assay (Table II). Compound **1** seemed especially active against the broad range of fungal test organisms. Benzoquinolinediones **2** and **3** also exhibited some antifungal activity, especially against the filamentous fungi *Trichophyton mentagrophytes, Helminthosporium* sp., and *Polyporus sanguineus* (Table II).

The results of the qualitative agar well-diffusion assay prompted a study to determine the minimum inhibitory concentrations (MICs) of each of the active compounds for each susceptible organism. The results of the MIC determinations correlate well with the initial qualitative results. Compound **1** had activity comparable to streptomycin sulfate against all of the bacterial test organisms (Table III). The MIC values for **2** and **3** were comparable to streptomycin sulfate for *B. subtilis* and *S. aureus*, but both **2** and **3** appear to be less active against *M. smegmatis* (Table III).

Based on a comparison of MIC values, compound **1** is at least comparable in antifungal activity to the standard amphotericin B against all of the fungal test organisms (Table IV). The benzoquinolinediones **2** and **3**, however, appear to be slightly less effective than either amphotericin B or compound **1** against most of the fungal test organisms (Table IV).

Benz[*g*]isoquinoline-5,10-dione (**1**) appears to have the most overall activity of the compounds tested for antibacterial and antifungal activity. Benzo[*g*]-quinoline-5,10-dione (**2**), which differs from **1** only in the position of the heterocyclic nitrogen, has a narrower spectrum of activity than **1**, especially as an antifungal agent, but is comparable in its quantitative activity, whereas benzo[*h*]quinoline-5,6-dione (**3**) is less active than either **1** or **2**. Anthraquinone (**4**), which does not possess a nitrogen-containing heterocyclic ring, was essentially inactive. Clearly, the presence of the nitrogen heterocyclic ring is important for antimicrobial activity and both the spectrum and degree of activity appear to be related to the position of the nitrogen in the heterocyclic ring. The antimicrobial activity appears also to be affected by the ring structure and/or quinone system present since **3** was less active than either **1** or **2**.

The antimicrobial activities correlate well with other studies on the biological activities of benzo[*g*]isoquinoline-5,10-dione (**1**) and its benzoquinolinedione isomers (**2, 3**) in which it was found that **1** was the most teratogenic and embryotoxic of the three compounds studied (3). Although the benzoquinolinediones have exhibited some interesting biological activities, there have been as yet no toxicological studies on these compounds.

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Phosphorus GABA Analogues as Potential Prodrugs

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Abstract: Analogues of γ-aminobutyric acid (GABA), wherein a P=O moiety is separated by three carbon atoms from an amino group, were incorporated into Schiff bases as potential acid-labile carrier molecules. These include 3-aminophenylphosphonic acid, its dimethyl ester and its previously unreported *N,N'*-diisopropylphosphonodiamide. A benzophenone derivative of GABA was also synthesized. A study of the degrees of *in vitro* hydrolysis of four Schiff bases indicated that lability of the C=N bond is determined by eletronic influences of ring substituents. All new products were tested for abilities to inhibit maximal electroshock- and subcutaneous pentylenetetrazol (Metrazol)-induced seizures in mice. Activity was found only in the former system with moderate inhibition displayed by two dimethyl ester and the GABA Schiff bases.

Anticonvulsant activity has recently been found to be associated with esters (**1b–1d**) of 3-aminophenylphosphonic acid **1a** (1, 2). In this report we describe the synthesis and testing of an additional derivative **1e** and Schiff bases (anils) **2a–e**, the latter being prepared by the incorporation of **1d** and **1a** into benzylidene derivatives. The 2,2'-dihydroxybenzophenone anil of γ-aminobutyric acid (GABA) **3** was also included in this study. All new products were tested for abilities to inhibit seizures induced in mice by maximal electroshock (MES) and subcutaneously administered pentylenetetrazol (Metrazol) (scMet) and for neurotoxicity. In addition, the degree of *in vitro* hydrolysis of four derivatives was investigated.

Background

The concept of Schiff bases as carrier molecules for biologically active amines has been applied in several previous investigations. Examples of these are cancer chemotherapeutic agents (3–5) and, more recently, in central nervous system (CNS) depressants (6) and GABA and its amide (GABAMIDE) (7, 8). GABA acts as an inhibitory neurotransmitter in the CNS and an

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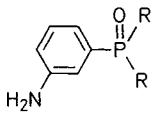
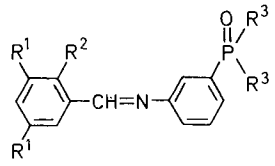


	R
1a	OH
1b	OMe
1c	OEt
1d	OiPr
1e	$NHCH(Me)_2$



	R^1	R^2	R^3
2a	H	OH	$NHCH(Me)_2$
2b	H	OH	OMe
2c	Br	OH	OMe
2d	H	COOH	OMe
2e	H	OH	OH

increase in its concentration in the brain is beneficial in several convulsive disorders. Being very hydrophilic GABA is, however, unable to penetrate the blood-brain barrier (9). In an attempt to transport GABAMIDE into the CNS, where it is supposedly converted into GABA, it has been derivatized as [[4-chlorophenyl) (5-fluoro-2-hydroxyphenyl)-methylene]amino]butamide (progabide) with the expectation that this Schiff base would then hydrolyze with release of the active amine. Certainly increased lipophilicity was achieved in progabide which has calculated log P (octanol/water) value of 3.94[a] and 4.11[b], somewhat in excess of the 2.0 ± 0.7 reported as optimum for CNS-acting agents (10). The prodrug nature of this agent is, however, ambiguous since one report on its activity indicates the appearance of GABA and GABAMIDE in the brain occurring within a few minutes (8) while another states that the conversion requires several hours (7). On both theoretical bases and indirect evidence from this present study the latter phenomenon is most likely.

Previous investigations of the effects of substitution of Schiff bases indicates that electron donating atoms or groups increase hydrolysis (11, 12). Progabide, possessing 2-OH, 3-F and 4′-Cl substituents with σ values of 1.22, 0.34 and 0.24, respectively, is probably quite stable. This is especially true since stability is enhanced by hydrogen bonding between the 2-hydroxyl group and the imino nitrogen (13). This bonding also increases lipophilicity in benzaldehydes and their anils by about 0.88 π[c].

Materials and Methods

Syntheses

Melting points were taken on a Thomas-Hoover apparatus and are corrected to reference standards. IR (KBr) spectra were measured in cm^{-1} on a Perkin-Elmer 283 spectrophotometer. ^1H-NMR spectra were measured in δ units on a Varian Associates FT-80A spectrometer using tetramethylsilane as the internal standard and deuterochloroform (**1e** and **2a–d**), dimethyl sulfoxide-d_6 (**3**) and deuterium oxide-NaOH (**2e**) as the solvents. UV-VIS spectra were recorded on a Perkin-Elmer 200 spectrophotometer using 1 cm cuvettes. A Beckman SS-2 meter was used to measure pH. Elemental analyses were performed for C, H and N on all new compounds by Atlantic Microlab Inc., Atlanta, GA and the results were within ±0.4 % of theoretical. Silica gel 60 (70–230 mesh) and a 25 × 500 mm column was used for chromatography.

N, N′-Diisopropyl-3-aminophenyl-phosphonodiamide (**1e**) – 3-Nitrophenylphosphonic acid was prepared by nitration of phenylphosphonic acid according the procedure of Kosolapoff (14) and converted to the dichloride with PCl_5 using the method of Freedman and Jaffe (15). Isopropylamine (15.3 g, 260 mmole) in CH_2Cl_2 (150 ml) was cooled to 5°C, and 3-nitrophenylphosphonic dichloride (15.6 g, 260 mmole) in CH_2Cl_2 (60 ml) was added dropwise. The reaction mixture was refluxed for three h and stirred overnight at 25°C, filtered and the filtrate rotary-evaporated to remove the solvent. The residue was purified by column chromatography using $CHCl_3$ as the eluant.

Compounds **2a–c** (Method A) – A solution of equimolar amounts of **1e** or **1b** (1) and salicylaldehyde or 3,5-dibromosalicylaldehyde in benzene was refluxed for 2 h after which time a theoretical amount of water collected in a Dean-Stark receiver. The reaction mixtures were rotary-evaporated to remove the benzene and the residues were recrystallized from EtOAc (**2a**) or CH_2Cl_2 (**2c**). **2b** was obtained by evaporation of its ether solution.

Compounds **2d, 2e** and **3** (Method B) – GABA, 3-aminophenylphosphonic acid (16) or **1b** (in 30 ml of benzene) was added to a solution prepared by reacting an equimolar (for **2d** and **3**) or a two-fold molar (for **2e**) quantity of sodium with EtOH or MeOH (for **2e**). An equimolar amount of 2,2′-dihydroxybenzophenone, salicylaldehyde or 2-carboxybenzaldehyde was added, and the mixtures were refluxed for 1–2 h. Rotary-evaporation to remove solvents gave residues which were dissolved in water and acidified with 1 N acetic acid (for **2d**) or citric acid (for **3**). The resulting precipitates in the case of **2d** and **3** were recrystallized from EtOH. For **2e** the solution of the residue was extracted with three-50 ml portions of $CHCl_3$, acidified with 1 N acetic acid and the precipitate washed with water and dried.

Hydrolysis Study

According to the procedure of Hodnett and Tai (5) samples of **2a,2b, 2e** and **3** were weighed and dissolved in a few drops of EtOH and quickly diluted with aqueous buffer (prepared from 0.01 M KH_2PO_4 and adjusted to pH 7.0 with 0.01 M NaOH solution) to make the solutions 2.5×10^{-3} M. The visible spectra were then recorded for samples of these solutions at 25°C. The wavelengths showing the greatest change in absorbance were selected as 440 and 425 nm for **2a** and **2e**, respectively, and the absorbances were recorded at intervals of 5 min for 1 h. The rate constants were calculated from the slopes as selected by the method of least squares. The correlation constants for **2a** and **2e** were 0.993 and 0.998, respectively. Compounds **2b** and **3** showed no changes in absorbance over any portion of their ultraviolet and infrared after several hours.

[a]From diphenylmethane (4.14), double bond (−0.03), aromatic OH (−0.67), aromatic Cl (0.71), aromatic F (0.14), propylamine (0.48), aliphatic amide (−1.71) and intramolecular hydrogen bonding (0.88).

[b]From 2-hydroxybenzophenone (3.53), butyramide (−0.21), aromatic Cl (0.71), aromatic F (0.14) and given the equivalence of O and N.

[c]An average of two calculations: salicylaldehyde (1.69) minus phenol (1.48), to which is added 2-CHO (−0.65) = 0.86 and salicylaldehyde minus benzaldehyde (1.45), to which is added a 2-OH (−0.67) = 0.91.

Anticonvulsant Testing

Anticonvulsant activity and neurological toxicity were evaluated by contractors of the Antiepileptic Drug Development Program administered by the National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, MD according to previously described procedures (17).

Results and Discussion

The Schiff bases were synthesized by two general methods and their physical properties are shown in Table I. The preparation of anils using benzaldehydes without a 2-hydroxyl group was attempted but, as has been previously reported (13), the products were less stable than those possessing this substituent. *o*-Carboxybenzaldehyde was condensed with **1b** with the expectation that the carboxyl group would produce a stabilizing influence in a manner similar to a hydroxyl moiety and this effect was realized in the anil **2d**. Compound **2b** occurred as the monohydrate form while **2e** was isolated as the high melting monosodium salt. The colorless aromatic amines **1a, 1b, 1e** and GABA formed yellow or orange (**2e**) anils with the exception of white **2d**.

Compound **1e** and its anil **2a** were included in this study to ascertain the effect of substitution of P-OH and P-OR groups by a phosphoramide moiety. The P-N bond is subject to acid catalyzed hydrolysis and, similar to GABAMIDE, would be expected to result in conversion *in vivo* to the acid. Thus, **1e** and **2a** are potential prodrug forms of **1a** and **2e**, respectively.

The *in vitro* hydrolysis of **2a, 2b, 2e** and **3** was studied by means of infrared spectroscopy. Compound **2a** and **2e** gave rates of 1.28×10^{-5} and 9.8×10^{-6} $M \cdot min^{-1}$, respectively, while **2b** and **3** displayed no evidence of hydrolysis. Compounds **2a, 2b** and **2e** differ only with regard to the amide, ester and acid nature of the P=O substituent. Their differences in abilities to undergo hydrolysis can be explained on the basis of the electronic effects of these moieties since electron donation favors this reaction. The 3-P (O) $(OH)_2$ group has a Hammett σ value of -0.02 and 0.25 in the PO_3^{-2} and PO_3H^- forms, respectively, while that of 3-P(O)$OCH_3)_2$ is 0.42σ (18). There are no such reported values for a 3-P (O)[NHCH $(CH_3)_2$] or homologous substituents but it should be relatively electron releasing since a 3-$NHCH_3$ is -0.30σ and a 3-P[$N(CH_3)_2$] is -0.03σ, while the presence of the P=O oxygen atom increases the values by about 0.23σ[d]. The stability of **3** towards hydrolysis can be attributed to both the hydrogen bonding and electron attracting (1.22σ each) influences of the 2- and 2′-hydroxyl groups.

The effects of **1e, 2a–e** and **3** in the inhibition of seizures induced in mice by MES and scMet are shown in Table II.The new 3-aminophenylphosphonic acid derivative **1e** was inactive in this test but a degree of anticonvulsant activity was displayed by Schiff bases **2b, 2d** and **3**. The greatest effect was noted with the former two anils which are derivatives of dimethyl 3-aminophenylphosphonate **1b**, the ester previously shown to possess the highest anticonvulsant properties (1). As was the case with the majority of the members of six chemical classes of organophosphorus compounds previously tested, this type of agent gave relatively low toxicities (2). Only **2e** in this present study displayed toxic symptoms during the rotorod test with all four mice dying after one-half hour from respiratory depression at a dose of 600 mg/kg. The amino acid **1a** from which **2e** was derived did not, however, produce toxicity up to four hours at this dose (1).

From the above data it appears that **2b**, unless activated *in vivo* by some mechanism, produces rapid seizure inhibition as the intact molecule. Similarly, unhydrolyzed progabide has been postulated as a form responsible for GABA receptor stimulation (8). It therefore, seems likely that neither drug serves as a prodrug but possesses intrin-

Table I. Physical Properties of **1e, 2a–e** and **3**

Compound	m.p., °C.	Formula	IR Spectra, cm^{-1}	NMR Spectra, δ
1e	146–147	$C_{12}H_{22}N_3OP$	3420, 3320 (NH_2)	1.10 (2d, 12H, $4CH_3$)
			3200 (NH)	3.19 (m, 4H, 2NHCH)
			1600 (arom. C=C)	4.45 (brs, 2H, NH_2)
			1170 (P=O)	6.99–7.17 (m, 4H, Ph)
2a	144–145	$C_{19}H_{26}N_3O_2P$	3400 (OH)	1.14 (d, 12H, $4CH_3$)
			3200 (NH)	2.47 (m, 2H, 2CH)
			1620 (C=N)	3.45 (m, 2H, 2NH)
			1570, 1475 (arom. C=C)	6.93–7.90 (m, 9H, OH, Ph)
			1170 (P=O)	8.65 (s, 1H, CH=N)
2b	44–45	$C_{15}H_{16}NO_4P \cdot H_2O$	3440 (OH)	3.69 (s, 3H, CH_3)
			1620 (C=N)	3.83 (s, 3H, CH_3)
			1590, 1490 (arom. C=C)	6.94–7.80 (m, 9H, OH, Ph)
			1245 (P=O)	8.65 (s, 1H, CH=N)
2c	148–149	$C_{15}H_{14}Br_2NO_4P$	3440 (OH)	3.74 (s, 3H, CH_3)
			1620 (C=N)	3.88 (s, 3H, CH_3)
			1270 (P=O)	7.49–7.79 (m, 7H, OH, Ph)
2d	164–165	$C_{16}H_{16}NO_5P$	3460 (OH)	8.59 (s, 1H, CH=N)
			1740 (C=O)	3.58 (s, 3H, CH_3)
			1605 (C=N)	3.72 (s, 3H, CH_3)
			1590 (arom. C =C)	7.19–7.84
			1240 (P=O)	(m, 1OH, COOH, CH=N, Ph)
2e	>300 (dec.)	$C_{13}H_{12}NO_4PNa$	3450 (OH)	6.65–7.59 (m, 9H, OH, Ph)
			2650, 2350, 1740 (P-OH)	9.70 (s, 1H, CH=N)
			1625 (C=N)	
			1600, 1580 (arom. C=C)	
			1170 (P=O)	
			480 (P–OH)	
3	195–196	$C_{17}H_{17}NO_4$	3200 (OH)	1.61–2.68 (m, 4H, $2CH_2$)
			1670 (C=O)	3.34 (t, 2H, CH_2)
			1610 (C=N)	
			1590, 1500 (arom. C=C)	6.50–7.51 (m, 8H, Ph)

[d] 4-P (O) $(OC_2H_5)_2$, 0.56σ vs. 4-P $(OC_2H_5)_2$, 0.33σ.

Table II. Inhibition of Seizures in Mice by **1e, 2a–e** and **3**

Compound	Anticonvulsant Activity[a]			
	MES[b]		ScMet[c]	
	0.5 h	4 h	0.5 h	4 h
1e	–	–	–	–
2a	–	–	–	–
2b	++	+	–	–
2c	–	–	–	–
2d	++	–	–	–
2e	–	–	–	–
3	+	–	–	–

[a]++ and + indicate activity at 300 and 600 mg/kg, respectively;
– signifies no activity observed at 600 mg/kg.
[b]Maximal electroshock seizure test.
[c]Subcutaneous pentylenetetrazol (Metrazol) seizure threshold test.

sic activity per se based on a comparison of the $\Sigma\sigma^*$ values of approximately 1.74[e] for stable **2b** with regard to the C=N and that of 2.01[f] for progabide. The inactivity displayed by **2c**, the dibromo derivative of active **2b**, and by **3**, the GABA derivative, is difficult to rationalize but this situation may be clarified by subsequent testing involving other *in vitro* and *in vivo* procedures. Compound **2b** may have an excessively high log P value, calculated as 4.40[g], for optimum effect as a centrally acting agent. While this present study constitutes an initial attempt to correlate electronic influences with prodrug activity of GABA and GABA analogue derivatives, there has been no investigation into the effect of hydrophilic-lipophilic balance on the absorption and distribution for these types of agents.

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[e]C_6H_4-2-OH [0.96 σ^* from C_6H_4 (0.75 σ^*) + 2-OH (1.34 σ^*) × 0.4^2] + 3-P (0) $(OCH_3)_2$ (0.42 σ^*) × 0.4^3].
[f]C_6H_4-4-Cl (0.87 σ^*) + C_6H_4-3-F (0.95 σ^*) + 2-OH [0.11 σ^* from OH (1.34 σ^*) × 0.4^2] + $(CH_2)_3C(O)NH_2$ [0.08 σ^* from $(CH_2)_2C(O)NH_2$ (0.19 σ^*) × 0.4].
[g]From salicylaldehyde (1.69), dimethyl phenylphosphonate, two aromatic Br (0.86 each) and given the equivalence of O and N.

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In vitro Metabolism of Bumetanide

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Abstract: A new metabolite of the diuretic drug bumetanide, the 4-[(4′-hydroxy)-phenoxy] analog (**7**), was identified in incubation mixtures of rat liver microsomes. Phenobarbital and clofibrate pretreatment to induce microsomal enzymes changed the relative amounts of the six metabolites formed. Compound **7** was the most prevalent metabolite after clofibrate pretreatment.

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Bumetanide [3-(*n*-butylamino)-4-phenoxy-5-sulfamoylbenzoic acid] (**1**), is a potent high ceiling diuretic belonging to the class of polar water soluble sulfonamides. Its diuretic activity varies greatly in different animal species. The drug is most potent in man and dog, followed by the rabbit, mouse and rat; the decrease in activity is correlated with an increased rate of metabolism (1).

Previous extensive *in vivo* studies in different animal species (2) led to the identification of five metabolites (**2, 3, 4, 5, 6**) (Fig. 1); the rat was the species that shows the highest metabolic rate (3). All of these metabolites are produced by metabolic oxidation of the *n*-butyl chain. These findings and the increased diuretic response to bumetanide in rats treated with several microsomal enzyme inhibitors (4) suggest that this drug is mainly metabolized by the microsomal mixed-function oxygenase system. Metabolites resulting from aromatic hydroxylation, either in the benzoic acid ring or in the phenoxy substituent, have not yet been reported. It has been postulated that electron withdrawing groups (e.g. carboxyl and aminosulfonyl) might be responsible for the lack of metabolic hydroxylation in the benzoic acid ring (5).

However, no explanation exists for the apparent lack of hydroxylation in the phenoxy ring, particularly in the rat,