N-*Hydroxy-imides. Part II.* Derivatives of Homophthalic and Phthalic Acids.*

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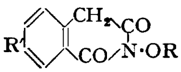
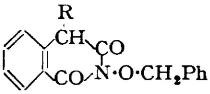
The *N*-benzyloxy- and *N*-hydroxy-imides of homophthalic, 4-chlorohomophthalic, 4-dimethylaminohomophthalic, phthalic, and naphthalic acids have been prepared. Further evidence on the structure of " phthaloxime " is presented.

It has been shown previously (Part I*) that the condensation of benzyloxyamine with dibasic acids yields *N*-benzyloxy-imides which can be catalytically hydrogenated to the *N*-hydroxy-imides or tautomeric products. This work has now been extended to the preparation of derivatives of some aromatic dibasic acids.

N-Benzyloxyhomophthalimide (I; $R = CH_2Ph$, $R' = H$) was readily prepared in high yield by this method but, although various solvents were used, only small yields of the imides could be obtained from 4-chloro- and 4-dimethylamino-homophthalic acid. The corresponding *N*-hydroxyimides were prepared by catalytic hydrogenation. Two attempts were made to prepare derivatives of the imide (I) bearing a basic substituent in the α-position. First, treatment of (I; $R = CH_2Ph$, $R' = H$) with benzenediazonium chloride gave the α-phenylazo-compound, reductively acetylated to the acetamido-imide (II, R = NHAc). The α-amino-imide could not, however, be obtained either by partial hydrolysis of this amide or by hydrogenation of the intermediate azo-compound. Condensation of the imide (I; $R = CH_2Ph$, $R' = H$) with *NN*-dimethyl-*p*-nitrosoaniline yielded the derivative (III) (cf. Buu-Hoï, *Bull. Soc. chim. France*, **1945**, **12**, 313) but this on hydrogenation gave *p*-aminodimethylaniline. The infrared absorption spectra of these benzyloxy- and hydroxy-compounds exhibit the two characteristic imide bands (see Table); in the solid state, these products are therefore represented by the structures (I; R = H, R' = H, Cl, or NMe_2) rather than as the tautomers (IV) and (V). This conclusion is of interest since the comparable *N*-hydroxy-αβ-dimethylglutaconimide exists as the enol (Part I).



(I)



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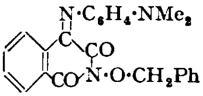
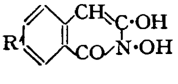
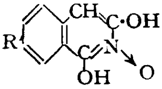


(III)

On titration with alkali both *N*-benzyloxy- and *N*-hydroxy-homophthalimides show pK_a values of *ca.* 8, which must therefore correspond to ionisation of the enolised CH_2·CO group; the *N*-hydroxy-group is an extremely weak acid (pK_a 11·9).



(IV)



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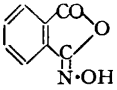
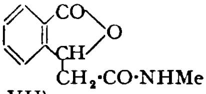


(VI)



(VII)

N-Hydroxyphthalimide was prepared similarly and found to be identical with " phthaloxime," obtained from phthalic anhydride and hydroxylamine. Earlier work on the structure of this product has been examined by Brady, Baker, Goldstein, and Harris (*J.*, 1928, 529; cf. Hurd, Buess, and Bauer, *J. Org. Chem.*, 1954, **19**, 1140) who formulated it as phthalic anhydride mono-oxime (VI). We have been unable to prepare the yellow " isomer " described by Brady *et al.* and earlier workers. Putokhin (*J. Russ. Phys. Chem. Soc.*, 1930, **62**, 2203) apparently obtained the same product from *N*-ethoxycarbonylphthalimide and hydroxylamine and regarded it as *N*-hydroxyphthalimide. This structure

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* The paper *J.*, 1955, 631, is regarded as Part I.

is indicated by the present method of preparation and is also supported by the following observations : (i) *N*-benzyloxy- and *N*-hydroxy-phthalimide show imide absorption bands similar to those of the *N*-ethyl-imide (see Table) though at somewhat higher frequencies (cf. Part I) ; (ii) the ultraviolet absorption spectra are also similar to those of phthalimide ; and, (iii) the pK_a value (7·0) is well outside the normal range for oximes (Parke and Davis, *Analyt. Chem.*, 1954, **26**, 642, give pK_a *ca.* 10—12).

In the hope of preparing analogous seven-membered ring imides from *o*-carboxycinnamic acid, the condensation of the acid with methylamine was first studied. The only product isolated, however, was (VII), the infrared spectrum showing bands at 1567, 1647, and 3367 cm.$^{-1}$ (CO·NH) and at 1761 cm.$^{-1}$ (phthalide ring ; cf. Grove and Willis, *J.*, 1951, 882). Gabriel and Michael (*Ber.*, 1877, **10**, 2203) obtained the parent phthalidylacetic acid by heating *o*-carboxycinnamic acid.

Absorption spectra and pK_a *values.*

	In ethanol		In soln., pH 8·9		Imide bands[a] (cm.$^{-1}$)	Other bands[a] 1640—2000 (cm.$^{-1}$)	pK_a
	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε			
(I; R = CH_2Ph, R′ = H)	2425	18,300	2450	15,400	1695	—	8·2[b]
	2930	2100					
	3080	2200	2800 *	2200	1727		
(I; R = R′ = H)	2250 *	10,600	2975	3900	1667	—	8·0, 11·9[b]
	2300	10,600			1727		
	2380 *	10,000					
(II; R = NHAc)	2450	22,100	2460	16,200	1709	1650	6·3[b]
	3000 *	2100	2825	3900	1751		
(I; R = CH_2Ph, R′ = Cl)	2325 *	19,300	3100	17,900	1690	—	8·48[c]
	3160	9800			1735 *		
(I; R = H, R′ = Cl)	3140	9000	2560	19,000	1701	1662	7·34[d]
			3025	9100	1742		
(I; R = CH_2Ph, R′ = NMe_2)	2470	26,600	2350	27,600	1694	—	9·90[e]
(I; R = H, R′ = NMe_2)	2360	14,200	2210	13,600	1717	—	8·97[f]
	2470 *	13,600	2630	10,900	1658		
			3300	3500			
Phthalimide	2150	41,000	—	—	—	—	—
	2295	16,200					
	2380	10,700					
	2910	1400					
N-Ethylphthalimide	—	—	—	—	1724	—	—
					1779		
N-Benzyloxyphthalimide ...	2220	47,200	—	—	1733	—	—
	2960	2100			1792		
N-Hydroxyphthalimide ...	2205	30,300	—	—	1745	1721	7·0[g]
	2980	1600			1795	1866	
N-Acetoxyphthalimide ...	2180	43,000	—	—	1751	1821[h]	—
	2375	9500			1792	1862	
	2950	1900					
N-Benzyloxynaphthalimide	2135	26,600	—	—	1692	—	—
	2340	37,900			1709		
	2355	12,800					
	4550	360					
N-Hydroxynaphthalimide	2360	38,400	—	—	1666	—	8·25[g]
	3350	11,900			1715		

* Inflection. [a] Nujol mulls. [b] 50% Dimethylacetamide. [c] 75% Ethanol. [d] 50% Ethanol. [e] 75% Dimethylformamide. [f] 50% Dimethylformamide. [g] 50% Methanol. [h] Acetate band.

EXPERIMENTAL

N-*Hydroxyphthalimide.*—Phthalic anhydride (2·0 g.) and benzyloxyamine (1·7 g.) were refluxed with xylene (50 c.c.) until no more water could be separated. Evaporation *in vacuo* and crystallisation from ethanol furnished needles of N-*benzyloxyphthalimide* (3·1 g. ; 90%) (Found : C, 71·7 ; H, 4·4 ; N, 5·3. $C_{15}H_{11}O_3N$ requires C, 71·1 ; H, 4·4 ; N, 5·5%). Hydrogenation of this imide (20 g.) in ethyl methyl ketone (100 c.c.) over palladised strontium carbonate (3 g. ; 5% Pd) yielded the *N*-hydroxy-imide (9·5 g. ; 74%), rods, m. p. 232—233° (decomp.), from ethyl methyl ketone (Found : C, 58·8 ; H, 3·1 ; N, 8·4. Calc. for $C_8H_5O_3N$: C, 58·9 ; H, 3·1 ; N, 8·6%). The melting point was not depressed on admixture with material prepared as described by Orndorff and Pratt (*Amer. Chem. J.*, 1912, **47**, 99); the infrared spectra of the samples were also identical. The acetate had m. p. 185—186° (Orndorff and Pratt give m. p. 183—185°).

N-*Hydroxynaphthalimide*.—Prepared in the same manner, N-*benzyloxynaphthalimide* (55%) separated from ethyl methyl ketone–light petroleum (b. p. 60—80°) in needles, m. p. 187—188° (Found: C, 75·0; H, 4·4; N, 4·9. $C_{19}H_{13}O_3N$ requires C, 75·2; H, 4·3; N, 4·6%). Catalytic debenzylation gave the hydroxy-imide which had m. p. 280—281° (from ethanol), undepressed on admixture with product prepared by Jaubert's method (*Ber.*, 1895, **28**, 362) (Found: C, 67·2; H, 3·3; N, 6·6. Calc. for $C_{12}H_7O_3N$: C, 67·6; H, 3·3; N, 6·6%).

N-*Hydroxyhomophthalimide*.—N-*Benzyloxyhomophthalimide* (83%), prepared by the same procedure, formed prismatic needles (from ethanol), m. p. 143—144° (Found: C, 71·8; H, 4·8; N, 5·4. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·2%). Hydrogenation afforded the *hydroxy-imide*, rods, m. p. 199—200°, from ethyl methyl ketone (Found: C, 61·4; H, 4·1; N, 7·8. $C_9H_7O_3N$ requires C, 61·0; H, 4·0; N, 7·9%).

4-*Dimethylaminohomophthalic Acid*.—4-Nitrohomophthalic acid (20·0 g.) (Ungnade, Nightingale, and French, *J. Org. Chem.*, 1945, **10**, 535) in methanol (100 c.c.) was hydrogenated in the presence of palladised strontium carbonate (2·0 g.; 5% Pd). When 3 mol. of hydrogen had been absorbed, formaldehyde (40 c.c.; 36%) was added and hydrogenation was continued. After addition of water (150 c.c.), the boiling solution was filtered; on cooling the *amino-acid* (13·2 g.) separated and formed thick parallelograms, m. p. 215—216° (decomp.), from methanol (Found: C, 59·2; H, 5·9; N, 6·3. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%).

4-*Chlorohomophthalic Acid*.—The nitro-acid (32 g.) in methanol (200 c.c.) was hydrogenated as before, water added, and the boiling solution filtered. Evaporation under reduced pressure gave the crude 4-aminohomophthalic acid which was dissolved in hydrochloric acid (250 c.c.; 2N) and diazotised by the addition of sodium nitrite (9·4 g.) in water (30 c.c.). The solution was added to cold cuprous chloride (from 160 g. of hydrated cupric sulphate) in concentrated hydrochloric acid. After 2 hr. the *chloro-acid* (16·0 g.) was filtered off and recrystallised from water forming needles, m. p. 191—192° (Found: C, 50·0; H, 3·3; Cl, 16·0. $C_9H_7O_4Cl$ requires C, 50·4; H, 3·3; Cl, 16·5%).

Substituted Homophthalimides.—Owing to insolubility, the condensation of 4-chloro- and 4-dimethylamino-homophthalic acids with benzyloxyamine failed except in boiling *o*-dichlorobenzene. The acid was dissolved in hot solvent and, after addition of the benzyloxyamine, the mixture was distilled slowly until no more water was eliminated (*ca.* 1/2 hr.). Evaporation under reduced pressure furnished the crude product which was recrystallised.

N-*Benzyloxy*-4-*chlorohomophthalimide* (40%) formed needles, m. p. 163—164°, from ethanol–ethyl methyl ketone (Found: C, 63·7; H, 4·0; N, 4·8; Cl, 12·1. $C_{16}H_{12}O_3NCl$ requires C, 63·8; H, 4·0; N, 4·7; Cl, 11·8%).

N-*Benzyloxy*-4-*dimethylaminohomophthalimide* (35%) separated from ethanol in plates, m. p. 158—160° (Found: C, 69·9; H, 6·0; N, 9·1. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·9; N, 9·0%).

The following were obtained by catalytic hydrogenation: 4-*Chloro*-N-*hydroxyhomophthalimide* (70%), needles, m. p. 215—216°, from ethyl methyl ketone (Found: C, 51·5; H, 3·1; N, 6·7; Cl, 16·9. $C_9H_6O_3NCl$ requires C, 51·5; H, 2·9; N, 6·6; Cl, 16·8%). 4-*Dimethylamino*-N-*hydroxyhomophthalimide*, yellow cubes, m. p. 158—159°, from ethanol (Found: C, 55·2; H, 6·0; N, 11·5. $C_{11}H_{12}O_3N_2,H_2O$ requires C, 55·5; H, 5·9; N, 11·8%). This compound could be sublimed unchanged at 130—150°/0·05 mm. (Found: C, 55·2; H, 6·0; N, 11·9%) but the spectra and especially pK_a values indicate that it is a hydrate and not a hydrolysis product.

N-*Benzyloxy*-α-*phenylazohomophthalimide*.—To *N*-benzyloxyhomophthalimide (2·0 g.) in sodium hydroxide solution (35 c.c.; 2N), acetic acid (3·5 c.c.) and benzenediazonium chloride solution (from aniline, 1·6 g.) were added, successively. The precipitate was crystallised from ethyl methyl ketone, giving red prisms of the *azo-compound* (0·9 g.), m. p. 214—215° (Found: C, 70·9; H, 4·7; N, 11·4. $C_{22}H_{17}O_3N_3$ requires C, 71·2; H, 4·6; N, 11·3%).

α-*Acetamido*-N-*benzyloxyhomophthalimide*.—The azo-compound (10 g.) was added in portions to a stirred mixture of zinc (10 g.), acetic acid (20 c.c.), and acetic anhydride (9 c.c.). Small portions of zinc and acetic anhydride were added at intervals until the yellow colour disappeared (8 hr.). The collected solid was washed with acetic acid (100 c.c.), and the combined filtrates evaporated under reduced pressure. Trituration of the residual gum with ether yielded the crude product (6·0 g.; m. p. 150—156°). The *acetamido-imide* crystallised from ethyl methyl ketone in needles, m. p. 172—173° (Found: C, 66·9; H, 4·6; N, 8·6; Ac, 13·1. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 5·0; N, 8·6; Ac, 13·3%).

N-*Benzyloxy*-α-p-*dimethylaminophenylimino*)*homophthalimide* (cf. Buu-Hoï, *Bull. Soc. chim. France*, 1945, **12**, 313).—*NN*-Dimethyl-*p*-nitrosoaniline (4·4 g.) in hot ethanol (60 c.c.) was added to a hot solution of *N*-benzyloxyhomophthalimide (7·9 g.) in ethanol (175 c.c.), and the mixture refluxed for 30 min. When the solution cooled the *imide* (8·6 g.) crystallised in violet, prismatic needles, m. p. 138—140° (Found: C, 71·8; H, 5·4; N, 10·4. $C_{24}H_{21}O_3N_3$ requires C, 72·2; H, 5·3; N, 10·5%).

Reaction of o-*Carboxycinnamic Acid with Methylamine.*—The acid (2 g.) and ethanolic methylamine (10 c.c.; 33%) were heated at 180° (bath) for 10 min., the solvent being allowed to distil off, and then at 225° for 10 min. Crystallisation of the residue from ether–methanol gave a product (0·4 g.), m. p. 138—142°. The pure N-*methylphthalidylacetamide* formed needles, m. p. 144—145°, from methanol (Found: C, 64·3; H, 5·4; N, 6·6. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%).

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