Absorption Studies. Absorption in Squirrel Monkeys. The esters were administered orally by intubation as solutions of the sodium salts in water (2 ml), at a dose of 25 mg/kg, to groups of five squirrel monkeys (Saimiri sciureus) weighing 500–1000 g. Venous blood samples were removed at 0.5, 1, 2, 4, and 6 hr after dosing. The blood samples were heparinized, stored at 4°, and assayed on the day of sampling.

Absorption in Human Volunteers. The compounds were administered in plain gelatin capsules without excipients to groups of ten healthy fasting volunteer subjects as a single oral dose corresponding to 500 mg of carbenicillin. Venous blood was taken 0.5, 1, 2, 3, and 4 hr after administration of the ester and urine was collected over a 6-hr period. In order to reduce hydrolysis *in vitro* sera were kept in an ice bath until microbiological assay which was usually commenced within 1 hr of collection of the specimens. The specimens of urine were examined for carbenicillin, unhydrolyzed ester, and penicilloic acid.

Microbiological Assay. The concentrations of carbenicillin found in body fluid specimens after administration of the esters were measured by standard large plate microbiological assay with *Pseudomonas aeruginosa* NCTC 10701 as assay organism.[6] This organism is sensitive to relatively low concentrations of carbenicillin but is insensitive to unhydrolyzed carbenicillin esters. Specimens of squirrel monkey blood or human sera were assayed against standard solutions of carbenicillin prepared in squirrel monkey blood or in pooled human serum. Urine specimens were assayed against carbenicillin standard solutions prepared in 0.05 *M* phosphate buffer, pH 7.0. The assay plates were incubated overnight at 30°, inhibition zone diameters measured, and the concentrations of carbenicillin derived from the standard lines.

Penicilloic Acid in Urine. The carbenicillin penicilloic acid concentrations in urine collected in the 6-hr period after administration of the esters to human volunteers were measured by an iodometric method.[7]

Unhydrolyzed Ester in Urine. The amounts of unhydrolyzed ester found in the urine of fasting subjects were measured by chromatography and bioautography, as described above (see section on hydrolysis by squirrel monkey tissue preparations). The inhibition zones formed by the urine specimens were measured and compared with those produced by buffer standard solutions of the esters.

Acknowledgment. The authors wish to thank Mr. F. P. Doyle, Director of Research, for his interest and enthusiasm in all phases of this work and for a number of valuable suggestions. We also thank Miss B. Ridley of our biochemical laboratory for measurement of hydrolysis rates.

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5-Aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols. A Novel Class of Anorectic Agents

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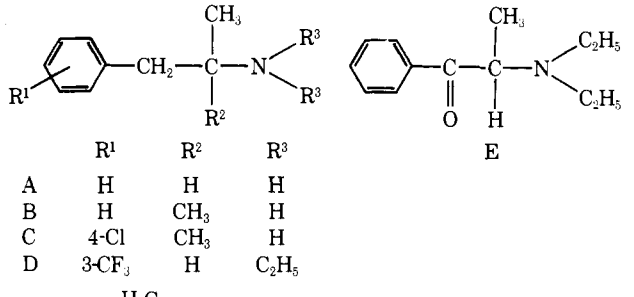
A series of 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (IV), prepared by the $LiAlH_4$ reduction of the corresponding 9b-aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones (II), was evaluated for suppression of food consumption in rats. One member of this series, 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (**6**, mazindol), was evaluated in squirrel and capuchin monkeys and found to have anorexic activity approximately equal to *d*-amphetamine.

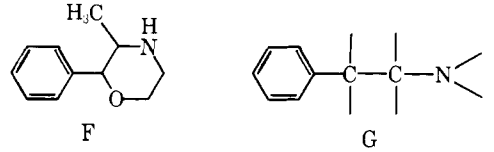
It has become increasingly apparent in recent years that obesity is a major health hazard in the United States and its control in individuals with diabetes and heart conditions is particularly desirable.[1] In the overall management of obesity the anorectic drugs[2] continue to occupy a useful role by diminishing the desire for intake of food.

At the time we began our work amphetamine (A), phentermine (B), chlorphentermine (C), fenfluramine (D), diethylpropion (E), and phenmetrazine (F) were the most widely used single drug entities in the United States and Europe for appetite control.[3] All of these drugs are characterized by the presence of a β-phenethylamine moiety G in their structure.



	R^1	R^2	R^3
A	H	H	H
B	H	CH_3	H
C	4-Cl	CH_3	H
D	3-CF_3	H	C_2H_5

E



F

G

It was the goal of our research effort to prepare an anorectic substance that did not contain a β-phenethylamine moiety as part of its structure. In the present work we present our findings on one such class, the 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols IV.†

Chemistry. Scheme I depicts the synthesis used to prepare the 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols IV reported in this paper. Condensation of a 2-benzoylbenzoic acid I with ethylenediamine gave the 9b-aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones II.[5] Treatment of II with $LiAlH_4$ in tetrahydrofuran (THF) gave the labile 9b-aryl-2,3,5,9b-tetrahydro-1*H*-imidazo[2,1-*a*]isoindol-5-ols III.[6] The latter compounds were not isolated but directly converted to IV by air oxidation[4c,7] in THF-CH_3OH.

It has been demonstrated by ultraviolet spectral data that 5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (IV, compound 1) exists as the tautomeric 2-(2-imidazolin-2-yl)benzophenone form IVa in acid solution.[6] An X-ray single-crystal structure analysis of 1·HBr has also confirmed the existence of the tautomeric form IVa in the

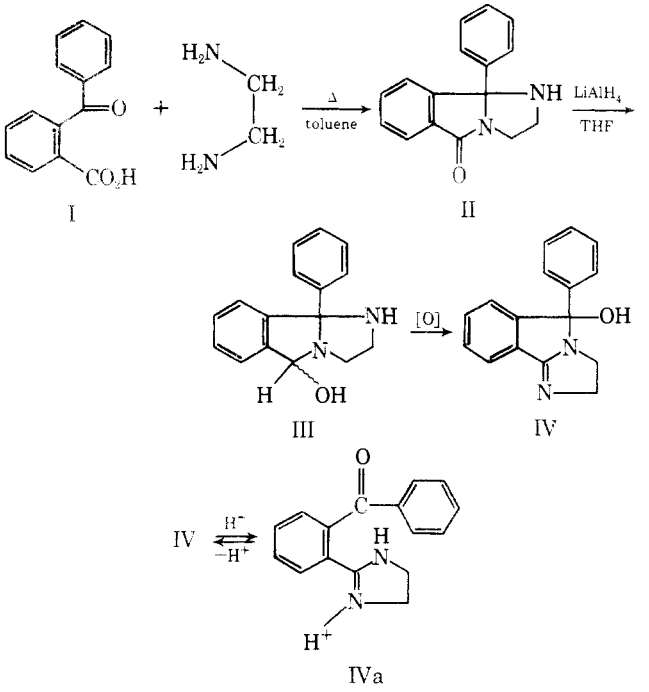
† Similar results have been published in the patent literature by groups from American Home Products and Hoffmann-La Roche.[4]

Table I. Ultraviolet Spectral Data for Some 2-Aroylbenzoic Acids (I) and 5-Aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (IV)[a]

	Maxima, mμ (ε)					
Compd IV	1	3	6	11	12	14
95% EtOH	258 (16,500) 264 (9,075) 268 (9,075) 275 (9,050)	265 (5,090) 270 (5,075) 276 (4,580)	223 (21,420) 268 (4,930) 276 (4,930)	271 (4050) 275 (4050)	227 (19,490) 275 (1,625) 283 (1,670)	270 (4,610) 275 (5,010)
95% EtOH–HCl	238 (12,650)	253 (13,400)	253 (12,210)	245 (14,200)	298 (14,135)	253 (13,200)
	Maxima, mμ (ε)					
Compd I	20	22	25	30	31	33
95% EtOH	241 (16,500)	247 (12,800)	258 (18,385)	243 (16,620) 276 (2,775)	284 (16,620)	256 (15,315)

[a] See chemical synthesis part of the Experimental Section for details.

Scheme I



solid state.[8] We have obtained the ultraviolet spectra of a selected group of IV analogs in 95% EtOH and 95% EtOH-HCl (Table I) and compared them with their corresponding 2-aroylbenzoic acid analogs (Table I). Examination of the data reveals that in 95% EtOH the closed tautomeric form IV exists. In 95% EtOH-HCl the ultraviolet spectrum of IV is similar to the 2-aroylbenzoic acids (see Table I) indicating that the benzophenone tautomer IVa exists in acid media.

Pharmacology. The anorexic activity, as measured by food consumption in rats, for the 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (IV) is listed in Table II. These data indicate that activity in this series of compounds was optimal when the phenyl ring of 1 contained one F or Cl atom in the 3′ (2, 5) or 4′ (3, 6) position. Placement of an F or Cl in the benzene portion of the imidazo[2,1-*a*]isoindole ring system (4, 7-9) led to substances weaker than 1. The presence of two Cl atoms in the 3′,4′ or 3′,5′ positions (14 and 15) gave compounds about as active as 1 while ring substitution (16 and 17) resulted in weakly active compounds. Addition of a CF_3 (10 and 11), OCH_3 (12), or C_6H_5 (13) substituent on the phenyl group of 1 lowered the anorexic activity. Replacement of the phenyl group in 1 by a 2-thienyl (18) or 2-pyridyl (19) group markedly reduced the activity.

On the basis of food consumption in rats and the overall pharmacological profile,[9] 5-(*p*-chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (6, mazindol) was selected for additional appetite suppression studies in rats and monkeys. In the Sprague-Dawley rat the anorexic ED_{50} (Table III) of 6 when compared with several selected anorectic agents was approximately equal to diethylpropion (E) and one-fourth that of *d*-amphetamine (A). When 6 was evaluated for anorexic activity in the squirrel or capuchin monkey, it was as effective as *d*-amphetamine (A) and four to five times more potent than the other standard agents (B-F).

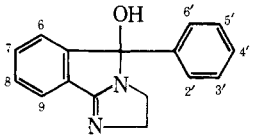
Experimental Section

Chemical Synthesis. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. For compounds 1-38 pmr spectra were obtained on a Varian Associates A-60 spectrometer in $CDCl_3$ or DMSO-d_6 and ir spectra (KBr) were determined using a Perkin-Elmer Infracord. In all cases the spectra were consistent with the assigned structure. The uv spectra for a selected group of compounds (Table I) were obtained in 95% EtOH or 95% EtOH-2 *N* HCl (9:1) solvent on a Cary Model 15 spectrophotometer. Thin-layer chromatography (tlc) was carried out on compounds 1-19 using glass plates coated with silica gel HF-254 (E. Merck AG) with the solvent system $CHCl_3$-MeOH (9:1) for the purpose of establishing homogeneity.

Pharmacology Testing. Acute Toxicity. The studies were carried out with paired male Royal Hart Wistar rats, 136-160 g, placed in 7 × 7 × 14 in. wire cages. The LD_{50} values (Table II) were obtained 72 hr post-administration of compounds using 20 rats per substances and estimated by probit analysis.

Appetite Suppression in Rats. Food consumption was determined using a modification of the free-feeding method described by Randall.[10] Male Royal Hart Wistar rats, 280-380 g, were individually housed in a room artifically illuminated 7 a.m. to 7 p.m. daily. The animals were chronically trained on a 4-hr feeding and 20-hr fasting schedule and prior to testing were deprived of food for 20 hr but allowed water *ad libitum*. Following oral administration of the substance a predetermined amount of ground food (Purina Lab Chow) was presented in a weighed ground food cannister. The changes in food consumption for the control and treated animals were determined 1 and 4 hr after presentation. The ED_{50} values were determined in Sprague-Dawley male rats, 150-200 g body weight, for the first 1-hr period and the total 4-hr session and defined as that dose of compound which suppressed food consumption by 50% when compared to controls. In all studies groups of ten rats were used per dose level with ED_{50} values determined using at least three dosage levels per compound.

Table II. 5-Aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols



No.	Substituent(s)	Mp, °C (recrystn solvent)[a]	Yield, %	Empirical formula	Analyses[b]	mg/kg po[c]	Food consumption, % of controls[c] 1 hr	Food consumption, % of controls[c] 4 hr	LD_{50}, mg/kg po[c]
1	None	200–202 (A)[d]	21	$C_{16}H_{14}N_2O$	C, H, N	50		47.8	300
2	3′-F	200–203 (B)	32	$C_{16}H_{13}FN_2O$	C, H, N	25	15	35.1	
3	4′-F	173–175 (B),[e] 192–195	29	$C_{16}H_{13}FN_2O$	C, H, N	25		54.3	200
4	7-F	206–208 (B)	28	$C_{16}H_{13}FN_2O$	C, H, N	25	30.3	65.4	40
5	3′-Cl	208–210 (C)	24	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	25	23.6	50.5	200
6	4′-Cl	184–185 (B),[e] 201–202	65	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	25	13.0	38.5	>400
7	6-Cl	224–226 (B)	36	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	50	67.5	68.8	>400
8	7-Cl	197–202 (B)	40	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	25	48.6	82.7	
9	8-Cl	210–215 (B)	15	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	25	60.1	86.4	
10	3′-CF_3	209–212 (B)	24	$C_{17}H_{13}F_3N_2O$	C, H, N	25	49.4	55.6	
11	4′-CF_3	210–212 (E)	21	$C_{17}H_{13}F_3N_2O$	C, H, N	50	49.0	69.4	353
12	4′-OCH_3	188–190 (C)	14	$C_{17}H_{16}N_2O_2$	C, H, N	50		87.2	>400
13	4′-C_6H_5	198–199 (B)	44	$C_{22}H_{18}N_2O$	C, H, N	50		119.6	>400
14	3′,4′-Cl_2	200–202 (B)	58	$C_{16}H_{12}Cl_2N_2O$	C, H, Cl, N	25	32.2	58.7	353
15	3′,5′-Cl_2	207–209 (B)	50	$C_{16}H_{12}Cl_2N_2O$	C, H, Cl, N	25	37.1	43.0	
16	7,8-Cl_2	195–198 (B)	25	$C_{16}H_{12}Cl_2N_2O$	C, H, Cl, N	25	76.7	85.3	
17	4′,7,8-Cl_3	188–190 (C)	21	$C_{16}H_{11}Cl_3N_2O$	C, H, Cl, O	25	59.7	87.8	
18	2-Thienyl[f]	152–153 (F)	15	$C_{14}H_{12}N_2OS$	C, H, N, S	25	54.6	85.6	>400
19	2-Pyridyl[g]	198–200 (B)	30	$C_{15}H_{13}N_3O$	C, H, N, O	50	78.4	100	
A	*d*-Amphetamine					5	20.1	68.0	71.0
E	Diethylpropion					25	18.2	43.6	>400
D	Fenfluramine					12.5	25.0	27.6	130

[a]Recrystallization solvents: A, MeOH-THF-H_2O; B, MeOH-THF; C, MeOH; D, THF-Et_2O; E, MeOH-Et_2O; F, THF-MeOH; G, EtOH-H_2O. [b]Unless otherwise stated analyses are within ±0.4% of the theoretical values. [c]See pharmacology testing in the Experimental Section for details. [d]Lit.[6] mp 194–196°. [e]The melting point was dependent on the rate of heating. In the Thomas-Hoover capillary melting point apparatus maintained at a setting of 6–7 the higher melting point was obtained. When the apparatus was preheated to 150° and set at 4 the lower melting point was obtained. [f]This is the 5-(2-thienyl)analog. [g] This is the 5-(2-pyridyl) analog.

Appetite Suppression in Squirrel Monkeys. The variable ratio food schedule of Ferster and Skinner[11] was used with some modification. Monkeys (0.75–3.5 kg) were placed in a sound attenuated chamber containing an "intelligence" panel equipped with a lever and a dipper for delivering 0.1–1.0 ml of orange juice. Pressing the lever periodically (but randomly as far as the animal is concerned) activates the dipper for dispensing liquid. The schedule used in the present studies required the animal to press the lever on the average of 15 times (VR-15 operant behavioral schedule) to receive the orange juice. This type of schedule produced a high rate of lever pressing (60–85 responses/min) and was very sensitive to anorexic substances. Each substance was tested in four monkeys by orally administering the test compound 0.5 hr prior to the start of the test session. All test sessions were conducted over a 90-min period. The anorexic ED_{50} was defined as that dose which suppressed lever pressing by 50% of the control rate over the 90-min session.

Appetite Suppression in Capuchin (Cebus) Monkeys. The VR-15 operant behavior schedule[11] as given above was used with slight modification. In addition to measuring lever responses, drinkometers were inserted in the manipulanda in order to determine possible differential effects of the compounds on lever-pressing behavior *vs.* effects on the animal's attempts to obtain the food reward. The anorexic ED_{50} was defined as that dose which suppresses licking behavior as measured by the drinkometer by 50% of control rate over a 90-min session.

2-Aroylbenzoic Acid Synthesis. Procedure A. Friedel-Crafts with Phthalic Anhydride. Following the respective literature procedures phthalic anhydride ws allowed to react with o-dichlorobenzene,[12] biphenyl,[13] thiophene,[14] and 3-chlorphthalic anhydride with benzene[15] in the presence of $AlCl_3$ to give compounds **52**, **51**, **56**, and **47**, respectively listed in Table V.

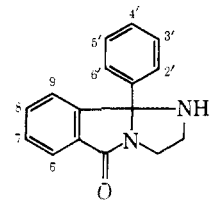
Table III. Anorexic ED_{50} Values

Compound	ED_{50}, mg/kg po: Sprague–Dawley rat[a] 1 hr	Sprague–Dawley rat[a] 4 hr	Squirrel monkey[a] (no. of trials)[b]	Capuchin monkey[a] (no. of trials)[b]
Mazindol (**6**)	7.81	25.8	0.25 (18)	0.42 (8)
d-Amphetamine[c] (A)	0.82	6.36	0.25 (21)	0.43 (9)
Phentermine[d] (B)	1.76	5.26	0.29 (19)	
Chlorphentermine (C)	4.69	8.07	2.0 (8)	1.64 (4)
Fenfluramine (D)				>2.00 (2)
Diethylpropion (E)	4.55	18.06	2.0[e] (8)	2.59 (4)
Phenmetrazine (F)				1.82 (4)

[a]See pharmacology testing in Experimental Section for details. [b]The ED_{50} values were measured 90 min post drug administration. [c]Administered as the sulfate salt. [d]Administered as the hydrochloride salt. [e]This ED_{50} was determined 15 min post-administration since the compound was found to be ineffective at longer time intervals.

Procedure B. Grignard Reaction with Phthalic Anhydride. To the Grignard reagent prepared from 13.4 g (0.55 mol) of magnesium shavings and 87.5 g (0.50 mol) of 3-bromofluorobenzene in 600 ml of dry THF there was added a solution of 81.5 g (0.55 mol) of phthalic anhydride in 1000 ml of C_6H_6 and 250 ml of THF over

Table IV. 9b-Aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones



No.	Substituent(s)	Mp, °C (recrystn solvent)[a]	Yield, %	Empirical formula	Analyses[b]
20	None	156–157 (A)[c]	68	$C_{16}H_{14}N_2O$	C, H, N
21	3′-F	144–145 (A)	85	$C_{16}H_{13}FN_2O$	C, H, N
22	4′-F	193–195 (B)[d]	76	$C_{16}H_{13}FN_2O$	C, H, N
23	8-F	152–153 (A)	70	$C_{16}H_{13}FN_2O$	C, H, N
24	3′-Cl	170–172 (C)[e]	80	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
25	4′-Cl	165–166 (A)[f]	85	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
26	7-Cl	193–194 (B)	81	$C_{16}H_{13}ClN_2O$	C, H, N
27	8-Cl	173–174 (A)	45	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
28	9-Cl	173–175 (D)	60	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
29	3′-CF_3	135–137 (F)[g]	85	$C_{17}H_{13}F_3N_2O$	C, H
30	4′-CF_3	191–193 (B)[h]	76	$C_{17}H_{13}F_3N_2O$	C, H, N
31	4′-OCH_3	161–162 (B)[i]	69	$C_{17}H_{16}N_2O_2$	C, H, N
32	4′-C_6H_5	200–202 (B)	67	$C_{22}H_{18}N_2O$	C, H, N
33	3′,4′-Cl_2	215–217 (D)	87	$C_{16}H_{12}Cl_2N_2O$	C, H, Cl, N
34	3′, 5′-Cl_2	204–207 (B)	72	$C_{16}H_{12}Cl_2N_2O$	C, H, Cl, N
35	7,8-Cl_2	185–187 (E)	55	$C_{16}H_{12}Cl_2N_2O$	C, H, Cl, N
36	4′, 7,8-Cl_3	218–219 (G)	43	$C_{16}H_{11}Cl_3N_2O$	C, H, Cl, N
37	2-Thienyl[j]	157–159 (H)[k]	55	$C_{14}H_{12}N_2OS$	C, H, S
38	2-Pyridyl[l]	105–107 (I)	54	$C_{15}H_{13}N_3O$	C, H, N

[a] Recrystallization solvents: A, EtOH–H_2O; B, MeOH; C, EtOH; D, EtOH–hexane; E, THF–Et_2O; F, MeOH–H_2O; G, CH_2Cl_2–Et_2O; H, EtOAc; I, acetone–pentane. [b] See footnote *b*, Table II. [c] Lit.[5] mp 155–157°. [d] Lit.[5] mp 193–195°. [e] Lit.[5] mp 175–177°. [f] Lit.[5] mp 165–166°. [g] Lit.[5] mp 140–142°. [h] Lit.[5] mp 193–194°. [i] Lit.[5] mp 159°. [j] This is the 9b-(2-thienyl) analog. [k] Lit.[5] mp 169°. [l] This is the 9b-(2-pyridyl) analog.

a 0.5-hr period (slightly exothermic). The mixture was stirred and refluxed for 15 hr, cooled to *ca.* 10°, and then hydrolyzed with 150 ml of saturated ammonium chloride solution. The organic layer was dried with $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was crystallized from EtOH–H_2O to give 78 g of 2-(*m*-fluorobenzoyl)benzoic acid (**40**, Table V). Following procedure B, 3-chlorobromobenzene,[5] 3-bromobenzotrifluoride,[5] and 4-bromobenzotrifluoride[16] gave compounds **43**, **48**, and **49**, respectively listed in Table V.

Procedure C. Chromium Trioxide Oxidation of Substituted 2-Methylbenzophenones. Step 1. Synthesis of Substituted 2-Methylbenzophenones. A. The Grignard reagent prepared from 43.0 g (0.25 mol) of 2-bromotoluene and 7.8 g (0.27 mol) of magnesium shavings in 250 ml of anhydrous THF was cooled in an ice bath and treated dropwise (2.0 hr) with a solution of 41.6 g (0.20 mol) of 3,5-dichlorobenzoyl chloride [bp 84–88° (5 mm); prepared from commercial acid and thionyl chloride] in 100 ml of THF. The reaction was processed as in procedure B to give 35.4 g (60%) of 3,5-dichloro-2′-methylbenzophenone (**58**): bp 169–175° (0.25 mm); nmr ($CDCl_3$) CH_3 at δ 2.32. *Anal.* ($C_{14}H_{10}Cl_2O$) C, H, Cl.

B. To a stirred mixture of 22.5 g (0.17 mol) of anhydrous aluminum chloride in 200 ml of C_6H_6 there was added (0.5 hr) a solution of 22.4 g (0.13 mol) of 5-fluoro-*o*-toluoyl chloride (prepared from the acid and thionyl chloride) in 50 ml of C_6H_6. The mixture was refluxed until the evolution of HCl gas ceased (*ca.* 45 min), cooled in an ice bath, and then poured onto a mixture of ice (500 g) and 200 ml of concentrated hydrochloric acid. The organic layer was separated, washed with 100 ml of H_2O, 100 ml of saturated sodium carbonate, and 150 ml of saturated NaCl solution, and then dried with anhydrous Na_2SO_4. Distillation gave 21 g (80%) of 5-fluoro-2-methylbenzophenone (**59**): bp 135–140° (0.5 mm); nmr ($CDCl_3$) CH_3 at δ 2.23. *Anal.* ($C_{14}H_{11}FO$) C, H.

In a similar manner 4-chloro-o-toluoyl chloride [prepared from the acid, mp 169–170° (C_6H_6–hexane) (lit.[16] mp 169.5–170°)] gave 91% of 4-chloro-2-methylbenzophenone (**60**): bp 150–155° (0.5 mm); nmr ($CDCl_3$) CH_3 at δ 2.32; $n^{20}D$ 1.6067. *Anal.* ($C_{14}H_{11}ClO$) C, H. 5-Chloro-o-toluoyl chloride [prepared from the acid, mp 171–172° (hexane) (lit.[18] mp 173°)] gave 79% of 5-chloro-2-methylbenzophenone (**61**): mp 42–43° (pentane); nmr ($CDCl_3$) CH_3 at δ 2.25. *Anal.* ($C_{14}H_{11}ClO$) C, H, Cl.

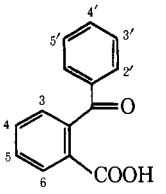
C. A stirred mixture of 91.5 g (0.69 mol) of anhydrous aluminum chloride and 200 g of 3,4-dichlorotoluene was treated (15 min) with a solution of 74 g (0.53 mol) of benzoyl chloride in 50 g of 3,4-dichlorotoluene. The mixture was refluxed until evolution of HCl gas ceased (1.5 hr) and after cooling to room temperature poured onto a mixture of 750 g of ice and 500 ml of concentrated hydrochloric acid. The organic phase was separated and washed with 200 ml of saturated NaCl solution and 150 ml of H_2O. Distillation gave 126.1 g (90%) of substance (**62**): bp 160–180° (0.75 mm); mp 82–96°. *Anal.* ($C_{14}H_{10}Cl_2O$) Cl. The nmr ($CDCl_3$) gave two CH_3 signals at δ 2.28 and 2.14 in an 85:15 ratio. The substance with the low-field CH_3 signal (85%) has been assigned as 4,5-dichloro-2-methylbenzophenone and the other component (15%) as 2,3-dichloro-5-methylbenzophenone. This mixture was used directly in step 2 to prepare **54**.

In a similar manner 250 g of 3,4-dichlorotoluene and 93 g (0.53 mol) of *p*-chlorobenzoyl chloride gave 150.7 g (95%) of a substance (**63**): bp 175–185° (0.50 mm); mp 78–87°. *Anal.* ($C_{14}H_9Cl_3O$) Cl. The nmr ($CDCl_3$) gave two CH_3 signals at δ 2.27 and 2.12 in a 90:10 ratio. The substance with the low-field CH_3 signal (90%) has been assigned as 2-methyl-4,4,5-trichlorobenzophenone and the other component as 5-methyl-2,3,4′-trichlorobenzophenone. The mixture was used directly in step 2 to prepare **55**.

Step 2. Chromium Trioxide Oxidation. To a stirred solution of 21.7 g (0.094 mol) of 4-chloro-2-methylbenzophenone and 130 ml of acetic acid there was added dropwise (2 hr) a solution of 25.4 g (0.25 mol) of chromium trioxide, 58 ml of H_2O, 95 ml of acetic acid, and 18 ml of concentrated H_2SO_4. The mixture was refluxed for 1 hr, cooled to room temperature, and poured onto a stirred mixture of *ca.* 1500 ml of ice–H_2O. After standing overnight the resultant solid was filtered off (19.7 g) and added to 500 ml of 2 *N* NaOH, and the entire solution was washed with 100 ml of toluene. The aqueous layer was acidified with concentrated HCl and allowed to stand *ca.* 15 hr in a cold room. There was obtained 2-benzoyl-5-chlorobenzoic acid (**45**, Table V).

In a similar manner 5-fluoro-2-methylbenzophenone, 5-chloro-

Table V. 2-Aroylbenzoic Acids



No.	Substituent(s)	Mp, °C (recrystn solvent)[a]	Procedure[b]	Yield, %	Empirical formula[c]
39	None		*d*		$C_{14}H_{10}O_3$
40	3′-F	145–147 (A)	B	66	$C_{14}H_9FO_3$[e]
41	4′-F		*d*		$C_{14}H_9FO_3$
42	4-F	115–117 (B)	C	49	$C_{14}H_9FO_3$[e]
43	3′-Cl	158–160 (C)[f]	B	60	$C_{14}H_9ClO_3$[g]
44	4′-Cl		*d*		$C_{14}H_9ClO_3$
45	5-Cl	169–172 (A)	C	65	$C_{14}H_9ClO_3$[g]
46	4-Cl	175–177 (D)	C	59	$C_{14}H_9ClO_3$[e]
47	3-Cl	228–230 (A)[h]	A	52	$C_{14}H_9ClO_3$[i]
48	3′-CF_3	164–166 (C)[j]	B	25	$C_{15}H_9F_3O_3$
49	4′-CF_3	176–178 (E)[k]	B	51	$C_{15}H_9F_3O_3$
50	4′-OCH_3		*d*		$C_{15}H_{12}O_4$
51	4′-C_6H_5	225–227 (F)[l]	A	56	$C_{20}H_{14}O_3$
52	3′,4′-Cl_2	185–187 (A)[m]	A	73	$C_{14}H_8Cl_2O_3$
53	3′,5′-Cl_2	180–181 (B)	C	60	$C_{14}H_8Cl_2O_3$[g]
54	4,5-Cl_2	206–208 (G)	C	51	$C_{14}H_8Cl_2O_3$[g]
55	4,4′,5-Cl_3	185–188 (G)	C	60	$C_{14}H_7Cl_3O_3$[g]
56	2-Thienyl	144–146 (H)[n]	A	65	$C_{12}H_8O_3S$
57	2-Pyridyl	228–229 (A)[o]	D	37	$C_{13}H_9NO_3$

[a] Recrystallization solvents: A, EtOH-H_2O; B, *i*-PrOH; C, C_6H_6; D, *i*-PrOH-H_2O; E, C_6H_6-hexane; F, HOAc; G, Et_2O-pentane; H, Et_2O. [b] The letters correspond to the procedures given under 2-aroylbenzoic acids in the Experimental Section. [c] See footnote *b*, Table II. [d] Obtained from the Aldrich Chemical Co. [e] Analyzed for C and H. [f] Lit.[5] mp 162–164°. [g] Analyzed for C, H, and Cl. [h] Lit.[15] mp 232.8–234.2°. [i] Analyzed for Cl. [j] Lit.[5] mp 166–168°. [k] Lit.[16] mp 176–178°. [l] Lit.[13] mp 226°. [m] Lit.[12] mp 191.2°. [n] Lit.[14] mp 145°. [o] Lit.[19] mp 229–230°.

2-methylbenzophenone, 3,5-dichloro-2′-methylbenzophenone, the mixture of 4,5-dichloro-2-methyl- and 2,3-dichloro-5-methylbenzophenone, and the mixture of 2-methyl-4,4′,5-trichloro- and 5-methyl-2,3,4′-trichlorobenzophenone gave the 2-aroylbenzoic acids **42**, **46**, **53**, **54**, and **55**, respectively (Table V).

Procedure D. 2-(Picolinoyl)benzoic Acid. To the Grignard reagent (N_2 atmosphere) prepared from 13.4 g (0.55 mol) of magnesium shavings and 94 g (0.55 mol) of 2-bromotoluene in 200 ml of Et_2O there was added 250 ml of anhydrous C_6H_6 followed by a solution of 39.6 g (0.37 mol) of 2-pyridinecarboxaldehyde in 150 ml of C_6H_6 over a 2-hr period. The mixture was refluxed for 2 hr, cooled in an ice bath, and then hydrolyzed with *ca.* 100 ml of a saturated ammonium chloride solution. The solution was dried with anhydrous $MgSO_4$ and filtered and the filtrate was distilled to give 49 g (43%) of 2-methyl-α-(2-pyridyl)benzyl alcohol (**64**): bp 134° (0.20 mm), that crystallized on standing, mp 55–57°. *Anal.* ($C_{13}H_{13}NO$) C, H, N.

A mixture of 49 g of **64**, 200 g of potassium permanganate, 5 g of NaOH, and 4.0 l. of H_2O was stirred and refluxed until the aqueous phase was colorless (5 hr). The salts were filtered off and the filtrate was acidified with 20% sulfuric acid. The filtrate was concentrated *in vacuo* and the resultant solid residue crystallized from EtOH-H_2O (1:1) to 18.8 g (37%) of 2-(picolinoyl)benzoic acid[19] (**57**, Table V).

9b-Aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones (II). General Procedure.[5b] A mixture of 0.10 mol of 2-aroylbenzoic acid, 0.20 mol of ethylenediamine, and 250 ml of toluene was stirred and refluxed in a flask equipped with a Dean-Stark tube. After the "water layer" (mixture of H_2O and diamine) in the side-arm remained constant (5–24 hr) the reaction mixture was allowed to cool to room temperature and the resultant solid was removed by filtration. If a solid was not obtained on cooling the solvent was removed *in vacuo* and the residue crystallized from an appropriate solvent. The compounds prepared by this procedure are listed in Table IV.

5-Aryl-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ols (IV). General Procedure. A stirred mixture of 0.10 mol of lithium aluminum hydride and 300 ml of anhydrous THF maintained under N_2 was cooled to an internal temperature of 20° and then treated dropwise with a solution of 0.10 mol of 9b-aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one (II) in 300 ml of THF at such a rate that the internal temperature was maintained at 20–25°. After the addition was completed the mixture was stirred *ca.* 6 hr at room temperature, cooled in an ice bath, and treated successively with 10 ml of 2 *N* NaOH, 15 ml of H_2O, and 30 g of anhydrous Na_2SO_4. The salts were filtered off and washed with *ca.* 50 ml of THF. The combined filtrates were concentrated *in vacuo* to give a solid. The solid was dissolved in 400 ml of anhydrous MeOH-THF (1:1) and stirred at room temperature for 4–6 days in a flask exposed to air and protected from moisture with a $CaCl_2$ drying tube. The resultant solid was filtered off and if necessary recrystallized from the appropriate solvent. The compounds prepared by this procedure are listed in Table II.

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Anorectic Agents. 2. Structural Analogs of 5-(*p*-Chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol

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A variety of structural modifications of the anorectic agent 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (1a) was prepared and evaluated for anorectic activity. All of the modifications resulted in complete or considerable loss of activity relative to 1a.

In the preceding paper[1] from our laboratories it was reported that 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (1) represent a novel class of anorectic agents. From this group of substances the *p*-chlorophenyl analog 1a (mazindol, Sanorex) was found to be an effective and potent appetite suppressant in humans.[2]

In an attempt to determine some of the structural features that are needed for anorectic activity in 1 we have prepared a series of compounds where ring A has been modified by (a) the introduction of a second double bond (3), (b) enlargement to a six- (8) and seven- (9) membered ring, and (c) an additional ring fused at the 2,3 position (12).

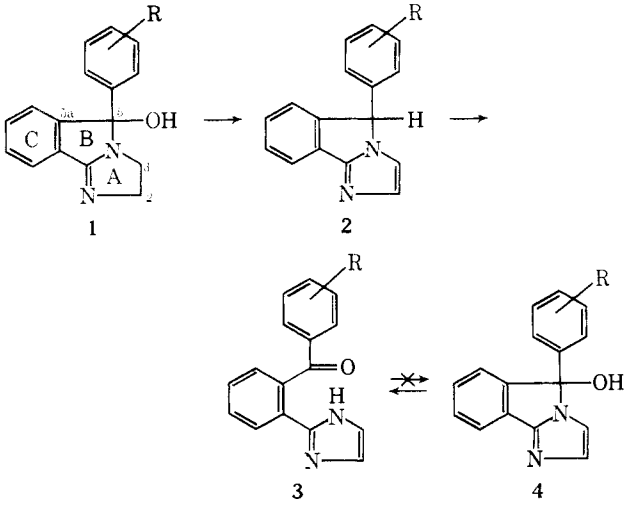
Two additional modifications, **14b** and **15b**, where the C_5-C_{5a} bond in 1 was opened and the aroyl group in 3 transferred to the imidazole N atom were also prepared and evaluated for anorectic activity.

Chemistry. The synthesis of the compounds needed for this study is described below.

Treatment of 1 with refluxing acetic acid resulted in the expected dehydration[3] to the 5-aryl-5*H*-imidazo[2,1-*a*]isoindoles **2**. Conversion of **2** to its sodium salt by sodium hydride in DMF followed by oxygenation[4] resulted in the formation of the 2-(2-imidazol-2-yl)benzophenones **3** rather than the tautomeric 5-aryl-5*H*-imidazo[2,1-*a*]isoindol-5-ols **4** (Scheme I). The structure of **3a** and **3b** was confirmed by ir, nmr, and the presence of a characteristic benzophenone uv maximum[5] at 258 and 260 mμ, respectively (Table I).

The condensation of a 2-aroylbenzoic acid with 1,3-di-

Scheme I



Scheme II