Synthesis of *N*-Hydroxymaleimide and *N*-Hydroxyitaconimide and their Related Derivatives

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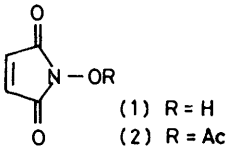
Thermolysis of alkyl and aryl carbonates of *N*-hydroxy-3,6-epoxy-1,2,3,6-tetrahydrophthalimide yielded the corresponding alkyl or aryl *N*-maleimidyl carbonates. The benzyl or phenyl carbonate afforded *N*-hydroxymaleimide, either by treatment with trifluoroacetic acid or by refluxing in methanol. *N*-Hydroxyitaconimide was obtained by dehydration of *N*-hydroxyitaconamic acid with dicyclohexylcarbodi-imide (DCC). The DCC dehydration of *N*-acetoxy- and *N*-benzyloxy-itaconamic acids produced iminofuranones, which could be rearranged to imides. Deacylation of *N*-acetoxymaleimide was unsuccessful, whereas aminolysis of *N*-acetoxyitaconimide yielded the *N*-hydroxyimide.

In order to continue our studies,[1,2] unsaturated cyclic *N*-hydroxyimides were required as polymeric acyl transfer agents.[3,4] Dehydration of *O*-substituted-*N*-hydroxymaleamic acids gives isoimides,[1,2,5] although *N*-substituted-maleamic acids produce either imides or isoimides, according to the dehydration conditions.[6-10] Some maleimides were prepared *via* the Diels–Alder adducts.[8,11,12]

RESULTS AND DISCUSSION

For *N*-hydroxymaleimide (1), we first attempted a reverse Diels–Alder reaction of *N*-hydroxy-3,6-epoxy-



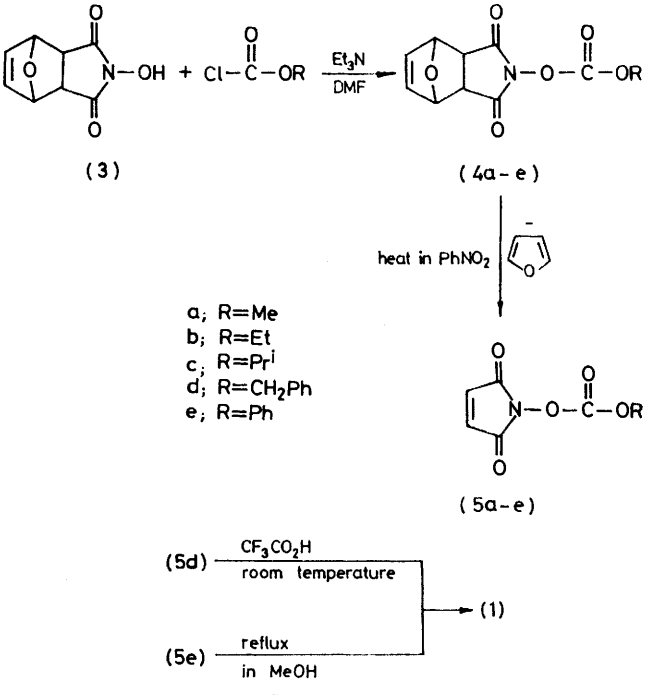
(1) R = H
(2) R = Ac

1,2,3,6-tetrahydrophthalimide (3). Only a trace amount of (1) was obtained; the *N*-hydroxy-function requires protection.

Deacylation of *N*-acetoxymaleimide (2) [12] was then tried: hydrolysis under acidic or basic conditions yielded a ring-opened product, *N*-hydroxymaleamic acid. No reaction occurred by merely heating in methanol, but an intractable oil was formed by addition of base. Aminolysis with cyclohexylamine or imidazole was also unsuccessful.†

As an alternative protecting group, a series of carbonates were examined, and the sequence is shown in Scheme 1.[4] Reaction of (3) with alkyl or phenyl chloroformates in DMF gave the corresponding carbonate esters (4a—e). Thermolysis of (4a—e) in nitrobenzene or bromobenzene at 155—160 °C yielded the *N*-maleimidyl carbonates (5a—e). Cleavage of the protecting group was carried out either by treating (5d) with trifluoroacetic acid, or by refluxing (5e) in methanol; both procedures gave (1) in good yield. The acidolysis was unsuccessful when applied to the other carbonates (5a—c, e), starting material being recovered. The methanolysis of (5a—d) was also unsuccessful, but addition of triethylamine to the methanol solution produced an oily substance, indicative of side-reactions.[13] In contrast, clean aminolyses were observed for the corresponding succinimide derivatives.[14,15]

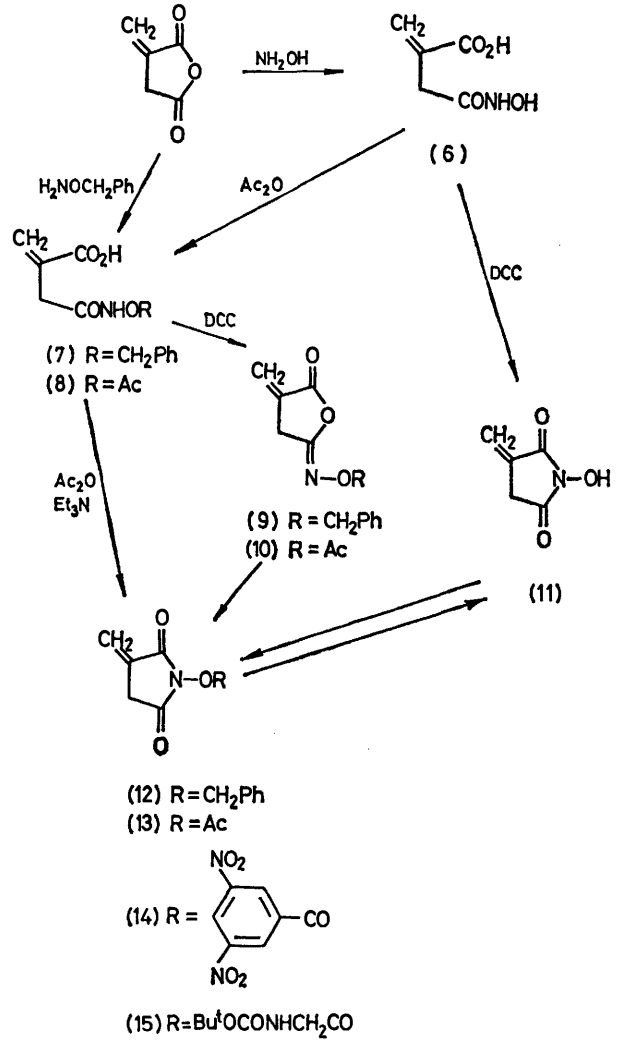
The above multi-step reaction made us explore more convenient routes to the desired imides. It is of interest to examine itaconic acid derivatives, since the exo-methylene system is expected to favour imide formation, because of the greater conformational freedom and less conjugative stabilisation relative to the maleamic system. Several itaconimides have been described in the literature,[16] but not many hydroxylamine derivatives. Scheme 2 depicts the reactions performed. Itaconic anhydride and hydroxylamine or benzyloxyamine gave the acids (6) and (7). Preferential attack at the methylene carbonyl group (CH_2CO) has been established previously.[17] Treatment of (6) with acetic anhydride without base gave the *O*-acylation product (8). Dehydration of the acids (7) and (8) with dicyclohexylcarbodi-imide (DCC) produced the isoimides (9)



Scheme 1

† Some reactions of maleimides with amines have been noted.[13]

and (10).[6,18] Similar dehydration of the parent acid (6) in dilute solution gave the desired imide (11) in 23% yield, suggesting that the imide formation is a facile process. Dehydration of the acids (7) and (8) by acetic anhydride–triethylamine yielded the imides (12) and (13). The rearrangement of (9) to (12) or (10) to (13) was effected by acetic acid–triethylamine or by mild heating. Aminolysis of the acetoxyimide (13) with



SCHEME 2

morpholine afforded the *N*-hydroxyimide (11). Furthermore, some active esters were prepared; (11) reacted with 3,5-dinitrobenzoyl chloride to give the benzoyl ester (14) and with t-butoxycarbonyl glycine in the presence of DCC to yield the amino-acid ester (15).

EXPERIMENTAL

I.r. spectra were recorded with a JASCO Model DS-403 G spectrometer. ^{1}H N.m.r. spectra were obtained with a JEOL Model C-60 HL spectrometer with $SiMe_4$ as internal standard. Microanalyses were performed by our Department with a Perkin-Elmer Model 240 elemental analyser.

Alkyl or Aryl N-(3,6-*epoxy*-1,2,3,6-*tetrahydrophthalimidyl*) *Carbonates* (4a—e). *N*-Hydroxy-3,6-epoxy-1,2,3,6-tetrahydrophthalimide (3) [12] (46.8 g, 0.258 mol) and Et_3N (26.3 g) were dissolved in DMF (130 ml). To this cooled and stirred solution was added dropwise the appropriate chloroformate (0.26 mol) during 1 h. After stirring for 2 h at room temperature, the precipitated Et_3NHCl was filtered off and the filtrate was poured into water (1.3 l) to precipitate the product. Additional product was obtained by dissolving the Et_3NHCl salt in water (1.3 l). The combined precipitated product was washed with water and dried, affording (4a—e). Common i.r. absorptions were at 1 820, 1 790, and 1 730 cm^{-1}. The following were obtained: the *methyl carbonate* (4a), in 71% yield (from CH_3CN), m.p. 176—177 °C (Found: C, 50.2; H, 3.8; N, 5.9. $C_{10}H_9NO_6$ requires C, 50.5; H, 3.9; N, 6.0%): the *ethyl carbonate* (4b), in 79% yield (from EtOH), m.p. 117—118 °C (Found: C, 52.2; H, 4.5; N, 5.6. $C_{11}H_{11}NO_6$ requires C, 52.2; H, 4.4; N, 5.5%): the *isopropyl carbonate* (4c), in 80% yield (from EtOH), m.p. 134—135 °C (Found: C, 53.7; H, 4.9; N, 5.2. $C_{12}H_{13}NO_6$ requires C, 53.9; H, 4.9; N, 5.2%): the *benzyl carbonate* (4d), in 71% yield (from EtOH), m.p. 140—141 °C (Found: C, 58.3; H, 3.7; N, 5.7. $C_{16}H_{13}NO_6$ requires C, 58.3; H, 3.7; N, 5.7%): and the *phenyl carbonate* (4e), in 82% yield (from Pr^{i}OH), m.p. 135—136 °C (Found: C, 59.8; H, 3.7; N, 4.7. $C_{15}H_{11}NO_6$ requires C, 59.8; H, 3.8; N, 4.7%).

Alkyl or Aryl N-*Maleimidyl Carbonates* (5a—e).—A solution of (4a—e) (0.15 mol) and t-butylcatechol (0.5 g) in nitrobenzene (80 ml) was heated for 30 min under reduced pressure (100 mmHg) in an oil-bath maintained at 155—160 °C. Nitrobenzene was then removed and the residue usually solidified as a crude product. Yields for (5a—c) were not optimized. Common i.r. absorptions were at 1 810, 1 790, and 1 730 cm^{-1}. The following maleimidyl carbonates were obtained: the *methyl carbonate* (5a), in 54% yield (from MeOH), m.p. 105—106 °C (Found: C, 42.1; H, 3.0; N, 8.2. $C_6H_5NO_5$ requires C. 42.4; H, 3.0; N, 8.2%): the *ethyl carbonate* (5b), in 51% yield as a liquid, b.p. 122 °C at 4 mmHg (Found: C, 45.4; H, 3.8; N, 7.5. $C_7H_7NO_5$ requires C, 45.4; H, 3.8; N, 7.6%): the *isopropyl carbonate* (5c), in 49% yield (from Pr^{i}OH), m.p. 77—78 °C (Found: C, 48.5; H, 4.6; N, 7.2. $C_8H_9NO_5$ requires C, 48.2; H, 4.7; N, 7.0%): the *benzyl carbonate* (5d), in 83% yield (from MeOH), m.p. 103—104 °C (Found: C, 58.3; H, 3.7; N, 5.7. $C_{12}H_9NO_5$ requires C, 58.3; H, 3.7; N, 5.7%): and the *phenyl carbonate* (5e), in 78% yield (from CCl_4), m.p. 98—99 °C, or in 92% yield by thermolysis in bromobenzene (Found: C, 56.7; H, 3.0; N, 6.0. $C_{11}H_7NO_5$ requires C, 56.7; H, 3.0; N, 5.8%).

N-*Hydroxymaleimide* (1).—(a) *Acidolysis.* Benzyl *N*-maleimidyl carbonate (5d) (2.0 g, 8.1 mmol) was dissolved in CF_3CO_2H (10 ml) and the mixture was kept at room temperature for 50 h. Evaporation of the solvent gave a solid, m.p. 124—126 °C (from toluene; 0.40 g, 44%); $\nu_{max.}$ 3 150 (N–OH) and 1 785—1 725 (imide) cm^{-1}; δ[$(CD_3)_2$CO] 6.80 (2 H, s, –CH=CH–).

(b) *Methanolysis.* A methanol solution (40 ml) of (5e) (7.0 g, 0.03 mol) was refluxed for 2 h and evaporated to give a residue which solidified with benzene–hexane (5 : 7). Recrystallization from hexane–THF gave (1) (2.7 g, 79%), m.p. 125—126 °C (Found: C, 42.6; H, 2.8; N, 12.1. $C_4H_3NO_3$ requires C, 42.5; H, 2.7; N, 12.4%).

(c) *Thermolysis.* A nitrobenzene solution (12 ml) of (3) (1.5 g, 8.3 mmol) was heated at 164 °C for 30 min. Evaporation of the solvent gave a residue of (1) (0.15 g, 16%), m.p. 118—120 °C.

3-(N-*Hydroxycarbamoyl*)-2-*methylenepropionic Acid* (6).—Itaconic anhydride (56 g, 0.50 mol) was added portionwise to a cooled and stirred solution of NH_2OH in MeOH [prepared by mixing NH_2OH·HCl (38 g) in MeOH (240 ml) with KOH (34 g, 85%) in MeOH (150 ml)]. The mixture was stirred at room temperature for 5 h, evaporated, washed with acetone, and dried to give (6) (59.6 g, 82%), m.p. 124—125 °C (from MeOH–benzene) (Found: C, 40.9; H, 4.9; N, 9.8. $C_5H_7NO_4$ requires C 41.4; H, 4.9; N, 9.7%); $\nu_{max.}$ 1 700 and 1 635 cm^{-1}; δ[$(CD_3)_2SO$] 2.98 (2 H, d, CH_2) and 5.73—6.28 (2 H, d, CH_2=).

3-(N-*Benzyloxycarbamoyl*)-2-*methylenepropionic Acid* (7).—Benzyloxyamine (6.2 g, 0.05 mol) was added dropwise to a cooled and stirred suspension of itaconic anhydride (5.6 g) in toluene (100 ml). The slurry was stirred for 3 h at room temperature, yielding (7) as a crude product (10.7 g, 91%), m.p. 122—123 °C (from AcOEt–hexane) (Found: C, 61.2; H, 5.7; N, 5.9. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.6; N, 6.0%); $\nu_{max.}$ 1 695 and 1 650 cm^{-1}; δ[$(CD_3)_2SO$] 2.97 (2 H, m, CH_2CO), 4.74 (2 H, s, CH_2Ph), 5.65—6.12 (2 H, m, CH_2=), and 7.32 (5 H, s, Ph).

3-(N-*Acetoxycarbamoyl*)-2-*methylenepropionic Acid* (8).—To a stirred solution of (6) (14.5 g, 0.10 mol) was added Ac_2O in AcOEt (70 ml). The suspension was stirred at room temperature for 20 h to give (8) as a crude product (15.7 g, 84%), needles (from AcOEt), m.p. 121—122 °C (Found: C, 45.5; H, 4.7; N, 7.7. $C_7H_9NO_5$ requires C, 44.9; H, 4.9; N, 7.5%); $\nu_{max.}$ 1 795 (N–OAc), 1 705, and 1 660 cm^{-1}; δ[$(CD_3)_2SO$] 2.13 (3 H, s, Me), 3.13 (2 H, s, CH_2), and 5.79—6.21 (2 H, d, CH_2=).

5-(*Benzyloxyimino*)-3-*methylene*-4,5-*dihydrofuran*-2(3H)-*one* (9).—A mixture of (7) (1.1 g, 4.7 mmol) and dicyclohexylcarbodi-imide (DCC) (0.97 g) in AcOEt (30 ml) was stirred for 3 h at 5 °C, and kept in the refrigerator overnight. Dicyclohexylurea (DCU) was filtered off, and the filtrate was concentrated. The residue was dissolved in AcOEt, and additional DCU was filtered off. Concentration of the filtrate gave (9) (from hexane). (0.64 g, 63%), m.p. 88—89 °C (Found: C, 66.2; H, 5.0; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%); $\nu_{max.}$ 1 815—1 795 and 1 680—1 660 (C=N) cm^{-1}; δ($CDCl_3$) 3.60 (2 H, m, CH_2CO), 5.03 (2 H, s, CH_2Ph), 5.58—6.42 (2 H, m, CH_2=), and 7.30 (5 H, s, Ph).

5-(*Acetoxyimino*)-3-*methylene*-4,5-*dihydrofuran*-2(3H)-*one* (10).—A mixture of (8) (2.0 g, 10.7 mmol) in AcOEt (80 ml) and DCC (2.2 g) in AcOEt (10 ml) was stirred for 3 h at 5 °C and kept in the refrigerator overnight. A residue obtained by the usual work-up gave (10) (from CCl_4) (0.70 g, 39%), m.p. 107—108 °C (Found: C, 49.5; H, 4.2; N, 8.1. $C_7H_7NO_4$ requires C, 49.7; H, 4.2; N, 8.3%); $\nu_{max.}$ 1 820 (N–OAc) and 1 765—1 700 (C=N) cm^{-1}; δ[$(CD_3)_2SO$] 2.14 (3 H, s, Me), 3.79 (2 H, t, CH_2), and 6.05—6.38 (2 H, t, CH_2=).

N-*Hydroxyitaconimide* (11).—A mixture of (6) (0.50 g, 3.4 mmol) and DCC (0.71 g) in acetone (100 ml) was stirred at room temperature for 15 h. The reaction mixture was treated in the same way as (9) to give a concentrated solution (1 ml), from which (11) crystallized as needles (0.10 g, 23%), m.p. 115—116 °C (from toluene) (Found: C, 47.2; H, 4.0; N, 11.0. $C_5H_5NO_3$ requires C, 47.2; H, 4.0; N, 11.0%); $\nu_{max.}$ 1 780 and 1 720 cm^{-1}; δ[$(CD_3)_2SO$] 3.35 (2 H, d, CH_2) and 5.67—6.15 (2 H, d, CH_2=).

N-*Benzyloxyitaconimide* (12).—A mixture of (7) (1.18 g, 5 mmol), Ac_2O (1.52 g), and Et_3N (0.10 g) in CH_2Cl_2 (40 ml) was stirred at room temperature for 4 h. The mixture was stirred with EtOH (2 ml) for an additional 2 h, washed with aqueous Na_2CO_3 and water, dried (Na_2SO_4), and evaporated to give (12) (1.02 g, 93%), m.p. 85—86 °C (from hexane–CH_2Cl_2) (Found: C, 66.1; H, 5.1; N, 6.2. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%); $\nu_{max.}$ 1 790 and 1 725 cm^{-1}; δ($CDCl_3$) 3.25 (2 H, t, CH_2CO), 5.15 (2 H, s, CH_2Ph), 5.58—6.35 (2 H, m, CH_2=), and 7.39 (5 H, s, Ph).

N-*Acetoxyitaconimide* (13).—A mixture of (6) (1.45 g, 0.01 mol), Ac_2O (3.1 g), and Et_3N (0.10 g) in AcOEt (40 ml) was stirred at room temperature for 24 h, concentrated, and chromatographed on silica gel with AcOEt as eluant. The first portion was collected (1.5 g, 89%). An additional column treatment followed by drying under vacuum gave an analytical sample as an oil (Found: C, 49.5; H, 4.4; N, 7.7. $C_7H_7NO_4$ requires C, 49.7; H, 4.2; N, 8.3%); $\nu_{max.}$ 1 815 (N–OAc), 1 785, and 1 735 cm^{-1}; δ($CDCl_3$) 2.17 (3 H, s, Me), 3.75 (2 H, t, CH_2), and 5.98—6.52 (2 H, t, CH_2=).

Isomerization.—Compound (9) (0.4 g) in CH_2Cl_2 was treated with AcOH (0.6 g) and Et_3N (0.2 g) at room temperature for 24 h to give the imide (12). Compound (10) was converted into (13) on standing in a desiccator for months or by heating at 80 °C for 8 h.

Aminolysis.—To a solution of (13) (0.88 g, 5 mmol) in CH_2Cl_2 (20 ml) was added dropwise morpholine (0.44 g) in CH_2Cl_2 (5 ml) and the solution was stirred at room temperature for 20 h. Removal of the solvent under vacuum gave an oil, which was extracted with hexane and CCl_4 and chromatographed on silica gel with MeOH as eluant. The first portion gave (11) as an oil (0.52 g, 79%), which crystallized on standing.

N-*Itaconimidyl*-3,5-*Dinitrobenzoate* (14).—To a solution of (11) (0.13 g, 1 mmol) and Et_3N (0.1 g) in THF (10 ml) was added portionwise 3,5-dinitrobenzoyl chloride (0.23 g, 1 mmol), the mixture stirred for 2 h at 5 °C, and kept overnight. Et_3NHCl was filtered off and the filtrate was concentrated. Trituration with CCl_4 gave (14) (0.25 g. 78%), m.p. 147—149 °C (from CCl_4) (Found: C, 44.4; H, 2.3; N, 13.0. $C_{12}H_7N_3O_8$ requires C, 44.9; H, 2.2; N, 13.1%); $\nu_{max.}$ 1 805, 1 780, and 1 740 cm^{-1}.

N-*Itaconimidyl t-Butyloxycarbonylglycinate* (15).—To a cooled and stirred solution of t-butyloxycarbonylglycine (0.70 g, 4 mmol) and (11) (0.51 g) in THF (15 ml) was added a solution of DCC (0.83 g) in THF (3 ml). After stirring for 5 h at −10 °C and for 20 h at room temperature, the usual work-up gave a residue which crystallized by addition of ether (15 ml) (0.69 g, 61%), m.p. 141—142 °C (from Bu^sOH–hexane) (Found: C, 50.9; H, 5.7; N, 9.9. $C_{12}H_{16}N_2O_6$ requires C, 50.7; H, 5.7; N, 9.9%); $\nu_{max.}$ 1 820, 1 790, 1 740, and 1 680 cm^{-1}.

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