and dried over $MgSO_4$. When the dry ether solution was treated with 7 *N* ethanolic HCl, a gummy solid precipitated. This hydrochloride was recrystallized from aqueous ethanol–ether.

N-(1,1-Dimethylpropynyl)-1-indanamine Hydrochloride (6). To a stirred mixture of 10.0 g (0.075 mole) of 1-indanamine, 9.5 g (0.09 mole) of Na_2CO_3 and 1.0 g of copper–bronze in 125 ml of acetone was added dropwise, 9.25 g (0.09 mole) of dimethylethynylcarbinyl chloride.[8] The reaction mixture was stirred at room temperature overnight before filtering the inorganic solids. The acetone was evaporated *in vacuo* and a small portion of the residue was converted to the hydrochloride with 7 *N* ethanolic HCl for analysis.

N-(1,1-Dimethylpropynyl)-N-methyl-1-indanamine Hydrochloride (7).—The above compound (**6**) was methylated with formic acid and paraformaldehyde[9] and converted to the hydrochloride.

N-Propynyl-1-indanamine Hydrochloride (2).—A mixture of 2.4 g (0.04 mole) of propargylamine and 3.3 g (0.02 mole) of 1-chloroindane in 25 ml of isopropyl alcohol was refluxed 6 hr. After cooling, the solid propargylamine hydrochloride was filtered and the filtrate was evaporated to dryness. The residue was converted to the hydrochloride.

Primary amines not commercially available were prepared by the formation of the oxime from the corresponding ketone, followed by catalytic reduction (5% Pd–C) of the oxime in AcOH–H_2SO_4 (19:1 by volume). A small portion of the base was converted to the hydrochloride for analysis.

The following compounds were prepared in this manner.

1,2,3,4-Tetrahydro-1-naphthylamine hydrochloride, mp 182–183°. *Anal.* Calcd for $C_{10}H_{13}N \cdot HCl$: C, 65.37; H, 7.64; N, 7.64. Found: C, 65.11; H, 7.74; N, 7.34.

6,7,8,9-Tetrahydro-5H-benzocyclohepten-5-amine hydrochloride, mp 277–278°. *Anal.* Calcd for $C_{11}H_{15}N \cdot HCl$: C, 66.80; H, 8.20; N, 7.08. Found: C, 67.05; H, 8.16; N, 6.97.

Acenaphthen-1-amine hydrochloride, mp 300°. *Anal.* Calcd for $C_{12}H_{11}N \cdot HCl$: C, 70.05; H, 5.84; N, 6.81. Found: C, 69.77; H, 5.94; N, 6.85.

Monoamine Oxidase Inhibitory Assay.—Comparative experiments were performed in which graded doses of the test substance (*N*-methyl-*N*-2-propynyl-1-indanamine hydrochloride (**1**) in this instance) and the standard, pargyline in 1% aqueous solution, were administered subcutaneously to two groups of three mice. After a period of 4 hr, 2.5 mg of methyl 17-*O*-(tetrahydro-2-pyranyl)reserpate as a 5% solution in polyethylene glycol diethylacetamide (4:1) was injected subcutaneously, and the animals were placed three to a cage in an activity recorder. The activity of the mice was recorded for a period of 90 min. A dosage ranging from 2.5 to 20 mg/kg sc of **1** was employed. An abrupt increase in the activity of the mice was observed when the dosage of **1** had reached 10 mg/kg. The observed increase in activity was greater than that produced by 100 mg/kg sc of pargyline and slightly less than that produced by 120 mg/kg. In a similar manner, products **2**–**13** were assayed and the results were expressed in decreasing order of activity of **1** in Table I. A second type of comparative study (as illustrated using **1**) was also made. Two groups of three mice (one of which served as a control) were injected subcutaneously with 2.5 mg/kg of methyl 17-*O*-(tetrahydro-2-pyranyl)reserpate. After 30 min when sedation and ptosis were quite obvious in all of the animals, one of the groups received 40 mg/kg sc of **1**. Within 30–40 min the animals so treated had become alert and active, and all evidence of ptosis had disappeared. The untreated controls were still deeply sedated, did not move about, and still showed marked ptosis. At a dose of 200 mg/kg pargyline produced no obvious decrease in the sedation or degree of ptosis when administered to animals previously treated with methyl 17-*O*-(tetrahydropyranyl)reserpate. At a dose of 400 mg/kg there was some reduction in sedation and the degree of ptosis, but the animals were still sluggish in their action and had not recovered to the degree approaching that noted after 20 mg/kg of **1**.

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Thyromimetics. VI. The Synthesis and Biological Screening of 3,5-Diiodothyroacetic and -propionic Acid Analogs

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Several 3,5-diiodothyroacetic and -propionic acids as well as certain of their ether and ester derivatives were prepared and examined for hypocholesteremic activity. The interesting 2′,3′-dimethyl compounds were studied further in other thyromimetic assays. The compounds, in general, had weak cholesterol-lowering activity although a desired separation of activities was evident in compounds IIIb, IVa, and IVb.

Jorgensen and co-workers[1,2] have shown within a series of dialkyl-3,5-diiodothyronines and 3,5-diiodo-4′-deoxythronines that the 2′,3′-dimethyl analogs were among the most active compounds. Subsequently, these workers[3] showed that the phenyl ether of 3,5-diiodotyrosine had cholesterol-lowering activity. Herman, Lee, and Parker,[4] in studying the hypocholesteremic activity of thyroxine-like compounds, have reported that 3,5-diiodo-3′,5′-dimethyl compounds have activity comparable to that of the corresponding 3,3′,5,5′-tetraiodo analogs. Other studies[5–7] have shown that alteration of the alanine side chain of 3,5-diiodothyronines has a significant effect on the nature and magnitude of the elicited biological responses. Thus, the synthesis of several dialkyl-3,5-diiodothyroacetic and -propionic acids, certain of their ether and ester derivatives, as well as the phenyl ethers of 4-hydroxy-3,5-diiodophenylacetic and -propionic acids was undertaken. Specifically, it was hoped that these compounds would lower plasma cholesterol levels without at the same time increasing calorigenic or cardiac responses. A second more

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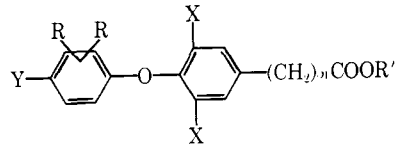
TABLE I

SUBSTITUTED 4-PHENOXYPHENYLACETIC AND -PROPIONIC ACIDS



Compd no.	n	X	Y	R	R′	Mp, °C[a]	Recrystn solvent	% yield	Formula	Calcd, % C	Calcd, % H	Calcd, % N or I	Found, % C	Found, % H	Found, % N or I
Ia	1	NO_2	H	H	C_2H_5	101–102	CH_3OH	61	$C_{16}H_{14}N_2O_7$	55.49	4.08	8.09	55.41	4.12	7.96
b	1	NO_2	OCH_3	2′,3′-CH_3	C_2H_5	122–124	C_2H_5OH	50	$C_{19}H_{20}N_2O_8$[b]	56.43	4.99	6.93	56.43	5.30	7.25
c	1	NO_2	OCH_3	5,6,7,8-(4H)[c]	C_2H_5	94–96	C_2H_5OH	47	$C_{21}H_{22}N_2O_8$	58.60	5.15	6.51	58.98	5.33	6.31
d	1	NO_2	OCH_3	3′,5′-CH_3	C_2H_5	83–85	C_2H_5OH	62	$C_{19}H_{20}N_2O_8$	56.43	4.99	6.93	56.56	5.07	6.59
e	2	NO_2	H	H	C_2H_5	84–86	80% CH_3OH	80	$C_{17}H_{16}N_2O_7$	56.66	4.48	7.78	56.55	4.55	7.86
f	2	NO_2	OCH_3	2′,3′-CH_3	C_2H_5	119–120	C_2H_5OH	73	$C_{20}H_{22}N_2O_8$	57.41	5.30	6.70	57.51	5.37	6.89
IIa	1	I	H	H	C_2H_5	105–106	CH_3OH	41	$C_{16}H_{14}I_2O_4$[d]	37.16	2.92	49.09	37.27	3.00	49.39
b	1	I	OCH_3	2′,3′-CH_3	C_2H_5	126–127	C_2H_5OH	72	$C_{19}H_{20}I_2O_4$[b]	40.31	3.56	44.83	40.46	3.58	44.79
c	1	I	OCH_3	5,6,7,8-(4H)[c]	C_2H_5	85–86	Aq C_2H_5OH	57	$C_{21}H_{22}I_2O_4$	42.59	3.74	42.86	42.81	3.76	43.26
d	1	I	OCH_3	3′,5′-CH_3	C_2H_5	Oil		78	$C_{19}H_{20}I_2O_4$						
e	2	I	H	H	C_2H_5	Oil		51	$C_{17}H_{16}I_2O_3$						
f	2	I	OCH_3	2′,3′-CH_3	C_2H_5	94–96	Aq CH_3OH	50	$C_{20}H_{22}I_2O_4$	41.40	3.82	43.75	41.85	4.14	43.59
IIIa	1	I	H	H	H	191–193	CH_3CN	93	$C_{14}H_{10}I_2O_3$	35.03	2.10	52.87	35.15	2.22	52.24
b	1	I	OH	2′,3′-CH_3	H	194–196	Aq C_2H_5OH	78	$C_{16}H_{14}I_2O_4$[b]	36.67	2.69	48.43	36.69	2.87	48.14
c	1	I	OH	5,6,7,8-(4H)[c]	H	218–219	$CH_3CO_2C_2H_5$–petr ether	75	$C_{18}H_{16}I_2O_4$	39.29	2.93	46.14	39.44	3.13	45.56
d	1	I	OH	3′,5′-CH_3	H	196–197	Aq C_2H_5OH	75	$C_{16}H_{14}I_2O_4$[e]	36.67	2.69	48.43	36.81	2.71	48.07
e	2	I	H	H	H	197–199	C_2H_5OH	56	$C_{16}H_{12}I_2O_3$	36.46	2.45	51.37	36.76	2.69	51.40
f	2	I	OH	2′,3′-CH_3	H	237–239	CH_3CN	40	$C_{17}H_{16}I_2O_4$	37.94	3.00	47.17	38.29	2.99	47.25
g	1	I	OCH_3	2′,3′-CH_3	H	178–179	Aq C_2H_5OH	67	$C_{17}H_{16}I_2O_4$	37.94	3.00	47.17	38.27	2.96	47.30
IVa	1	I	OH	2′,3′-CH_3	$(CH_2)_2N(C_2H_5)_2$	206–208	Acetone–hexane	94	$C_{22}H_{29}I_2NO_4$[f]	40.05	4.28	38.47	40.37	4.33	38.35
b	1	I	OCH_3	2′,3′-CH_3	$(CH_2)_2N(C_2H_5)_2$	195–197	CH_3OH–$(C_2H_5)_2O$	80	$C_{23}H_{29}I_2NO_4$[f]	41.00	4.49	37.67	41.16	4.69	37.43

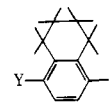
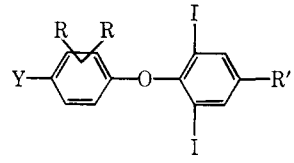
[a] Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected. [b] Reported previously by B. Blank and C. M. Greenberg, U. S. Patent 3,210,413 (Oct 5, 1965). [c] This is  . [d] Hemihydrate. [e] Reported by W. Siedel, H. Nahm, and J. König, German Patent 1,072,998 (Jan 14, 1960). [f] Hydrochloride.

TABLE II

RELATIVE THYROMIMETIC ACTIVITIES[a]



Compd no.	Y	R	R′	Plasma total cholesterol	Oxygen consumption	Heart wt increase	Antigoitrogenic
IIIa	H	H	CH_2COOH	Inactive			
b	OH	2′,3′-CH_3	CH_2COOH	0.06–0.09	0.014	0.013	0.01
c	OH	5,6,7,8-(4H)[b]	CH_2COOH	0.025			
d	OH	3′,5′-CH_3	CH_2COOH	0.025			
e	H	H	CH_2CH_2COOH	Inactive			
f	OH	2′,3′-CH_3	CH_2CH_2COOH	0.008			
g	OCH_3	2′,3′-CH_3	CH_2COOH	0.038			
IVa	OH	2′,3′-CH_3	$CH_2COOCH_2CH_2N(C_2H_5)_2$	0.10–0.15	0.014	0.015	0.01
b	OCH_3	2′,3′-CH_3	$CH_2COOCH_2CH_2N(C_2H_5)_2$	0.017	0.006	0.003	Inactive
Va	H	H	L-$CH_2CH(NH_2)COOH$	0.005[c]			
b	OH	2′,3′-CH_3	L-$CH_2CH(NH_2)COOH$	0.10–0.24[c]	0.16[d]		0.12[d]

[a] Activity is expressed in terms of L-T_3 having an arbitrary value of 1. [b] This compound is 4-(4-hydroxy-5,6,7,8-tetrahydronaphthoxy)-3,5-diiodophenylacetic acid. [c] This value is comparable to that reported in ref 3. [d] Value taken from ref 3.

general goal of this investigation was to determine if previous structure–activity correlations were valid.

The syntheses followed the well-established pathways described by Wilkinson[8] and Kharasch and coworkers[9] for the preparation of 3,5-diiodothyroacetic and -propionic acids. The methoxyphenols required in these syntheses as well as the ether and ester derivatives IIIg, IVa, and IVb were obtained using previously described routes. The reactions are summarized in Chart I, while the compounds prepared, together with appropriate physical constants and analytical data, are presented in Table I.

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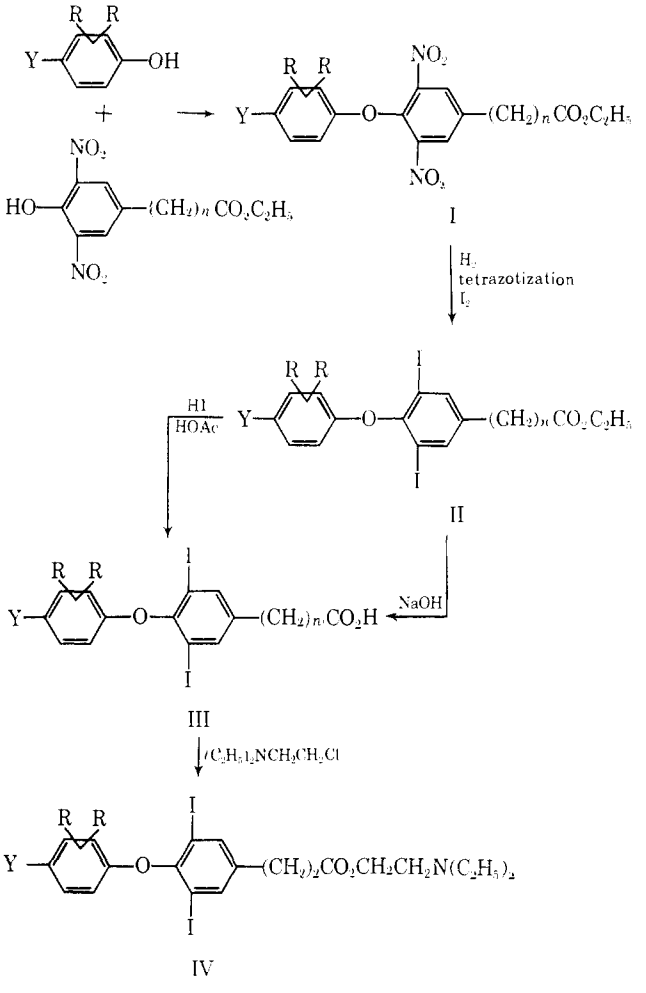
Experimental Section

Methoxyphenols.—2,3-Dimethyl-4-methoxyphenol was prepared from 2,3-dimethylphenol as described by Jorgensen and

CHART I



Kaul.[4] 3,5-Dimethyl-4-methoxyphenol was obtained according to the directions of Baker and Brown.[10] 5,6,7,8-Tetrahydronaphthalene-1,4-diol was prepared from the Diels–Alder adduct of butadiene and 1,4-benzoquinone[11] and was then methylated to give 5,6,7,8-tetrahydro-4-methoxy-1-naphthol.[12]

Ethyl 3,5-Dinitro-4-phenoxyphenylacetates and -propionates (Ia–f).—A solution of equimolar amounts of ethyl 4-hydroxy-3,5-dinitrophenylacetate[8] or -propionate[9] and *p*-toluenesulfonyl chloride in pyridine was stirred and heated on a steam bath for 10 min. The appropriate phenol was added and the mixture was stirred under reflux for 2 hr. The products were isolated and purified as described earlier.[13]

Ethyl 3,5-Diiodo-4-phenoxyphenylacetates and -propionates (IIa–f).—Reduction, tetrazotization, and iodination were performed using well-known procedures.[8,9,13]

3,5-Diiodo-4-phenoxyphenylacetic and -propionic Acids (IIIa–f).—Hydrolysis of the esters II was effected with a 1:1 mixture of hydriodic and acetic acids. After refluxing for 4–6 hr the solutions were cooled, diluted with water, and cooled further, and the resulting precipitates were filtered, washed with water, and recrystallized.

3,5-Diiodo-4-(4-methoxy-2,3-xylyloxy)phenylacetic Acid (IIIg).—A solution of IIb in aqueous ethanol containing dilute NaOH solution was stirred 1 hr at room temperature. The solution was diluted with water, acidified, cooled, and filtered. The product was washed with water and recrystallized.

β-Diethylaminoethyl 3,5-diiodo-4-phenoxyphenylacetate hydrochlorides (IVa and b) were prepared from the acids IIIa and g using the method of Horenstein and Pählicke.[13,14]

Biological Screening.—The compounds were screened for hypocholesteremic activity in rats fed a diet containing 2% cholesterol and 1% cholic acid.[15] Compounds which demonstrated significant activity in this assay were then examined for calorigenic,[16,17] cardiac-stimulatory,[17] and antigoitrogenic[15,18] activities. The results are shown in Table II.

Discussion

The compounds in this study had weak hypocholesteremic and thyromimetic activity compared to 3,3′,5-triiodo-L-thyronine (L-T_3), with the most active compound, IVa, being 0.01–0.15 as potent as L-T_3 in various assays. From the data in Table II the following conclusions can be drawn: (1) changing the alanine side chain of Va and b to an acetic or propionic acid causes a decrease in hypocholesteremic activity (compare Va and b with IIIa, b, e, and f); (2) conversion of Vb to the acetic acid analog IIIb causes a desirable separation of activities, IIIb being 6–9 times more potent as a cholesterol-lowering substance than as a stimulator of calorigenic effects or myocardial hypertrophy; (3) conversion of IIIb to the diethylaminoethyl ester IVa causes an increase in cholesterol-lowering activity without a concomitant rise in calorigenic rate or heart weight; (4) methylation of IIIb and IVa to the methyl ethers IIIg and IVb causes a decrease in hypocholesteremic activity and in the case of IVb causes a decrease in all activities with a slight separation of activities; (5) the acetic acid side chain seems to be more desirable than the propionic acid side chain when measured by hypocholesteremic activity (IIIb *vs.* IIIf); and (6) the 2′,3′-dimethyl modification is more desirable than either the 3′,5′-dimethyl or tetrahydronaphthyl modifications when measured by hypocholesteremic activity (compare IIIb with IIId and e).

In summary it can be said that the current studies confirm previous findings that methyl ethers are less potent than their phenolic counterparts[6,13] and that the nature of the side chain in thyroxine-like compounds has an effect on the type and magnitude of the biological response they produce.[5–7]

Acknowledgment.—We wish to thank members of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories for elemental analyses.

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