

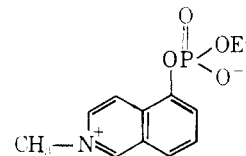
TABLE I
 SUBSTITUTED 3,4,5-TRIMETHOXYBENZYLETHYLENEDIAMINES

No.	R	Mp, °C (mm)	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd	Found	Calcd	Found	Calcd	Found
1	N(C ₂ H ₅) ₂	170-181 (0.35)	59.8	C ₂₁ H ₃₁ N ₃ O ₃	67.53	67.90	8.37	8.35	11.15	11.86
2	Pyrolidino	146-160 (0.27)	39.7	C ₂₁ H ₂₉ N ₃ O ₃	67.90	68.16	7.84	8.34	11.31	11.16
3	Piperidino	205-215 (0.35)	56.2	C ₂₃ H ₃₁ N ₃ O ₃	68.54	68.35	8.11	8.04	10.90	10.80
4	Morpholino	180-195 (0.35)	27.2	C ₂₁ H ₂₉ N ₃ O ₄	65.00	65.12	7.54	7.55	10.85	10.65

at reduced pressure. The fraction distilling at 163-171° (0.40 mm) was collected; yield 12.3 g (71.6%). A disuccinate derivative had mp 136.5°.

Anal. Calcd for C₁₉H₂₇N₃O₃: C, 66.02; H, 7.88; N, 12.16. Found: C, 65.72; H, 7.52; N, 11.93. Calcd for C₂₇H₃₉N₃O₇ (disuccinate): N, 7.23. Found: N, 7.12.⁷

The physical constants, yields, and analyses of additional 3,4,5-trimethoxybenzylethylenediamines, prepared in a manner similar to that described above, are given in Table I.



Our results support this view. It is therefore necessary to avoid heating these compounds in the presence of a nucleophilic agent such as I⁻ but it is safe to heat in the presence of anionic such as picrate and *p*-toluenesulfonate.

O-Diethyl Phosphoryl Esters of Quaternary and Tertiary Aminophenols¹

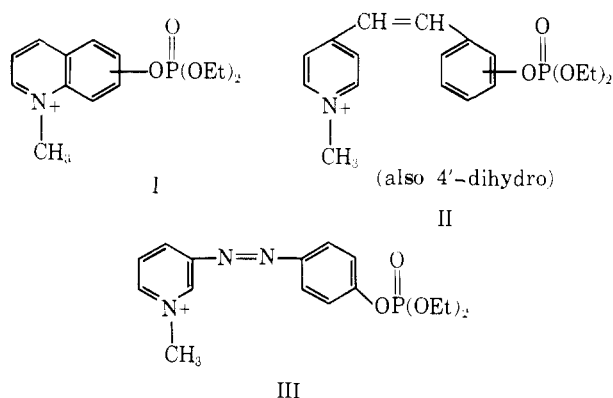
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Tertiary esters of phosphoric acid which contain a rather acidic alcohol or phenol residue are inhibitors of acetylcholinesterase and other hydrolytic enzymes. Acetylcholinesterase in its reactions with other types of compounds reacts much more rapidly with compounds containing a quaternary ammonium or substituted ammonium function in the leaving group than it reacts with similar compounds lacking this structure.

It would seem then that O-diethyl phosphoryl esters of aminophenols might be interesting compounds for this field of study. Although this principle is widely recognized, only a few compounds of this type have been previously prepared,²⁻⁴ and we have therefore undertaken the preparation of a number of new ones. The compounds are of the types I, II, III, and some bis-quaternary compounds containing a dimethylene ether bridge, -CH₂OCH₂-, between the two ring nitrogens (see Table I).



The general procedure was to diethylphosphorylate the aminophenol and then to quaternize the amine with methyl *p*-toluenesulfonate. The product is not obtained with methyl iodide, and Andrews² suggested that the resulting product might be the following betaine.

(1) This work supported by the Division of Research Grants and Fellowships of the National Institutes of Health, Grant NB00573-18 and Program Project Grant GM09069-04; by the U. S. Public Health Service and Research Career Award GM-K3-15, 012; and by National Science Foundation Grant GB 2817.

(2) K. J. M. Andrews, F. R. Atherton, F. Bergel, and A. L. Morrison, *J. Chem. Soc.*, 1638 (1954).

(3) F. Hobbiger, *Brit. J. Pharmacol.*, **9**, 159 (1954).

(4) L. E. Tammelin, *Acta Chem. Scand.*, **11**, 1340 (1957).

Experimental Section

Quinolinols and 5-isoquinolinol were commercial products. Stilbazoles were prepared according to the method of Papa, *et al.*⁵ The 4,3' derivative, not previously prepared was also obtained by this method; yield 74%, mp 225°.

Anal. Calcd for C₁₃H₁₁NO: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.93; H, 5.53; N, 7.13.

The 4,4'-hydroxystilbazole was reduced to the dihydrostilbazole with sodium amalgam at reflux (temperature for 6 hr in methanol containing sodium methoxide using the one-half amount of NaHg; yield 70%).

4-(3-Pyridylazo)phenol was prepared by coupling 3-pyridine-diazonium chloride with phenol in aqueous alkali. The product was precipitated by neutralization with acid; yield 81%; recrystallized from methanol, mp 219°.

Anal. Calcd for C₁₁H₈N₂O: C, 66.32; H, 4.55; N, 21.10. Found: C, 65.87; H, 4.35; N, 20.58.

Diethyl Phosphorylation.—The procedure using diethyl phosphoryl chloride was slightly modified after Andrews, *et al.*² Sodium methoxide was used instead of sodium ethoxide and the reaction mixture was not heated. After 1 hr at room temperature the reaction mixture was diluted with H₂O and the product was extracted with ether. After washing (NaOH, H₂O) the ether layer was dried (Na₂SO₄) in the presence of charcoal. The ether was evaporated and the crude product was sufficiently pure to be used for subsequent preparations without distillation. Yields varied from 25 to 60%. Picrates were prepared for identification.

Quaternization.—The N-methyl quaternary salts were prepared by heating the diethyl phosphate ester with 50% excess methyl *p*-toluenesulfonate in dimethylformamide (DMF) on a steam bath. The crude product was precipitated with ether. If the product was relatively high melting, it was recrystallized from acetone. If it was an oil, or oily, it was transformed into the picrate by dissolving in hot water or methanol and adding hot aqueous sodium picrate. The picrates separated on cooling. The picrates were recrystallized from methanol. The yields ranged from 50 to 75%.

To check Andrews' hypothesis that methyl iodide might yield the betaine, the diethyl phosphoryl ester of 5-isoquinolinol was heated for 1 hr on a steam bath with excess methyl iodide in DMF. The solution was cooled and a lemon-colored precipitate, mp 238°, insoluble in acetone, was obtained with ether. The compound was very soluble in water and gave a negative iodide test with AgNO₃. The analysis agrees with the betaine hydrate.

Anal. Calcd for C₁₂H₁₄NO₃·H₂O: C, 50.52; H, 5.66; N, 4.91; P, 10.86. Found: C, 50.07; H, 6.13; N, 4.93; P, 10.91.

Bisquaternary Compounds Containing an N,N'-Dimethylene Ether Bridge.—Bis(chloromethyl) ether was transformed to the iodide with excess NaI in acetone. NaCl was filtered off and the O-diethyl phosphorylated tertiary amine in acetone solution was added. A dilute aqueous solution of sodium picrate was

(5) D. Papa, E. Schwenk, and E. Klingsberg, *J. Am. Chem. Soc.*, **73**, 253 (1951).

TABLE I^a

No.	b	c	R	Y	Mp, °C ^d	Solvent of recrystn	Formula	Calcd, %					Found, %						
								C	H	N	P	S	C	H	N	P	S		
Diethyl Phosphoryl Esters of Quinolinols, Hydroxystilbazoles, 4,4'-Hydroxydihydrostilbazole, and 4-(3-Pyridylazo)phenol																			
1	3	...	H	...	159	EtOH													
2	3	...	CH ₃	...	111 ^e	H ₂ O													
3	5	...	H	...	157	MeOH													
4	5	...	CH ₃	...	117	MeOH-Et ₂ O	C ₂₀ H ₂₁ N ₄ O ₁₁ P	45.81	4.04	10.69	5.91		46.23	3.96	10.56	5.72			
5	6	...	H	...	178	MeOH													
6	6	...	CH ₃	...	137	MeOH	C ₂₀ H ₂₁ N ₄ O ₁₁ P	45.81	4.04	10.69	5.91		46.00	3.83	10.54	5.87			
7	7	...	H	...	168	MeOH													
8	7	...	CH ₃	...	92	MeOH	C ₂₀ H ₂₁ N ₄ O ₁₁ P	45.81	4.04	10.69	5.91		46.27	3.95	10.70	6.01			
9	8	...	H	...	123	H ₂ O													
10	8	...	CH ₃	...	107	H ₂ O	C ₂₀ H ₂₁ N ₄ O ₁₁ P	45.81	4.04	10.69	5.91		45.86	4.43	10.68	5.96			
11	5 ^f	...	H	...	141	MeOH													
12	5 ^f	...	CH ₃	...	133	MeOH													
13	5 ^f	...	CH ₃	...	129 ^g	Me ₂ CO	C ₂₁ H ₂₂ NO ₇ PS	53.95	5.61	3.00	6.63	6.86	53.79	5.37	2.97	6.34	6.47		
14	4	2	H	CH=CH	154	MeOH													
15	4	2	CH ₃	CH=CH	157	MeOH	C ₂₄ H ₂₅ N ₄ O ₁₁ P	50.01	4.37	9.72	5.37		49.95	4.04	9.88	5.38			
16	4	3	H	CH=CH	163	MeOH													
17	4	3	CH ₃	CH=CH	127	MeOH	C ₂₄ H ₂₅ N ₄ O ₁₁ P	50.01	4.37	9.72	5.37		50.05	3.86	9.66	5.44			
18	4	4	H	CH=CH	141	MeOH													
19	4	4	H	CH=CH	121 ^g	Me ₂ CO-Et ₂ O													
20	4	4	CH ₃	CH=CH	152	MeOH													
21	4	4	CH ₃	CH=CH	168	Me ₂ CO	C ₂₆ H ₂₆ NO ₇ PS	57.79	5.82	2.70	5.96	6.17	57.75	5.76	2.90	5.80	6.06		
22	4	4	H	CH ₂ CH ₂	103	MeOH-H ₂ O													
23	4	4	CH ₃	CH ₂ CH ₂	77	MeOH-H ₂ O	C ₂₄ H ₂₇ N ₄ O ₁₁ P	49.83	4.71	9.69	5.36		49.68	4.81	9.67	5.25			
24	3	4	H	N=N	133	MeOH													
25	3	4	H	N=N	115 ^g	MeOH-Et ₂ O													
26	3	4	CH ₃	N=N	104	EtOH	C ₂₂ H ₂₂ N ₆ O ₁₁ P	45.68	4.01	14.53	5.36		45.85	4.40	14.35	5.31			
Bisquaternary Compounds Containing the Bridge CH ₂ OCH ₂ between the Two Ring Nitrogen Atoms																			
27	6	193	Me ₂ CO													
28	5 ^f	134	EtOH-Me ₂ CO	C ₄₀ H ₄₀ N ₈ O ₂₂ P ₂	45.20	3.79	10.55	5.83		44.95	3.67	10.70	5.88			
29	4	2	...	CH=CH	197	MeOH	C ₄₈ H ₄₈ N ₈ O ₂₂ P ₂	49.41	4.15	9.60	5.31		50.20	4.68	9.78	4.57			
30	4	3	...	CH=CH	129	MeOH	C ₄₈ H ₄₈ N ₈ O ₂₂ P ₂	49.41	4.15	9.60	5.31		49.26	4.21	9.63	4.92			
31	4	4	...	CH=CH	192	MeOH	C ₄₈ H ₄₈ N ₈ O ₂₂ P ₂	49.41	4.15	9.60	5.31		49.64	4.48	9.39	5.29			
32	4	4	...	CH ₂ CH ₂	87	MeOH													

^a The formula weight of all compounds except those containing CH=CH and N=N, which were not tested, was correct to 1.5% by the picrate method. ^b This number refers to the quinoline or pyridine rings. ^c This number refers to the benzene ring. ^d Melting points were taken on a Uni-Melt apparatus. ^e Previously reported;² softens at 108–110°, melts at 135–137°. ^f Isoquinolinol. ^g *p*-Toluenesulfonate.

added a few minutes later, and much of the solvent was evaporated at room temperature. The crude picrate was obtained by cooling and was recrystallized from methanol.

Analysis for Picrate.—All the picrates except those containing the chromophores CH=CH and N=N were analyzed by measuring the optical density at 415 mμ of a solution at about 2×10^{-5} M in 10% ethanol. The method was standardized with picric acid and a few drops of dilute alkali. All compounds were correct with $\pm 1.5\%$ which is about the accuracy of the method. The identity of the unquaternized esters in those compounds containing a chromophore rests upon the correct analyses of the quaternized derivatives.

6,12-Diphenyldibenzo[b,f][1,5]diazocines

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Since 2,8-dichloro-6,12-diphenyldibenzo[b,f][1,5]diazocine was shown to have hormonelike activity,¹ a number of analogs were

(1) Pharmacological data on some of the compounds described will be published at a later date; see also G. W. Duncan, S. C. Lyster, and J. B. Wright, *Proc. Soc. Exptl. Biol. Med.*, **120**, 725 (1965).

prepared. In two cases^{2,3} 6,12-diphenyldibenzodiazocines were formed by heating the corresponding 2-aminobenzophenone hydrochlorides. We have found that dibenzodiazocines can be prepared conveniently and in good yields from 2-aminobenzophenones when Lewis acids are used as condensing agents.

Experimental Section

All melting points are corrected. Ultraviolet spectra were determined in isopropyl alcohol using a Cary 14 spectrophotometer.

General Procedure.⁴—The corresponding 2-aminobenzophenone was dissolved in an inert solvent, the catalyst was added, and the solution was heated under reflux for the time indicated. After cooling, the solution was washed with aqueous sodium hydroxide, and the solvent was removed *in vacuo*. In each case the crystalline reaction product was recrystallized from a mixture of methylene chloride and alcohol to give pale yellow prisms.

Acknowledgement.—We are indebted to Dr. V. Toome and Mr. S. Traiman for the spectrophotometric determinations and to Dr. Al Steyermark and his staff for the microanalyses.

(2) A. Sondheimer, *Chem. Ber.*, **29**, 1272 (1896).

(3) A. Giacalone, *Gazz. Chim. Ital.*, **65**, 120 (1935); *Chem. Abstr.*, **29**, 5450^g (1935).

(4) Variations of the condensing agents and solvents gave different yields of the respective product. One representative example for the preparation of each compound is shown in Table I on the following page.