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®.

TABLE I

6,7,8,9-TETRAHYDRO-5H-DIBENZ[*d*,*f*]AZONINES

Compd	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
2b	Oil	61		$C_{23}H_{23}N$	
2b·HCl	230–231.5 dec	98	Me_2CO	$C_{23}H_{23}N \cdot HCl$	C, H, Cl
2c	Oil	57		$C_{27}H_{31}NO_4$	
2c·HCl	129 dec	92	H_2O	$C_{27}H_{31}NO_4 \cdot HCl$	C, H, N
3b	Oil			$C_{16}H_{17}N$	
3b·HCl	283.5–286 dec	93	*i*-PrOH	$C_{16}H_{17}N \cdot HCl$	C, H, Cl
3c	104–106		60–90° petr ether	$C_{20}H_{25}NO_4$	C, H, N
3c·HCl·*i*-PrOH[a]	125–127	95	*i*-PrOH	$C_{20}H_{25}NO_4 \cdot HCl \cdot C_3H_8O$	C, H, N, Cl
4b[b]	Oil			$C_{17}H_{19}N$	
4b·HCl	256–257 dec	76	*i*-PrOH	$C_{17}H_{19}N \cdot HCl$	C, H, Cl
4c	84.5–86.5	86	Petr ether	$C_{21}H_{27}NO_4$	C, H, N
4c·H_2SO_4	130–132	98	H_2O	$C_{21}H_{27}NO_4 \cdot H_2SO_4$	C, H, N
5c	166.5–168.5[c]	76	EtOH	$C_{21}H_{26}BrNO_4$	

[a] This salt forms a stable 2-propanolate that loses the solvent very slowly at 100° *in vacuo*. The nmr spectrum shows the presence of exactly 1 mole of *i*-PrOH: δ 1.05 [J = 6.5 cps, 6 H, $(CH_3)_2C$], 1.67–2.31 [broad and diffuse, 8 H, $(CH_2CH_2)_2N$], 3.77, 3.79, 3.83, 3.85 (4 CH_3O), 6.32, 6.63, 6.68, 7.05 (4 arom), 8.95 (broad, 2 H, NH_2^+). [b] After this work had been completed, compound **4b** (as the hydrobromide) was described in a paper by K. Kotera, *et al.*, *Shionogi Kenkyusho Nempo*, **17**, 88 (1967). [c] Lit.[6] mp 166–167°.

TABLE II

6,7-DIHYDRO-5H-DIBENZ[*c*,*e*]AZEPINES

Compd	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
2a	147–149	81	Aq *i*-PrOH	$C_{20}H_{27}NO_4$	C, H, N
2a·HCl	256–257 dec	98	*i*-PrOH–Et_2O	$C_{20}H_{27}NO_4 \cdot HCl$	C, H, N, Cl
3a	Oil			$C_{18}H_{21}NO_4$	
3a·HCl	274–276 dec	85	*i*-PrOH–Et_2O	$C_{18}H_{21}NO_4 \cdot HCl$	C, H, N, Cl
4a	179–181	88	Aq EtOH	$C_{19}H_{23}NO_4$	C, H, N
4a·HCl	247–249 dec	80	Aq *i*-PrOH	$C_{19}H_{23}NO_4 \cdot HCl$	C, H, N

after filtering or decanting from the insoluble primary amine hydrobromides. The dibenzazonines (**4b**,**c**) were best prepared by heating the reactants in a suitable solvent at 140–145° for a reaction period of 4–6 hr.[10] Under these conditions, yields of 40–50% were obtained, and in the case of **2b**, 61% has been consistently obtained after a study of the reaction variables. The dibenzazonines were contaminated with a complicated mixture of primary and secondary amines and a fair amount of neutral material that undoubtedly resulted from the formation of vinylbiphenyls and their subsequent polymerizations. The pure tertiary amines were isolated by chromatographic procedures.

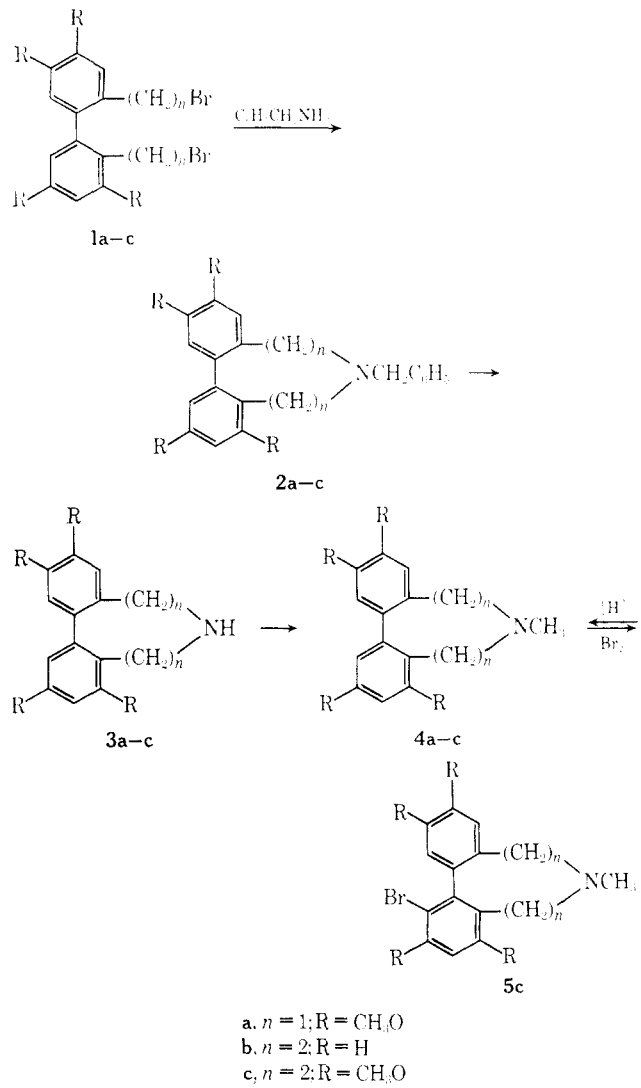
Table III summarizes the biological data which have been obtained for this series of compounds. The alkaloid protostephanine exerts a moderately strong and persistent hypotensive effect. Most of the other compounds show some CNS activity. In the limited series of compounds listed no obvious effect of the methoxyl groups on activity is discernible.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are corrected. Ir were determined on a Beckman IR-5 recording spectrophotometer; nmr spectra were determined on a Varian A-60 spectrometer (TMS) and recorded in parts per million (δ). Where analyses are indicated only by the symbols of the elements, satisfactory analytical results were obtained for those elements within ±0.3% of the theoretical values. The ir and nmr data were consistent with the postulated structures.

General Procedure for the Preparation of a Dibenzazepine. 6-Benzyl-6,7-dihydro-2,3,8,10-tetramethoxy-5H-dibenz[*c*,*e*]azepine (2a) and the Hydrochloride.—Of the methods described by Wenner,[8] the following was preferred for up to 0.5-mole reactions. Ten millimoles of **1a** and 30 mmoles of benzylamine in 75 ml of C_6H_6 were mixed at room temperature. A mildly exothermic reaction ensued with almost immediate separation of benzylamine hydrobromide. After 18 hr, tlc[11] showed that the starting material had disappeared entirely. The precipitate was removed by filtration and the filtrate was freed of solvent and excess benzylamine by distillation [up to 100° (10–15 mm)], leaving a pale

CHART I



(10) There seems to be no evidence of reaction at room temperature.

(11) Performed on silica gel G using EtOH–Et_2O–NH_4OH (90:10:2) as developer.

TABLE III

BIOLOGICAL ACTIVITIES OF SELECTED DIBENZAZEPINES AND DIBENZAZONINES

	Activity, mg/kg[a]									
Compd	Writhing test	Inflamed foot	Antiedema	Hot plate	Anti-obesity	Blood pressure[b]	Anti-bacterial	S180 tumor[c]	Ehrlich tumor[c]	Toxicity[d]
3a·HCl	200 NE	200	100 NE				40 NE	NE	NE	300
3b·HCl	70	50–100	200 NE	39			40 NE	NE	NE	126
3c·HCl·*i*-C_3H_8O	200 NE	200	100	49		−30 (3)	40 NE	NE	NE	158
4a·HCl	80	200 (±)[e]	100	200	25–35	−40 (5)	40 NE	NE	NE	158
4b·HCl	52	200	100 (±)[e]	200 NE		4 NE	40 NE	NE	NE	141
4c·HCl	200 NE	100	100	200 NE	50 NE	−45 (66)	40 NE	25–50 sl[f]	NE	141
5c					50 NE			NE	NE	200

[a] The values in the table are the doses required to elicit an effect in the stated test. A value followed by NE means that no effect was observed at the indicated dose. [b] Effect of a 4-mg dose iv; the value in parentheses is the duration of the effect in minutes. [c] Titrated to the toxic dose. [d] Ip mice. [e] Doubtful response. [f] Dose administered ip; the effect, though weak, was reproducible.

amber syrup that crystallized on cooling. The free base was recrystallized twice from aqueous *i*-PrOH, yield 3.3 g, 81% (CHN). The base was converted by conventional means to the hydrochloride which was recrystallized from *i*-PrOH to constant melting point (CHClN).

General Procedure for the Preparation of a Dibenzazonine. 7-Benzyl-6,7,8,9-tetrahydro-5H-dibenz[*d*,*f*]azonine (2b·HCl).—The dibromide (**1b**) (55.2 g, 0.15 mole) was refluxed with 72.7 g (0.68 mole) of benzylamine in 1 l. of dry xylene[12] for 6 hr. To the cooled suspension, 500 ml of H_2O was added followed by sufficient concentrated HCl to make the mixture distinctly acid whereupon a heavy viscous amber oil separated. The oil and aqueous layers (both under the xylene) were removed and the xylene was washed with three 150-ml portions of 1 *N* HCl. The combined oil and aqueous washes were made alkaline with an excess of 40% NaOH and the oil that separated was collected in three 150-ml portions of C_6H_6. After drying (anhydrous K_2CO_3) and distillation of the solvent at reduced pressure, 44 g of a halogen-free amber syrup remained. This syrup was dissolved in 100 ml of C_6H_6 and the solution was passed over 500 g of alumina.[13] The column was washed with 2.5 l. of C_6H_6. Removal of the solvent from the combined eluates gave 29.8 g of a very pale yellowish syrup which was shown by tlc[11] to be homogeneous. The base was converted to the hydrochloride with *i*-PrOH–HCl and, after two evaporations with *i*-PrOH, an off-white crystalline precipitate was obtained. This salt was dissolved in 75 ml of warm EtOH, 500 ml of Et_2O was added to the solution, and on slow cooling overnight a mass of white crystals was obtained. These were filtered and washed with Et_2O; yield 32 g, 61% (CHCl).

General Procedure for the Hydrogenolysis of 2a, b, or c. Preparation of 6,7-Dihydro-2,3,8,10-tetramethoxy-5H-dibenz[*c*,*e*]azepine (3a·HCl).—The hydrochloride of **2a** (18.4 g, 0.047 mole) was dissolved in 220 ml of HOAc and shaken under 3.16 kg/cm² of H_2 at 60° in the presence of 1 g of 10% Pd-C catalyst. H_2 uptake was complete after 14 hr. The catalyst was removed by filtration and the solvent distilled in the rotary evaporator. After reevaporation with H_2O, a white crystalline residue remained. This was recrystallized from 125 ml of boiling H_2O and yielded 12.3 g, 85% (C,H,N).

Norprotostephanine (3c) was prepared by hydrogenolysis of the base **2c** in HOAc at 30–45°. After removing the catalyst by filtration and distillation of the solvent in the rotary evaporator, a crystalline precipitate was obtained. Slightly more than the stoichiometric amount of concentrated HCl was added, followed by *i*-PrOH, and the mixture was taken to dryness in the rotary evaporator. After two more evaporations with *i*-PrOH the residue was crystalline. Recrystallization from *i*-PrOH gave **3c·HCl** containing 1 mole of *i*-PrOH. The free base prepared from the hydrochloride in the usual way is crystalline.

Protostephanine (4c).—The following procedure is a more convenient variation of the published method.[2] Compound **3c** (as the HCl·*i*-PrOH salt, 2.75 g) was dissolved in 200 ml of HOAc along with 0.7 g of 37% CH_2O and 0.65 g of anhydrous NaOAc. The mixture was shaken under 3.52 kg/cm² of H_2 in the presence of 0.5 g of PtO_2 at 35° for 5.75 hr. After removal of the catalyst by filtration and distillation of the solvent in the rotary evaporator, the free base was isolated in the usual manner. It was dissolved in 20 ml of C_6H_6 and the solution was passed over 20 g of alumina[13] using 200 ml of C_6H_6 to wash the column. From the combined eluates 2.24 g of an oil was obtained. It was dissolved in the minimal amount of 60–90° petroleum ether and when the solution was cooled in an ice bath, there was obtained 1.92 g of protostephanine, 86%, identical (melting point, mixture melting point, and tlc[11]) with that previously described.[2]

13-Bromoprotostephanine (5c).—Protostephanine (1.0 g, 2.8 mmoles) in 15 ml of HOAc was treated with a solution of 0.45 g (2.8 mmoles) of Br_2 in 5 ml of HOAc. After 30 min, the very pale yellow solution was poured into water and 40% NaOH solution was added to pH 11. The gum that separated was dissolved in 20 ml of C_6H_6, and the solution was washed with H_2O to neutrality and dried (K_2CO_3). Distillation of the solvent gave a pale yellow solid that was recrystallized from 25 ml of EtOH to yield very uniform pale buff rhomboids, 0.93 g.

Biological Procedures.—The substances described in this paper were subjected to a variety of biological screening procedures which included the hot plate[14] and writhing test[15] for analgetic properties, the yeast inflamed foot[16] and the carrageenin antiedema[17] test for antiinflammatory activity, and the prevention of tetrabenazine-induced ptosis.[18] Antiappetite effects and blood pressure effects were measured by methods described by Randall, *et al.*[19] In addition, the compounds were screened in mice against the following infections: *Staphylococcus aureus*, *Proteus vulgaris*, *Candida albicans*, *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Coxsackie SK* virus. The effects on tumors, S180 and the solid Ehrlich tumor, were also studied.

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(12) The xylene was dried over anhydrous alumina (Woelm I) for at least 24 hr.

(13) Woelm, grade I.

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