They were tested against Walker carcinosarcoma 256, Sarcoma 180, Friend virus leukemia, and Lewis lung carcinoma. Available biological data on all of these compounds suggest that they are nontoxic but inactive in the tested systems.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. The analyses were performed by Midwest Microlaboratories, Inc., Indianapolis, Ind. All amines were purified either by distillation or crystallization from appropriate solvents.

1,3-Bis(aralkyl)-2-(N-aryl- or alkylamino)-1,3,2-diazaphosphorine 2-Oxides (Table I).—The synthesis of these compounds is illustrated well by two basic procedures which shall be referred to as procedure A and procedure B.

Procedure A is typified by the synthesis of 1,3-bis(*p*-chlorobenzyl)-2-(N-piperidyl)-1,3,2-diazaphosphorine 2-oxide. 1,3-Bis(*p*-chlorobenzyl)-2-chloro-1,3,2-diazaphosphorine 2-oxide, 5.0 g (0.012 mole), was dissolved in 75 ml of benzene. Piperidine, 2.1 g (0.025 mole), was added dropwise to the refluxing solution over a 20-min period and a precipitate formed at once. After the complete addition of the amine, the reaction mixture was refluxed for 15 min and allowed to cool. The piperidine hydrochloride, 1.38 g (0.011 mole), was collected by filtration. The benzene from the filtrate was removed completely under reduced pressure and the resulting oil was dissolved in a minimum of acetonitrile. After setting for several days at 0°, 4.5 g of white crystals were collected by filtration (mp 110–112°). On recrystallization of a small sample, a pure solid, melting at 111–113° was obtained. The crude yield was 80.5%.

Anal. Calcd for $C_{29}H_{35}Cl_2N_3OP$: N, 9.30. Found: N, 9.46.

Procedure B is illustrated by the preparation of 1,3-bis(*p*-chlorobenzyl)-2-(N-aziridyl)-1,3,2-diazaphosphorine 2-oxide. Aziridine (0.54 g, 0.012 mole), and 2 ml of triethylamine in benzene were added dropwise, over a 15-min period, to a benzene solution of 5.0 g (0.012 mole) of the 1,3-bis(*p*-chlorobenzyl)-2-chloro-1,3,2-diazaphosphorine 2-oxide. A precipitate of triethylamine hydrochloride formed at once and refluxing was continued for 15 min after complete addition of the amine solution. The solid hydrochloride was removed by filtration and the benzene was completely removed under reduced pressure to give 4.0 g (79% yield) of a white solid. The product was recrystallized from acetonitrile to give 3.0 g of pure product in 59% yield, mp 72–74°.

Anal. Calcd for $C_{19}H_{22}Cl_2N_3OP$: N, 10.24. Found: N, 10.14.

Scopoletin, an Antispasmodic Component of *Viburnum opulus* and *prunifolium*

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The genus *Viburnum* contains several notable species, particularly *opulus* and *prunifolium*, which were used in American Indian therapeutics.[1] Their utilization has persisted into recent times[2] but their efficacy has been questioned frequently. We have verified both to have a reasonably high order of antispasmodic activity and that this is due to several compounds.[3]

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(2) "The Dispensatory of the United States of America," A. Osol and G. E. Farrar, Ed., 25th ed, J. B. Lippincott Co., Philadelphia, Pa., 1960.

Until recently[4-6] chemical explorations of *V. opulus* and *V. prunifolium* have been limited and largely inconclusive, especially with respect to biologically active components. Our work on the antispasmodic and cytotoxic components of these plants has required large quantities of extracts and in their fractionation we have obtained crystalline scopoletin from both, a finding contradictory to earlier work.[5]

A determination of whether scopoletin had antispasmodic properties was made using an *in vitro*, estrone-primed and barium chloride stimulated rat uterus preparation.[3] The compound was found to be reasonably active and the average bath concentration required to produce a 50% decrease in contraction amplitude, $1D_{50}$, of single uterine horns was 0.09 mg/ml. A qualitatively similar effect was noted in whole animal experiments utilizing oxytocin- and ergonovine-promoted uterine contractions. The smooth muscle relaxant property of scopoletin is an unusual effect for coumarin compounds, but not surprising in view of the number which show activity as nonspecific vasodilators.[7]

Experimental Section

V. prunifolium.—Root bark (42 kg) was extracted with distilled water in an Eppenbach stirrer. The aqueous filtrate was extracted with CH_2Cl_2 to yield 9.5 g (0.08%) of fluorescent red oil. The crude product was put on a 3 × 7 cm column of 50 g of Woelm activity grade I neutral alumina and eluted with 600 ml of redistilled $CHCl_3$. Evaporation of the solvent gave 5.3 g (0.04%) of bright yellow fluorescent oil. It was dissolved in 50 ml of cold methanol, cooled to 5°, and centrifuged for 15 min to precipitate the waxes. The suspension was filtered to give 4.5 g (0.04%) of oil. It was dissolved in 20 ml of $CHCl_3$, concentrated to 7 ml, and cooled to 5° for 24 hr to yield slightly yellow needles, mp 195–205°. The product was washed with cold $CHCl_3$ and crystallized from 5% methanol-$CHCl_3$ to yield 50 mg (4×10^{-4}%) of scopoletin, mp 210° dec,[8] mp 204–205°,[5] mmp 211°.

V. opulus.—Root bark (22.5 kg) was extracted to yield 126 g (0.56%) of oil. When chromatographed as above 103 g (0.46%) of brown oil was obtained. The crude product was mixed with sand and extracted with petroleum ether (bp 30–50°, alumina purified) for 280 hr. The extract was concentrated to 250 ml, diluted to 500 ml with ethyl ether, cooled to 10°, and extracted with cold 1 *N* NaOH. The extract was immediately acidified with 6 *N* HCl and back extracted with ethyl ether to yield 38.8 g (0.17%) of light brown oil which was refrigerated to precipitate 0.17 g (7.5 × 10^{-3}%) of light yellow scopoletin. On crystallization from methanol–water the melting point was 204.5–205.5°.

Thin Layer Chromatography of Scopoletin.—Purity and completeness of separation were determined using Merck silica gel G and H cast into 20 cm × 17 mil films from 28.5% distilled water slurries. The films were methanol washed by upward development, stored at 100° for 12 hr, desiccated, and then activated for 0.5 hr at 100° just prior to use. The solvent system used was water-saturated ethyl ether; R_f (plate G) 0.28, (plate H) 0.44.

Bioassay of Scopoletin.—Potency was determined using a micro version of the reported method.[3] The total bath volume was 10 ml and regular uterine contractions were induced with just sufficient 1% $BaCl_2$ to produce maximum effect. Scopoletin was dissolved in propylene glycol to give 5 mg/ml and cumulative dose–response experiments were performed. Bath concentrations of 0.025, 0.050, 0.100, and 0.150 mg/ml were used. For each con-

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(7) T. O. Soine, *J. Pharm. Sci.*, **53**, 231 (1964).

(8) W. Karrer, "Konstitution und Vorkommen der Organischen Pflanzenstoffe," Birkhäuser Verlag, Basel, 1958, p 537.

centration 16 relaxation determinations were made; the average values gave a straight line with ID_{50} at 0.09 mg/ml.

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Synthesis of Substituted 2-(2-Biphenylyl)ethylamines as Potential Analgetics[1]

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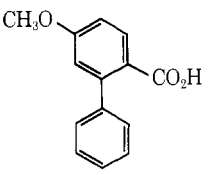
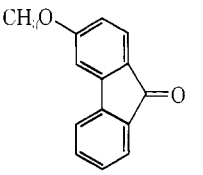
Analgetic activity may be observed with certain aralkylamines, especially with those compounds that may be considered as derivatives of phenethylamine.[2] A special case of this class of compounds is that of β-biphenylylethylamines, which may also be considered as simplified fragments of the morphine molecule.[3] Goldschmidt and Veer[4] have examined a number of simple β-biphenylylethylamines, which failed to show any analgetic activity. It appeared of interest to synthesize some 2-(5-methoxy- and -5-hydroxy-2-biphenylyl)ethylamines; these compounds constitute simplified structures derived from the morphine molecule, an important feature being the presence of the phenolic or ether oxygen *para* to the ethylamine chain.

5-Methoxy-2-biphenylcarboxylic acid (**1**) was used as the starting material for the synthesis of the title compounds. The corresponding demethylated acid, 5-hydroxy-2-biphenylcarboxylic acid, has been obtained by cleavage of 3-hydroxyfluorenone.[5] In a similar manner the acid **1**, mp 173–175°, was prepared by alkali fusion in diphenyl ether[6] of 3-methoxyfluorenone (**2**).[7] The same structure **1** has recently been assigned to an acid, mp 98–103°, obtained by treating 7-bromo-4-methoxy-2-phenyltropone with sodium methoxide.[8] The acid of mp 173–175° is, however, different from the isomer **3**, mp 88–90°,[9] which could also result from cleavage of the fluorenone **2**. An attempt to prepare the acid **1** by alkaline hydrolysis of the known 5-methoxy-2-biphenylcarbonitrile[10] gave a neutral product, identified as being the corresponding amide **4**.[11] This amide was also obtained by treating the chloride of **1** with ammonia, which left no doubt as to the structure attributed to this acid and, accordingly, as to the position of the carboxyl group.



1



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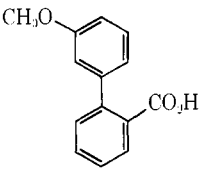
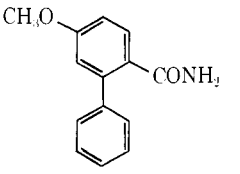
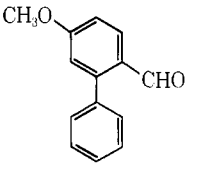


3

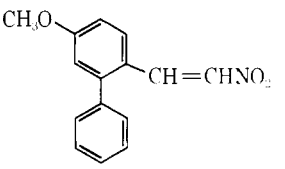


4

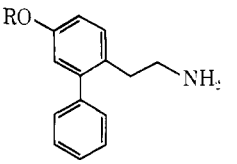
The primary amines **7** and **8** were obtained *via* the aldehyde **5**. The acid **1** was converted into the corresponding aldehyde either by Rosenmund reduction of its chloride, or by decomposition of its benzenesulfonylhydrazide following the method of McFadyen and Stevens.[12] The same aldehyde was also obtained, though in less satisfactory yield, by the method of Stiles and Sisti,[13] starting with 5-methoxy-2-biphenyl iodide[14] (see Experimental Section). The nitrostyrene **6** was readily prepared by the action of nitromethane on the aldehyde **5** and was then reduced by lithium aluminum hydride to the amine **7**, isolated as the hydrochloride. Demethylation of the methoxyamine **7** with hydrobromic acid afforded the phenolic amine **8**.



5



6



7, R = CH_3
8, R = H

The acid **1** was converted, by the Arndt–Eistert reaction, to the ethyl ester of the homologous acid, 5-methoxy-2-biphenylacetic acid. Reduction of the ester with lithium aluminum hydride afforded 2-(5-methoxy-2-biphenylyl)ethanol, which was then converted into the corresponding bromide. Reaction of the bromide with the appropriate amines in alcohol gave the sub-

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