[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER[1]]

SALTS AND DERIVATIVES OF *CIS*-Δ^4-TETRAHYDROPHTHALIC ACID[2]

LEONARD M. RICE,[3] MARTIN RUBIN, JEAN SCHOLLER, AND E. EMMET REID

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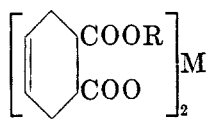
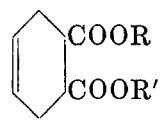
The divalent metal salts of the half esters of phthalic acid (1) have high solubility in lipids and are of some medicinal interest (2). The possible utility of this type of metal organic compound as a carrier of radioisotopes and as a therapeutic agent led us to prepare a variety of similar compounds derived from *cis*-Δ^4-tetrahydrophthalic acid.

The types of compounds prepared in this study were: salts of the half esters of *cis*-Δ^4-tetrahydrophthalic acid (I); the corresponding symmetrical and asymmetrical diesters (II); the phthalamic acids (III); and the imides (IV).



I



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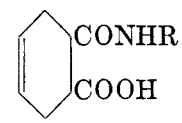
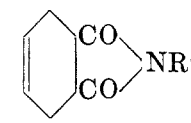


III



IV

The desired salts of the half esters of *cis*-Δ^4-tetrahydrophthalic acid (I) were obtained by interaction of the sodium salts of the half esters and the appropriate metal salts in aqueous solution followed by extraction with chloroform. Concentration of the chloroform extracts yielded the products as viscous oils or glasses. The required half esters were readily obtained by reaction of *cis*-Δ^4-tetrahydrophthalic anhydride and the alcohol (3).

Symmetrical esters (II) were prepared by interaction of the anhydride and alcohol in the presence of an acidic catalyst (4). The asymmetric esters resulted from the reaction of the silver salts of the half esters with alkyl halides in benzene.

Primary and secondary amines reacted with *cis*-Δ^4-tetrahydrophthalic anhydride at room temperature to give the tetrahydrophthalamic acids (III). At 150° N-decyltetrahydrophthalamic acid was converted by ring closure with elimination of water to the corresponding imide. The Δ^4-tetrahydrophthalamic acid was regenerated by mild alkaline hydrolysis. Utilization of the amino acids glycine, alanine, and methionine as the amine moiety provided the corresponding imides which showed surprising water solubility and stability to vacuum-distillation. The attempted condensation of the anhydride with β-isopropylaminopropionitrile, however, led to N-isopropyltetrahydrophthalimide and acryl-

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[3] Abstracted from a thesis submitted to the Graduate School of Georgetown University in partial fulfillment for the Degree of Master of Science.

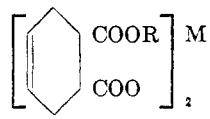
onitrile by scission of the secondary amine. This reversal of the cyanoethylation of isopropylamine is not an unexpected finding for this type of compound (5).

N-decyl-4-aminonaphthalimide was prepared from 4-aminonaphthalic anhydride and *n*-decylamine. Reduction with lithium aluminum hydride, as in an analogous compound (6), resulted in replacement of the carbonyl by methylene groupings.

EXPERIMENTAL

General procedures for monoalkyl esters of cis-Δ⁴-tetrahydrophthalic acid. Equimolar amounts of *cis*-Δ⁴-tetrahydrophthalic anhydride and the appropriate alcohol were heated to 110–130° for 15 minutes. The reaction products were dissolved in a sodium carbonate

TABLE I

SALTS OF MONOESTERS OF *cis*-Δ⁴-TETRAHYDROPHTHALIC ACID 

R	COPPER, %		MAGNESIUM, %		NICKEL, %		COBALT, %		CALCIUM, %	
	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_3	14.8	15.3	6.2	6.3	13.8	14.0				
C_2H_5	13.9	16.1[a]	5.8	6.0	13.0	13.1				
n-C_3H_7	13.0	13.4	5.5	5.9	12.2	11.7				
n-C_5H_{11}	11.7	11.2	4.9	4.6	10.9	11.7				
n-C_6H_{13}	11.1	10.4	4.6	4.8	10.4	11.0				
n-C_7H_{15}	10.6	10.1	4.2	4.7	9.9	9.9				
n-C_8H_{17}	10.2	9.9	4.1	4.3	9.5	9.2	9.5	9.5		
n-C_9H_{19}	9.7	10.1	4.0	4.0	9.1	8.5				
n-$C_{10}H_{21}$	9.3	9.3	3.8	4.0	8.7	8.3	9.1	11.8		
n-$C_{12}H_{25}$	8.7	8.4	3.5	3.8	8.0	7.5				
n-$C_{14}H_{29}$	8.0	7.7	3.2	3.6	7.4	7.3				
n-$C_{16}H_{33}$	7.5	7.2	3.0	3.1	6.9	6.8				
n-$C_{18}H_{37}$	7.0	6.6	2.5	3.1	6.5	6.6				
β-*tert*-Butylthioethyl[b]	10.0	9.9	4.0	4.3	10.3	10.1			6.5	6.3

[a] Probably due to basic salt's impurity. Analysis repeated four times.

[b] Free acid m.p. 98–101°. "Acid Number". Calc'd: 286. Found: 281. Recrystallized from acetone.

solution and precipitated by addition of hydrochloric acid, extracted with benzene or ether, concentrated, and recrystallized from dilute alcohol or acetone (3).

Copper salts: Table I. Interaction of 11.0 g. of the acid ester, dissolved in excess 10% sodium hydroxide and adjusted to the alkaline side of phenolphthalein with acetic acid, with a solution of 10.0 g. of cupric chloride in 50 ml. of water, added slowly and with good stirring, caused the precipitation of the copper salts as amorphous solids or viscous oils. The salts were removed, dissolved in chloroform, and this solution washed with sodium bicarbonate and water, and concentrated to dryness *in vacuo*.

Magnesium, nickel, calcium, cobalt salts: Table I. The lower alkyl salts prepared by the above procedure were water-soluble, (to R = C_3H_7), and isolation was achieved by concentration of the aqueous reaction mixture to dryness followed by extraction of the residue with chloroform. The work-up of the chloroform extract was as described above for the copper salts. The higher alkyl ester salts were prepared as described for the copper salts.

Preparation of symmetrical diesters: Table II. These esters were prepared by the following general method: The anhydride (0.3 mole) and the appropriate alcohol (0.8 mole) were added to a mixture of 300 ml. of toluene and 0.5 ml. of concentrated sulfuric acid. The toluene was distilled off and dried over sodium sulfate and then recirculated through the system. After four hours the excess toluene and alcohol were stripped off under reduced

TABLE II

ESTERS OF *cis*-Δ^4-TETRAHYDROPHTHALIC ACID

R′	R	FORMULA	B.P., °C./MM.	CARBON		HYDROGEN	
				Calc'd	Found	Calc'd	Found
ASYMMETRICAL							
Ethyl	Decyl	$C_{20}H_{34}O_4$	148–152/0.3	70.96	71.10	10.12	10.11
Benzyl	Octyl	$C_{23}H_{32}O_4$	189–193/0.7	74.15	74.19	8.66	8.71
SYMMETRICAL; R = R′							
Hexyl		$C_{20}H_{34}O_4$	146–148/0.2	70.96	70.95	10.12	9.88
Heptyl		$C_{22}H_{38}O_4$	163–168/0.7	72.08	71.83	10.42	10.45
Octyl		$C_{24}H_{42}O_4$	195–197/0.7	73.05	72.86	10.73	10.76
Nonyl		$C_{26}H_{46}O_4$	195–201/0.5	73.88	74.04	10.97	10.81
Decyl		$C_{28}H_{50}O_4$	200–206/0.3	74.62	74.91	10.96	10.80

TABLE III

N-SUBSTITUTED *cis*-Δ^4-TETRAHYDROPHTHALAMIC ACIDS

R	R′	FORMULA	M.P., °C.	ACID NUMBER		NITROGEN		MAGNESIUM SALT	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
H	Butyl[a]	$C_{12}H_{19}NO_3$	90–91	224	225	6.25	5.97	5.10	5.50
H	Hexyl[a]	$C_{14}H_{23}NO_3$	91–92	253	254	5.53	5.35		
H	Decyl[a]	$C_{18}H_{31}NO_3$	90–91	302	304	4.52	4.71		
H	Dodecyl[a]	$C_{20}H_{35}NO_3$	70–72	337	347	4.15	4.30		
H	Phenyl[b]	$C_{14}H_{15}NO_3$	96–98	245	250	5.71	5.58		
H	Benzyl[b]	$C_{15}H_{17}NO_3$	98–100	259	256	5.42	5.41	4.4	4.1
H	Diethylaminoethyl HCl[b]	$C_{14}H_{25}ClN_2O_2$	211–213	—	—	9.17	9.36		
Butyl	Butyl[b]	$C_{16}H_{27}NO_3$	74–75	281	282	4.98	5.03		
Morpholino[c]		$C_{12}H_{17}NO_4$	142–143.5	239	236	5.86	5.81	4.8	4.9
Cyclohexyl	Cyclohexyl[c]	$C_{20}H_{31}NO_3$	178–180	333	343	4.20	4.13	3.5	3.3

[a] No solvent. Recrystallized from dilute ethanol. [b] In acetone. Recrystallized from dilute ethanol. [c] Heated to 150°. Recrystallized from ethanol.

pressure, the residue washed with water, sodium carbonate solution, again with water, and dried over magnesium sulfate. Upon vacuum-distillation the esters were obtained as colorless liquids.

Preparation of asymmetrical esters: Table II. The octyl or decyl half esters were converted to silver salts by the addition of an aqueous solution of silver nitrate to the phen-

olphthalein-neutralized solution of the sodium salts. These products were filtered, washed with water, dissolved in benzene and dried by azeotropic distillation. The appropriate alkyl iodide was added to the dried benzene solution and the mixture refluxed overnight. The precipitated silver iodide was removed, the solution concentrated to half its volume, washed with water, sodium carbonate solution, again with water, dried over magnesium sulfate, and fractionated *in vacuo*.

Cis-Δ⁴-tetrahydrophthalamic acids: Table III. The amine and anhydride in equimolar amounts were mixed either in the absence of a solvent or in some cases in acetone. When the initial reaction was over the mixture was allowed to stand several hours. In cases where acetone was used as a solvent water was added to turbidity and the mixture chilled. The products were then recrystallized from a suitable solvent.

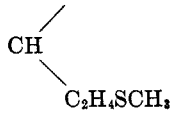
TABLE IV

N-ALKYL-*cis*-Δ⁴-TETRAHYDROPHTHALIMIDES

R	FORMULA	M.P., °C.	B.P., °C./MM.	NITROGEN	
				Calc'd	Found
H	$C_8H_9NO_2$	136	—	9.26	9.18
Hexyl	$C_{14}H_{21}NO_2$	—	131–134/1.5	5.95	6.05
Decyl	$C_{18}H_{29}NO_2$	—	163–165/0.7	4.81	5.00
Dodecyl	$C_{20}H_{33}NO_2$	—	165–170/0.2	4.38	4.50
Diethylaminoethyl	$C_{14}H_{22}N_2O_2$	—	112–116/0.25	11.18	10.91

TABLE V

N-*cis*-Δ⁴-TETRAHYDROPHTHALIMIDES FROM AMINO ACIDS

R	FORMULA	B.P., °C./MM.	ACID NUMBER		NITROGEN		CARBON		HYDROGEN		MAGNESIUM SALT	
			Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_2COOH	$C_{10}H_{11}NO_4$	160–165/0.3	209	213	6.7	6.7	57.41	57.51	5.30	5.42	5.5	5.9
C_2H_4COOH	$C_{11}H_{13}NO_4$	180/0.75	222	225	6.3	6.4	59.33	59.18	5.82	6.00	4.5	4.7
	$C_{13}H_{17}NO_4S$	175/0.3	283	290	5.0	4.9	55.10	55.26	6.05	6.27	4.1	4.2

Conversion of N-decyl-cis-Δ⁴-tetrahydrophthalamic acid to N-decyl-cis-Δ⁴-tetrahydrophthalimide. The acid (10 g.) was heated in benzene, toluene, or xylene for one hour with no conversion to the imide. When 10 g. of the acid was heated in an oil-bath at 150° for 15 minutes the liberation of water was observed. After one hour at this temperature the residue was distilled under a vacuum; the product, b.p. 163°/0.7 mm., weighed 7.3 g.

Anal. Calc'd for $C_{18}H_{29}NO_2$: N, 4.81. Found: N, 4.84.

On standing at room temperature for three hours in 0.100 *N* alcoholic sodium hydroxide solution the imide had an indicated saponification equivalent of 290: Theory 292. Acidification of the alkaline solution precipitated the N-decyl-*cis*-Δ⁴-tetrahydrophthalamic acid (m.p. 90–91°) which did not depress the melting point of an authentic sample.

Preparation of cis-Δ⁴-tetrahydrophthalimide. Tetrahydrophthalic anhydride (0.5 mole) was mixed with 200 ml. of 28% ammonium hydroxide, the mixture was refluxed for 15 min-

utes and then gradually heated to 300°. The reaction mixture was kept at this temperature for 15 minutes and poured while hot into a mortar. When cold the product was ground to a fine powder and recrystallized three times from ethanol, m.p. 136°.

Preparation of imides from primary amines: Table IV. Tetrahydrophthalic anhydride (0.3 mole) and the appropriate amine (0.3 mole) were mixed and heated to 180° for three hours. After cooling the product was diluted with ether, washed with sodium carbonate solution, 10% hydrochloric acid, and water. The solution was then dried over magnesium sulfate, concentrated and vacuum-distilled.

Preparation of imides from amino acids: Table V. Equimolar quantities of the amino acid and the anhydride were heated at 190–200° for 30 minutes. After cooling to 100° the mixture was distilled under a vacuum; the product was obtained as a clear viscous liquid which solidified in the receiver.

Reaction of β-isopropylaminopropionitrile with cis-Δ^4-tetrahydrophthalic anhydride. A mixture of 44.8 g. of the aminonitrile and 60.8 g. of the anhydride was heated in an oil-bath at 180–200° and all volatile material was collected. After one hour no more distillate was obtained. The residue was dissolved in ether, washed with water, dried over magnesium sulfate, and distilled under a vacuum. The product had b.p. 100–105°/0.3 mm. The recorded b.p. for N-isopropyltetrahydrophthalimide is 99–100°/0.5 mm. There was no depression in melting point of an authentic sample (7).

Anal. Calc'd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8.
Found: C, 68.0; H, 7.9.

In theory, 76 g. of this imide should have been formed; there was obtained 70 g. plus 3 g. of residue. The distillate which separated into two layers on standing totaled 24 g. The lower layer (6 g.) was identified as water (theory 7 g.). The upper layer (18 g.) was fractionated to give 16 g., b.p. 75–76°, shown to be acrylonitrile (theory 21 g.); recorded b.p. 78°.

Anal. Calc'd for C_3H_3N: C, 67.9; H, 5.7.
Found: C, 68.5; H, 5.9.

Preparation of 4-amino-N-decylnaphthalimide. A mixture of 0.1 mole of 4-aminonaphthalic anhydride and 0.1 mole of decyl amine was heated at 200° for four hours and poured while hot into a mortar. After cooling the product was ground to a fine powder, washed with 10% hydrochloric acid, and recrystallized from benzene, m.p. 176°.

Anal. Calc'd for $C_{22}H_{28}N_2O_2$: N, 7.95. Found: 7.74.

Reduction of 4-amino-N-decylnaphthalimide. Anhydrous ether, 200 ml., was refluxed with 4 g. of lithium aluminum hydride for two hours. Ten grams of the imide in a Soxhlet extractor was gradually transferred to the reaction flask on overnight reflux of the ether solution. The excess hydride was decomposed with water, and the mixture acidified with dilute hydrochloric acid. The aqueous layer was made alkaline with sodium hydroxide solution and the amine extracted with benzene. The extracts and the ether layer were combined and dried over magnesium sulfate. The solution was concentrated to half its volume and the product was purified by recrystallization from benzene, m.p. 139–140°.

Anal. Calc'd for $C_{22}H_{32}N_2$: N, 8.61. Found: N, 8.41.

WASHINGTON 7, D. C.

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