system as the next larger ion, naphtho(2,1-*b*)quinolizinium, is 1/3.4 times as active.

In an aliphatic system, such as the trimethylalkylammonium compounds, the difference in activity between the *n*-propyl ($I_{50}3 \times 10^{-3}$) and *n*-heptyl ($I_{50}6 \times 10^{-4}$) homologs (4 carbon atoms different) was 5 times and between the *n*-butyl ($I_{50}2 \times 10^{-3}$) and *n*-heptyl homologs (3 carbon atoms different), was 3.3 times.[5] The effect on activity of adding three carbon atoms both to the "aliphatic" series and the first two compounds in the "aromatic" series now examined is practically the same. This suggests that the effect of adding 3 extra carbon atoms, to either lengthen an aliphatic chain or to go from a pyridinium system to a quinolizinium one, is non-specific and, in both cases, increases activity by increasing the number of van der Waals' interactions. However, when the increase in activity brought about by the addition of 4 carbon atoms to the "aliphatic" series is compared with the difference in activity between the quinolizinium ion and its benzhomolog the situation is different. The marked increase in activity which occurs in the 'aromatic' series suggests that the adsorption of the benzo-*b*-quinolizinium ion onto acetylcholinesterase is more specific than other quaternary ammonium ions. This conclusion is supported by the fact that naphtho(2,1-*b*) quinolizinium bromide is less active than acridizinium bromide even though it has 4 more carbon atoms.

Acknowledgment.—The quinolizinium compounds were prepared in the Pharmacy Department by J. M. Midgley.

(5) F. Bergmann and A. Shimoni, *Biochem. Biophys. Acta*, **10**, 49 (1953).

Esters of Farnesylacetic Acid

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A series of new alkyl and aryl farnesylacetates, prepared by standard methods described in the Experimental part, have been found to exhibit preventive and curative activity on different gastric ulcers in guinea pigs when administered parenterally in small doses; they had no autonomic action.[2] Table I lists the physical properties of the most interesting compounds prepared, as well as the anti-ulcer activity at the dosage levels used.[3] The anti-ulcer activity of the compounds was measured in terms of inhibition and cure of experimental gastric ulcer produced by histamine in guinea pigs pretreated with the antihistaminic, tripelennamine. The procedural details have been described in previous publications.[4]

The most promising of these esters, geranyl farnesylacetate[5] had an i.v. LD_{50} in mice of 2821 mg./kg. (confidence limits, 95%). The i.p. LD_{50} was higher than 4000 mg./kg., the oral LD_{50} higher than 8000 mg./kg. Chronic administration of this drug to growing young rats (70 mg./kg./day) for 91 days did not interfere with normal development. No blood dyscrasias or macroscopic or microscopic alterations of the vital organs were observed on necropsy.

Anti-ulcer tests with geranyl farnesylacetate revealed no local action on the gastric mucosa. The prophylactic doses in the restrained rat was 50 mg./kg. s.c., in reserpine ulcer (rat) 20 mg./kg. i.p. and in the fasting rat 10 mg./kg. i.p. No activity was found in the Shay ulcer in the rat up to 200 mg./kg. The drug relaxes the isolated guinea pig ileum, apparently unspecifically, at a rate of one-ninth that of papaverine. The compound is practically not anticholinergic (2780 times less than atropine), nor antihistaminic (1305 times less than diphenhydramine), or antinicotinic (126 times less than hexamethonium). No analgetic or anti-inflammatory effects have been noted. The mechanism of the rather specific anti-ulcer activity has not yet been elucidated.

Experimental

Preparations of Esters. Method A.—An alcoholic solution of potassium hydroxide (0.5 mole per mole of ester) was added to an alcoholic solution of alkyl farnesylmalonate[6] and the mixture was allowed to stand at room temperature for about 30 hr. After removal of alcohol, acidification, and extraction with ether, the residue was decarboxylated by heating *in vacuo* for 4 hr. at 150°. It then was dissolved with ether and washed with sodium carbonate or some other weakly alkaline agent. After removal of the ether, it was distilled *in vacuo*.

B.—One mole of an ester of farnesylacetoacetic[7] acid was added to an alcoholic solution of 1 mole of the appropriate sodium alkoxide and refluxed for 2 hr. After removal of the alcohol, the residue was dissolved in water, extracted with ether, dried, and distilled.

C.—Farnesylacetic acid[6b,7b] was esterified by refluxing either with a large excess of the proper alcohol or with a small excess, but in benzene solution. It is advisable to add a little hydrochloric acid or *p*-toluenesulfonic acid as catalyst. After removal of the solvent and washing with a weakly alkaline agent, the ester was distilled *in vacuo*.

D.—Silver farnesylacetate was prepared by adding an aqueous solution of silver nitrate to a solution of farnesylacetic acid in 0.5 *N* ammonium hydroxide. After drying in the dark, the salt was dissolved in boiling benzene and a benzene solution of alkyl iodide was added. After boiling for 9 hr. and removal of the solvent and filtration, the residue was distilled *in vacuo*.

E.—Ketene was passed into ice-cooled farnesylacetic acid until a small excess was absorbed. After heating *in vacuo* for 5 hr. at 160°, a large excess of alcohol (or a small excess of alcohol and benzene as solvent) was added and refluxed for 11 to 15 hr. After dilution with ether and washing with an alkaline agent, the solvent was removed and the residue distilled *in vacuo*.

F.—Farnesylacetyl chloride is prepared by adding without heating a small excess of a benzene solution of thionyl chloride to farnesylacetic acid and refluxing for 2 hr. It distils *in vacuo* with slight decomposition. For the subsequent reactions, the fraction passing at 145–155° (0.7–1 mm.) was used.

Farnesylacetyl chloride was added dropwise to a solution of the alcohol and an excess of dimethylaniline in anhydrous benzene, the mixture was then refluxed for 8 hr. and worked up.

(1) To whom inquiries should be addressed.

(2) E. Adami, *Experientia*, **18**, 461 (1962).

(3) E. Adami, E. Marazzi-Uberti, and C. Turba, *Medicina Experimentalis*, **7**, 171 (1962).

(4) E. Marazzi-Uberti and C. Turba, *ibid.*, **4**, 284 (1961); **5**, 9 (1961).

(5) Gefarnate (International non-proprietary name, proposed to W.H.O.).

(6) For ethyl farnesylmalonate see: (a) P. Dietrich and E. Lederer, *Compt. rend.*, **234**, 637 (1952); *Helv. Chim. Acta*, **35**, 1148 (1952). Dibutyl farnesylmalonate boiled at 137–145° (0.02–0.03 mm.).

(7) Ethyl farnesylacetoacetate has been used as an intermediate by various authors, but has never been isolated in the pure state; *cf.* (a) L. Ruzicka and G. Firmenich, *Helv. Chim. Acta*, **22**, 392 (1939); (b) A. Caliezi and H. Schinz, *ibid.*, **35**, 1649 (1952); (c) A. Mondon, *Chem. Ber.*, **88**, 724 (1955).

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	$C_{20}H_{32}O_2$	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.

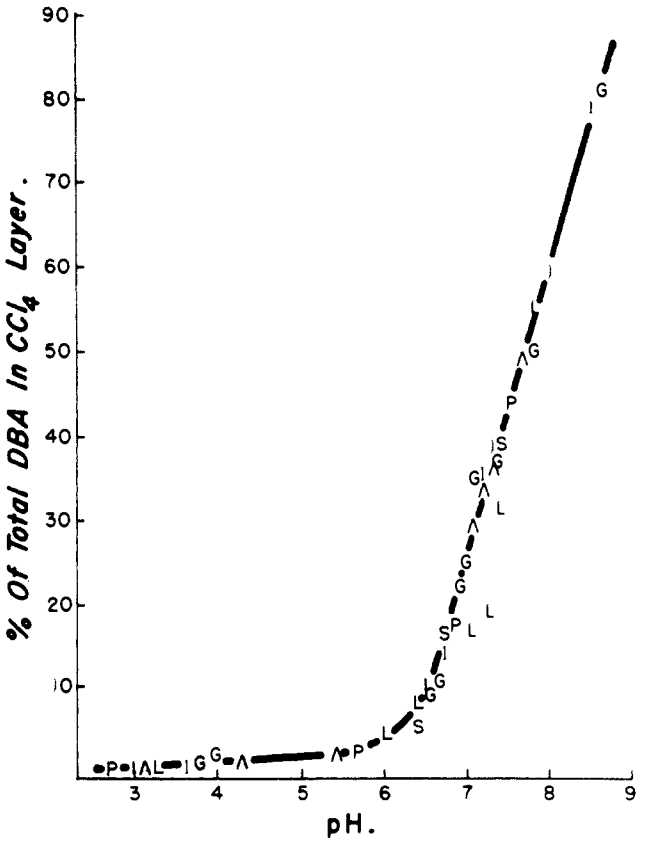

Fig. 1.—The symbols for amino acids indicate the percentage of DBA in the CCl_4 phase when that particular amino acid is present. Symbols for amino acids; G,glycine; A, alanine; L, leucine; I, isoleucine; P, phenylalanine; S, serine.

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).