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Reactions of Phthalaldehydic Acid

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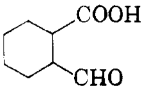
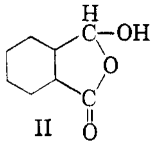
The uncatalyzed reactions of phthalaldehydic acid with a number of alcohols, thiols, amines, amides, sulfonamides, ureas, carbamates, and acid anhydrides have been studied. The unusually high reactivity of phthalaldehydic acid is demonstrated and evidence is presented to show that the free acid and most of its derivatives exist in the phthalide form.

Phthalaldehydic acid, first reported by Racine in 1886,[1] has received only limited attention, perhaps because the earlier methods of preparation were quite tedious and generally resulted in poor yields. The recent development of a satisfactory and convenient process for the preparation of phthalaldehydic acid[2] led to a systematic study of its reactions. This paper reports reactions of phthalaldehydic acid with several classes of compounds.

Phthalaldehydic acid is often represented as having an aldehyde and an acid group (I). The tautomeric 3-hydroxyphthalide form (II) has been suggested,[1] and the material has been reported to exist in both the open and ring-closed form depending upon the solvent and temperature.[3,4]



I



II

The infrared[5] spectrum of the material used in this study has many features which indicate that phthalaldehydic acid exists in the 3-hydroxyphthalide form both in the solid state and in aqueous solution. From a comparison of its spectrum (Fig. 1A) with that of terephthalaldehydic acid (Fig. 1B), it is apparent that differences other than those of ring substitution must exist. An "alcoholic" OH absorption (3.01μ) is found in phthalaldehydic acid and the typical COOH doublet (3.73μ and 3.93μ) found in terephthalaldehydic acid is absent. Also, the carbonyl frequency is that of a lactone rather than that of an acid or aldehyde. In addition, two strong bands are found at longer wavelengths (9.33μ and 11.00μ) which do not appear in the spectrum of terephthalaldehydic acid. Since the intensity, broadness, and wave-length region of these absorptions suggest C—O stretching motions, they have been tentatively assigned to the antisymmetric and symmetric C—O—C stretch, respectively, of the phthalide ring. Of course, these assignments are probably not true descriptions of the actual motions of the atoms involved in these vibrations, as such motions are complex and not easily described in simple terms. As is shown below, these absorptions are not due to C—OH since they are also found in thio- and amino-phthalides.

A water solution spectrum[6] of phthaldehydic acid (Fig. 1C) clearly indicates the presence of lactone carbonyl at 5.73μ. The antisymmetric C—O—C stretch of the ring is also observed. This is strong evidence that the acid remains in the phthalide form in aqueous solutions. The symmetric C—O—C stretch at 11μ is masked by the water absorption.

The derivatives prepared in the present study all retain the phthalide configuration. However in some cases, particularly from reactions with alcohols, 10–15% of the product may be in the open form. The three absorption bands—lactone carbonyl, antisymmetric C—O—C stretch, and symmetric C—O—C stretch—are found in all phthalide derivatives and may be used in their identification. Their sensitivity (particularly that of the symmetric C—O—C stretch absorption at 11μ) to the group attached in the "3" position can further be used to characterize that group.

The out-of-plane hydrogen deformation band characteristic of *ortho* substituted aromatics occurs at 13.35μ in phthalaldehydic acid and between 13.2μ and 13.9μ in its derivatives. In many phthalides three other bands appear in this region similar to those found in phthalaldehydic acid at 12.75μ, 14.00μ, and 14.43μ. Their variation in position and relative intensity, however, limits their usefulness in structure determination.

Although the infrared absorption of phthalaldehydic acid indicates it to be 3-hydroxyphthalide, the compound has some of the properties which would be expected of the open form (I). Thus the material undergoes the Cannizzaro reaction,[7] forms

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[1] S. Racine, *Ber.*, 19, 778 (1886).

[2] J. D. Head and O. D. Ivins, U. S. Patent 2,748,162 (1956).

[3] Ng. Ph. Buu-Hoï and Che-Kin Lin, *Compt. rend.*, 209, 221 (1939).

[4] M. M. Shemyakin, *Zhur. Obshchei Khim.*, 13, 290 (1943).

[5] With the exception of the water solution, the infrared spectra illustrated were obtained by the usual Nujol mull technique. Spectra were obtained on a double-beam infrared spectrometer with sodium chloride optics designed and built by L. W. Herscher of the Spectroscopy Laboratory, the details of which will be published soon.

[6] Obtained in a barium fluoride cell (0.036 mm.) compensated with water.

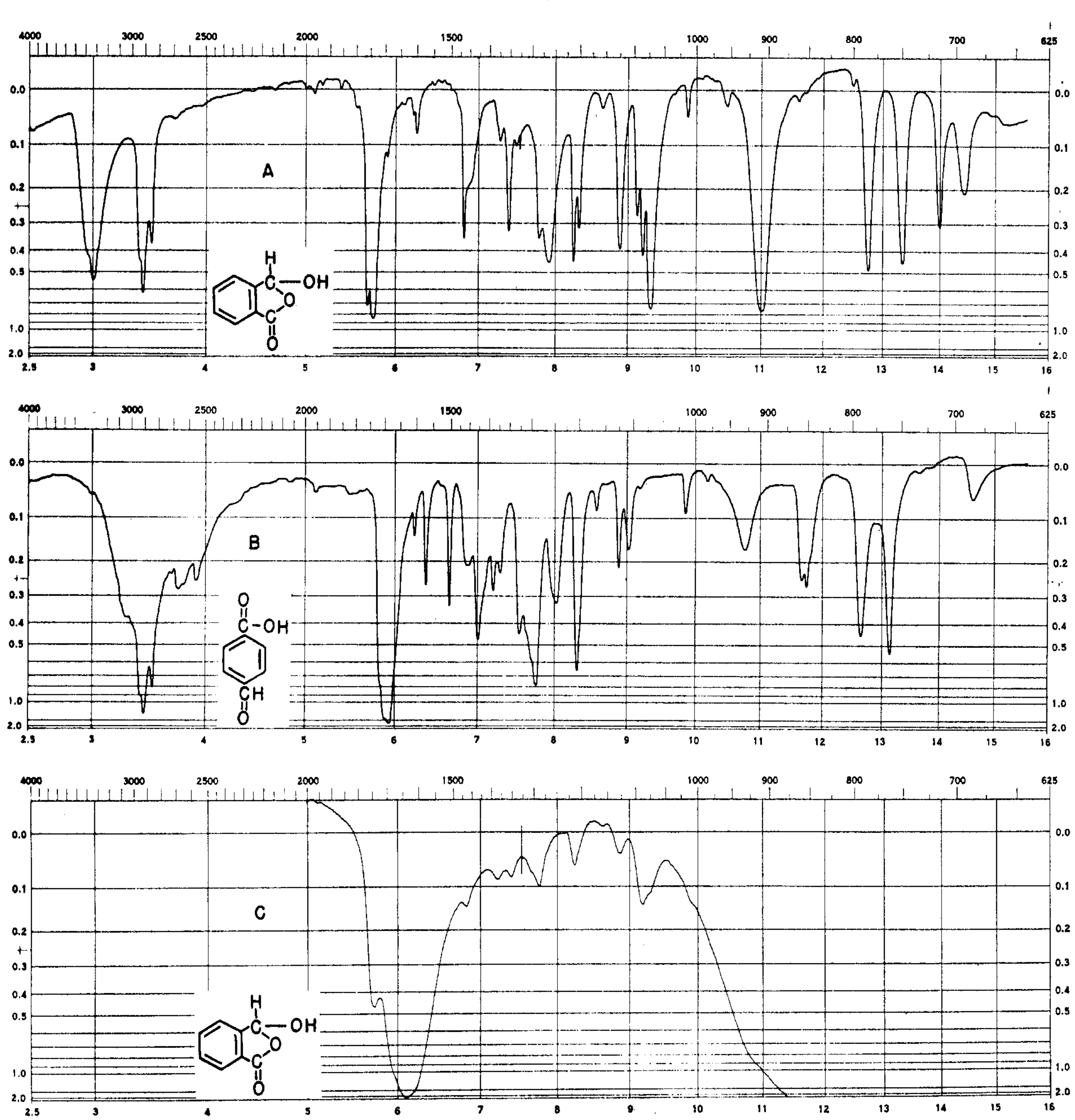

FIG. 1. INFRARED SPECTRA: A—Phthalaldehydic acid. B—Terephthalaldehydic acid. C—Phthalaldehydic acid-water solution. Nujol absorption bands appear at 3.42μ, 6.85μ, and 7.28μ

an oxime,[8] and reacts with ammoniacal silver solution.[8] Its ionization constant (2.76×10^{-5})[9] is of the expected order for an *ortho* substituted benzoic acid.

However, the interaction of the aldehyde and acid groups results in unusual properties. For example, the anomalous behavior of salicylic acid in forming two liquid layers with water[10] has also been observed with phthalaldehydic acid.[11] Another result of this interaction, which is of greater significance, is the unusual chemical reactivity of phthalaldehydic acid. In general, it can be said that phthalaldehydic acid has a reactivity which approaches that of an acid chloride or anhydride for every reactant except water. This property is illustrated by its reactions with a wide variety of compounds.

Phthalaldehydic acid has been reported to react with methyl and ethyl alcohol on long heating without a catalyst.[8,12,13] It is now apparent that relatively short reaction times are required and, in fact, that an equilibrium mixture is approached on

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(7) A. Hamburger, *Monatsh.*, **19**, 430 (1898).

(8) S. Racine, *Ann.*, **239**, 80 (1887).

(9) J. Tirouflet, *Compt. rend.* **236**, 1426 (1953).

(10) N. V. Sidgwick and E. K. Ewbank, *J. Chem. Soc.*, **119**, 979 (1921).

(11) N. V. Sidgwick and H. Clayton, *J. Chem. Soc.*, **121**, 2263 (1922).

(12) H. Meyer, *Monatsh.*, **25**, 497 (1904).

(13) S. Gabriel, *Ber.*, **49**, 1612 (1916).

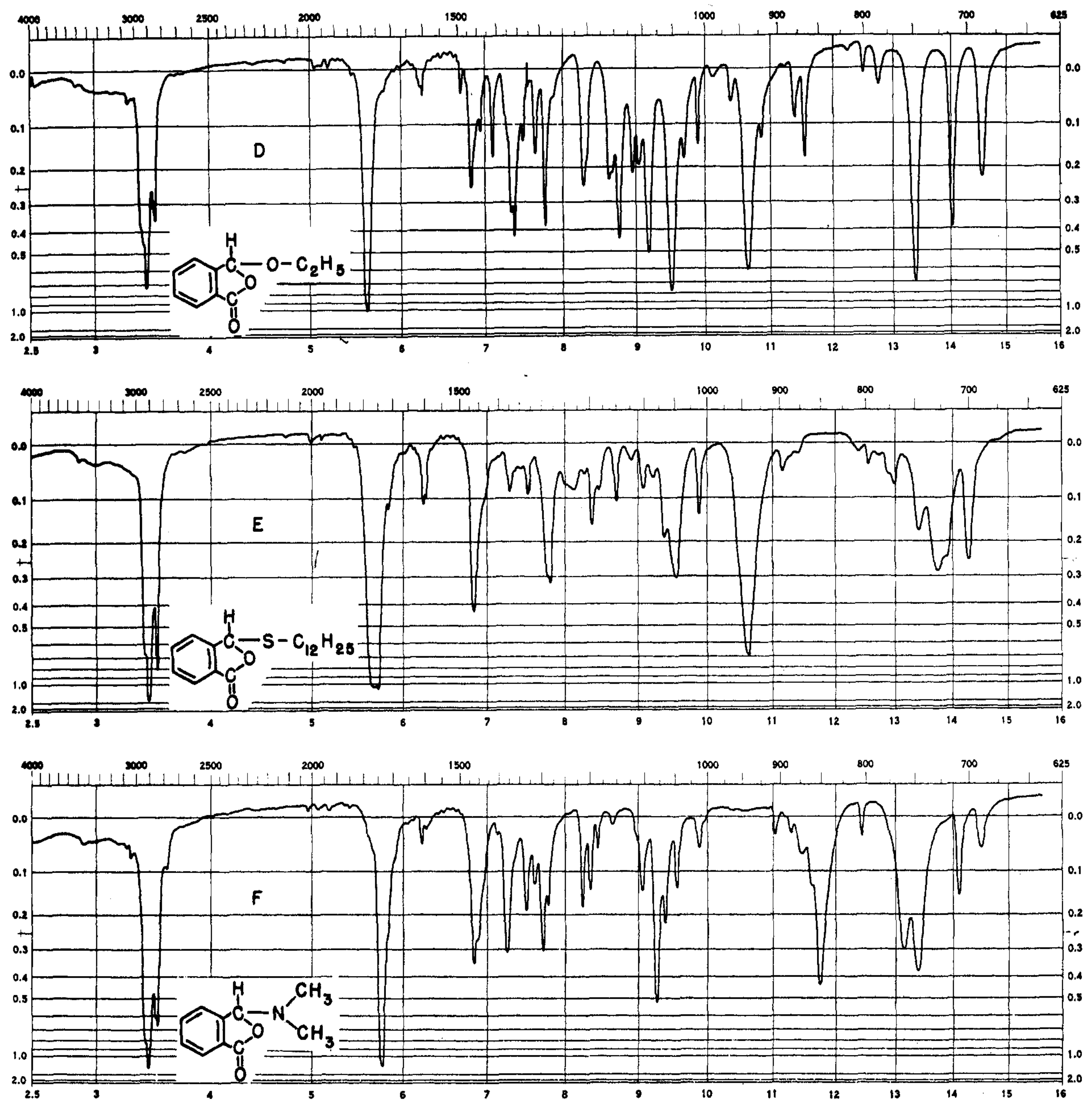

FIG. 1. INFRARED SPECTRA: D—3-Ethoxyphthalide. E—3-Dodecylthiophthalide. F—3-Dimethylaminophthalide. Nujol absorption bands appear at 3.42μ, 6.85μ, and 7.28μ

refluxing in a lower alcohol for 1 to 2 hr. (Table I). In contrast, equilibrium is attained only after several days of refluxing acetic acid with ethanol,[14] although the acids have similar ionization constants.

Phthalaldehydic acid has been reacted with a variety of alcohols and glycols to prepare 3-alkoxy- and 3,3′-alkylenedioxydiphthalides. With the lower alcohols, the solutions were homogeneous and about 75% yields of III were obtained. With higher alcohols, the water produced in the reaction separated from the reaction product and somewhat higher yields resulted. When the water was removed from the mixture by distillation, quantitative yields were obtained.

TABLE I

REACTION OF PHTHALALDEHYDIC ACID WITH PROPYL ALCOHOL AT REFLUX[a]

Time (hours)	% 3-Propoxyphthalide[b]
1/2	72
1	79
2	84
4	87
8	88
23	88

[a] Five moles of propyl alcohol per mole of acid. [b] Determined by titration of aliquots.

When an alkoxy group is substituted in the 3-position of a phthalide, the carbonyl absorption is found to lie very close to 5.61μ although in some

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(14) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd Ed., Reinhold Publishing Co., New York, 1956, p. 130.

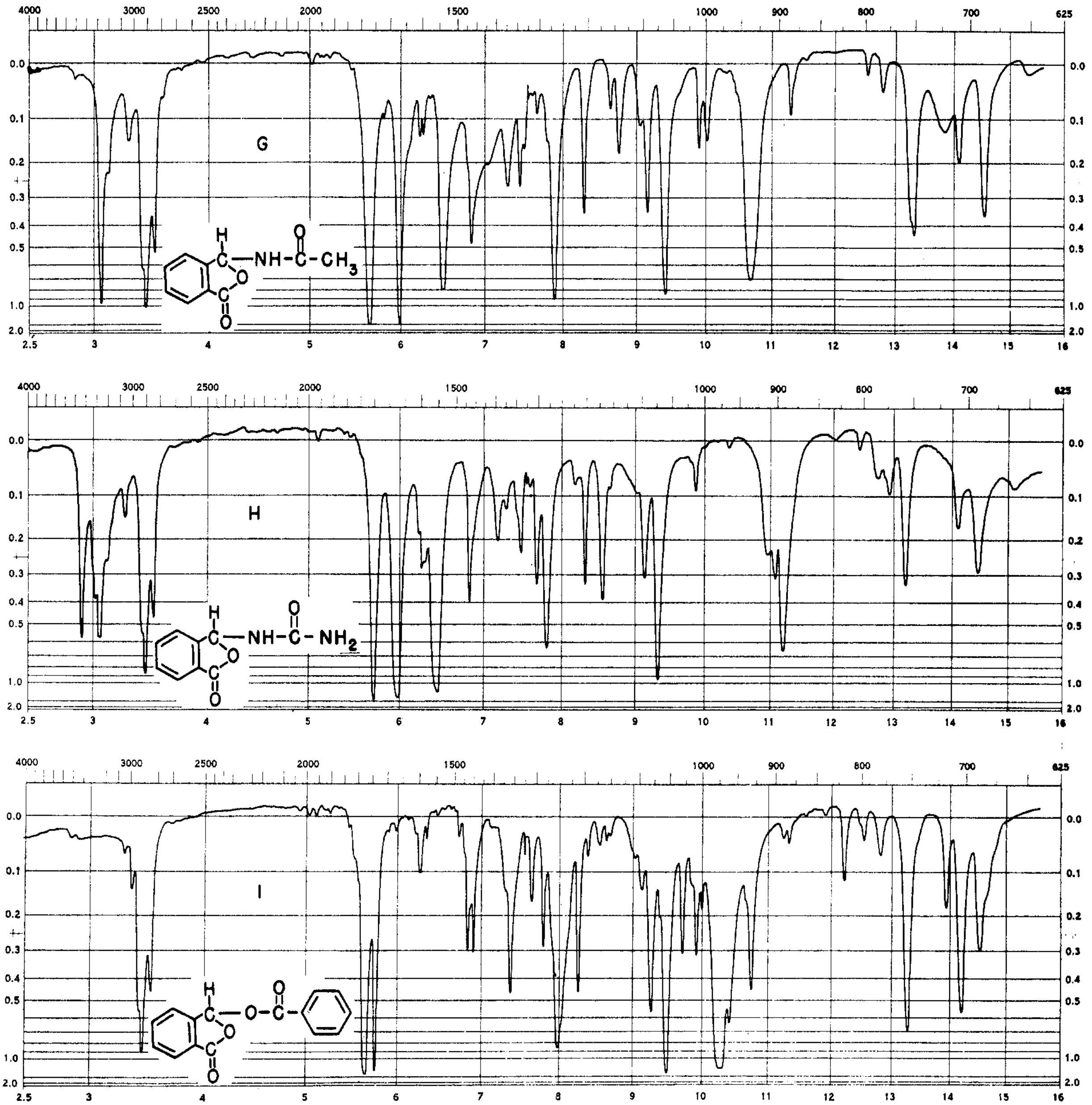

FIG. 1. INFRARED SPECTRA. G—3-Acetamidophthalide. H—3-Ureidophthalide. I—Phthalidyl benzoate. Nujol absorption bands appear at 3.42μ, 6.85μ, and 7.28μ

crystals it may be as high at 5.68μ. The antisymmetric C—O—C stretch absorption lies between 9.38μ and 9.52μ; the symmetric, between 10.38μ and 10.82μ. In addition, the alkoxyphthalides and phthaldehydic acid show a strong band near 8.90μ which has been tentatively assigned to the C—O stretch of the oxygen in the "3" position. The spectrum of 3-ethoxyphthalide (Fig. 1D) is typical of the oxyphthalides.

Fel'dman[15,16] prepared 3-(*p*-nitrophenylthio)-phthalide by reaction of phthalaldehydic acid with *p*-nitrobenzenethiol in acetic acid in the presence of hydrogen chloride as a catalyst. In the present study it has been found that no catalyst is required and, in fact, the reaction with mercaptans and thiophenols is analogous to the reaction with alcohols.

The spectra of the thiophthalides are essentially the same as those of their oxygen analogs, with the exception of the out-of-plane hydrogen deformation absorption which occurs near 13.75μ as contrasted with 13.40μ in the oxyphthalides. The absence of a band at 8.90μ supports the assignment of that band to the C—O stretch of the "3" oxygen in the oxyphthalides. The spectrum of 3-dodecylthiophthalide (Fig. 1E) is typical of this group.

3-Anilinophthalide (V; R = H, R′ = phenyl) has been prepared earlier by reaction of phthalalde-

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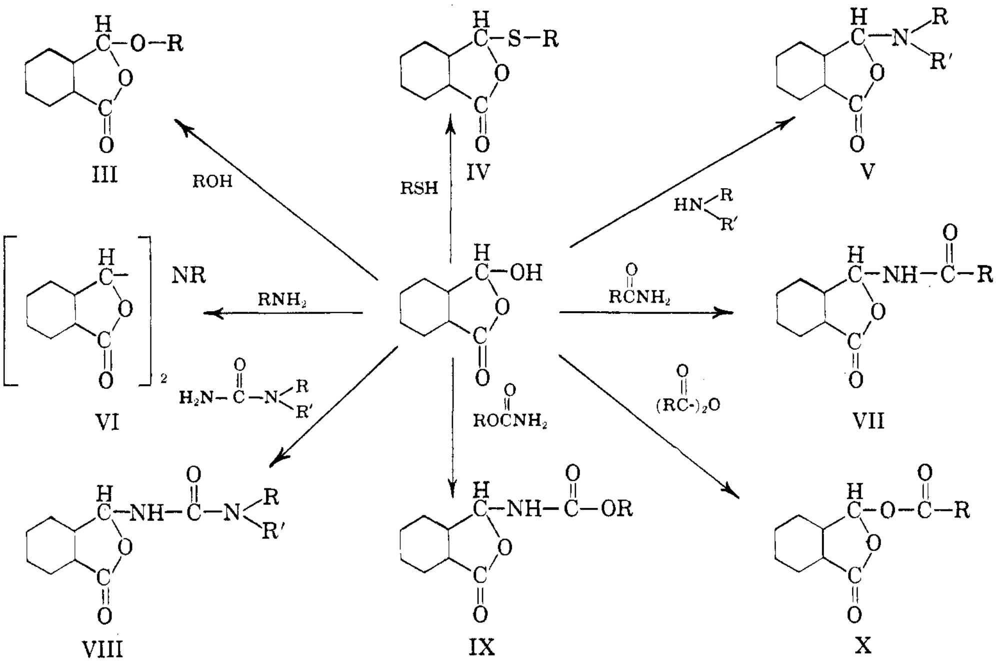
[15] I. K. Fel'dman, *Doklady Akad. Nauk. S.S.S.R.*, 65, 857 (1949).

[16] I. K. Fel'dman and T. I. Gurevich, *Zhur. Obshchei Khim.*, 21, 1540 (1951).



hydic acid with aniline.[8] It has now been found that high yields of this product are obtained within minutes from the reaction with aniline in acetone or alcohol, or even with aniline hydrochloride in water. The reaction has been extended to a variety of primary and secondary aryl, mixed alkylaryl, and secondary alkylamines with comparable results. The high order of reactivity cannot be explained by anil formation since amines such as dimethylamine, diphenylamine and N-methylaniline react readily.

The aminophthalides are characterized principally by their strong symmetric C—O—C stretch between 11.10μ and 11.80μ (Fig. 1F, 3-dimethylaminophthalide). The antisymmetric C—O—C stretch occurs between 9.12μ and 9.52μ while the carbonyl is found between 5.62μ and 5.83μ. No absorption has been found which can be correlated reliably with the C—N stretch.

With unhindered primary alkylamines and ammonia the only products obtained were 3,3'-iminodiphthalides (VI) resulting from the reaction of two moles of phthalaldehydic acid with one of amine. Significant variation in the ratio of the reactants did not alter the latter reaction except when a large excess of the amine was used. In these cases the amine salt of phthalaldehydic acid was produced. When sterically hindered primary alkylamines were employed, 3-alkylaminophthalides (V; R = H, R' = alkyl) were produced. Two highly hindered amines, dicyclohexylamine and 1,1,2,2-tetramethylbutylamine, formed only salts with phthalaldehydic acid.

When two phthalides are attached to the same nitrogen atom, the spectrum in the 11–12μ region usually becomes complex, possibly due to a resonance splitting of the symmetric C—O—C stretch. For this reason it is sometimes difficult to assign a particular absorption to that vibration. The antisymmetric C—O—C stretch and carbonyl bands shift very little, if at all, from their positions in the other aminophthalides.

Phthalaldehydic acid reacts with alkyl and aryl acid amides upon heating to form 3-amidophthalides (VII). The reaction has been extended to arylsulfonamides with comparable results. However, the reaction apparently is limited to amides in which the amide nitrogen is unsubstituted since *N*-methylacetamide did not react under the conditions used.

The carbonyl and antisymmetric C—O—C stretching absorptions in amido, sulfonamido and thioamidophthalides are essentially unchanged from the aminophthalides, appearing in the regions 5.62μ to 5.72μ, and 9.30μ to 9.48μ respectively. The symmetric C—O—C stretch, however, is found at shorter wave lengths (10.33μ–10.85μ) than in the aminophthalides. The absorptions associated with amides, sulfonamides, etc., are affected slightly, if at all, by the phthalide ring. Figure 1G, 3-acetamidophthalide, is typical of the spectra of this group.

Urea or substituted ureas which contain one —NH_2 group reacted readily with phthalaldehydic acid to give 3-ureidophthalides (VIII). Nearly quantitative yields were obtained within a few minutes in hot aqueous solution. The reaction of phthalaldehydic acid with ethyl carbamate was comparable to the reaction with urea.

Racine,[17] who first reacted phthalaldehydic acid with urea, reported the product to be α-(carbamoylimino)-*o*-toluic acid. However, the infrared spectra of the products prepared from urea and sub-

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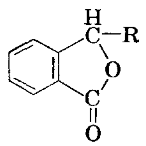
[17] S. Racine, *Compt. rend.*, 106, 947 (1888).

TABLE II
3-SUBSTITUTED PHTHALIDES



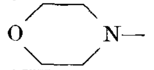
Name	R	M.P.,^{a} °C.	Yield, %	Empirical Formula	Analysis							
					Calculated				Found			
					C	H	N	S	C	H	N	S
Ethoxy	$CH_3CH_2O—$	64–65	73^{b}	$C_{10}H_{10}O_3$	Lit. m.p. 66°^{c} (64°^{d})							
Allyloxy	$CH_2=CHCH_2O—$	^{e}	70	$C_{11}H_{10}O_3$	69.46	5.30			69.28	5.65		
Isopropoxy	$(CH_3)_2CHO—$	61–62	69	$C_{11}H_{12}O_3$	68.73	6.29			68.50	6.36		
Propoxy	$CH_3CH_2CH_2O—$	32–33	61	$C_{11}H_{12}O_3$	68.73	6.29			68.14	6.30		
tert-Butoxy	$(CH_3)_3CO—$	77–79	62	$C_{12}H_{14}O_3$	69.88	6.84			69.81	7.25		
Cyclohexyloxy	cyclo-$C_6H_{11}O—$	79–81	73	$C_{14}H_{16}O_3$	72.39	6.94			72.12	7.20		
Benzyloxy	$C_6H_5—CH_2O—$	47–50	79	$C_{15}H_{12}O_3$	74.98	5.04			74.43	5.26		
n-Octyloxy	$CH_3(CH_2)_6CH_2O—$	^{f}	93^{b}	$C_{16}H_{22}O_3$	73.25	8.45			73.14	8.23		
n-Hexadecyloxy	$CH_3(CH_2)_{14}CH_2O—$	65–66	95	$C_{24}H_{38}O_3$	76.96	10.23			76.90	10.48		
sec-Butylthio	$CH_3CH_2CH(CH_3)S—$	47–48	91^{b}	$C_{12}H_{14}O_2S$	64.83	6.35		14.42	64.92	7.02		14.78
p-Chlorophenylthio	*p*-Cl-$C_6H_4—S—$	120–121	79	$C_{14}H_9ClO_2S$	12.81 (Cl)			11.59	13.04 (Cl)			12.04
Phenylthio	$C_6H_5—S—$	102–103	77	$C_{14}H_{10}O_2S$	69.40	4.16		13.24	69.38	4.55		13.45
1,1,2,2-Tetramethylbutylthio	$CH_3CH_2C(CH_3)_2C(CH_3)_2S—$	65–66	52	$C_{16}H_{22}O_2S$	69.02	7.97		11.52	69.19	7.95		11.71
n-Dodecylthio	$CH_3(CH_2)_{10}CH_2S—$	36–38	98	$C_{20}H_{30}O_2S$				9.59				9.73
n-Octadecylthio	$CH_3(CH_2)_{16}CH_2S—$	68–69	77	$C_{26}H_{42}O_2S$				7.66				8.11
Dimethylamino	$(CH_{22})N—$	89–90	77	$C_{10}H_{11}NO_2$	67.78	6.26	7.91		67.73	5.88	7.66	
Morpholino		127–128	99	$C_{12}H_{13}NO_3$			6.39				6.20	
tert-Butylamino	$(CH_3)_3CNH—$	134–136	84	$C_{12}H_{15}NO_2$			6.83				6.87	
2,4,5-Trichloroanilino	2,4,5-$Cl_3C_6H_2NH—$	209–210	80	$C_{14}H_8Cl_3NO_2$			4.26	32.37 (Cl)			4.33	32.22 (Cl)
o-Chloroanilino	*o*-$Cl—C_6H_4NH—$	170–171	85	$C_{14}H_{10}ClNO_2$			5.39	13.65 (Cl)			5.38	14.23 (Cl)
m-Nitroanilino	*m*-$NO_2C_6H_4NH—$	227–229	74	$C_{14}H_{10}N_2O_4$			10.35				10.24	
Anilino	$C_6H_5NH—$	180–181^{g}	94	$C_{14}H_{11}NO_2$	74.66	4.92	6.22		74.98	4.93	6.29	
p-Hydroxyanilino	*p*-$HOC_6H_4NH—$	181–183	93	$C_{14}H_{11}NO_3$			5.81				5.97	
p-Sulfamoylanilino	*p*-$H_2NSO_2C_6H_4NH—$	262–264	97	$C_{14}H_{12}N_2O_4S$			9.21	10.54			9.12	10.79
o-Carboxyanilino	*o*-$HOOC—C_6H_4NH—$	211–212(*d*)	93	$C_{15}H_{11}NO_4$			5.20				5.07	
Benzylamino	$C_6H_5CH_2NH—$	86–89	99	$C_{15}H_{13}NO_2$	75.30	5.48	5.86		75.70	5.74	5.77	
N-Methylanilino	$C_6H_5N(CH_3)—$	158–159	73	$C_{15}H_{13}NO_2$	75.30	5.48	5.86		75.43	5.02	5.81	
p-Acetylanilino	*p*-$CH_3COC_6H_4NH—$	246–247	97	$C_{16}H_{13}NO_3$			5.24				5.29	
N-(2-Chloroallyl)-anilino	$C_6H_5N(CH_2CCl=CH_2)—$	120–121	85	$C_{17}H_{14}ClNO_2$			4.67	11.83 (Cl)			4.78	11.60 (Cl)
o-Carboethoxyanilino	*o*-$C_2H_5OOCC_6H_4NH—$	163–164	70	$C_{17}H_{15}NO_4$			4.71				4.85	
2-Naphthylamino	2-$C_{10}H_7NH—$	208–209	91	$C_{18}H_{13}NO_2$			5.09				4.77	
p-(1,1-Dimethylpropyl)anilino	*p*-$C_2H_5(CH_3)_2CC_6H_4NH—$	200–202	93	$C_{19}H_{21}NO_2$			4.74				4.70	
Diphenylamino	$(C_6H_5)_2N—$	137–138	58	$C_{20}H_{15}NO_2$	79.72	5.02	4.65		79.87	4.65	4.52	
1,2-Diphenylhydrazino	$C_6H_5NHN(C_6H_5)—$	196–198	70	$C_{20}H_{16}N_2O_2$			8.85				8.54	
Acetamido	$CH_3CONH—$	218–220	72	$C_{10}H_9NO_3$	62.82	4.75	7.33		62.74	4.92	7.24	
Thioacetamido	$CH_3CSNH—$	180–182	42	$C_{10}H_9NO_2S$			6.76	15.47			6.87	15.79

TABLE II (Cont'd)

Name	R	M.P.,* °C.	Yield, %	Empirical Formula	Analysis Calculated C	Calculated H	Calculated N	Calculated S	Found C	Found H	Found N	Found S
2,2-Dichlorobutyramido	$C_2H_5CCl_2CONH—$	169–171	47	$C_{12}H_{11}Cl_2NO_3$			4.86	24.61 (Cl)			4.73	24.20 (Cl)
p-Bromobenzenesulfonamido	p-$BrC_6H_4SO_2NH—$	211–212	94	$C_{14}H_{10}BrNO_4S$			3.80	21.71 (Br)			3.83	21.66 (Br)
Benzenesulfonamido	$C_6H_5SO_2NH—$	178–180	62	$C_{14}H_{11}NO_4S$			4.84	11.08			4.87	11.29
Benzamido	$C_6H_5CONH—$	175–177	89	$C_{15}H_{11}NO_3$	71.14	4.38	5.53		71.57	4.53	5.58	
Phenylacetamido	$C_6H_5CH_2CONH—$	223–225	75	$C_{16}H_{13}NO_3$			5.24				5.20	
Caprylamido	$CH_3(CH_2)_6CONH—$	131–133	69	$C_{16}H_{21}NO_3$			5.09				5.20	
Ureido	$H_2NCONH—$	243–244(*d*)[h]	96	$C_9H_8N_2O_3$			14.58				14.38	
3-Methylureido	$CH_3NHCONH—$	229–230(*d*)	97	$C_{10}H_{10}N_2O_3$	58.24	4.89	13.59		58.28	4.88	13.72	
Ethyl 3-oxo-1-phthalancarbamate	$CH_3CH_2OCONH—$	171–172	74	$C_{11}H_{11}NO_4$			6.33 1438				6.24	
3-Ethylureido	$C_2H_5NHCONH—$	213–215(*d*)	99[b]	$C_{11}H_{12}N_2O_3$			12.72				12.53	
3-Phenylureido	$C_6H_5NHCONH—$	217–218(*d*)	88[b]	$C_{15}H_{12}N_2O_3$			10.45				10.39	
3-Benzylureido	$C_6H_5CH_2NHCONH—$	214–215(*d*)	50	$C_{16}H_{14}N_2O_3$			9.92				9.90	
Acetate[i]	$CH_3COO—$	62–63	96	$C_{10}H_8O_4$	Lit. m.p. 60–63[j] (71°[c])							
Propionate[i]	$C_2H_5COO—$	72–74	96	$C_{11}H_{10}O_4$	64.07	4.89			63.68	4.70		
Hexanoate[i]	$CH_3(CH_2)_4COO—$	47–48	96[b]	$C_{14}H_{16}O_4$	67.73	6.50			68.44	6.87		
Benzoate[i]	$C_6H_5COO—$	129–130	39	$C_{15}H_{10}O_4$	70.86	3.97			70.97	4.18		

[a] Melting points are uncorrected. [b] Yield of technical grade material. [c] See Reference (8). [d] See Reference (12). [e] B.p. 128–129° (2 mm.) [f] B.p. 171–172° (5 mm.) [g] M.p. reported 174°, see reference (8). [h] M.P. reported for α-(carbamoylimino)-*o*-toluic acid 240° (d), see Reference (17). [i] Phthalidyl ester. [j] See Reference (19).

stituted ureas indicate that they retain the phthalide form. The bands associated with the phthalide ring are in the following regions: carbonyl, 5.62μ–5.82μ; antisymmetric C—O—C stretch, 9.32μ–9.53μ; symmetric C—O—C stretch, 10.75μ–11.20μ. The latter band can be used to distinguish them from the carbamates in which the symmetric C—O—C stretch of the phthalide ring is at shorter wavelengths (10.30μ–10.90μ). The spectrum of 3-ureidophthalide, Fig. 1H, is typical of the urea derivatives.

Phthalidyl acetate (X; R = CH_3) has been prepared by the reaction of phthalaldehydic acid with acetic anhydride in a sealed tube at 200°.[8] The use of sodium acetate[18] and sulfuric acid[19] as catalysts has been reported. We have found that it can be prepared in good yield simply by heating the materials and distilling the acetic acid from the mixture as it forms. A number of other acid anhydrides gave comparable results. The use of a mixture of acetic anhydride and benzoic acid gave the benzoate (X; R = C_6H_5).

Phthalidyl esters are similar to the alkoxyphthalides in the carbonyl and antisymmetric C—O—C stretch absorptions; 5.62μ–5.68μ and 9.35μ–9.52μ respectively. As in the other derivatives, the symmetric C—O—C stretch serves to characterize the group. This absorption occurs near 10.25μ in the four esters studied. The ester carbonyl absorption (as distinguished from the phthalide carbonyl absorption) is found to be between the carbonyl frequencies of aliphatic and phenyl esters of the same acid. The spectrum of phthalidyl benzoate (Fig. 1I) is typical of these compounds.

EXPERIMENTAL

Preparation of phthalaldehydic acid. Phthaldehydic acid was prepared in 90% yield by photochlorination of *o*-xylene to α,α,α,α′,α′-pentachloro-*o*-xylene,[20] followed by hydrolysis in constant boiling hydrochloric acid containing 10% ferric chloride.[2] Purification was accomplished by recrystallization from water. The purity of the phthalaldehydic acid used in this study was 97% or better by titration.

Preparation of terephthalaldehydic acid. *p*-Xylene was photochlorinated in the side chains to a mixture of tetra-, penta- and hexachloro- *p*-xylenes. The mixture was subjected to fractional distillation and the fraction of b.p. 160–162° (10 mm.) recrystallized from 95% ethanol to obtain α,α,α,α′,α′-pentachloro-*p*-xylene, m.p. 43–45°.

Anal. Calcd. for $C_8H_5Cl_5$: Cl, 63.7. Found: 63.4.

α,α,α,α′,α′-Pentachloro-*p*-xylene was hydrolyzed in constant boiling hydrochloric acid containing 10% ferric chloride. The insoluble product was recrystallized from 95% alcohol to give a 43% yield of terephthalaldehydic acid. The material melted over a wide range above 240°. Neutral equivalent calculated for $C_8H_6O_3$ was 150.1, found 149.8. The oxime was prepared (90% yield), m.p. 215–216° (reported 208–210°[21]); neutral equivalent, 164.1 (theoretical 165.1).

3-Ethoxyphthalide. A solution of 150 g. (1.0 mole) of phthal-

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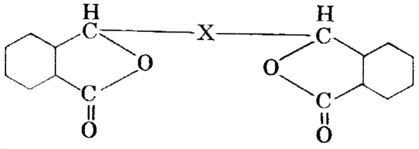
(18) L. Seekles, *Chem. Weekblad*, **20**, 261 (1923).

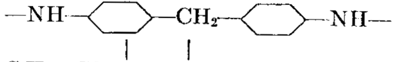
(19) L. Seekles, *Rec. trav. chim.*, **43**, 329 (1924).

(20) A. Colson and H. Gautier, *Ann. chim. et phys.*, [6] **11**, 29 (1887).

TABLE III

3,3′-SUBSTITUTED DIPHTHALIDES



Name	—X—	M.P.[a] °C.	Yield %	Empirical Formula	Analysis Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
Ethylenedioxy	—OCH_2CH_2O—	94–96	99[b]	$C_{18}H_{14}O_6$	66.25	4.33		66.26	4.44	
Butynylenedioxy	—OCH_2—C≡C—CH_2O—	144–147	78[c]	$C_{20}H_{12}O_6$	68.97	3.47		69.01	3.53	
1,2-Dimethylethylenedioxy	—$OCH(CH_3)CH(CH_3)O$—	188–190	66	$C_{20}H_{18}O_6$	67.79	5.12		68.34	5.42	
Imino	—NH—	209–210	57	$C_{16}H_{11}NO_4$	68.32	3.94	4.98	68.16	4.10	4.95
Methylimino	$CH_3N<$	231–233	78	$C_{17}H_{13}NO_4$			4.74			5.24
2-Bromoethylimino	$BrCH_2CH_2N<$	168–171	77	$C_{18}H_{14}BrNO_4$			3.60			3.39
2-Hydroxyethylimino	$HOCH_2CH_2N<$	185–187	88	$C_{18}H_{15}NO_5$			4.31			4.23
Allylimino	CH_2=$CHCH_2N<$	153–154	87	$C_{19}H_{13}NO_4$			4.39			4.34
2-Methoxyethylimino	$CH_3OCH_2CH_2N<$	140–141	64	$C_{19}H_{17}NO_5$			4.13			4.12
sec-Butylimino	$CH_3CH_2(CH_3)CHN<$	218–220	81	$C_{20}H_{19}NO_4$			4.15			3.86
p-Phenylenediimino	*p*-NH—C_6H_4—NH—	258–261	93	$C_{22}H_{16}N_2O_4$	70.96	4.23	7.52	70.74	4.13	7.44
Cyclohexylimino	cyclo$C_6H_{11}N<$	188–190	36	$C_{22}H_{20}NO_4$			3.86			3.85
Benzylimino	$C_6H_5CH_2N<$	140–141	37	$C_{23}H_{17}NO_4$			3.77			3.75
n-Octylimino	$CH_3(CH_2)_6CH_2N<$	109–110	84	$C_{24}H_{27}NO_4$			3.56			3.21
Ethylenebis(butylimino)	$C_4H_9NCH_2CH_2NC_4H_9$	152–153	70	$C_{26}H_{32}N_2O_4$			6.42			6.46
Methylenebis(p-phenyleneimino)		190–192	91	$C_{29}H_{22}N_2O_4$			6.06			6.00
Ethylenebis(benzylimino)	C_6H_5—$CH_2NCH_2NCH_2$—C_6H_5	172–173	85	$C_{32}H_{28}N_2O_4$			5.55			5.34
n-Hexadecylimino	$CH_3(CH_2)_{14}CH_2N<$	91–92	86	$C_{32}H_{43}NO_4$			2.77			2.67

[a] Melting points are uncorrected. [b] Technical material, m.p. 86–89°C. [c] Technical material, m.p. 134–138°C.

aldehydic acid in 300 ml. of 95% ethanol was refluxed for 7 hr. The solution was cooled and poured into cold water and 129 g. of product obtained as a white crystalline solid, m.p. 62–64° (73% yield). Recrystallization of a small sample from 86–100° petroleum ether gave material which melted at 64–65° (80% recovery). Reported m.p. 66°[8] (64°).[12]

3,3'-Ethylenedioxydiphthalide. A mixture of 375 g. (2.50 moles) of phthalaldehydic acid and 77.5 g. (1.25 moles) of ethylene glycol was heated to 145° at 15 mm. over a 1-hr. period. It was held at 140–150° and 15 mm. for 1 hr., heated to 210° during the following hour, and cooled. The viscous residue amounted to 400 g. (99%) of 3,3'-ethylenedioxydiphthalide. After standing one year the material had solidified, m.p. 86–89°.

The preparation of the 3-alkoxyphthalides from the lower alcohols was similar to the preparation of 3-ethoxyphthalide. Equivalent amounts or an excess of the desired alcohol were used with reaction times of 2–7 hr. at reflux temperatures. With the higher alcohols, equivalent amounts of the reactants, and reaction times of 2–3 hr. at reflux temperatures were employed. The liquid products were taken up in benzene, isolated, and fractionally distilled while the solids were recrystallized from petroleum ether or alcohol if desired. The preparation of the glycol derivatives was comparable to the preparation of 3,3'-ethylenedioxydiphthalide.

3-n-Dodecylthiophthalide. A mixture of 40.5 g. (0.2 mole) of 1-dodecanethiol and 30 g. (0.2 mole) of phthalaldehydic acid was heated at reflux (105–115°) for 2 hr. The cooled mixture was poured into water and the insoluble oil taken up in benzene. The benzene was removed by distillation leaving 66 g. (99%) of 3-*n*-dodecylthiophthalide as a residue. On standing the material solidified, m.p. 36–38°.

The preparation of the other thiophthalides was similar except that some of the higher melting derivatives formed solids instead of oils when mixed with water. The solid desivatives were collected by filtration and recrystallized rrom aqueous alcohol.

3-Anilinophthalide. A solution of 37.5 g. (0.25 mole) of phthalaldehydic acid and 32.4 g. (0.25 mole) of aniline hydrochloride in 125 ml. of water was heated at 95° for 0.5 hr. Crystalline solid separated and was isolated from the cooled mixture. The solid was recrystallized from aqueous acetone, and 45.5 g. (81%) of 3-anilinophthalide, m.p. 180–181°, was obtained. Reported m.p. 174°.[8]

A solution of 75 g. (0.5 mole) of phthalaldehydic acid in 100 ml. of warm acetone was added to a warm solution of 46 g. (0.5 mole) of aniline in 100 ml. of acetone. Heat was evolved and crystalline 3-anilinophthalide precipitated (105 g., 94%).

The procedure for the preparation of the phthalide derivatives from primary arylamines and diamines, mixed alkylarylamines, N,N'-disubstituted ethylenediamines and hydrazines was similar to the latter example. In some cases a heating period of up to 1 hr. and removal of some of the solvent was required.

3-Dimethylaminophthalide. A solution of 45 g. (0.3 mole) of phthalaldehydic acid in 60 g. of a 25% aqueous solution of dimethylamine (0.3 mole) was heated to 95° for 1 hr. while the volume was reduced to one half by evaporation. Crystalline solid formed and 41 g. (77%) of 3-dimethylaminophthalide, m.p. 89–90°, was isolated from the cold mixture.

3-Diphenylaminophthalide. A solution of 30 g. (0.2 mole) of phthalaldehydic acid and 33.8 g. (0.2 mole) of diphenylamine in 150 ml. of benzene was heated and the benzene partially evaporated over a 4-hr. period. On cooling, 35 g. (58%) of 3-diphenylaminophthalide, m.p. 137–138°, crystallized.

In a similar manner with reaction times of 0.5 to 4 hr., the secondary alkyl and arylamine derivatives of phthalaldehydic acid were prepared. This procedure was also applied to the sterically hindered primary alkylamines such as benzyl and tert-butylamine. When the product was a liquid, a low melting solid, or soluble in benzene, the solvent was removed to recover the derivative as a residue.

3,3'-n-Octyliminodiphthalide. A solution of 25.8 g. (0.2 mole) of *n*-octylamine in 100 ml. of benzene was cooled while 60 g. (0.4 mole) of phthalaldehydic acid was added in small portions over a 5-min. period. The resulting solution was heated on the steam bath for 2 hr. while the benzene partially evaporated. Crystalline 3,3'-*n*-octyliminodiphthalide, m.p. 109–110°, precipitated on cooling the solution (45.5 g., 58%). The filtrate from isolation of the solid was heated and the majority of the benzene evaporated. On cooling, 20 g. (26%) of 3,3'-*n*-octyliminodiphthalide was obtained. The total yield was 65.5 g. (84%).

In a comparable manner a variety of 3,3'-iminodiphthalides was prepared. In a few cases water was used as the solvent and slightly lower yields were obtained.

3-Acetamidophthalide. A mixture of 150 g. (1.0 mole) of phthalaldehydic acid and 59 g. (1.0 mole) of acetamide was heated to 120° for 0.5 hr. The molten reaction mixture solidified at this time and the water present was evaporated under reduced pressure. The crude solid (198 g.) was washed with aqueous acetone. 3-Acetamidophthalide, m.p. 218–220°, was obtained in a yield of 137.5 g. (72%).

3-Benzenesulfonamidophthalide. A mixture of 67 g. (0.43 mole) of benzenesulfonamide and 64 g. (0.43 mole) of phthalaldehydic acid was heated to 130° for 3 hr. The mixture was cooled to 100° and poured into cold water whereupon 103.5 g. of crude solid precipitated. The material was recrystallized from 95% ethanol and 76 g. (62%) of 3-benzenesulfonamidophthalide, m.p. 178–180°, was obtained.

In a similar manner the other 3-amido- and sulfonamidophthalides were prepared.

3-(3-Methylureido)phthalide. A solution of 29.6 g. (0.4 mole) of methylurea in 50 ml. of hot water was slowly added to a hot solution of 60 g. (0.4 mole) of phthalaldehydic acid in 250 ml. of water. An insoluble precipitate formed immediately and after completion of the addition (10 min.), the mixture was cooled and filtered. 3-(3-Methylureido)phthalide, m.p. 229–230°(d) was obtained (79.5 g., 97%).

The same procedure was used for the preparation of all of the ureidophthalides.

Ethyl 3-oxo-1-phthalancarbamate. A solution of 44.5 g. (0.5 mole) of ethyl carbamate and 75 g. (0.5 mole) of phthalaldehydic acid in 250 ml. of 2-butanone was heated to reflux for 4 hr. The 2-butanone was allowed to distill and the residue poured into cold water. Ethyl 3-oxo-1-phthalancarbamate, m.p. 171–172°, precipitated (81 g., 74.%).

Phthalidyl acetate. A mixture of 61 g. (0.6 mole) of acetic anhydride and 75 g. (0.5 mole) of phthaldehydic acid was heated at 140–160° for 3 hr. while 22 g. (73%) of acetic acid distilled. The reaction mixture was cooled and poured into water whereupon a solid precipitated. A total of 92 g. (96%) of phthalidyl acetate, m.p. 62–63°, was obtained. Reported m.p. 60–63°[8] (71°[19]).

In a similar manner other phthalidyl esters were prepared, although in some cases the reaction was carried out under reduced pressure to aid the distillation of the acid byproduct.

Phthalidyl benzoate. A mixture of 60 g. (0.40 mole) of phthalaldehydic acid, 55 g. (0.45 mole) of benzoic acid and 46 g. (0.45 mole) of acetic anhydride was heated at 150–200° over a 2.5 hr. period while 36 g. (75%) of acetic acid distilled. The mixture was cooled to 80° and poured into water whereupon 107 g. of a crude solid precipitated. The solid was recrystallized twice from 2 l. of 86–100° petroleum ether to give 50 g. (48%) of phthalidyl benzoate, m.p. 118–121°. A 5.0 g. sample was recrystallized from 50 ml. of 95% ethanol and 4.1 g. (82% recovery) of phthalidyl benzoate, m.p. 129–130°, was obtained.

Solubilities. In general the phthalide products are not soluble in water or petroleum ether. They are soluble in organic solvents such as acetone, alcohol, and benzene. The solubility decreases as the complexity and molecular weight increase.

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