and L-prolylglycyl-L-phenylalanyl-O-acetyl-L-seryl-L-prolyl-L-phenylalanyl-L-citrulline methyl ester hydrobromide (2.2 g.). The crude solid solidified from acetonitrile to yield 1.4 g., m.p. 118–120°, $[\alpha]^{23}D$ −54.4° (*c* 0.5, dimethylformamide); lit.[2] m.p. 155–160° (sintering 115°), $[\alpha]^{20}D$ −61.3° (*c* 0.99, dimethylformamide).

Anal. Calcd. for $C_{61}H_{81}N_{15}O_{17}\cdot 3H_2O$: C, 54.25; H, 6.49; N, 15.56. Found: C, 54.32; H, 6.35; N, 15.02.

Carbobenzoxynitro-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-L-phenylalanyl-L-histidine (XIIA).—The protected nonapeptide methyl ester (2.4 g., 0.002 mole) was dissolved in 20 ml. of methanol and 2.5 ml. of *N* sodium hydroxide was added. The mixture was allowed to stand 2.5 hr. and was evaporated *in vacuo*. The residue was partitioned between 75 ml. of water and 75 ml. of ethyl acetate. The aqueous layer was separated and acidified with *N* hydrochloric acid to precipitate a small amount of oil which solidified, 0.3 g., m.p. 140° with preliminary softening.

Anal. Calcd. for $C_{58}H_{73}N_{15}O_{15}\cdot H_2O$: C, 56.27; H, 6.11; N, 16.97. Found: C, 56.02; H, 6.28; N, 16.94.

Carbobenzoxynitro-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-L-phenylalanyl-L-citrulline (XIIB) was prepared by hydrolysis of 1 g. of the protected methyl ester in methanolic sodium hydroxide to yield 0.65 g. of amorphous solid, m.p. 125–130°.

Anal. Calcd. for $C_{58}H_{77}N_{15}O_{16}\cdot H_2O$: C, 55.38; H, 6.31; N, 16.70. Found: C, 55.46; H, 6.62; N, 15.74.

L-Arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-L-phenylalanyl-L-histidine (9-Histidine Bradykinin) (XIIIA).—Carbobenzoxynitro-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-L-phenylalanyl-L-histidine (250 mg.) was hydrogenated in glacial acetic acid–methanol over palladium black in the usual manner. The mixture was filtered and evaporated *in vacuo*. The residue was dissolved in water, filtered, shell frozen, and lyophilized to give 220 mg. of a solid which gave a single spot on electrophoresis in acetate buffer, pH 5.6, 3 hr. at 30 ma.

Anal. Calcd. for $C_{50}H_{68}N_{14}O_{11}\cdot CH_3COOH\cdot 4H_2O$: C, 52.20; H, 6.46; N, 17.75. Found: C, 52.59; H, 6.76; N, 15.77.

L-Arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-L-phenylalanyl-L-citrulline (9-Citrulline Bradykinin) (XIIIB).—Hydrogenation of 500 mg. of the protected citrulline nonapeptide in the same manner yielded 275 mg. of water-soluble solid, $[\alpha]^{22}D$ −79° (*c* 0.85, *N* acetic acid), lit.[2] $[\alpha]^{22}D$ −88.7° (*c* 1, *N* acetic acid).

Anal. Calcd. for $C_{50}H_{72}N_{14}O_{12}\cdot 2CH_3COOH\cdot 4H_2O$: C, 51.70; H, 7.08; N, 15.65. Found: C, 51.00; H, 6.8; N, 15.40.

Acknowledgment.—We are indebted to Mr. C. E. Childs and his staff for the microanalyses and to Mrs. Carola Spurlock and Mrs. Vivien Lee for the optical rotations.

Thyromimetics. III. The Synthesis and Relative Thyromimetic Activities of Some 4′-Ethers of Iodinated Thyronines and Thyroalkanoic Acids

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4′-Methyl, ethyl, and β-diethylaminoethyl ethers of several thyroxine-like compounds were prepared by treating suitable intermediates with base and dialkyl sulfates or β-diethylaminoethyl chloride. Protecting groups were hydrolyzed to yield the desired ethers (IIa–f, Va–d, and VIa and b) which were screened for their ability to lower plasma cholesterol levels in rats fed a cholesterol–cholic acid diet. Interesting compounds were studied further for their ability to stimulate oxygen consumption and/or to increase heart weight. A comparison of these results with the values from the cholesterol-lowering screen gave some indication of whether the compounds had a desired separation of activities.

During the study in our Laboratories of various classes of thyroxine-like compounds for their thyromimetic activities, it was noted that by controlling the administered dose of the methyl ether of 3,3′,5-triiodothyropropionic acid a good separation between calorigenic and antigoitrogenic responses could be obtained in the rat.[1] This initial observation coupled with the report by Herman, Lee, and Parker[2] that 4′-methyl ethers of thyromimetic substances often possess a large separation between the minimum effective hypocholesteremic dose and the dose which causes weight loss in animals prompted us to prepare a few examples of methyl ethers in an earlier study.[3] These results were encouraging enough that several additional 4′-methoxy compounds have now been screened for their cholesterol-lowering activity. In addition, two 4′-ethyl ethers were prepared to determine what effects a larger alkyl group in the 4′-position would have on biological activity. Moreover, since the preparation of β-diethylaminoethyl esters of several iodinated thyroalkanoic acids resulted in compounds with good hypocholesteremic activity,[3] the cholesterol-lowering activity of some representative 4′-β-diethylaminoethyl ethers was determined. It was hoped that a study of these types of structures would reveal compounds that would prove to be potent hypocholesteremic agents in man at doses which would cause no calorigenic or cardiac distress.

The methyl and ethyl ethers of thyroalkanoic acids (IIa–f) used in this study were prepared by treating the requisite acids (I) with either dimethyl or diethyl sulfate in the presence of aqueous base.[3] Diethylaminoethyl ethers (IV) were prepared from the requisite thyroalkanoic acid ethyl esters (III) on treatment with sodium methoxide and β-diethylaminoethyl chloride. These intermediates (IV) were then converted to the desired ethers (V) upon hydrolysis with hydrochloric acid.

In some instances the intermediate esters (IV) were isolated, purified, and characterized as their hydrochlorides. In other instances they were hydrolyzed directly to V.

The methyl ethers VIa and b of 3,3′,5-triiodo-D and L-thyronine were prepared *via* their N-benzoyl methyl esters as indicated by Tomita, *et al.*[4]

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

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

(3) B. Blank, F. R. Pfeiffer, C. M. Greenberg, and J. F. Kerwin, *J. Med. Chem.*, **6**, 560 (1963).

(4) K. Tomita, H. A. Lardy, D. Johnson, and A. Kent, *J. Biol. Chem.*, **236**, 2981 (1961).

Experimental[5]

Chemistry. Preparation of 4'-Methoxy and Ethoxy Acids (IIa–f).—These compounds were prepared as described previously.[3]

Iodinated Thyroalkanoic Acid Ethyl Esters (IIIa–d). A.—A mixture of 0.015 mole of thyroalkanoic acid (I), 10 ml. of absolute ethanol, 0.2 g. of *p*-toluenesulfonic acid monohydrate, and 70 ml. of chloroform was heated and stirred under reflux in such a manner that the water formed was azeotropically removed. Heating and stirring were continued overnight. The cooled solution was washed with water, dried over sodium sulfate, and the solvent was evaporated. Recrystallization of the residue gave the desired ester.

B.—A solution of 0.01 mole of I in 150 ml. of absolute ethanol was saturated with dry hydrogen chloride with cooling. The alcohol was removed and the residue was evaporated twice again with fresh portions of ethanol. The residue was then recrystallized.

4'-Diethylaminoethyl-3,5-diiodo- and 3,3',5-Triiodothyroacetic and Propionic Acid Ethyl Esters and Hydrochlorides (IVa and b).—A mixture of 4 mmoles of III and 5 mmoles of sodium methoxide in 10 ml. of absolute ethanol was stirred for 30 min. at room temperature. To the stirred mixture was added a solution of 5 mmoles of β-diethylaminoethyl chloride[3] in 8 ml. of dry toluene. The mixture was refluxed for 3 hr. and left standing at room temperature overnight. The precipitated sodium chloride was filtered and washed with a little dry ethanol. The filtrate was taken to dryness at reduced pressure and the resulting sirup was taken up in ether. The ethereal solution was filtered from a small amount of insoluble material and the ether was evaporated. The residue of crude product was either hydrolyzed directly to the acid V or was used to prepare the hydrochloride IV. In the latter cases the ethereal solution was filtered and saturated with dry hydrogen chloride and the precipitated hydrochloride was filtered and washed with ether. It was occasionally necessary to triturate the hydrochloride with ethyl acetate to produce a solid that was readily filterable. Analytical samples of IV were obtained by recrystallization from the solvents listed in Table I.

4'-Diethylaminoethyl-3,5-diiodo- and 3,3',5-Triiodothyroacetic and Propionic Acids (Va–d).—A solution of 2 mmoles of IV in 20 ml. of a 1:1 mixture of acetic and hydrochloric acids was refluxed for 4 hr. The solution was cooled, diluted with ice–water, and adjusted to pH 5–6 with 10% sodium hydroxide with cooling. The resulting gum or solid was dissolved in 1-butanol saturated with water and the butanolic solution was washed with water and dried over sodium sulfate. Most of the butanol was removed and the product was precipitated by cooling or the addition of ether. Further purification was effected by recrystallization.

Biological Screening.—The methods employed for determining plasma total cholesterol, oxygen consumption, and heart weight increase have been reported previously.

Cholesterol-lowering ability was determined in male rats fed a diet containing 2% cholesterol and 1% cholic acid. The drug was administered subcutaneously for 7 days, on the 8th day the animals were sacrificed and cholesterol values were determined.[1,6]

Calorigenic assays were carried out on rats which had been treated subcutaneously for 10 days with the test compound. On the 11th day total body oxygen consumption values were obtained by the method of Holtkamp, *et al.*[7]

For the heart weight assays the agents were administered subcutaneously to groups of adult male rats (250–300 g.) for a period of 10 days. The animals were sacrificed on the 11th day; the entire heart was removed, cut open, and the clotted blood removed by blotting on filter paper. The hearts were weighed and the relative weights (mg./100 g. body weight) determined.[8] Groups of saline-treated and 3,3',5-triiodo-L-thyronine (L-T_3)-treated rats were studied concurrently and served as the controls and reference, respectively.

Effects on oxygen consumption and heart weight increase were determined by administering at least four doses of the agent to be tested as well as the reference compound (L-T_3) to groups of rats (6–8) in each assay. The results of the assays were statistically tested for significance and parallelism by the usual methods as described by Finney.[9] Since there was no evidence of a lack of parallelism in any assay, an average slope was calculated for the two response lines in each assay and the results were plotted using the method of parallel regression analysis.

The results are shown in Table II and are expressed in terms of L-T_3 having an arbitrary value of one. Several closely related nonetherified compounds (Ia–d and VII) have been included for comparison.

$$\text{Activity} = \frac{\text{dose of L-T}_3\text{ which causes a significant response}^{10}}{\text{dose of test compound which causes a comparable response}}$$

Discussion

A study of the results in Table II shows that of the ethers studied, the methyl ethers of 3,3',5-triiodo- and 3,5-diiodo-3'-isopropylthyroacetic acids (IIa and d) were the most potent hypocholesteremic agents. Increasing the side chain to three or four carbon atoms (Ib and c, IIb and c) caused between a 3- and 100-fold decrease in cholesterol-lowering activity. Also of interest was the marked depression in the hypocholesteremic activities of the methyl ethers of triiodo-D- and L-thyronine as compared to the unetherified substances (compare VIa and b with VII and L-T_3).

The 3'-isopropyl compounds Id and IId had activities comparable to the corresponding 3'-iodo compounds Ia and IIa, confirming previous findings[3,11] that an isopropyl group can replace the 3'-iodine atom without loss of potency.

A comparison of the ethyl ether of 3,3',5-triiodothyropropionic acid with the corresponding methyl ether (IIf with IIb) shows this modification to have little or no effect on hypocholesteremic activity.

The four β-diethylaminoethyl ethers studied (Va–d) all showed poor activity whether they were di- or triiodo derivatives or whether they possessed acetic or propionic acid side chains. This is in marked contrast to the activities shown by comparable β-diethylaminoethyl esters.[3]

As pointed out earlier, a useful thyromimetic hypocholesteremic agent should cause a significant depression in plasma cholesterol at doses which cause no calorigenic (measured by changes in oxygen consumption) or cardiac changes (measured by increases in heart weight). Therefore, a comparison of the relative thyromimetic activities of several of the most interesting compounds has been carried out by determining a series of ratios in which activity in the cholesterol-lowering screen has been compared with activity in the oxygen consumption and/or heart weight studies. These values are shown in the last two columns of Table II. The larger the ratio, the greater is the apparent separation of activities.

Although methylation of the desamino compounds Ia–d to form the ethers IIa–d did not, in general, cause a marked change in cholesterol-lowering ability, the

(5) All melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected.

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

(7) D. E. Holtkamp, S. Ochs, C. C. Pfeiffer, and A. E. Heming, *Endocrinology*, **56**, 93 (1955).

(8) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls, *Am. J. Physiol.*, **205**, 821 (1963).

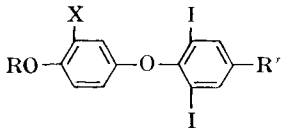
(9) D. J. Finney, "Statistical Method in Biological Assay," Hafner Publishing Company, New York, N. Y., 1952.

(10) For plasma total cholesterol values 50 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 ($P = 0.01$). A dose of 1.5–3.0 μg./kg./day of L-T_3 consistently causes such a depression.

(11) B. Blank, F. R. Pfeiffer, C. M. Greenberg, and J. F. Kerwin, *J. Med. Chem.*, **6**, 554 (1963).

TABLE I

ESTERS AND ETHERS OF IODINATED THYRONINES AND THYROALKANOIC ACIDS

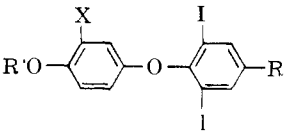


Compd.	No.	R	X	R'	M.p., °C.	Recrystn. solvent	% Yield	Formula	References to starting materials	% Calcd. C	% Calcd. H	% Calcd. I	% Found C	% Found H	% Found I
II	a	CH_3	I	CH_2COOH	164–166	CH_3OH	48	$C_{15}H_{11}I_3O_4$[a]	*b,c,d*	28.33	1.74	59.87	28.41	1.89	59.92
	b	CH_3	I	$(CH_2)_2COOH$	224–226	CH_3OH	60	$C_{16}H_{13}I_3O_4$	*e*	..	..	*f*	..	..	..
	c	CH_3	I	$(CH_2)_3COOH$	183–185	C_2H_5OH	74	$C_{17}H_{15}I_3O_4$	*g*	30.75	2.28	..	30.93	2.67	..
	d	CH_3	*i*-C_3H_7	CH_2COOH	142–144	Aq. C_2H_5OH	74	$C_{18}H_{18}I_2O_4$	*f*	..	..	*f*	..	..	..
	e	C_2H_5	H	$(CH_2)_2COOH$	154–155	95% C_2H_5OH	50	$C_{17}H_{16}I_2O_4$	*e,h,i,j,k*	37.94	3.00	47.17	37.77	2.93	47.12
	f	C_2H_5	I	$(CH_2)_2COOH$	192–193	95% C_2H_5OH	73	$C_{17}H_{15}I_3O_4$	*e*	30.75	2.28	57.34	31.03	2.57	57.07
III	a	H	H	CH_2COOEt	156–158	sublimed	95	$C_{16}H_{14}I_2O_4$	*b,c,d,h,l*	36.67	2.69	48.43	37.26[m]	2.79	48.31
	b	H	I	CH_2COOEt	134–136	95% C_2H_5OH	88	$C_{16}H_{13}I_3O_4$	*b,c,d*	29.57	2.02	58.57	29.86	2.31	58.49
	c	H	H	$(CH_2)_2COOEt$	137–139	50% Aq. C_2H_5OH	93	$C_{17}H_{16}I_2O_4$	*e,h,i,j,k*	37.94	3.00	47.17	38.05	3.00	46.85
	d	H	I	$(CH_2)_2COOEt$	155–156	Aq. C_2H_5OH	86	$C_{17}H_{15}I_3O_4$	*e*	30.75	2.28	57.34	30.72	2.30	57.32
IV	a	$Et_2NCH_2CH_2$	H	$(CH_2)_2COOEt$	185–187	*i*-C_3H_7OH	64	$C_{23}H_{30}ClI_2NO_4$		41.00	4.49	37.67	40.93	4.54	37.22
	b	$Et_2NCH_2CH_2$	I	$(CH_2)_2COOEt$	177–179	$CHCl_3$–petr. ether	63	$C_{23}H_{29}ClI_3NO_4$		34.55	3.66	47.61	34.48	3.70	47.40
V	a	$Et_2NCH_2CH_2$	H	CH_2COOH	192–194	*n*-C_4H_9OH	48[n]	$C_{20}H_{23}I_2NO_4$		40.36	3.90	42.64	40.28	3.85	42.55
	b	$Et_2NCH_2CH_2$	I	CH_2COOH	193–196	*n*-C_4H_9OH	19[n]	$C_{20}H_{22}I_3NO_4$		33.31	3.08	52.80	33.50	3.39	52.92
	c	$Et_2NCH_2CH_2$	H	$(CH_2)_2COOH$	124–126	*i*-C_3H_7OH	29	$C_{21}H_{25}I_2NO_4$		41.40	4.14	41.66	41.64	4.21	41.32
	d	$Et_2NCH_2CH_2$	I	$(CH_2)_2COOH$	170–172	THF–H_2O	50	$C_{21}H_{24}I_3NO_4$		34.31	3.29	51.79	34.63	3.30	51.57
VI	a	CH_3	I	D-$CH_2CH(NH_2)COOH$	234–236[o]	C_2H_5OH–H_2O[p]	78	$C_{16}H_{14}I_3NO_4$	*q*	28.90	2.12	57.25	29.11	2.44	56.91
	b	CH_3	I	L-$CH_2CH(NH_2)COOH$	229–230[o]	C_2H_5OH–H_2O[p]	87	$C_{16}H_{14}I_3NO_4 \cdot H_2O$[a]	*r*	28.14	2.36	55.74	28.37	2.40	55.35

[a] Also reported in ref. 4. [b] C. R. Harington and R. Pitt-Rivers, *Biochem. J.*, **50**, 438 (1952). [c] J. H. Wilkinson, *ibid.*, **63**, 601 (1956). [d] W. Siedel, H. Nahm, and J. König, German Patent 1,072,998 (January 14, 1960). [e] J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, 2467 (1951). [f] See ref. 3. [g] Although there are several reports dealing with the testing of 3,3',5-triiodothyrobutyric acid (material supplied by the Cyclo Chemical Co.), the only reported synthesis of this compound is the result of an incubation study [T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **81**, 871 (1959)]. 3,3',5-Triiodothyrobutyric acid was prepared in our Laboratories by the controlled iodination of 3,5-diiodothyrobutyric acid [N. Kharasch and S. H. Kalfayan, *J. Org. Chem.*, **21**, 929 (1956)], m.p. 159–160° (aq. CH_3OH). Calcd.: C, 29.56; H, 2.02; I, 58.57. Found: C, 29.72; H, 2.19; I, 58.66. [h] R. I. Meltzer, D. M. Lustgarten, and A. Fischman, *ibid.*, **22**, 1577 (1957). [i] K. Tomita and H. A. Lardy, *J. Biol. Chem.*, **219**, 595 (1956). [j] S. Wawzonek, S. C. Wang, and P. Lyons, *J. Org. Chem.*, **15**, 593 (1950). [k] N. Kharasch, S. H. Kalfayan, and J. D. Arterberry, *ibid.*, **21**, 925 (1956). [l] H. Ziegler and C. Marr, *ibid.*, **27**, 3335 (1962). [m] This compound was prepared by both methods A and B, recrystallized from several solvent systems and/or sublimed to give materials which all had the same melting point and which after repeated analyses always analyzed high for carbon. Paper chromatography shows the material to be homogeneous. We can offer no explanation for the high carbon analyses. [n] Over-all yield from III. [o] With decomposition. [p] Recrystallized from a hot ethanolic solution containing a few drops of concentrated hydrochloric acid by the addition of hot water and hot 2 *N* sodium acetate solution to pH 5–6. [q] Prepared from N-acetyl-3,5-dinitro-D-tyrosine [made by the method reported by J. Elks and G. J. Waller, *J. Chem. Soc.*, 2366 (1952); W. K. Warburton, *ibid.*, 2651 (1961)] using the route employed by J. R. Chalmers, G. T. Dickson, J. Elks, and B. A. Hems, *ibid.*, 3424 (1949), for the preparation of thyroxine. Recently, H. Nahm and W. Siedel [*Chem. Ber.*, **96**, 1 (1963)] have described the preparation of 3,3',5-triiodo-D- and L-thyronine by the resolution of N-formyl-3,3',5-triiodo-DL-thyronine. [r] Prepared from N-acetyl-3,5-dinitro-L-tyrosine by the route used for the D-isomer.

TABLE II

RELATIVE THYROMIMETIC ACTIVITIES[a]



Compd.	No.	R′	X	R	Plasma total cholesterol	Oxygen consumption	Heart weight increase	Cholesterol-lowering / O_2 consump.	Cholesterol-lowering / heart wt. increase
I	a	H	I	CH_2COOH	0.300	0.075	0.097	4.0	3.1
	b	H	I	$(CH_2)_2COOH$	.100	.100	.017	1.0	5.9
	c	H	I	$(CH_2)_3COOH$	.040	.010	.029	4.0	1.4
	d	H	*i*-C_3H_7	CH_2COOH	.600	.067	.160	9.0	3.8
II	a	CH_3	I	CH_2COOH	.430	.033	.030	13.0	14.0
	b	CH_3	I	$(CH_2)_2COOH$	.050	.015	.007	3.3	7.2
	c	CH_3	I	$(CH_2)_3COOH$	.005	.005	.003	1.0	1.5
	d	CH_3	*i*-C_3H_7	CH_2COOH	.400	.022	.040	18.2	10.0
	e	C_2H_5	H	$(CH_2)_2COOH$	<0.006				
	f	C_2H_5	I	$(CH_2)_2COOH$	.060	.009		6.7	
V	a	$(C_2H_5)_2NCH_2CH_2$	H	CH_2COOH	.006				
	b	$(C_2H_5)_2NCH_2CH_2$	I	CH_2COOH	.006				
	c	$(C_2H_5)_2NCH_2CH_2$	H	$(CH_2)_2COOH$	.006				
	d	$(C_2H_5)_2NCH_2CH_2$	I	$(CH_2)_2COOH$	<0.006				
VI	a	CH_3	I	D $CH_2CH(NH_2)COOH$	.090	.022	.020	4.0	4.5
	b	CH_3	I	L $CH_2CH(NH_2)COOH$	.120	.500		0.2	
VII		H	I	D $CH_2CH(NH_2)COOH$	.490	.250	.082	2.0	6.0

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

finding of particular interest was that the methyl ethers had a relatively low order of activity in the calorigenic and heart weight tests. The apparent exception to this rule is the thyrobutyric acid derivative IIc.

The data in Table II show that the methyl ethers IIa and IId have the greatest separation of thyromimetic activities of the compounds in this study. However, since the 4′-hydroxy compounds Ia and b have displayed undesirable side effects in clinical trials at doses which were required to depress cholesterol levels,[12-17] the question still to be resolved is how large a separation in activities must be seen in laboratory animals before one can choose an agent for clinical study with some degree of certainty. Further clinical trials should furnish this answer.

In summary it can be said that the formation of the 4′-methyl ethers of 3,3′,5-triiodo- and 3,5-diiodo-3′-isopropylthyroalkanoic acids generally leads to compounds which have a greater degree of separation between cholesterol-lowering activity and either calorigenic or cardiac effects than the corresponding non-etherified materials (compare Ia,b, and d with IIa,b, and d). This apparent separation of activities also implies that the hypocholesteremic activity of these thyromimetics is probably not mediated through any action on protein synthesis as has been indicated recently to be the case for the calorigenic and cardiac effects elicited by thyromimetics.[18,19]

Acknowledgment.—We wish to express our thanks to Carol A. Bocher, Roger O'Connor, Leo F. Mansor, and Mrs. Barbara B. Lewis for technical assistance and to Mrs. Doris A. Ralston and staff for elemental analyses.

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