Analogs of Luminol. Synthesis and Chemiluminescence of Two Methoxy-Substituted Aminophthalic Hydrazides

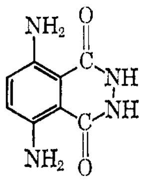
EMIL H. WHITE AND MAURICE M. BURSEY[1]

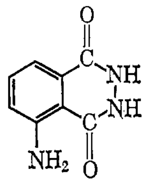
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

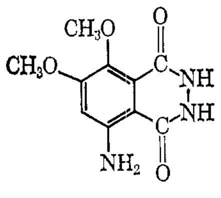
Received January 13, 1966

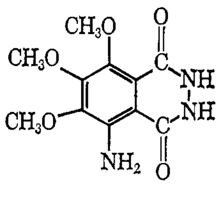
The synthesis of two analogs of luminol, containing two and three methoxy groups, respectively, is described. These compounds exceed luminol in chemiluminescence efficiency by 13 and 30% in dry dimethyl sulfoxide. A match of their chemiluminescence spectra and the fluorescence spectra of the corresponding phthalate ions indicates that, just as for luminol, the appropriately substituted phthalate ion is the emitting species. A strong dependence of the quantum yield of chemiluminescence on the solvent was found.

Few studies of cumulative substituent effects in chemiluminescence have been reported. In 1937, the hydrazides of 3-substituted phthalic acids were examined by Drew and Pearman, who noted a positive correlation between the electron-releasing abilities of several substituents and chemiluminescence intensity in water for the hemoglobin-catalyzed oxidation by hydrogen peroxide.[2] Similarly, Philbrook and Maxwell showed that the intensities of chemiluminescence of a series of 14 derivatives of lophine in a dimethyl sulfoxide-water mixture could be related by Hammett's equation.[3] Other factors can negate the correlation, however. On the basis of a normal cumulative effect, compound I should be more efficient than luminol (II). Yet Drew and Pearman noted that it is much less efficient, presumably as the result of destruction of the aromatic ring made susceptible to oxidation by the amino groups.[4] To circumvent this particular difficulty, we have synthesized compounds III and IV, in which the oxidation to quinonoid derivatives is blocked. As outlined in the discussion section, these compounds are more efficient than luminol, but the chemiluminescence is rather sensitive to hydrogen-bonding effects.


I

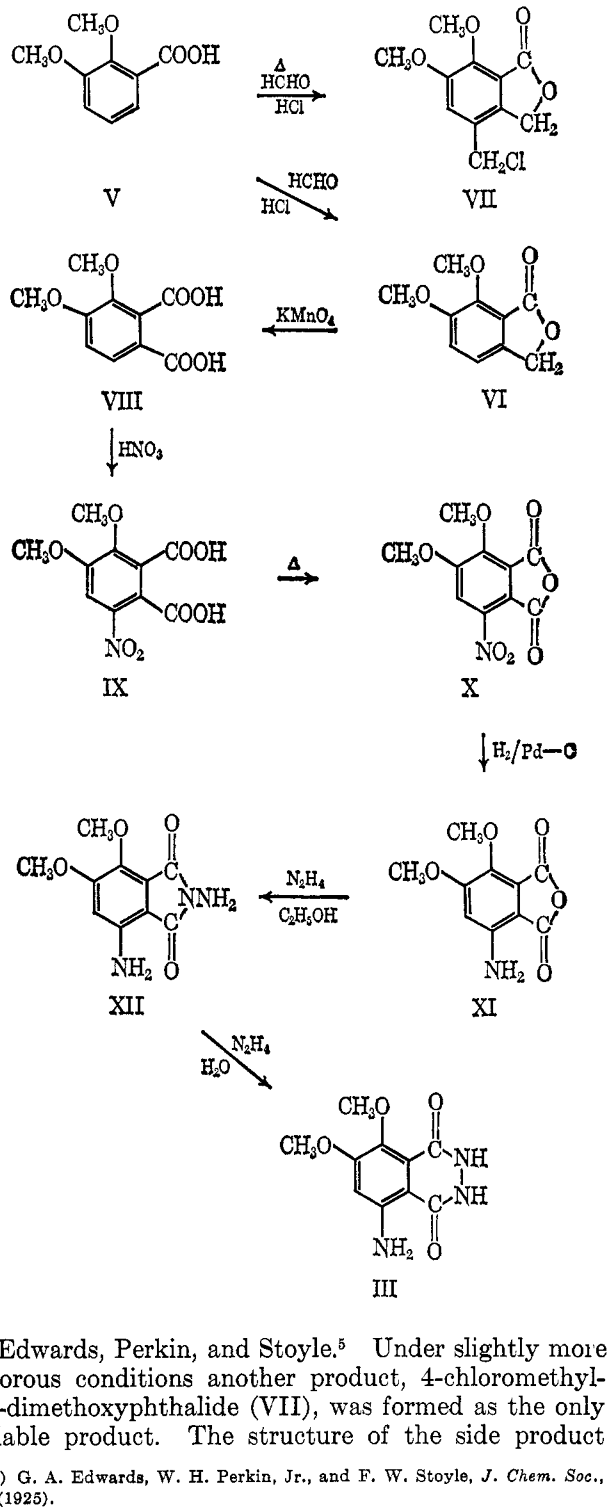

II


III


IV

For the synthesis of 8-amino-2,3-dihydro-5,6-dimethoxyphthalazine-1,4-dione (III), meconine (6,7-dimethoxyphthalide) (VI) was prepared by heating 2,3-dimethoxybenzoic acid (V) (Scheme I) with formaldehyde and hydrochloric acid according to the method of Edwards, Perkin, and Stoyle.[5] Under slightly more vigorous conditions another product, 4-chloromethyl-6,7-dimethoxyphthalide (VII), was formed as the only isolable product. The structure of the side product

SCHEME I



---

[1] National Science Foundation Cooperative Graduate Fellow, 1960–1963.

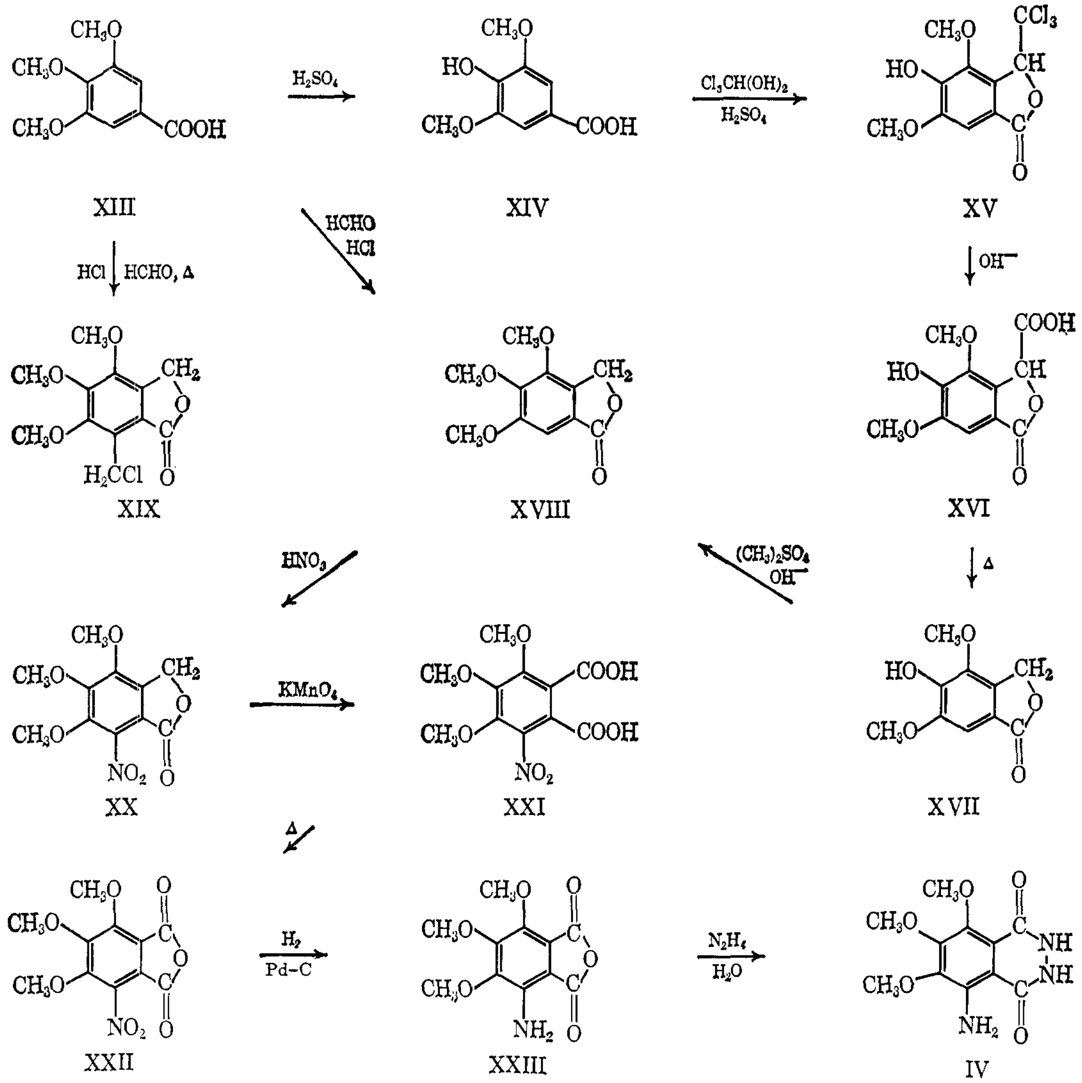
[2] H. D. K. Drew and F. H. Pearman, *J. Chem. Soc.*, 586 (1937).

[3] G. E. Philbrook and M. A. Maxwell, *Tetrahedron Letters*, **No. 19**, 1111 (1964).

[4] E. Erdmann, *Chem. Ber.*, **37**, 2906 (1904).

[5] G. A. Edwards, W. H. Perkin, Jr., and F. W. Stoyle, *J. Chem. Soc.*, 195 (1925).

Scheme II



(VII) was indicated by elementary analysis, formation of silver chloride with ethanolic silver nitrate, agreement of the infrared and ultraviolet spectra with expected values, and comparison of nmr data for this compound and 6,7-dimethoxyphthalide (see Experimental Section). The position of the chloromethyl group is suggested by electronic and steric factors which would favor attack of a chloromethyl carbonium ion at the 4-position over attack at the 5-position of compound VI. The chloromethyl compound (VII) might afford a convenient synthesis of 4,5-dimethoxybenzene-1,2,3-tricarboxylic acid, but no further studies were made of it.

Hemipinic acid (3,4-dimethoxyphthalic acid, VIII), obtained by basic permanganate oxidation of the dimethoxyphthalide, was nitrated in acetic acid to give 3,4-dimethoxy-6-nitrophthalic acid (IX);[6] the position of the nitro group had been established by identification of IX with the oxidation product of nitroopianic acid (2,3-dimethoxy-6-formyl-5-nitrobenzoic acid),[6] and in turn the nitro and formyl groups of this compound had been shown to be adjacent by formation of a substituted indigo on heating with acetone in base.[7] The acid was not isolated, but the reaction mixture was sublimed to give 3,4-dimethoxy-6-nitrophthalic anhydride (X). The nitro anhydride was reduced with hydrogen in the presence of palladium to 6-amino-3,4-dimethoxyphthalic anhydride (XI), previously obtained from the corresponding acid;[8] the anhydride was heated with hydrazine in ethyl alcohol, producing an N-aminoimide, 2,4-diamino-6,7-dimethoxy-1,3-dioxoisoindoline (XII), instead of the desired hydrazide. Drew and Hatt[9] and Drew and Pearman[10] have found that five-membered N-aminoimides are normally intermediates in the formation of six-membered phthalazinediones (*e.g.*, XI → XII → III). In the present case, a more prolonged treatment with hydrazine or treatment under more vigorous conditions gave the desired hydrazide (III) in high yield.

The synthesis of 5-amino-2,3-dihydro-6,7,8-trimethoxyphthalazine-1,4-dione (IV) followed a somewhat different route. Alimchandani and Meldrum's five-step synthesis[11] of 4,5,6-trimethoxyphthalide (XIII–XVIII) (Scheme II) was repeated to obtain authentic material. A shorter procedure, however, based on the successful use of chloromethylation in the previous synthesis (*i.e.*, treatment of 3,4,5-trimethoxybenzoic

---

[6] R. Wegscheider and P. von Rušnov, *Monatsh.*, **29**, 289 (1908).

[7] C. Liebermann, *Chem. Ber.*, **19**, 351 (1886).

[8] F. D. Faltis and F. Kloiber, *Monatsh.*, **53/54**, 620 (1929).

[9] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

[10] H. D. K. Drew and F. H. Pearman, *ibid.*, 26 (1937).

[11] R. L. Alimchandani and A. N. Meldrum, *ibid.*, **117**, 964 (1920).

TABLE I

COMPARISON OF CHEMILUMINESCENCE AND FLUORESCENCE SPECTRA OF HYDRAZIDES AND PHTHALATE IONS

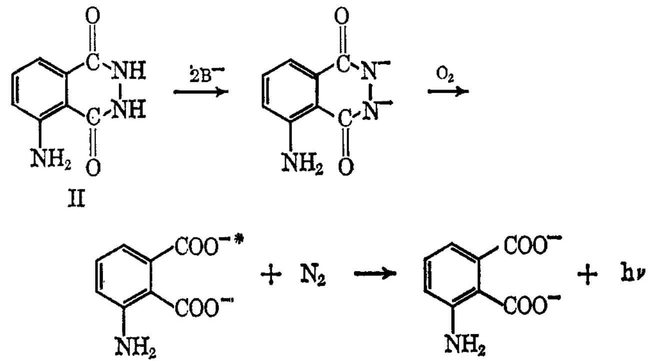
Solvent	Chemiluminescence max, mμ	Fluorescence max of phthalate, mμ	Fluorescence max of product soln, mμ
Dimethoxy hydrazide (III)			
DMSO[a]	465	465	465
H_2O-DMSO, 17:83 mole %[b]	465, 405[c]	465, 405[c]	465, 405[c]
H_2O[d]	405	405	440
Trimethoxy hydrazide (IV)			
DMSO[a]	465	465	465
H_2O-DMSO, 17:83 mole %[b]	465	465 (sh 405)	465 (sh 405)
H_2O[d]	405	405	440

[a] $+KO_2$. [b] +KOH. [c] In the chemiluminescence spectrum the 465-mμ peak was more intense than the 405; the fluorescence spectrum of the phthalate and product solutions had the 405-mμ peak as the more intense. [d] Cu^{2+}-NH_3-H_2O_2-H_2O.

acid (XIII) with formaldehyde and HCl in aqueous dioxane) yielded the phthalide (XVIII) directly. A more vigorous chloromethylation procedure gave a new product, 7-chloromethyl-4,5,6-trimethoxyphthalide (XIX), whose structure was deduced from the elementary analysis, spectral characteristics (see Experimental Section), and chemical behavior.

The trimethoxyphthalide (XVIII) was then nitrated by a known procedure[12] yielding 7-nitro-4,5,6-trimethoxyphthalide (XX), which was oxidized to 3-nitro-4,5,6-trimethoxyphthalic acid (XXI) with basic permanganate. Sublimation of the acid produced 3-nitro-4,5,6-trimethoxyphthalic anhydride (XXII), which was reduced in the presence of palladium to 3-amino-4,5,6-trimethoxyphthalic anhydride (XXIII). On reflux with aqueous hydrazine this produced IV; infrared spectral evidence was gained for the formation of an N-aminoimide as an intermediate in this last reaction, but no attempt was made to isolate it.

Chemiluminescence.—The course of the chemiluminescent oxidation of luminol (II) has been demonstrated to be consistent with the scheme below.[13] The evidence for the aminophthalate ion as the emitting species is the match between the chemiluminescence spectrum of luminol and the fluorescence spectrum of aminophthalate in pure solvents;[14] similar data have recently been obtained for other chemiluminescent cyclic hydrazides.[15] Similar studies were carried out for the new hydrazides. The chemiluminescence maxima in dimethyl sulfoxide and water were compared with the fluorescence spectra of the corresponding substituted phthalate anion, prepared in solution (Table I).


II

The data are also compared with fluorescence of the reaction mixture after chemiluminescence had ceased. These data are strongly reminiscent of the data for luminol.[14] In dimethyl sulfoxide and in water the emitting species is presumably the substituted phthalate ion because of the similarity of the spectral curves; in mixed solvents, two peaks are observed, and the peak at longer wavelength is more intense in chemiluminescence spectra than in fluorescence spectra, as is the case with luminol itself. Interference with solvation by departing nitrogen in chemiluminescence has been suggested as an explanation of this nonidentity.[14]

The final product of the reaction appears to depend on the solvent. In dimethyl sulfoxide and aqueous dimethyl sulfoxide solutions, fluorescence data indicate that the substituted phthalate ion is indeed the final product in each case. Paper chromatographic results also support the substituted phthalate ion as the sole fluorescent product of the reaction.

In the aqueous hydrogen peroxide system, although the emitter still appears to be the excited phthalate ion, the fluorescence data indicate that some other material is the end product. Paper chromatographic results again support some new product, formed either to the complete (dimethoxy) or partial (trimethoxy) exclusion of the phthalate. This is not surprising, since luminol itself reacts cleanly in the Cu^{2+}-H_2O_2 system only at 0°, and our products might be less stable than aminophthalate. These products have not yet been fully investigated, but they might have been formed by decarboxylation reactions.

Quantum Yields for Chemiluminescence.—Data for the relative quantum yields in dimethyl sulfoxide and partly aqueous or alcoholic solutions are presented in Table II for luminol, the dimethoxy compound, and the trimethoxy compound. In the absence of hydrogen-bonding effects (*i.e.*. in dry dimethyl sulf-

TABLE II

CHEMILUMINESCENT EFFICIENCIES RELATIVE TO LUMINOL[a]

	Rel efficiency				
	DMSO	DMSO–*t*-BuOH 96:4[b]	DMSO–H_2O 87:13[b]	DMSO–H_2O 70:30[b]	H_2O
Luminol	1.00	0.40	0.32	0.25	0.23
Dimethoxy hydrazide (III)	1.13	0.012	0.05	0.037	0.024
Trimethoxy hydrazide (IV)	1.30	0.052	0.50	0.44	0.052

[a] Base: for DMSO, KO_2; DMSO-*t*-BuOH, *t*-BuOK; DMSO-H_2O, KOH; NH_3-Cu^{2+}-H_2O_2. [b] Respective mole per cent.

---

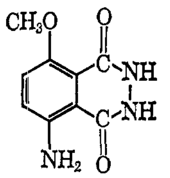
[12] F. Weygand, H. Weber, and E. Maekawa, *Chem. Ber.*, **90**, 1879 (1957).

[13] E. H. White, O. Zafiriou, H. H. Kägi, and J. H. M. Hill, *J. Am. Chem. Soc.*, **86**, 940 (1964).

[14] E. H. White and M. M. Bursey, *ibid.*, **86**, 941 (1964).

[15] K.-D. Gundermann, W. Horstmann, and G. Bergmann, *Ann.*, **684**, 127 (1965).

oxide) the polysubstituted compounds are more efficient than luminol itself; the dimethoxy hydrazide emits 1.13 times as much light and the trimethoxy compound emits 1.30 times as much. In water they are disappointingly weaker. In water our compounds may be compared with "monomethoxyluminol" XXIV, which has been studied by Gundermann and Drawert.[16]



XXIV

In water, this compound is oxidized by hydrogen peroxide with hemin catalyst to yield 22% as much light as luminol under similar conditions. Our dimethoxy hydrazide is only 10% as efficient as luminol in an aqueous system, and the value for the trimethoxy compound is 22%.

The variability of these trends suggests that another factor, the solvation of the emitting species, plays an important role in the quantum yield of a condensed-phase chemiluminescent reaction.

Luminol, which is only one-fourth as efficient in water as in dimethyl sulfoxide, is also less efficient in systems which contain a little *t*-butyl alcohol. The primary interaction with the solvent is, therefore, not one involved with the dielectric constant, which decreases in the series water > dimethyl sulfoxide > *t*-butyl alcohol but is better described as a hydrogen-bonding effect. Solvents which can hydrogen bond to the substrate molecule lower its efficiency, either because they lead to the formation of new, less fluorescent ions, or because the "supermolecule" formed by the substrate and the hydrogen-bonded solvent molecules supplies many more modes of vibration through which the excited state may be degraded. In this fashion the excited state has less probability of decaying by the emission of a photon.

The new dimethoxy hydrazide appears to be subject to this hydrogen-bonding effect to a greater extent than luminol, presumably because there are more sites for this bonding. Its efficiency in water is only 2% of that in anhydrous sulfoxide. The trimethoxy hydrazide is a shade less subject to hydrogen bonding than the preceding compound; its efficiency in water is 4% of its anhydrous efficiency. It is also not so sensitive to small amounts of water in the solvent.

The chemiluminescent efficiency of these compounds is in reasonable agreement with the effect expected for electron-donating substituents on the basis of previously observed correlations. However, the solvent effect makes it clear that the comparison of different compounds must be made on data obtained from use of a common solvent.

Experimental Section

General.—Elemental analyses were performed by Mr. Joseph Walter in this laboratory. All melting points were taken in a Hershberg-type apparatus and are uncorrected. Alcoa alumina (F-20, 80–200 mesh) was used for chromatography. Petroleum ether (Phillips purified), bp 30–50°, was distilled before use. Ultraviolet spectra were recorded on a Beckman DK-2 recording instrument with matched 1-cm cells.

Since traces of fluorescent impurities would render spectral data useless, especial care was observed in preparation of all amino compounds, and these were repeatedly recrystallized until no visible trace of any fluorescent by-product could be detected by paper chromatography (Whatman No. 1 paper, 8:1:1 95% ethanol–concentrated aqueous ammonia–water).

2,3-Dimethoxybenzoic acid (V) (Aldrich Chemical Co., Inc.) was recrystallized from water: mp 121.6–123.6° (lit.[17] 120–122°).

6,7-Dimethoxyphthalide (VI).—The procedure was based on that of Edwards, Perkin, and Stoyle.[5] A mixture of 50 g (270 mmoles) of 2,3-dimethoxybenzoic acid (V), concentrated hydrochloric acid (200 ml), and 37% formaldehyde (135 ml) was boiled for 15 min, filtered, diluted with 200 ml of water, and cooled to yield crystals which were dissolved in chloroform and extracted with dilute sodium bicarbonate solution. Evaporation of solvent gave 7.5 g of the product; the oil which had been filtered off was worked up similarly, yielding product (9.0 g) of lower purity. Both samples were recrystallized to give 15 g of product (77 mmoles, 28%): mp 100.2–100.6° (lit.[5] 102°); λ_{max}^{EtOH} 303 mμ (ϵ 4740); nmr, τ 2.77, 2.93 (centers of gravity for an AB pattern, relative area, 2), τ 4.77 (2), τ 5.91 (3), τ 6.08 (3), all singlets except as noted.

4-Chloromethyl-6,7-dimethoxyphthalide (VII).—A mixture of 107 g (590 mmoles) of 2,3-dimethoxybenzoic acid (VI), 290 ml of 37% formaldehyde, and 540 ml of concentrated hydrochloric acid was boiled until the solution became cloudy (8 min). The oil which formed on cooling was filtered off. This procedure was repeated three times with the remaining solution. The oil was sublimed, giving product, which was recrystallized from methanol (25 g, 103 mmoles, 18%): mp 99.6–103.0°; λ_{max}^{EtOH} 313 mμ (ϵ 4900); nmr, τ 2.85 (1), τ 4.82 (2), τ 5.47 (2, broadened), τ 5.94 (3), τ 6.10 (3), all singlets; precipitate with 2% alcoholic $AgNO_3$ within 30 sec.

Anal. Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57. Found: C, 54.69; H, 4.52.

3,4-Dimethoxyphthalic Acid (VIII).—To a solution of 7.5 g (39 mmoles) of 6,7-dimethoxyphthalide (VI) in 20 ml of 5% sodium hydroxide was added potassium permanganate (8.3 g in 250 ml of water). After 3 days the reaction mixture was filtered, acidified to pH 1 (concentrated hydrochloric acid), clarified (sodium bisulfite solution), and flash evaporated. The residue was extracted with hot isopropyl alcohol, which was flash evaporated to give product, recrystallized from water (9.0 g, 34.5 mmoles, 89% as the dihydrate); mp 185.5–186.5° (rapid) (lit.[5] 177°); λ_{max}^{EtOH} 253 mμ (ϵ 14,300), 285 sh (ϵ 3680).

3,4-Dimethoxy-6-nitrophthalic Anhydride (X).—The phthalic acid was prepared by a modification of the method of Wegscheider and von Rušnov.[6] Fuming nitric acid (2 ml) was added over 5 min to a solution of 3,4-dimethoxyphthalic acid (VIII) (1.52 g, 5.8 mmoles) in 4 ml of glacial acetic acid at 90°. After 30 min the reaction mixture was cooled overnight and the product was filtered off; additional product was obtained by concentration of the filtrate. Total product was sublimed twice at 150–160°, dissolved in chloroform, washed with dilute sodium bicarbonate solution, and recrystallized from benzene: (1.38 g, 5.5 mmoles, 95%), mp 155.2–155.4° (lit.[18,19] 145°, 154–155°); λ_{max}^{EtOEt} 246 mμ (ϵ 10,300), 325 (ϵ 4500).

6-Amino-3,4-dimethoxyphthalic Anhydride (XI).—A solution of 1.74 g (6.9 mmoles) of 3,4-dimethoxy-6-nitrophthalic anhydride (X) in 200 ml of ethyl acetate was hydrogenated with 1.4 g of 10% palladium on charcoal in two lots, flash evaporated, crystallized (1.2 g, 5.4 mmoles, 78%), and recrystallized from ethanol: mp 225° dec (rapid heating), (lit.[8] 190–210°, depending on rate of heating); λ_{max}^{EtOEt} 231 mμ (ϵ 20,300), 261 (ϵ 22,800), 392 (ϵ 6150).

Anal. Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06. Found: C, 54.04, H, 3.83.

2,4-Diamino-6,7-dimethoxy-1,3-dioxoisoindoline (XII).—A mixture of 310 mg (1.4 mmoles) of 6-amino-3,4-dimethoxyphthalic anhydride (XI) and 80 mg (2.5 mmoles) of 95% hydrazine in 25 ml of 95% ethyl alcohol was refluxed for 1 hr, cooled to room temperature, filtered, dried (300 mg, 1.3 mmoles,

---

[16] K.-D. Gundermann and M. Drawert, *Chem. Ber.*, **95**, 2018 (1962).

[17] I. M. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

[18] H. Grüne, *Chem. Ber.*, **19**, 2299 (1886).

[19] R. Wegscheider and H. Strauch, *Monatsh.*, **29**, 305 (1908).

91%), not immediately soluble in cold aqueous sodium hydroxide: mp 264–265° dec (rapid heating); $\lambda_{\max}^{\mathrm{EtOH}}$ 230 mμ (ε 17,200), 267 (ε 13,600), 397 (ε 4470). An analytical sample was recrystallized from ethanol.

Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67. Found: C, 50.81; H, 4.36.

8-Amino-2,3-dihydro-5,6-dimethoxyphthalazine-1,4-dione (III).—A mixture of 500 mg (2.2 mmoles) of 6-amino-3,4-dimethoxyphthalic anhydride (XI) and 5 ml of 95% hydrazine in 20 ml of water was refluxed for 3 hr, cooled, adjusted to pH 5 with glacial acetic acid, and cooled overnight in the refrigerator. The hydrazide was filtered and washed with cold water. Concentration of the filtrate produced a second crop after cooling (430 mg, 1.8 mmoles, 81%). A sample for analysis was recrystallized from 1:2 dimethylformamide–water. It was easily soluble in cold aqueous sodium hydroxide: darkens at 240–260°, mp 290–292° dec (rapid heating); $\lambda_{\max}^{6\,N\ \mathrm{NH_4OH}}$ end absorption, 220 mμ (ε >110,000), 322 (ε 7350), 355 (ε 8100).

Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; Found: C, 50.37; H, 4.55.

3,4,5-Trimethoxybenzoic acid (XIII) (Columbia Organic Chemicals Co., Inc.) was recrystallized from water and then from ethanol: mp 169.0–170.6° (lit. 166°).

The multistep procedure of Alimchandani and Meldrum[11] was used to convert this material *via* syringic acid (XIV) sequentially to 4,6-dimethoxy-5-hydroxy-3-trichloromethylphthalide (XV), mp 172–173° (lit.[11] 172–173°); 4,6-dimethoxy-5-hydroxyphthalide-2-carboxylic acid (XVI), mp 185–186° (lit.[11] 187°); 4,6-dimethoxy-5-hydroxyphthalide (XVII), mp 142–143° (lit.[11] 144°); 4,5,6-trimethoxyphthalide (XVIII), mp 133–134.5° (lit.[11] 135–136°). The following procedures are more convenient, however.

4,5,6-Trimethoxyphthalide (XVIII).—A mixture of 10 g (47 mmoles) of 3,4,5-trimethoxybenzoic acid (XIII), 25 ml of 37% formaldehyde, and 40 ml of concentrated hydrochloric acid was boiled for 10 min and cooled in the refrigerator. Total product was filtered, washed with cold water, dried under vacuum, dissolved in chloroform, and washed with aqueous sodium bicarbonate. The chloroform was evaporated, yielding an oil which solidified and which was recrystallized from ethyl acetate several times (7.2 g, 32 mmoles, 68%), infrared spectrum identical with that of the material produced by the literature method.[14] After sublimation at 120–130°, it had mp 134–136° and did not depress the melting point of a sample prepared by the multistep procedure: $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (ε 8500), 296 (ε 4110).

Alternate Method.—To a solution of 100 g (0.47 mole) of 3,4,5-trimethoxybenzoic acid (XIII) in 600 ml of dioxane was added a mixture of 250 ml of 37% formaldehyde and 450 ml of concentrated hydrochloric acid. The reaction mixture was heated on the steam bath for 1 hr, cooled for 10 min, and poured into 2500 ml of water. After 12 hr, the product was dissolved in 300 ml of chloroform and washed with 1 *N* sodium hydroxide. Evaporation of the chloroform left a residue, mp 127–134°, amounting to 51.5 g. Recrystallization from ethyl acetate once yielded 48 g of the phthalide, mp 136–137°. Concentration of the mother liquors gave another 3 g, mp 133–134.5°. Total yield was 51 g (0.23 mole, 49%).

7-Chloromethyl-4,5,6-trimethoxyphthalide (XIX).—A mixture of 30 g (140 mmoles) of 3,4,5-trimethoxybenzoic acid (XIII), 75 ml of 37% formaldehyde, and 125 ml of concentrated hydrochloric acid was boiled for 15 min and cooled, and 100 ml of chloroform was added. This extract was washed with 1 *N* sodium bicarbonate and evaporated. The residue was sublimed, yielding 28.5 g of colorless material, mp 70–90°. Thin layer chromatography (silica gel G, 1:4 ethyl acetate–benzene) indicated the presence of two compounds, the minor one being 4,5,6-trimethoxyphthalide; these were not separated by attempted fractional crystallization and fractional sublimation.

The crude product (11 g) was chromatographed over alumina. Product was eluted with 19:1 petroleum ether–benzene (8.5 g, 31 mmoles, 22%), followed by 4,5,6-trimethoxyphthalide (2 g), and was recrystallized from ethyl acetate: mp 83.5–85.5°; $\lambda_{\max}^{\mathrm{EtOH}}$ 258 mμ (ε 8370), 298 (ε 3950); nmr spectrum, τ 4.78 (2), τ 4.95 (2), τ 6.00 (9, irregular multiplet), all singlets except as noted; precipitate with 2% alcoholic $AgNO_3$ within 30 sec.

Anal. Calcd for $C_{12}H_{13}ClO_5$: C, 52.85; H, 4.80. Found: C, 53.07; H, 4.87.

7-Nitro-4,5,6-trimethoxyphthalide (XX).—This was prepared by the procedure of Weygand, Weber, and Maekawa,[12] mp 115–116° (lit.[12] 116–116.5°): $\lambda_{\max}^{\mathrm{EtOH}}$ 250 mμ (ε 7450), 293 sh (ε 2990). One preparation had mp 118–119° after recrystallization.

3-Nitro-4,5,6-trimethoxyphthalic Acid (XXI).—To a solution of 5.7 g (21 mmoles) of 7-nitro-4,5,6-trimethoxyphthalide (XX) in 40 ml of 10% KOH was added 7.7 g potassium permanganate in 250 ml of water. After 22 hr at 25°, the reaction mixture was filtered, acidified to pH 1 (concentrated hydrochloric acid), clarified (sodium bisulfite solution), flash evaporated, and extracted three times with boiling acetone. Evaporation of the acetone and crystallization from water gave product (5.5 g, 17 mmoles, 82% as the monohydrate). Recrystallized analytical samples had mp 177.5–178° dec; $\lambda_{\max}^{\mathrm{EtOH}}$, vague shoulder at *ca.* 245 mμ (ε 7550), 295 (ε 1510).

Anal. Calcd for $C_{11}H_{11}NO_9 \cdot H_2O$: C, 41.39; H, 4.10. Found: C, 41.42; H, 4.06.

3-Nitro-4,5,6-trimethoxyphthalic Anhydride (XXII).—The 3-nitro-4,5,6-trimethoxyphthalic acid (XXI) (3.0 g, 9.4 mmoles) was sublimed twice at 175°. A chloroform solution of the sublimate was cooled and extracted with dilute sodium bicarbonate (2.0 g, 7.2 mmoles, 77%). An analytical sample, mp 90–91°, was recrystallized once from chloroform–heptane and once from ethyl acetate–heptane: $\lambda_{\max}^{\mathrm{EtOEt}}$ 238 mμ (ε 18,300), 320 (ε 2500).

Anal. Calcd for $C_{11}H_9NO_8$: C, 46.65; H, 3.20. Found: C, 46.91: H, 3.34.

3-Amino-4,5,6-trimethoxyphthalic Anhydride (XXIII).—A solution of 3 g (11 mmoles) of 3-nitro-4,5,6-trimethoxyphthalic anhydride (XXII) in 500 ml of ethyl acetate was hydrogenated with 0.7 g of 10% palladium on charcoal, filtered, and flash evaporated. The product (1.8 g) was recrystallized from tetrahydrofuran–pentane. Another crop (0.3 g), obtained by concentration of the mother liquors, showed traces of a second spot on paper chromatography: total yield, 2.1 g (8.5 mmoles, 77%). An analytical sample was recrystallized twice from tetrahydrofuran–pentane and had mp 121–122°; $\lambda_{\max}^{\mathrm{EtOEt}}$ 235 mμ (ε 18,200), 259 (ε 21,300), 298 (ε 2400), 390 (ε 6900).

Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.16; H, 4.38. Found: C, 51.97; H, 4.44.

5-Amino-2,3-dihydro-6,7,8-trimethoxyphthalazine-1,4-dione (IV).—A solution of 1.00 g (3.9 mmoles) of 3-amino-4,5,6-trimethoxyphthalic anhydride (XXIII) in 50 ml of 12% aqueous hydrazine was refluxed for 5 hr, cooled, and adjusted to pH 1 (concentrated hydrochloric acid). A mixed precipitate of hydrazine hydrochloride and the product was cooled, filtered, redissolved, taken to pH 4, and flash evaporated at 40–50°. The residue was washed with about 8 ml of water. The inorganic material dissolved, leaving the phthalazinedione (0.7 g, 2.8 mmoles, 68%), which was filtered and washed with a few milliliters of water. The analytical sample, mp 174–175°, was recrystallized from water and had $\lambda_{\max}^{6\,N\ \mathrm{NH_4OH}}$ 230 mμ (ε 28,000), 318 (ε 7100), 358 (ε 8300).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.90. Found: C, 49.78, H, 4.88.

Total Quantum Yield Measurement.—A brass sleeve was constructed to slide over a Photovolt photomultiplier detector (Model 520 A) arm so that another circular brass sleeve, into which the chemiluminescence cell fit snugly, opened directly above the aperture before the detector tube. A simple diaphragm, consisting of a circular copper disk with a circular aperture in the center, was placed in the sleeve over the detector to diminish the total amount of light reaching the detector from the reaction. The chemiluminescence cell for room temperature measurements sat atop this diaphragm. Oxygen entered through an inlet after passing through a column of Tel-Tale silica gel and Ascarite to remove water and carbon dioxide. The sample was injected from a syringe into a port in darkness; in some cases, the dimethyl sulfoxide solution was admitted to the cell before measurement began, and aqueous base was added in darkness. The lower part of the cell was wrapped on the sides with asbestos to permit a secure fit in the circular brass sleeve.

The Photovolt photomultiplier detector was adapted to integrate the light input directly. The assembled apparatus was tested occasionally for light leaks by a blank run in the dark. That it was tight was indicated by the lack of upward drift (<1% of chart width on the most sensitive scale) even after 4–6 hr of accumulated "exposure". No downward drift (<1% of chart width on the most sensitive scale) was observed when the meter was left at *ca.* 90 units for 4–6 hr; this indicated that there was no leak in the capacitor of the integrator circuit. All experiments were performed in a room whose temperature was maintained at 22 ± 2°. A number of experiments were repeated either at the same time or on different days to compare their reproducibility, and variations determined from measurements on a standard solution on a day-to-day basis, were corrected by insertion of the proper figure in the calculations.

Fluorescence and Chemiluminescence Measurements.—Data were recorded with an Aminco-Bowman spectrophotofluorometer (American Instrument Co., Inc.) using Vitroseal tubes. Dimethyl sulfoxide (Matheson Coleman and Bell) was stirred for several hours over KOH pellets and then distilled from the same flask at vacuum pump pressure. The fluorescence of the distillate was then checked; it could not be reduced by fractional freezing, but shaking with potassium superoxide appeared to reduce fluorescence. Solvent fluorescence was insignificant at the exciting wavelengths used to determine fluorescence of the species of interest.

Spectra in anhydrous dimethyl sulfoxide were recorded after the addition of about 50 mg of KO_2 (personal gift of Professor Paul H. Emmett) to a 3-ml sample of a standard solution. For the partially aqueous systems, standard 0.5 N NaOH was pipetted into the tube, the proper amount of standard hydrazide solution or corresponding anhydride solution in dimethyl sulfoxide pipetted in, the tube was swirled until no striations of light were noted, and the spectrum was recorded. The aqueous spectra were recorded in a solution 1 N in NH_4OH and 0.12 N in Cu^{2+}. To this chilled mixture, 30% H_2O_2 was added dropwise while the tube sat in the spectrophotofluorometer so that emission of light had ceased before addition of the succeeding drop. The spectrum of the final product was recorded after a second run in an ice bath, and the spectrum of the corresponding phthalate was recorded from a sample of a solution of the anhydride dissolved overnight in dilute Na_2CO_3 solution.

Acknowledgment.—We wish to thank the National Institutes of Health (GM-10849) for its support of this work.

Compounds of Phosphorus and Fluorine. IV. Reaction of 1-Chloro-2,3,3,4,4,5,5-heptafluorocyclopentene with Trialkyl Phosphites and Other Nucleophilic Reagents[1]

ARLEN W. FRANK

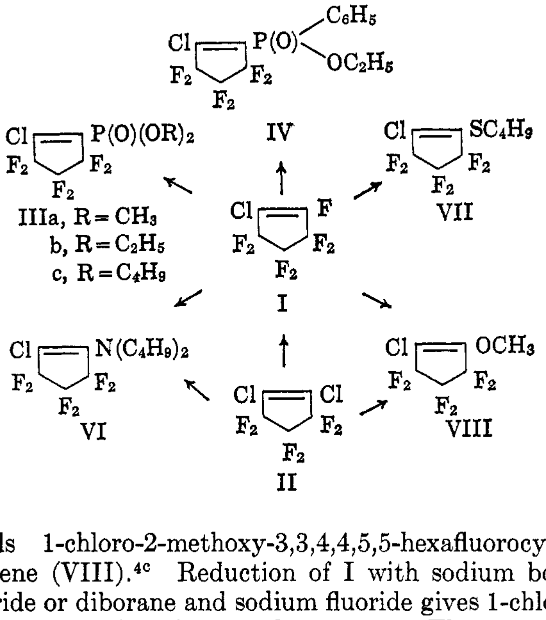
Research Center, Hooker Chemical Corporation, Niagara Falls, New York 14302

Received December 1, 1965

1-Chloro-2,3,3,4,4,5,5-heptafluorocyclopentene (I) reacts readily with nucleophilic reagents, giving the products of displacement of vinylic fluorine. The chlorine atom is retained in every case. The reaction of I with trialkyl phosphites provides a direct synthesis of the dialkyl 2-chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonates (III), compounds first described in the preceding paper in this series. Diethyl phenylphosphonite reacts similarly, giving a phosphinate ester (IV). Dibutylamine reacts with I to give the same product (VI) which is obtained from dibutylamine and 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene (II), but under much milder conditions. I also reacts readily with methanol and with butyl mercaptan in ether solution in the presence of triethylamine, giving the known ether, VIII, or the new compound, butyl 2-chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-yl sulfide (VII). The mechanism of the displacement of fluorine *vs.* chlorine is discussed.

In part II of this series it was shown that trialkyl phosphites cannot be made to react with 1,2-dichloroperfluorocycloalkenes in a 1:1 ratio. The products are diphosphonates, regardless of the order of addition or the ratio of reactants.[2] A monophosphonate was, however, later prepared by an indirect synthesis involving the cleavage of one of the C–P bonds in a diphosphonate.[1] In the present paper a direct synthesis of monophosphonates is described, employing 1-chloro-2,3,3,4,4,5,5-heptafluorocyclopentene (I) as the starting material. This and other reactions of I with various nucleophilic reagents to be discussed are sketched in Chart I.

CHART I



The chemistry of I reported in the literature is meager, as the compound has not been generally available. In our laboratories it is prepared by the partial fluorination of 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene (II) with potassium fluoride in dimethylformamide.[3,4] Further fluorination gives perfluorocyclopentene, with displacement of the remaining chlorine atom,[3,4] but in all of the other reactions the chlorine atom is preserved. The reaction of I with methanol in the presence of lithium chloride or potassium bifluoride yields 1-chloro-2-methoxy-3,3,4,4,5,5-hexafluorocyclopentene (VIII).[4c] Reduction of I with sodium borohydride or diborane and sodium fluoride gives 1-chloro-2H-3,3,4,4,5,5-hexafluorocyclopentene.[5] The reaction of I with hydrogen chloride gives II and trichloropentafluorocyclopentene.[6]

In the present work, I was found to react smoothly with trimethyl phosphite, triethyl phosphite, tributyl

---

[1] Part III: A. W. Frank, *J. Org. Chem.*, **31**, 1521 (1966).

[2] Part II: A. W. Frank, *ibid.*, **30**, 3663 (1965).

[3] Unpublished work by Dr. R. L. K. Carr.

[4] (a) A similar method was described by A. Henne and J. Sedlak, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., 1960, p 16 M. See also (b) A. Henne, U. S. Patent 3,024,290 (March 6, 1962); *Chem. Abstr.*, **56**, 15333 (1962); (c) N. A. Edelson, Ph.D. Thesis, Cornell University, 1962; (d) J. T. Maynard, *J. Org. Chem.*, **28**, 112 (1963).

[5] (a) D. J. Burton and R. L. Johnson, *J. Am. Chem. Soc.*, **86**, 5361 (1964); (b) R. L. Johnson and D. J. Burton, *Tetrahedron Letters*, 4079 (1965).

[6] C. F. Baranauckas and R. L. K. Carr, U. S. Patent 3,193,587 (July 6, 1965); *Chem. Abstr.*, **63**, 14724 (1965).