Anal. ($C_{43}H_{56}N_6O_{10}S_2$) C, H, N, S. Asp, 0.98; Pro, 1.00; Gly, 0.98; Bzl-Cys, 1.00.[25]

Z-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH$_2$.—The Z group was removed from the protected pentapeptide with HBr in AcOH, and the chain was lengthened by the addn of Z-L-Gln-ONP,[15,24] as described in ref 8. The protected hexapeptide amide was secured in 88% yield. It was homogeneous by tlc, R_f (A) 0.66, (B) 0.64; mp 198–201°; $[\alpha]^{30}D$ −42° (*c* 1, DMF). *Anal.* ($C_{48}H_{64}N_{10}O_{12}S_2$) C, H, N, S. Asp, 0.97; Glu, 1.01; Pro, 1.06; Gly, 0.93; Bzl-Cys, 0.98.[25]

Z-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH$_2$.—The lengthening of the chain from the hexapeptide derivative to the protected heptapeptide followed the procedure in ref 8. The product, mp 201–204°, was obtd in 90% yield, homogeneous in the tlc systems A and B with R_f values 0.69 and 0.67, respectively, $[\alpha]^{30}D$ −37.9° (*c* 1, DMF). *Anal.* ($C_{57}H_{73}N_{11}O_{13}S_2$) C, H, N, S. Asp, 1.00; Glu, 1.00; Pro, 1.00; Gly, 0.95; Phe, 1.03; Bzl-Cys, 0.98.[25]

Z-L-Tyr(Bzl)-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH$_2$.—This protected octapeptide was prepared according to the procedure used for the synthesis of lysine-vasopressin.[8] The product, mp 215–219°, was secured in 87% yield, in homogeneous form: tlc, R_f A, 0.72, B, 0.70; $[\alpha]^{30}D$ −39.8° (*c* 1, DMF). *Anal.* ($C_{73}H_{88}N_{12}O_{15}S_2$) C, H, N, S. Asp, 0.98; Glu, 1.00; Pro, 1.00; Gly, 0.97; Tyr, 0.96; Phe, 1.04; Bzl-Cys, 1.01.[25]

Z-L-Cys(Bzl)-L-Tyr-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH$_2$.—The procedure in ref 8 was followed with the notable exception that diisopropylethylamine[9] rather than Et_3N was used for the neutralization of HBr. Also, the fully protected nonapeptide was isolated by diln of the reaction mixt with 95% EtOH instead of EtOAc: yield, 82%; mp 218–221°; $[\alpha]^{30}D$ −42.8° (*c* 1, DMF). Homogeneous on tlc, R_f (A) 0.66. *Anal.* ($C_{76}H_{93}N_{13}O_{16}S_3$) C, H, N, S. Asp, 1.00; Glu, 0.97; Pro, 0.98; Gly, 0.92; Tyr, 0.98; Phe, 1.06; Bzl-Cys, 2.05.[25]

8-L-Homolysine-vasopressin.—A sample (0.20 g) of the protected nonapeptide was dissolved in liq NH_3 (*ca.* 0.2 l.) and treated at the bp of the soln with small pieces of Na until the blue color persisted for about 3 min. A few drops of AcOH were added, the NH_3 was allowed to evap to a small vol, and the rest of the solvent was removed *in vacuo* by evapn from the solid state. The residue was dissolved in O_2-free H_2O (0.3 l.) and aerated at pH 6.5 for several hr until the reaction for SH group (sodium nitroferricyanide) neg. The pH was adjusted to 4 with AcOH, and the soln was passed through a column (2.4 × 13 cm) of Amberlite IRC-50 in H^+ cycle. The column was washed with 0.25% AcOH (0.4 l.) and H_2O (25 ml). The cyclic peptide was eluted with a mixt of pyridine, AcOH, and H_2O (30, 4, and 70 ml). The eluate was concd *in vacuo*, and the resulting syrup was dild with H_2O (15 ml). A small amt of solid sepd and was removed by filtration. The soln was applied on a column of CM-cellulose (Whatman CM-23, 18 g) that was pretreated with 0.5 *N* NaOH and 0.5 *N* HCl and was equilibrated with 0.05 *M* NH_4OAc. The column was packed under pressure to 2.5 × 20 cm. For elution, a linear gradient of NH_4OAc (0.05–0.5 *M*, 500–500 ml) was used. Fractions of 6 ml were collected at a flow rate of 50 ml/hr. The hormone analog was eluted in fractions 45–48, as detected by uv absorption at 280 nm. From the total absorption, a yield of 78% was calcd (based on the protected nonapeptide amide). The soln was concd *in vacuo* to about 30 ml and lyophilized. The residue was dissolved in 0.25% AcOH (6.5 ml), the soln was applied to a Sephadex G-25 column (2.5 × 30 cm) and eluted with the same solvent. Fractions were collected at 10-min intervals at a flow rate of 36 ml/hr. The purified product was detected in fractions 23–28°. The soln was lyophilized, redissolved in 0.25% AcOH, and relyophilized. The white fluffy solid was dried *in vacuo* over NaOH and P_2O_5 overnight: yield, 84 mg; $[\alpha]^{30}D$ −23° (*c* 1, 1 *N* AcOH). Homogeneous on paper chromatograms, in *n*-BuOH–AcOH–H_2O (4:1:5), R_f 0.35; in *n*-BuOH–pyridine–AcOH–H_2O (30:20:6:24), R_f 0.56. On paper electrophoresis at pH 4.2 (0.1 *M* pyridine acetate) at 24 V/cm, 8-L-homolysine-vasopressin traveled toward the cathode as a single spot, 12.5 cm in 2 hr. *Anal.* ($C_{47}H_{67}N_{13}O_{12}S_2 \cdot 2CH_3COOH \cdot 4H_2O$) C, H, N. (Best fit obtd for solvation with $4H_2O$). Asp, 1.01; Glu, 1.00; Pro, 1.01; Gly, 1.00; 0.5-Cys, 1.98; Tyr, 1.01; Phe, 1.03; homolysine, 1.04.[25]

(25) In the quant amino acid analysis of the protected intermediates, tosylhomolysine, incompletely hydrolyzed, interfered with the detn of NH_3. Therefore, no values are reported for these 2 constituents. In the hydrolysate of 8-L-homolysine-vasopressin, homolysine was detd on the short column of the Beckman-Spinco amino acid analyzer, but with the "B" buffer (pH 4.28) as eluent.

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Thyroxine Analogs. 21.[1] *o*- and *m*-L-Thyroxine and Related Compounds

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Thyroxine analogs with the phenolic OH group ortho or meta to the ether O were synthesized and tested for thyroid hormonal activity in the rat antigoiter assay. 3-[4-(3-Hydroxyphenoxy)-3,5-diiodophenyl]-L-alanine (*m*-3,5-diiodo-L-thyronine) was found to be active, while the corresponding ortho isomer was inactive. *m*-L-Thyroxine was inactive, and *o*-L-thyroxine was weakly active in both thyromimetic and thyroxine antagonist tests. Blocking of the 4′ position with a Me group in *o*- and *m*-3,5-diiodo-L-thyronine produced inactive compounds. The 2′,4′-dihydroxyphenyl ether of 3,5-diiodo-L-tyrosine was also inactive. These results are consistent with 4′-hydroxylation *in vivo* producing active metabolites of *m*-3,5-diiodo-L-thyronine and of *o*-L-thyroxine, and offer an alternate explanation to the concept that the potential for *o*-quinoid oxidation is associated with the biological activity of *o*-L-thyroxine.

Niemann[2] has proposed that the potential for the phenolic ring of thyroxine (**1**) to undergo reversible oxidation to a quinoid form (**2**) is related to its biological activity. In support of this hypothesis, *o*-DL-thyroxine[3] (**3**) showed low thyroxine-like activity, while *m*-DL-thyroxine[4] (**4a, b**) was inactive.[5] The activity of **1** and **3** was related to their potential for oxidation to *p*- and *o*-quinoid forms, resp, whereas the inactive meta analog (**4a, b**) could not be oxidized in this manner. Structure **4a** was originally assigned to *m*-DL-thyroxine, but the isomeric 4′,6′-I_2 substitution pattern of **4b** was later considered to be more likely for this compound[2] and for

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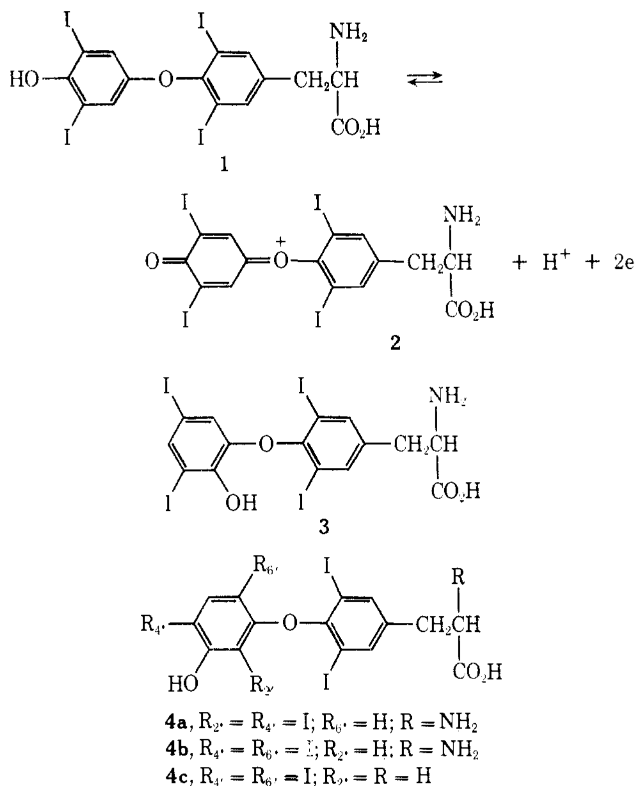
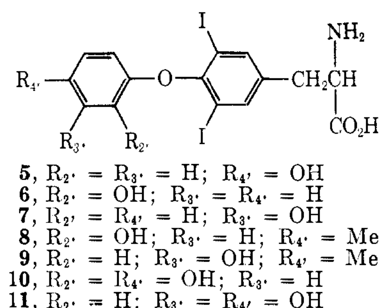


the related analog with a propionic acid side chain[6] (**4c**).

Recent studies[7] on 1- and 2-naphthyl ethers of 3,5-diiodo-L-tyrosine showed that only those hydroxynaphthyl ethers which could undergo quinoid oxidation, or their potential metabolic precursors,[8] were thyromimetic, in support of the Niemann hypothesis.[2] In addition, the relative spatial position of the alanine-bearing ring and the phenolic OH group was found to be important, activity being associated with a para (4-hydroxy-1-naphthyl ether) or a near-para (6-hydroxy-2-naphthyl ether) relationship between the phenolic OH group and ether O.[7] The steric importance for the relative position of the phenolic OH in the naphthyl ether series is in contrast to its apparent lack of importance in *o*-DL-thyroxine. Therefore, the L isomers of *o*-thyroxine (**3**) and *m*-thyroxine (**4b**) were prepared for testing for thyroxine-like activity, and for physical measurements to determine the iodine-substitution pattern of *m*-thyroxine. In view of the thyroxine-like activity for 3,5-diiodo-L-thyronine[9,10] (**5**), the synthetic intermediates to *o*- and *m*-L-thyroxine (**3,4b**) *o*- and *m*-3,5-diiodo-L-thyronine (**6,7**) were also tested for thyroxine-like activity. Analogs of **6** and **7**, with a Me group in the 4′ position (**8,9**) were prepared and tested as compounds in which the 4′ position was blocked to metabolic hydroxylation. The 2′,4′-dihydroxy analog (**10**) was also prepared for comparison with its active isomer, 3′-hydroxy-3,5-diiodothyronine[11,12] (**11**).



The syntheses of the thyroxine analogs followed standard methods,[8,13,14] as described in the Experimental Section. Table I lists the synthetic intermediates.

The ir spectrum of *m*-L-thyroxine was compared with those of the 2′,3′,4′-Me_3Ph and 2′,4′,5′-Me_3Ph ethers of 3,5-diiodophenylalanine.[15] The aromatic substitution pattern of the 2′,3′,4′-Me_3Ph ether corresponds to that of **4a**, while the 2′,4′,5′-Me_3Ph ether corresponds to **4b**. *m*-L-Thyroxine and the 2′,4′,5′-Me_3 analog were lacking the strong peak at 800 cm^{-1} present in the 2′,3′,4′-Me_3 analog, which was assigned to the two adjacent aromatic H atoms. Strong peaks in the 880- to 835-cm^{-1} region were present in *m*-L-thyroxine (865, 835 cm^{-1}) and in the 2′,4′,5′-Me_3 analog (875, 845 cm^{-1}), which were lacking in the 2′,3′,4′-Me_3Ph ether. *m*-L-Thyroxine closely resembled the 2′,4′,5′-Me_3Ph ether in the 1000- to 800-cm^{-1} region, adding support to the assignment of structure **4b** to *m*-L-thyroxine.

Biological Results and Discussion.[16,17]—Table II summarizes the results of tests for thyroxine-like and thyroxine antagonist activity in the rat antigoiter assay.

As indicated by the studies of Niemann and Mead[3,5] on *o*-DL-thyroxine, the L isomer **3** was 0.3% as active as L-thyroxine. The synthetic intermediate, *o*-3,5-diiodo-L-thyronine (**6**), was inactive. *m*-L-thyroxine (**4b**), in agreement with the findings of Niemann and Redemann[4,5] on the DL isomer, was inactive. However, its synthetic intermediate, *m*-3,5-diiodo-L-thyronine (**7**), was 1% as active as L-thyroxine.

The activity of *m*-3,5-diiodo-L-thyronine (**7**) cannot be explained directly on the basis of the Niemann hypothesis,[2] since it cannot be oxidized to a quinoid form. However, if metabolic 4′-hydroxylation occurs, activity would be expected since 3′-hydroxy-3,5-diiodo-L-thyronine (**11**) is 1.5% as active as L-thyroxine.[12] Iodination of **7** to form *m*-L-thyroxine (**4b**), or by otherwise blocking the 4′ position to metabolic attack, as with the 4′-Me analog (**9**), leads to the expected loss of biological activity.

o-L-Thyroxine (**3**) and *o*-3,5-diiodo-L-thyronine (**6**) have free 4′ positions which could be metabolically hydroxylated. In *o*-3,5-diiodo-L-thyronine, it would be expected that the 2′-OH would direct metabolic oxidation to the 3′ or 5′ positions. Even if 4′-hydroxylation were to occur *in vivo*, 2′-hydroxy-3,5-diiodo-L-thyronine

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TABLE I

SUBSTITUTED PHENYL ETHERS OF N-ACETYL-3,5-DINITRO-L-TYROSINE ETHYL ESTER AND OF N-ACETYL-3,5-DIIODO-L-TYROSINE ETHYL ESTER

L-4-R_1O-3,5-$R_2C_6H_2CH_2CH(NHAc)CO_2Et$

No.	R_1	R_2	Mp, °C	Yield, %	Optical rotation,[a] deg	Formula	Analysis[b]
12	2'-MeO-C_6H_4	NO_2	97–98	45	+26.0	$C_{20}H_{21}N_3O_9$	C, H
13	3'-MeO-C_6H_4	NO_2	102–103	43	+21.1	$C_{20}H_{21}N_3O_9$	C, H
14	2'-MeO-4'-MeC_6H_3	NO_2	150–153	46	+45.5	$C_{21}H_{23}N_3O_9$	C, H
15	3'-MeO-4'-MeC_6H_3	NO_2	145–147	44	+38.8	$C_{21}H_{23}N_3O_9$	C, H
16	2',4'-(MeO)$_2$-C_6H_3	NO_2	154–156	70	+44.8	$C_{21}H_{23}N_3O_{10}$	C, H
17	2'-MeO-C_6H_4	I	127–129	50	+49.7	$C_{20}H_{21}I_2NO_5$	C, H
18	3'-MeO-C_6H_4	I	107–108	43	+50.7	$C_{20}H_{21}I_2NO_5$	C, H
19	2'-MeO-4'-MeC_6H_3	I	132–134	24	+47.1	$C_{21}H_{23}I_2NO_5$	C, H, I
20	3'-MeO-4'-MeC_6H_3	I	137–138	43	+51.1	$C_{21}H_{23}I_2NO_5$	C, H
21	2',4'-(MeO)$_2$-C_6H_3	I	105–107	22	+46.8	$C_{21}H_{23}I_2NO_6$	C, H, I

[a] $\alpha^{25}D$ (c 2.0, $CHCl_3$). [b] Anal. results were within 0.4% of the calcd values.

TABLE II

SUBSTITUTED PHENYL ETHERS OF 3,5-DIIODO-L-TYROSINE

L-4-RO-3,5-$I_2C_6H_2CH_2CH(NH_2)CO_2H$

No.	R[a]	Mp, °C dec	Yield, %	Optical rotation,[b] deg	Antigoiter activity: Thyroxine-like[c]	Antigoiter activity: Thyroxine antagonist[d]
6	2'-HO-C_6H_4	224–228	41	+20.1	0	I
3	2'-HO-3',5'-$I_2C_6H_2$	232–236	60	e	0.3[f]	A
7	3'-HO-C_6H_4	222–229	87	+17.6	1	N
4b	3'-HO-4',6'-$I_2C_6H_2$	201–205	81	e	0	I
8	2'-HO-4'-MeC_6H_3	215–218	52	+17.3	0	N
9	3'-HO-4'-MeC_6H_3	235–243	26	+15.9	0	I
10	2',4'-(HO)$_2$-C_6H_3	223–245	23	+15.1	0	N
11	3',4'-(HO)$_2$-C_6H_3[g]				1.5[g]	N

[a] Compds **6**, **7** ($C_{15}H_{13}I_2NO_4$); **3**, **4b** ($C_{15}H_{11}I_4NO_4$); **8**, **9** ($C_{16}H_{15}I_2NO_4$); **10** ($C_{15}H_{13}I_2NO_5$) were anal. for C, H, and I. The values obtd were within 0.4% of the calcd values. [b] $[\alpha]^{26}D$ (c 2.0, 1 N HCl–EtOH, 1:1 v/v). [c] Relative to L-thyroxine as 100 on a molar basis. [d] Tested at a 200:1 molar ratio of analog to L-thyroxine. I = inactive (no statistically significant increase in thyroid weight over that of the group of rats receiving 3.0 μg/100 g body weight of L-thyroxine alone). A = Active (compd **3** produced a 31% reversal of the L-thyroxine effect). N = not tested. [e] Too insol in aq HCl–EtOH to obtain optical rotation. [f] 1% of L-thyroxine in O_2 consumption assay on thyroidectomized rats (personal communication, Dr. S. B. Barker). [g] R. W. Doskotch and H. A. Lardy, *J. Amer. Chem. Soc.*, **80**, 6230 (1958).

(**10**) was shown to be inactive. Blocking the 4' position in o-3,5-diiodo-L-thyronine with Me (**8**), also produced an inactive compound. Iodination of **6** to yield the weakly active o-L-thyroxine (**3**), introduced I atoms into the 3' and 5' positions. These would tend to direct metabolic hydroxylation to the 4' position. The resulting metabolite, 2'-hydroxy-L-thyroxine, could account for the weak biological activity, and its structure would conform with the steric requirement of para hydroxylation for thyromimetic activity.[7]

Bruice[6] has concluded that stabilization of an oxidation product of thyroxine by a quinoid form is not a requisite to biological activity, since m-thyropropionic acid (**4c**) showed thyroxine-like properties in initiating metamorphosis of the larvae of the bullfrog *Rana catesbeiana*. The greatly enhanced absorption of the lipophilic thyropropionic acid analogs by tadpoles emersed in test solutions of such compounds,[18] the high toxicity of **4c** which required special experimental conditions, the inability to induce metamorphosis in other tadpole species without toxic effects, the lack of tests in mammals, and the ability for iodinated compounds to induce metamorphosis in tadpoles,[19] even though they lack thyromimetic properties in mammalian systems,[20] place in doubt general conclusions based on this test system.

Biological data on thyroxine-like activity in mammals, and the results of the present study, are consistent with a structural requirement for potential oxidation to a quinoid form, with steric restrictions to a para or near-para position for the phenolic OH relative to the ether O, for significant biological activity.

Compounds **3**, **4b**, **6**, and **9** were also tested as thyroxine antagonists[10] at a molar ratio of analog to L-thyroxine of 200:1 (Table II). In addition to its weak thyroxine-like properties, o-L-thyroxine was active as a thyroxine antagonist, causing a 31% reversal of the reduction in thyroid weight produced by thyroxine in the thiouracil-treated rat.

Experimental Section[21]

Substituted Phenols.—Guaiacol, resorcinol monomethyl ether, and creosol were fractionally distd through an efficient column

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and shown to be homogeneous by glc on a diethylene glycol succinate column at 117°.

3-Methoxy-4-methylphenol was prepd by diazotization and acid hydrolysis of 3-methoxy-4-methylaniline,[22] crystd from C_6H_6 and ligroin, mp 59.5–61.5°, lit.[22] bp 136–137° (20 mm). *Anal.* ($C_8H_{10}O_2$) C, H. 2,4-Dimethoxyphenol was prepd by Baeyer-Villiger oxidn of 2,4-dimethoxyacetophenone,[23] mp 25–28°, lit.[24] 28°.

Substituted Ph Ethers of N-Acetyl-3,5-dinitro-L-tyrosine Et Ester (Table I, 12–16).—A 3-fold excess of the appropriate substituted phenol was condensed with N-acetyl-3,5-dinitro-L-tyrosine Et ester by the Meltzer[14] modification of the method of Barnes[13] to form the dinitrodiphenyl ethers **12–16**. Crystd from EtOH.

Substituted Ph Ethers of N-Acetyl-3,5-diiodo-L-tyrosine Et Ester (Table I, 17–21).—The dinitro compds **12–16**) were hydrogenated, tetrazotized, and decompd in aq I_3^- soln by standard methods.[8,13,14] Compds **19–21** were formed in aq I_3^- soln which contd twice as much H_2O as in the standard procedure in order to prevent the formation of side products with an extraneous ir peak at 2100 cm^{-1} in **20**, or with high I analyses in **19** and **21**. The crude product was dissolved in C_6H_6 and chromatogd on acid-washed alumina, using increasing concns of $CHCl_3$ or of Et_2O in C_6H_6. Fractions eluting with 10–25% $CHCl_3$ in C_6H_6 were crystd from acetone (**17**) or EtOH (**18**). Compds **19–21** were eluted with 20–50% Et_2O in C_6H_6 and crystd from EtOH.

Substituted Ph Ethers of 3,5-Diiodo-L-tyrosine (Table II, 6–10).—The diiodo methoxyphenyl ethers (**17–21**, 1 g) were hydrolyzed to the amino acids **6–10** by heating in const-boiling HI (6 ml) and AcOH (20 ml) under reflux for 6 hr, except compd **21** which was heated under reflux for 8 hr. The soln was evapd to dryness at 60–70° under reduced pressure. The residue was dissolved in a small amt of H_2O. The soln was filtered, aq AcONa was added to pH 4.9, and the soln was refrigerated overnight. The ppt was collected and dissolved in HCl, and aq AcONa was added to pH 4.9, yielding a granular solid.

3-[4-(2-Hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]-L-alanine (o-L-thyroxine, 3).—The procedure of Niemann and Mead[3] for the synthesis of *o*-DL-thyroxine was used. A soln of I_2 (140 mg, 0.55 mmole) in 6 ml of 1 *M* KI was added dropwise during 7 min to a well-stirred soln of *o*-3,5-diiodo-L-thyronine (**6**, 139 mg, 0.27 mmole) in 5 ml of 7 *N* NH_4OH and cooled in an ice bath. Stirring was contd for 30 min, then $NaHSO_3$ was added to reduce unreacted I_2. Dil aq HCl was added until the soln was at pH 3.0. After refrigeration overnight the ppt was collected by filtration, dissolved in 7 *N* NH_4OH, reptd at pH 3.0, washed with cold H_2O, and dried at 100° (1 mm) over P_2O_5 to yield 124 mg (60%) of *o*-L-thyroxine (**3**) (see Table I).

3-[4-(3-Hydroxy-4,6-diiodophenoxy)-3,5-diiodophenyl]-L-alanine (m-L-thyroxine, 4b).—*m*-3,5-Diiodo-L-thyronine (**7**, 278 mg, 0.53 mmole) was iodinated as described for the prepn of **3** to yield 331 mg (81%) of **4b**.

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8-Substituted Theophyllines. *In Vitro* Inhibition of 3′,5′-Cyclic Adenosine Monophosphate Phosphodiesterase and Pharmacological Spectrum in Mice

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A series of 8-substituted theophylline derivatives was tested for *in vitro* 3′,5′-cyclic AMP phosphodiesterase (PDE) inhibition. The unbranched derivatives, Me to *n*-Hex (**2–7**), cyclopropyl (**12**), cyclobutyl (**13**), cyclopentyl (**14**), *i*-Pr (**10**), and *i*-Bu (**11**) were more potent inhibitors than theophylline (T). The *n*-heptyl (**8**) and 4-hydroxybutyl (**9**) were inactive. *In vitro* activity was influenced by H_2O and lipid solubility as well as by the size and configuration of the substituent. The symptomatology pattern in mice changed from CNS stimulation (T) to pronounced depression (**7**). Compds **4**, **5**, **12**, and **14** were active antidepressants; **4**, **7**, and **10** were effective against pentylenetetrazole-induced mortality. Antiedema activity was present in **4**, **5**, **6**, **11**, **12**, and **13**. Marked hyperglycemic responses were induced by **5**, **6**, and **7**. CNS depression and hyperglycemia appear to be directly related to *in vitro* PDE inhibition. The other activities are not readily explained, but an involvement in some aspect of the cyclic AMP–adenyl cyclase-PDE–Ca^{2+} system is suggested.

The methylxanthines (caffeine and theophylline) are established cyclic AMP phosphodiesterase (PDE) inhibitors. As such they are capable of exerting characteristic effects in certain *in vitro* systems, *e.g.*, stimulate exocrine pancreas[1] and gastric[2] secretion, increase lipolysis,[3] produce a negative inotropic effect on rat portal vein,[4] simulate the effect of vasopressin in the toad bladder,[5] etc.

To date their proven *in vivo* effects pertinent to PDE inhibition have been limited. Hynie, *et al.*,[3] have established the lipolytic action of theophylline (T) in rats, and Malamud[6] obtained a stimulation of DNA synthesis in the parotid gland of the mouse. It is fairly well ascertained that insulin release induced in the rat by T is the result of increased cyclic AMP levels.[7] Otherwise, the majority of their pharmacological effects has been secondary, *i.e.*, potentiation of the activity of a primary compound such as the hormone epinephrine. Potentiation of this nature has been accepted as evidence of cyclic AMP involvement.[8]

Cyclic AMP has been implicated in a wide variety of physiological processes, as has been indicated to some extent above. To explain the manner in which these different effects result from intracellular production

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