation of *N*-substituted amic acids, the most general appear to be dicyclohexylcarbodiimide[5] (but see below) and ethyl chloroformate–triethylamine.[5] Other methods include acetyl chloride–triethylamine,[5,12] trifluoroacetic anhydride[13,15] and acetic anhydride–sodium acetate[16] but each is capable of producing either maleimides or maleisoimides, or sometimes both together, depending upon the substrate and precise reaction conditions. Reactions conducted at low temperature tend to favour isoimide formation and it is likely that isoimides are usually the primary reaction products but subsequently isomerise to the thermodynamically-favoured[17] imide under base catalysis.

In order further to explore the features which promote isoimide formation we first repeated the reaction of benzylamine with citraconic anhydride but omitted the cobalt naphthenate from the cyclisation step. The yield of crude products was *ca.* 10% lower than for the same reaction performed in the presence of the metal salt but the product distribution, assayed by ^{1}H NMR spectroscopy, was virtually identical to that of the previous reaction (ratio of compounds **1**, **3** and **4** was *ca.* 1:5:12). All further cyclisation reactions were therefore carried out in the presence of trace amounts of cobalt naphthenate.

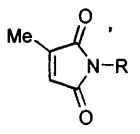
To examine the effect of an aromatic amine, aniline was used in place of benzylamine in the reaction as described above, and isoimides (compounds **5** and **6**) were again found to be the predominant products. For convenience the cyclisation reaction with acetic anhydride–cobalt naphthenate was carried out on the preformed *N*-phenylcitraconamic acids as a *ca.* 44:56 mixture of the isomers **10** and **12**. In this case the reaction mixture was not readily analysed by ^{1}H NMR spectroscopy, but isolated yields of the isoimides **5**[10a] and **6**[10a] were *ca.* 40 and 25%, respectively, together with a trace amount of *N*-phenylcitraconimide **2**.[3] An authentic sample of the latter compound was readily obtained as a single product by heating together aniline and citraconic anhydride in glacial acetic acid under reflux. When the isomerically pure citraconamic acid **10** (obtained by brief treatment of the mixed isomers with trifluoracetic acid[9]) was subjected to the cobalt naphthenate–acetic anhydride cyclisation, the isoimide **5** was obtained in 61% yield after crystallisation. The imide **2**, could not be detected in the reaction mixture. Thus the reaction course seems not to be significantly influenced by the nature of the amine reactant.

Since a single methyl substituent had been shown to exert such a marked effect, it was logical to examine the reaction with dimethylmaleic anhydride. Both the *N*-phenylimide **13** and isoimide **15** have been reported previously[18] but since our interest at the outset had been focussed on *N*-alkylimides, we used benzylamine as the model amine. As in the work described above, we used the preformed amic acid **17**. This compound precipitated readily when ethereal solutions of benzylamine and dimethylmaleic anhydride were mixed, but the NMR spectrum and subsequent reactions showed that the precipitate was contaminated by free benzylamine and the starting anhydride (see below). Previous workers[18] had reported being unable to obtain the corresponding *N*-phenyl amic acid and purification of the crude material was not attempted in view of the known spontaneous tendency of dimethylmaleic acid derivatives to cyclise.[19]

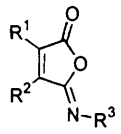
When the amic acid **17** was heated under reflux in acetic acid, the imide **14** was readily isolated. In an attempt to generate an authentic sample of the isoimide **16**, a suspension in methylene dichloride of the amic acid **17** was treated with dicyclohexylcarbodiimide. The crude products were obtained in only 15% combined yield, apparently because of the poor solubility of the amic acid, but surprisingly comprised a mixture of the imide **14** and a second component, subsequently confirmed to be the isoimide **16**, in a ratio of *ca.* 4:5. Formation of imides during carbodiimide-mediated cyclisation of amic acids is unusual and we are aware of only two previous examples. Plouvier *et al.*[20] obtained a mixture of imide and isoimide from cyclisation of an *N*-(pyrrol-3-yl)maleamic acid, while Ramirez *et al.*[21] obtained only imides from a range of *N*-alkylmaleamic acids when 1-hydroxybenzotriazole was present during the cyclisation reaction. When the crude amic acid **17** in DMA was treated with cobalt naphthenate and acetic anhydride, the reaction product contained a mixture of the isoimide **16**, dimethylmaleic anhydride and *N*-acetylbenzylamine, from which the isoimide was easily purified by chromatography. The imide **14** could not be detected among the reaction products either by TLC or ^{1}H NMR spectroscopy.

In the light of all these results, products from the reaction previously described[1] of benzylamine with maleic anhydride were reexamined and were found to contain *N*-benzylmaleimide and *N*-benzylmaleisoimide in the ratio 86:14. The small singlet at δ 4.80 in the ^{1}H NMR spectrum (benzylic protons of the isoimide) had previously been overlooked and was not present in a sample of *N*-benzylmaleimide prepared by heating maleic anhydride and benzylamine under reflux in glacial acetic acid.[1,4] Despite this finding, the earlier conclusion[1] that the DMA–acetic anhydride procedure gave the better yield of *N*-benzylmaleimide remains formally valid, although the differential between this and the glacial acetic acid procedure is reduced to 71 *vs.* 56% after correction for the isoimide content.

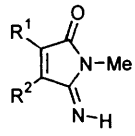
The acetic anhydride–DMA procedure (with or without added cobalt naphthenate) now joins the extensive list of



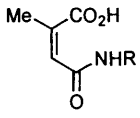
1 R = CH_2Ph
2 R = Ph

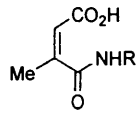


3 R^1 = Me, R^2 = H, R^3 = CH_2Ph
4 R^1 = H, R^2 = Me, R^3 = CH_2Ph
5 R^1 = Me, R^2 = H, R^3 = Ph
6 R^1 = H, R^2 = Me, R^3 = Ph



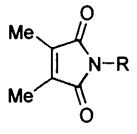
7 R^1 = Me, R^2 = H
8 R^1 = H, R^2 = Me

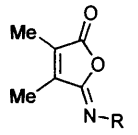




9 R = CH_2Ph
10 R = Ph

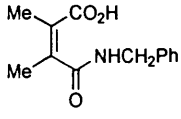
11 R = CH_2Ph
12 R = Ph





13 R = Ph
14 R = CH_2Ph

15 R = Ph
16 R = CH_2Ph



17

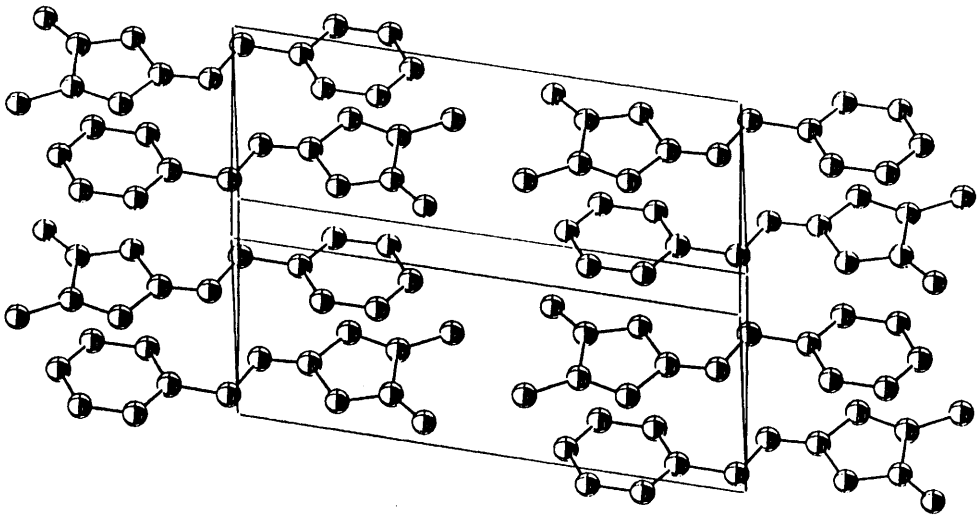


Fig. 1 ORTEP[24] drawing of compound **3** with 50% probability ellipsoids, showing the crystal packing

reagents which are capable of yielding either imides or isoimides depending upon the precise reaction conditions and the structure of the maleamic acid. In common with other reagents, the reaction tends towards imide formation at higher temperature, as shown when the benzylamine–citraconic anhydride cyclisation was performed at 100 °C. Under these conditions the ratio of imide **1** to combined isoimides **3** and **4** was 1:1.4, compared to 1:19 at 75 °C. The more striking phenomenon is the effect of a single methyl substitution which changes the imide–isoimide ratio (for cyclisation at ~75 °C) from 86:14 for maleic anhydride to 5:95 for citraconic anhydride. Evidently the balance between kinetic and thermodynamic control is very finely poised in these reactions and the empirical conclusion is that the products from any new combination of anhydride and amine should be carefully examined to determine the imide–isoimide ratio. The results reported here suggest that no such assessment was made in the work described by Kiefer and Haug[2] and the purity of their products must be viewed with caution. Our data suggest that steric repulsion between substituents on the olefinic carbons of the intermediate amic acid, which presumably results in steric compression of the carboxy and amide groups, favours formation of the kinetic isoimide product. It would be of interest to examine maleamic acids prepared from the anhydrides of cycloalkene-1,2-dicarboxylic acids in 5-, 6- and 7-membered rings, where the changing ring size would be expected to alter the distance between the carboxy and amide groups.

Finally, the geometry of the carbon–nitrogen double bond in the isoimides described here deserves brief comment. Sauers and Relles[7] studied several *N*-arylmaleisoimides by NMR methods and concluded that the *Z*-isomer was the predominant form (80–92%). Capraro *et al.*,[12a] in a reference to unpublished data, indicated that the same is true for *N*-alkylmaleisoimides (88–96%). An X-ray diffraction analysis of the *N*-benzylcitraconisoimide **3** confirmed the *Z*-stereochemistry in the solid state, as shown in Fig. 1, which also shows the antiparallel disposition of molecules within the crystal. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.†

None of the *N*-benzylisoimides **3**, **4** or **16** prepared in this work showed clear evidence of the presence of a minor *E*-stereoisomer in solution, although in the absence of reference NMR data for expected chemical shifts this cannot be a definitive statement. The *N*-phenylcitraconisoimides **5** and **6** have been previously described[10a] but no comment was made on their stereochemistry. In our hands the 3-methyl isomer **5** showed ^{1}H NMR signals for a major and minor isomer (ratio *ca.* 10:1), consistent with the distribution found by Sauers and Relles[7] for *N*-arylmaleisoimides. However the ^{1}H NMR spectrum of the 4-methyl isomer **6** appeared to represent a single species, which is reasonable since steric crowding between the methyl and phenyl groups would be expected to destabilise the *E*-isomer of this compound.

Experimental

General methods

Analyses were carried out by MEDAC Ltd., Brunel University, Uxbridge. NMR spectra were determined on a JEOL FX90Q spectrometer for solutions in deuteriochloroform and with tetramethylsilane as internal standard; *J* values are given in Hz. Merck 9385 silica gel was used for flash chromatography. Light petroleum was the fraction boiling between 40–60 °C. Cobalt naphthenate was purchased from Fluka, Gillingham, Dorset. Organic extracts were dried over anhydrous Na_2SO_4.

1-Benzyl-3-methyl-2,5-dihydropyrrole-2,5-dione 1

A solution of benzylamine (266 mg, 2.5 mmol) and citraconic (methylmaleic) anhydride (224 mg, 2 mmol) in glacial acetic acid (5 cm^3) was heated under reflux for 2 h. The acetic acid was evaporated under reduced pressure and a solution of the residue in ethyl acetate was washed with aq. $NaHCO_3$, dilute aq. HCl and brine, dried and evaporated to leave the imide **3** as a colourless oil (350 mg, 87%), bp 210 °C (Kugelrohr oven temp.)/1 mmHg (lit.,[3] 189–190 °C/26 mmHg); ν_{max}(CH-Cl_3)/cm^{-1} 1775 (w), 1710 (vs), 1435, 1405 and 860; δ_H 7.28 (5 H, br s, ArH), 6.30 (1 H, q, *J* 1.7, H-4), 4.63 (2 H, s, CH_2) and 2.05 (3 H, d, Me); δ_C 171.4 (C-2), 170.4 (C-5), 145.6 (C-3), 136.4 (phenyl C-1), 128.6 (C-4), 128.2, 127.7 and 127.3 (phenyl C-2 to 6), 41.4 (CH_2) and 10.9 (Me).

1-Phenyl-3-methyl-2,5-dihydropyrrole-2,5-dione 2

Compound **2** was prepared from aniline and citraconic anhydride as described for compound **1**, mp 98–99 °C (lit.,[3] 98 °C); δ_H 7.30–7.64 (5 H, m, ArH), 6.47 (1 H, q, *J* 1.7, H-4) and 2.16 (3 H, d, Me).

5-Benzylimino-3-methyl-2,5-dihydrofuran-2-one 3 and 5-benzylimino-4-methyl-2,5-dihydrofuran-2-one 4

A solution of citraconic anhydride (492 mg, 4.4 mmol) in dry DMA (4 cm^3) was added dropwise under nitrogen to a stirred solution of benzylamine (457 mg, 4.3 mmol) in dry DMA (2

† For details of the CCDC deposition scheme, see 'Instructions to Authors', *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1 .

cm^3) and the solution was warmed to 60 °C over 20 min. An aliquot (0.21 cm^3) of a solution of cobalt naphthenate (20 mm^3) in DMA (1 cm^3) was added, followed by dropwise addition of acetic anhydride (0.84 cm^3) and the solution was stirred at 70–80 °C for 2 h, then cooled and poured into water. The precipitated solid was extracted into EtOAc and the organic extract was washed with aq. $NaHCO_3$, dilute aq. HCl and brine, dried and evaporated under reduced pressure. TLC analysis [silica gel; EtOAc–light petroleum (20:80)] showed two major spots and flash chromatography in the same solvent yielded a less polar fraction (0.30 g) almost pure (^{1}H NMR) and a more polar fraction (0.12 g) which on rechromatography gave a homogeneous compound (0.07 g). The less polar material crystallised from light petroleum to yield the *isoimide* **4** as needles, mp 110–111 °C (Found: C, 71.6; H, 5.5; N, 6.9. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); λ_{max}(EtOH)/nm 234 (ε/dm^3 mol^{-1} cm^{-1} 12 300); ν_{max}(Nujol)/cm^{-1} 1790, 1695, 1380, 1245, 915, 855, 840 and 730; δ_H 7.40 (5 H, br s, ArH), 6.30 (1 H, q, *J* 1.7, H-3), 4.79 (2 H, s, CH_2) and 2.20 (3 H, d, Me); δ_C 166.2 (C-2), 154.2 (C-4), 153.4 (C-5), 138.5 (phenyl C-1), 128.5, 127.9 and 127.0 (phenyl C-2 to 6), 123.1 (C-3), 53.0 (CH_2) and 11.8 (Me). The small amount of the imide **1** which co-chromatographed with isoimide **4** was removed during crystallisation.

The more polar fraction was the isoimide **3** but the compound was more conveniently prepared as follows. A solution of isomerically pure citraconamic acid **9**[9] (985 mg, 4.3 mmol) in DMA (6 cm^3) was warmed to 60 °C under nitrogen, then treated with cobalt naphthenate and acetic anhydride as described above, stirred at 70–80 °C for 2 h and worked up as above. The crude product was purified by flash chromatography [EtOAc–light petroleum (20:80)] to yield the *isoimide* **3** (0.44 g, 51%) which crystallised from light petroleum as laths, mp 83–84 °C (Found: C, 71.6; H, 5.5; N, 6.9. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); λ_{max}(EtOH)/nm 241 (ε/dm^3 mol^{-1} cm^{-1} 17 400); ν_{max}(Nujol)/cm^{-1} 1790, 1695, 915 and 730; δ_H 7.36 (5 H, br s, ArH), 6.89 (1 H, q, *J* 1.7, H-4), 4.78 (2 H, s, CH_2) and 2.09 (3 H, d, Me); δ_C 168.2 (C-2), 151.5 (C-5), 139.6 (C-3), 138.4 (phenyl C-1), 135.6 (C-4), 128.6, 127.9 and 127.1 (phenyl C-2 to 6), 53.1 (CH_2) and 10.9 (Me).

(*Z*)-2-Methyl-4-oxo-4-phenylaminobut-2-enoic acid 10

The crude mixed amic acids (3.6 g) from the reaction of aniline and citraconic anhydride[9] were dissolved in trifluoroacetic acid (35 cm^3) at room temp. After 5 min the TFA was evaporated under reduced pressure and the residue was crystallised from 95% EtOH to yield the amic acid **9** (1.49 g), mp (sealed tube) 151–152 °C (lit.,[9] 170–172 °C). Despite the discrepancy in melting point, the ^{1}H NMR spectrum of the product was fully in agreement with the published data[9] for the pure isomer.

5-Phenylimino-3-methyl-2,5-dihydrofuran-2-one 5 and 5-phenylimino-4-methyl-2,5-dihydrofuran-2-one 6

The pure amic acid **10** was cyclised as described above and the reaction product was diluted with water. The precipitated solid was washed with water and dried *in vacuo*, then crystallised from light petroleum to yield the isoimide **5** as pale yellow laths (61%), mp 109–110 °C (lit.,[10a] 107 °C), ν_{max}(Nujol)/cm^{-1} 1785, 1575, 775 and 690; δ_H 7.24–7.52 (5 H, m, ArH), 6.84 and 7.01 [total 1 H, 2 × q, *J* 1.7, H-4(*Z*) and H-4(*E*)], 2.09 and 2.13 [total 3 H, 2 × d, Me(*E*) and Me(*Z*)]. The *E*:*Z* ratio was approx. 1:9.

The isoimide **6** was obtained by cyclisation of the mixed amic acids[9] from reaction of aniline with citraconic anhydride as described above and the crude reaction product was flash chromatographed [EtOAc–light petroleum (85:15)] to give a less polar and a more polar fraction. The latter contained principally the isoimide **5** together with a small proportion of the imide **2**. The less polar fraction (25%) was crystallised from light petroleum to give the isoimide **6** as pale yellow plates, mp 66–66.5 °C (lit.,[10a] 66 °C); ν_{max}(Nujol)/cm^{-1} 1790, 1685, 1250, 900 and 850; δ_H 7.29–7.47 (5 H, m, ArH), 6.34 (1 H, q, *J* 1.6, H-3) and 2.29 (3 H, d, Me).

(*Z*)-2,3-Dimethyl-4-oxo-4-benzylaminobut-2-enoic acid 17

A solution of benzylamine (0.96 g, 9 mmol) in dry diethyl ether (30 cm^3) was added dropwise to a mechanically-stirred solution of dimethylmaleic anhydride (1.26 g, 10 mmol) in dry diethyl ether (100 cm^3). The solution was stirred for a further 2 h then filtered, and the filtered solid was washed with diethyl ether and dried *in vacuo* to give the crude amic acid **17** (1.25 g) which was used without further purification.

1-Benzyl-3,4-dimethyl-2,5-dihydropyrrole-2,5-dione 14

A solution of the crude amic acid **17** (0.58 g) in glacial acetic acid (5 cm^3) was heated under reflux for 2 h then cooled and concentrated under reduced pressure. A solution of the residue in EtOAc was washed with dilute aq. HCl, aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was flash chromatographed [EtOAc–light petroleum (15:85)] and crystallised from light petroleum to give the *imide* **14** as rhombs (0.21 g, 40%), mp 43.5–44 °C (Found: C, 72.6; H, 6.1; N, 6.5. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%); λ_{max}(EtOH)/nm 228 (ε/dm^{-3} $mol\,cm^{-1}$ 14 900); ν_{max}(Nujol)/cm^{-1} 1710, 1430, 1405, 1365, 1100, 967, 740, 730 and 695; δ_H 7.30 (5 H, br s, ArH), 4.63 (2 H, s, CH_2) and 1.95 (6 H, s, Me).

5-Benzylimino-3,4-dimethyl-2,5-dihydrofuran-2-one 16

A solution of the crude amic acid **17** (0.93 g, 4 mmol) in dry DMA (5.6 cm^3) was stirred under nitrogen at room temp. and treated with an aliquot (0.195 cm^3) of a solution of cobalt naphthenate (20 mm^3) in DMA (1 cm^3), followed by dropwise addition of acetic anhydride (0.78 cm^3). The solution was warmed to 70 °C over 10 min and stirred at that temp. for 2 h, then cooled and diluted with water. The mixture was extracted with EtOAc and the organic extract was washed with aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was flash chromatographed [EtOAc–light petroleum (12:88)] to give a less polar and a more polar fraction. The latter (40 mg) was shown to be dimethylmaleic anhydride (^{1}H NMR, TLC). In addition the ^{1}H NMR spectrum of the crude product showed the presence of *N*-acetylbenzylamine, but this compound remained on the chromatography column in the elution solvent used here. The isolated, less polar fraction (250 mg, 29%) was crystallised from light petroleum to give the *isoimide* **16** as needles, mp 109–110 °C (Found: C, 72.4; H, 6.05; N, 6.5. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%); λ_{max}(EtOH)/nm 246 (ε/dm^3 mol^{-1} cm^{-1} 15 600); ν_{max}(Nujol)/cm^{-1} 1790, 1700, 960 and 730; δ_H 7.32 (5 H, br s, ArH), 4.77 (2 H, s, CH_2), 2.08 (3 H, s, Me) and 1.97 (3 H, s, Me).

Crystal data and structure determination for compound 3

$C_{12}H_{12}NO_2$, M = 202.23, triclinic, space group $P\bar{1}$, a = 7.121(3), b = 12.814(7), c = 5.983(3) Å, V = 522.5(4) $Å^3$, Z = 2, D_c = 1.285 g cm^{-3}, $F(000)$ = 214, μ(Mo-Kα) = 0.088 mm^{-1}, crystal size 0.90 × 0.40 × 0.05 mm.

Intensity data were collected at 293 K on a Rigaku AFC6S four-circle diffractometer with graphite-monochromated Mo-Kα X-radiation, λ = 0.7107 Å. Equivalent reflections were merged and only Lorenz and polarisation corrections were applied. The structure was solved by direct method using SHELXS[22] and refined on F^2 using SHELXL.[23] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a rigid model.‡ Full-matrix least-

‡ The rigid model has C_{sp2}–H = 0.93 Å, $C_{sp3}(CRH_2)$–H = 0.96 Å, $C_{sp3}(CH_3)$–H = 0.97 Å and N_{sp2}–H = 0.86 Å with $U_{iso}\{H[C_{sp2}]\}$ = $U_{iso}\{H[C_{sp3}(CRH_2)–H]\}$ = $1.2U_{eq}(C_{sp2})$, $U_{iso}\{H[C_{sp3}(CH_3)–H]\}$ = $1.5U_{eq}(C_{sp3})$ and $U_{iso}H[N_{sp2}]\}$ = $1.2U_{eq}(N_{sp2})$.

squares refinement of 138 parameters for 1838 independent reflections [$I \geqslant \sigma(I)$] in the range $2.97 < \theta < 25.00°$ gave $R_F = 0.0617$ and ${}_wR_I = 0.1320$.§

§ $R_F = \Sigma[|F_o| - |F_c|]/\Sigma|F_o|$ and ${}_wR_I = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{\frac{1}{2}}$ and the weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0709P)^2 + 0.0964P]$ where $P = [\max(I_{obs}, 0) + 2F_c^2]/3$.

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