2-(4-Biphenylyl)ethylamines: Potential Cardiovascular and CNS Agents

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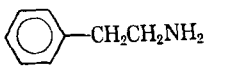
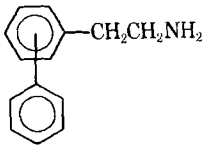
The syntheses of some 2-(4-biphenylyl)ethylamines are described. The results of preliminary pharmacological tests are reported.

MANY NATURALLY occurring substances which incorporate the phenylethylamine (I) or hydrogenated phenylethylamine moieties in their structures possess interesting biological properties. Ephedrine (1), morphine (2), and bulbocapnine (3) are such examples. The latter two substances also contain the biphenylylethylamine (II) group. Whereas extensive investigations (4–6) have been directed toward the synthesis of phenylethylamines, little effort (7, 8) has been expended in studies of biphenylylethylamines. Consequently, it was of interest to



I



II

determine whether compounds such as II possess central nervous system and cardiovascular properties similar to the phenylethylamines. Moreover it was anticipated that some of the biphenylylethylamines would possess CNS effects similar to morphine and/or bulbocapnine.

The synthetic approaches utilized for the preparation of the biphenylylethylamines are outlined in Scheme I.

The biphenylylethylamines (VIII) were prepared by either the reduction of the corresponding nitriles (VII) or the reduction and hydrolysis of phthalimido-ketones (X). The nitriles were obtained from the corresponding amides (VI).

The biphenylylhydroxyethylamines (XII) were prepared from the chloroacetylbiphenyls (IX). The latter were converted to the phthalimido-ketones (X), reduced with sodium borohydride to the phthalimido-alcohols (XI), and then hydrolyzed to the biphenylylhydroxyethylamines (XII). Alternately, the phthalimido-alcohols were synthesized from the corresponding chloro-alcohols (XIII). The latter also were utilized for the preparation of the *N*-isopropyl derivatives (XIV).

Pharmacological Results[1]—Acute effects after intraperitoneal injection of four compounds (X*b*, IV*a*, V*a*, VI*a*) were observed in albino mice. The LD_{50} values ranged from greater than 1.0 Gm./Kg. for IV*a*, to 261 mg./Kg. for V*a*. No deaths were observed for X*b* or for VI*a* at dosages of 2.1 and 1.0 Gm./Kg., respectively. All of these compounds appeared to produce a mild to moderate sedative effect, but none showed hypnotic or anesthetic levels of CNS depression. Higher (and especially lethal) dose levels of V*a* caused excitation and clonic convulsions. Signs of peripheral vasodilation were noted for compound IV*a* at well below toxic dosages. Signs of pain reflex inhibition led to further examination of IV*a* and V*a* by writhing test in mice. The ED_{50}'s for inhibition of writhing were 300 to 400 mg./Kg. for IV*a* and 112 mg./Kg. for V*a*.

Acute effects after oral administration of VIII*b* were observed in albino mice and rats by several methods. The LD_{50} for VIII*b* was 56 mg./Kg. Toxic doses of VIII*b* caused hyperpnea, muscle weakness, mydriasis, and subconvulsive to clonic convulsive manifestations. At low dosage VIII*b* produced a transient hypotensive effect in anesthetized rats, followed by a slight hypertensive effect. Blood pressure response to standard neurohumoral agents was unaffected by VIII*b*. The latter did not show activity in the hot plate analgesia test, the maximal electroshock anticonvulsant test, or an avoidance-escape behavior test. Compound VIII*b* decreased spontaneous motor activity at all dosage levels, but had only slight ability to increase hexobarbital sleeping time.

EXPERIMENTAL[2]

N-[4-(3′-Chloro-4′-methoxy)biphenylylthioacetyl]morpholine (IVa)—A method similar to that of

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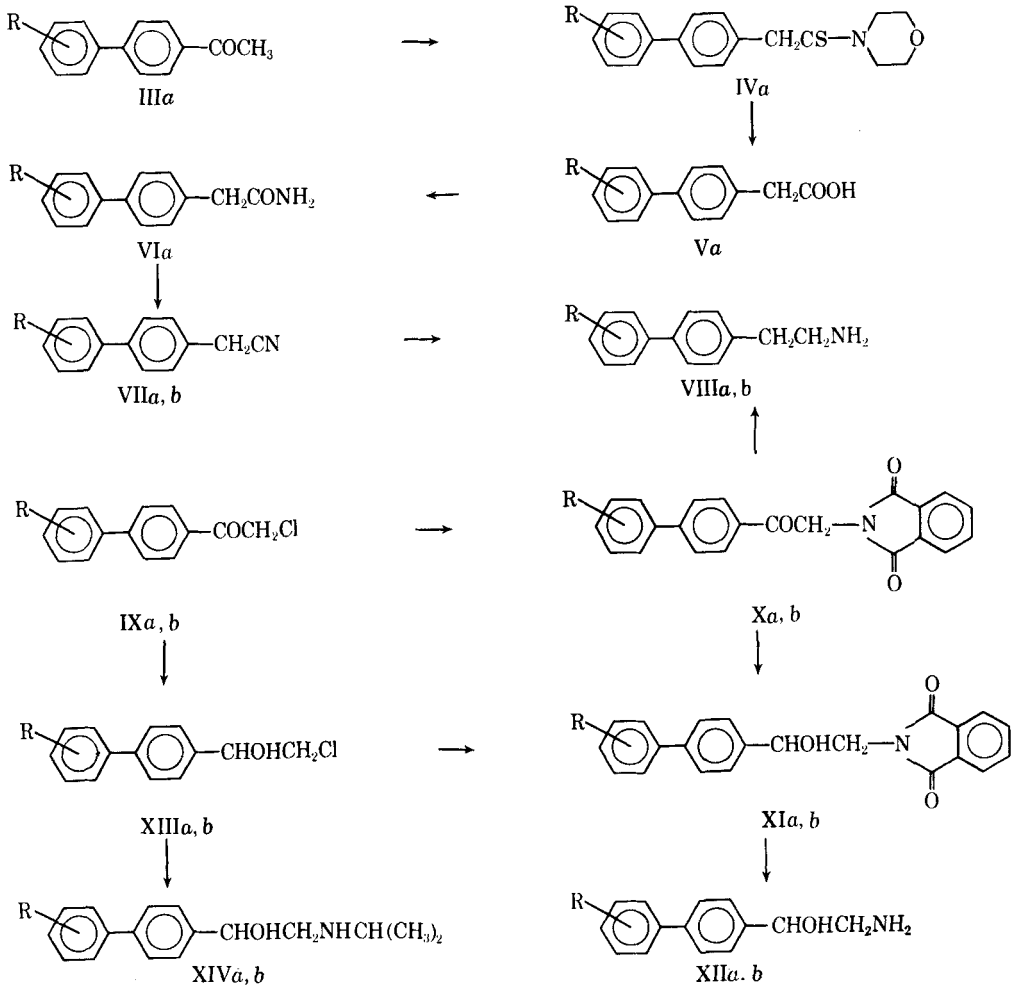
[1] The authors are grateful to Dr. W. Marvin Davis for the pharmacological data of compounds X*b*, IV*a*, V*a*, and VI*a*. Compound No. VIII*b* was evaluated by Hazleton Laboratories, Inc., Falls Church, Va. under contract No. PH 43-63-555 to the Psychopharmacology Service Center.

[2] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137 infracord spectrophotometer using KBr pellets.



Biphenyls (*a* refers to R = 3-chloro-4-methoxy; *b* refers to R = H).

Scheme I

Schwenk and Papa (9) was employed. A mixture of 63.9 Gm. (0.245 mole) of 4-(3-chloro-4-methoxyphenyl)acetophenone (III*a*) (16), 12.5 Gm. (0.4 mole) of sulfur, and 75 ml. of morpholine was heated under reflux for 8 hr. The hot reaction mixture was poured into 300 ml. of methanol and the solid that separated was removed by filtration. The solid was triturated with cold methanol and then recrystallized, $\lambda_{max.}^{KBr}$ 1490, 1260 cm.$^{-1}$.

2-[4-(3′-Chloro-4′-methoxy)biphenylyl]acetic Acid (Va)—A solution consisting of 25.3 Gm. (0.07 mole) of *N*-[4-(3′-chloro-4′-methoxy)biphenylylthioacetyl] morpholine (IV*a*), 16 Gm. of sodium hydroxide, 75 ml. of water, and 110 ml. of ethanol was refluxed for 8 hr. The ethanol was distilled and the residue diluted with water and acidified to pH 2. The solid was removed by filtration, digested with boiling water and recrystallized.

2-[4-(3′-Chloro-4′-methoxy)biphenylyl]acetamide (VIa)—A finely ground mixture of 5.53 Gm. (0.02 mole) of 2-[4-(3′-chloro-4′-methoxy)biphenylyl]acetic acid (V*a*) and 1.52 Gm. (0.02 mole) of thiourea was gradually heated to 200–210° and maintained at this temperature for 1.5 hr. as described by Rehman, Medrano, and Mittal (10). The reaction mixture was cooled, digested with boiling water, and filtered. The brown crystalline solid was triturated with dilute alkali, removed by filtration, and then washed with water. The solid was digested with boiling ethanol, cooled, and removed by filtration; $\lambda_{max.}^{KBr}$ 1640, 1650, 3100, 3280 cm.$^{-1}$.

2-[4-(3′-Chloro-4′-methoxy)biphenylyl]acetonitrile (VIIa)—A mixture of 0.72 Gm. (0.0025 mole) of 2-[4-(3′-chloro-4′-methoxy)biphenylyl] acetamide (VI*a*) and 0.4 Gm. of phosphorus pentoxide was heated at 220–240° in an oil bath for 8 hr. The cooled reaction mixture was extracted with ether. The evaporation of the solvent left 0.15 Gm. (23%) of solid which was recrystallized; $\lambda_{max.}^{KBr}$ 2220 cm.$^{-1}$.

N-(4-Phenylphenacyl)phthalimide (Xa)—The procedure employed was adapted from that described by Sheehan and Bolhofer (11). A solution of 23 Gm. (0.1 mole) of 4-phenylphenacyl chloride in 200 ml. of *N*,*N*-dimethylformamide was treated with 20 Gm. (0.11 mole) of potassium phthalimide. The mixture, after remaining at room temperature for 3 hr., was treated with 500 ml. of water and then extracted with chloroform. The chloroform extract was washed with dilute alkali and water, respectively, and then dried over anhydrous sodium sul-

fate. The solid obtained after distillation of the chloroform solution was washed with ether and recrystallized.

2-(4-Biphenylyl)ethylamine Hydrochloride (VIIIb)—*Method A*—The method described by Nystrom (12) was modified slightly and followed. 4-Biphenylylacetonitrile (13) (7.9 Gm., 0.041 mole) was transferred *via* a Soxhlet extractor into a refluxing mixture of lithium aluminum hydride, anhydrous aluminum chloride, and dry ether (prepared by the rapid addition of a solution of 5.5 Gm. of aluminum chloride in 120 ml. of ether to 2.0 Gm. of lithium aluminum hydride in 80 ml. of ether). The reaction mixture was stirred during and 1 hr. after the transfer of the nitrile into the reaction flask. The reaction mixture, after remaining at room temperature for 16 hr. (during which it was stirred periodically), was treated dropwise with 15 ml. of water and then acidified with 60 ml. of 6 *N* hydrochloric acid. The solid was removed by filtration, washed with ether, and then recrystallized.

Method B—A suspension of 22 Gm. (0.065 mole) of *N*-(4-phenylphenacyl)phthalimide (X*b*) in 350 ml. of methanol was treated with 7.7 ml. of 95% hydrazine and then heated under reflux for 1 hr. The mixture was treated with a methanolic solution of sodium methoxide (prepared from 7.0 Gm. of sodium and 150 ml. of methanol) and then distilled to remove the methanol. Thereafter the mixture was treated with 7.5 ml. of hydrazine and 100 ml. of diethylene glycol. The mixture was refluxed over a free flame for 1 hr. and thereafter the low-boiling material and water were removed by distillation. The reaction mixture was heated to 195–200° and kept at this temperature for 4 hr. The reaction mixture was cooled, diluted with water, and extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulfate. The hydrochloride was prepared in the usual manner and recrystallized. Admixture with the product obtained by Method A showed no depression in the melting point.

4-Phenylstyrene—In the preparation of 2-(4-biphenylyl)ethylamine (Method B) when the heating was continued up to 210–220°, 3.76 Gm. (52%) of a faintly yellow distillate was obtained which solidified. Recrystallization of the solid from methanol gave colorless flakes; m.p. 108–110°, λ_{max}^{KBr} 905, 995, 1625, 2990 cm.$^{-1}$ [lit. (22) m.p. 119°].

Anal.—Calcd. for $C_{14}H_{12}$: C, 93.3; H, 6.7. Found: C, 92.9; H, 6.9.

2-[4-(3′-Chloro-4′-methoxy)biphenylyl]ethylamine (VIIIa)—2-[4-(3′-Chloro-4′-methoxy)biphenylyl]acetonitrile (VII*a*) was reduced with lithium aluminum hydride in the presence of anhydrous aluminum chloride as described for the preparation of 2-(4-biphenylyl)ethylamine (VIII*b*, Method A). The amine was isolated as its sulfate and recrystallized.

α-Chloromethyl-4-biphenylylcarbinol (XIIIb)—A modification of the procedure described by Chaikin and Brown (14) was utilized. To a solution of 4-phenylphenacyl chloride (10 Gm., 0.05 mole) in 125 ml. dioxane were added alternatively and in divided portions 5 Gm. of sodium borohydride and 75 ml. ethanol. The mixture was stirred at room temperature for 18 hr. The solvent was distilled under reduced pressure, the residue was treated with 10% hydrochloric acid, and then exhaustively extracted with chloroform. The extract was washed twice with water and dried over anhydrous sodium sulfate. The solid obtained after removal of chloroform was recrystallized.

N-[2-Hydroxy-2-(4-biphenylyl)ethyl]phthalimide (XIb)—*Method C*—A solution of 1.8 Gm. (0.0077 mole) of α-chloromethyl-4-biphenylylcarbinol (XIII*b*) in 25 ml. of 2-methoxyethanol was treated with 1.5 Gm. of potassium phthalimide and then refluxed for 1 hr. The reaction mixture was cooled and diluted with 150 ml. of water. The solid was removed by filtration, digested with hot methanol, and then recrystallized.

Method D—The procedure described for the preparation of XIII*b* was followed using 7 Gm. (0.02 mole) of *N*-[4-phenylphenacyl]phthalimide, 175 ml. dioxane, 3.5 Gm. of sodium borohydride, and 100 ml. of methanol.

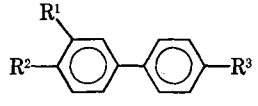
2-Hydroxy-2-(4-biphenylyl)ethylamine Hydrochloride (XIIb)—The procedure employed was adapted from that described by Barber and Wragg (15). A solution of *N*-[2-hydroxy-2-(4-biphenylyl) ethyl]phthalimide (10 Gm., 0.03 mole) in a mixture of 70 ml. chloroform and 70 ml. ethanol was treated with 7 ml. of hydrazine hydrate (50% aqueous solution). The reaction mixture was refluxed for 48 hr. and then left at room temperature for 48 hr. The solvent was distilled under reduced pressure. The residue was stirred for 2 hr. with a mixture of 50 ml. 2 *N* ammonia, 60 ml. of water, and 70 ml. of chloroform. The chloroform layer was separated and extracted with 10% hydrochloric acid. The acid layer was washed twice with chloroform; the solid obtained after distillation of the water under reduced pressure was recrystallized.

α-Isopropylaminomethyl-4-biphenylylcarbinol Hydrochloride (XIVb)—To a solution of α-chloromethyl-4-biphenylylcarbinol (10 Gm., 0.05 mole) in 100 ml. of ethanol was added dropwise a solution containing 1 Gm. of sodium hydroxide, 3 ml. of water, 80 ml. of ethanol, and 15 ml. of isopropylamine. The reaction mixture was stirred at room temperature for 18 hr. The solvent was distilled under reduced pressure and the residue treated with water and exhaustively extracted with ether. The ether extract was washed twice with water and then extracted with 10% hydrochloric acid. The acid layer was concentrated under reduced pressure; the residue was recrystallized.

2-Chloro-4′-(3-chloro-4-methoxy)phenylacetophenone (IXa)—A mixture of 5.5 Gm. (0.025 mole) of 3-chloro-4-methoxybiphenyl (16), 40 ml. of dry carbon disulfide, and 2.4 ml. of chloracetyl chloride was treated with 3.8 Gm. of anhydrous aluminum chloride by a procedure similar to that described by Buu-Hoi, Sy, and Riche (16). The reaction mixture was poured onto crushed ice and the solid that separated was extracted with chloroform. The chloroform extract was washed with an aqueous solution of sodium bicarbonate and thereafter dried over anhydrous magnesium sulfate. The solvent was distilled under reduced pressure and the residual red oil crystallized from ethanol.

N-[4-3′-Chloro-4′-methoxy)phenylphenacyl]-phthalimide (Xa)—The method described by Sheehan and Bolhofer (11) was modified slightly. A solution of 2-chloro-4′-(3-chloro-4-methoxy)phenyl acetophenone (20 Gm., 0.068 mole) in 170 ml. *N,N*-dimethylformamide was treated with 13.6 Gm.

TABLE I—BIPHENYLS



No.	R1	R2	R3	% Yield	M.P.° C. (Recrysn. Solvent)[a]	Molecular Formula	Analysis, % Calcd. C	H	Cl	N	Found C	H	Cl	N
IV*a*	Cl	OCH_3	$CH_2CSNC_4H_8O$[b]	84	152–154 (A)	$C_{19}H_{20}ClNO_2S$[c]	63.0	5.6	9.8	3.9	63.0	5.7	10.0	3.8
V*a*	Cl	OCH_3	CH_2CO_2H	73	167–168 (A)	$C_{15}H_{13}ClO_3$	65.1	4.7	12.8		65.0	4.8	12.8	
VI*a*	Cl	OCH_3	CH_2CONH_2	83	245–247 (D)	$C_{15}H_{14}ClNO_2$	65.3	5.1	12.9	5.1	65.1	5.3	13.0	5.0
VII*a*	Cl	OCH_3	CH_2CN	23	82–83 (M)	$C_{15}H_{12}ClNO$	69.9	4.7	13.8	5.4	69.4	4.8		5.4
VIII*a*	Cl	OCH_3	$(CH_2)_2NH_2$	70	237–240 (W)	$C_{30}H_{34}Cl_2N_2O_6S$[d, e]	58.0	5.5	11.4	4.5	58.0	5.5	11.5	4.6
VIII*b*	H	H	$(CH_2)_2NH_2$	87[f], 13[g]	245 (W)	$C_{14}H_{16}ClN$[h]	71.9	6.9	15.1	6.0	71.9	6.5	15.1	6.0
IX*a*	Cl	OCH_3	$COCH_2Cl$	63	108–110 (E)	$C_{15}H_{12}Cl_2O_2$	61.0	4.1	24.0		60.4	4.3	24.2	
X*a*	Cl	OCH_3	$COCH_2N(CO)_2C_6H_4$[i]	85	239–241 (EA)	$C_{23}H_{16}ClNO_4$	68.1	4.0	8.7	3.5	68.0	4.2	8.6	3.4
X*b*	H	H	$COCH_2N(CO)_2C_6H_4$[i]	31	198–200 (A)	$C_{23}H_{15}NO_3$	77.4	4.4		4.1	77.5	4.4		4.2
XI*a*	Cl	OCH_3	$CHOHCH_2N(CO)_2C_6H_4$[i]	60	186–187 (EA)	$C_{23}H_{18}ClNO_4$	67.7	4.5	8.7	3.4	67.3	4.9	8.9	3.5
XI*b*	H	H	$CHOHCH_2N(CO)_2C_6H_4$[i]	69[j], 13[k]	184.5–185 (AW)	$C_{22}H_{17}NO_3$	77.0	5.0		4.1	76.9	5.6		4.1
XII*a*	Cl	OCH_3	$CHOHCH_2NH_2$	20	180–182 dec. (E)	$C_{16}H_{17}Cl_2NO_2$[h]	57.3	5.5	22.6	4.5	56.8	5.5		4.4
XII*b*	H	H	$CHOHCH_2NH_2$	34	209–211 dec. (E)	$C_{14}H_{16}ClNO$[h]	67.3	6.5	14.2	5.6	7.1	6.6		5.2
XIII*a*	Cl	OCH_3	$CHOHCH_2Cl$	72	92–93 (H)	$C_{15}H_{14}Cl_2O_2$	60.6	4.8	23.9		60.6	4.9	24.1	
XIII*b*	H	H	$CHOHCH_2Cl$	83	78–80 (C)	$C_{14}H_{13}ClO$	72.3	5.6	15.2		72.1	5.4	15.1	
XIV*a*	Cl	OCH_3	$CHOHCH_2NHCH(CH_3)_2$	33	186–188 dec. (E)	$C_{18}H_{23}Cl_2NO_2$[h]	60.7	6.5	19.9	3.9	60.6	6.5	19.7	4.0
XIV*b*	H	H	$CHOHCH_2NHCH(CH_3)_2$	48	175–177 (ER)	$C_{17}H_{22}ClNO$[h]	70.0	7.6	12.2	4.8	69.7	7.7		4.6
XV*a*	Cl	OCH_3	$(CH_2)_2NHCOCH_3$	60	172–174 (MW)	$C_{17}H_{18}ClNO_2$	67.2	6.0	11.7	4.6	67.0	6.2	11.4	4.6
XV*b*	H	H	$(CH_2)_2NHCOCH_3$	90[l]	143–144 (MW)	$C_{16}H_{17}NO$	80.3	7.2		5.9	80.2	7.3		6.0
XVI*a*	Cl	OCH_3	$CH_3CONH(CH_2)_2C_6H_5$	30	144 (E)	$C_{23}H_{22}ClNO_2$	72.7	5.8	9.3	3.7	72.7	5.7	9.2	3.6
XVII*b*	H	H	$(CH_2)_2NHCOCH_2C_6H_5$	49	161–162 (MW)	$C_{22}H_{21}NO$	83.8	6.7		4.4	83.7	6.6		4.6

[a] A = acetic acid; AW = acetic acid–water; C = cyclohexane; D = *N*,*N*-dimethylformamide; E = ethanol; EA = ethyl acetate; ER = ethanol–ether; H = *n*-hexane; M = methanol; MW = methanol–water; W = water. [b] NC_4H_8O = morpholino. [c] Calcd. for S, 8.86; Found, 8.77. [d] Sulfate. [e] Calcd. for S, 5.16; Found, 5.58. [f] Method A. [g] Method B. [h] Hydrochloride. $COCH_2N(CO)_2C_6H_4$ = phthalimido. [j] Method C. [k] Method D. [l] Methods E and F.

(0.073 mole) of potassium phthalimide. The reaction mixture was stirred at room temperature for 18 hr. and then treated with 500 ml. of water. The solid that separated was removed by filtration, washed several times with water, dried, and then recrystallized.

N-{2-Hydroxy-2-[4-(3'-chloro-4'-methoxy)biphenylyl]ethyl}phthalimide (XIa)—The procedure described for the preparation of XIII*b* was followed using 10 Gm. (0.025 mole) of *N*-[4-(3'-chloro-4'-methoxy)phenylphenacyl]phthalimide, 750 ml. of dioxane, 6 Gm. of sodium borohydride, and 250 ml. of methanol.

2-Hydroxy-2-[4-(3'-chloro-4'-methoxy)biphenylyl]ethylamine Hydrochloride (XIIa)—The procedure for the preparation of XII*b* was followed using 1 Gm. (0.002 mole) of *N*-{2-hydroxy-2-[4-(3'-chloro-4'-methoxy)biphenylyl]ethyl}phthalimide, 10 ml. of chloroform, 10 ml. of ethanol, and 1 ml. of hydrazine hydrate (50% aqueous solution).

α-Chloromethyl-4-(3'-chloro-4'-methoxy)biphenylylcarbinol (XIIIa)—The procedure described for the preparation of XIII*b* was followed using 2.95 Gm. (0.01 mole) of 4-(3'-chloro-4'-methoxy)phenylphenacylchloride, 25 ml. of dioxane, 1 Gm. of sodium borohydride, and 15 ml. of methanol.

α-Isopropylaminomethyl-4-(3'-chloro-4'-methoxy)biphenylylcarbinol Hydrochloride (XIVa)—The procedure described for the preparation of XIVb was followed using 4 Gm. (0.013 mole) of α-chloromethyl-4-(3'-chloro-4'-methoxy)biphenylylcarbinol, and 10 ml. of isopropylamine.

N-[2-(4-Biphenylyl)ethyl]acetamide (XVb)—*Method E*—A suspension of 0.1 mole of 2-(4-biphenylyl)ethylamine (VIII*b*) or its hydrochloride in 15% aqueous ethanol, treated with acetic anhydride and sodium acetate, in the usual manner provided the amide.

Method F—A suspension of 19.3 Gm. (0.1 mole) of 4-biphenylylacetonitrile in 50 ml. of freshly distilled acetic anhydride was hydrogenated at 22 p.s.i. with 0.6 Gm. of platinum oxide catalyst according to a modification of the procedure described by Carothers and Jones (17). After 17 hr. the reaction mixture was treated with water; the crystalline solid was collected by filtration and recrystallized.

2-Phenyl-N-(4-biphenylylethyl)acetamide (XVIIb)—A solution of 1.5 Gm. (0.0076 mole) of 2-(4-biphenylyl)ethylamine (VIII*b*) in 5 ml. of pyridine was treated with 2 ml. of phenylacetyl chloride and set aside at room temperature for 25 hr. The amide was isolated in the usual manner and recrystallized.

N-{2-[4-(3'-Chloro-4'-methoxy)biphenylyl]ethyl}acetamide (XVa)—A solution of 0.68 Gm. (0.0026 mole) of 2-[4-(3'-chloro-4'-methoxy)phenylyl]acetonitrile (VII*a*) in 10 ml. of acetic anhydride was hydrogenated at 15 p.s.i. with 0.1 Gm. of platinum oxide catalyst for 12 hr. according to the procedure described for XV*b*, (Method F); $\lambda_{max.}^{KBr}$ 1285, 1545, 1645, 3250 cm.$^{-1}$.

2-[4-3'-Chloro-4'-methoxy)biphenylyl]-N-(phenethyl)acetamide (XVIa)—2-[4-(3'-Chloro-4'-methoxy)biphenylyl]acetyl chloride was prepared in the usual manner from 7.1 Gm. (0.026 mole) of the acid (V*a*) and 7 ml. of redistilled thionyl chloride. A suspension of the acid chloride in 20 ml. of pyridine was treated with 3.2 Gm. of phenethylamine and then allowed to remain at room temperature for 24 hr. The product was isolated in the usual manner.

Pharmacological Tests—Adult male albino mice were utilized for gross symptomologic characterization concurrently with lethality determination. Observations continued for 3–4 hr. after injection and further checks were made daily thereafter for 3 days. Compounds injected intraperitoneally were in aqueous solution or were in acacia suspensions. The one injected intravenously was dissolved in 10% ethanol and the one given orally was suspended in 0.5% methylcellulose. LD_{50} and ED_{50} values were determined using the method and tables of Horn (18).

Blood pressure studies in male albino rats utilized urethan anesthesia, carotid artery cannulation, and recordings *via* a Sanborn pressure transducer.

Analgesia measures used in mice were the benzoquinone writhing test (19) or the hot plate method (20). The standard maximal electroshock testing procedure (21) was utilized. Locomotor activity was recorded in a commercial photocell activity device.

The analytical data for the biphenyls are given in Table I.

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Keyphrases

2-(4-Biphenylyl)ethylamines—synthesis
Pharmacological activity—biphenylethylamines
LD_{50} values—biphenylethylamines
IR spectrophotometry—structure