and acylated as previously described[3] with 260 mg (0.90 mmol) of Boc-Gly-Gly-Gly (I) and 186 mg (0.90 mmol) of DCCI in 20 ml of purified DMF[10] since Boc-Gly-Gly-Gly was not soluble in CH_2Cl_2. Complete acylation was achieved using a single 12-hr reaction. The peptide was cleaved from the polymer and hydrogenated as described[3] giving 125 mg. The crude peptide was dissolved in 5 ml of 0.05 *M* NH_4OAc–1 *M* AcOH and applied to a 2.5 × 100 cm column of Sephadex-C25-SE (NH_4^+) packed in the same buffer. The column was eluted at 34 ml/hr with a gradient of NH_4OAc in 1 *M* AcOH using a concentration change of 3.3×10^{-4} *M*/ml starting from 0.05 *M*. The effluent was monitored at 280 mμ and the fractions from the center of the main peak were pooled and lyophilized giving 40 mg. After further purification *via* the picrate salt[2,11] there was 30 mg of white powder, homogeneous on tlc, R_fV: 0.57, R_fVII: 0.33 (detected with Pauly reagent). A 72-hr acid hydrolysate had the following amino acids: Gly, 2.99; Tyr, 0.96; Ile, 1.00; His, 1.00; Pro, 1.00; Phe, 0.99; peptide content, 81%. A 48-hr acid hydrolysate incubated with L-amino acid oxidase (Worthington)[3] had the following amino acids: Gly 2.23, Tyr 0.00, Ile 0.00, His 0.06, Pro 1.00, Phe 0.00.[12]

ηAoc-Tyr-Ile-His-Pro-Phe (IV).—Boc-Tyr(Bzl)-Ile-His(Bzl)-Pro-Phe-polymer[3] (0.9 g, 0.15 mmol), was deprotected and acylated as before with 155 mg (0.60 mmol) of Boc-ηAoc (II) and 125 mg (0.60 mmol) of DCCI in 20 ml of CH_2Cl_2. The peptide was cleaved from the polymer and hydrogenated as previously described[3] giving 140 mg. This crude product was dissolved in 5 ml of 0.1 *M* NH_4OAc–1 *M* AcOH and applied to a 2.5 × 100 cm column of Sephadex-C25-SE (NH_4^+) packed in the same buffer. The column was eluted at 34 ml/hr with a gradient of NH_4OAc in 1 *M* A AcOH using a concentration change of 2.0×10^{-4} *M*/ml starting from 0.1 *M*. The effluent was monitored at 280 mμ and the fractions from the main peak which were homogeneous on tlc in solvents VI and VII were pooled and lyophilized to give 60 mg. After further purification *via* the picrate salt,[2,11] there was 47 mg of chromatographically homogeneous material, R_fVI: 0.70, R_fVII: 0.32 (detected with Pauly reagent). A 72-hr acid hydrolysate had the following amino acids; ηAoc, 1.00; Tyr, 0.97; Ile, 1.02; His, 1.04; Pro, 1.00; Phe, 0.99; peptide content, 96%. ηAoc emerged from the short (5.3 cm) column of the analyzer 20 ml after arginine and had a color value which was 23% that of leucine. A 48-hr acid hydrolysate incubated with L-amino acid oxidase[3] had the following amino acids: ηAoc, 0.80; Tyr, 0.00; Ile, 0.00; His, 0.09; Pro, 1.00; Phe, 0.00.

Acknowledgment.—We are grateful to Dr. D. Nitecki for her helpful discussions during the course of this work.

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(11) Both peptides described in this paper gave gummy picrate salts which were decomposed very slowly by the ion exchange resin AG 1 × 2 (acetate) in 1 *M* AcOH. In this case, the procedure described in ref 2 was modified so that the precipitated salt was dissolved in 1 ml of AcOH, H_2O was added until slightly turbid then the AG 1 × 2 (acetate) was added.

(12) These values were corrected for the amount of racemization occurring when a mixture of these amino acids was subjected to the same hydrolytic conditions.

Thyroxine Analogs. XIX.[1] 3,5-Dimethyl-3′-isopropyl-DL-thyronine

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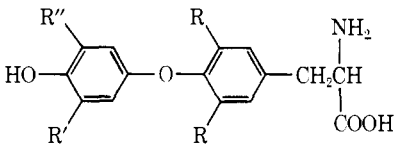
The iodine atoms of the thyroid hormones, L-thyroxine (L-T_4, **1**) and 3,5,3′-triiodo-L-thryonine (L-T_3, **2**),



1, R = R′ = R″ = I
2, R = R′ = I; R″ = H
3, R = Me; R′ = I; R″ = H
4, R = Me; R′ = *i*-Pr; R″ = H
5, R = R′ = R″ = Me

have been replaced, in part, by alkyl or aryl groups, with retention of hormonal activity.[2]

Hormonal activity is also retained by a partial or complete replacement of I by other halogen atoms, particularly Br,[3] or by a combination of Br and alkyl groups, *e.g.*, 3,5-dibromo-3′-isopropyl-L-thyronine.[4] The *i*-Pr group substitution produces an analog more potent than the parent compound when it replaces the 3′-I atom of L-T_3(**2**).[2e,g] *i*-Pr group replacement of the 3,5-I atoms of L-T_3, however, results in loss of hormonal activity.[1,5] The Me group is the only nonhalogen substituent yet reported to be capable of replacing the 3,5-iodines of L-T_3 with retention of thyroxine-like properties. 3,5-Dimethyl-3′-iodo-DL-thyronine (**3**) has been reported to show about 3% the activity of L-T_4 in the rat antigoiter assay.[6] Because of the uniqueness of this finding, it was felt desirable to carry out an independent resynthesis and biological evaluation of **3**.

The establishment or rejection of an essential role for halogen in the hormonal actions of L-T_4 and L-T_3 could aid in a better understanding of the events which initiate the hormonal response. Thus, the heavy atom perturbation theory, whereby I participates in energy transfer mediated by its excitability to the long-lived highly reactive triplet state,[7] could not be valid if a completely alkyl-substituted thyronine proved to be hormonally active. Because of the activities of 3,5-diiodo-3′-isopropyl-L-thyronine (500–1200% L-T_4) and of 3,5-dimethyl-3′-iodo-DL-thyronine (**3**, 3% L-T_4), 3,5-dimethyl-3′-isopropyl-DL-thyronine (**4**) was selected for synthesis as a potentially active halogen-free thyronine derivative. Previous studies indicated that 3,5,3′5′-tetramethyl-DL-thyronine (**5**) was inactive,[8] or possessed questionable weak activity.[6] A reevaluation of **5** at high dose levels in the antigoiter assay was therefore included in the present study.

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TABLE I

RAT ANTIGOITER ASSAY OF 3,5-DIMETHYL-DL-THYRONINES

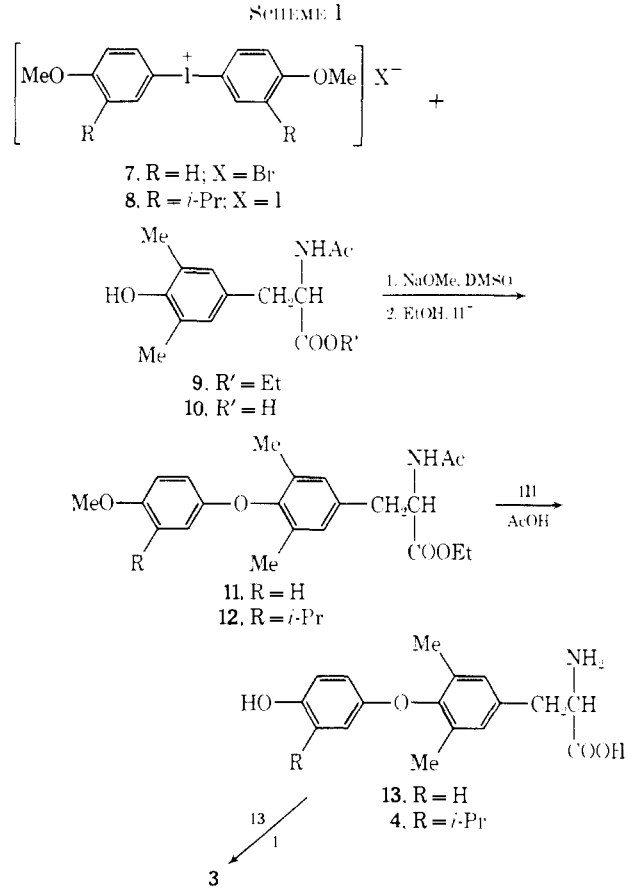
No.	Name	Dosage level[a]	Thyroid Weight, mg/100 g of Body Weight — Animals Treated With Thyroxine[b] — Untreated animals[c]	Thiouracil only	1.6 μg/100 g	2.0 μg/100 g	2.8 μg/100 g	4.0 μg/100 g	Test compound	Potency percent of L-thyroxine
3	3,5-Dimethyl-3′-iodo-DL-thyronine	25:1	12.9 ± 2.1[d]	23.7 ± 5.6			9.1 ± 1.5		8.4 ± 1.2	4
		10:1	10.3 ± 1.2	37.8 ± 8.4	20.8 ± 2.2	12.1 ± 4.2		7.3 ± 1.1	19.2 ± 7.3	5
		50:1	10.3 ± 1.2	37.8 ± 8.4	20.8 ± 2.2	12.1 ± 4.2		7.3 ± 1.1	7.1 ± 2.1	4
4	3,5-Dimethyl-3′-isopropyl-DL-thyronine	10:1	11.9 ± 1.6	26.2 ± 4.5		12.9 ± 4.0	11.3 ± 3.0	8.8 ± 0.6	27.8 ± 3.6	0
		20:1	11.9 ± 1.6	26.2 ± 4.5		12.9 ± 4.0	11.3 ± 3.0	8.8 ± 0.6	31.0 ± 5.4	0
		50:1	11.9 ± 1.6	26.2 ± 4.5		12.9 ± 4.0	11.3 ± 3.0	8.8 ± 0.6	30.9 ± 5.6	0
5	3,5,3′,5′-Tetramethyl-DL-thyronine[e]	200:1	9.0 ± 1.1	27.0 ± 6.1		13.7 ± 1.9	12.9 ± 4.5	6.6 ± 1.6	29.8 ± 6.4	0
1 + T_4	3,5-Dimethyl-3′-isopropyl-DL-thyronine and 2.0 μg/100 g of L-T_4[c,f]	100:1	10.3 ± 1.2	37.8 ± 8.4	20.8 ± 2.2	12.1 ± 4.2		7.3 ± 1.1	8.3 ± 1.7	Antag[g]
		200:1	10.3 ± 1.2	37.8 ± 8.4	20.8 ± 2.2	12.1 ± 4.2		7.3 ± 1.1	8.3 ± 1.5	Antag[g]
6 + T_4	*n*-Butyl 3,5-diiodo-4-hydroxybenzoate and 2.0 μg/100 g L-T_4[c,f]	100:1	10.3 ± 1.2	37.8 ± 8.4	20.8 ± 2.2	12.1 ± 4.2		7.3 ± 1.1	9.9 ± 1.1	Antag[g]
		500:1	10.3 ± 1.2	37.8 ± 8.4	20.8 ± 2.2	12.1 ± 4.2		7.3 ± 1.1	12.1 ± 3.9	Antag[g]

[a] Molar ratio over the intermediate level of thyroxine, 2.0 or 2.8 μg/100 g. [b] This group received normal feed. All other animals received 0.3% thiouracil in their feed. Sodium L-thyroxine pentahydrate. [d] All figures are means for six animals + standard deviation. [e] Provided by Dr. H. J. Bielig, see ref 8b. Assay for thyroxine antagonistic activity. [g] Reversal of thyroxine effect not significant.

Hormonal blocking action is a possible property of analogs, particularly in those with stereochemical similarity to the natural hormones, combined with the potential for strong receptor associations, and low biological activity. The alkyl thyronine, **4**, was therefore tested as an antagonist to L-T_4 in the antigoiter assay. Butyl 3,5-diiodo-4-hydroxybenzoate (**6**) has been well characterized for its antagonistic effects on L-T_4 in rodent O_2 consumption tests.[9] Since no reports exist on the antagonistic properties of **6** in the antigoiter test, this compound was included in the present biological study.

The synthetic route used is shown in Scheme I. Attempts to condense the diaryliodonium halide **8** with *N*-acetyl-3,5-dimethyl-DL-tyrosine ethyl ester (**9**) in the presence of Cu powder and Et_3N,[10] or with KO-*t*-Bu,[6] yielded only 2-isopropyl-4-iodoanisole, and no diaryl ether. Therefore, *N*-acetyl-3,5-dimethyltyrosine (**10**) was converted into its Na salt with NaOMe. MeOH was removed, and the condensation with the diaryliodonium halide **8** was carried out in DMSO. The crude *N*-acetyl diaryl ether was esterified with EtOH to facilitate purification as the *N*-acetyl ethyl ester (**12**). Hydrolysis with HI in AcOH yielded 3,5-dimethyl-3′-isopropyl-DL-thyronine (**4**). A similar series of reactions afforded 3,5-dimethyl-DL-thyronine (**13**) which was iodinated in aq $EtNH_2$ to yield 3,5-dimethyl-3′-iodo-DL-thyronine (**3**).

SCHEME I



Biological Results (Table I) and Discussion.—At three different dose levels and in two independent assays, 3,5-dimethyl-3′-iodo-DL-thryonine (**3**) was confirmed in its thyroxine-like activity in the rat antigoiter test.[11] A consistent level of 4–5% the activity of L-T_4 was found, in good agreement with the previous report[6] of about 3%. 3,5-Dimethyl-3′-isopropyl-DL-thyronine (**4**), however, was completely inactive, as was 3,5,3′,5′-tetramethyl-DL-thyronine (**5**) when tested at dose levels higher than those previously used. Thus, two compounds containing structural elements which permitted T_4-like activity, as long as halogen was present in the molecule, were completely devoid of T_4-like effects when halogen was absent. This indicates that halogen, or at least a structural element more halogen-like than the alkyl group, is an essential component for thyroid hormonal activity. Further, it appears that the location of the halogen, on either the phenolic or the alanine-bearing ring, is not critical. An alter-

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nate possibility is that the halogens on the alanine-bearing ring are uniquely essential for the direct hormonal effect, since 3,5-dimethyl-3′-iodo-DL-thyronine (**3**) might be producing its T_4-like actions by an indirect mechanism. Possible indirect actions in the intact animal test system used, include inhibition of enzyme systems inactivating the thyroid hormones, such as the deiodinases, or the displacement of hormone from tissue binding sites. The possibility of an indirect action of **3** is currently under study.

3,5-Dimethyl-3′-isopropyl-DL-thyronine (**4**) was inactive as an antagonist to L-T_4 in the antigoiter assay. Butyl 3,5-diiodo-4-hydroxybenzoate (**6**) was also inactive as an antagonist to L-T_4 in the antigoiter assay, even at the high molar dose ratio of 500 to 1.

Experimental Section[12]

***N*-Acetyl-3,5-dimethyl-4-(3-isopropyl-4-methoxyphenoxy)-phenyl-DL-alanine Ethyl Ester** (**12**).—*N*-Acetyl-3,5-dimethyl-DL-tyrosine[13] (6.8 g, 0.027 mol) was dissolved in 33 ml of 1.17 *N* NaOMe in MeOH. The MeOH was removed under reduced pressure and the residual Na salt dried *in vacuo* at 27°. Anhydrous DMSO (50 ml) was added, followed by 16.5 g (0.03 mol) of di-(3-*i*-propyl-4-methoxyphenyl)iodonium iodide.[2d] After stirring overnight at 110°, the solvent was removed by distillation and the residue dissolved in AcOEt and extracted with dilute NaOH. The aq extract was acidified, and extracted with AcOEt. After drying ($MgSO_4$) the AcOEt was removed under reduced pressure and the residue dissolved in 200 ml of dry $CHCl_3$ containing 0.9 g of *p*-toluenesulfonic acid and 8 ml of abs EtOH. The solution was heated under reflux for 24 hr, H_2O produced being removed by passage through a molecular sieve. The solvent was removed under reduced pressure, the residue was dissolved in Et_2O, then washed with 10% Na_2CO_3, 10% NaOH, H_2O, and dried ($MgSO_4$). Refrigeration of the filtered solution yielded 0.8 g (7%) of small crystals, which were recrystallized from MeOH–Et_2O: mp 180–181°; tlc (BuOH: MeOH: AcOH; H_2O, 9:1:1:1) one spot, R_f 0.88; nmr spectrum was as expected.[14] *Anal.* ($C_{25}H_{33}NO_5$) C, H, N.

***N*-Acetyl-3,5-dimethyl-4-(4-methoxyphenoxy)phenyl-DL-alanine Ethyl Ester** (**11**).—This compound was prepared in the same manner as **12** from 6 g (0.025 mol) of *N*-acetyl-3,5-dimethyl-DL-tyrosine (**10**) dissolved in 30 ml of 1.17 *N* NaOMe in MeOH. After removal of MeOH and dissolution of the residue in 50 ml of DMSO, a total of 31.5 g (0.075 mol) of di-(4-methoxyphenyl)-iodonium bromide[15] (**7**) was added in portions over 48 hr to the stirred solution maintained at 90°. After filtration and evaporation of solvent, the residue was dissolved in AcOEt and extracted with 10% NaOH. The aq extract was acidified, extracted with AcOEt and the AcOEt extract dried ($MgSO_4$) and evaporated under reduced pressure. The residual *N*-acetyl acid was esterified as described for **12**, to yield 860 mg (9%) of a colorless oil which was homogeneous by tlc and showed the expected spectral characteristics (nmr, ir, uv). The oil was hydrolyzed to yield the amino acid **13** without further purification.

3,5-Dimethyl-4-(3-isopropyl-4-hydroxyphenoxy)phenyl-DL-alanine Hydriodide (**4**).—The *N*-acetyl ethyl ester (**12**, 0.427 g, 0.001 mol) was heated under reflux (N_2 atmosphere) for 4 hr with 10 ml AcOH and 15 ml 47% HI. The free amino acid was too soluble in H_2O for isolation by isoelectric precipitation at pH 5.5. The solution was evaporated under reduced pressure to yield the HI salt, which crystallized as needles from H_2O (0.40 g, 90%): mp 250–260° dec; tlc (BuOH: MeOH: AcOH: H_2O, 9:1:1:1) one spot. *Anal.* ($C_{20}H_{26}INO_4$) C: calcd, 50.97; found, 50.44; H, N.

3,5-Dimethyl-4-(3-iodo-4-hydroxyphenoxy)phenyl-DL-alanine (**3**).—3,5-Dimethyl-DL-thyronine[6,15] (**13**) was obtained in the same manner as **4**, by HI–AcOH hydrolysis of **11**. Iodination of 120 mg (0.4 mmol) of **13** in 10 ml of 33% $EtNH_2$ was carried out[6] with 101 mg of I_2 in 0.2 g of aq KI to yield 125 mg (70%) of **3**, mp 215° dec (Lit.[6] 212–214° dec). *Anal.* ($C_{17}H_{18}INO_4 \cdot H_2O$) C, H, I.

Acknowledgments.—We thank Mr. Ahmad Parvez for the synthesis of butyl 3,5-diiodo-4-hydroxybenzoate, and for assistance in the conduct of rat antigoiter assays.

(12) Melting points (corrected) were determined with a Thomas-Hoover capillary melting point apparatus. Microanalyses were performed by the Microanalytical Laboratory, Dept. of Chemistry, University of California, Berkeley, Calif. Nmr spectra were obtained in $CDCl_3$ on a Varian A-60A (Me$_4$Si). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

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Central Nervous System Activity of Ethyl 1-Naphthylalkylcarbamates

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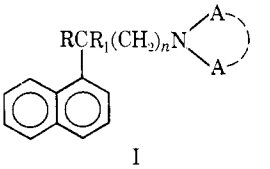
Our interest in the field of naphthalene chemistry, together with the recent availability of primary 1-naphthylalkylamines,[1] has led us to synthesize an extensive series of ethyl 1-naphthylalkylcarbamates of structure I, in which R was H, or alkyl, or aminoalkyl; R_1 was $NHCO_2Et$ or CH_2NHCO_2Et; NAA was a tertiary amino group; n = 2–4. The new substances (Table I) were obtained from the corresponding amines by reaction



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with excess $ClCO_2Et$, the reaction time depending on the steric hindrance of the amines.

All of the new compounds were submitted to an investigation of their CNS activity which included studies of behavioral effects,[2] action on pentobarbital sleeping time,[3] and analgetic,[4,5] anticonvulsant,[3] antidepressant (reserpine antagonism),[6] and antitremor (oxotremorine antagonism)[7] actions. In all the experiments, the drugs were tested in mice at the oral dose of 100 mg/kg.

Of all the substances tested 8, **12**, **17**, **20**, **21**, **26**, and

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