barrier preparations seemed to spread the oster oil. In these instances, the reaction extended over the area covered by the barrier rather than being confined to the site of the oster oil application.

DISCUSSION

The procedure of using sensitized guinea pigs to test barrier protection against allergic contact dermatitis depends upon producing a pronounced and predictable contact dermatitis in response to exposure to the allergen. Oster oil proved to be a fairly satisfactory oil-soluble allergen. DNFB is a potent oil-soluble allergen, but its use is limited to application areas where the animal cannot ingest the substance and there would be difficulty in testing more than one barrier per animal at any one time. None of the water-soluble potential allergens tested thus far has produced a satisfactory response and further work must be done before this method can be used to test barrier protection against water-soluble substances. Four of these barriers had been tested previously by an *in vitro* procedure involving solubility in oster oil (10). The *in vitro* results were in agreement with these *in vivo* data.

Reactions are much more intense if a defatting solution is used prior to application of the oster oil than if no defatting solution is used ($P < 0.001$), and with all allergens, the hair should be clipped before each application. The animals varied one from another in response to each allergen. Guinea pig No. 5 reacted very strongly to oster oil and responded only moderately to DNFB, whereas guinea pig No. 3 showed low sensitivity to oster oil and intense reactions to DNFB. In some instances the reaction was more severe 48 hours following application of the allergen than at the 24-hour period and further investigation will include time-reaction intensity studies. Unless the investigator uses a large group of animals, testing is necessarily slow because of the time necessary for the skin to clear after each positive reaction. The procedure could be improved with development of a more objective method of reading reactions.

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Hypocholesteremic Agents I. (*p*-Acetamidophenoxy)acetic Acid Derivatives

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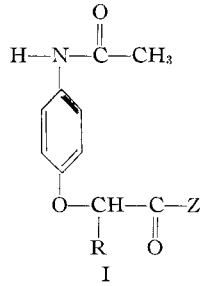
A series of (*p*-acetamidophenoxy)acetic acid derivatives (I) has been examined for hypocholesteremic effects, and significant activity was noted with R as lower alkyl and Z as an amide function.

It has been proposed that the hypercholesteremic state is stress-mediated (1). Since acetophenetidin purportedly influences adrenal activity via its effect on the pituitary (2) derivatives (I) of this compound have been examined, particularly for the influence on serum cholesterol levels.

Related systems have been assessed as hypocholesteremic agents (3) and for other pharmacological effects (4, 5).

For the preparation of the compounds, *p*-hydroxyacetanilide was reacted with the α-bromoester, of the formula $RHBrCCOOC_2H_5$, in acetone under reflux, employing potassium carbonate as an acid binder, to give I, Z = $—OC_2H_5$. Ammonolysis of the esters afforded the amides, and hydrolysis yielded the acids.

The hypocholesteremic effect was evaluated in guinea pigs given 30 mg./Kg. subcutaneous doses of the test compounds at the beginning of the experiment, twenty-four hours later, and finally, forty-eight hours later. Serum cholesterol levels were established at the initiation of the experiment and at the following time intervals thereafter: six, forty-eight, and seventy-two hours. The reduction (in



I

Z = —OH, $—OC_2H_5$
—NH_2, $—NHC_2H_5$
$—NH(CH_2)_2N(C_2H_5)_2$
$—NH(CH_2)_2OH$
R = H, $CH_3—$, $C_2H_5—$

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TABLE I.—(*p*-ACETAMIDOPHENOXY)ACETIC ACID DERIVATIVES (I)

Compound No.	Z	M. P., °C.[a]	R. S.[b]	Yield,[c] %	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
	(R = H)										
1[e]	—OH	175–177	A	32	$C_{10}H_{11}NO_4$	57.4	57.4	5.3	5.1	6.7	6.8
2[f]	—OC_2H_5	104–105	A	53	$C_{12}H_{15}NO_4$	60.8	60.2	6.4	6.0	5.9	6.3
3[g]	—NH_2	197–199	A	56	$C_{10}H_{12}N_2O_3$	57.7	57.4	5.8	5.8	13.5	13.5
4	—NHC_2H_5	202–203	A	39	$C_{12}H_{16}N_2O_3$	61.0	61.3	6.8	6.9	11.9	12.0
5	—$NH(CH_2)_2N(C_2H_5)_2$	73–75	B	27	$C_{16}H_{25}N_2O_3$	62.5	62.8	8.2	7.9	13.7	13.8
	($R = CH_3$—)										
6	—OH	173–174	A	51	$C_{11}H_{13}NO_4$	59.2	59.1	5.9	5.7	6.3	6.4
7	—OC_2H_5	[h]		61	$C_{13}H_{17}NO_4$	62.1	62.4	6.8	7.0	5.6	5.7
8	—NH_2	200–202	C	52	$C_{11}H_{14}N_2O_3$	59.5	59.1	6.4	6.1	12.6	12.6
9	—NHC_2H_5	164–167	A	33	$C_{13}H_{18}N_2O_3$	62.4	62.3	7.3	7.1	11.2	11.5
10	—$NH(CH_2)_2N(C_2H_5)_2$	126–129	A	44	$C_{17}H_{27}N_3O_3$	63.5	63.8	8.5	8.4	13.1	12.8
11	—$NH(CH_2)_2OH$	149–153	A	13	$C_{13}H_{18}N_2O_4$	58.6	58.9	6.8	6.8	10.5	10.9
	($R = C_2H_5$—)										
12	—OH	137–138	D	10	$C_{12}H_{15}NO_4$	60.8	61.1	6.4	6.4	5.9	6.3
13	—OC_2H_5	[i]		57	$C_{14}H_{19}NO_4$	63.4	63.1	7.2	7.3	5.3	5.7
14	—NH_2	208–211	A	67	$C_{12}H_{16}N_2O_3$	61.0	60.3	6.8	6.8	11.9	12.3
15	—NHC_2H_5	159–162	A	49	$C_{14}H_{20}N_2O_3$	63.6	64.0	7.6	7.3	...	...
16	—$NH(CH_2)_2N(C_2H_5)_2$	126–128	B	10	$C_{18}H_{29}N_3O_3$	64.5	64.5	8.7	8.8	12.5	12.8

[a] Melting points were established on a Fisher-Johns apparatus. [b] R. S. = recrystallizing solvent; A = acetonitrile; B = water; C = methanol; D = methyl ethyl ketone. [c] Yields are based on recrystallized or distilled product. [d] Analyses were performed by Weiler and Strauss, Oxford, England. [e] Reported, Beilstein XIII, p. 465, m. p. 175–176°. [f] Reported, *ibid.*, m. p. 103–104°. [g] Reported, *ibid.*, m. p. 202–208°. [h] B. p. 186–192° (0.03 mm.). [i] B. p. 182–184° (0.01 mm.).

%) from the cholesterol level at the initiation of the experiment was noted.

Responses showing a hypocholesteremic effect of more than 30% were observed with the following compounds: compound number ($LD_{min.}$): 8 (750), 10 (>1,000), 11 (750), 16 (>1,000), with the highest activity (46% reduction) being noted with compound 16. This compound also afforded a 31% reduction in cholesterol at 60 mg./Kg., p. o.

Structure-activity relationships indicate that for significant hypocholesteremia in I, that R be substituted as lower alkyl, and Z be substituted to provide an amide function. See Table I.

Other pharmacological responses of interest were local anesthetic effect (ED_{50}, 15 mg./ml.) (6) with compound 10, and adrenergic block (6) with compound 13.

EXPERIMENTAL[1]

Ethyl α-(4-Acetamidophenoxy)butyrate (Compound 13).—A mixture of 30.2 Gm. (0.2 mole) of *p*-hydroxyacetanilide, 39.0 Gm. (0.2 mole) of ethyl α-bromobutyrate, and 27.6 Gm. (0.2 mole) of potassium carbonate in 150 ml. of acetone was heated under reflux, with stirring, for ten hours. When cool, the solvent was removed and the residue was dissolved in ether and washed successively with 5% aqueous sodium carbonate and water. After drying (anhydrous magnesium sulfate) and removal of ether, distillation gave 30 Gm. (57%) of product, b. p. 182–184° (0.1 mm.).

[1] Typical procedures are given, data appearing in Table I are not reproduced.

N-(2-Diethylaminoethyl)-α-(*p*-acetamidophenoxy)propionamide (Compound 10).—Ethyl α-(*p*-acetamidophenoxy)propionate (7.0 Gm., 0.02 mole), 16.2 Gm. (0.14 mole) of 2-diethylaminoethylamine, and 0.5 ml. of 25% sodium methylate in methanol were placed in a flask fitted with a 10-cm. fractionating column and distilling head, and heated at 140° for nine hours. The temperature was then raised to 160° and the formed ethanol distilled out. After repeating this heating and distillation procedure, excess amine was removed and the residue on trituration with ether granulated, and on recrystallization (acetonitrile) yielded 4.0 Gm. (44%) of product.

α-(*p*-Acetamidophenoxy)propionic acid (Compound 6).—Ethyl α-(4-acetamidophenoxy)propionate (7.0 Gm., 0.028 mole) was refluxed for four hours with 23.9 ml. (0.028 mole) of 1.17 *N* aqueous sodium hydroxide. When cool, on acidification, the product separated.

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