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SYNTHESIS AND SOME REDUCTIONS OF *ENDO*- AND *EXO*-3,6-EPOXY-Δ^4-TETRAHYDROPHTHALIC ANHYDRIDE

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Abstract—The synthesis of *endo*-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride from the *endo*-adduct of furan and maleic acid is described. Reduction of *endo*- and *exo*-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride with sodium borohydride gave the corresponding lactones, while catalytic hydrogenation over 10% Pd/C gave anhydride and/or hemi-acylals, depending on the solvent.

The Diels-Alder reaction of furan and maleic anhydride gives rise to the formation of *exo*-adduct **1**, as has been shown by Woodward and Baer.[1] The reaction was investigated by Anet[2] with NMR and found to proceed in a non-stereospecific way. Initially, *exo*-adduct **1** is formed twice as fast as *endo*-adduct **2**, but after a while—due to instability of *endo*-adduct **2**—only the thermodynamically favoured *exo*-adduct **1** is present in the reaction mixture. Anet was once able to isolate almost pure **2**, but could not reproduce this result.

endo-Acid **3** being available,[3] it seems obvious to try to convert **3** into *endo*-adduct **2**. We could accomplish this conversion by treating **3** with acetic anhydride-pyridine for 5 min at 0–5°, affording *endo*-compound **2** in 60–70% yield. The compound is stable in crystalline form and shows a m.p. 80–82°† (dec). During repeated scanning of the NMR spectrum (Table 1) of *endo*-adduct **2** in DMSO-d_6, the compound decomposed by a retrograde Diels-Alder reaction, which could be seen from appearance of signals of furan and maleic anhydride. Upon scanning the spectrum again after 1 hr, signals of furan, maleic anhydride and *exo*-adduct **1** were visible. In spite of instability‡ of *endo*-adduct **2** in solution, we were able to carry out some reactions with this compound.

Catalytic hydrogenation of **2** over 10% Pd/C catalyst at low temperature—to suppress retrograde Diels-Alder reaction—gave the known saturated *endo*-anhydride **4**, whose structure was confirmed by its NMR spectrum (Table 1). Reduction of **2** with $NaBH_4$ in DMF at 0°—a suitable method for reducing cyclic anhydrides to lactones[4,5]—afforded lactone **5**. Similar reactions of *exo*-adduct **1** led to the formation of anhydride **8** and lactone **9**. Catalytic hydrogenation of lactone **9** in ethyl acetate afforded lactone **12**.

Table 1. Chemical shifts of some 3,6-epoxy-Δ^4-tetrahydro- and hexahydro-phthalic anhydrides

	C_1H, C_2H	C_3H, C_6H	C_4H, C_5H
1	3·19[a], 3·25[b]	5·47[a], 5·34[b]	6·62[a], 6·53[b]
2	3·90[a], 3·77[b]	5·4[a], 5·43[b]	6·63[a], 6·53[b]
4	3·77[a]	5·0[a]	1·35–1·95[a]
8	3·40[a]	4·92[a]	1·68[a]

[a]DMSO-d_6.
[b]CD_3CN (see ref 4).

Catalytic hydrogenation of **1** over 10% Pd/C catalyst shows a remarkable solvent dependency. Hydrogenation in acetone, DMF or isopropanol gave anhydride **8**, while hydrogenation in ethanol or methanol led to the formation of hemi-acylal **10** which—according to the NMR spectrum—is present in the cyclic form completely. Hydrogenation in acetic acid under the same conditions gave a mixture of anhydride **8** and cyclic hemi-acylal **10**. Hydrogenation of anhydride **4** in ethanol over 10% Pd/C catalyst afforded hemi-acylal **6**.

The solvent dependency on catalytic hydrogenation of substituted succinic anhydrides has already been noticed by McCrindle *et al*,[6,7] who found that, if a relative large amount of Adams catalyst was used, formation of hemi-acylal, γ-lactone and/or 2-methylcarboxylic acid was dependent on substrate, solvent and time of reduction. Hydrogenation of **1** e.g. in ethyl acetate gave cyclic hemi-acylal **10** and lactone **12**, while hydrogenation in acetic acid afforded lactone **12** and 2-methylcarboxylic acid **13**.[6,7] We could reduce phthalic

[a]Taken in part from the forthcoming doctorate dissertation of T. A. Eggelte.
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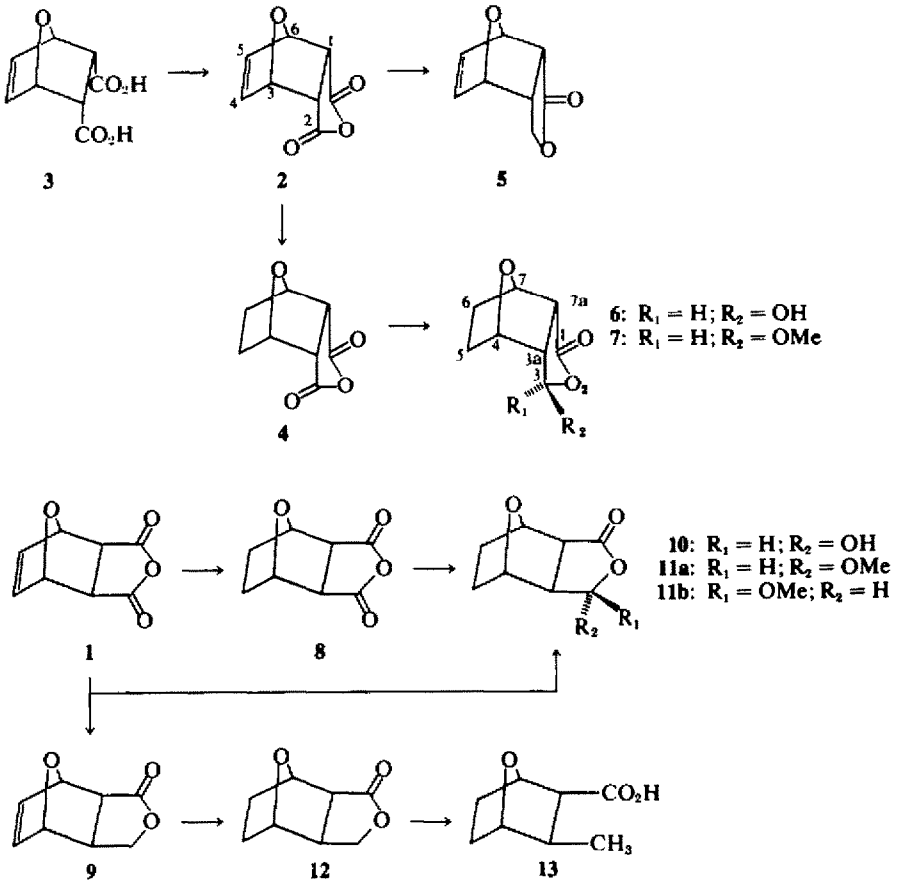
†Circa 70° was reported by Anet.[2]
‡Anet[2] reported appreciable dissociation after 5 min.



anhydride smoothly to *o*-toluic acid in several solvents (acetone, DMF, isopropanol, ethanol) when 10% Pd/C was used as catalyst. Use of PtO_2 is known to give several products due to attack on the aromatic ring,[8] while use of other catalysts requires more severe conditions.[9,10]

In both **6** and **10** the OH group at $C_{(3)}$ is *cis* with respect to the $C_{(3a)}$ proton, which follows from the NMR spectra showing a singlet for the $C_{(3)}$ proton in **6** and a doublet ($J_{3,3a} = 2$ Hz) in **10**. In both cases reduction has taken place from the less hindered *exo*-side, but in the case of **6**—due to unfavourable sterical interaction of the OH group with the $C_{(5)}$ *endo*-proton–the OH group is isomerized *via* the aldehyde-carboxylic acid from the *trans* to the *cis* position with respect to the $C_{(3a)}$ proton. Refluxing hemi-acylal **6** in methanol in presence of a catalytic amount of *p*-toluenesulphonic acid afforded the pseudo-ester **7**. Similar reaction of **10** gave—according to the NMR spectrum—a mixture of pseudo-esters **11a** and **11b** in a ratio 6:1. The isomers could be separated by column chromatography and further purified by recrystallisation from cyclohexane. Configuration assignment is based on the coupling constant $J_{3,3a}$. (**11a** $J_{3,3a} = 1\frac{1}{2}$ Hz, **11b** $J_{3,3a} = 6\frac{1}{2}$ Hz).

EXPERIMENTAL

All m.ps are uncorrected. Analyses were carried out by Mr. H. Pieters of the Microanalytical Department of this Laboratory. IR spectra were recorded on Unicam SP 200 and Perkin Elmer 125 spectrometers. NMR spectra were measured on a Varian Associates Model A-60 and HA-100 instrument.

exo-3,6-*Epoxy*-Δ^4-*tetrahydrophthalic anhydride* (**1**). *exo*-Adduct **1** was prepared according to the method described,[11] yield: 85%, white needles, m.p. 120–121°(Lit.[1] 125°); IR (KBr): 1855 and 1790 cm^{-1} (anhydride C=O).

endo-3,6-*Epoxy*-Δ^4-*tetrahydrophthalic anhydride* (**2**). *endo*-Acid **3** (1·0 g) was added to a mixtue of pyridine (0·75 ml) and Ac_2O (1·0 ml); the mixture was stirred for 5 min at 0–5°. After addition of ether, *endo*-adduct **2** (635 mg; 70%) was obtained by filtration; m.p. 80–82° (dec); IR (KBr): 1855 and 1770 cm^{-1} (anhydride C=O). (Found: C, 57·9; H, 3·5. $C_8H_8O_4$ requires: C, 57·83; H, 3·64%).

endo-3,6-*Epoxy-hexahydrophthalic anhydride* (**4**). *endo*-Adduct **2** (300 mg) was added to prehydrogenated 10% Pd/C catalyst (50 mg) in 40 ml acetone at −5–0° and hydrogenated for 40 min at 4 atm in a Parr apparatus. Filtering off the catalyst, evaporation of the solvent and addition of ether afforded *endo*-anhydride **4** (210 mg; 70%) after filtration. M.p. 166–167°; Lit.[1] 169–170°. IR (KBr): 1855 an 1785 cm^{-1} (anhydride C=O).

endo-4,7-*Epoxy*-Δ^5-*tetrahydrophthalide* (**5**). To $NaBH_4$ (180 mg) in DMF (18 ml) at 0° *endo*-adduct **2** (0·5 g) was

added and the mixture stirred for 40 min. Evaporation of the solvent gave a solid residue of the borate complex, which was hydrolysed with 1 M H_2SO_4. The hydrolysate was extracted several times with chloroform an the combined extracts were washed with water and sat NaCl aq and dried over $MgSO_4$.

Evaporation of the solvent gave lactone **5** (253 mg, 55%), m.p. 108–109° (recrystallized from cyclohexane/EtOAc); IR (KBr): 1760 cm^{-1} (lactone C=O); NMR ($CDCl_3$, 100 MHz); δ 3·1–3·45 (*m*) (C_{3a}—H), 3·5 (C_{7a}—H, $J_{3a,7a}$ = 9½ Hz), 3·76 ($C_{3\alpha}$—H, $J_{3\alpha,3\beta}$ = 10 Hz, $J_{3\alpha,3a}$ = 3 Hz), 4·26 ($C_{3\beta}$—H, $J_{3\beta,3a}$ = 8½ Hz), 5·10 (*d*) (C_4—H, $J_{3a,4}$ = 4½ Hz), 5·25 (*d*) (C_7—H, $J_{7,7a}$ = 5 Hz), 6·28 (*s*) (C_5— and C_6—H). (Found: C, 63·1; H, 5·3. $C_8H_8O_3$ requires: C, 63·15; H, 5·30%).

endo-3-*Hydroxy*-4,7-*epoxyhexahydrophthalide* (**6**). *endo*-Anhydride **4** (5·0 g) was hydrogenated in dry EtOH (200 ml) over 10% Pd/C (500 mg) for 17 hr at 4 atm in a Parr apparatus. The reaction was started at 0° and allowed to warm up to room temp during hydrogenation. Filtering off the catalyst, evaporation of the solvent and treatment of the residue with ether gave hemi-acylal **6** (4·15 g, 82%): m.p. 138–140·5°; IR (KBr): 3300 cm^{-1} (—OH), 1720 broad band with shoulder at 1770 cm^{-1} (hemi-acylal C=O); NMR (DMSO-d_6, 100 MHz); δ 1·3–1·9 (*m*) (C_5-methylene and C_6-methylene) 2·76 (C_{3a}—H, $J_{3a,4}$ = 6 Hz), 3·36 (C_{7a}—H, $J_{3a,7a}$ = 10½ Hz, $J_{7a,7}$ = 6½ Hz), 4·7 (C_4—H and C_7—H), 5·75 (*s*) (C_3—H). (Found: C, 56·5; H, 6·0. $C_8H_{10}O_4$ requires: C, 56·46; H, 5·92%).

endo-3-*Methoxy*-4,7-*epoxyhexahydrophthalide* (**7**). Hemi-acylal **6** (480 mg) was refluxed in MeOH (10 ml) for 4 hr in presence of a catalytic amount of *p*-toluenesulphonic acid. Evaporation of the solvent gave pseudo-ester **7a** as a colourless oil, which slowly crystallized; m.p. 68·5–70° (recrystallized from cyclohexane): IR ($CHCl_3$): 1775 cm^{-1} (pseudo-ester, lactone C=O); NMR ($CDCl_3$, 100 MHz): δ 1·75 (*s*) (C_5-methylene and C_6-methylene) 2·95 (C_{3a}—H, $J_{3a,7a}$ = 10 Hz, $J_{3a,4}$ = 5½ Hz), 3·36 (C_{7a}—H, $J_{7a,7}$ = 6 Hz), 4·75 and 4·83 (C_4—H and C_7—H), 5·19 (*s*) (C_3—H). (Found: C, 58·5; H, 6·4. $C_9H_{12}O_4$ requires: C, 58·69; H, 6·57%).

exo-3,6-*Epoxyhexahydrophthalic anhydride* (**8**). *exo*-Adduct **1** (50 g) was hydrogenated in DMF (150 ml) over 10% Pd/C catalyst (2·5 g) for 5 hr. After addition of ether (100 ml the mixture was filtered over hyflo and the solvents evaporated, giving anhydride **8** (49 g; 98%); m.p. 115–116° (after sublimation); lit.[1] 116–117°); IR (KBr): 1870, 1814 and 1770 cm^{-1} (anhydride C=O).

exo-4,7-*Epoxy*-Δ⁴-*tetrahydrophthalide* (**9**). To $NaBH_4$ (2·16 g) in DMF (30 ml) at 0° *exo*-adduct **1** (10 g) in DMF (50 ml) was added in 30 min and stirred for 3 hr at room temp. After evaporation of the solvent a solid residue of the borate complex was obtained, which was hydrolysed with 1 M H_2SO_4 (150 ml). The hydrolysate was extracted several times with chloroform and the combined extracts were washed and dried over $MgSO_4$. Evaporation of the solvent gave lactone **9** (6·5 g, 71%); m.p. 91–92° (recrystallized from cyclohexane/EtOAc); IR ($CHCl_3$): 1760 cm^{-1} (lactone C=O); NMR (DMSO-d_6, 100 MHz); δ 2·55–2·75 (*m*) (C_{3a}—H), 2·82 (C_{7a}—H, $J_{3a,7a}$ = 8½ Hz), 4·10 (C_3—H_β, $J_{3\alpha,3\beta}$ = 9½ Hz, $J_{3\beta,3a}$ = 3½ Hz), 4·42 (C_3—H_α, $J_{3\alpha,3a}$ = 8½ Hz), 5·0 (*s*) (C_4—H), 5·07 (*s*) (C_7—H), 6·46 (*s*) (C_5—H and C_6—H). (Found: C, 63·0; H, 5·4. $C_8H_8O_3$ requires: C, 63·15; H, 5·30%).

exo-3-*Hydroxy*-4,7-*epoxyhexahydrophthalide* (**10**). *exo*-Anhydride **8** (0·5 g) was hydrogenated as described for *endo*-anhydride **4**. After working up hemi-acylal **10** (500 mg) was obtained. Instead of **8**, *exo*-adduct **1** could be used for hydrogenation, giving similar results, m.p. 175–176° (recrystallized from cyclohexane/EtOAc); lit.[7] 180–181°; IR (KBr): 3260 cm^{-1} (—OH), 1730 cm^{-1} broad band with shoulder at 1770 cm^{-1} (hemi-acylal C=O); NMR (DMSO-d_6; 60 MHz): δ 1·54 (*s*) (C_5-methylene an C_6-methylene), 2·40 (C_{3a}—H), 3·02 (C_{7a}—H, $J_{3a,7a}$ = 8 Hz), 4·62 (C_4—H), 4·75 (C_7—H), 5·51 (*d*) (C_3—H, $J_{3,3a}$ = 2 Hz), 7·3–7·7 (OH). (Found: C, 56·3; H, 6·0. $C_8H_{10}O_4$ requires: C, 56·46; H, 5·92%).

exo-3-*Methoxy*-4,7-*epoxyhexahydrophthalide* (**11**) Hemi-acylal **10** (1·0 g) was refluxed in MeOH (15 ml) for 1 hr in presence of a catalytic amount of *p*-toluenesulphonic acid. After evaporation of solvent **11** was obtained as a colourless oil, which consisted—according to TLC an NMR spectrum—of two isomers. The isomers **11a** an **11b** could be separated on a silica gel column—using chloroform as eluent—and further purified by recrystallization from cylohexane.

Compound **11a**; m.p. 64·5–66°. IR ($CHCl_3$): 1770 cm^{-1} (pseudo-ester, lactone C=O); NMR ($CDCl_3$, 100 MHz): δ 1·35–1·9 (C_5-methylene and C_6-methylene 2·49 (C_{3a}—H), 2·90 (C_{7a}—H, $J_{3a,7a}$ = 8 Hz), 3·47 (*s*) (OMe), 4·70 (C_4—H), 4·80 (C_7—H), 5·18 (*d*) (C_3—H, $J_{3,3a}$ = 2½ Hz). (Found: C, 58·8; H, 6·5. $C_9H_{12}O_4$ requires: C, 58·69; H, 6·57%).

Compound **11b**; m.p. 116–118°. IR ($CHCl_3$) 1770 cm^{-1} (pseudo-ester, lactone C=O); NMR ($CDCl_3$, 100 MHz): δ 1·25–1·95 (C_5-methylene and C_6-methylene), 2·69 (C_{3a}—H), 2·89 (C_{7a}—H, $J_{3a,7a}$ = 8½ Hz), 3·56 (*s*) (OCH_3) 4·9 (C_4—H), 5·05 (C_7—H), 5·41 (*d*) (C_3—H, $J_{3,3a}$ = 6½ Hz). (Found: C, 58·7; H, 6·6%).

exo-4,7-*Epoxyhexahydrophthalide* (**12**). Lactone **9** (1·0 g) was hydrogenated in EtOAc (75 ml) over 10% Pd/C catalyst (100 mg) for 2 hr. Filtering off the catalyst and evaporation of the solvent gave lactone **12** (940 mg); m.p. 120–120·5° (recrystallized from cyclohexane); lit.[7] 126–127°; IR (KBr): 1770 cm^{-1} (lactone C=O). NMR ($CDCl_3$, 100 MHz): δ 1·35–1·95 (C_5-methylene and C_6-methylene) 2·6–2·9 (*m*), (C_{3a}—H and C_{7a}—H), 4·0–4·25 (C_3—H_β), 4·25–4·5 (C_3—H_α), 4·54 (C_4—H), 4·81 (C_7—H).

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