

937. The Catalytic Hydrogenation of Substituted Succinic Anhydrides.

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A series of substituted succinic anhydrides has been hydrogenated in the presence of platinum. In addition to the corresponding butyrolactones, the intermediate hemiacylals were, in certain cases, obtained in good yields. Unexpectedly 2-methyl-carboxylic acids are obtained as major products when the solvent is acetic acid. A limited study has been made of the relation between anhydride structure and product composition.*

THE literature records the reduction of 1,2-dicarboxylic anhydrides under a variety of conditions. The usual product is the lactone which results from reduction of one carbonyl group to methylene. Thus phthalic anhydride with zinc and acetic acid,¹ Raney nickel,² or lithium aluminium hydride³ gives phthalide, but sodium in pentyl alcohol⁴ or hydrogen in presence of platinum and acetic acid⁵ gives hexahydrophthalide, the corresponding hydroxy-acid, and hexahydro-*o*-toluic acid.

There are far fewer instances of the reduction of non-aromatic anhydrides, but these include reduction of succinic anhydride to butyrolactone (12%) by sodium amalgam,⁶ and reduction of the tetrahydromethylphthalic anhydride (I) by lithium aluminium hydride to the lactone (II). More recently the reduction of cyclo-octene-1,2-dicarboxylic anhydride to the corresponding saturated lactone with platinum has been observed,⁸ and this most closely parallels our findings. It is also relevant that sodium borohydride has been shown to effect reduction of a cyclic hemiacylal⁹ to the lactone. The results which follow disclose two aspects of anhydride reduction which appear to be new. We have found that catalytic hydrogenation of substituted succinic anhydrides with a platinum catalyst can give the hemiacylal, $-\text{CO}\cdot\text{O}\cdot\text{CO}- \longrightarrow -\text{CH}(\text{OH})\cdot\text{O}\cdot\text{CO}-$, and the 2-methyl-carboxylic acid, $-\text{CO}\cdot\text{O}\cdot\text{CO} \longrightarrow \text{CH}_3 \text{H}_2\text{OC}-$, as major products, the exact course of the reaction depending upon the substrate, solvent, and time of reduction.

Our interest in this subject arose from our observation that the Diels-Alder adduct (III)¹⁰ of 2-acetoxymethylenecyclopentadiene and maleic anhydride (the *endo*-configuration is assigned on the basis of precedent¹¹) formed a tetrahydro-derivative in more than 90% yield when it was hydrogenated in the presence of Adams catalyst in ethyl acetate. The reduction product was shown to have structure (IV) or (V) by virtue of its stability to boiling ethanol, loss of the characteristic succinic anhydride doublet in its infrared spectrum, and smooth reconversion into the anhydride (III; without ethylenic linkage) on consumption of one oxygen-equivalent of chromic acid. That the tetrahydro-compound existed as the hemiacylal tautomer was shown by the absence in the infrared spectrum of aldehydic and carboxylic absorption and the presence in solution of well-defined bands at 1770 (hemiacylal) and 1750 (acetate) cm^{-1} . The lactone (VI) was isolated as a very minor by-product (~2%). However, when acetic acid was used as solvent, further hydrogenation removed all the initially

* See McC Crindle, Overton, and Raphael, *Proc. Chem. Soc.*, 1961, 313.

¹ Wislicenus, *Ber.*, 1884, **17**, 2178.

² Theilacker and Kalenda, *Annalen*, 1953, **584**, 87.

³ Weygand, Kinkel, and Tiejn, *Chem. Ber.*, 1950, **83**, 394.

⁴ Einhorn, *Annalen*, 1898, **300**, 172.

⁵ Willstätter and Jaquet, *Ber.*, 1918, **51**, 773.

⁶ Rodd, "Chemistry of Carbon Compounds," Vol. IB, Elsevier, Amsterdam, 1952, p. 796.

⁷ Granger and Techer, *Compt. rend.*, 1960, **250**, 142.

⁸ Sicher, Sipos, and Jonas, *Coll. Czech. Chem. Comm.*, 1961, **26**, 262.

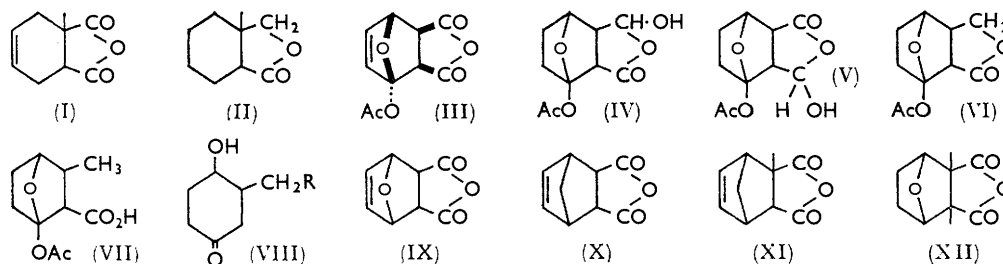
⁹ Weinberg, Utzinger, Arigoni, and Jeger, *Helv. Chim. Acta*, 1960, **43**, 236.

¹⁰ Clauson-Kaas and Elming, *Acta Chem. Scand.*, 1952, **6**, 560; Cava, Wilson, and Williams, *J. Amer. Chem. Soc.*, 1956, **78**, 2303.

¹¹ Woodward and Baer, *J. Amer. Chem. Soc.*, 1948, **70**, 1161; Kwart and Vosburgh, *ibid.*, 1954, **76**, 5400.

formed hemiacylal, the products being comparable amounts of the lactone (VI) and, surprisingly, the methyl acid (VII). Similar hydrogenation of the hemiacylal (IV) itself led to a 2 : 1 mixture of lactone and methyl acid; the lactone (VI) remained unchanged in comparable hydrogenation conditions.

A decision as to which of the anhydride carbonyl groups of (III) had been reduced was based on hydrolysis and decarboxylation of the lactone (VI) and the acid (VII)



by alkali to the ketones (VIII; R = OH) and (VIII; R = H), respectively, characterised as the crystalline 2,4-dinitrophenylhydrazones. That all three reduction products were simply related followed from the conversion of the hemiacylal into both the lactone and the methyl acid.

Our results appeared to us to be of interest for three reasons. First, absence of previous similar observations seemed surprising in view of the numerous instances¹² of the hydrogenation of Diels–Alder adducts, although the proportion of catalyst used in our experiments was in excess of that normally employed. Secondly, the one-step formation of acyl-hemiacylals from anhydrides might offer practical advantages over the usual, more tedious methods.¹³ Thirdly, the unexpected formation of a 2-methyl carboxylic acid from an alicyclic (as distinct from an aromatic) anhydride appeared to require the novel hydrogenolysis of an apparently unactivated oxygen function.

The effect of change of structure on product composition was explored by reduction of the adducts (IX), (X), and (XI), representing simple structural variations on (III). In the first two cases exhaustive hydrogenation in ethyl acetate gave only the lactone (or hydroxy-acid). The hemiacylal was obtained if reduction was stopped after a shorter time or if a smaller proportion of catalyst was used. With the adducts (III) and (XI), the hemiacylal was the major product at completion. On the other hand, reduction of cantharidin (XII) in ethyl acetate led almost exclusively to the lactone. These results preclude simple correlation of hydrogenation products with the structure of the starting anhydride.

Hexahydrophthalic anhydride was reduced to hexahydrophthalide in ethyl acetate and to a mixture of the phthalide and hexahydro-*o*-toluic acid in acetic acid. Succinic anhydride similarly gave butyrolactone as a major product but even in ethyl acetate this was accompanied by butyric acid in minor amount. Cyclobutane-1,2-dicarboxylic anhydride was unique in giving the methyl acid as the only isolable product of reduction.

Camphoric anhydride in ethyl acetate gave a mixture of hydroxy-acids corresponding to α - and β -campholides (1 : 2), the latter, as might be expected, arising in excess. In acetic acid no appreciable hydrogen uptake occurred.

A number of proposals could be made to rationalise our results, but they would hardly be justified in view of the qualitative nature of our observations and the limited knowledge concerning the mechanism of catalytic hydrogenations in general.

¹² *E.g.*, (a) Woodward and Lofffield, *J. Amer. Chem. Soc.*, 1941, **63**, 3167; (b) Jenkins and Costello, *ibid.*, 1946, **68**, 2733; (c) Bailev, Haworth, and McKenna, *I.*, 1954, 967.

¹³ Warner and Moe, *J. Amer. Chem. Soc.*, 1948, **70**, 3470; Johnson, Linstead, and Whetstone, *J.*, 1950, 2219.

EXPERIMENTAL

M.p.s were taken on the Kofler block. Infrared absorption spectra were determined, unless otherwise stated, in Nujol with the Perkin-Elmer 13 (by Dr. G. Eglington and his colleagues) and the Infracord spectrophotometer. Microanalyses were carried out by Mr. J. M. L. Cameron, B.Sc., and his associates. Light petroleum refers to the fraction of b. p. 60–80° unless otherwise stated. Ethyl acetate and acetic acid were of "AnalaR" grade. The catalyst used throughout was Adams platinum oxide (Johnson Matthey and Co., London). Silica gel (B.D.H., London) was used for chromatography unless otherwise stated.

Hydrogenation of the Anhydride (III).—(a) The anhydride (1.5 g.) and Adams catalyst (200 mg.) were shaken in ethyl acetate (40 ml.) at 20°. 1 mol. of hydrogen (160 ml.) was taken up very rapidly and a further 1.3 mol. (200 ml.) during 16 hr. Removal of catalyst and solvent afforded 7-acetoxy-4,7-epoxyhexahydro-3-hydroxyphthalide (IV) (1.3 g.), needles (from methanol), m. p. 206–207° (Found: C, 52.75; H, 5.0. $C_{10}H_{12}O_6$ requires C, 52.65; H, 5.3%), ν_{\max} 3265 cm^{-1} (OH), (in $CHCl_3$) 1770 (CO of hemiacylal) and 1750 cm^{-1} (OAc).

The hemiacylal (IV) was recovered unchanged from refluxing ethanol after 30 min. The dihydro-adduct (4-acetoxy-4,7-epoxyperhydrophthalic anhydride), when similarly treated, afforded the *monoethyl ester*, needles (from ethyl acetate), m. p. 148°, of one of the corresponding diacids (Found: C, 52.9; H, 6.0. $C_{12}H_{16}O_7$ requires C, 52.95; H, 5.9%).

The hemiacylal (IV) (120 mg.) was further reduced with catalyst (55 mg.) in acetic acid (20 ml.). Unchanged material was removed by crystallisation from benzene. Chromatography over silica afforded (ether–benzene, 1:200) the lactone (VI) (54 mg.) and (ether–benzene, 1:20) 2-acetoxy-2,5-epoxy-6-methylcyclohexanecarboxylic acid (VII) (26 mg.) (see below).

(b) The adduct (III) (250 mg.) was hydrogenated as in (a), and the hemiacylal (IV) (190 mg.), m. p. 205–207°, obtained by crystallisation from ethyl acetate. Chromatography of the residue in benzene furnished 7-acetoxy-4,7-epoxyhexahydrophthalide (VI) (4 mg.), prisms (from light petroleum), m. p. 142–143° (Found: C, 56.55; H, 5.5. $C_{10}H_{12}O_5$ requires C, 56.5; H, 5.7%), ν_{\max} 1740 cm^{-1} (superimposed γ -lactone and acetate).

The lactone (VI) (200 mg.) and sodium hydroxide (400 mg.) in water (5 ml.) were refluxed for 1 hr., and the cooled solution was acidified and treated with 2,4-dinitrophenylhydrazine (500 mg.) in 5N-hydrochloric acid (2 ml.) for 3 min. at 95°. The product extracted with chloroform was chromatographed in benzene over alumina (grade 5). Ethyl acetate–chloroform (1:10) eluted the 2,4-dinitrophenylhydrazone, needles (from ethyl acetate–light petroleum), m. p. 158–160°, of 4-hydroxy-3-hydroxymethylcyclohexanone (VIII; R = OH) (Found: C, 48.35; H, 4.95; N, 17.2. $C_{13}H_{16}N_4O_6$ requires C, 48.15; H, 4.95; N, 17.3%).

The lactone (VI) was shaken with an equal weight of catalyst in acetic acid. There was no hydrogen uptake and the lactone was recovered unchanged.

(c) The anhydride (III) (210 mg.) was reduced with catalyst (100 mg.) in acetic acid (30 ml.), uptake being complete in 6 hr. Removal of catalyst and solvent and chromatography of the residue (195 mg.) in benzene afforded (ether–benzene, 1:200) the lactone (VI) (69 mg.), (ether–benzene, 1:20) 2-acetoxy-2,5-epoxy-6-methylcyclohexanecarboxylic acid (VII), forming needles, m. p. 147–150°, when sublimed at 120°/0.1 mm. (Found: C, 56.25; H, 6.35. $C_{10}H_{14}O_5$ requires C, 56.05; H, 6.6%), ν_{\max} 2500–2700 (OH of CO_2H), 1740 (OAc) and 1695 cm^{-1} (CO_2H). Further elution with ethyl acetate gave a mixture of hemiacylal (28 mg.) and methyl acid (10 mg.).

The dihydro-anhydride (cf. III) (610 mg.), when reduced similarly, afforded the lactone (298 mg.) and the methyl acid (272 mg.), but no hemiacylal.

When the methyl acid was hydrolysed as for the lactone, the product afforded the 2,4-dinitrophenylhydrazone, needles (from ethyl acetate–light petroleum), m. p. 169–172°, of 4-hydroxy-3-methylcyclohexanone (VIII; R = H) (Found: C, 50.55; H, 5.4; N, 17.8. $C_{13}H_{16}N_4O_5$ requires C, 50.65; H, 5.25; N, 18.2%).

The methyl acid (50 mg.) was heated at 200° during 5 min. Sublimation of the product at 80°/0.1 mm. afforded a lactone (prisms from benzene–light petroleum), m. p. 83–84° (Found: C, 62.3; H, 6.4. $C_8H_{10}O_3$ requires C, 62.3; H, 6.55%), ν_{\max} 1760 (γ -lactone?) and 1705 cm^{-1} (cyclohexanone).

Hydrogenation of the Anhydride (IX).—(a) The anhydride¹⁴ (1 g.) and catalyst (200 mg.) in

¹⁴ Diels and Alder, *Ber.*, 1929, **62**, 554.

ethyl acetate (50 ml.) consumed 2.2 mol. of hydrogen during 6 hr. Chromatography of the product afforded the following compounds: (i) with benzene, 4,7-epoxyhexahydrophthalide (210 mg.), needles (from ethyl acetate-light petroleum), m. p. 126—127° (Found: C, 62.35; H, 6.5. $C_8H_{10}O_3$ requires C, 62.3; H, 6.55%), ν_{\max} 1745 cm^{-1} (γ -lactone); (ii) with chloroform, 4,7-epoxyhexahydro-3-hydroxyphthalide (767 mg.), cubes (from ethyl acetate-light petroleum), m. p. 180—181° (Found: C, 56.6; H, 6.0. $C_8H_{10}O_4$ requires C, 56.45; H, 5.9%), ν_{\max} 3200 (OH) and 1720 cm^{-1} (CO of hemiacylal), (in $CHCl_3$) 1765 cm^{-1} (CO of hemiacylal).

(b) The adduct (IX) (1 g.) was hydrogenated as above but in acetic acid, 1 mol. of hydrogen being absorbed rapidly and a further 2.1 mol. during 20 hr., whereafter uptake ceased. Chromatography as in (a) furnished (i) the lactone (with ether-benzene, 1:20) (650 mg.); (ii) 3,6-epoxy-2-methylcyclohexanecarboxylic acid (270 mg.), rods (from ethyl acetate-light petroleum), m. p. 142—143° (Found: C, 61.35; H, 7.7. $C_8H_{12}O_3$ requires C, 61.5; H, 7.75%), ν_{\max} 2700—3200 (OH of CO_2H) and 1690 cm^{-1} (CO_2H). When the lactone, m. p. 126—127°, was shaken with half its weight of catalyst for 6 hr., there was no hydrogen uptake and the lactone was recovered unchanged.

Hydrogenation of Anhydride (X).—This anhydride ¹⁵ (550 mg.) was reduced in ethyl acetate with 20% of its weight of catalyst. The product gave on chromatography (i), with benzene, the known dihydro-anhydride (140 mg.), (ii) hexahydro-4,7-methylenephthalide (145 mg.), prisms (from light petroleum), m. p. 148—149° (Found: C, 70.95; H, 7.85. $C_9H_{12}O_2$ requires C, 71.0; H, 7.9%), ν_{\max} 1760 cm^{-1} (γ -lactone), (iii) with chloroform hexahydro-3-hydroxy-4,7-methylenephthalide (135 mg.), plates (from ethyl acetate light-petroleum), m. p. 120—121° (Found: C, 64.0; H, 7.4. $C_9H_{12}O_3$ requires C, 64.25; H, 7.2%), ν_{\max} 3290 (OH) and 1740 cm^{-1} (CO of hemiacylal), and (iv) with acetone, the hydroxy-acid (80 mg.), ν_{\max} 3430 (OH), 2500—2800 (OH of CO_2H), and 1705 cm^{-1} (CO_2H), corresponding to the lactone of m. p. 120—121° into which it was converted when heated at 80° in benzene for 1 hr.

When this reduction was repeated with 40% of catalyst by weight, only the lactone and the corresponding hydroxy-acid were obtained.

Hydrogenation of the Anhydride (XI).—This adduct ¹⁵ (500 mg.) and catalyst (150 mg.) in ethyl acetate (30 ml.) furnished on chromatography (i) by benzene, hexahydro-3a(or 7a)-methyl-4,7-methylenephthalide (84 mg.) (from light petroleum), m. p. 130—131° (Found: C, 71.95; H, 8.55. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.5%), ν_{\max} 1765 cm^{-1} (γ -lactone), and, (ii) by chloroform, hexahydro-3-hydroxy-3a(or 7a)-methyl-4,7-methylenephthalide (288 mg.), plates (from ethyl acetate-light petroleum), m. p. 182—183° (Found: C, 65.9; H, 7.65. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.5%), ν_{\max} 3270 (OH) and 1735 cm^{-1} (CO of hemiacylal).

This hemiacylal (100 mg.), hydrogenated with an equal weight of catalyst in ethyl acetate, afforded unchanged material (48 mg.) and lactone (43 mg.).

Hydrogenation of Cantharidin (XII).—Cantharidin (305 mg.) was hydrogenated with the catalyst (500 mg.) in ethyl acetate (75 ml.), 2 mol. being taken up during 4 hr. Chromatography gave (i) 4,7-epoxyhexahydro-3a,7a-dimethylphthalide (252 mg.), needles (from ethyl acetate-light petroleum), m. p. 132—134° (sublimation) (Found: C, 65.95; H, 7.4. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.75%), and (ii) 4,7-epoxyhexahydro-3-hydroxy-3a,7a-dimethylphthalide (32 mg.), prisms (from ethyl acetate-light petroleum), m. p. 152—154° (sublimation) (Found: C, 60.85; H, 6.9. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%).

Hydrogenation of cis-Hexahydrophthalic Anhydride.—*cis*-Hexahydrophthalic anhydride ^{12b} (310 mg.) and catalyst (195 mg.) in ethyl acetate (30 ml.) gave a product that was kept on Woelm acid alumina (grade V) during 18 hr. (to cyclise hydroxy-acid to lactone) and then eluted as follows: (i) benzene-light petroleum (1:20) gave oily hexahydrophthalide (73 mg.), characterised as the *S*-benzylthiouronium salt, prisms (from ethyl acetate), m. p. 166°, of the corresponding hydroxy-acid (Found: C, 59.45; H, 7.6; N, 8.65. $C_{16}H_{24}N_2O_3S$ requires C, 59.25; H, 7.45; N, 8.65%); (ii) ethyl acetate gave 2-methylcyclohexanecarboxylic acid (110 mg.), characterised as the *S*-benzylthiouronium salt, prisms (from ethyl acetate), m. p. 168—170° (Found: C, 62.15; H, 7.6; N, 8.6. $C_{16}H_{24}N_2O_2S$ requires C, 62.3; H, 7.85; N, 9.0%).

Hydrogenation of Succinic Anhydride.—Succinic anhydride (2 g.) and catalyst (1 g.) in ethyl acetate (100 ml.) absorbed 2 mol. of hydrogen in 24 hr. The solvent was removed through a short Vigreux column, and the residue [ν_{\max} 3200—3500, 2500—2800, and 1700 cm^{-1} (hydroxy-acid)] was heated on the steam-bath for 3 hr. to lactonise hydroxy-acid, and dried. Distillation

¹⁵ Diels and Alder, *Annalen*, 1928, **460**, 98.

at 150—160°/760 mm. gave butyric acid (240 mg.) and a residue of butyrolactone (1.6 g.), both having correct infrared spectra.

Hydrogenation of cis-Cyclobutane-1,2-dicarboxylic Anhydride.—The anhydride¹⁶ (1.24 g.), catalyst (630 mg.), and ethyl acetate (70 ml.) absorbed 3 mol. of hydrogen in 4 hr. The oily product (1.15 g.) consisted almost exclusively of 2-methylcyclobutanecarboxylic acid characterised as the *S*-benzylthiouronium salt, prisms (from ethyl acetate), m. p. 164—167° (Found: C, 59.7; H, 6.95; N, 10.3. C₁₄H₂₀O₂N₂S requires C, 60.0; H, 7.2; N, 10.0%). Attempts to demonstrate the presence of the hemiacetyl as the 2,4-dinitrophenylhydrazone, or of the hydroxy-acid as the 4-nitrobenzyl ester, or the anilide were unsuccessful.

Hydrogenation of Camphoric Anhydride.—(—)-Camphoric anhydride (2 g.), catalyst (1 g.), and ethyl acetate (100 ml.) absorbed 1.5 mol. of hydrogen in 18 hr. Chromatography separated the product into unchanged camphoric anhydride (800 mg.) and a mixture of hydroxy-acids (1.2 g.) corresponding to α - and β -campholide. The mixture (876 mg.) crystallised from ethyl acetate, affording α -campholenic acid (412 mg.), m. p. 119°,¹⁷ which was converted by hot 0.1N-sulphuric acid into α -campholide, m. p. 206—210°, $[\alpha]_D -24^\circ$ (*c* 1.5) (infrared spectrum identical with that of an authentic sample¹⁸). From the mother-liquor the known β -campholenic acid¹⁷ (220 mg.), m. p. 113—115°, separated on dilution with light petroleum. This was converted into β -campholide¹⁹ (we are most grateful to Professor Salmon-Legagneur, Rennes, for an authentic specimen), m. p. 215—219°, $[\alpha]_D +29^\circ$ (*c* 0.9), the infrared spectrum being identical with that of authentic sample. Lactonisation of the oily residue (240 mg.) from the β -campholenic acid mother-liquors and chromatography furnished α -campholide (65 mg.) and β -campholide (90 mg.).

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¹⁶ Buchman, Reims, Skei, and Schlatter, *J. Amer. Chem. Soc.*, 1942, **64**, 2696.

¹⁷ Salmon-Legagneur and Vene, *Bull. Soc. chim. France*, 1937, **4**, 448.

¹⁸ Baeyer and Villiger, *Ber.*, 1899, **32**, 3625.

¹⁹ Haller and Blanc, *Compt. rend.*, 1905, **141**, 697; Bredt, *J. prakt. Chem.*, 1917, **95**, 63.