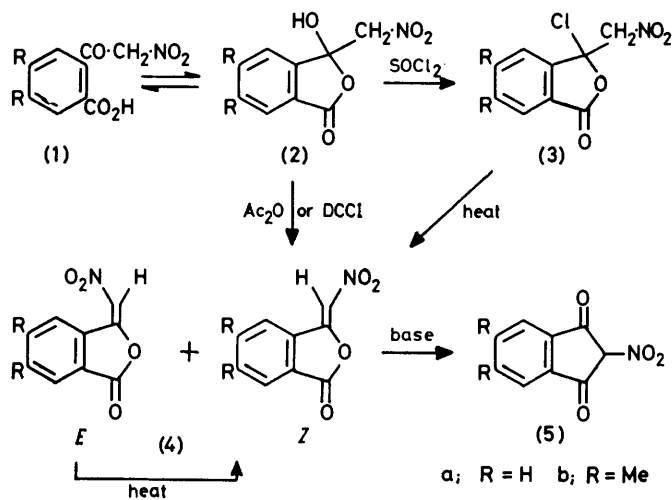


Cyclisation of 2-(Nitroacetyl)benzoic Acids

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The cyclisation of 2-(nitroacetyl)benzoic acids (1) gives mixtures of (*E*)- and (*Z*)-3-(nitromethylene)phthalides (4), unambiguously identified by n.m.r. spectroscopy. Rearrangement of either isomer with tertiary base provides a novel route to 2-nitroindane-1,3-diones (5).

RECENT work on 2-(nitroacetyl)benzoic acids (1) and their esters has shown that the antiallergic activity of these compounds may reflect, at least in part, their ability to undergo biocyclisation to 2-nitroindanediones (5), these compounds having been shown to be of potential value in the treatment of allergic diseases.^{1,2} We investigated cyclisation reactions of the acids (1) in the



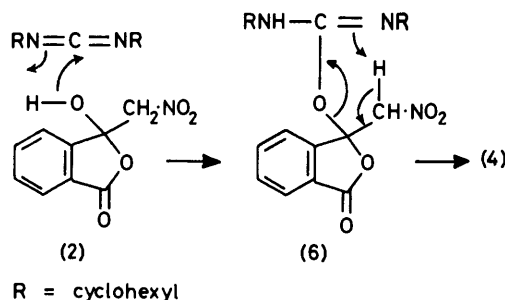
SCHEME 1

hope that these compounds might provide alternative intermediates for the synthesis of the indanediones (5). This paper describes these reactions and the base-induced rearrangement of the resulting 3-(nitromethylene)phthalides (4) (Scheme 1).

Treatment of 2-(nitroacetyl)benzoic acid (1a) and its dimethyl homologue (1b) with thionyl chloride led, *via* their hydroxy-lactone tautomers (2), to the cyclic chlorides (3a and b), identified from their i.r. spectra and their ready thermal elimination of hydrogen chloride to give the 3-(nitromethylene)phthalides (4). The interaction of the chlorides (3) with tertiary base also effected this elimination, together with formation of some 2-nitroindanedione (5), the latter rearrangement suggesting a useful new route to the dione (5). Reinvestigation of the dehydration of (1a) with acetic anhydride^{3,4} resulted in a high yield of (*Z*)-3-(nitromethylene)phthalide (4a), together with a little of the *E*-isomer. The latter was readily converted into the thermodynamically more

stable *Z*-isomer on extended refluxing in acetic anhydride. A similar reaction with (1b) gave the *Z*-isomer of (4b) as the only isolated product. Since α -phenyl- β -nitroalcohols are known to undergo ready elimination of water,⁵ the dehydration of (1) under milder conditions with *NN'*-dicyclohexylcarbodi-imide (DCCI) was attempted. Treatment of (1a) with DCCI at 0 °C rapidly resulted in a 1 : 1 mixture of the two geometric isomers of (4a), which on heating was converted entirely into the *Z*-form. Similarly, the reaction of (1b) afforded an equimolar mixture of isomers of (4b) from which the pure *Z*-isomer could be isolated after thermal equilibration in acetic anhydride. No nitroindanedione (5) was isolated from the reaction of (1a or b) with either dehydrating agent, although the rearrangement of (4) to (5) was readily accomplished in good yield either by brief treatment in boiling pyridine or by triethylamine in chloroform at room temperature. Attempts to rearrange (4) with methanolic sodium methoxide yielded only the methyl esters of (1).

A suggested mechanism for the dehydration by DCCI is illustrated in Scheme 2. Attack by the hydroxy-group of (2) at the imide carbon atom is envisaged to give an intermediate carbamate (6), which then loses *NN'*-dicyclohexylurea *via* a cyclic mechanism similar to



SCHEME 2

that postulated for the dehydration of β -hydroxyketones.⁶

The geometric configurations of the *E*- and *Z*-nitroolefins (4a and b) were elucidated from their ¹H n.m.r. spectra; their i.r. and mass spectra showed only minor differences. The n.m.r. spectra of the *E*-isomers showed the C-4 proton resonance at low field (Table), owing to

¹ D. R. Buckle, N. J. Morgan, J. W. Ross, H. Smith, and B. A. Spicer, *J. Medicin. Chem.*, 1973, **16**, 1334.

² D. R. Buckle, B. C. C. Cantello, N. J. Morgan, H. Smith, and B. A. Spicer, *J. Medicin. Chem.*, 1975, **18**, 733.

³ L. P. Zalukaev, *J. Gen. Chem. (U.S.S.R.)*, 1956, **26**, 1039.

⁴ S. Gabriel, *Ber.*, 1903, **36**, 570.

⁵ H. H. Baer and L. Urbas in 'The Chemistry of the Nitro and Nitroso Groups,' part 2, ed. S. Patai, Interscience, 1970, p. 104.

⁶ E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, 1968, **90**, 3245.

the anisotropic effect of the nitro group (*cf.* cyanomethyl-nephthalides⁷ and acetonilidene-phthalides⁸). Unambiguous assignment of the vinylic proton signal for each isomer of (4b) was made by selective deuterium enrichment. Furthermore, addition of *ca.* 0.4 mol.

Partial 90 MHz ¹H n.m.r. spectra of geometric isomers of the (nitromethylene)phthalides (4)

Compound	δ	Assignment
(Z)-(4a) ^a	8.10 (2 H, m)	4-, 7-H
	7.91 (2 H, m)	5-, 6-H
	7.89 (1 H, s)	vinylic CH
(E)-(4a) ^a	8.85 (1 H, d, d)	4-H
	8.00 (3 H, m)	5-, 6-, 7-H
	7.77 (1 H, s)	vinylic CH
(Z)-(4b) ^b	7.81 (1 H, s)	7-H
	7.51 (1 H, s)	4-H
	7.21 (1 H, s)	vinylic CH
(E)-(4b) ^b	8.62 (1 H, s)	4-H
	7.81 (1 H, s)	7-H
	7.51 (1 H, s)	vinylic CH

^a In 3 : 1 CDCl₃-(CD₃)₂SO. ^b In CDCl₃.

equiv. of the lanthanide shift reagent Eu([²H₉]fod)₃ to the isomeric mixture of (4b) effected complete resolution of the aromatic and vinylic signals, from which individual assignments could be made (Table).

EXPERIMENTAL

I.r. spectra were measured for dispersions in Nujol (Perkin-Elmer 157 spectrophotometer). N.m.r. spectra were determined with a Perkin-Elmer R32 (90 MHz) instrument for solutions in CDCl₃, (CD₃)₂SO, or combinations thereof.

2-(Nitroacetyl)benzoic Acids.—2-(Nitroacetyl)benzoic acid (1a) and its 4,5-dimethyl homologue (1b), were prepared in high yield by mild hydrolysis of the respective methyl esters as previously described,² or more directly, albeit in lower yield, by the method of Gabriel.⁴

3-Chloro-3-(nitromethylene)phthalide (3a).—Thionyl chloride (1.1 g, 0.009 mol) was added to a solution of the acid (1a) (1.05 g, 0.005 mol) in dry dichloromethane (10 ml) and the mixture was heated at reflux for 1 h. The solvent and excess of thionyl chloride were removed *in vacuo* and the residue was recrystallised from toluene to give 3-chloro-3-(nitromethylene)phthalide (0.98 g, 86%), m.p. 107—109°; ν_{\max} . 1 790 and 1 570 cm⁻¹; δ (CDCl₃) 7.81 (4 H, m) and 5.30 (2 H, s) (Found: C, 47.8; H, 2.65; N, 6.15. C₈H₆ClNO₄ requires C, 47.5; H, 2.65; N, 6.15%).

3-Chloro-5,6-dimethyl-3-(nitromethylene)phthalide (3b).—Thionyl chloride (2.2 g, 0.018 5 mol) was added to a suspension of the acid (1b) (2.25 g, 0.009 5 mol) in dry dichloromethane (20 ml) and the mixture was refluxed until clear (2.5 h). Removal of the solvent and excess of thionyl chloride *in vacuo* afforded an off-white solid which was recrystallised from benzene-light petroleum (b.p. 40—60 °C) to give the chlorophthalide (1.46 g, 60%), m.p. 94—96°, ν_{\max} . 1 790 and 1 560 cm⁻¹; δ (CDCl₃) 7.71 (1 H, s), 7.47 (1 H, s), 5.23 (2 H, s), 2.45 (3 H, s), and 2.40 (3 H, s) (Found: C, 52.0; H, 3.8; Cl, 13.45; N, 5.6. C₁₁H₁₀ClNO₄ requires C, 51.7; H, 3.95; Cl, 13.85; N, 5.5%).

Both chlorophthalides (3a and b) readily lost hydrogen

⁷ J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc. (C)*, 1971, 2424.

chloride either on heating or on brief treatment with hot pyridine.

Dehydrations with Acetic Anhydride.—(i) 3-(Nitromethylene)phthalide (4a). A mixture of the acid (1a) (1.1 g, 0.005 3 mol) and acetic anhydride (5 ml) was heated at 140 °C for 1.5 h and then cooled. The precipitated yellow solid was filtered off and dried to give (Z)-3-(nitromethylene)phthalide (0.708 g, 70%), m.p. 209—210° (lit.,³ 205—206°), ν_{\max} . 1 805 cm⁻¹, δ [CDCl₃-(CD₃)₂SO 3 : 1] 8.10 (2 H, m), 7.91 (2 H, m), and 7.89 (1 H, s); *m/e* 191 (M⁺), 185, 161, 133, and 104. From the mother liquor material (0.215 g, 21%) of m.p. 145—146° was obtained, the n.m.r. spectrum of which showed it to be *ca.* 64% (E)- and 36% (Z)-3-(nitromethylene)phthalide. Refluxing this mixture in acetic anhydride afforded pure Z-isomer in quantitative yield. A similar reaction at vigorous reflux gave no detectable E-isomer.

(ii) 5,6-Dimethyl-3-(nitromethylene)phthalide (4b). A solution of the acid (1b) (2.37 g, 0.01 mol) in acetic anhydride (15 ml) was heated at reflux for 10 min, then evaporated under reduced pressure. Treatment of the residue with ethanol followed by filtration gave the (nitromethylene)phthalide (4b) (1.82 g, 83%) as yellow crystals. Recrystallisation from glacial acetic acid gave material of m.p. 211—212°, ν_{\max} . 1 805 cm⁻¹. The n.m.r. spectrum (see main text) showed it to be pure (Z)-5,6-dimethyl-3-(nitromethylene)phthalide, δ (CDCl₃) 7.81 (1 H, s), 7.51 (1 H, s), 7.21 (1 H, s), and 2.44 (6 H, s); *m/e* 219 (M⁺), 161, 132, and 117 (Found: C, 60.25; H, 4.1; N, 6.4. C₁₁H₉NO₄ requires C, 60.3; H, 4.15; N, 6.4%).

Dehydrations with NN'-Dicyclohexylcarbodi-imide (DCCI).—(i) 3-(Nitromethylene)phthalide (4a). To a cold (0 °C), stirred solution of the acid (1a) (0.418 g, 0.002 mol) in dry acetone (15 ml) was added DCCI (0.453 g; 10% excess) in one portion, and the mixture was stirred in ice for a further 2 h. The precipitated dicyclohexylurea was filtered off and washed well with acetone, and the combined filtrate and washings were evaporated to give crude product (0.416 g) shown by n.m.r. to be a 1 : 1 mixture of E- and Z-isomers of 3-(nitromethylene)phthalide. Recrystallisation from glacial acetic acid gave 0.38 g (quantitative) of pure Z-isomer, m.p. 211°. Several repeat runs also gave the (statistical) 1 : 1 ratio of E- and Z-isomers.

(ii) 5,6-Dimethyl-3-(nitromethylene)phthalide (4b). To an ice-cold solution of the acid (1b) (0.474 g, 0.002 mol) in dry acetone (15 ml) was added a slight excess of DCCI (0.452 g), in one portion. After a further 2 h at 0 °C the precipitated solid was collected and washed well with acetone and the combined filtrate and washings evaporated to give 0.435 g (quantitative) of material of m.p. 177° (decomp.). The n.m.r. spectrum showed this to be a 1 : 1 mixture of E- and Z-(nitromethylene)phthalides. Heating in acetic anhydride followed by recrystallisation from ethanol or acetic acid gave pure Z-isomer, m.p. 211—212°.

5,6-Dimethyl-3-(nitro[²H]methylene)phthalide.—A solution of the acid (1b) (0.5 g) in dry chloroform (15 ml) containing a little NN-dimethylformamide (1 ml) was shaken with 99.6% deuterium oxide (5 × 1 ml) and then evaporated to dryness. The residue was dried by azeotropic removal of water with dry benzene and dissolved in dry acetone (15 ml). After cooling in ice an excess of DCCI (0.477 g) was added and the mixture stirred at 0 °C for 2 h. The precipitated urea was filtered off and washed with dry acetone and the filtrate and washings were evaporated to dryness. Re-

⁸ P. A. Chopard, R. F. Hudson, and R. J. G. Searle, *Tetrahedron Letters*, 1965, 2357.

crystallisation from ethanol (charcoal) afforded the *E*- and *Z*-phthalides (0.335 g, 76%), m.p. 177—178°; ν_{\max} 2 300, 1 815, and 1 805 cm^{-1} . Mass spectral analysis indicated *ca.* 70% incorporation of deuterium.

Reaction of Phthalic Anhydride with Nitromethane.—Phthalic anhydride (30 g, 0.2 mol) was dissolved in dry ether (3 l) and the solution cooled to 0 °C. Nitromethane (24 g, 0.4 mol) was added with stirring followed by sodium methoxide [from sodium (4.6 g, 0.2 mol)] in methanol (100 ml). A pink gelatinous slurry was formed, which was stirred at 0 °C for 6 h and left overnight. The separated solid was extracted into water (500 ml) and acidified with concentrated hydrochloric acid. The resulting mixture was extracted with ether and the dried extracts were evaporated to an oily mixture of 2-(nitroacetyl)benzoic acid and methyl hydrogen phthalate. For synthetic purposes the components of this mixture were not separated but were refluxed with acetic anhydride (60 ml) for 90 min to convert the nitroacetyl derivative into the (nitromethylene)phthalide (4a). Evaporation afforded a yellow solid which after trituration with ethanol (50 ml) was recrystallised from acetic acid to give 3-(nitromethylene)phthalide (5.4 g, 14%); m.p. 205—206° (see above for spectral data).

Reaction of 4,5-Dimethylphthalic Anhydride with Nitromethane.—In a similar manner to that described above, 4,5-dimethylphthalic anhydride (17.6 g, 0.1 mol) was converted into 5,6-dimethyl-3-(nitromethylene)phthalide (4b) (2.63 g, 12%), m.p. 211—212° (from acetic anhydride).

2-Nitroindane-1,3-dione.—A mixture of 3-(nitromethylene)phthalide (4a) (0.25 g, 0.0013 mol) and triethylamine (2 ml) in chloroform (8 ml) was stirred at 25 °C for 18—24 h, and then evaporated *in vacuo*. Addition of 5*N*-hydrochloric acid to the residue resulted in precipitation of the indanedione as yellow crystals (63%), m.p. 113° (lit.,¹ 113—114°; lit.,⁹ 113°).

5,6-Dimethyl-2-nitroindane-1,3-dione.—5,6-Dimethyl-3-(nitromethylene)phthalide (4b) (0.22 g, 0.001 mol) was treated with a solution of triethylamine (2.0 ml) in chloroform (2 ml) over 18 h at 25 °C and the yellow solution was then evaporated to half its bulk *in vacuo*. Dilution with 5*N*-hydrochloric acid then precipitated the title compound as a yellow crystalline solid (80.5%), m.p. 111—113° (lit.,¹ 113—114°).

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⁹ G. Vanags, *Ber.*, 1936, **19**, 1066.