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

Acknowledgments.—The authors are grateful to Dr. V. C. Runeckles, Imperial Tobacco Company of Canada, for authentic scopoletin, to Dr. A. H. Nathan, and to Mr. C. V. Vanderkolk of the Upjohn Company, Kalamazoo, Mich., for extractions. This research was supported by Grant AM 07147 of the National Institutes of Health, U. S. Public Health Service.

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

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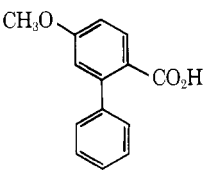
Analgetic activity may be observed with certain aralkylamines, especially with those compounds that may be considered as derivatives of phenethylamine.[2] A special case of this class of compounds is that of β-biphenylylethylamines, which may also be considered as simplified fragments of the morphine 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.



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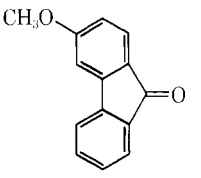

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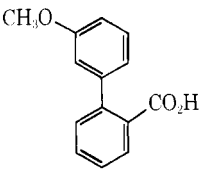

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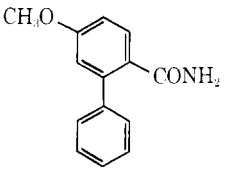

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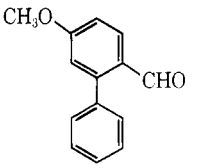
The primary amines **7** and **8** were obtained *via* the aldehyde **5**. The acid **1** was converted into the corresponding aldehyde either by Rosenmund reduction of its chloride, or by decomposition of its benzenesulfonylhydrazide following the method of McFadyen and Stevens.[12] The same aldehyde 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**.



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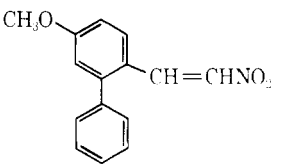

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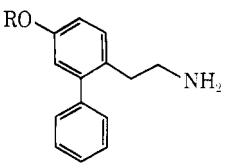

7, R = CH_3
8, R = H

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-

(1) For a preliminary communication of this work see G. Tsatsas, A. Psarrea-Sandris, and C. Sandris, *Compt. Rend.*, **258**, 943 (1964).

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(3) J. Lee, ref 2, p 438.

(4) S. Goldschmidt and W. L. C. Veer, *Rec. Trav. Chim.*, **67**, 489 (1948).

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(11) After the preliminary communication of this work appeared,[1] J. R. E. Hoover, A. W. Chow, R. J. Stedman, N. M. Hall, H. S. Greenberg, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.*, **7**, 245 (1964), reported the preparation of **1**, mp 174–175.5°, by hydrolysis of the corresponding nitrile under more drastic conditions.

(12) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936).

(13) M. Stiles and A. J. Sisti, *J. Org. Chem.*, **25**, 1691 (1960).

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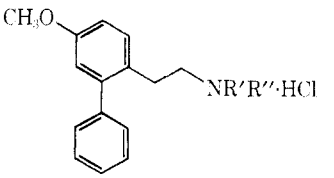
TABLE I
N-SUBSTITUTED 2-(5-METHOXY-2-BIPHENYLYL)ETHYLAMINES (HYDROCHLORIDES)



No.	NR'R''	Yield,[a] %	Mp, °C	Formula	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N
9	Diethylamino	40	161–162	$C_{19}H_{26}ClNO$	71.33	8.20	11.08	4.38	71.22	8.13	11.14	4.43
10	Morpholino	43	200–203	$C_{19}H_{24}ClNO_2$	68.34	7.24	10.62	4.20	68.25	7.27	10.64	4.21
11	Piperidino	34	181–182	$C_{20}H_{26}ClNO$	72.37	7.89	10.69	4.22	72.45	8.02	10.59	4.16
12	Isopropylamino	44	159–160	$C_{18}H_{24}ClNO$	70.70	7.90	11.59	4.58	70.67	7.98	11.78	4.63

[a] Yields refer to analytically pure hydrochlorides.

stituted ethylamines **9–12**, isolated as their hydrochlorides (see Table I).

The LD_{50} of the hydrochlorides of the compounds **7–12**, evaluated on mice, were found to be between 30 and 50 mg/kg. Analgetic activity was examined by the Haffner, and d'Amour and Smith tests. The doses used were equal to one-fifth of the LD_{50}; each product was dissolved in water and the solution was immediately injected subcutaneously. Under these conditions no analgetic effect was noted for any of the compounds tested.

Experimental Section[15]

5-Methoxy-2-biphenylcarboxylic Acid (1).—A mixture of 23.8 g of 3-methoxyfluorenone (**2**),[7] 94 g of KOH pellets, and 330 ml of diphenyl ether was heated at 170–180° during 6 hr with vigorous stirring. To the cooled mixture were added equal volumes of water and ether; after separation of the organic phase, the aqueous phase was acidified with concentrated HCl and extracted twice with ether. The ether extracts were washed with a saturated solution of NaCl, the ether was evaporated, the residue was dissolved in a dilute solution of NaOH, and the solution was treated with charcoal and again acidified with concentrated HCl. The solid formed was extracted with ether and after evaporation of the solvent was recrystallized from ethanol, yielding 11.6 g (45%), mp 173–175° (*cf.* lit.[11] mp 174–175.5°).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.69; H, 5.29. Found: C, 73.50; H, 5.30.

This acid, treated with a cold solution of concentrated H_2SO_4 for 0.5 hr and the solution diluted with water, gave crystals of **3-methoxyfluorenone,** mp and mmp 99° (lit.[7] mp 99°).

5-Methoxy-2-biphenylcarboxamide (4). A. From 5-Methoxy-2-biphenylcarbonitrile.—The nitrile[10] (3 g) was refluxed with 10 ml of 30% alcoholic KOH for 16 hr. After distillation of the alcohol, the residue was taken with water and extracted ($CHCl_3$), the solvent was evaporated, and the solid obtained was recrystallized from ethanol yielding 2.5 g (77%) of a substance, mp 182–183°.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.76; N, 6.16. Found: C, 73.85; H, 5.82; N, 6.48.

The aqueous phase after acidification and extraction with ether gave a small amount of a solid which, recrystallized from ethanol–water, had mp 171°. The melting point was not depressed when mixed with 5-methoxy-2-biphenylcarboxylic acid.

B. From 5-Methoxy-2-biphenylcarboxylic Acid (1).—The acid (0.7 g) was converted into the chloride by reaction with $SOCl_2$. Treatment of the chloride with aqueous ammonia gave a precipitate which was filtered, washed with water, and recrystallized from ethanol; mp and mmp 181–183°.

5-Methoxy-2-biphenylcarboxaldehyde (5). A. From the Chloride of 5-Methoxy-2-biphenylcarboxylic Acid.—The chloride from 6.2 g of **1** was reduced in 30 ml of refluxing xylene with stirring, in the presence of 0.9 g of 5% Pd–$BaSO_4$ catalyst and 0.1 ml of freshly prepared quinoline–sulfur regulator.[16] After cooling, the catalyst was removed by decantation, the solution was treated with charcoal, and the solvent was distilled. The oily residue yielded 3.7 g (64%) of a colorless liquid, bp 147° (1 mm), which solidified, mp 37–38°.

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 78.82; H, 5.67.

B. From the Benzenesulfonylhydrazide of 5-Methoxy-2-biphenylcarboxylic Acid.—Acid **1** (8 g) was esterified with an ethereal solution of diazomethane. After evaporation of the solvent the **methyl ester** was distilled under reduced pressure, bp 150° (2 mm).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.30; H, 5.70.

The methyl ester (8.3 g) was refluxed during 5 hr with 12 g of 98% hydrazine in 15 ml of ethanol. After cooling and addition of water the **hydrazide** was extracted with ether. The oil obtained was not purified further.

Benzenesulfonyl chloride (5.6 g) was added in portions to a stirred solution of the crude hydrazide (7.5 g) in 25 ml of pyridine at 0°. The mixture was allowed to stand overnight and was then poured into a mixture of ice and concentrated HCl. The yellow precipitate formed was filtered and recrystallized from methanol, yielding 9.2 g of the benzenesulfonylhydrazide, mp 216–218°.

Anal. Calcd for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.32. Found: C, 62.80; H, 4.80; N, 7.46.

Anhydrous Na_2CO_3 (13.5 g) was added to the benzenesulfonylhydrazide in 65 ml of ethylene glycol at 160°. After 1 hr, when the initial reaction had subsided, hot water was added, and the mixture cooled. Ether extraction, followed by evaporation of the solvent and distillation under reduced pressure, yielded 4.8 g of the aldehyde **5** (64% yield, based on **1**), mp and mmp 37–38°.

C. From 5-Methoxy-2-biphenyl Iodide.—For the transformation of this iodide to the aldehyde **5** the procedure given by Stiles and Sisti[13] was followed. The iodide[14] (42.6 g) was converted into the corresponding organomagnesium compound and this on reaction with *p*-dimethylaminobenzaldehyde afforded the corresponding **secondary alcohol,** 13.6 g (30%), mp 126–128°, after recrystallization from benzene–petroleum ether (bp 50–70°). A second recrystallization gave an analytical sample, mp 139–140°.

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.40; H, 6.97; N, 4.33.

Decomposition of 7 g of the secondary alcohol by the diazonium salt of sulfanilic acid afforded on distillation 2.65 g (60%) of the aldehyde **5**, mp and mmp 36–38°.

1-Nitro-2-(5-methoxy-2-biphenylyl)ethylene (6).—A mixture of 4.8 g of **5**, 1.2 ml of nitromethane, 0.15 ml of benzylamine, and 12 ml of ethanol was stirred at 50° for 20 hr. After cooling, the solid which separated was filtered and recrystallized from ethanol: 4.0 g (70%), mp 102–104°. The analytical sample, obtained by a second recrystallization from ethanol, had mp 107–109°.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.13; N, 5.48. Found: C, 70.38; H, 5.13; N, 5.37.

2-(5-Methoxy-2-biphenylyl)ethylamine (7).—The nitro compound **6** (3.8 g) was reduced with 2.3 g of $LiAlH_4$ in 150 ml of anhydrous ether. The mixture was refluxed with stirring for 4

(15) Melting point and boiling point values are not corrected.

(16) E. Mosettig and R. Mozingo, *Org. Reactions*, **4**, 368 (1948).

hr and hydrolyzed with 2.3 ml of water, 2.3 ml of a 15% solution of NaOH, and 7 ml of water. The precipitate formed was filtered and thoroughly washed with ether. After drying and evaporation of the ether, the amine was obtained as an oily residue. The **hydrochloride,** formed with an alcoholic solution of HCl, was recrystallized from absolute ethanol yielding 1.95 g (50%), mp 188–189°.

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.31; H, 6.88; N, 5.31. Found: C, 68.08; H, 6.88; N, 5.11.

2-(5-Hydroxy-2-biphenylyl)ethylamine (8).—The hydrochloride (2.2 g) of **7** was refluxed with 33 ml of 48% HBr for 5 hr. After concentration under vacuum, the red oily residue was dissolved in a small amount of water and treated with a saturated solution of $NaHCO_3$. Continuous extraction with ether gave a solid material which was converted into the hydrochloride with an ethereal solution of HCl. After recrystallization from absolute ethanol–anhydrous ether, the **hydrochloride** presented mp 209° dec, yield 1.55 g (74%).

Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.34; H, 6.46; Cl, 14.20; N, 5.60. Found: C, 67.22; H, 6.30; Cl, 14.50; N, 5.40.

Ethyl 5-Methoxy-2-biphenylacetate.—Acid **1** (11.4 g) was transformed into the chloride by reaction with 10 g of oxalyl chloride in 30 ml of benzene. After the usual treatment, the acid chloride was dissolved in 30 ml of anhydrous benzene, and the solution was added dropwise with stirring in a cooled ethereal solution of excess diazomethane. The mixture was left overnight at room temperature and the solvents were evaporated under vacuum. The **diazo ketone** thus obtained, a yellow solid of mp 72–75°, was dissolved in 150 ml of absolute ethanol, the solution was heated at 55–60°, and an alcoholic suspension of Ag_2O (prepared from 2.5 g of $AgNO_3$ and 2 *N* NaOH) was added in portions. The mixture was then refluxed for 15 min, treated with charcoal, and filtered, and the solvent was evaporated. Distillation of the residue yielded 7.8 g of the **ester** (58% yield, based on the acid), bp 184° (2 mm).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.39; H, 6.60.

Saponification of the ester with alcoholic NaOH afforded the corresponding **acid,** mp 114° (lit.[10] mp 115–116°).

2-(5-Methoxy-2-biphenylyl)ethanol.—The above ester (12.7 g) was reduced in 150 ml of anhydrous ether with 4.8 g of $LiAlH_4$. After decomposition of the complex with water and 3% H_2SO_4, the organic phase was separated, the solvent was evaporated and the residue was distilled under reduced pressure yielding 8.95 g (84%) of the alcohol, bp 160° (1 mm).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.02. Found: C, 78.88; H, 7.20.

2-(5-Methoxy-2-biphenylyl)ethyl Bromide.—A solution of 1.4 ml of PBr_3 in 6 ml of benzene was added dropwise in a cooled solution of 8.9 g of 2-(5-methoxy-2-biphenylyl)ethanol in 8 ml of anhydrous benzene. The mixture was kept in an ice bath for 3 hr, then warmed at 60° for 3 hr, cooled, and poured into crushed ice. The organic layer was separated, washed successively with 10% NaOH, 10% HCl, and water, and dried, and the solvent was evaporated. The residue yielded on distillation 7 g (61%) of the bromide, bp 166° (1 mm).

Anal. Calcd for $C_{15}H_{15}BrO$: C, 61.86; H, 5.20; Br, 27.44. Found: C, 62.06; H, 5.09; Br, 27.10.

The method used to prepare the amines **9–12** (see Table I) is illustrated by the following procedure.

N,N-Diethyl-2-(5-methoxy-2-biphenylyl)ethylamine (9).—2-(5-Methoxy-2-biphenylyl)ethyl bromide (3 g) in 20 ml of absolute ethanol was refluxed with 3.7 g of diethylamine for 4 hr. The ethanol was distilled, and the residue was taken up with saturated $NaHCO_3$ and extracted with ether. After washing, drying, and evaporating the ether, the yellow oil was converted into the **hydrochloride** with alcoholic HCl. The salt was recrystallized from absolute ethanol–anhydrous ether; yield 1.3 g of white needles (see Table I).

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Analogs of 2,6-Pyridinedimethanol Bis(N-methylcarbamate)

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Recently, Shimamoto and co-workers have described the pharmacology of a new bradykinin antagonist, 2,6-pyridinedimethanol bis(N-methylcarbamate) ($R_1 = R_2 = CH_3NHCO_2CH_2$ in the general structure of Table I), which exhibited powerful antiatherosclerotic properties when fed orally to rabbits.[1,2] Further studies[3,4] have led to the claim that the compound has beneficial effects on human vascular occlusive diseases associated with atherosclerosis, and that it is useful in the treatment of inflammatory disorders such as rheumatic fever and rheumatoid arthritis.

It should be noted that 2,6-pyridinedimethanol bis(N-methylcarbamate) and related compounds[5] show structural resemblances to a series of substituted-propanol carbamates with antiinflammatory properties.[6] Other pyridinemethanol carbamates have been tested for sedative and anticonvulsive activities.[7]

We have now prepared additional carbamate and urea analogs of 2,6-pyridinedimethanol bis(N-methylcarbamate) and these are listed in Tables I–VI. All the compounds were prepared by standard procedures.

Pharmacology.—All the compounds were found to be inactive when tested orally in rats for possible antiinflammatory activity, using the carrageenin-induced edema technique.[8] Representative compounds of the various structural types were also tested for an inhibitory effect on the reversed passive cutaneous anaphylactic reaction in guinea pigs,[9] with only compounds **29, 50,** and **123** showing activity.

Experimental Section[10]

Unless indicated otherwise, the alcohols, thiols, amines, isocyanates, isothiocyanates, and carbamoyl chlorides used to prepare the carbamates and ureas in Tables I–VI were obtained from commercial sources.

Acyl Isocyanates.—Acetyl isocyanate was prepared from acetyl chloride and silver cyanate.[11] Chloroacetyl isocyanate, butyryl

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(10) Melting points were determined with a variety of equipment and are uncorrected.

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