TABLE I

ESTERS OF FARNESYLACETIC ACID  CO_2R

R	Formula	Method of preparation	B.p. °C.	B.p. mm.	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Antiulcer activity[a] Subcutaneous mg./kg.		Antiulcer activity[a] Oral mg./kg.	
Methyl	$C_{18}H_{30}O_2$	E, G	108–110	0.08	77.42	10.62	77.65	10.86	2.5	0	2.5	0
Ethyl	$C_{19}H_{32}O_2$	A, B, C, D, E, F	114–115	0.06	78.20	10.81	78.03	11.03	2.5	+	2.5	+
Propyl	$C_{20}H_{34}O_2$	E, F	130–135	0.1	78.49	11.03	78.38	11.18	2.5	0	2.5	0
n-Butyl	$C_{21}H_{36}O_2$	A, C, E, F	127–130	0.1	78.53	10.99	78.69	11.32	2.5	0	2.5	0
Isoamyl	$C_{22}H_{38}O_2$	E, F	145–149	0.1	79.07	11.20	78.98	11.45	2.5	−	2.5	0
3,7-Dimethyloctyl (tetrahydrogeranyl)	$C_{27}H_{48}O_2$	E, F	183–185	0.15	80.29	11.63	80.14	11.96	2.5	+		
n-Dodecyl	$C_{29}H_{52}O_2$	C, E, F	193–197	0.06	80.40	11.75	80.49	12.11	2.5	0	2.5	0
Cyclohexyl	$C_{28}H_{38}O_2$	E, F	156–161	0.1	79.63	10.88	79.71	11.05	2.5	+	2.5	0
Allyl	$C_{26}H_{32}O_2$	E, F, H	116–118	0.15	78.91	10.28	78.89	10.59	2.5	+	2.5	0
Geranyl	$C_{27}H_{44}O_2$	E, F	165–168	0.05	81.06	11.05	80.94	11.07	1.25	+	1.25	+
Farnesyl	$C_{32}H_{52}O_2$	E, F	200–203	0.05	81.68	10.95	81.99	11.18	2.5	0	2.5	+
Phytyl	$C_{37}H_{66}O_2$	E, F	226–230	0.08	81.52	11.90	81.85	12.25	2.5	0	2.5	+
Propargyl	$C_{20}H_{30}O_2$	E, F	122–128	0.07	79.43	9.98	79.42	10.00	2.5	+	2.5	0
Phenyl	$C_{23}H_{32}O_2$	E, F	162–170	0.15	81.05	9.31	81.13	9.47	2.5	0	2.5	0
Cinnamyl	$C_{26}H_{36}O_2$	E, F	195–200	0.15	81.71	9.47	82.06	9.54	2.5	+	2.5	0

[a] + Positive significant improvement in comparison with the controls ($P \leq 0.05$); − negative significant aggravation in comparison with the controls ($P \leq 0.05$); 0 no effect ($P > 0.05$); negative results do not exclude a positive result at higher dosages.

G.—An ethereal solution of diazomethane was added to a cooled ethereal solution of farnesylacetic acid.

H.—An ethereal solution of 45% boron trifluoride (3.5 g.) was added to a cooled ethereal mixture of the alcohol (0.07 mole) and of farnesylacetic acid (0.04 mole). After refluxing for 2 hr. and removal of excess alcohol *in vacuo*, the residue was dissolved in ether, washed with 10% sodium carbonate solution, and fractionated *in vacuo*.

Chemical Models of Drug–Receptor Interaction. II

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In an earlier paper[1] it was reported that amino acids displace the distribution of diethylaminoethanol (DEA) between water and carbon tetrachloride toward the aqueous phase. The qualitative and quantitative aspects of this phenomenon were interpreted in terms of electrostatic attraction and hydrogen bonding between DEA and amino acids, and conclusions were drawn regarding drug–receptor interaction in general, considering DEA as a model for drugs and the amino acids as models for receptor protein.

Another drug model, related to DEA and a higher homolog of it, is dibutylaminoethanol (DBA). One may expect this base, with its larger alkyl groups, to favor carbon tetrachloride in the distribution more than does DEA. In fact, although the pK_a of DBA (9.67) is not very different from that of DEA (9.58), the distribution of the former between water and carbon tetrachloride (solid curve in Fig. 1) turned out to be far more on the side of carbon tetrachloride. Even at pH 7, where DBA is practically all ionic, 25% of it is in the carbon tetrachloride layer at equilibrium.

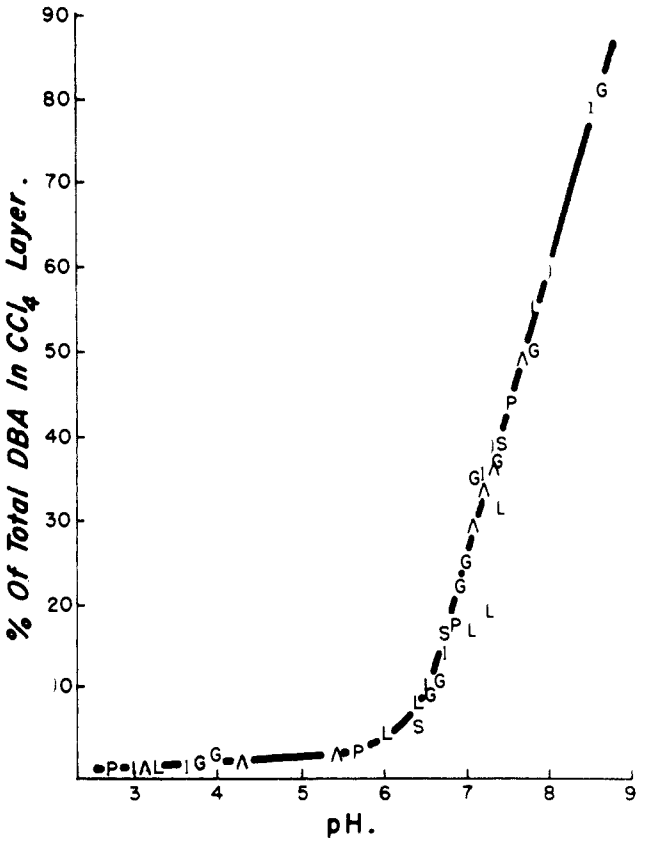

Fig. 1.—The symbols for amino acids indicate the percentage of DBA in the CCl_4 phase when that particular amino acid is present. Symbols for amino acids; G,glycine; A, alanine; L, leucine; I, isoleucine; P, phenylalanine; S, serine.

One must expect amino acids to be less able to bind DBA than DEA under the conditions of these experiments since the carbon tetrachloride layer in effect competes for DBA with the amino acids in the aqueous phase. On the other hand, the possibility of van der Waals bonding between the butyl groups of DBA and large hydrocarbon groups in amino acids might permit

(1) A. Gero and L. A. Shropshire, *J. Med. Pharm. Chem.*, **3**, 299 (1961).

some binding of DBA by such amino acids as leucine, isoleucine, and phenylalanine.

To test these expectations, the experiments described in the first paper were repeated with DBA instead of DEA, using glycine, alanine, leucine, isoleucine, phenylalanine, and serine as amino acids, serine being included in order to test the ability of the strongly hydrogen-bonding OH group to overcome the competition of the carbon tetrachloride. In the experiments with DEA, the OH group proved a potent binding factor in both serine and threonine.

As expected, none of these amino acids showed any binding of DBA in the pH range 8.5 to 10.2 where binding of DEA is quite pronounced.[1] There was, however, unmistakable binding of DBA by leucine in the pH range 7.0 to 7.5 where both DBA and leucine are predominantly cationic and where consequently, from the results obtained with DEA, one would predict no binding at all (Fig. 1). That binding does nevertheless occur can hardly be attributed to anything but van der Waals bonding between the butyl groups of DBA and the isobutyl group of leucine. As would be expected of van der Waals bonding, leucine binds DBA much more weakly than DEA, giving rise to a maximum binding coefficient [DBA–leucine complex]/([DBA][leucine]) = 2.2, against 9.7 for the DEA–leucine complex.

That isoleucine shows no binding at any pH may perhaps be attributed to steric hindrance: the branching in the alkyl chain near the polar end of the amino acid molecule interferes with the close approach of the DBA required for binding. The same may apply to phenylalanine.

If these considerations are valid, the experiments reported here may be said to provide a model for several known factors of drug–receptor interaction, namely, the role of van der Waals bonding between drug and receptor, the role of steric factors, and the importance of solubility effects. In cases for which the present instance can serve as a model, a lipophilic phase (carbon tetrachloride here, fat in the organism) can compete for the drug with the receptor, while the opposite should be true for receptors in body fats. It should be noted that these results also are a model of specificity. In the experimental arrangement used here, the amino acids could distinguish between two compounds as closely related in both structure and basicity as DEA and DBA, binding the former and rejecting the latter.

Thyroxine Analogs. X.[1] 3,5-Diamino-, 3,5-Dicyano-, and 3,5-Dicarboxy-DL-thyronines

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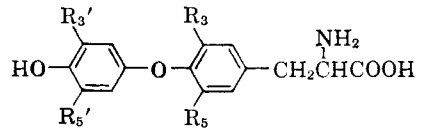
It has been established that analogs of the naturally occurring thyroid hormones in which the iodine atoms at positions 3 and 5 have been replaced by methyl groups (Ia)[3] and by halogens other than iodine (Ib)[4] retain significant thyroxine-like activity. Thyronine derivatives with a single iodine atom in the alanine bearing ring (Ic) show thyroxine antagonist properties[5,6]; 3,5-dinitrothyronines (Id) have been found to possess neither thyroxine-like nor thyroxine antagonist properties.[7]



Ia: $R_3 = R_5 = CH_3$, $R_3' = I$, $R_5' = H$
Ib: $R_3 = R_5 = Br$, $R_3' = I$, $R_5' = H$; $R_3 = R_3' = I$, $R_5 = R_5' = Cl$
Ic: $R_3 = R_3' = I$, $R_5 = R_5' = H$
Id: $R_3 = R_5 = NO_2$, $R_3' = R_5' = I$
Ie: $R_3 = R_5 = COOH$, $R_3' = R_5' = H$

In studies relative to substituent requirements in the alanine bearing ring of the thyronine nucleus, we have prepared additional 3,5-disubstituted analogs: 3,5-diamino-DL-thyronine (IV), 3,5-diamino-3′-methyl-DL-thyronine (VII), and 3,5-dicyano-DL-thyronine (XIII). The diamino analogs, IV and VII, were assayed for thyromimetic activity and IV was tested for antithyroxine effect. Barnes, *et al.*,[8] have reported the synthesis of 3,5-dicarboxy-L-thyronine. Since this material does not appear to have been evaluated biologically, we have prepared 3,5-dicarboxy-DL-thyronine (Ie), and have tested it both for thyroxine-like and for antithyroid effect.

Synthesis.—Chalmers, *et al.*,[9] have described the preparation of the L-isomer of the dinitrothyronine derivative II and the corresponding diamino derivative III. From DL-III, 3,5-diamino-DL-thyronine (IV) has been prepared by hydrolysis with hydriodic acid. Since a substituent such as iodine at position 3′ is required for maximum potency in the thyronine series, iodination of 3,5-diamino-DL-thyronine (IV) was attempted, using iodine in aqueous ethylamine[3] and iodine monochloride in aqueous hydrochloric acid. Neither an iodinated product nor reactant could be isolated due to rapid formation of dark polymeric material.

It has been shown[10,11] that 3,5-diiodothyronines bearing a 3′-methyl substituent possess a high order of thyromimetic potency. On this basis, it was felt that 3,5-diamino-3′-methyl-DL-thyronine (VII) should disclose any activity which might be present in the

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