5-α-Hydroxybenzyluracil (VI).—5-Benzoyluracil (V) (0.075 g., 0.25 mole) was added to a solution of potassium borohydride (0.037 g.) in 2 ml. of water. The mixture was stirred vigorously for about 10 min. at room temperature and then for a further 5 min. at 100°. On acidifying with 3 *N* hydrochloric acid and cooling in ice there was obtained 0.03 g. (40%) of a white solid. It was recrystallized from ethanol, m.p. 221–223°, R_f 0.59.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.63; N, 12.84. Found: C, 60.79; H, 4.84; N, 12.78. Ultraviolet absorption: λ_{max} 265 mμ (ε 7624), λ_{min} 235 mμ (0.1 *N* HCl). λ_{max} 288 mμ (ε 6235), λ_{min} 250 mμ (0.1 *N* NaOH). Compounds X and XI were synthesized in the same manner.

Paper Chromatography.—The pyrimidines reported here were chromatographed on Whatman No. 1 paper by the descending technique in the butanol–water (86:14 v./v.) solvent system of Markham and Smith.[18] The chromatogram was run 18–20 hr. at room temperature and air dried, and the spots were located by means of a Mineralight ultraviolet lamp.

Biological Data.—Compounds V and VI along with 5-benzyluracil and 5-hydroxymethyluracil were tested against a wild strain and also a uracil-requiring mutant of *Escherichia coli* at a final concentration of 25 and 100 γ/ml. During the course of an 8 hr. period both the control and the analog containing cultures showed the same rate of growth, indicating no inhibition of growth by these analogs. With the uracil-requiring mutant of *E. coli* the experiments were carried out under growth-limiting concentrations of uracil (1.0 ml). All the compounds reported here have been submitted to the National Cancer Testing Service to test for antitumor activity.

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Acknowledgment.—We wish to express our gratitude to the U. S. Public Health Service (CY 3231) for financial assistance.

Thyromimetics. I. The Synthesis and Hypocholesteremic Activity of Some 3′ and 3′,5′-Alkyl and Aryl-3,5-diiodothyronines

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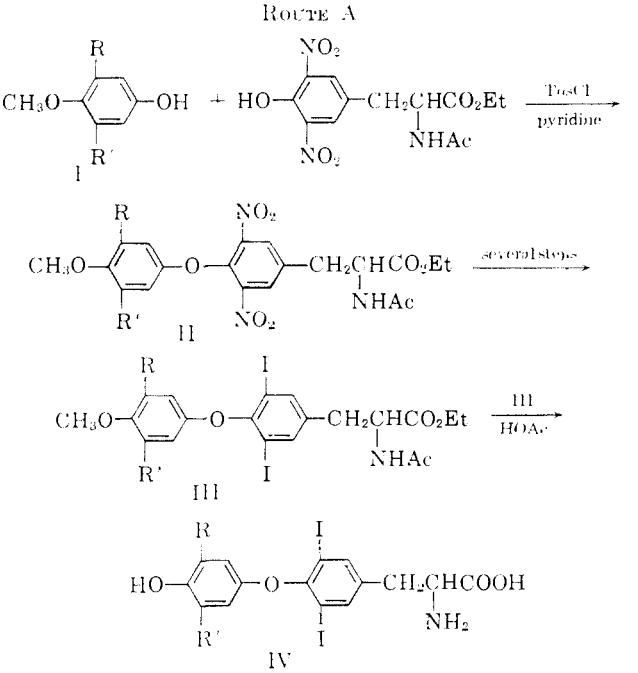
The syntheses of a number of alkyl and aryl derivatives of 3,5-diiodothyronine are described. Diphenyl ether intermediates required for these syntheses were prepared by one of two general procedures. The ability of the final compounds (IVa–h and XIa, d) to lower plasma cholesterol levels in rats fed a cholesterol–cholic acid diet is also reported.

The possibility that high serum cholesterol levels may in some way be involved in the etiology of atherosclerosis has led many investigators to study agents which cause a decrease in serum cholesterol. Thyromimetic compounds, as a class, have been among the most intensively studied of these agents.

Therefore, a number of compounds related to thyroxine and triiodothyronine had been prepared in our laboratories as part of a continuing program of chemical synthesis to provide compounds for biological evaluation as potential hypocholesteremic agents.[1–3] However, in light of the current interest in thyroxine-like compounds having alkyl groups, usually methyl groups, in place of iodine atoms[4–13] it seemed of interest to extend this approach and to prepare other alkyl derivatives of thyroxine and triiodothyronine. The studies of Jorgensen and his coworkers[6–8,12–14] in trying to determine what structural features are important for thyrominetic activity led us to prepare a series of 3′ and 3′,5′-alkyl and aryl-3,5-diiodothyronines for testing as cholesterol-lowering agents.

The compounds were prepared by two general routes. The first of these (route A) followed closely the method of synthesis developed by Chalmers, *et al.*,[15] for the preparation of thyroxine.

ROUTE A



(1) C. M. Greenberg, C. A. Bocher, J. F. Kerwin, S. M. Greenberg, and T. H. Lin, *Am. J. Physiol.*, **201**, 732 (1961).

(2) C. M. Greenberg, L. F. Mansor, C. A. Bocher, H. L. Saunders, and J. F. Kerwin, *Endocrinology*, **70**, 365 (1962).

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(9) E. Van Heyningen, *J. Org. Chem.*, **26**, 3850 (1961).

(10) C. S. Pittman, H. Shida, and S. B. Barker, *Endocrinology*, **68**, 248 (1961).

(11) R. G. Herman, C. C. Lee, and R. Parker, *Arch. Intern. Pharmacodyn.*, **133**, 284 (1961).

(12) E. C. Jorgensen and R. A. Wiley, *J. Med. Pharm. Chem.*, **5**, 1307 (1962).

(13) E. C. Jorgensen, P. A. Lehmann, C. Greenberg, and N. Zenker, *J. Biol. Chem.*, **237**, 3832 (1962).

(14) (a) E. C. Jorgensen and P. A. Lehman, *J. Org. Chem.*, **26**, 894, 897 (1961); (b) E. C. Jorgensen and P. Slade, *J. Med. Pharm. Chem.*, **5**, 729 (1962).

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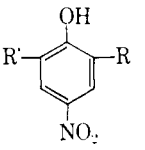
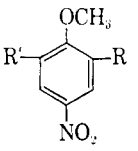
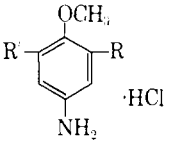
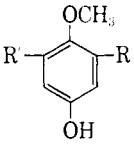
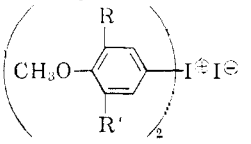
TABLE I

Compd. no.	R	R′	M.p., °C.	Recrystal. solvent	% yield	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Substituted *p*-Nitrophenols												
												
VIa	C_2H_5	H	73–75	CCl_4–pet. ether	58	$C_8H_9NO_3$	[a]					
b	*i*-C_3H_7	H	84–85	CCl_4–pet. ether	67	$C_9H_{11}NO_3$	[b]					
c	*i*-C_4H_9	H	88–89	Ligroin	84	$C_{10}H_{13}NO_3$	61.53	6.71	7.18	61.88	6.74	7.12
d	C_6H_5	H	121–123	Aq. HOAc	87	$C_{12}H_9NO_3$	[c]					
e	C_6H_5	C_6H_5	115	EtOH	72	$C_{18}H_{13}NO_3$	[d]					
f	Cyclo-C_6H_{11}	H	155–157[e]	Toluene	[e,f]	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	65.47	6.71	6.26
Substituted *p*-Nitroanisoles												
												
VIIa	C_2H_5	H	B.p., 134–135 (3 mm.)	.....	74	$C_9H_{11}NO_3$	59.66	6.12	7.73	59.34	6.08	7.81
b	*i*-C_3H_7	H	B.p. 147–148 (8 mm.)	.....	82	$C_{10}H_{13}NO_3$	61.53	6.71	7.18	61.66	6.90	7.34
c	*i*-C_4H_9	H	B.p. 120° (0.5 mm.)	.....	84	$C_{11}H_{15}NO_3$	63.14	7.23	6.69	63.32	7.27	6.83
d	C_6H_5	H	92–93	EtOH	77	$C_{13}H_{11}NO_3$	[c]					
e	C_6H_5	C_6H_5	152–154	EtOH–$CHCl_3$	69	$C_{19}H_{15}NO_3$	[d]					
Substituted *p*-Aminoanisoles												
												
VIIIa	C_2H_5	H	196–198	Sublimed twice	72	$C_9H_{14}ClNO$	57.60	7.52	18.89[h]	57.63	7.63	18.74[h]
b	*i*-C_3H_7	H	210–212	EtOH–$(C_2H_5)_2O$	76	$C_{10}H_{16}ClNO$	59.55	8.00	17.58[h]	59.26	7.94	17.71[h]
c	*i*-C_4H_9	H	162–164	EtOH–$(C_2H_5)_2O$	97	$C_{11}H_{18}ClNO$	61.24	8.41	16.44[h]	61.30	8.33	16.61[h]
d	C_6H_5	H	237–239	EtOH–$(C_2H_5)_2O$	89	$C_{13}H_{14}ClNO$	66.24	5.99	15.04[h]	66.55	6.24	14.70[h]
e	C_6H_5	C_6H_5	242–244	$CHCl_3$–pet. ether	85	$C_{19}H_{18}ClNO$	73.19	5.82	11.37[h]	72.85	5.94	11.35[h]
Substituted *p*-Methoxyphenols												
												
Ia	C_2H_5	H	126–130[g]	*i*-C_3H_7OH	43	$C_{16}H_{14}N_2O_7$[g]	55.49	4.08	8.09	55.74	4.16	8.05
b	*i*-C_3H_7	H	B.p. 137–139 (8 mm.)		58							
			92–93[g]	EtOH		$C_{17}H_{16}N_2O_7$[g]	56.67	4.48	7.78	56.64	4.41	7.81
c	*i*-C_4H_9	H	B.p. 161–163 (16 mm.)		44							
			85–87[g]	Skelly-L		$C_{18}H_{18}N_2O_7$[g]	57.75	4.85	7.48	57.50	4.70	7.39
d	C_6H_5	H	b.p. 200–203 (8 mm.)		26							
			149–150[g]	C_2H_5OH		$C_{20}H_{14}N_2O_7$[g]	60.92	3.58	7.10	60.43	3.69	6.83
e	C_6H_5	C_6H_5	166–167	Toluene	45	$C_{19}H_{16}O_2$	82.58	5.84		82.56	5.74	

[a] See ref. 18b and E. C. S. Jones and J. Kenner, *J. Chem. Soc.*, 1842 (1933). [b] Fileti, *Gazz. chim. ital.*, **16**, 117 (1886). [c] See ref. 18c. [d] See ref. 18b. [e] J. F. Bartlett and C. E. Garland, *J. Am. Chem. Soc.*, **55**, 2064 (1933), describe the preparation of a mononitro-*o*-cyclohexylphenol. It was reported to be a red oil, b.p. 144–146°. [f] During distillation most of the material decomposed, b.p. 205–210° (4 mm.). [g] For the 3,5-dinitrobenzoate. [h] Chlorine analyses.

TABLE II

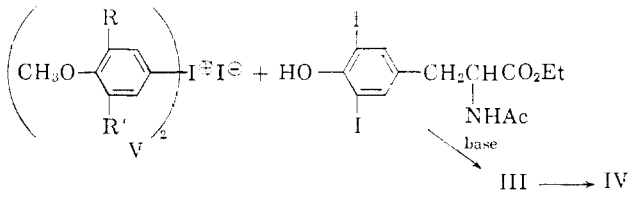
SUBSTITUTED DI-(*p*-ANISYL) IODONIUM IODIDES



Compd. no.	R	R'	M.p., °C.	Recrystal. solvent	% yield	Method used	Formula	Calcd., % C	Calcd., % H	Calcd., % I	Found, % C	Found, % H	Found, % I
Va	CH_3	H	179–181	CH_3OH	10	1	$C_{16}H_{18}I_2O_2$	38.73	3.66	51.16	38.73	3.86	50.78
b	C_2H_5	H	155–157	Acetone	15	2	$C_{18}H_{22}I_2O_2$	41.24	4.23	48.42	41.38	4.11	48.54
c	*i*-C_3H_7	H	164–166	THF–$(C_2H_5)_2O$	86	2	$C_{20}H_{26}I_2O_2$	43.50	4.75	45.96	43.32	4.62	46.03
d	*t*-C_4H_9	H	177–178	DMF–H_2O	86	2	$C_{22}H_{30}I_2O_2$	45.53	5.21	43.73	45.59	5.49	44.02
e	Cyclo-C_6H_{11}	H	167–168	CH_3OH	83	2	$C_{26}H_{34}I_2O_2$	49.38	5.42	40.14	49.28	5.55	40.02
f	*i*-C_3H_7	*i*-C_3H_7	160–162	DMF–H_2O	33	2	$C_{26}H_{38}I_2O_2$	49.07	6.02	39.88	49.33	5.94	40.05

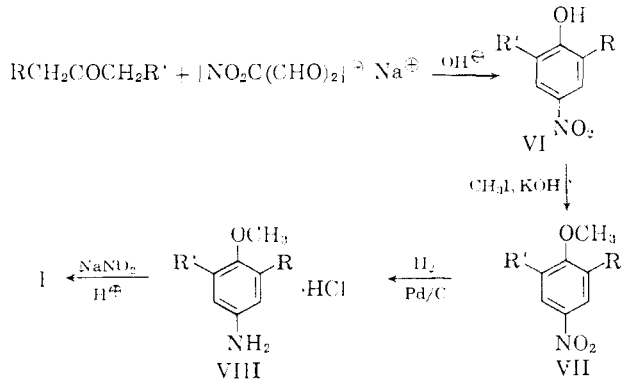
The second route (route B) was based on a synthesis of thyroxine developed by Hillman.[16] More recently this approach has been extended by other workers.[12,17]

ROUTE B



The choice of routes was determined to a large extent by the availability of the required intermediates. It was our experience that III could usually be prepared more conveniently by route A. However, in those cases where the required *p*-methoxyphenols (I) could be secured only by long and laborious procedures, route B proved to be a useful and convenient alternative.

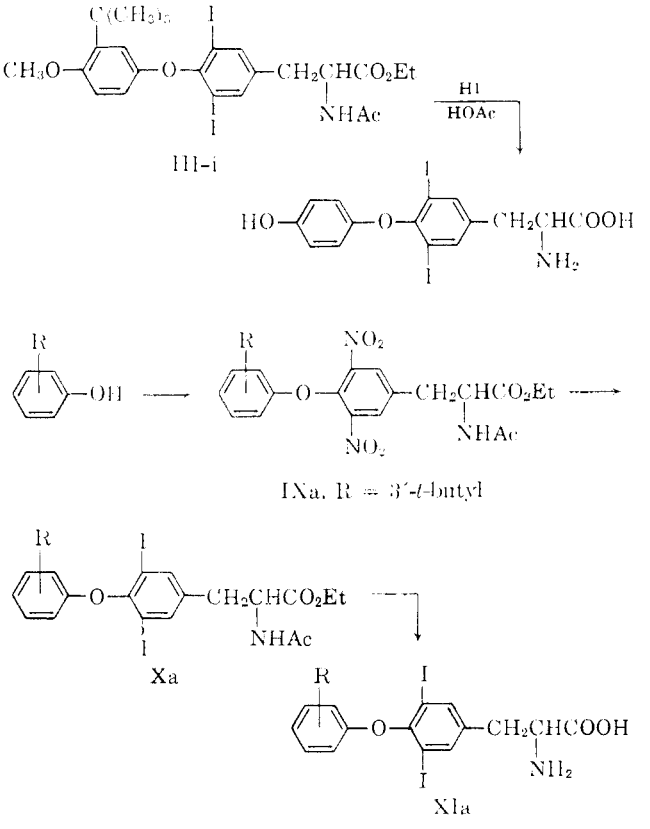
For the preparation of I a longer and more devious route than is usually employed for such compounds was chosen in order to fix unambiguously the position of the alkyl groups in the final compounds. The method utilized was originally described by Hill and his associates[18] and has recently been employed by Armstrong, *et al.*,[19] for the preparation of 2,6-di-*n*-octylhydroquinone.



Conversion of Ia–e to IIa–e and thence to IVa–e proceeded in a straightforward manner.[15]

The ethers (V) used in route B were prepared by the procedure of Plati[20] (method 1) for di-(*p*-anisyl)iodonium bromide or that of Beringer and his coworkers[21] (method 2) for the preparation of di-(*p*-anisyl)iodonium halides. Using these methods the iodonium iodides listed in Table II were prepared.

Conversion of V to III was accomplished in methanol solution on treatment with N-acetyl-3,5-diiodotyrosine ethyl ester in the presence of triethylamine and copper powder.[11a] IV was then obtained as in route A by removing the protecting groups with a mixture of hydriodic and acetic acids. In the case of the 3′-*t*-butyl derivative (IIIi) this acid treatment caused the loss of the *t*-butyl group as evidenced by the isolation of 3,5-diiodothyronine. The identity of the diiodothyronine



(16) (a) G. Hillman, *Z. Naturforsch.*, **11b**, 449 (1956); (b) G. Hillman, U. S. Patent 2,886,592 (May 12, 1959).

(17) (a) P. F. Bevilacqua, J. T. Plati, and W. Wenner, U. S. Patent 2,895,927 (July 21, 1959); (b) A. Dibbo, L. Stephenson, T. Walker, and K. Warburton, *J. Chem. Soc.*, 2615 (1961).

(18) (a) H. B. Hill and J. Torrey, *Am. Chem. J.*, **22**, 89 (1899); (b) H. B. Hill, *ibid.*, **24**, 1 (1900); (c) H. B. Hill and W. J. Hale, *ibid.*, **33**, 8 (1911).

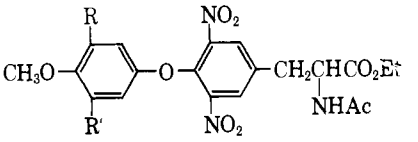
(19) E. C. Armstrong, R. L. Bent, A. Loria, J. R. Thirtle, and A. Weissberger, *J. Am. Chem. Soc.*, **82**, 1928 (1960).

(20) J. T. Plati, U. S. Patent 2,839,583 (June 17, 1958).

(21) F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Marsallo, M. Mausner, and E. Sommer, *J. Am. Chem. Soc.*, **81**, 342 (1959).

TABLE III

SUBSTITUTED 3,5-DINITROTHYRONINE DERIVATIVES

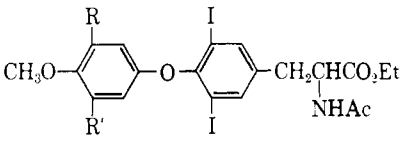


Compd. no.	R	R'	M.p., °C.	% yield	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIa-DL	C_2H_5	H	125–127	40	$C_{22}H_{25}N_3O_9$	55.58	5.30	8.84	55.56	5.36	9.15
IIa-L	C_2H_5	H	109–110	57	$C_{22}H_{25}N_3O_9$	$[\alpha]^{25}D$	+50.7°	(*c* 0.5)[b]	55.63	5.12	8.62
IIb-DL	*i*-C_3H_7	H	128–130	37	$C_{23}H_{27}N_3O_9$	56.44	5.56	8.59	56.28	5.61	8.73
IIb-D	*i*-C_3H_7	H	104–105	31	$C_{23}H_{27}N_3O_9$	$[\alpha]^{25}D$	−42.3°	(*c* 0.8)	56.52	5.50	8.65
IIb-L	*i*-C_3H_7	H	107–109	55	$C_{23}H_{27}N_3O_9$	$[\alpha]^{25}D$	+41.6	(*c* 1.0)	56.62	5.61	8.62
IIc-L	*i*-C_4H_9	H	107–109	55	$C_{24}H_{29}N_3O_9$	57.25	5.81	8.35	57.52	5.94	8.36
						$[\alpha]^{25}D$	+43.9	(*c* 0.7)			
IId-DL	C_6H_5	H	175–177	69	$C_{26}H_{25}N_3O_9$	59.65	4.81	8.03	59.55	4.92	8.00
IIe-DL	C_6H_5	C_6H_5	175–178	75	$C_{32}H_{29}N_3O_9$	64.10	4.88	7.01	63.77	4.99	7.05

[a] All compounds were recrystallized from ethanol, except IIb-D (aq. EtOH). [b] All rotations were determined in chloroform.

TABLE IV

SUBSTITUTED 3,5-DIIODOTHYRONINE DERIVATIVES



Compd. no.	R	R'	M.p., °C.	Recrystal. solvent	% yield	Route used	Formula	Calcd., % C	Calcd., % H	Calcd., % I	Found, % C	Found, % H	Found, % I
IIIa-DL	C_2H_5	H	129–131	Aq. C_2H_5OH	30	A	$C_{22}H_{23}I_2NO_5$	41.46	3.95	39.83	41.46	3.96	39.16
IIIa-L	C_2H_5	H	114–116	C_2H_5OH	48	B	$C_{22}H_{23}I_2NO_5$	$[\alpha]^{25}D$	+52.2 (*c* 0.5)[a]		41.57	3.75	39.62
IIIb-DL	*i*-C_3H_7	H	119–121	Aq. C_2H_5OH	52	A	$C_{23}H_{27}I_2NO_5$	42.42	4.18	38.97	42.43	4.31	38.90
IIIb-D	*i*-C_3H_7	H	119–120	Aq. C_2H_5OH	73	A	$C_{23}H_{27}I_2NO_5$	$[\alpha]^{25}D$	−42.4 (*c* 0.7)		42.68	4.32	38.70
IIIb-L	*i*-C_3H_7	H	129–131	C_2H_5OH	72	A	$C_{23}H_{27}I_2NO_5$	$[\alpha]^{25}D$	+47.3 (*c* 1.0)		42.56	4.30	38.98
IIIc-L	*i*-C_4H_9	H	141–143	C_2H_5OH	45	A	$C_{24}H_{29}I_2NO_5$	43.33	4.39	38.15	43.44	4.29	38.25
								$[\alpha]^{25}D$	+48.3 (*c* 1.1)				
IIId-DL	C_6H_5	H	128–130	C_2H_5OH	36	A	$C_{26}H_{23}I_2NO_5$	45.57	3.68	37.04	45.41	3.66	36.95
IIIe-DL	C_6H_5	C_6H_5	182–184	Aq. C_2H_5OH	44	A	$C_{32}H_{29}I_2NO_5$	50.48	3.84	33.34	50.65	3.78	32.74
IIIf-DL	CH_3	H	118–120	C_2H_5OH	34	B	$C_{21}H_{23}I_2NO_5$	40.47	3.72	40.73	40.53	3.82	40.48
IIIg-DL	Cyclo-C_6H_{11}	H	143–144	$(C_2H_5)_2O$–pet. ether	45	B	$C_{26}H_{31}I_2NO_5$	45.17	4.52	36.71	45.18	4.47	36.46
IIIh-DL	*i*-C_3H_7	i-C_3H_7	147–148	Aq. C_2H_5OH	18	B	$C_{26}H_{33}I_2NO_5$	45.04	4.80	36.61	45.29	4.91	36.68
IIIi-DL	*t*-C_4H_9	H	137–139	C_2H_5OH	48	B	$C_{24}H_{29}I_2NO_5$	43.33	4.39	38.15	43.65	4.38	38.18

[a] All rotations were determined in chloroform.

was confirmed by elemental analysis, paper chromatography, and a comparison of its melting point with that of an authentic sample prepared in our laboratory.

To gain some further insight into the course of this reaction the corresponding 4′-deoxy compound (XIa) was prepared. In this case hydrolysis with hydriodic and acetic acids occurred without dealkylation. This implies that the loss of the *t*-butyl group in the 4′-hydroxy series in some way involves the 4′-hydroxy group. This reaction has not yet been investigated any further.

Three other 4′-deoxy compounds (XIb, c, and d, where R is 2′, 3′, and 4′-phenyl, respectively) were also prepared in a manner completely analogous to that used in the preparation of XIa.

Experimental[22]

Preparation of Substituted *p*-Nitrophenols (VI) (Table I).—A solution of the required ketone in alcohol was added to an aqueous solution of an equimolar amount of the sodium salt of nitromalondialdehyde.[23] A 1 *M* excess of dilute sodium hydroxide was added and the mixture was stirred at room temperature for 24 hr. The alcohol was removed by heating the mixture on a steam bath and the aqueous solution was cooled and acidified with dilute hydrochloric acid. The products were either filtered and recrystallized directly or were extracted into ether. The ethereal solutions were washed with base to separate phenolic material from other nonacidic material. Acidification of the alkaline washes followed by recrystallization yielded VI.

Preparation of Substituted *p*-Nitroanisoles (VII) (Table I).—To a stirred suspension of powdered potassium hydroxide in ethanol (about 2% w./v.) was added an equimolar amount of VI. The mixture was heated to reflux and an equimolar amount of methyl iodide was added slowly. After heating for 2 hr. an additional amount of methyl iodide equal to one-half that originally added was introduced slowly into the reaction mixture and stirring and heating were continued overnight. The alcohol was removed and the residue was dissolved in a mixture of ether and water. The layers were separated and the ethereal layer was washed consecutively with water, 10% sodium bisulfite, water, 10% sodium hydroxide, and again with water. After drying over magnesium sulfate the ethereal solution was evaporated and the residue was either recrystallized or distilled.

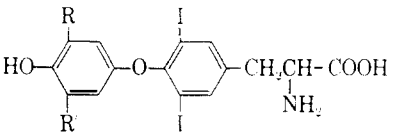
Preparation of Substituted *p*-Aminoanisoles (VIII) (Table I).—The substituted *p*-nitroanisoles (VII) dissolved in ethanol were

(22) All melting points were taken in a Thomas–Hoover melting point apparatus and are corrected.

(23) P. E. Fanta, *Org. Syn.*, **32**, 95 (1952).

TABLE V

SUBSTITUTED 3,5-DIIODOTHYRONINES

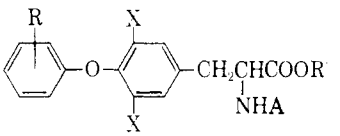


Compd. no.	R	R'	M.p., °C.[a]	Recrystal. solvent[b]	%, yield	R_f[c]	Formula	Calcd., %, C	H	I	Found, %, C	H	I
IVa-DL	C_2H_5	H	232–234	C_2H_5OH–H_2O	58	0.53	$C_{17}H_{17}I_2NO_4$[d]	36.32	3.23	45.16	36.58	3.25	44.83
IVa-L	C_2H_5	H	252–254	C_2H_5OH–H_2O	67	.53	$C_{17}H_{17}I_2NO_4$	36.91	3.10	45.89	37.16	3.22	45.29
								$[\alpha]^{25}D$	−45.0 (*c* 0.5)[e]				
IVb-DL	*i*-C_3H_7	H	202–204	C_2H_5OH–H_2O	42	.61	$C_{18}H_{19}I_2NO_4$[d]	37.54	3.50	44.05	37.71	3.53	
									N, 2.43			N, 2.39	
IVb-L	*i*-C_3H_7	H	225–226	C_2H_5OH–H_2O	84	.61	$C_{18}H_{19}I_2NO_4$[d]	$[\alpha]^{25}D$	+23.2 (*c* 0.8)		37.52	3.56	44.12
IVb-D	*i*-C_3H_7	H	216–218	C_2H_5OH–H_2O	10	.65	$C_{18}H_{19}I_2NO_4$	38.12	3.38	44.75	38.45	3.59	44.69
								$[\alpha]^{25}D$	−28.5° (*c* 0.4)				
IVc-L	*i*-C_4H_9	H	239–241	C_2H_5OH–H_2O	80	.64	$C_{19}H_{21}I_2NO_4$[f]	38.66	3.76	43.01	38.90	3.90	43.08
								$[\alpha]^{25}D$	−27.1 (*c* 1.1)				
IVd-DL	C_6H_5	H	219–221	C_2H_5OH–H_2O	89	.59	$C_{21}H_{17}I_2NO_4$[f]	40.73	3.09	41.00	40.86	2.88	41.34
IVe-DL	C_6H_5	C_6H_5	233–235	Aq. CH_3CO_2H	50		$C_{27}H_{21}I_2NO_4$[d] CH_3CO_2H	46.67	3.51	34.01	46.73	3.74	34.18
IVf-DL	CH_3	H	246–248	C_2H_5OH–H_2O	57	.47	$C_{16}H_{15}I_2NO_4$[e]	35.06	2.94	46.31	35.15	3.21	45.98
IVg-DL	Cyclo-C_6H_{11}	H	203–205	C_2H_5OH–H_2O	20	.61	$C_{21}H_{23}I_2NO$	41.54	3.82	41.80	41.39	3.97	42.19
IVh-DL	*i*-C_3H_7	*i*-C_3H_7	235–236	C_2H_5OH–H_2O	65	.67	$C_{21}H_{25}I_2NO_4$	41.40	4.56	41.66	41.30	4.24	42.31

[a] All compounds melted with decomposition. [b] All compounds except IVe were recrystallized from hot ethanolic solutions containing a few drops of concd. hydrochloric acid by the addition of hot water and hot 2 *N* sodium acetate solution to pH 5–6. [c] Paper chromatograms were prepared in an isoamyl alcohol–*t*-amyl alcohol–6 *N* NH_3 system (1:1:2) and were developed by spraying with ninhydrin: I. B. Eisdorfer and W. C. Ellenbogen, p. 42B, Abstracts of the 131st National Meeting of the American Chemical Society, Miami, Florida, April, 1957. [d] Hemihydrate. [e] All rotations were determined in ethanol–1 *N* hydrochloric acid (3:1 by volume). [f] Monohydrate.

TABLE VI

SUBSTITUTED 4'-DEOXY-3,5-DINITRO AND 3,5-DIIODO-DL-THYRONINE DERIVATIVES



Compd. no.	R	R'	X	A	M.p., °C.	Recrystal. solvent	%, yield	Formula	Calcd., %, C	H	N	Found, %, C	H	N
IXa	3'-*t*-C_4H_9	C_2H_5	NO_2	$COCH_3$	87–89	Aq. C_2H_5OH	42	$C_{23}H_{27}N_3O_8$	58.34	5.75	8.88	58.32	5.83	8.91
b	2'-C_6H_5	C_2H_5	NO_2	$COCH_3$	223–224	CH_3CN	56	$C_{29}H_{23}N_3O_8$	60.85	4.70	8.52	60.83	4.90	8.57
c	3'-C_6H_5	C_2H_5	NO_2	$COCH_3$	140–142	*i*-C_3H_7OH	64	$C_{29}H_{23}N_3O_8$	60.85	4.70	8.52	61.07	4.80	8.59
d	4'-C_6H_5	C_2H_5	NO_2	$COCH_3$	144–146	C_2H_5OH	74	$C_{29}H_{23}N_3O_8$	60.85	4.70	8.52	61.02	4.99	8.61
									C	H	I	C	H	I
Xa	3'-*t*-C_4H_9	C_2H_5	I	$COCH_3$	91–93	Aq. C_2H_5OH	61	$C_{23}H_{27}I_2NO_4$	43.48	4.28	39.95	43.76	4.35	40.00
b	2'-C_6H_5	C_2H_5	I	$COCH_3$	172–175	Aq. C_2H_5OH	23	$C_{25}H_{23}I_2NO_4$	45.82	3.54	38.73	46.14	3.69	38.55
c	3'-C_6H_5	C_2H_5	I	$COCH_3$	149–151	Aq. CH_3OH	23	$C_{25}H_{23}I_2NO_4$	45.82	3.54	38.73	45.97	3.57	38.97
d	4'-C_6H_5	C_2H_5	I	$COCH_3$	170–172	50% aq. C_2H_5OH	27	$C_{25}H_{23}I_2NO_4$	45.82	3.54	38.73	45.81	3.75	38.98
XIa	3'-*t*-C_4H_9	H	I	H	225–227	C_2H_5OH–H_2O[a]	87	$C_{19}H_{21}I_2NO_3$[b]	39.81	3.86	44.21	39.68	4.00	44.42
b	2'-C_6H_5	H	I	H	215–217	C_2H_5OH–H_2O[a]	20	$C_{21}H_{17}I_2NO_4$[b]	42.44	3.05	42.72	42.54	3.39	42.57
c	3'-C_6H_5	H	I	H	234–236	C_2H_5OH–H_2O[a]	65	$C_{21}H_{17}I_2NO_3$	43.10	2.93	43.37	43.25	3.19	42.96
d	4'-C_6H_5	H	I	H	239–240	C_2H_5OH–H_2O[a]	[c]	$C_{21}H_{17}I_2NO_3$[d]	41.82	3.18	42.05	41.83	3.04	41.56
e	4'-C_6H_5	H	I	$COCH_3$	250–251	Aq. CH_3CO_2H	40	$C_{23}H_{19}I_2NO_4$	44.04	3.05	40.47	44.26	3.37	40.16

[a] These compounds were recrystallized from hot ethanolic solutions containing a few drops of concd. hydrochloric acid by the addition of hot water and hot 2 *N* sodium acetate solution to pH of 5–6. [b] Hemihydrate. [c] Material was obtained by hydrolyzing XIe. [d] Monohydrate.

reduced in a Parr apparatus in the presence of 10% Pd/C (1.0 g./0.1 mole of nitro compound) under an initial pressure of 3–4 atm. of hydrogen. When the reduction had been completed, the catalyst was removed, the solvent was evaporated, and the residue was taken up in benzene and evaporated. This last operation was repeated 2–3 times with fresh portions of benzene to remove traces of water. The residue was taken up in a small volume of ether and saturated with dry hydrogen chloride. The precipitated hydrochloride was filtered, washed with ether, and recrystallized.

Preparation of *p*-Methoxyphenols (I) (Table I).—To a stirred slurry of 40 ml. of concentrated sulfuric acid and ice was added 0.2 mole of VIII. To this stirred, cooled mixture was added in portions 15 g. of sodium nitrite dissolved in a small volume of water. Stirring and cooling were continued for 15 min. after all the sodium nitrite had been added. The diazonium solution was added dropwise with stirring to a refluxing solution of 340 ml. of sulfuric acid in 680 ml. of water. Stirring and heating were continued further for 15 min. after all the diazonium solution had been added. The mixture was cooled and extracted several times with benzene. The benzene solution was washed with 10% sodium hydroxide and then with water until the aqueous washes

were neutral. The aqueous layers were combined and acidified with dilute hydrochloric acid. The resulting phenol, if a solid, was filtered and recrystallized; if a liquid it was extracted into benzene and the benzene solution was washed with water, dried over magnesium sulfate, and evaporated. The residue was then distilled *in vacuo*.

Preparation of Substituted Di-(*p*-anisyl)iodonium Iodides (V) (Table II). Method 1.—A solution of iodyl sulfate[20] prepared from 0.08 mole of iodine and 0.18 mole of iodine pentoxide in 500 ml. of acetic acid was cooled with stirring to 15°. The requisite anisole (0.2 mole) was added dropwise while the temperature was maintained at 15° by intermittent cooling. Cooling was discontinued and the solution was allowed to warm to room temperature as the iodyl sulfate dissolved (about 2.5 hr.). The mixture was filtered to remove a small amount of insoluble material and the filtrate was diluted with a large volume of water containing excess potassium iodide and a little sodium bisulfite. The solid which separated upon cooling was filtered, washed with ether, and recrystallized.

Method 2.—To a solution of iodine trifluoroacetate[21] in 50 ml. of acetic anhydride cooled to −10° was added a solution of the required anisole (0.2 mole) in a mixture of 80 ml. of acetic anhydride, 15 ml. of trifluoroacetic acid, and 0.5 ml. of water at such a rate that the temperature was kept below −5°. The mixture was stirred an additional 15 min. at −5° and then was stored in a refrigerator overnight. The following day the dark brown mixture was stirred for 3 hr. at room temperature before the solvents were removed at 40° (1–2 mm.). After the residue was dissolved in 350 ml. of methanol, the methanolic solution was diluted with 75 ml. of 10% sodium bisulfite and 100 g. of potassium iodide in 600 ml. of water. A precipitate which soon appeared was filtered, washed with a 6:1 petroleum ether–ether mixture, and recrystallized.

Preparation of IIa-e and IXa-d (Tables III and VI).—A solution of 0.045 mole of N-acetyl-3,5-dinitrotyrosine ethyl ester[15,24] and 0.045 mole of *p*-toluenesulfonyl chloride in 100 ml. of pyridine was heated on a steam bath for 10 min. with stirring. I or a substituted phenol (for the preparation of IXa–d) (0.10 mole) was added and the solution was stirred under reflux for 2 hr. The pyridine was removed *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was washed successively with dilute hydrochloric acid, water, 10% sodium hydroxide, and again with water. The chloroform solution was dried, the solvent was removed, and the residue was recrystallized.

Preparation of IIIa-e and Xa–d (Tables IV and VI). Route A.—A solution of II or IX (0.015 mole) in 150 ml. of acetic acid was reduced in a Parr apparatus in the presence of 1.5 g. of 10% Pd/C under an initial pressure of 3–4 atm. of hydrogen. When the reduction was complete, the catalyst was removed by filtration and the filtrate was added to a stirred, cooled nitrosyl sulfuric acid solution (prepared by slowly adding 5.9 g. of sodium nitrite to a mixture of 125 ml. of sulfuric acid and 50 ml. of acetic acid at 60–70°) at such a rate that the temperature was maintained at 0–5°. After all the amine had been added the tetrazonium solution was stirred and cooled an additional hr. It was then added rapidly to a stirring mixture of 13.2 g. of sodium iodide, 16.5 g. of iodine, and 3.0 g. of urea in 275 ml. of water and 275 ml. of chloroform. Stirring was continued for 1–2 hr. at room temperature and the layers were separated. The aqueous layer was extracted several times with chloroform and the combined chloroform phases were washed in turn with water, 10% sodium bisulfite, water, 5% sodium bicarbonate, and water. After drying over calcium chloride the chloroform solution was distilled. The residue was purified either by recrystallization or by elution with chloroform from a column packed with Woelm acid alumina (anionotropic, grade 1). Evaporation of the chloroform effluents yielded a material which was crystalline or which crystallized upon the addition of solvent.

Preparation of IIIa-L and IIIf–i (Table IV). Route B.—A mixture of 0.018 mole of V, 0.01 mole of N-acetyl-3,5-diiodotyrosine ethyl ester,[25] 1.5 ml. of triethylamine, and 0.1 g. of copper powder in 120 ml. of methanol was stirred vigorously at room temperature for 24 hr. The mixture was filtered and the filtrate was evaporated to a sirup. The sirup was dissolved in benzene and the benzene solution was shaken for 5 min. with dilute hydrochloric acid. Precipitated triethylamine hydrochloride was removed by filtration. The filtrate was placed in a separatory funnel and the organic layer was separated. After washing with water, 10% sodium hydroxide, and again with water the benzene solution was dried over sodium sulfate and distilled. The residue was crystallized by trituration with solvent or was chromatographed as described under route A.

Preparation of IVa-h and XIa-c (Tables V and VI).—A mixture of III or X in a solution made up of equal volumes of hydriodic (hydrochloric for X) and acetic acids (20 ml./g. of III or X) was heated under reflux for 4 hr., cooled, and poured into 4 volumes of ice–water. Aqueous sodium hydroxide was added to pH 5–6 and the precipitated solid was cooled, filtered, washed with water, and recrystallized.

Preparation of XId.—A suspension of 3 g. (4.6 mmoles) of Xd in 35 ml. of acetic acid and 35 ml. of hydrochloric acid was heated and stirred under reflux for 2 hr. During this time the solid dissolved and reprecipitated. The mixture was cooled, diluted with water, and adjusted to pH 5 with 40% sodium hydroxide. The solid was filtered, washed with water, and recrystallized from aqueous acetic acid to give 1.2 g. of amide (XIe), m.p. 250–251° dec.

A mixture of 700 mg. of XIe in 25 ml. of acetic acid and 25 ml. of hydrochloric acid was refluxed for 20 hr. (the solid never completely dissolved). The mixture was cooled, and filtered to give after drying 600 mg. of material, m.p. 246° dec. The material was purified by two isoelectric reprecipitations; yield 400 mg. of XId, m.p. 239–240° dec.

Hydrolysis of IIIi.—A mixture of 750 mg. of IIIi in 10 ml. of hydriodic and 20 ml. of acetic acids was refluxed for 4 hr. The product was isolated and purified as described for IVa–h; yield 400 mg. of 3,5-diiodo-DL-thyronine monohydrate, m.p. 259–261° dec.

Anal. Calcd. for $C_{15}H_{13}I_2NO_4 \cdot H_2O$: C, 33.17; H, 2.78; I, 46.74. Found: C, 33.52; H, 2.94; I, 46.95.

Biochemical Screening.—The compounds were screened for their ability to lower plasma cholesterol levels in rats fed a diet containing 2% cholesterol and 1% cholic acid.

L-Triiodothyronine (L-T_3) or the test compounds were injected subcutaneously, once daily for 7 days to groups of 8 adult male Sprague–Dawley rats having a fasting body weight of 270–290 g. and fed a diet consisting of 2% cholesterol, 1% cholic acid, 4% Alphacel, 4% vitamins and minerals, 20% protein, 20% hydrogenated fat, and 49% carbohydrate. Appropriate controls were also run. The animals were fasted for 18 hr. on the 7th day, and sacrificed by decapitation on the 8th day. Blood collections and cholesterol determinations were made in a manner similar to that reported previously.[2] The results are shown in Table VII and are expressed in terms of L-T_3 having an arbitrary value of 1.

$$\text{activity} = \frac{\text{dose of L-}T_3\text{ which decreases plasma total cholesterol at least 38 mg./100 ml.}^{26}}{\text{dose of test compound which lowers plasma total cholesterol to a comparable extent}}$$

TABLE VII

PLASMA CHOLESTEROL VALUES

Cmpd. No.	Activity[a]
IVa-DL	0.50
IVb-DL	1.00
IVb-D	0.15
IVb-L	1.30
IVc-L	0.50
IVd-DL	.35
IVe-DL	< .001
IVf-DL	.07
IVg-DL	.03
IVh-DL	< .001
XIa-DL	.04
XId-DL	.03

[a] Activity is expressed in terms of L-T_3 having an arbitrary value of 1.

(24) J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, 2467 (1951).

(25) J. H. Barnes, E. T. Burrows, J. Elks, B. A. Hems, and A. G. Long, *ibid.*, 2824 (1950).

(26) It has been shown statistically using pooled samples from thyromimetic-treated and control animals that a plasma total cholesterol difference of 38 mg./100 ml. is required for significance ($P = 0.01$).[1] A dose of 1.5–3.0 μg./kg./day of L-T_3 consistently causes such a depression.

As can be seen from Table VII several compounds (IVa-DL, IVb-DL, IVb-L, and IVc-L) have noteworthy activity. Compound IVb-L is particularly interesting since it appears to be more potent than L-T_3. A more detailed study of the activity in several thyromimetic assay procedures of most of the compounds listed in Table VII will be described shortly.[27]

(27) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls, *Am. J. Physiol.*, in press.

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Thyromimetics. II. The Synthesis and Hypocholesteremic Activity of Some β-Diethylaminoethyl Esters of Iodinated Thyroalkanoic Acids

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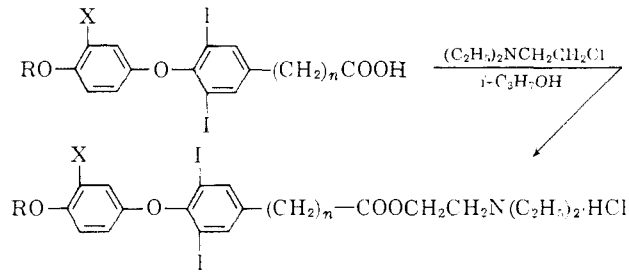
The synthesis of a number of β-diethylaminoethyl esters of iodinated thyroalkanoic acids is described. The ability of these compounds to lower plasma cholesterol levels in rats fed a cholesterol-cholic acid diet is also reported. A study of the hypocholesteremic activity of the compounds tested indicates that maximum activity is found in those compounds with a two-carbon side chain and a 3′-iodine atom or isopropyl group (VII, VIII, and XIII).

Although the relationship between serum cholesterol levels and the occurrence of atherosclerosis has not been conclusively demonstrated, the implications are such that the search for hypocholesteremic agents is currently being carried out by many investigators. In the search for a useful cholesterol-lowering agent much attention has been devoted to thyromimetic agents with current interest centering on the D-isomers of thyroxine and 3,3′,5-triiodothyronine and iodinated thyroacetic, -formic, and -propionic acids.[1-9]

While most of these compounds have some effect on serum cholesterol levels in animals few have proved satisfactory for use in man.

In an effort to obtain agents which have a specific hypocholesteremic action with few or no side effects a series of diethylaminoethyl esters of various iodinated thyroalkanoic acids was prepared (Table I). Several 4′-methyl ethers were also prepared since it appears that these derivatives often possess a large separation between the minimum effective hypocholesteremic dose and the dose which causes weight loss in animals.[7] Since it had been demonstrated in our laboratories that an isopropyl group can be substituted for iodine in the 3′-position of 3,5-diiodothyronine without causing any loss in hypocholesteremic activity,[10] the 3′-isopropyl analog XIII of the β-diethylaminoethyl ester of 3,3′,5-triiodothyroacetic acid (VII) was prepared to see if this relationship proved true in this series also.

To prepare the esters listed in Table I the requisite acids were treated with β-diethylaminoethyl chloride in dry 2-propanol.[11]



R = H or CH_3; X = H, I, or i-C_3H_7; n = 0, 1, 2

The 3′-isopropyl compound XIII was prepared using the sequence of reactions shown in Chart I.

Ethyl 3,5-diiodo-4-(3-isopropyl-4-methoxyphenoxy)-phenylacetate (XVI) was first prepared using a procedure (XIV → XV → XVI) similar to that reported by Wilkinson[12] in the preparation of 3,5-diiodothyroacetic acid. The intermediate XVI was prepared subsequently without isolation more expediently from the iodonium salt XVII as shown (XVII → XVI) using the method of Ziegler and Marr.[13] Basic hydrolysis of XVI yielded the methoxy acid XIX which in turn could be converted to the hydroxy acid XVIII on treatment with a mixture of acetic and hydriodic acids. The acid XVIII, however, was usually prepared directly from XVI as shown. Treatment of the acids XVIII and XIX with β-diethylaminoethyl chloride as described yielded the corresponding basic esters XIII and XX. Unfortunately, we were unable to purify XX to the point where satisfactory analytical data could be obtained.

Those 4′-methoxy acids whose syntheses had not been reported were readily prepared using dimethyl sulfate and aqueous sodium hydroxide (Table II).

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