THE TETRAHYDROPHTHALIC ACIDS

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CONTENTS

I. INTRODUCTION

This review is concerned mainly with the chemical and physical properties of the isomeric tetrahydrophthalic acids and their derivatives, especially the anhydrides, imides, and esters.

The tetrahydrophthalic acids and their derivatives have been subjected to various systems of nomenclature by the authors who have discussed them. Representative names are given in table 1. In the more recent indices of *Chemical Abstracts* the compounds are listed as cyclohexenedicarboxylic acids and their derivatives, but in earlier indices they are also listed under the tetrahydrophthalic acids. Both general systems of naming have been used in Beilstein's *Handbuch* (25). In this review it will be convenient to use the name tetrahydrophthalic acid and to designate the position of the double bond by the Δ notation.

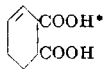
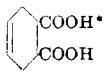
No other review has dealt specifically with the isomeric tetrahydrophthalic acids. Some of the synthetic methods have been covered in reviews of the Diels–Alder reaction (55, 76, 102), and some of the useful applications of derivatives of the Δ^4 acid have been included in practical reviews on maleic anhydride adducts (56, 57). For this review the literature has been covered through 1954.

II. STRUCTURE AND IDENTITY

The currently accepted (9, 115) assignments of structure to the known tetrahydrophthalic acids and anhydrides are given in table 2. In the earlier literature,

TABLE 1

Representative names used for the tetrahydrophthalic acids

Formula of Acid	Names
	1-Cyclohexene-1,2-dicarboxylic acid Δ^1, 1,2-Cyclohexenedicarboxylic acid Δ^1-Tetrahydrophthalic acid 3,4,5,6-Tetrahydrophthalic acid
	2-Cyclohexene-1,2-dicarboxylic acid Δ^2,1,2-Cyclohexenedicarboxylic acid Δ^2-Tetrahydrophthalic acid 2,3,4,5-Tetrahydrophthalic acid
	3-Cyclohexene-1,2-dicarboxylic acid Δ^3,1,2-Cyclohexenedicarboxylic acid Δ^3-Tetrahydrophthalic acid 1,2,3,4-Tetrahydrophthalic acid
	4-Cyclohexene-1,2-dicarboxylic acid Δ^4,1,2-Cyclohexenedicarboxylic acid Δ^4-Tetrahydrophthalic acid 1,2,3,6-Tetrahydrophthalic acid

* The carboxyl groups can be either cis or trans with respect to each other.

TABLE 2

Melting points of the tetrahydrophthalic acids and anhydrides (9, 115)

Isomer	Melting Point		Isomer	Melting Point	
	Acid	Anhydride		Acid	Anhydride
	°C.	°C.		°C.	°C.
Δ^1	120	74	*trans*-Δ^3	218	140
Δ^2	215	79	*cis*-Δ^4	166	104
cis-Δ^3	174	59	*trans*-Δ^4	172	188

particularly that referred to in the main series of Beilstein's *Handbuch* (25), the *cis*- and *trans*-Δ^3 isomers are designated incorrectly as the corresponding Δ^4 isomers. The *trans*-Δ^3 acid was originally synthesized (14) by the reduction of phthalic acid and the incorrect Δ^4 structure was assigned on the basis of the fact that no succinic acid was isolated from the oxidation of the acid. The *cis*-Δ^3 anhydride was prepared by isomerization of the *trans*-Δ^3 anhydride at 220°C. It was first considered to be the Δ^3 isomer (14), and then it was incorrectly designated as the *cis*-Δ^4 isomer (13). The correct structures were clearly established by the use of the Diels–Alder synthesis (102). The *cis*-Δ^4 anhydride was prepared by the reaction of maleic anhydride with butadiene, and the structure was established by oxidation to *meso*-1,2,3,4-butanetetracarboxylic acid (9, 51). Derivatives of the *trans*-Δ^4 acid were prepared by the reaction of butadiene with various derivatives of fumaric acid (9, 79, 80, 81). The structure of the acid was established by oxidation to *dl*-1,2,3,4-butanetetracarboxylic acid (9). A mixture of the *cis*- and *trans*-Δ^3 acids was prepared by the reaction of 2,4-pentadienoic

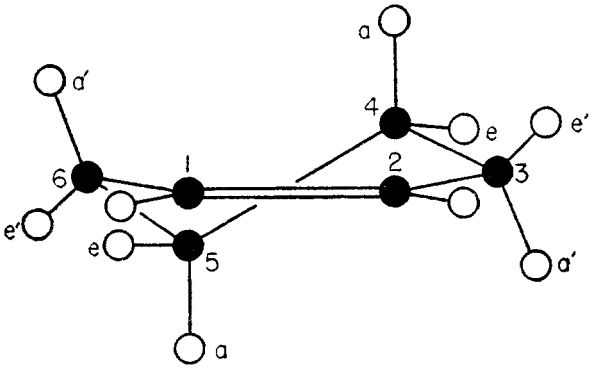


FIG. 1. The chair form of the cyclohexene ring

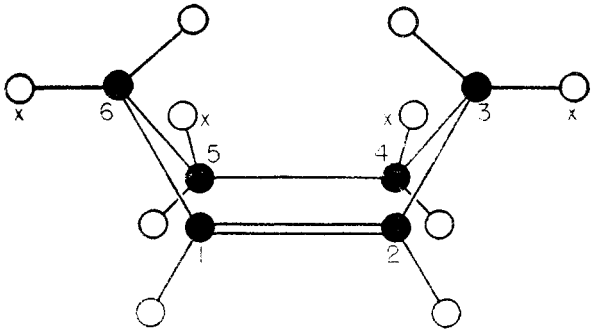


FIG. 2. The boat form of the cyclohexene ring

acid with acrylic acid (10). Their properties identified them with the acids earlier believed to be the *cis*- and *trans*-Δ^4 isomers. A tetrahydrophthalic acid (anhydride melting at 70°C.) to which the Δ^3 structure was incorrectly assigned (1, 2, 3, 5, 6, 25) appears, on the basis of its properties and those of its derivatives, to have been an impure preparation of the Δ^1 isomer.

III. STEREOCHEMISTRY

Although extensive structural determinations have not been carried out, it has been possible to treat the stereochemistry of substituted cyclohexenes (21, 22, 23, 24, 77, 104) in a fashion analogous to that used for cyclohexanes (103). Figure 1 shows the chair form or "half chair" form and figure 2 the boat form or "half boat" form which are possible for the cyclohexene ring (21). Only the cis configuration about the double bond is possible in a six-membered ring. The trans configuration would give rise to too much strain (50).

As in the case of the cyclohexane ring the chair form is the more stable (24). Only carbon atoms 4 and 5 of the cyclohexene ring have well-defined equatorial bonds (e) and axial bonds (a), which before 1954 were designated as polar bonds (p). The bonds of carbon atoms 3 and 6 can be designated as either axial (a')

TABLE 3

Relative positions of carbonyl group attachment in the tetrahydrophthalic acids and their derivatives

Isomer	Open-chain Derivatives					Fused-ring Derivatives				
	Ring conformation	Position of C=O				Ring conformation	Position of C=O			
		C	Bond	C	Bond		C	Bond	C	Bond
Δ^1	Chair	1		2		Chair	1		2	
Δ^2	Chair	2		3	a′	Boat	2		3	*x*
						Chair	2		3	e′
cis-Δ^3	Chair	3	a′	4	e	Chair	3	a′	4	e
	Chair	3	e′	4	a	Chair	3	e′	4	a
trans-Δ^3	Chair	3	a′	4	a	Chair	3	e′	4	e
cis-Δ^4	Chair	4	e	5	a	Boat	4	*x*	5	*x*
						Chair	4	e	5	a
trans-Δ^4	Chair	4	a	5	a	Chair	4	e	5	e

or equatorial (e′) on the basis of what they would be if the double bond were saturated (21, 104).

In table 3 are tabulated the most likely conformations for the various tetrahydrophthalic acids and their derivatives. The conformations listed for open-chain derivatives, such as the acids themselves and their esters, are based on the assumption that the chair form would be favored over the boat form (24) and that the large groups would be as far apart as possible (103). The conformations suggested for fused-ring derivatives such as anhydrides or imides are based on the ability of the carbonyl groups to be as close together as possible so that the ring fusions would be relatively strainless. For some of the fused-ring systems the boat conformation may be more stable for the cyclohexene ring, since the ring fusion would be less strained than that with the best chair conformation. The bonds labeled X in the boat form of figure 2 are somewhat analogous to the equatorial bonds (e and e′) of the chair form in figure 1.

Although the most likely conformation of the *cis*-Δ^4 acid is asymmetric, the mobility of the ring would be expected to make successful resolution unlikely. Such an attempted resolution was unsuccessful (31).

Since all conformations of the *trans*-Δ^4 acid, the *cis*- and *trans*-Δ^3 acids, and the Δ_2 acids are asymmetric, with no conversions possible between enantiomers merely by changes of ring conformation, it would be expected that all of these acids could be resolved successfully. Samples of (+)-*trans*-Δ^4-tetrahydrophthalic acid, melting point 169–170°C. and $[\alpha]_D^{21}$ = 1.02–11.65°, have been prepared by way of the (−)-menthyl ester (80, 81). Resolution of *trans*-Δ^3-tetrahydrophthalic acid yielded the (+) acid, m.p. 165°C. and $[\alpha]_D^{25}$ = +115.2°; (+) anhydride, m.p. 128°C. and $[\alpha]_D^{25}$ = +6.6°; (−) acid, m.p. 167°C. and $[\alpha]_D^{25}$ = −97.4° (4). It was also reported (4) that the *dl*-form of the *trans*-Δ^3 acid had an appreciable rotation, so these latter values are of doubtful reliability. The other acids have not been subjected to any type of resolution.

TABLE 4

Wavelengths in microns of the main infrared absorption bands of tetrahydrophthalic anhydrides*

Δ^1	Δ^2	*cis*-Δ^3	*cis*-Δ^4	*trans*-Δ^4
3.34 W	3.36 W	3.30 M	3.35 M	3.39 W
3.42 M	3.43 M	3.41 M	3.50 W	3.50 W
3.56 W	3.55 W	3.53 W	3.58 W	3.60 W
5.44 S	5.43 S	5.40 S	5.40 S	5.42 S
			5.50 S	
5.63 S	5.62 S	5.66 S	5.63 S	5.63 S
5.99 M	5.98 S			5.85 W
				6.13 W
6.84 M	6.80 M			
6.99 S	7.02 M	6.93 M	6.96 M	6.93 M
7.39 W	7.37 W	7.40 W	7.25 W	7.30 W
7.62 W	7.50 W	7.65 M	7.42 W	7.42 W
7.86 S†	7.79 M	7.83 M	7.62 M	7.77 S
8.16 W	8.01 S	8.04 S	8.10 S	8.05 M
				8.30 M
8.52 M	8.62 S	8.62 W	8.41 S	8.50 S
8.82 W	8.83 S†	8.76 W	8.73 M	8.71 S
9.21 S	9.20 M	9.22S	9.17 S	8.86 M
9.33 M	9.35 M			
9.64 M	9.59 M	9.60 S	9.62 M	9.58 M
	10.08 S	9.86 S†	10.07 S†	
10.47 M	10.43 S	10.38 S	10.42 S	10.60 W
		10.72 S		10.80 M
11.17 S	11.04 S	10.99 S	10.80 S	11.16 S
		11.45 W		
11.70 W	11.78 M	11.58 W		
11.87 W	12.24 M	12.38-12.52 W		12.53-14.02 W
14.40 M	14.04 M	14.76-14.82 M	14.60 W	
			15.25 M	15.20 M

* The relative intensities of the bands have been roughly designated as strong (S), medium (M), and weak (W).

† These bands were used in the quantitative analysis of mixtures of the anhydrides obtained in isomerization with phosphorus pentoxide or sulfuric acid (16).

IV. PHYSICAL PROPERTIES OF THE ACIDS AND THEIR DERIVATIVES

A. Properties of the acids and anhydrides

The melting points of the acids and their anhydrides are listed in table 2. Simple heating of the acids above their melting points was usually sufficient for the preparation of the anhydrides as derivatives. In cases where this type of treatment led to rearrangement (see Section VI,B) milder reactions with acetyl chloride and similar reagents were effective. Hot water was usually sufficient for the conversion of the anhydride to the acid.

The infrared absorption spectra of the Δ^1, Δ^2, *cis*-Δ^3, *cis*-Δ^4, and *trans*-Δ^4 anhydrides have been measured (16, 17). The spectra differed enough so that the spectrum of a mixture could be used for the determination of its composition (16). In table 4 are listed the principal infrared absorption bands observed for these anhydrides (17).

The heat of formation of the Δ^2 acid was determined to be 881.3 kcal. at constant volume and 881.6 kcal. at constant pressure (121).

TABLE 5

Dissociation constants (K_1) at 25°C. of the tetrahydrophthalic acids

Isomer	K_1	Reference	Isomer	K_1	Reference
Δ^1	5.9×10^{-4}	(15)	*cis*-Δ^3	6.2×10^{-6}	(5)
Δ^{1*}	5.81×10^{-4}	(1)	*trans*-Δ^3	1.18×10^{-6}	(15)
Δ^2	7.4×10^{-5}	(15)	*trans*-Δ^3	1.30×10^{-6}	(5)
Δ^2	7.6×10^{-5}	(117)			

* This sample was assigned the Δ^3 structure, but its properties indicate that it was probably impure Δ^1 acid.

In table 5 are tabulated the dissociation constants (K_1) of various tetrahydrophthalic acids at 25°C. These constants were determined by electrical conductance measurements. On the basis of the catalysis of the inversion of sucrose by the acid salt of the Δ^2 acid, the K_2 of this acid at 100°C. was reported as 3.2×10^{-7} (117).

The molar refractions and the dispersions of the Δ^1, Δ^2, *cis*-Δ^3, and *trans*-Δ^3 anhydrides in ethyl alcohol have been reported (6). The isomer reported to be Δ^3 (but which was probably impure Δ^1) was also included, and its properties were consistent with its identification as impure Δ^1.

The crystalline forms of the Δ^1 acid (14), the Δ^2 acid, and the *cis*- and *trans*-Δ^3 acids have been investigated and have been used in identification (62).

B. Properties of derivatives other than anhydrides

Solid derivatives (other than anhydrides) of the acids are listed in table 6. Liquid derivatives are given in table 7.

Esters were made by direct esterification of either the anhydrides or the acids. Amides were made by the reaction of ammonia or amines with the anhydrides except for the *N*-butylmonoamide of the Δ^2 acid, which was prepared by the Beckmann rearrangement of the oxime of sedononic acid (6-valeroyl-1-cyclohexenecarboxylic acid) (40). The imides were prepared from the amides or by the reaction of amines with the anhydride. The Δ^1 nitriles were prepared by dehydration of the amide (52).

The Δ^2 acid chloride was prepared by the reaction of the acid and phosphorus pentachloride (68).

A number of derivatives of the Δ^4 acids such as esters (64, 80, 81), the trans chloride (81), the trans dinitrile (129), the cis-*N*-isobutylimide (64), and the cis anhydride (55) were made directly by the Diels–Alder synthesis with butadiene and the corresponding derivatives of maleic and fumaric acids. Similarly, ethyl 2-cyano-3-cyclohexenecarboxylate was synthesized directly by the reaction of ethyl acrylate with 2,4-pentadienonitrile (118).

The hexahydrophthalic acids and anhydrides were prepared by hydrogenation (47, 67) or reduction (12, 14) of the tetrahydrophthalic acids and anhydrides and by direct cyclization reactions (115).

The dibromides were generally prepared by direct addition of bromine. The chlorohydrin and the bromohydrin of the Δ^1 acid and chlorohydrins of the Δ^4

TABLE 6

Solid derivatives of the tetrahydrophthalic acids

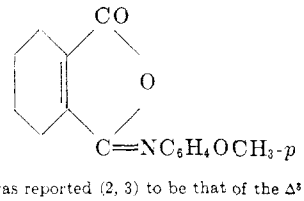
Derivative	Isomer	Melting Point	Reference
		°C.	
Monomethyl ester	*cis*-Δ^4	81.2–83.1	(125)
Monoethyl ester	*cis*-Δ^4	86.0–86.9	(125)
Monopropyl ester	*cis*-Δ^4	48.2–50.5	(125)
Monobutyl ester	*cis*-Δ^4	52.2–54.2	(125)
Monoamyl ester	*cis*-Δ^4	47.1–49.0	(125)
Monohexyl ester	*cis*-Δ^4	48.5–49.5	(125)
Monoheptyl ester	*cis*-Δ^4	38.0–39.9	(125)
Monoöctyl ester	*cis*-Δ^4	36.5–37.1	(125)
Monononyl ester	*cis*-Δ^4	42.9–44.5	(125)
Monodecyl ester	*cis*-Δ^4	51.2–52.1	(125)
Monoundecyl ester	*cis*-Δ^4	50.8–52.0	(125)
Monodocecyl ester	*cis*-Δ^4	58.0–59.0	(125)
Monotridecyl ester	*cis*-Δ^4	61.0–61.8	(125)
Monotetradecyl ester	*cis*-Δ^4	65.3–66.0	(125)
Monopentadecyl ester	*cis*-Δ^4	66.1–66.8	(125)
Monohexadecyl ester	*cis*-Δ^4	70.1–70.7	(125)
Monoheptadecyl ester	*cis*-Δ^4	70.0–71.0	(125)
Monooctadecyl ester	*cis*-Δ^4	73.4–74.4	(125)
Mono-*dl*-menthyl ester	*trans*-Δ^4	101–103	(81)
Mono-(−)-menthyl ester[a]	(+)-*trans*-Δ^4	75–85	(80)
Monocinnamyl ester	*cis*-Δ^4	87–88	(97)
Mono-2-chloroethyl ester	*cis*-Δ^4	66–68	(98)
Monodimethylaminoethyl ester	*cis*-Δ^4	133–134	(113)
Monodiethylaminoethyl ester	*cis*-Δ^4	83–84	(113)
Monodibutylaminoethyl ester	*cis*-Δ^4	Glass	(113)
Monomorpholinoethyl ester	*cis*-Δ^4	141–143	(113)
Monopiperidinoethyl ester	*cis*-Δ^4	148–149	(113)
Monopyrrolidinoethyl ester	*cis*-Δ^4	160–161	(113)
Monophthalimidoethyl ester	*cis*-Δ^4	129–30	(113)
Mono-3-diethylaminopropyl ester	*cis*-Δ^4	Glass	(113)
Mono-2-pyridylethyl ester	*cis*-Δ^4	134–136	(113)
Dimethyl ester	*trans*-Δ^4	39–40	(14)
Bis(3-chloro-1-propyl) ester	*cis*-Δ^4	74.5–76	(98)
Bis(diethylaminoethyl) ester	*cis*-Δ^4	166–171	(113)
Dinitrile	Δ^1	90	(52)
Dinitrile	*trans*-Δ^4	125	(129)
Monoamide, ammonium salt	Δ^1	142–145	(52, 82)
N-*n*-Butylmonoamide	Δ^2	171	(40)
N-*n*-Butylmonoamide	*cis*-Δ^4	90–91	(114)
N-*n*-Hexylmonoamide	*cis*-Δ^4	91–92	(114)
N-*n*-Decylmonoamide	*cis*-Δ^4	90–91	(114)
N-*n*-Dodecylmonoamide	*cis*-Δ^4	70–72	(114)
N-Phenylmonoamide	Δ^1	155	(106)
N-Phenylmonoamide	*cis*-Δ^4	96–98	(114)
N-*p*-Hydroxyphenylmonoamide	Δ^1	170–175	(106)
N-*p*-Methoxyphenylmonoamide	Δ^1	150–155	(106)
N-*p*-Ethoxyphenylmonoamide	Δ^1	145	(106)
N-Benzylmonoamide	*cis*-Δ^4	98–100	(114)
Hydrochloride of *N*-(2-dimethylaminoethyl) monoamide	*cis*-Δ^4	211–213	(114)
Cyanoamide	Δ^1	167–170	(52)
Diamide	Δ^1	208	(52)
Imide	Δ^1	169–170	(82)
Imide	Δ^2	170–175	(52)
		172–173	(82)
Imide	*cis*-Δ^3	148	(118)
Imide	*trans*-Δ^3	232–233	(82)
Imide	*cis*-Δ^4	136–138	(59, 82, 114)
N-Phenylimide	Δ^1	137	(106)
N-*p*-Hydroxyphenylimide	Δ^1	178	(106)
N-*p*-Methoxyphenylimide	Δ^1	95[b]	(3, 106)
N-*p*-Methoxyphenylimide	Δ^2	71	(3)
N-*p*-Methoxyphenylimide	*trans*-Δ^3	128	(3)
N-*p*-Ethoxyphenylimide	Δ^1	137	(106)
N-2-Chloro-5-nitrophenylimide	*cis*-Δ^4	—	(36)

TABLE 6—*Concluded*

Derivative	Isomer	Melting Point	Reference
N-Trichloromethylmercaptoimide[e]	*cis*-Δ^4	170–171	(71, 75)
		172–173	(72, 73)
		177	(120)
(−)-Quinine salt[d]	(+)-*trans*-Δ^3	151	(4)
(−)-Quinine salt[e]	(−)-*trans* Δ^3	174	(4)
Hexahydro acid	*cis*-	192	(115)
Hexahydro acid	*trans*-	221	(115)
Hexahydro anhydride	*cis*-	32	(115)
Hexahydro anhydride	*trans*-	143	(115)
Dibromide[f]	Δ^1	[g] [h]	(14)
Dibromide[f]	Δ^2	225	(14)
Dibromide[f]	*trans*-Δ^3	[g]	(14)
Dibromide	*cis*-Δ^4	220–221	(127)
		222–223	(59)
Dibromide of anhydride	*cis*-Δ^4	138.5–139.5	(127)
Dibromide of dimethyl ester[f]	Δ^1	83–84 } [i]	(14)
		123–124 }	
Dibromide of dimethyl ester[f]	Δ^2	73–74	(14)
Dibromide of dimethyl ester[f]	*trans*-Δ^3	116–117	(14)
Bromohydrin[j]	Δ^1	180	(12)
Chlorohydrin	Δ^1	186	(65)
Chlorohydrin of anhydride	*cis*-Δ^4	164–165	(59)
Glycol	Δ^1	184, 178[i]	(65)
		178–180[k]	(12)
Hydrated double bond	Δ^1	178	(65)
Epoxide	Δ^1	Oil	(65)
Epoxide, fenchylamine salt	Δ^1	197	(65)
Epoxide of anhydride	*cis*-Δ^4	204–205	(59)
cis-Δ^2-Octalin-9,10-dicarboxylic acid[l]	Δ^1	203	(8)
		190	(33)
cis-Δ^2-Octalin-9,10-dicarboxylic anhydride[l]	Δ^1	67–68	(8, 33)
Adipic acid[m]	Δ^1	149	(14)
meso-1,2,3,4-Butanetetracarboxylic acid[m]	*cis*-Δ^4	188–189	(9, 51)
dl-1,2,3,4-Butanetetracargoxylic acid[m]	*trans*-Δ^4	235–237	(9, 79)

[a] $[\alpha]_D^{15} = -47.1°$.

[b] The derivative melting at 95°C. was colorless. A yellow isomer melting at 108°C. was also reported (106). It was formed slowly at 75–80°C. and was reported (83) to be:



Another derivative melting at 88°C. was reported (2, 3) to be that of the Δ^3 acid. It was probably the derivative of impure Δ^1 acid.

[c] This derivative is a fungicide known as Captan.

[d] $[\alpha]_D^{25} = -112.5°$.

[e] $[\alpha]_D^{25} = -149.6°$.

[f] No analysis was given for this derivative.

[g] No melting point was given for this derivative.

[h] A dibromide was reported (2) for the isomer believed to be the Δ^3 acid which was probably an impure sample of the Δ^1 acid. Its melting point was 187°C.

[i] Two diastereomers of this derivative were isolated.

[j] This derivative crystallized with 0.5 H_2O.

[k] This derivative crystallized with 2 H_2O.

[l] This derivative was prepared by a Diels–Alder addition with butadiene.

[m] This derivative was prepared by oxidation.

TABLE 7

Liquid derivatives of the tetrahydrophthalic acids

Derivative	Isomer	Boiling Point	References
		°C.	
Acid chloride	Δ^2	129/14 mm.	(68)
Acid chloride	*trans*-Δ^4	114–115/8 mm.	(81)
Monoallyl ester[a]	*cis*-Δ^4	(b)	(97)
Mono(2-phenoxyethyl) ester[c]	*cis*-Δ^4	205–215/0.5 mm.	(101)
Dimethyl ester	Δ^1	(b)	(14)
Dimethyl ester	Δ^2	(b)	(14)
Dimethyl ester[d]	*cis*-Δ^4	120–122/5 mm.	(41, 42)
Diethyl ester[e]	Δ^1	160/14 mm.	(78)
Diethyl ester[f]	Δ^2	155/12 mm.	(78)
Diethyl ester[g]	*cis*-Δ^4	129–131/5 mm.	(41, 42)
		133–137/5 mm.	(34)
Diethyl ester	Mixture	170–182/14 mm.	(112)
Di-*n*-propyl ester	*cis*-Δ^4	140–141/5 mm.	(34)
Di-*n*-butyl ester	*cis*-Δ^4	186–192/18 mm.	(34)
Di-*n*-butyl ester	mixture	163–165/1 mm.	(110)
Di-*n*-pentyl ester	*cis*-Δ^4	163–165/5 mm.	(34)
Di-*n*-hexyl ester	*cis*-Δ^4	146–148/0.2 mm.	(114)
Di-*n*-heptyl ester	*cis*-Δ^4	163–169/0.7 mm.	(114)
Di-*n*-octyl ester	*cis*-Δ^4	195–197/0.7 mm.	(114)
Di-*n*-nonyl ester	*cis*-Δ^4	195–201/0.5 mm.	(114)
Bis(3,5,5-trimethylhexyl) ester[h]	*cis*-Δ^4	197–198/1.5 mm.	(35)
Di-*n*-decyl ester	*cis*-Δ^4	200–206/0.3 mm.	(114)
Ethyl *n*-decyl ester	*cis*-Δ^4	148–152/0.3 mm.	(114)
Benzyl *n*-octyl ester	*cis*-Δ^4	189–193/0.7 mm.	(114)
Diallyl ester[i]	*cis*-Δ^4	150–152/8 mm.	(97)
Bis(2-methylallyl) ester[j]	*cis*-Δ^4	150–160/4.5 mm.	(97)
Digeranyl ester[k]	*cis*-Δ^4	234–244/3.5 mm.	(97)
Bis(2-chloroallyl) ester[l]	*cis*-Δ^4	185–190/18 mm.	(97)
Bis(2-chloroethyl) ester[m]	*cis*-Δ^4	185–190/7 mm.	(98)
Bis(1-chloro-2-propyl) ester[n]	*cis*-Δ^4	178–188/5.5 mm.	(98)
Bis(1,3-dichloro-2-propyl) ester[o]	*cis*-Δ^4	230–240/5 mm.	(98)
Ethyl 2-cyano-3-cyclohexenecarboxylate[p]	*cis*-Δ^3	77–79/0.2 mm.	(118)
N-Allylimide	*cis*-Δ^4	127–129/3 mm.	(101)
N-Isopropylimide	*cis*-Δ^4	99–100/0.5 mm.	(101)
N-*n*-Butylimide[q]	*cis*-Δ^4	129–131/3 mm.	(101)
		123.5–124/2 mm.	(122)
N-Isobutylimide	*cis*-Δ^4	117–119/2 mm.	(64, 101)
N-*n*-Hexylimide	*cis*-Δ^4	131–134/1.5 mm.	(114)
N-Benzylimide	*cis*-Δ^4	175–178/0.5 mm.	(101)
N-*n*-Decylimide	*cis*-Δ^4	163–165/0.7 mm.	(114)
N-*n*-Dodecylimide	*cis*-Δ^4	165–170/0.2 mm.	(114)
N-(2-Dimethylaminoethyl) imide	*cis*-Δ^4	112–116/0.25 mm.	(114)
N-Carboxymethylimide	*cis*-Δ^4	160–165/0.3 mm.	(114)
N-(2-Carboxyethyl) imide	*cis*-Δ^4	180/0.75 mm.	(114)
N-(1-Carboxy-3-methylmercaptopropyl) imide	*cis*-Δ^4	175/0.3 mm.	(114)
Dimethyl ester of chlorohydrin	*cis*-Δ^4	152–154/0.5 mm.	(59)
Diethyl ester of chlorohydrin	*cis*-Δ^4	146/0.5 mm.	(59)
Di-*n*-butyl ester of chlorohydrin	*cis*-Δ^4	160/1.0 mm.	(59)
Diallyl ester of chlorohydrin	*cis*-Δ^4	186–188/0.4 mm.	(59)
Dimethyl ester of epoxide	*cis*-Δ^4	112/0.6 mm.	(59)
Diethyl ester of epoxide	*cis*-Δ^4	120/0.3 mm.	(59)
Di-*n*-butyl ester of epoxide	*cis*-Δ^4	160–164/0.8 mm.	(59)
Diallyl ester of epoxide	*cis*-Δ^4	133–136/0.3 mm.	(59)
Allyl ethyl ester of epoxide	*cis*-Δ^4	141–144/1.0 mm.	(59)

[a] $n_D^{25} = 1.4971$.

[b] No boiling point was given for this sample.

[c] $n_D^{25} = 1.5230$.

[d] $n_D^{25} = 1.4700$.

[e] $n_D^{20} = 1.4743$; $d_4^{20} = 1.0782$.

[f] $n_D^{20} = 1.4700$; $d_4^{20} = 1.0760$.

[g] $n_D^{25} = 1.4605$–1.4610 (41, 42).

[h] $n_D^{25} = 1.4628$.

[i] $n_D^{25} = 1.4840$; $d_{25}^{25} = 1.09$.

[j] $n_D^{25} = 1.4693$; $d_{25}^{25} = 1.03$.

[k] $n_D^{25} = 1.4902$; $d_{25}^{25} = 0.94$.

[l] $n_D^{25} = 1.5039$; $d_{25}^{25} = 1.24$.

[m] $n_D^{25} = 1.4933$; $d_{25}^{25} = 1.25$.

[n] $n_D^{25} = 1.4837$; $d_{25}^{25} = 1.18$.

[o] $n_D^{25} = 1.5103$; $d_{25}^{25} = 1.32$.

[p] $n_D^{20} = 1.4727$.

[q] $n_D^{25} = 1.5001$; $d^{35} = 1.0723$ g./ml. Viscosity at 35°C. = 0.2996 poise. Surface tension at 35°C. = 34.7 dynes/cm. Interfacial tension against water at 35°C. = 11.4 dynes/cm. Solubility in water at 35°C. = 0.226 g./ml. (122).

esters were prepared by the addition of the elements of the corresponding hypohalous acid (12, 59, 65). The chlorohydrins of the Δ^1 acid and the Δ^4 anhydride were prepared by the opening of oxide rings with hydrogen chloride (59, 65). The glycols of the Δ^1 acid were prepared from the oxide or the halohydrin (12, 65). The lower-melting isomer was assigned the trans configuration, since it was possible to obtain it very slightly resolved (65), but such an assignment is doubtful (see Section VII,B). The 1-hydroxy-1,2-cyclohexanedicarboxylic acid expected from the hydration of the Δ^1 acid was prepared indirectly by way of the cyanohydrin of 2-cyclohexanonecarboxylic acid (65).

The epoxides of the Δ^1 acid and of the Δ^4 esters were synthesized by the reactions of the chlorohydrins with base (59, 65). The epoxides of the Δ^4 anhydride and of the Δ^4 esters were prepared by the epoxidation of the double bond with peracetic acid (59).

The oxidative cleavages of the double bonds to give open-chain acids were carried out with either potassium permanganate or nitric acid.

The salts of the tetrahydrophthalic acids have not been extensively investigated. The lower solubility of the cadmium salt of the Δ^1 acid compared with that of the Δ^2 acid has been used as a rough method of analysis of mixtures (78). The monosodium salt of the Δ^1 acid is relatively insoluble in water and can be easily obtained pure (37).

Salts of divalent metal ions with monoalkyl esters of *cis*-Δ^4-tetrahydrophthalic acid have been prepared (108, 114, 124, 125). Alkyl groups as small as methyl and as large as octadecyl have been used. Salts have been prepared with copper(II), nickel(II), cobalt(II), magnesium, barium, and calcium. Monododecyl *cis*-Δ^4-tetrahydrophthalate has been investigated more extensively than the other esters. Its pK at 25°C. was 6.53 ± 0.08 (124). Its cobalt(II) salt has been found to be a useful derivative for distributing Co^{60} into oil (108, 124).

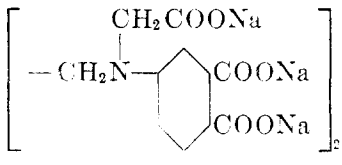
V. USES OF ACIDS AND THEIR DERIVATIVES

Partial reviews of useful applications of tetrahydrophthalic acid derivatives along with those of other maleic anhydride-diene adducts are available (56, 57) and should be consulted for details concerning types of derivatives used for industrial applications.

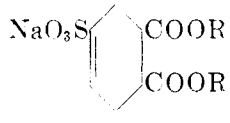
Dialkyl esters of *cis*-Δ^4-tetrahydrophthalic acid prepared either by direct esterification (19, 34, 119) or by Diels–Alder reactions of maleates (64, 95) have been reported to be useful as solvents and plasticizers. The use of chlorinated alcohols in the preparation of the esters leads to products reported to be useful as stabilizers and insecticides (98). This sort of property is also claimed for the allyl-type ester of the *cis*-Δ^4 acid (97), and these esters can also be used in copolymers (7, 97). Polyesters of the *cis*-Δ^4 acid have been prepared and have been reported as useful in many applications (45, 58, 69, 70, 88, 99). Copolymers of such polyesters with styrene have also been reported (58). Polyesters made from the *trans*-Δ^4 acid have been reported to have different properties from those observed for the polyesters of the *cis*-Δ^4 acid (84).

The addition of hydrogen chloride to dimethyl *cis*-Δ^4-tetrahydrophthalate gave the corresponding chloro compound, which was not isolated but was treated with ethylenediamine and sodium chloroacetate and then was saponified to yield the wetting agent shown in formula I (30). The salts of sulfonated esters such as II have also been reported (63, 89) to be useful as wetting agents.

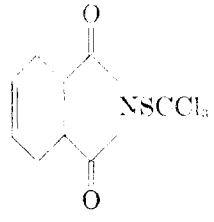
The *N*-alkylimides of the *cis*-Δ^4 acid have been investigated as possible insect repellents and insecticides (101). Of these the *N*-*n*-butylimide appears to be the most promising as a repellent (11, 49, 116, 122). The newly developed fungicide Captan is *N*-trichloromethylmercapto-*cis*-Δ^4-tetrahydrophthalimide (III). It is made (71, 72, 73, 75, 120) by the reaction of trichloromethanesulfenyl chloride with the sodium salt of the *cis*-Δ^4 imide, which is produced (61, 74, 96) from the anhydride.



I



II



III

Besides being a fungicide, Captan is reported to stimulate plant growth (73). The *cis*-Δ^4 acid itself has been reported (109) to promote the growth of a strain of hemolytic streptococus. On the other hand, a tetrahydrophthalic acid whose structure was not specified has been reported (38, 39) as toxic to plants. Since these experiments were carried out before the Diels–Alder synthesis was in use, this acid may have been the mixture of Δ^2- and *trans*-Δ^3-tetrahydrophthalic acids obtained by the reduction of phthalic acid with sodium amalgam (13, 14) or it may have been the Δ^1 acid synthesized from hydropyromellitic acid (12).

The dialkylaminoalkyl esters and half-esters of the *cis*-Δ^4 acid have been found to be hypotensive agents (113).

VI. METHODS OF SYNTHESIS OF THE ACIDS

A. *Diels–Alder reaction*

The original reports on the Diels–Alder reaction included the synthesis of *cis*-Δ^4-tetrahydrophthalic anhydride (46, 47). The Diels-Alder reaction itself has been amply covered by reviews (76, 102). The specific application of the method to the synthesis of the *cis*-Δ^4 anhydride has also been thoroughly covered and compilations of references are available (43, 55). A method of analysis for 4-vinylcyclohexene as a contaminant in the anhydride preparation has been developed (123).

The *cis*-Δ^4 acid is usually synthesized indirectly by way of the anhydride, but there has been one report of the direct synthesis of the acid from maleic acid (64). Esters (64, 69, 70, 95) and substituted imides (64) have also been prepared di-

rectly by the Diels–Alder reaction of the corresponding derivative of maleic acid. It has been reported, however, that such reactions of maleate esters were preceded by isomerization to fumarate esters (80).

The *cis*-Δ^4-tetrahydrophthalaldehyde has been prepared by the Diels–Alder reaction of malealdehyde with butadiene (66). This compound on oxidation by silver oxide gave the *cis*-Δ^4 acid.

Fumaric acid has been used in the Diels–Alder reaction to give the *trans*-Δ^4 acid (79, 81, 84). Esters (80), the acid chloride (81), and the dinitrile (129) have been prepared from the analogous derivatives of fumaric acid by reaction with butadiene.

A mixture of the *cis*- and *trans*-Δ^3 acids with the cis acid predominating in the ratio of 4.5:1 was prepared by the Diels–Alder reaction of 2,4-pentadienoic acid with acrylic acid (10). Similarly, ethyl 2-cyano-3-cyclohexenecarboxylate, which yielded the *cis*-Δ^3 imide on treatment with sulfuric acid, was synthesized by the reaction of 2,4-pentadienonitrile with ethyl acrylate (118).

The Diels–Alder reaction of 1-acetoxy-1,3-butadiene with maleic anhydride yielded 3-acetoxy-4-cyclohexene-1,2-dicarboxylic anhydride, which gave 2,4-cyclohexadiene-1,2-dicarboxylic acid when treated with sulfuric acid. This dihydrophthalic acid was hydrogenated preferentially at the 4-position to yield the Δ^2-tetrahydrophthalic acid (9).

The reaction of butadiene with acetylenedicarboxylic acid was carried out at fairly high temperatures to yield mostly 1,4-cyclohexadiene-1,2-dicarboxylic anhydride, which was hydrogenated at the 4-position to yield Δ^1-tetrahydrophthalic anhydride (8).

B. Isomerization reactions

Two types of isomerization are possible with the tetrahydrophthalic acids and their derivatives. There can be a shift in the position of the double bond and there can be a cis-trans isomerization of the carboxyl groups,— or rather of the hydrogen atoms on the alpha carbon atoms.

With base the Δ^1 acid (14, 16, 60, 78) and the *cis*-Δ^3 acid (13, 118) have been reported to isomerize to the Δ^2 isomer. It has been reported (60) that the base-catalyzed isomerization of the Δ^1 acid to the Δ^2 acid was reversible, but no experimental evidence was cited (78).

The only similar base-catalyzed isomerization of the Δ^4 isomer is mentioned in connection with the oxidative cleavage by base to yield 3-carboxypimelic acid or pimelic acid (see Section VII,B). Such a cleavage is best explained on the basis of an initial isomerization to the Δ^2 isomer, which was not isolated (105).

When the Δ^2 acid or anhydride was heated around 220–230°C. the Δ^1 anhydride was the product (14). A similar treatment of the *trans*-Δ^3 anhydride gave rise to the *cis*-Δ^3 anhydride (14).

With relatively small amounts of phosphorus pentoxide or concentrated sulfuric acid as a catalyst the *cis*-Δ^4 anhydride was isomerized rapidly to the *cis*-Δ^3 isomer, which in turn was isomerized more slowly to the Δ^2 isomer and eventually to the Δ^1 isomer. It was possible to obtain a mixture of anhydride isomers of

minimum solidification point (around 0°C.) which had about 60 per cent *cis*-Δ^3 anhydride with the rest of the composition about equally distributed among the starting anhydride and the other two isomers formed. It was also possible to obtain a product which was mostly the Δ^1 anhydride. The composition of isomer mixtures was determined by means of infrared spectra (16).

C. Miscellaneous methods

The first synthesis of a tetrahydrophthalic acid was that of the Δ^1 isomer (12). A mixture of hydropyromellitic acid and isohydropyromellitic acid was prepared by the action of sodium amalgam on pyromellitic acid. Slow distillation of this mixture yielded Δ^1-tetrahydrophthalic anhydride, which was converted to the acid by water.

The application of reduction by sodium amalgam to phthalic acid gave a mixture of the Δ^2- and the *trans*-Δ^3-tetrahydrophthalic acids (13, 14). The Δ^1 acid (14) and the *cis*-Δ^3 acid (13) were synthesized from these by the isomerization methods already described in Section VI,B.

The cyanohydrin of ethyl cyclohexanone-2-carboxylate was hydrolyzed to 1-hydroxycyclohexane-1,2-dicarboxylic acid, which was dehydrated when heated to yield Δ^1-tetrahydrophthalic anhydride (65).

The dehydrohalogenation of 2,2′-dibromosuberic acid with strong base gave 1,5-hexadiene-1,6-dicarboxylic acid as the main product. Both Δ^2-tetrahydrophthalic acid and Δ^1-tetrahydrophthalic acid were also isolated, the former in greater amount (60).

Diethyl tetrahydrophthalate, reported to be mostly the Δ^4 isomer, was obtained from the reaction of acetylene with ethyl acrylate in the presence of $[(C_6H_5)_3P]_2 \cdot CuCl$ (111, 112). Low yields of a dibutyl tetrahydrophthalate resulted from the reaction of acetylene with butanol and carbon monoxide (110).

The chlorination of diethyl *cis*-hexahydrophthalate in the presence of benzoyl peroxide has been reported to give low yields of diethyl Δ^1-tetrahydrophthalate, while the trans isomer gave diethyl Δ^2-tetrahydrophthalate (107). In each case these were the only products isolated. The reaction was interpreted as involving inversion of configuration during chlorination at one of the alpha carbon atoms, followed by trans elimination.

The reaction of *trans*-decalin with oxygen at 100°C. resulted in a 1–2 per cent yield of Δ^1-tetrahydrophthalic acid (93). It is surprising that the acid was obtained as a product which crystallized from the decalin. The usual product obtained when the acid is heated either with or without a solvent is the anhydride. In fact, the anhydride is often the product which crystallizes from aqueous solutions of the acid (14, 37).

VII. REACTIONS OF THE ACIDS AND THEIR DERIVATIVES

A. Carboxyl reactions

The usual carboxyl reactions can be expected of the acids, with the presence of two carboxyl groups on adjacent carbon atoms modifying the results obtained. The formation of the cyclic anhydrides is the reaction that is most easily carried

out. Heating with or without a dehydrating agent is usually effective in bringing about this change. In some cases, however, rearrangement of the double bond or cis-trans isomerization takes place under the conditions of anhydride formation, as was discussed in Section VI,B. The anhydrides are listed in table 2. Because of the ease of anhydride formation acid chlorides have not usually been prepared. Two of them are listed in table 7, however.

The reaction of an alcohol with an anhydride will lead directly to a monoester. Further reaction, especially with an acid catalyst or the acid-catalyzed reaction of the alcohol with the tetrahydrophthalic acid, will lead to a diester. Both types of esters are listed in tables 6 and 7. Polyesters have been made by the interaction of either the anhydrides or the acid with polyhydric alcohols (56, 57, 58, 84, 88, 99). Monoesters of the *cis*-Δ^4 acid with monoglycerides have been used in synthesizing polyesters (69, 70). The reaction of the *cis*-Δ^4 anhydride with polymers containing epoxy groups has also been used to make polyesters (45).

The direct action of an amine or ammonia on one of the anhydrides will give a monoamide. This type of product can be heated or the original reaction can be run at higher temperature to give the imide. The products of these reactions are listed in tables 6 and 7.

The Δ^1 diamide has been dehydrated to give both monocyano and dicyano derivatives, which are listed in table 6 (52).

Displacement reactions of the sodium salts of the imides with reactive halides would be expected to be a successful means of synthesis. Only the fungicide Captan, *N*-trichloromethylmercapto-*cis*-Δ^4-tetrahydrophthalimide, has thus far been prepared in this way (71, 72, 73, 75, 120), however.

A Friedel–Crafts type of reaction of the *cis*-Δ^4 imide and formaldehyde with *p*-nitrochlorobenzene in the presence of sulfuric acid gave rise to *N*-(2-chloro-5-nitrobenzyl)-*cis*-Δ^4-tetrahydrophthalimide (36). This reaction illustrates another possible method for alkylating the nitrogen of the imides.

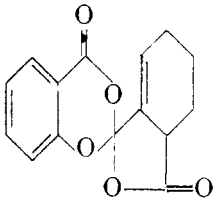
Hydrolysis of the anhydrides could be effected by hot water. In the case of the Δ^1 acid, however, the anhydride often crystallized from fairly concentrated aqueous solutions (14, 37). Hydrolysis of esters, amides, and imides generally requires acidic or basic catalysts. Again these reaction conditions often give rise to isomerization, as was discussed in Section VI,B.

The action of phenylmagnesium bromide on the *cis*-Δ^4 anhydride gave a 74 per cent yield of 2-benzoyl-4-cyclohexenecarboxylic acid (53). Similarly, the action of benzylmagnesium chloride on the Δ^2 anhydride has been reported (27) to give 3,3-dibenzyl-4,5,6,9-tetrahydrophthalide. With alkylmagnesium halides the Δ^2 anhydride and Δ^2 acid as well have been reported (28, 29) to give addition followed by reduction, so that 3-alkyl-4,5,6,9-tetrahydrophthalides were the products.

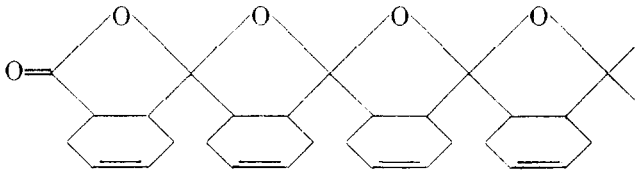
The action of the Δ^2 anhydride on benzene in the presence of anhydrous aluminum chloride gave the expected Friedel–Crafts reaction product 2-benzoyl-2-cyclohexenecarboxylic acid (26). There was no reported interaction involving the double bond.

The acid chloride of the Δ^2 acid with anhydrous aluminum chloride gave a complex from which the acid chloride was released unchanged when treated with ice (68). The acid chloride of the Δ^2 acid has also been reported (68) to react with the disodium salt of salicyclic acid to yield the lactone-anhydride derivative IV.

When the *cis*-Δ^4 anhydride was heated polymeric substances were obtained (57, 94, 99). In one case the product was reported (57, 99) as being formed with the evolution of carbon dioxide. Its structure was formulated as in V. No mention of loss of carbon dioxide was made for the other case, where the tentative structures given involved addition reactions of the carbon–carbon double bond with the anhydride group (94). Such additions of an anhydride to a double bond are unlikely in the absence of a Friedel–Crafts catalyst. Also, the seven-membered rings suggested would be unlikely.



IV



etc.

V

Most of the reduction reactions which have been carried out on the tetrahydrophthalic acids and their derivatives have involved the carbon–carbon double bond (see Section VII,B). Catalytic hydrogenations of the Δ^1 anhydride (91) and of the Δ^2 anhydride (92) have been reported to yield the corresponding tetrahydrophthalides, however. This resistance of the double bond to hydrogenation in the isomers with double bonds conjugated to carboxyl functions should be investigated more thoroughly than it has. In the case of the Δ^2 anhydride it was by no means established which of the two carbonyl groups was reduced.

The reduction of the *cis*-Δ^4 acid by lithium aluminum hydride gave *cis*-Δ^4-tetrahydrophthalyl alcohol, which was acetylated to the diacetate. Pyrolysis of the acetate gave the unusual conjugated diene, 4,5-dimethylenecyclohexene, which could easily be isomerized to *o*-xylene (18).

The reduction of the dinitrile of the Δ^1 acid by sodium in isoamyl alcohol has been reported to give low yields of tetracyclohexenotetraazaporphin (52).

The action of hypochlorite ion or of hypobromite ion on Δ^2-tetrahydrophthalimide has been reported to give none of the expected Hofmann bromoamide rearrangement. Instead, the ring was cleaved and mixtures of acids were obtained (92).

B. Addition reactions of the carbon–carbon double bond

The catalytic hydrogenation of derivatives of the *cis*-Δ^4 acid seems to give a straightforward reaction to yield the corresponding derivatives of *cis*-hexahydro-

phthalic acid. This type of reaction has been successfully carried out on the anhydride (67, 99, 100, 126), the methyl and ethyl ester (41, 42), the sodium salt (47), and the imide (118). The same result was obtained with the *cis*-Δ^3 imide also (118). The reduction of the Δ^1 acid by hydriodic acid gave *trans*-hexahydrophthalic acid (12, 14), while sodium amalgam gave a mixture of the cis and trans acids (14).

The addition of bromine to the tetrahydrophthalic acids appears to have been a successful reaction in general (14, 59, 127) except that the dibromide of the Δ^1 acid could not be isolated directly (14). It was prepared by hydrolysis of the dibromide of the dimethyl ester. Rough determinations of the rates of addition of bromine to the tetrahydrophthalic anhydrides showed the *cis*-Δ^3 isomer to be the most reactive, with the other isomers studied arranging themselves in the following order of decreasing reactivity: Δ^2, *trans*-Δ^3, and Δ^1. On the basis of the data in table 5, this order of decreasing reactivity is the same as the order of increasing acid strength of the corresponding acids (5).

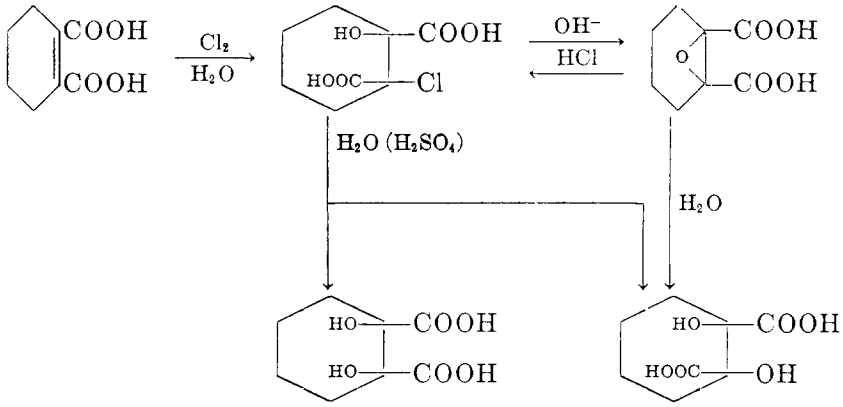
Although a quantitative measurement of the reactions of bromine with the Δ^1 and the Δ^2 acid in chloroform showed almost instantaneous reactions, the use of iodine solution—presumably as iodine chloride or iodine bromide—did not lead to successful determinations with either acid (78).

The addition of chlorine to the *cis*-Δ^4 anhydride in glacial acetic acid gave rise to 4-chloro-Δ^4-tetrahydrophthalic anhydride, m.p. 123–124°C. (127). When the reaction was carried out in water the corresponding acid, m.p. 173–175°C., was isolated. The same acid and anhydride could also be prepared by way of the Diels–Alder reaction of maleic anhydride with chloroprene. The chlorination of the *cis*-Δ^4 anhydride has also been reported to yield polymeric products (127), particularly when chloroform or carbon tetrachloride was used as the solvent (59). In the light of a reaction of chlorine with anhydrides which was recently reported (32) this formation of polymers is not surprising. The chlorine attacks the anhydride to yield an acyl halide and an acyl hypohalite, which adds rapidly to any available double bond. Such a reaction series applied to an unsaturated dicarboxylic anhydride would be expected to yield polymeric products.

The only other derivative of a tetrahydrophthalic acid for which direct chlorination has been reported is Captan (*N*-trichloromethylmercapto-*cis*-Δ^4-tetrahydrophthalimide). This reaction led to a product with approximately two additional chlorine atoms per molecule. There was evidence that both addition and substitution took place (71, 120). In all of these cases of chlorination of the Δ^4 acid or its derivatives, the apparent substitution of chlorine for hydrogen may be addition of chlorine followed by elimination of hydrogen chloride.

Both chlorine and bromine have been added to the Δ^1 acid in water to give the 1-chloro-2-hydroxy-1,2-cyclohexanedicarboxylic acid melting at 186°C. (65), and the 1-bromo-2-hydroxy-1,2-cyclohexanedicarboxylic acid melting at 180°C. (12). Such additions would be expected to be stereospecific and trans. Each of the halohydrin products underwent displacement of the halogen by water to yield 1,2-dihydroxy-1,2-cyclohexanedicarboxylic acid. From the

chlorohydrin two diastereomers were reported (65), one melting at 184°C. and the other at 178°C. From the bromohydrin only one product, melting at 178–180°C., was obtained (12). The chlorohydrin underwent a stereospecific oxide ring closure under the action of base. The *cis*-epoxide formed was an oil which reacted stereospecifically with hydrogen chloride to give back the same chlorohydrin. It was also reported (65) that the epoxide reacted with water to give only the *cis*-1,2-dihydroxy-1,2-cyclohexanedicarboxylic acid. While such an oxide ring opening would be expected to be stereospecific, it would also be expected to take place with inversion of configuration (128). Thus, the configuration of the dihydroxy acid would be expected to be trans not cis; the epoxide must be cis because the trans form is too strained (20). Also, the dihydroxy acid should have the same configuration as the chlorohydrin which was formed by the opening of the oxide ring with inversion and by the trans addition to the double bond. The only basis reported for designating the isomers of the dihydroxy acid as cis or trans was the fact that one of them could be obtained with slight optical activity so the trans configuration was assigned to it (65). Small amounts of optically active impurities could have accounted for the results, however. On the basis of the expected configurations the reactions were as follows:



The *cis*-Δ^4 anhydride has been treated (59) with peracetic acid under anhydrous conditions (54) to yield the corresponding epoxide. The action of water caused polymer formation. Anhydrous hydrogen chloride gave the chlorohydrin. Esters of the *cis*-Δ^4 acid were converted to the corresponding epoxides by direct epoxidation with peracetic acid or by the action of base on the corresponding chlorohydrins (59).

The Diels–Alder reaction of the Δ^1 anhydride with butadiene in a sealed tube at temperatures ranging from 160°C. to 180°C. yielded *cis*-Δ^2-octalin-9,10-dicarboxylic anhydride (8, 33). The use of other dienes has not been reported, nor has the reaction been run with derivatives of the Δ^2 acid, which is the other acid with the double bond conjugated with a carboxyl function.

The products of addition to the double bonds of the tetrahydrophthalic acids are listed in tables 6 and 7.

Two other addition reactions have been described. One was the addition of hydrogen chloride to dimethyl *cis*-Δ^4-tetrahydrophthalate. The product was not isolated but was used directly in a series of displacement reactions for the preparation of a wetting agent (30).

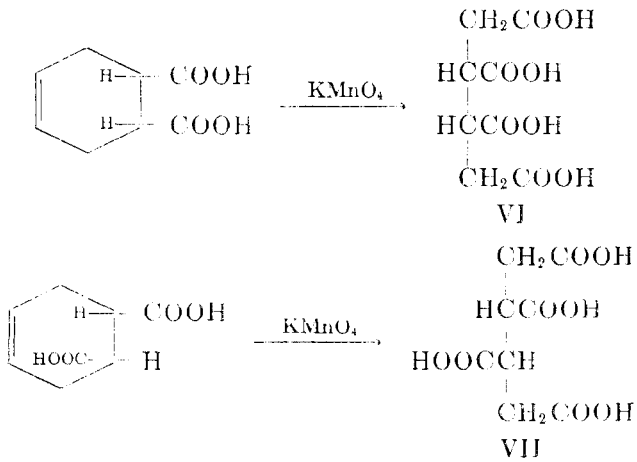
The other was a reaction of ethoxide ion with diethyl Δ^1-tetrahydrophthalate which was found to go to the extent of 12.5 per cent when heated for 4 hr. in ethyl alcohol. Presumably the product was ethyl 1-ethoxycyclohexane-1,2-dicarboxylate but none was isolated pure. The reaction was followed by the determination of ethoxyl groups in the mixed ester product. The Δ^2 ester did not undergo a similar change (78).

The action of concentrated sulfuric acid or of chlorosulfonic acid on the *cis*-Δ^4 anhydride led to a sulfonated unsaturated product which could be esterified either partially or completely (89). Similar results were obtained by esterification followed by sulfonation (63, 89). The products were isolated as sodium salts.

Although maleic anhydride and *endo-cis*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride have been reported (44) to react at 260°C. with linseed oil and to form addition polymers, *cis*-Δ^4-tetrahydrophthalic anhydride did not react.

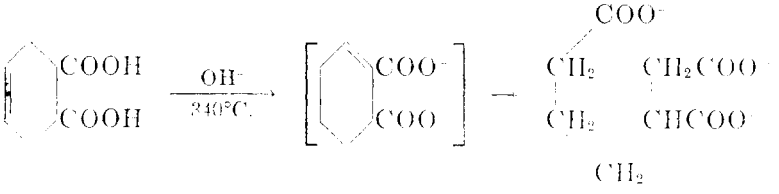
C. Oxidation reactions

Oxidation of the Δ^1 acid by potassium permanganate led to adipic acid, while the Δ^2 acid gave oxalic acid, succinic acid, and possibly glutaric acid (14). The only other well-defined products isolated from the complete oxidation of the double bonds of tetrahydrophthalic acids were the *meso*-1,2,3,4-butanetetracarboxylic acid (VI) from the *cis*-Δ^4 acid by reaction with potassium permanganate (48, 51, 57, 99) or with nitric acid (9), and the *dl*-1,2,3,4-butanetetracarboxylic acid (VII with its enantiomer) from the *dl-trans*-Δ^4 acid by reaction with potassium permanganate (9, 79).



It has been reported that the *cis*-Δ^4 acid underwent an oxidative cleavage to 3-carboxypimelic acid when heated at 340°C. with aqueous sodium hydroxide

(105). With fused sodium hydroxide at the same temperature the product was pimelic acid. Such a cleavage can best be explained on the basis of isomerization of the Δ^4 isomer to the Δ^2 isomer under the influence of the base, as discussed in Section VI,B.



D. Dehydrogenation and related reactions

Isomerization of the double bond in the various tetrahydrophthalic acids and their derivatives is discussed in Section VI,B. The rearrangement of the double bond of the *cis*-Δ^4 anhydride on interaction with phosphorus pentoxide or concentrated sulfuric acid (16) is particularly interesting in the light of results reported (79, 80) for the reactions of some substituted tetrahydrophthalic anhydrides with relatively large amounts of phosphorus pentoxide. The reactions were carried out with various dimethyl-Δ^4-tetrahydrophthalic anhydrides to yield the corresponding xylenes and carbon monoxide (86). With 1,4,5-trimethyl-Δ^4-tetrahydrophthalic anhydride the product was 1,2,4-trimethylbenzene (85). Presumably the unsubstituted tetrahydrophthalic anhydride would be expected to give benzene under these conditions, but the reaction was not reported.

Closely related to the reactions involving either hydrogenation or rearrangement is the reaction reported (87) for *cis*-Δ^4-tetrahydrophthalic acid with certain metal catalysts. With palladium black in boiling tetrahydrofuran there was a disproportionation to yield two moles of hexahydrophthalic acid to one mole of phthalic acid.

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