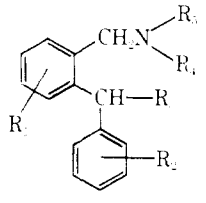

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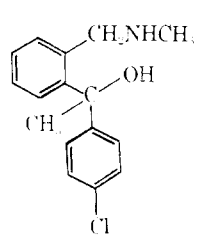

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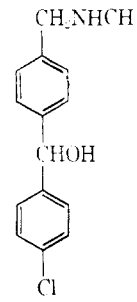

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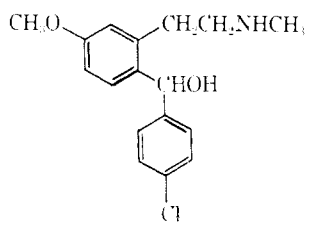

37

in pyridine (135 ml) with $PhSO_2Cl$ (5.4 g) in the usual way. The crude sulfonamide (9 g) was methylated with MeI (4.5 g) in EtOH (100 ml) in the presence of 2 g of NaOH (60°, 4 hr): yield 5.6 g (43%); mp 108–109° (EtOH). *Anal.* ($C_{29}H_{30}ClNO_3S$) C, H, Cl, N, S.

4-Chloro-4′-methylaminomethylbenzhydrol.—The above benzenesulfonylamine (15.5 g) was heated in a mixture of 150 ml of concd H_2SO_4 plus H_2O (60 ml) at a bath temp of 180° for 2.5 hr. The mixture was poured on ice, made alkaline with concd NaOH, and extracted with five 200-ml portions of EtOAc. The extract was purified on silica using $CHCl_3$–MeOH–NH_3, 90:9:1, as eluent. The fraction corresponding to a tlc R_F value 0.3, consisting of 4-chloro-4′-(methylaminomethyl)benzophenone, was reduced with LAH (THF) in the usual way: yield 3.5 g (30%); hydrochloride, mp 203°. *Anal.* ($C_{15}H_{16}ClNO \cdot HCl$) C, H, Cl, N.

4-Chloro-2′-(2-methylaminoethyl)-4′-methoxybenzhydrol (37).—A mixture of 75 g of 1-*p*-chlorophenyl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline ($C_{17}H_{18}ClNO$, mp 95°, prepd by Pictet–Spengler synthesis, followed by N-methylation) and 750 ml of Ac_2O was refluxed for 45 min. The mixture was dec on ice–NH_3 and worked up in the usual way. The resulting pale oil [99 g, 97%; *N,O*-diacetyl-4-chloro-4′-methoxy-2′-(methylaminoethyl)benzhydrol, bp 230° (0.005 mm)] was used without purification for the following step.

A mixture of 50 g of the diacetyl compd, 500 ml of *n*-PrOH, and 200 ml of 50% KOH was refluxed for 18 hr. After cooling the solution was dild with H_2O (500 ml), satd with NaCl, and extd with EtOAc. The residue crystallized from Me_2CO: yield 33 g (84%); mp 110°. *Anal.* ($C_{17}H_{20}ClNO_2$) C, H, Cl, N.

Anorectic Activity, Inhibition of Food Consumption in Trained Rats.—Sprague–Dawley male rats (80 ± 10 g) were preconditioned to a daily 4-hr feeding period (11 AM–3 PM). The rats were grouped 3 to a cage; H_2O *ad libitum*. The food was presented in the form of a wet paste prepared from powdered Purina Laboratory Chow. The amount of food consumed was measured by weighing the containers before and after the 4-hr feeding period. This feeding schedule was maintained until the daily food consumption per group did not vary more than 5 g. The rats weighed 120 ± 10 g after 8 days of conditioning.

The food consumption of each group on the day prior to drug testing was taken as the control value for that group. The food consumption on the test day was measured and expressed as a per cent of the control value. Two untreated groups of 3 rats each, served as controls on each test day. Two test groups of 3 rats were used for each dosage point. The drug was administered in H_2O by gavage 1 hr prior to the feeding period.

Table I shows the results of several known anorectics and of **9** in this method. The relative anorectic potencies of a number of benzhydrols in relation to **9** (=1) are shown in Table II. A (−) indicates that reduction in food consumption was less than 20% in doses approaching toxicity.

Results and Discussion

Among the variations in R_2, only those with Cl, F, CF_3, and, to some extent, MeS groups show activity. Minor structural changes lead to abolition of anorectic activity. For instance, primary or tertiary amines of this series do not affect the feeding behavior of rats. Interestingly, variations, which in the sympathomimetic amphetamine series lead to increased or prolonged activity, *e.g.*, carbamate formation, result also in loss of activity. The same is true for the homolog **37**, which—as an ortho-substituted phenethylamine—could have been expected to be active, (even though it is not strictly comparable with **9** because of its MeO group). These results indicate, that the mechanism of action of these new appetite suppressants differs significantly from the classical anorexigenic agents. This is borne out also by the detailed pharmacology of **5** and **9**.[6]

Acknowledgment.—The authors are grateful for the technical assistance of Mrs. A. Thomas, Miss E. Dubois, Mr. A. Bauer, and Mr. K. Grozinger.

Tranquilizing Drugs. Carbamates of 4-(4-Hydroxypiperidino)-4′-fluorobutyrophenone and Analogs

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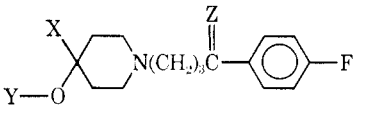
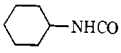
In the course of other work we had occasion to synthesize 4-(4-hydroxypiperidino)-4′-fluorobutyrophenone (**1**) which produced some interesting CNS effects in mice, such as behavioral depression, muscle relaxation, and blockade of the conditioned avoidance response (CAR) and escape response (ER) at oral doses of 50 and >200 mg/kg, respectively. Clinically **1** failed to live up to its animal activity spectrum and was essentially devoid of any useful therapeutic properties even in high doses.[1] We felt that metabolism of the secondary OH, such as oxidation might account for this discrepancy between animal and human data and, therefore, proceeded with the synthesis of "protected" OH derivatives in the form of their carbamates and tertiary alcohols, which would be resistant to metabolic degradation.

The tertiary alcohols **3** and **4** were prepared by alkylating 4-methyl-4-piperidinol with 4-chloro-4′-fluorobutyrophenone and 4-chloro-1,1-ethylenedioxy-1-(*p*-

(1) D. M. Gallant, M. P. Bishop, and R. Guerrero-Figueroa, *Curr. Ther. Res.*, **10**, 244 (1968).

TABLE I
CARBAMATES AND PARENT ALCOHOLS[a]



Compd	X	Y	Z	Formula	Mp or bp(mm), °C	Minimal effective dose (MED_{50}) in mice, mg/kg CAR block	ER block
1	H	H	O	$C_{15}H_{20}FNO_2$	88	50	200
2	H	H	$(CH_2O)_2$	$C_{18}H_{25}FN_2O_4$	115–117	5	10
3	Me	H	O	$C_{16}H_{22}FNO_2$	80.5–82	5	20
4	Me	H	$(CH_2O)_2$	$C_{18}H_{26}FNO_3$	130 (0.002)[b]	10	20
5	*m*-$CF_3C_6H_4$	H	O			0.5	5–10
6	H	NH_2CO	O	$C_{16}H_{21}FN_2O_3$	152–154	10	40
7	H	MeNHCO	O	$C_{17}H_{23}FN_2O_3$	97–98	5	10
8	H	EtNHCO	O	$C_{18}H_{25}FN_2O_3$	103.5–104.5	10	50
9	H	*i*-PrNHCO	O	$C_{19}H_{27}FN_2O_3$	105–105.5	1.6 4.1 (rats)	120 35 (rats)
10[c]	H	*i*-PrNHCO	$(CH_2O)_2$	$C_{25}H_{35}FN_2O_8$	180–182	5	40
11	Me	*i*-PrNHCO	O	$C_{20}H_{29}FN_2O_3$	89–90	6	25–50
12[c]	Me	*i*-PrNHCO	$(CH_2O)_2$	$C_{26}H_{37}FN_2O_8$	182–183 dec	2	25
13	H	*n*-BuNHCO	O	$C_{20}H_{29}FN_2O_3$	87–88.5	15	40
14	H	CH_2=$CHCH_2NHCO$	O	$C_{19}H_{25}FN_2O_3$	93.5–94	10	50
15	H	CH≡CCH_2NHCO	O	$C_{19}H_{23}FN_2O_3$	119–120	6	25
16	H		O	$C_{22}H_{31}FN_2O_3$	121–122.5	20	75
17	H	*m*-ClC_6H_4NHCO	O	$C_{22}H_{24}ClFN_2O_3$	125–126	50	50
18	H	*p*-ClC_6H_4NHCO	O	$C_{22}H_{24}ClFN_2O_3$	135–137	50	100
19	H	*p*-$NO_2C_6H_4NHCO$	O	$C_{22}H_{24}FN_3O_5$	154–155	10	20
20	H		O	$C_{20}H_{27}FN_2O_4$	175–180 (0.4)[b]	50	50

[a] Satisfactory analyses on C, H, and N were obtained for all of these compounds. [b] Temperatures given are not true boiling points but those of the air bath, at which the materials were collected. [c] As hydrogen fumarate.

fluorophenyl)butane, respectively. The carbamates were synthesized by two general procedures: (A) conversion of an alcohol into the chloroformate, followed by treatment with an amine; and (B) reaction of an alcohol with an isocyanate. Method A is particularly practical where an isocyanate is not available.

A large number of *N*-alkyl, *N*-alicyclic, *N*-aryl carbamates, and carbamates derived from heterocyclic secondary amines were synthesized and tested orally in mice, and in some instances in rats. The CNS activities of the carbamates decrease with increase in the bulk of the N-substituents in the alkyl, alicyclic, and heterocyclic amine series. The *N*-arylcarbamates do not produce any significant activities at all. Some typical compounds are given in Table I.

The carbamate of **1** in blocking the CAR and ER in rats with a fourfold dosage spread between the two types of activities. Optimum activities were obtained with the *N*-isopropylcarbamate **9**, which was 12 times as active as **1** in the CAR test and exhibited a ninefold dosage spread in the avoidance and escape response tests. Any of the other molecular modifications failed to approach **9** in activity by rather wide margins.

The tertiary alcohol **3** was 10 times as potent as the secondary alcohol **1**. Interestingly, the *N*-isopropylcarbamate of **3** (**11**) did not produce any further increase in potency as had been the case for the *N*-isopropylcarbamate of **1** (**9**). This would tend to indicate that the secondary alcohol **1** is possibly more susceptible to metabolic degradation than either the tertiary alcohol **3** or the carbamate **9**.

Of all active carbamates, **9** appeared to have the most desirable activity spectrum in that CAR block occurred at doses well below those required to produce behavioral depression, muscle relaxation, blockade of escape response, and hypotension. In that sense, the compound resembled trifluperidol (**5**), although its MED_{50} was 10 times that of the latter.[2]

Compound **9** has now been tested in a limited number of severely chronic schizophrenic patients by Gallant, *et al.*,[3] and found to be effective in the therapeutic dosage range of 100–200 mg daily. It was said to produce only mild side effects in the studies. Similar results are also reported by Sugerman,[4] and by Angus, *et al.*[5]

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt and are uncorrected. Microanalyses were conducted by the Aldrich Analytical Division on an F and M Model 185 CHN analyzer.

4-Piperidyl Chloroformate Hydrochlorides.—A soln of a 1-substituted or 1,4-disubstituted 4-piperidinol in anhyd C_6H_6 or PhMe was rapidly satd with $COCl_2$, and the mixture stirred for several hours. The pptd product was collected, washed with the same solvent, and dried at reduced pressure.

Carbamates. Procedure A. From 4-Piperidyl Chloroformates.—A mixture of a chloroformate·HCl prepd above, an amine

(2) A comparison of these two compounds has been reported by R. Guerrero-Figueroa, M. M. Rye, D. M. Gallant, and C. L. Morse, *Curr. Ther. Res.*, **11**, 121 (1969).

(3) D. M. Gallant, M. P. Bishop, R. Guerrero-Figueroa, and L. O'Meallie, *ibid.*, **11**, 456 (1969).

(4) A. A. Sugerman, *ibid.*, **11**, 775 (1969).

(5) J. W. S. Angus, S.-H. Go, and G. M. Simpson, *ibid.*, **11**, 779 (1969).

(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 recrystaln 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.

Acknowledgment.—We thank Mr. John F. Hoops and Mrs. Margaret M. Weber for their valuable technical assistance.

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.[5] mp 44°).

Biphenylen-2-aldehyde (2).—The acid chloride from biphenylene-2-carboxylic acid[7] (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.[5] yield <10%, lit.[5] mp 78–79°.

2-(2-Aminopropyl)biphenylene (3).—To a soln of biphenylen-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°, *m/e* (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.* ($C_{14}H_{13}NO$) 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-

(1) Supported by Grant GM-12781 from the National Institute of General Medicine, National Institutes of Health.

(2) (a) To whom all inquiries should be addressed; (b) National Defense Education Act Fellow, 1966–1969.

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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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