TABLE IV

INTRAPERITONEAL ACUTE TOXICITY AND ANALGETIC ACTIVITY OF 2-QUINOLIZIDINYL ESTERS[a]

Compd[b]	ED$_{50}$, mg/kg (95% confidence limits)	Slope	LD$_{50}$, mg/kg[c] (95% confidence limits)	Slope
Axial acetate (IVb)	13.7 (10.0–18.8)	1.44	109.9 (76.3–158.3)	1.53
Equatorial acetate (IIIb)	20 ($^1/_5$ at 20 mg/kg)		97.0 (78.3–120.3)	1.35
Equatorial propionate (IIIc)	3.0 (1.3–6.8)	3.14	69.1 (51.3–93.4)	1.63
			84.0 (65.8–107)	1.22
Axial propionate (IVc)	2.4 (1.4–4.1)	1.80	100 (64.1–156)	1.44
			124 (78.5–196)	1.90
Meperidine	6.4 (4.3–9.6)	1.39	145 (95–225)	1.10

[a] Five female mice (ICR strain) per dose. [b] Hydrochlorides. [c] LD$_{50}$ observation period = 2 hr.

(15.6%) of white needles, mp 117–178°, bringing the total yield of IVa to 16.27 g (39.6%).

Fractions 36–46, eluted with 50:50 Me$_2$CO–anhydrous Et$_2$O, gave 7.31 g (19%) of product, mp 114–116°. The sample was recrystallized from petroleum ether to give 5.6 g (14.5%) of 2(e)-hydroxy-2(a)-phenylquinolizidine (IIIa), mp 119–120°. Admixture of the material with IVa showed a significant melting point depression (90–95°). Anal. (C$_{15}$H$_{21}$NO) C, H, N.

Esters of Hydroxyphenylquinolizidines (Table III).—A solution of 0.01 mole of the appropriate epimeric hydroxyphenylquinolizidine in 10 ml of Ac$_2$O or propionic anhydride and 40 ml of pyridine was refluxed for 18 hr. The mixture was cooled to room temperature and treated with crushed ice and excess solid K$_2$CO$_3$, respectively. The aqueous mixture was extracted with two 250-ml portions of Et$_2$O. The ethereal solution was evapo-

rated and the residual oil either was distilled or converted to hydrochlorides or picrates in the usual manner and recrystallized. The ir spectra showed no OH but strong C=O absorption at 1725 cm^{-1}. Samples of the free bases of VI and VII for nmr studies were obtained by elution chromatography using Woelm grade I neutral alumina and petroleum ether as the eluent.

Phosphorus Analogs of Nitrogenous Drugs. II.[1] 10H-Dibenzo[1,4]thiaphosphorins as Central Nervous System Depressants

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In an effort to delineate the electronic properties of the tricyclic nucleus which are important to chlorpromazine-type biological activity, 10-(3-dimethylaminopropyl)-10H-dibenzo[1,4]thiaphosphorin, its oxide, and three analogous oxides, substituted at the 2 position with Cl, SMe, and OMe groups, respectively, have been synthesized. Ultraviolet spectral data are presented to show that extensive delocalization of the 3p electrons on the phosphorus atom in the phosphine would be expected. The compounds are shown to depress spontaneous activity in mice in the 30–50-mg/kg dosage range, and a possible correlation between biological activity and electronic properties of the nucleus, as revealed by uv spectral data, are discussed.

The important biological properties associated with the phenothiazine tranquilizers, of which chlorpromazine is the prototype, are well known and have been reviewed extensively.[2] In an initial attempt aimed at definition of optimum stereoelectronic properties in the tricyclic nucleus the title compounds, of which 1 is the prototype, in which phosphorus replaces the ring nitrogen have been synthesized and submitted to preliminary biological evaluation. Several related oxides 2 have also been prepared and tested. We elected to insert phosphorus into these systems because its close chemical relationship to nitrogen would be expected to affect the chemical properties of the aromatic nucleus in a very subtle manner. These small changes should be observ-

able chemically, by observing the spectroscopic properties of the system, as well as biologically.

Perusal of the uv spectral data for the first six compounds in Table I will show that the unshared electrons of nitrogen adjacent to an aromatic system interact with the aromatic π electrons to cause a bathochromic shift in the λ_{max} and a pronounced increase in the ϵ_{max}. The effect is more pronounced in Ph$_2$NH than in PhNH$_2$, but reduced in Ph$_2$N(CH$_2$)$_3$NMe$_2$, perhaps because the alkyl chain interferes with coplanarity of the two benzenoid rings. The 3p orbital accommodating the unshared electrons of phosphorus is much larger than the corresponding 2p orbital of nitrogen and, in some situations, this results in striking chemical differences between analogous nitrogen and phosphorus compounds. For example, the phosphorus analog of pyridine is not known,[3] apparently because in this sp^2-bonded system the overlap of the 3p phosphorus electrons with those in the carbon 2p orbitals is so poor that little or no resonance stabilization is afforded. However, in the present case, the uv data for Ph$_3$P in
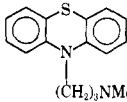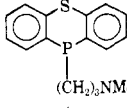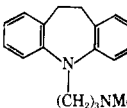
(1) (a) Part I: R. A. Wiley and H. N. Godwin, *J. Pharm. Sci.*, **54**, 1063 (1965). (b) J. H. C. was a Predoctoral Fellow of the Public Health Service, 1963–1967. (c) The authors gratefully acknowledge the assistance of Dr. C. K. Erickson in the biological studies.

(2) (a) M. Gordon in "Psychopharmacological Agents," Vol. 2, M. Gordon, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) K. Stach and W. Poldinger, *Fortsch. Arzneimittelforsch.*, **9**, 129 (1966); (c) P. B. Bradley in "Physiological Pharmacology, A Comprehensive Treatise," Vol. 1, W. S. Root and F. G. Hofmann, Ed., Academic Press, New York, N. Y., 1963, p 417.

(3) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 3.

Table I suggest that the unshared phosphorus electrons interact with the aromatic π electrons, since its spectral characteristics are very similar to those of closely analogous amines. Therefore, the hypothesis that 10H-dibenzo[1,4]thiaphosphorins should rather closely resemble analogous phenothiazines appeared tenable.

TABLE I

Uv Data

Compd	λ_{max}^{MeOH}, mμ	ϵ_{max}
PhH	203	7,400
PhNH$_2$	230	8,600
Ph$_2$NH	281	19,200
Ph$_3$P	264	12,000
Ph$_2$S	249	11,400
Ph$_2$N(CH$_2$)$_3$NMe$_2$ (13)	248	8,350
Ph$_2$P(CH$_2$)$_3$NMe$_2$ (12)	248	8,900
(promazine)	254	30,000
(1)	263	4,750
(imipramine)	253	8,700

SCHEME I

a, R = H
b, R = Cl
c, R = SMe
d, R = OMe

The synthesis of these compounds was carried out as shown in Scheme I. The benzenethiol 3[4] was condensed with 4 to yield the disulfide 5; it was found that for this reaction far better yields were obtained in the NaHCO$_3$–DMF system[5] than by earlier KOH–EtOH procedures. Reduction of 5 with Sn–HCl[6] afforded 6 in good yield. This substance was diazotized with nitrosylsulfuric acid[7] to form 7, which was smoothly converted to 8 under Sandmeyer conditions. Diazotization of 6 with HNO$_2$ in aqueous solution afforded only minute yields of 7, apparently due to the fact that 6 is very weakly basic.

Preparation of 9 was best achieved as shown,[8] and this substance was allowed to react under Michaelis conditions[9] with the chloroamine 10 to give 11. It was found that yields of 11 obtained in this way were critically dependent on time, solvent, and work-up conditions (toluene, 4–8 hr, and direct distillation of the reaction mixture being optimal).

After a number of other approaches were unsuccessfully pursued, cyclization to obtain the phosphine oxides 2 was effected using a procedure modeled after
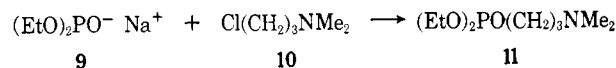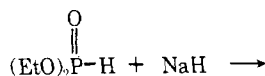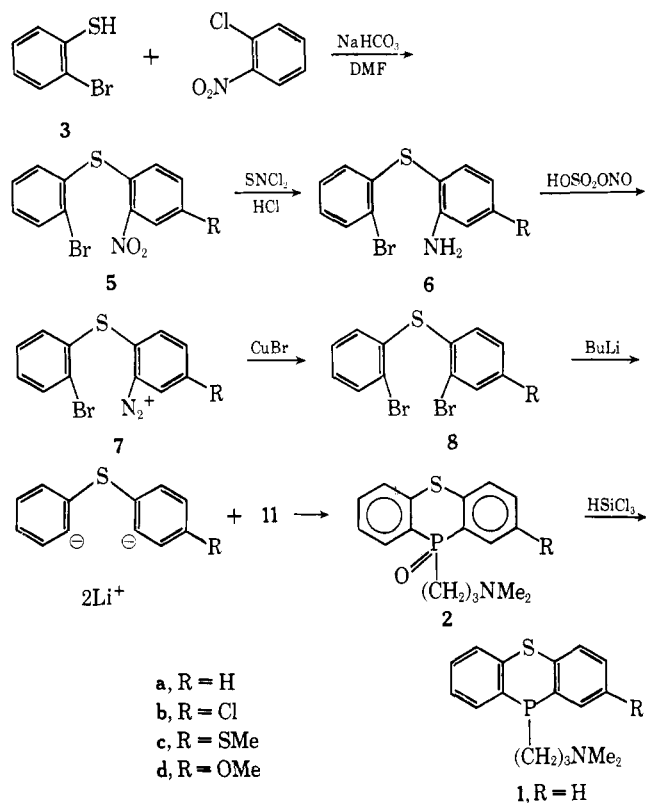
that of Burger and Shelver,[10] in which excess BuLi was employed. In the one case where sufficient sample was available, reduction of the oxide 2 produced a good yield of the desired cyclic phosphine 1.

Biological Results.—In order to explore the capability of these substances to cause generalized CNS depression, their ability to depress the level of spontaneous activity in mice was determined. Groups of three animals were used, the drug was administered intraperitoneally, and the number of counts generated by the treated animals interrupting ir light beams was compared with that of saline-injected controls concomitantly determined. Details of the procedure have been published.[11] It is not inferred that this procedure constitutes a reliable index of chlorpromazine-type activity, but phenothiazine-type tranquilizers are very active in the assay. In order to exclude the possibility that phenobarbital-type sedation might explain these results, more elaborate studies will be necessary.

The results obtained for these compounds are presented in Table II, along with the data for Ph$_2$N(CH$_2$)$_3$-NMe$_2$, the amine analog of a previously reported[1a] phosphine. Biological data for this amine do not appear to have been previously reported.

(4) A. J. Saggiomo, P. N. Craig, and M. Gordon, J. Org. Chem., 23, 1906 (1958).

(5) H. Oelschlager, W. Toporski, P. Schmersahl, and C. Welsch, Arch. Pharm., 296, 107 (1963).

(6) H. H. Hodgson and W. Rosenberg, J. Soc. Dyers Colourists, 46, 267 (1930).

(7) H. H. Hodgson and J. Walker, J. Chem. Soc., 1620 (1933).

(8) R. G. Harvey, T. C. Myers, H. I. Jacobson, and E. V. Jensen, J. Am. Chem. Soc., 79, 2612 (1957).

(9) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950, p 16.

(10) A. Burger and W. H. Shelver, J. Med. Pharm. Chem., 4, 225 (1961).

(11) D. G. Wenzel and L. L. Broadie, Arch. Int. Pharmacodyn. Ther., 159, 154 (1966).

TABLE II

BIOLOGICAL RESULTS. DEPRESSION OF
SPONTANEOUS ACTIVITY IN MICE

Compd	Dose, mg./kg. ip	Obsn time, min	% depression
1	10	30	0
	30	30	58
2a	30	50	0
	50	50	49
2b	30	30	40
	50	30	60
2c	50	30	83
2d	50	30	45
Ph$_2$P(CH$_2$)$_3$NMe$_2$ (12)[1a]	10	30	89
Ph$_2$N(CH$_2$)$_3$NMe$_2$ (13)	75	30	59

Discussion

It is interesting to note that the diphenylphosphine derivative 12 is a significantly more potent CNS depressant than its amine counterpart 13, for which doses less than 75 mg/kg were ineffective. Since promazine is active in this assay at dose levels of about 1 mg/kg, it was surprising to note that the phosphorin 1, although active, was not as potent as 12. As was noted previously[1a] for the oxide of 12, the oxide of 1 (2a) is also active, although somewhat less so than the parent phosphine. Surprisingly, the other phosphine oxides 2, which bear substituents associated with high activity in the phenothiazine series, all display about the same level of activity as the unsubstituted oxide (2a).

A possible explanation for these data in terms of molecular electronic structure as reflected in the uv spectrum may be advanced. It is not claimed that uv spectral data reflect definitive properties of the aromatic nucleus; this would require much more extensive data and calculations. On the other hand, the uv spectrum is a sensitive and generally reliable guide to the extent of electron delocalization in aromatic systems. In the case at hand, it is seen that the diphenylphosphine derivative 12 and its amine analog 13 exhibit almost identical spectral maxima. When these two compounds are compared to their respective tricyclic analogs, it is seen that a bathochromic shift is encountered in both cases, but the very large increase in molecular absorptivity observed in the phenothiazine series fails to appear in the phosphine 1. This indicates generally that, although the electronic transitions are similar in both cases, the probability of the transition in the phosphine is much less, and that this difference in electronic properties may be the reason the phenothiazines are more active CNS depressants.

The ingenious hypothesis advanced by Stach and Poldinger[2b] to explain in chemical terms the difference between chlorpromazine-type and imipramine-type drugs, namely that the former are only "bent" out of coplanarity, while the latter are both "bent" and "twisted," may also bear on this point. It is clear that, in addition to the stereochemical context in which the Stach and Poldinger hypothesis was framed, this bending and twisting would have important effects on the extent of π-electron delocalization as well. It was therefore of interest to compare the uv spectrum of 1 to that of imipramine.[12] This was done, and a striking

similarity was observed. Since imipramine displays weak tranquilizing power in addition to its antidepressant effect, it will be of great interest to determine whether 1 exhibits antidepressant-type activity. This and other aspects of these studies are in progress.

Experimental Section[13]

2'-Bromo-2-nitrodiphenyl Sulfides (5).—The 4-substituted 3-nitrothioanisole (0.20 mol) and 2-bromobenzenethiol (0.20 mol) were dissolved in 250 ml of DMF. NaHCO$_3$ (0.24 mol) was added and the resulting suspension was heated for 6 hr at 70°. The mixture was cooled to 25° and filtered, and the precipitate was washed with 100 ml of CHCl$_3$. The combined filtrates were concentrated on the steam bath under a stream of air to afford a black residue. The product was isolated by chromatography on Al$_2$O$_3$. The following new sulfides 5 were prepared: R = SCH$_3$, mp 90–90.5°, C, H, Br, S analyses; R = OCH$_3$, mp 67.5–68°, C, H, Br, S analyses.

2-Amino-2'-bromodiphenyl Sulfides (6).—To a solution of SnCl$_2$ (10 g) in 15 ml of HCl was added the 2'-bromo-2-nitrodiphenyl sulfide 5 (4.55 mmol) followed by 15 ml of 95% EtOH. The suspension was heated for 4 hr at 70–80°, cooled to 25°, and extracted three times with 50-ml portions of C$_6$H$_6$, and the combined extracts were dried (MgSO$_4$). The mixture was filtered and the solvent was concentrated in vacuo to afford crude product. Purification was effected by chromatography on Al$_2$O$_3$. The following new sulfides 6 were prepared: R = SCH$_3$, mp 115.5–115.8°, C, H, N analyses; R = OCH$_3$, mp 79–80°, C, H, N analyses.

2,2'-Dibromodiphenyl Sulfides (8).—NaNO$_2$ (0.06 mol) was added in small portions to 29 ml of H$_2$SO$_4$. The mixture was shaken vigorously after each addition. After addition was completed, the mixture was heated to 70° to dissolve the remaining NaNO$_2$ and then was cooled to 15°.

A solution of the 2-amino-2'-bromodiphenyl sulfide 6 (0.055 mol) in 100 ml of glacial HOAc was added slowly to the diazotization solution below 20°. After addition was completed, the flask was rinsed with 36 ml of glacial HOAc. The mixture was stirred for an additional 30 min below 20° and then was added to a suspension of CuBr (10 g) in 40 ml of 48% HBr. The flask was rinsed with two 25-ml portions of glacial HOAc. The mixture was heated for 1 hr at 80°, cooled to 25°, partially neutralized by the slow addition of 100 ml of NH$_4$OH, and extracted three times with 100-ml portions of CHCl$_3$. The combined CHCl$_3$ extracts were washed three times with 50-ml portions of 10% NH$_4$OH and once with 50 ml of H$_2$O and then dried (MgSO$_4$). The mixture was filtered and the solvent was concentrated in vacuo to afford crude product, which was purified by chromatography on Al$_2$O$_3$. The following new sulfides 8 were obtained: R = H, mp 67.5–68°, C, H, Br, S analyses; R = Cl, semisolid, C, H, S analyses; R = SCH$_3$, mp 72°, C, H, Br analyses; R = OCH$_3$, mp 107°, C, H, Br analyses.

Diethyl (3-Dimethylaminopropyl)phosphonate (11).—Sodium diethyl phosphite was prepared by the procedure of Harvey and coworkers,[8] using 0.6 mole of diethyl phosphite. The reaction mixture containing this substance was cooled to 25° while 1-chloro-3-dimethylaminopropane (0.92 mol), generated from the hydrochloride, in 100 ml of PhCH$_3$ was added. The mixture was heated at reflux for 8 hr, and then was cooled to 25°. Excess NaH was hydrolyzed by the dropwise addition of 20 ml of H$_2$O. The mixture was filtered and dried (MgSO$_4$), and the solvent was concentrated in vacuo to afford crude product (113.41 g). This was distilled to give the product (95.12 g), collected at 90–120° (1.0–2.0 mm), lit.[14] bp 83° (0.16 mm).

(12) F. Haefliger [J. Can. Psychiat. Assoc., 4 (Suppl), S69–S74 (1959)] has called attention to the fact that phenothiazines exhibit an additional low-intensity uv band about 300 mμ, which is not present in imipramine. No such band is seen in the phosphine 1. Although the existence of these bands

will have to be kept in mind in future work, it is our opinion that the large changes in molar absorptivity in the 250-mμ band, which apparently results from similar electronic transitions in both species, represent a potentially more useful correlation.

(13) Representative synthetic procedures are noted only for hitherto unreported compounds or where totally new methods were employed. For other substances, observed physical constants agreed with those reported. Melting points were taken in a Thomas–Hoover Unimelt apparatus and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. All analytical samples had ir and nmr spectra in agreement with their assigned structures.

(14) T. C. Myers and A. O. Jibril, J. Org. Chem., 22, 180 (1957).

10-(3-Dimethylamino-1-propyl)-10H-dibenzo[1,4]thiaphosphorin 10-Oxides (2).—To 150 ml of C_6H_{14} and 200 ml of C_6H_6 (both dried over Na) was added a solution of n-BuLi (0.117 mol in hexane) under N_2. To this was added a solution of 2,2'-dibromodiphenyl sulfide (0.05 mole) in 50 ml of C_6H_{14}. After the solution was stirred at 25° for approximately 15 min it became yellow and a white precipitate began to form. The mixture was heated at reflux for 4 hr, and then was cooled to 25°. A solution of diethyl (3-dimethylaminopropyl) phosphonate (0.05 mol) in 50 ml of C_6H_{14} was added. During addition the precipitate dissolved and the yellow solution became deep red. The solution was stirred for 15 hr at 25°, cooled to 0°, and hydrolyzed by the addition of 50 ml of 5% HCl and the layers were separated. The organic layer was extracted twice with 50-ml portions of 5% HCl. The combined acid extracts were washed once with 50 ml of C_6H_{14}, made basic by the addition of 10% NaOH, and extracted with three 50-ml portions of $CHCl_3$, and the combined $CHCl_3$ extracts were dried ($MgSO_4$). The mixture was filtered and the solvent was concentrated *in vacuo* to afford a mixture of the product and starting phosphonate.

The mixture was heated with 50 ml of concentrated HCl for 8 hr at 80°, cooled to 25°, and made basic with 10% NaOH. The suspension was extracted with three 50-ml portions of $CHCl_3$, and the combined $CHCl_3$ extracts were dried ($MgSO_4$). The desiccant was separated by filtration and the solvent was concentrated *in vacuo* to afford still impure product (1.60 g). The impure product was dissolved in 100 ml of C_6H_6 and extracted with three 50-ml portions of 50% HCl, and the combined acid extracts were made basic with 10% NaH. The suspension was extracted with four 50-ml portions of $CHCl_3$ and the combined

$CHCl_3$ extracts were dried ($MgSO_4$). The mixture was filtered and the solvent was concentrated *in vacuo* to afford almost pure semisolid product. Chromatography of this material on Al_2O_3, eluting with C_6H_6–$CHCl_3$ (1:1), gave the product as a semisolid. Attempted drying at 45° *in vacuo* resulted in decomposition. In this way, the following phosphine oxides **10** were obtained: R = H (C, H; N: calcd, 4.18; found, 4.69), R = Cl (H, N; C: calcd, 55.21; found, 54.41), R = SCH_3 (N; C: calcd, 56.67; found, 56.07; H: calcd, 6.34; found, 6.87), R = OCH_3 (C, H, N).

10-(3-Dimethylaminopropyl)-10H-dibenzo[1,4]thiaphosphorin (1).—In a 1-l. flask dried with a flame after assembly was placed a solution of $HSiCl_3$ (0.20 mol) in 180 ml of C_6H_6 (dried over Na). Upon addition of a solution of **2a** (0.13 mol) in 100 ml of C_6H_6, a precipitate formed. The suspension was heated at reflux for 4 hr, cooled to 0°, and hydrolyzed by the dropwise addition of 250 ml of 20% NaOH, and the layers were separated. The aqueous layer was extracted with two 50-ml portions of $CHCl_3$ and the combined organic solutions were dried ($MgSO_4$). The desiccant was separated by filtration and the solvent was concentrated *in vacuo* to afford the crude product (3.80 g). The crude product was extracted with 100 ml of C_6H_{14}, filtered, and concentrated *in vacuo* to afford a residue (3.52 g). This residue was dissolved in 100 ml of C_6H_{14}, cooled to $-20°$ overnight, decanted from an oil which separated, and concentrated *in vacuo* to afford almost pure semisolid product (3.29 g). Chromatography of a portion of this (0.50 g) on Al_2O_3, eluting with C_6H_6–$CHCl_3$ (7:3), afforded the product (0.39 g). *Anal.* N; C: calcd, 65.78; found, 66.27; H: calcd, 6.28; found, 7.27. Attempted drying at 45° *in vacuo* resulted in decomposition.

The Synthesis and Biological Properties of Some Dibenzazepines and Dibenzazonines Related to Protostephanine

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The synthesis and biological properties of some 6,7-dihydro-2,3,8,10-tetramethoxy-5H-dibenz[c,e]azepines, some 6,7,8,9-tetrahydro-5H-dibenz[d,f]azonines, and the 2,3,10,12-tetramethoxy derivatives of the latter, which include protostephanine and its nor derivative, are described.

Recently, a synthesis of protostephanine (**4c**) one of the minor alkaloids of *Stephania japonica* Miers was described.[1,2] This paper reports some of the biological properties of protostephanine and some closely related dibenzazonines and dibenzazepines which were prepared by the scheme shown in Chart I.

2,2'-Bis(2-bromoethyl)-3,4',5,5'-tetramethoxybiphenyl[2] (**1c**) was treated with benzylamine to give 7-benzyl-6,7,8,9-tetrahydro-2,3,10,12-tetramethoxy-5H-dibenz[d,f]azonine (**2c**). Hydrogenolysis of the benzyl group yielded the nor base **3c**, which was methylated reductively[3] to **4c**[4] using formaldehyde and hydrogen. Bromoprotostephanine (**5c**),[5] a compound previously described in the course of degradative experiments on the alkaloid,[6] was also prepared by the action of bromine on **4c** in AcOH. Table I describes the dibenzazonines reported in this paper.

In order to assess the biological effect of the four methoxyl groups in this series, the corresponding unsubstituted 6,7,8,9-tetrahydro-5H-dibenz[d,f]azonines **2b**, **3b**, and **4b** were prepared using the same procedures, but starting with 2,2'-bis(2-bromoethyl)biphenyl[7] (**1b**).

Since **1a** was available as an intermediate for the preparation of **1c**, it was used to prepare[8] 6-benzyl-6,7-dihydro-2,3,8,10-tetramethoxy-5H-dibenz[c,e]azepine (**2a**) which in turn furnished **3a** and **4a**. These compounds are lower homologs of protostephanine and, in addition, since they are tetramethoxy derivatives of the adrenergic blocking agent azapetine phosphate,[9] a consideration of their pharmacology falls rightly within the scope of the present work. Table II summarizes the pertinent physical data on these dibenzazepines.

The dibenzazepines of type **2a** were generally obtained in yields of the order of 80–90% in a mildly exothermic reaction that was complete in approximately 18 hr at room temperature. The products were obtained by distillation of solvent and excess primary amine

(1) B. Pecherer and A. Brossi, *Helv. Chim. Acta*, **49**, 2261 (1966).

(2) B. Pecherer and A. Brossi, *J. Org. Chem.*, **32**, 1053 (1967).

(3) W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).

(4) This incidentally constitutes another synthesis of protostephanine (**4c**). In ref 2, the direct condensation of **1c** with methylamine to give **4c** was reported, but the procedure described here is more convenient and productive of better yields.

(5) Correct name: 13-bromo-6,7,8,9-tetrahydro-2,3,10,12-tetramethoxy-7-methyl-5H-dibenz[d,f]azonine.

(6) H. Kondo, T. Watanabe, and K. Takeda, *Itsuu Kenkyusho Nempo*, **3**, 45 (1952); *Chem. Abstr.*, **47**, 12755 (1953).

(7) K. Mislow, S. Hyden, and H. Schaefer, *J. Am. Chem. Soc.*, **84**, 1449 (1962).

(8) This general procedure for the preparation of 6-substituted 6,7-dihydro-5H-dibenz[c,e]azepines was first used by W. Wenner, *J. Org. Chem.*, **16**, 1475 (1951); **17**, 1451 (1952).

(9) Active ingredient in Ilidar[R].