

The Reaction of Piperazine-2,5-dione with 2-Formylbenzoic Acid

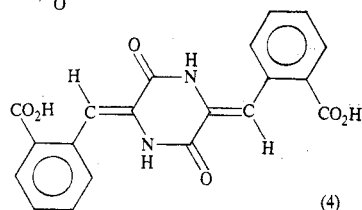
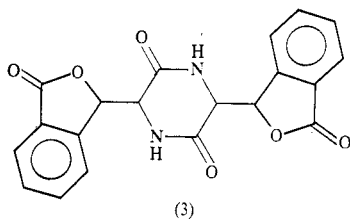
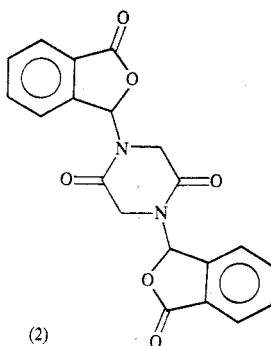
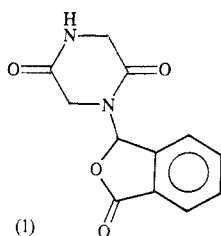
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Abstract

Reaction of piperazine-2,5-dione with 2-formylbenzoic acid in the presence of triethylamine gives three products: 1-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)piperazine-2,5-dione, its 1,4-bis analogue which had previously been identified as the 3,6-compound, and 2,2'-[3,6-dioxopiperazine-2,5-diylidene-bis(methylidene)]bis(benzoic acid). The latter compound is shown by ^1H and ^{13}C n.m.r. spectroscopy to be the *Z,Z* isomer.

From the reaction of piperazine-2,5-dione with 2-formylbenzoic we have isolated three products. The first of these is the 1 : 1 adduct, 1-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)piperazine-2,5-dione (1). The carbonyl stretching frequency (1790 cm^{-1}) showed that it was a lactone and, once the formula was known, its structure was determined from the ^1H n.m.r. spectrum. This showed only one NH signal but two methylene AB patterns, one of which was only revealed as such at 600 MHz.



The second product was the bis analogue (2). Its ^1H n.m.r. spectrum showed a single peak, somewhat broadened, for the phthalidyl methine hydrogens and eight peaks in the region δ 3.3-3.85, arising from the two methylenes. Compound (2)

can exist in (\pm) and *meso* forms, in each of which the hydrogens of each pair will be diastereotopic and thus give rise to an AB pattern of four lines.

Compound (2) was previously reported¹ as the bis-lactone (3) but our structure evidence makes it clear that condensation has occurred at the nitrogens of the piperazinedione rather than at the methylene carbons. 2-Formylbenzoic acid is known to react in this way with other amides, for example urea² and isatin.³

The final reaction product was the bis-acid (4), which had been previously identified¹ as a product of this reaction. The *Z,Z* stereochemistry is deduced from the ¹H n.m.r. spectrum which shows a single olefinic hydrogen signal, the chemical shift of which is comparable to that in (*Z*)-3-benzylidenepiperazine-2,5-dione.⁴ In compound (4), the carboxyl groups have deshielded the olefinic hydrogens by about 0.7 ppm, an amount which corresponds to the chemical shift difference between cinnamic acid⁵ and 2-carboxycinnamic acid.⁶

The stereochemistry of compound (4) is confirmed by the observation that, in a fully coupled ¹³C n.m.r. spectrum, both carbonyl carbon signals are doublets with *J* 3.0 Hz. This is consistent with the olefinic hydrogen and the ring carbonyl existing in a *cis* relationship, because a much larger coupling would be expected⁷ for the *trans*.

Experimental

Melting points were determined with a Reichert hot-stage microscope apparatus, and are uncorrected. Infrared spectra were recorded for paraffin mulls with a Jasco IRA-1 grating spectrophotometer. Mass spectra were measured at 70 eV with a V.G. Micromass 70/70F mass spectrometer with source temperature 200°. ¹H n.m.r. spectra were recorded, with tetramethylsilane as internal standard, in a Perkin-Elmer R32 (90 MHz) spectrometer. Higher-field spectra were recorded on Bruker WM 200 spectrometer and on the 141 kG spectrometer at the Carnegie Mellon University, Pittsburgh.

Reaction of Piperazinedione with 2-Formylbenzoic Acid

Piperazine-2,5-dione (2.85 g, 25.0 mmol), 2-formylbenzoic acid (4.37 g, 25.0 mmol), anhydrous sodium acetate (2.05 g, 25.0 mmol) and acetic anhydride (5.10 g, 50.0 mmol) were heated for 5 h at 140–150° in an oil bath. The mixture was poured into hot water and the insoluble brown precipitate, dipthalidylpiperazinedione (1.80 g), was washed with water and dried in air. The filtrate was boiled with decolorizing charcoal, filtered, and allowed to cool. Acidification with 2 M HCl gave a pale brown precipitate of the diacid (4). This acid (0.38 g) was recovered by filtration and the filtrate was extracted with dichloromethane (2 × 150 ml). The dichloromethane was dried and evaporated to give a pale yellow solid (0.65 g, 11%) which, purified by boiling with absolute ethanol, gave 1-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)piperazine-2,5-dione, m.p. 243.5–244.5°. The compound retained water and acceptable combustion analyses could not be obtained (Found: M^+ , 246.063 \pm 0.002. $C_{12}H_{10}N_2O_4$ requires M^+ , 246.064). Infrared: ν_{\max} 3200, 1790, 1680 cm^{-1} . ¹H n.m.r. δ 3.229, 1H, d, J_{gem} 16.2 Hz, H 6; 3.569, 1H, d, J_{gem} 16.2 Hz, H 6; 4.014, 2H, AB pattern with J_{gem} 17.1 Hz, $\Delta\delta$ 0.036, H 3; 7.574, 1H, s, H 3'; 7.6–8.0, 4H, m, aromatic H; 8.289,

¹ Hashimoto, T., and Oyama, S., *Yakugaku Zasshi*, 1954, **74**, 1287.

² Raeine, S., *C. R. Acad. Sci.*, 1888, **106**, 947.

³ Rees, C. W., and Sabet, C. R., *J. Chem. Soc.*, 1965, 680.

⁴ Shin, C., Hayakawa, M., Suzuki, T., Ohtsuka, A., and Yoshimura, J., *Bull. Chem. Soc. Jpn*, 1978, **51**, 550.

⁵ Varian Associates 'High Resolution NMR Spectra Catalog' (Varian: Palo Alto 1962). Spectrum 230.

⁶ Elvidge, J. A., and Jones, D. E. H., *J. Chem. Soc. C*, 1967, 2059.

⁷ Bystrov, V. F., *Prog. Nucl. Magn. Reson. Spectrosc.*, 1976, **10**, 41.

1H, s, NH (exchanges with D₂O). ¹³C n.m.r. δ 44.54 (t) and 44.67 (t), C3 and C6; 82.38 (d), C3'; 123.4 (d), 125.29 (d), 126.92 (s), 130.88 (d), 135.04 (d), 143.43 (s), aromatic C; 165.08 (s), 166.77 (s), 168.01 (s), carbonyl C. Mass spectrum m/z 246, 245, 218, 217, 201, 148, 133.

1,4-Bis(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)piperazine-2,5-dione (2)

Isolated from the reaction described above, m.p. > 260°. Infrared ν_{\max} 1775, 1680 cm⁻¹. The ¹H n.m.r. spectrum ((CD₃)₂SO) showed two components in ration 5 : 3, presumably as the result of different solubilities because (\pm) and *meso* compounds should have formed in equal amounts. Major component δ 3.52 and 3.91, AB pattern, J 16.3 Hz; 7.48, s, H3'; 7.7-8.0, m, aromatic. Minor component δ 3.56 and 3.82, AB pattern, J 16.4 Hz; 7.51, s, H3'; 7.7-8.0, m, aromatic. Mass spectrum m/z 378, 316, 133.

2,2'-[3,6-Dioxopiperazine-2,5-diylidenebis(methylidyne)]bis(benzoic acid) (4)

Isolated from the reaction described above, m.p. > 260°. Infrared ν_{\max} 2400-3200br, 1700, 1635 cm⁻¹. Mass spectrum m/z 189 (doubly charged), 143. ¹H n.m.r. (CF₃COOH) δ 8.22, 2H, s. The corresponding hydrogen in (*Z*)-3-benzylidenepiperazine-2,5-dione is found at δ 7.45 (this work), cf. δ 7.41 (lit.⁴). ¹³C n.m.r. of (4) in (CD₃)₂SO: δ 109.8 (d), CH; 126.9 (d), 128.2 (d), 128.8 (d), 129.8 (s), 132.8 (d), 136.0 (s), aromatic C; 127.7 (s), C2,5; 161.4 (s), CO; 162.9 (s), COOH.

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