(1 molar equiv), and Et_3N (2 molar equiv) in anhyd C_6H_6 or CH_2Cl_2 was stirred for several hours. After washing the reaction mixture with H_2O and drying ($MgSO_4$), the organic phase was concd to dryness *in vacuo* to afford the product in 60–95% yield. Solid products were purified by recrystn from appropriate solvents, such as EtOAc, C_6H_6, and heptane. Liquid products were purified by fractionation on a kugelrohr distln apparatus.

The following modification was used with gaseous amines and NH_3. The anhyd amine was introduced into a suspension of the chloroformate·HCl in C_6H_6 for 30 min and the reaction mixture worked up as described above. For the preparation of *N*-unsubstituted carbamates, concd NH_4OH may also be used instead of NH_3 gas.

Procedure B. From 4-Piperidinols.—A 1-substituted or 1,4-disubstituted 4-piperidinol and an isocyanate in molar equivalent amounts were refluxed in anhyd C_6H_6 for 2 hr. Evaporation of the reaction soln *in vacuo* afforded the carbamate in 82–94% yield. The products were purified as in procedure A.

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Some Biphenylene Derivatives with Pharmacophoric Side Chains[1]

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The observation that the sterically strained ring system, [2.2]paracyclophane, served as a favorable matrix for pharmacodynamically active derivatives,[3] turned our attention to another strained ring system, biphenylene. We are describing a number of biphenylene derivatives with typical pharmacophoric side chains, synthesized by traditional methods (see Experimental Section). Preliminary pharmacologic tests[4] of some of the target compounds revealed weak CNS signs but no noteworthy properties.

Experimental Section

Melting points were determined in a Hoover-Thomas capillary melting point bath preheated to 15° below the melting point, and are corrected. Ir spectra were recorded on a Perkin-Elmer spectrophotometer Model 337 (KBr), nmr spectra on a Varian Model A-60 (TMS). Both ir and nmr spectra were taken of all compounds and were as expected. Analyses, performed by Galbraith Laboratories, Knoxville, Tenn., were within ±0.4% of calcd values.

Biphenylen-1- and -2-aldehyde were prepared by improvements over published[5,6] directions, with much better yields.

Biphenylen-1-aldehyde (1).—An Et_2O soln of 1-lithiobiphenylene,[7] from 10 g (0.07 mole) of biphenylene, was cooled to 5°, and 15 g (0.11 mole) of HCONHMe[8] in dry Et_2O was added dropwise. The mixture was refluxed for 3 hr and cooled and 25 g of ice and 50 ml of 2 *N* HCl were added. The Et_2O layer, combined with Et_2O washings, was washed ($NaHCO_3$, H_2O) and then stirred with a 40% $NaHSO_3$ soln for 12 hr. The solid addition product was filtered, washed (Et_2O), decomposed with aq Na_2CO_3 and the aldehyde worked up by ether extraction: yield 4.5 g (36%), mp 51–52° (*cf.* lit.[5] yield, 17%, lit.[6] mp 44°).

Biphenylen-2-aldehyde (2).—The acid chloride from biphenylene-2-carboxylic acid[5] (6 g, 0.03 mole) and $SOCl_2$ was dissolved in Diglyme under N_2 at −70°. A soln of $LiAl(O\text{-}t\text{-}Bu)_3$,[9] from 1.5 g of LAH, 13 ml of *t*-BuOH, and 50 ml of Diglyme, was added slowly over 1 hr. The soln was allowed to warm to 26° and poured into ice, the pptd solid was filtered off, dissolved in Et_2O, stirred with $NaHSO_3$ soln, and worked up as for the 1-isomer; yield 4 g (74%), mp 75–77°; lit.[6] yield <10%, lit.[5] mp 78–79°.

2-(2-Aminopropyl)biphenylene (3).—To a soln of biphenylene-2-aldehyde (**2**, 2 g, 11 mmoles) in a slight excess of $EtNO_2$, 4–5 drops of *n*-$BuNH_2$ was added. The mixture was heated at 90° for 3 hr and cooled until the nitroethene crystallized. This product was filtered off and purified partially by one crystallization from Et_2O–petr ether, mp 107–108°, ir (cm^{-1}) 1645 (C=C), 1520 (NO_2). It was dissolved in dry Et_2O and the soln added dropwise at 0°, under N_2, to a soln of LAH (0.5 g, 13 mmoles) in Et_2O (50 ml). After 10 hr refluxing the mixture was worked up as usual. The HCl salt of **3**, from EtOH–Et_2O, weighed 0.8 g (33%), mp 227–229°. *Anal.* ($C_{15}H_{16}ClN$) C, H.

1-(2-Aminopropyl)biphenylene (4) was prepared analogously from **1** *via* the oily 1-(2-nitro-1-propenyl)biphenylene (ir spectra as expected). The HCl salt of **4** had mp 223–225° from EtOH–Et_2O; yield 20%. *Anal.* ($C_{15}H_{16}ClN\cdot 0.5C_2H_5OH$) C, H.

1-(2-Amino-1-hydroxyethyl)biphenylene (5).—A mixture of 1.8 g (10 mmoles) of aldehyde **1** in enough $MeNO_2$ to effect soln and 2 ml of satd aq $NaHCO_3$ was stirred at 26° for 1 week. Et_2O was added, the layers were separated, and the Et_2O soln was stirred with aq $NaHSO_3$ to remove unchanged **1**. After filtering **1**·$NaHSO_3$ and drying (Na_2SO_4) the Et_2O soln furnished 1.4 g of oily 1-(1-hydroxy-2-nitroethyl)biphenylene [ir (cm^{-1}) 3450 (OH), 1550 (NO_2)] which was reduced in dry Et_2O with LAH (0.13 g, 3 mmoles) at 0°, and then at reflux for 12 hr. Work-up furnished oily **5** which was converted into the HCl salt. Recrystallization gave 0.7 g (28%) of salt, mp 225–228°, ms (70 eV) 211 (M^+). *Anal.* ($C_{14}H_{14}ClNO$) C, H.

The isomeric **2-(2-amino-1-hydroxyethyl)biphenylene (6)** was prepared similarly from aldehyde **2**. The crude oily intermediate 2-(1-hydroxy-2-nitroethyl)biphenylene showed ir 3400 (OH) and 1500 cm^{-1} (NO_2). Crystalline **6**·HCl had mp 209–210° dec (from EtOH–Et_2O), mass spectrum (70 eV) *m/e* 211 (M^+). An analytical sample of the free amino alcohol was obtained from the salt with base, ether extraction, and work-up. The low-melting substance crystallized from Et_2O–C_6H_{14}. *Anal.* ($C_{14}H_{15}NO$) C, H.

2-Chloroacetylbiphenylene (7).—Biphenylene (5 g, 33 mmoles) in 250 ml of CS_2 was added dropwise to a stirred slurry of 5 g of anhyd $AlCl_3$ and 50 g of $ClCH_2COCl$ in 400 ml of dry CS_2. The deep-red mixture was warmed gently for 1 hr but never above 40°. After being stirred for another 15 hr, it was cooled in ice, and 200 ml of 18% HCl was added slowly. The mixture was filtered, the aq layer extd with CS_2, the combined CS_2 solns were washed (H_2O), dried (Na_2SO_4), and evapd. The residual red solid weighed 6 g (80%). It was sublimed (20 mm) to give yellow crystals, mp 134–135°, ir as expected. *Anal.* ($C_{14}H_9ClNO$) C, H.

2-(3-*N*,*N*-Dimethylaminopropionyl)biphenylene (8).—A soln of 1.5 g (7.6 mmoles) of 2-acetylbiphenylene,[7] 0.75 g (9 mmoles) of $Me_2NH_2^+Cl^-$, 0.6 g (20 mmoles) of paraformaldehyde, and 50 ml of *i*-AmOH was refluxed for 45 min. A few drops of ethereal HCl were added, the mixture was cooled to 0° and diluted (Et_2O). The crystals that formed were filtered, washed (a little H_2O, Et_2O), and recrystd (EtOH). The salt, **8**·HCl, had mp 204–205° dec, ir as expected, mass spectrum (70 eV) *m/e* 251 (M^+). *Anal.* ($C_{17}H_{18}ClNO$) C, H.

In one batch of this Mannich reaction, using a large excess of paraformaldehyde, a second material was obtained as the major reaction product. A soln of 5 g (26 mmoles) of 2-acetylbiphenylene, 19.5 g (650 mmoles) of paraformaldehyde, 24.5 g (310 mmoles) of $Me_2NH_2^+Cl^-$, and 150 ml of *i*-AmOH was treated as described in the preparation of **8**. On recrystallization of the crude hydrochloride only a little **8**·HCl pptd out. Concentra-

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(4) These tests were carried out by Smith Kline and French Laboratories. We are grateful for permission to publish their results.

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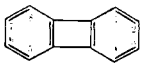
TABLE I

PHARMACOLOGIC PROPERTIES OF SOME BIPHENYLENE DERIVATIVES[a]

Compound No. of base		Dose, mg/kg	Tetrabenazine antagonism	Vehicle	Remarks, number of animals
3	2-$CH_2CH(CH_3)NH_2 \cdot HCl$	200	Yes (ptosis)	PEG + MeC	Slight exophthalmos (3/3), mydriasis (3/3)
8	2-$CO(CH_2)_2NMe_2 \cdot HCl$	200	No	PEG + MeC	No apparent effects (3/3)
12	2-$COCH_2NC_5H_{10} \cdot HCl$	200	No	PEG + MeC	Moderate ptosis (1/3), low posture, moderate decrease in motor activity, bradypnea (1/3), prostration (1/3), intention tremors, dyspnea (1/3), respiratory arrest (1/3), death (1/3), ataxia (2/3), high posture (1/3), slight exophthalmos (2/3), abnormal gait (1/3), weak grasp reflex (1/3), moderate hypothermia (1/3)
13	2-$CHOHCH_2NC_5H_{10} \cdot HCl$	25		PEG + MeC	Slight hypertonia (2/3)
		50			No overt signs (3/3)
		100			High body posture (3/3), fine body tremors (2/3), piloerection (1/3), abnormal gait (2/3), moderate hypersensitivity to touch (3/3), marked salivation (1/3), toe-walking (1/3)
		200	No		Fine body tremors (3/3), high body posture (3/3), moderate hypersensitivity to touch (1/3), abnormal gait (3/3), marked salivation (2/3), marked rhinorrhea (1/3), descended testes (1/3)
14	1-$O(CH_2)_2NEt_2 \cdot HCl$	200	No	H_2O	Slight hypersensitivity (1/3), slight decrease in motor activity (1/3), moderate ptosis (1/3)
15	2-$O(CH_2)_2NEt_2 \cdot HCl$	200	No	EtOH	High body posture (1/3), slight increase in motor activity (1/3), slight exophthalmos (2/3), slight mydriasis (1/3)

[a] All compounds were administered once orally to male Wistar rats (210–275 g), usually at 200 mg/kg, in H_2O or a mixture of 5% polyethylene glycol (PEG 400) and 95% methylcellulose (Methocel). Overt effects and tetrabenazine antagonism were recorded. For the latter effect, one animal of each dose level was injected ip with 15 mg of tetrabenazine/kg 3 hr after dosing. Tetrabenazine is 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-3-isobutyl-2-oxo-11b*H*-benzo[*a*]quinolizine.

ion of the EtOH–Et_2O mother liquors furnished 1.5 g of a yellow crystalline material which was (erroneously, *vide infra*) believed to be more **8**·HCl and was reduced directly with 0.3 g (8 mmoles) of LAH in dry Et_2O for 1 hr. After the usual work-up by decomposition with H_2O, drying (Na_2SO_4), and *acidification* with Et_2O–HCl, 0.8 g of a salt was obtained, mp 205–208° (from EtOH–Et_2O), mass spectrum (70 eV) *m/e* 283 (M^+). *Anal.* ($C_{18}H_{19}Cl_2N$): calcd C, 67.51; H, 5.97. Found, C, 67.61; H, 6.25.

This salt must be 2-(1-chloro-2-methylene-3-dimethylaminopropyl)biphenylene·HCl (**9**) (Ar = 2-biphenylyl). It must

$$\underset{\mathbf{9}}{ArCHClC(=CH_2)CH_2NMe_2 \cdot HCl} \xrightarrow{NaOH} ArCHOHC(=CH_2)CH_2NMe_2$$

10

have originated from the Mannich product, $ArCOCH(CH_2NMe_2)_2$ by LAH reduction which effected both reduction of the keto group (*cf.* **13**) and deamination in the alkaline medium.[10]

When an aq soln of **9** was made basic with 10% NaOH, the amino alcohol **10** was obtained in 50% yield, mp 84–85°; *m/e* (70 eV) 265 (M^+). *Anal.* ($C_{18}H_{19}NO$): calcd C, 81.47; H, 7.21. Found: C, 80.95; H, 7.48.

2-(3-Dimethylamino-1-hydroxypropyl)biphenylene (**11**).—The base **8** was reduced with LAH as described for the reduction of **13** below. The resulting amino alcohol **11** was converted into its HCl salt in Et_2O; yield 55%, mp 170–171° dec (from EtOH–Et_2O); *m/e* (70 eV) 253 (M^+). *Anal.* ($C_{17}H_{20}ClNO$) C, H.

2-Piperidinoacetylbiphenylene (**12**).—A soln of 7 (2.5 g, 11 mmoles) and 2 ml of piperidine in dry C_6H_6 was allowed to stand overnight, filtered from pptd piperidine·HCl, and washed (H_2O). Shaking the C_6H_6 soln with 10% aq HCl gave a yellow ppt (3.1 g, 88%) of **12**·HCl. The free base, liberated with NaOH in H_2O, was recrystd from Et_2O–pet ether, mp 112–114°. *Anal.* ($C_{19}H_{19}NO$) C, H.

2-(1-Hydroxy-2-piperidinoethyl)biphenylene (**13**).—To a soln of LAH (0.2 g, 5 mmoles) in dry Et_2O was added dropwise, at 0° under N_2, a soln of 1.1 g (4 mmoles) of **10** in 40 ml of Et_2O. After stirring at 26° for 1 hr, H_2O was added, and the Et_2O soln was filtered, dried (Na_2SO_4), and worked up. Ethereal HCl pptd 0.7 g (56%) of **13**·HCl, mp 230–232° (from EtOH–Et_2O). *Anal.* ($C_{19}H_{22}ClNO$) C, H.

1-(2-Diethylaminoethoxy)biphenylene (**14**).—A mixture of 1-hydroxybiphenylene[9] (2.5 g, 15 mmoles), NaH (1 g, 20 mmoles, 50% in mineral oil), and 50 ml of dry PhMe was refluxed for 5 hr, and then cooled. A soln of 2.5 g (20 mmoles) of $Et_2N(CH_2)_2Cl$ in dry PhMe was added, and the mixture stirred and refluxed for 19 hr. It was decompd with ice–dil HCl and extd (Et_2O). The aq layer was made basic (10% NaOH) and the product extd into Et_2O, dried, and worked up. The oily base was converted into the hydrochloride in dry Et_2O, yield 1.5 g (33%), mp 145–147° (from EtOH–Et_2O), *m/e* (70 eV) 267 (M^+). *Anal.* ($C_{18}H_{22}ClNO$) C, H.

2-(2-Diethylaminoethoxy)biphenylene (**15**) was prepared similarly from 2-hydroxybiphenylene.[11] The salt **15**·HCl crystallized from EtOH–Et_2O, mp 135–136.5°, *m/e* (15 eV) 267 (M^+), yield 31%. *Anal.* ($C_{18}H_{22}ClNO$) C, H.

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