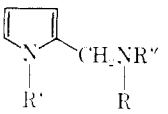
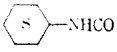
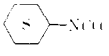
TABLE I



No.	R	R′	R″	Pyrrole compd	Electrophile	Method[a]	Mp, °C	Recrystn solvent	% yield	Formula	Activity[b]
3	CH_2CO	H	CH_3	1a	$(CH_3CO)_2O$	D	74–76	Et_2O	56	$C_8H_{12}N_2O$	+ +
4	C_6H_5CO	H	CH_3	1a	C_6H_5COCl	A	87–89	Et_2O	59	$C_{13}H_{14}N_2O$	+ +
5	*p*-ClC_6H_4CO	H	CH_3	1a	*p*-ClC_6H_4COCl	A	146–147	EtOH	22	$C_{13}H_{13}ClN_2O$	−
6	*p*-FC_6H_4CO	H	CH_3	1a	*p*-FC_6H_4COCl	A	141–143	EtOH	49	$C_{13}H_{13}FN_2O$	−
7	3,4,5-$(CH_3O)_3C_6H_2CO$	H	CH_3	1a	3,4,5-$(CH_3O)_3C_6H_2COCl$	A	122–124	EtOH	76	$C_{16}H_{20}N_2O_4$	+
8	$C_6H_5CH_2CO$	H	CH_3	1a	$C_6H_5CH_2COCl$	A	87–89	EtOH	29	$C_{14}H_{16}N_2O$	−
9	$(C_6H_5)(CH_3CO_2)CHCO$	H	CH_3	1a	$(C_6H_5)(CH_3CO_2)CHCOCl$	A	117–119	Et_2O–cyclohexane	77	$C_{16}H_{18}N_2O_3$	−
10	C_2H_5OCO	H	CH_3	1a	C_2H_5OCOCl	A	Oil		31	$C_9H_{12}N_2O_2$	+ +
11	*p*-$CH_3C_6H_4SO_2$	H	CH_3	1a	*p*-$CH_3C_6H_4SO_2Cl$	A	86–88	EtOH	61	$C_{13}H_{16}N_2O_2S$	−
12	C_6H_5NHCO	H	CH_3	1a	C_6H_5NCO	B	78–81	Et_2O–petr ether	48	$C_{13}H_{13}N_3O$	+ +
13	$CH_3(CH_2)_4NHCO$	H	CH_3	1a	$CH_3(CH_2)_4NCO$	B	43–45	Et_2O–cyclohexane	79	$C_{13}H_{23}N_3O$	+
14		H	CH_3	1a		B	105–107	Et_2O	87	$C_{14}H_{13}N_3O$	−
15	C_6H_5NHCS	H	CH_3	1a	C_6H_5NCS	B	132–134		86	$C_{13}H_{13}N_3S$	−
16	$CH_3(CH_2)_4NHCS$	H	CH_3	1a	$CH_3(CH_2)_4NCS$	B	54–55	Et_2O–petr ether	51	$C_{13}H_{23}N_3S$	−
17	$H_2NCOCH_2CH_2$	H	CH_3	1a	$CH_2{=}CHCONH_2$ O	C	123–125	EtOH	55	$C_{14}H_{17}N_3O$	−
18	$C_6H_5CH(OH)CH_2$	H	CH_3	1a	$C_6H_5CHCH_2$ O	E, F	72–74	Cyclohexane	1–20 2–67	$C_9H_{13}N_3O$	−
19	3,4,5-$(CH_3O)_3C_6H_2CH_2$	H	CH_3	1a		E	88–90	EtOH	56	$C_{16}H_{23}N_3O_3$	−
20	CH_3CO	H	C_2H_5	1b	$(CH_3CO)_2O$	D	67–69		75	$C_9H_{14}N_2O$	− +
21	C_6H_5CO	H	C_2H_5	1b	C_6H_5COCl	A	58–60	Et_2O–cyclohexane	26	$C_{14}H_{16}N_2O$	−
22	C_6H_5NHCO	H	C_2H_5	1b	C_6H_5NCO	B	87–89	Et_2O	65	$C_{14}H_{17}N_3O$	−
23	C_6H_5NHCS	H	C_2H_5	1b	C_6H_5NCS	B	96–98	Petr ether	100	$C_{13}H_{17}N_3S$	− +
24	*p*-ClC_6H_4CO	H	$CH_3(CH_2)_2$	1c	*p*-ClC_6H_4COCl	A	59–61	Et_2O–petr ether	39	$C_{13}H_{15}ClN_2O$	−
25	C_6H_5NHCO	H	$CH_3(CH_2)_2$	1c	C_6H_5NCO	B	123–125		78	$C_{13}H_{18}N_3O$	− +
26	*p*-ClC_6H_4CO	CH_3	CH_3	1d	*p*-ClC_6H_4COCl	A	55–57	Cyclohexane	74	$C_{13}H_{15}ClN_2O$	−
27	*p*-$CH_3C_6H_4SO_2$	CH_3	CH_3	1d	*p*-$CH_3C_6H_4SO_2Cl$	A	117–119	$(CH_3OCH_2)_2$	77	$C_{20}H_{18}N_2O_2S$	−
28	C_6H_5NHCO	CH_3	CH_3	1d	C_6H_5NCO	B	129–131	EtOH–Et_2O	57	$C_{19}H_{17}N_3O$	−

[a] Where oils or gums were obtained employing the listed methods, crystallization was induced by trituration with an appropriate organic solvent (usually petroleum ether, cyclohexane or ether). [b] CNS depressant activity (standard mouse dose range study): + = activity below 500 mg/kg po; ++ = activity below 250 mg/kg; − = inactive.

Method A.—To an ice-cooled and stirred solution of the pyrrole compd (0.1 mole), Et_3N (0.3 mole), and C_6H_6 (300 ml), a solution of acid chloride (0.1 mole) in C_6H_6 (100 ml) was added dropwise over a 2-hr period. The reaction mixture was stirred for 6 hr and let stand overnight. The $Et_3N \cdot HCl$ formed was extracted from the C_6H_6 solution with H_2O (200 ml). The organic layer was dried (Na_2SO_4) and filtered, followed by concentration under reduced pressure.

Method B.—A mixture of the pyrrole compd (0.05 mole) and the appropriate isocyanate (0.05 mole) or isothiocyanate (0.05 mole) in C_6H_6 (200 ml) was permitted to stand at room temp for 16 hr. The solvents were removed under reduced pressure.

Method C. A mixture of the pyrrole compd (0.1 mole) and the α,β-unsaturated compd (0.1 mole) and C_6H_6 (300 ml) was stirred and refluxed for 10 hr. The reaction mixture was permitted to stand 16 hr at room temp during this period. Compd **17** was deposited while **18** was obtained as an oil after removing the solvent and purified by passing through a neutral silica column using EtOH as a solvent.

Method D.—To a cooled and stirred solution of the pyrrole compd (0.1 mole) dissolved in C_6H_6 (300 ml) under N_2, a solution of anhydride (0.1 mole) dissolved in C_6H_6 (200 ml) was added dropwise. After the addition was complete, the reaction was stirred for 12 hr, followed by extraction with two 100-ml portions of 10% aq NaOH and 100 ml of H_2O. The C_6H_6 layer was dried (Na_2SO_4), filtered, and coned under reduced pressure.

Method E.—To a cooled and stirred slurry of LAH (4 g) in THF (400 ml), a solution of the pyrrole compd (0.004 mole) dissolved in THF (200 ml) was added dropwise. After the addition was complete, the reaction mixture was refluxed for 5 hr. While cooling in an ice bath, the excess LAH was decomposed by the dropwise addition of a 10% NaOH solution (25 ml) and a satd Na_2SO_4 solution (25 ml). The reaction mixture was permitted to stir for 30 min followed by the addition of solid Na_2SO_4 (15 g). The reaction mixture was filtered and the filter cake washed several times with hot THF. The filtrate was dried (Na_2SO_4), filtered, and coned under reduced pressure.

Method F.—A solution of the pyrrole compd (0.1 mole), styrene oxide (0.1 mole) dissolved in Et_2O (200 ml) was permitted to stand for 8 days at room temp. The Et_2O was evaporated and the resulting oil (**18**) heated on the steam bath for 2 hr.

A New Group of Anorexigenic Compounds

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The therapy of obesity is either based on reducing diets or on drugs which diminish the desire for food intake in excess of the energy expenditure—or most successfully—a combination of both. Anorexigenic agents presently in use are phenethylamine derivatives comprising the structural elements aryl-C-C-N[1-3] which show varying degrees of stimulation.

* To whom correspondence should be addressed.

(1) A. Engelhardt, *Acta Neuroveg.*, **24**, 647 (1963).
(2) D. Lorenz, *Mitt. Deut. Pharm. Ges. Pharm. Ges. DDR*, **36**, 269 (1966).
(3) G. Ebrhart and H. Rushig, "Arzneimittel," Verlag Chemie, Weinheim, 1968, p 139.

TABLE I

Compd	Oral dose causing 50% reduction in food consumption[a] $ED_{50} \pm S_{EM}$[b] (mg/kg)
Amphetamine	8.8 ± 2.5
Fenfluramine	6.8 ± 2.1
Diethylpropion	40.0 ± 8.4
Cloforex	45.0 ± 14.6
Phenmetrazine	54.0 ± 8.1
Compound 9	57.0 ± 11.0
Wy 5244[c]	60.2 ± 9.5

[a] 24 rats per test. [b] S_{EM} = Standard error of mean. [c] 5-*p*-Chlorophenyl[6,7]benz-1,4-diazocine. See ref 4 and M. I. Gluckmann, *Pharmacologist*, **7**, 146 (1965).

Experimental Section[7]

Compounds **1–34**[8] and **35**[9] were prepared according to published methods. The preparation of **36** was straightforward, except for the hydrolysis of the benzenesulfonylmethylaminomethylbenzhydrol with H_2SO_4, where oxidn to the benzophenone occurred, requiring an additional step of reduction. Compound **37** was prepared by ring cleavage of the substituted tetrahydroisoquinoline with Ac_2O, a method already employed for cleavage of tetrahydrocarbolines,[10] isoindolines,[8] and dihydroisobenzofurans.[9]

4-Chloro-4′-(methylaminomethyl)benzhydrol (36). 4-Chloro-4′-aminomethylbenzhydrol.—4-Chloro-4′-cyanobenzophenone (12.8 g) was reduced with LAH (THF) (4 g), in the usual way: yield 11.5 g (86%); mp 90° from EtOH–Et_2O–pet ether; hydrochloride, mp 240–245° (EtOH). *Anal.* ($C_{14}H_{14}ClNO \cdot HCl$) C, H, Cl, N.

4-Chloro-4′-(*N*-methyl-*N*-benzenesulfonylaminomethyl)benzhydrol.—The primary amine described above (8.1 g) was acylated

TABLE II

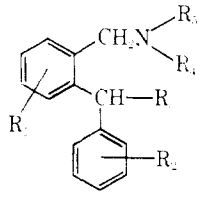
No.	R_1	R_2	R_3	R_4	R_5	Rel anorectic act.
1	H	H	OH	H	CH_3	(−)
2	H	4-CH_3	OH	H	CH_3	(−)
3	H	4-OCH_3	OH	H	CH_3	(−)
4	H	4-SCH_3	OH	H	CH_3	0.6
5	H	4-F	OH	H	CH_3	1.0
6	5-Cl	H	OH	H	CH_3	(−)
7	H	2-Cl	OH	H	CH_3	(−)
8	H	3-Cl	OH	H	CH_3	0.7
9	H	4-Cl	OH	H	CH_3[a]	1.0
10	H	4-Cl	OH	H	CH_3[b]	1.5
11	H	4-Cl	OH	H	CH_3[c]	0.8
12	4,5-$(OCH_3)_2$	4-Cl	OH	H	CH_3	(−)
13	H	4-Cl 3-CF_3	OH	H	CH_3	1.2
14	H	4-Br	OH	H	CH_3	0.7
15	H	3-CF_3	OH	H	CH_3	1.2
16	H	H	OH	H	H	(−)
17	5-Cl	H	OH	H	H	(−)
18	H	4-Cl	OH	H	H	(−)
19	H	4-Cl	OH	H	C_2H_5	(−)
20	H	4-Cl	OH	H	*n*-Bu	0.5
21	H	4-Cl	OH	H	*i*-Bu	(−)
22	H	4-Cl	OH	H	$CH_2C_6H_5$	(−)
23	H	4-Cl	OH	H	C_6H_{11}	(−)
24	H	4-Cl	OH	CH_3	CH_3	(−)
25	H	4-CH_3	$OCOCH_3$	$COCH_3$	CH_3	(−)
26	H	4-Cl	$OCOCH_3$	$COCH_3$	CH_3	(−)
27	H	4-Cl	OH	$CO_2C_2H_5$	CH_3	(−)
28	H	4-F	OH	$CO_2C_2H_5$	CH_3	(−)
29	5-Cl	H	OH	$CO_2C_2H_5$	H	(−)
30	5-Cl	H	$CO_2C_2H_5$	$CO_2C_2H_5$	H	(−)
31	H	4-Cl	$CO_2C_2H_5$	$CO_2C_2H_5$	H	(−)
32	H	4-Cl	H	H	CH_3	(−)
33	H	4-Cl	OC_2H_5	H	CH_3	0.5
34	H	4-Cl	CH_3	H	CH_3	(−)
35	See formula					1.0
36	See formula					(−)
37	See formula					(−)

[a] Racemate. [b] Dextrorotatory isomer. [c] Laevorotatory isomer.

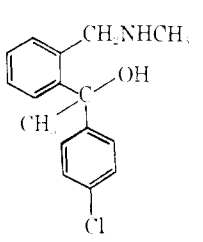
Only in the last few years have isolated examples of compounds with different structures become known, which compounds were claimed to have anorexigenic properties.[4,5] We wish to report the relationship between structure and anorexigenic activity in a group of substituted aminomethylbenzhydrols, which differ chemically and pharmacologically[6] from the typical appetite suppressants.

(4) C. K. Cain, *Annu. Rep. Med. Chem.*, **1967**, 50 (1968).
(5) E. DeFelice, S. Bronstein, A. Cohen, *Curr. Ther. Res. Clin. Exp.* **11**, 256 (1969).
(6) J. T. Oliver, to be published.

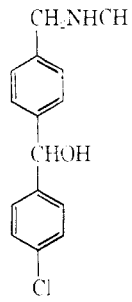
(7) Melting points were taken on a Fisher-Jones apparatus and are uncorrected. Microanalyses were performed by Dr. C. Daesslé, Montreal. All analytical samples have nmr spectra in agreement with their structures. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.
(8) K. Freter and M. Götz, *Can. J. Chem.*, in press (1970).
(9) K. Freter, E. Dubois, and A. Thomas, *J. Heterocycl. Chem.*, **7**, 159 (1970).
(10) K. Freter, H. H. Hübner, H. Merz, H. D. Schroeder, and K. Zeile, *Justus Liebigs Ann. Chem.*, **684**, 159 (1965).



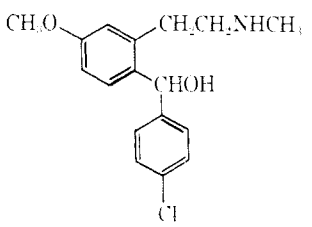
1–34



35



36



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.* ($C_{21}H_{29}ClNO_3S$) 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. Bauch, 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).