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_4Si). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

(13) E. C. Jorgensen and R. A. Wiley, *J. Pharm. Sci.*, **52**, 122 (1963).

(14) P. A. Lehman and E. C. Jorgensen, *Tetrahedron*, **21**, 363 (1965).

(15) A. Dibbo, L. Stephenson, T. Walker, and W. K. Warburton, *J. Chem. Soc.*, 2645 (1961).

Central Nervous System Activity of Ethyl 1-Naphthylalkylcarbamates

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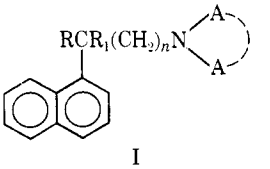
Our interest in the field of naphthalene chemistry, together with the recent availability of primary 1-naphthylalkylamines,[1] has led us to synthesize an extensive series of ethyl 1-naphthylalkylcarbamates of structure I, in which R was H, or alkyl, or aminoalkyl; R_1 was $NHCO_2Et$ or CH_2NHCO_2Et;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



I

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

(1) G. Pala, A. Donetti, C. Turba, and S. Casadio, *J. Med. Chem.*, **13**, 668 (1970).

(2) S. Irwin, Communication at the Gordon Research Conference on Medicinal Chemistry, New London, N. H., Aug 3–7, 1959.

(3) E. Marazzi-Uberti, C. Turba, and C. Bianchi, *J. Pharm. Sci.*, **55**, 1105 (1966).

(4) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol. Chemother.*, **9**, 280 (1954).

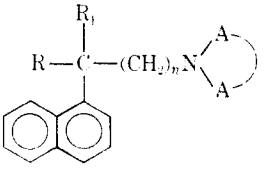
(5) J. Y. P. Chen and H. Beckman, *Science*, **113**, 631 (1951).

(6) S. Garattini, A. Giachetti, A. Jori, L. Pieri, and L. Valzelli, *J. Pharm. Pharmacol.*, **14**, 509 (1962).

(7) A. Burger, "Selected Pharmacological Testing Methods," Vol. 3, Marcel Dekker, Inc., New York, N. Y., 1968, p 337.

TABLE I

1-NAPHTHYLALKYLCARBAMATES



Compd	R	R1	NR2	Reflux time, hr	Yield, %[a]	Bp (mm), °C	Formula[b]
1	*i*-C_3H_7	$NHCO_2Et$	$(CH_3)_2N(CH_2)_2$	8	65.6	*c*	$C_{21}H_{30}N_2O_2$
2	*i*-C_3H_7	$NHCO_2Et$	*d*	8	78.4	*c*	$C_{24}H_{34}N_2O_2$
3	H	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	3	65.4	190–192 (0.3)	$C_{19}H_{26}N_2O_2$
4	CH_3	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	8	56.2	*c*	$C_{20}H_{28}N_2O_2$
5	*i*-C_3H_7	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	5	77	*c*	$C_{22}H_{32}N_2O_2$
6	*sec*-C_4H_9	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	5	39.2	*c*	$C_{23}H_{34}N_2O_2$
7	$(CH_3)_2N(CH_2)_2$	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	8	74	*c*	$C_{25}H_{35}N_3O_2$
8	*i*-C_3H_7	CH_2NHCO_2Et	$CH_3(C_2H_5)N(CH_2)_2$	5	82.2	*c*	$C_{25}H_{34}N_2O_2$
9	*i*-C_3H_7	CH_2NHCO_2Et	$(C_2H_5)_2N(CH_2)_2$	5	82	*c*	$C_{24}H_{36}N_2O_2$
10	*sec*-C_4H_9	CH_2NHCO_2Et	$(C_2H_5)_2N(CH_2)_2$	5	60.8	*c*	$C_{25}H_{38}N_2O_2$
11	*i*-C_3H_7	CH_2NHCO_2Et	$(i\text{-}C_3H_7)_2N(CH_2)_2$	5	60	*c*	$C_{26}H_{40}N_2O_2$
12	CH_3	CH_2NHCO_2Et	*e*	8	53.3	*c*	$C_{22}H_{30}N_2O_2$
13	*i*-C_3H_7	CH_2NHCO_2Et	*e*	5	63.4	*c*	$C_{24}H_{34}N_2O_2$
14	*sec*-C_4H_9	CH_2NHCO_2Et	*e*	5	48.8	*c*	$C_{25}H_{36}N_2O_2$
15	*e*	CH_2NHCO_2Et	*e*	8	41	*c*	$C_{27}H_{39}N_3O_2$
16	H	CH_2NHCO_2Et	*d*	3	81.5	215–218 (0.5)	$C_{22}H_{30}N_2O_2$
17	CH_3	CH_2NHCO_2Et	*d*	5	67	*c*	$C_{23}H_{32}N_2O_2$
18	*i*-C_3H_7	CH_2NHCO_2Et	*d*	5	81.4	*c*	$C_{25}H_{36}N_2O_2$
19	*d*	CH_2NHCO_2Et	*d*	5	80	*c*	$C_{29}H_{43}N_3O_2$
20	CH_3	CH_2NHCO_2Et	*f*	5	88	*c*	$C_{22}H_{30}N_2O_3$
21	*i*-C_3H_7	CH_2NHCO_2Et	*f*	5	55.7	*c*	$C_{24}H_{34}N_2O_3$
22	*f*	CH_2NHCO_2Et	*f*	10	66.4	*c*	$C_{27}H_{39}N_3O_4$
23	CH_3	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_3$	5	80.2	*c*	$C_{21}H_{30}N_2O_2$
24	*sec*-C_4H_9	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_3$	3	43.5	*c*	$C_{24}H_{36}N_2O_2$
25	*i*-C_3H_7	CH_2NHCO_2Et	*g*	3	66.6	*c*	$C_{26}H_{38}N_2O_2$
26	*sec*-C_4H_9	CH_2NHCO_2Et	*h*	5	92.7	*c*	$C_{26}H_{38}N_2O_2$
27	*sec*-C_4H_9	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_4$	5	56.6	*c*	$C_{25}H_{38}N_2O_2$
28	*i*-C_3H_7	CH_2NHCO_2Et	*i*	5	80.4	*c*	$C_{27}H_{40}N_2O_2$
29	*i*-C_3H_7	CH_2NHCO_2Et	*j*	4	76.2	*c*	$C_{26}H_{38}N_2O_3$

[a] Crude product. [b] All compounds were analyzed for C, H, N and the analytical results were within ±0.4% of the theoretical values. [c] Waxy product. [d] 2-Piperidinoethyl. [e] 2-(1-Pyrrolidinyl)ethyl. [f] 2-Morpholinoethyl. [g] 3-Piperidinopropyl. [h] 3-Morpholinopropyl. [i] 4-Piperidinobutyl. [j] 4-Morpholinobutyl.

29 prolonged pentobarbital sleeping time at 40 mg/kg ip. However, this effect had only slight pharmacological significance. Compounds **12** and **20** displayed some activity in the antireserpine test but were less active than imipramine. In none of the other assays did the compounds exert any noteworthy activity.

Experimental Section[8]

The intermediate amines were prepared as previously described.[1]

Ethyl 1-Naphthylalkylcarbamates.—A solution of the appropriate amine (0.1 mol) and $ClCO_2Et$ (0.15 mol) in anhydrous C_6H_6 (190 ml) was refluxed in the presence of K_2CO_3 (0.15 mol). The reaction mixture was extracted with 10% HCl, the acid solution made alkaline with 10% NaOH, and the precipitate which formed extracted (Et_2O). The ethereal solution was washed (H_2O) until neutral, dried (Na_2SO_4), and evaporated to dryness to give an oily or waxy product.

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(8) Boiling points are uncorrected.

Synthesis and Endocrine Activity of Some 3-Aza-*A*-homopregnenes

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The nucleotide, cyclic 3′,5′-adenosine monophosphate (cyclic AMP), is a naturally occurring intracellular constituent that has been shown to influence a wide variety of physiological functions.[1-3] Hormones and

(1) M. A. Rizack, *J. Biol. Chem.*, **239**, 392 (1964).
(2) E. W. Sutherland and T. W. Rall, *Pharmacol. Rev.*, **12**, 265 (1960).
(3) S. Tarui, K. Nanaka, Y. Ikura, and K. Shima, *Biochem. Biophys. Res. Commun.*, **13**, 329 (1963).