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Central Nervous System Depressants—III. 2- and 4-Allyloxy-3,5-Disubstituted Benzoic Acids and Derivatives*

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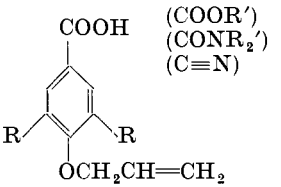
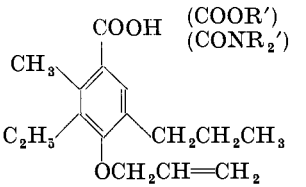
In the preceding articles,[1, 2] it was reported that a considerable number of 4-allyloxy-3,5-dialkylbenzoic acids, esters, amides and nitriles (I; R = propyl, isopropyl, ethyl and methyl) greatly increase the sleeping time of mice given small doses of hexobarbital. We have now extended the series by replacing the alkyl groups with halogens (I; R = chlorine or iodine) and by the introduction of a methyl group into the 2-position (II).

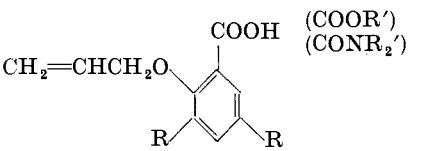


(I)



(II)

Furthermore, we have prepared a series of analogues in which the allyloxy group is in the 2-position instead of the 4-position (III).

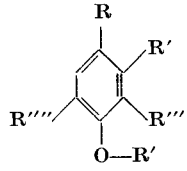


(III)

Although many of these compounds were highly active, they were in general less active than the corresponding derivatives described in the preceding articles.[1, 2]

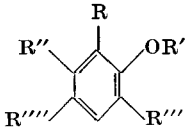
* Presented in part before the Division of Medicinal Chemistry, American Chemical Society, September 1959, Abstracts p. 11-0.

Table I. Pharmacological properties



No.	R	R′	R″	R‴	R⁗	Toxicity LD50[a]	% Increase in hexobarbital sleeping time[b]	% Decrease in motor activity[c]
1	COOH	H	H	Cl	Cl	650	40	
2	COOH	$CH_2CH{=}CH_2$	H	Cl	Cl	460	100	
3	$COOCH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	Cl	Cl	300	80	
4	$CONH_2$	$CH_2CH{=}CH_2$	H	Cl	Cl	650	⩾900[d]	99
5	COOH	H	H	I	I	1000	60	17
6	COOH	$CH_2CH{=}CH_2$	H	I	I	200	50	−7
7	$COOCH_2CH_3$	$CH_2CH{=}CH_2$	H	I	I	>1000	100	11
8	$CONH_2$	$CH_2CH{=}CH_2$	H	I	I	>1000	290	10
9	$CON(C_2H_5)_2$	$CH_2CH{=}CH_2$	H	I	I	>1000	428	32
10	CH_3	H	H	$C(CH_3)_3$	$C(CH_3)_3$	200	80	6
11[7]	CHO	H	H	$C(CH_3)_3$	$C(CH_3)_3$	>1000	140	23
12	CH=NOH	H	H	$C(CH_3)_3$	$C(CH_3)_3$	650	117	−1
13	C≡N	H	H	$C(CH_3)_3$	$C(CH_3)_3$	>1000	100	31
14	$COOC_2H_5$	H	CH_3	C_2H_5	H	770	150	0
15	$COOC_2H_5$	$CH_2CH_2CH_3$	CH_3	C_2H_5	H	840	200	
16	COOH	$CH_2CH_2CH_3$	CH_3	C_2H_5	H	530	100	
17	$COOC_2H_5$	$CH_2CH{=}CH_2$	CH_3	C_2H_5	H	650	100	3
18	$COOC_2H_5$	H	CH_3	C_2H_5	$CH_2CH{=}CH_2$	>1000	50	12
19	$COOC_2H_5$	H	CH_3	C_2H_5	$CH_2CH_2CH_3$	>1000	110	12
20	COOH	$CH_2CH{=}CH_2$	CH_3	C_2H_5	$CH_2CH_2CH_3$	300	290	−2
21	$COOCH_3$	$CH_2CH{=}CH_2$	CH_3	C_2H_5	$CH_2CH_2CH_3$	300	320	23
22	$CONH_2$	$CH_2CH{=}CH_2$	CH_3	C_2H_5	$CH_2CH_2CH_3$	>1000	>680[e]	77
23	$CON(C_2H_5)_2$	$CH_2CH{=}CH_2$	CH_3	C_2H_5	$CH_2CH_2CH_3$	533	1215	25

Table I (*continued*)



No.	R	R′	R″	R‴	R″″	Toxicity LD50[a]	% Increase in hexobarbital sleeping time[b]	% Decrease in motor activity[c]
24	$COOCH_3$	$CH_2CH{=}CH_2$	H	H	H	>1000	150	19
25	$COOCH_3$	H	H	$CH_2CH{=}CH_2$	H	530	10	
26	$COOCH_3$	$CH_2CH{=}CH_2$	H	$CH_2CH{=}CH_2$	H	>1000	650	34
27	$COOCH_3$	H	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	530	440	
28	$COOCH_3$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	230	110	
29[g]	COOH	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	170	220	30
30	$COOCH_3$	$CH_2CH{=}CH_2$	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	650	1230	26
31	COOH	$CH_2CH{=}CH_2$	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	650	480	41
32	$CONH_2$	$CH_2CH{=}CH_2$	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	>1000	1656	22
33	$CONH_2$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	>1000	170	18
34[g]	COOH	H	CH_3	$CH(CH_3)_2$	H	200	30	2
35[f]	$COOCH_3$	H	CH_3	$CH(CH_3)_2$	H	420	80	35
36	$COOCH_2CH{=}CH_2$	H	CH_3	$CH(CH_3)_2$	$CH_2CH{=}CH_2$	650	350	20
37	COOH	H	CH_3	$CH(CH_3)_2$	$CH_2CH{=}CH_2$	200	50	3

[a] Toxicities were obtained by Mr. Wm. Veldkamp and staff. The compounds were administered to mice intraperitoneallly. The values (mg/kg) are approximations with an accuracy of about +100% to −50%.

[b] The compounds were dissolved or suspended in aqueous carboxymethylcellulose in doses representing 20% of their LD50's and injected intraperitoneally into mice. Thirty minutes later the mice were injected interperitoneally with 100 mg/kg of hexobarbital sodium. Loss of righting reflex was used as a criterion of sleep. The action of the compound is expressed as the percentage increase in sleeping time over that of controls. The controls, given hexobarbital alone, slept for approximately 14 min.

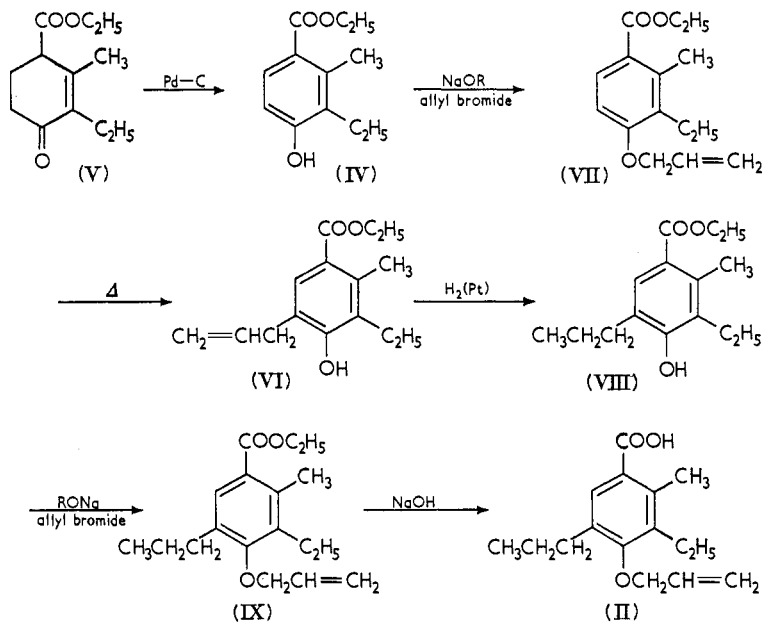
[c] The compounds were dissolved or suspended in aqueous carboxymethylcellulose in doses equal to 20% of their LD50's and injected intraperitoneally into mice. Thirty minutes later the effect on motor activity was determined using the technique of Dews.[5] Individual mice were put in the actophotometers and the number of breaks in the light beams was determined during a 5-min period. The action of the compounds is expressed as the percentage decrease in activity from the controls.

[d] 970% increase in 10% of LD50.

[e] 700% increase at 10% of LD50.

[f] This methyl ester[4] was prepared in poor yield by esterification of *o*-thymotinic acid[3] with methanol and hydrogen chloride.

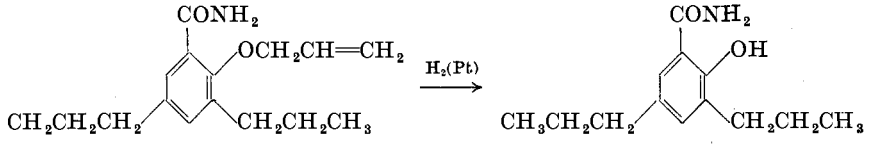
The halogen-containing compounds were prepared from 3,5-dichloro- and iodo-4-hydroxybenzoic acids obtained from commercial sources. For the series of 3-ethyl-2-methyl-4-alkoxy compounds, the key starting compound was ethyl 3-ethyl-2-methyl-4-hydroxybenzoate (IV). This was prepared by aromatization of 2-ethyl-3-methyl-4-carbethoxy-2-cyclohexenone[3] (V). The 5-allyl compound (VI) was prepared by Claisen rearrangement of the 4-allyloxy derivative (VII) and was then



hydrogenated to the propyl compound (VIII). This was converted to the allyl ether (IX) and hydrolyzed to the acid (II) from which a number of derivatives were prepared.

The series of *ortho* allyloxy derivatives was obtained from methyl salicylate by repeated Claisen rearrangement of the allyl ethers[4]. The allyl groups in methyl 3,5-diallyl-4-hydroxybenzoate hydrogenated smoothly to propyl groups. However, in an attempt to hydrogenate 2-allyloxy-3,5-dipropylbenzamide (XI) to the corresponding 2-propoxy amide the allyl group was cleaved giving

the hydroxy amide (XII). Infrared spectra* were obtained on all pure products and in all cases were consistent with the proposed structures.



(XI) (XII)

Experimental†

Allyl 4-allyloxy-3,5-dichlorobenzoate (No. 3) and 4-allyloxy-3,5-dichlorobenzoic acid (No. 2). To a solution of sodium (18·4 g, 0·8 mole) in methanol (250 ml) was added a methanolic solution of 3,5-dichloro-4-hydroxybenzoic acid (No. 1) (83 g, 0·4 mole). To this allyl bromide (242 g, 2·0 moles) was slowly added with stirring, and the mixture was stirred for 1 h at room temperature and for 2 h under reflux. Most of the solvent was distilled under reduced pressure. Ether was added and the mixture was extracted with cold dilute sodium hydroxide. The ether solution was washed with water, saturated salt solution and dried over sodium sulphate. After filtration and removal of the solvent, the residue was distilled giving the allyl ester (No. 3) (34·6 g, 30 per cent) as a colourless liquid, b.p. 112°/0·005 mm, n_D^{25} 1·5423.

Anal. Calcd. for $C_{13}H_{12}Cl_2O_3$: C, 54·37; H, 4·21; Cl, 24·70. Found: C, 54·92; H, 4·74; Cl, 24·72.

Acidification of the basic aqueous extract gave the acid (No. 2) (62·4 g, 63 per cent), m.p. 162–168°. This same acid was obtained in 94 per cent yield by saponification of the pure allyl ester (No. 3).

In another run the allyl ester was not isolated but the reaction mixture was hydrolyzed with sodium hydroxide giving a 99 per

* Infrared spectra are by Dr. James L. Johnson and staff of our Department of Physical and Analytical Chemistry.

† Melting points were taken in capillary tubes with a partial immersion thermometer and are uncorrected. Elemental analyses and neutral equivalents are by Mr. William Struck and staff of our Department of Physical and Analytical Chemistry.

cent yield of the acid, m.p. 163–164°. Recrystallization of this acid from ethanol gave colourless crystals, m.p. 168–168·5°.

Anal. Calcd. for $C_{10}H_8Cl_2O_3$: C, 48·61; H, 3·26; Cl, 28·70. Found: C, 48·89; H, 3·46; Cl, 28·63.

4-Allyloxy-3,5-dichlorobenzamide (*No. 4*). A solution of 4-allyloxy-3,5-dichlorobenzoic acid (No. 2) (58 g, 0·244 mole) (m.p. 163–164°) in benzene (100 ml) and thionyl chloride (100 ml) was heated under reflux until the evolution of gas ceased. The solvent was distilled under reduced pressure and 100 ml more benzene was added and distilled leaving a yellow oil. To this was carefully added 28 per cent ammonium hydroxide (600 ml). A white solid separated immediately. The lumps were broken up, the mixture was allowed to stand for three days, and filtered giving 51·17 g of solid. This was recrystallized from benzene giving a nearly white solid (42·1 g, 73 per cent), m.p. 134–135°.

4-Allyloxy-3,5-diiodobenzoic acid (*No. 6*). 4-Hydroxy-3,5-diiodobenzoic acid (156 g, 0·4 mole) and methanol (100 ml) were placed in a 2-l. flask. The flask was fitted with a stirrer, reflux condenser and two dropping funnels. In one was placed sodium methoxide from sodium (29·6 g, 1·2 mole) and methanol (400 ml). In the other was placed allyl bromide (182 g, 1·5 mole). One-half of the sodium methoxide solution was added with stirring followed by one-half of the allyl bromide. The mixture was heated under reflux with stirring until it tested neutral. Then one-half of the remainder of the sodium methoxide and allyl bromide were added and refluxing was continued until neutral. The remainder of the sodium methoxide and allyl bromide were added and refluxing was continued for 5 h when it again tested neutral. Most of the solvent was distilled under reduced pressure, methanol (150 ml) and aqueous sodium hydroxide (150 ml) were added and the mixture was heated under reflux for 2 h to hydrolyze the esters formed in the reaction. Part of the solvent was distilled, water was added, and the mixture was extracted with two portions of ether. The aqueous solution was acidified giving a white solid (167·6 g), m.p. 184–185°. This was recrystallized from aqueous ethanol yielding colourless crystals (161·1 g, 93·6 per cent), m.p. 188·5–189°.

Anal. Calcd. for $C_{10}H_8I_2O_3$: C, 27·93; H, 1·88; I, 59·03. Found: C, 28·00; H, 2·22; I, 58·80.

Ethyl 4-allyloxy-3,5-diiodobenzoate (*No. 7*). A mixture of

4-allyloxy-3,5-diiodobenzoic acid (No. 6) (45·1 g, 0·105 mole), thionyl chloride (34 ml) and benzene (34 ml) was heated under reflux with stirring for 2·5 h. The solid dissolved in about 15 min. The solvent was distilled under reduced pressure, the crystalline acid chloride was dissolved in benzene (100 ml) and absolute ethanol (200 ml), and pyridine (10 ml) was added. After refluxing for 1 h, the solvent was distilled and the solid residue was mixed with ether and washed with dilute hydrochloric acid, water, cold aqueous sodium hydroxide, twice with water and finally with saturated salt solution. After drying over sodium sulphate and filtering the solvent was distilled leaving a crystalline residue. This was recrystallized from ethanol giving colourless crystals (33·0 g, 68·5 per cent), m.p. 72–74°.

Anal. Calcd. for $C_{12}H_{12}I_2O_3$: C, 31·47; H, 2·64; I, 55·41. Found: C, 31·79; H, 2·89; I, 55·11.

4-Allyloxy-3,5-diiodobenzamide (*No. 8*). Crude acid chloride, prepared as above from the acid (No. 6) (45·1 g, 0·105 mole) was dissolved in benzene (100 ml) and absolute ether (100 ml) and ammonia was passed in with stirring until saturated. A white solid separated. This was shaken with water and the remaining white solid was collected on a filter, washed with water and dried giving 48·3 g of product, m.p. 174·5–176°. Recrystallization from ethanol gave colourless crystals (39·89 g, 88·8 per cent), m.p. 179–180°.

Anal. Calcd. for $C_{10}H_9I_2NO_2$: C, 28·00; H, 2·11; N, 3·27; I, 59·17. Found: C, 28·43; H, 2·40; N, 3·30; I, 59·70.

4-Allyloxy-3,5-diiodo-N,N-*diethylbenzamide* (*No. 9*). Crude acid chloride was prepared as above from the acid (No. 6) (45·1 g, 0·105 mole), was dissolved in benzene (100 ml) and added slowly to diethylamine (30 g, 0·4 mole) with stirring. The mixture was heated under reflux for 15 min, cooled, diluted with ether and washed with dilute hydrochloric acid, water, dilute sodium hydroxide, twice with water and finally with saturated salt solution. After drying over sodium sulphate, filtering and distilling the solvent a crystalline residue was obtained. This was recrystallized from aqueous ethanol giving a white solid (34·8 g, 68·2 per cent), m.p. 98–99°.

Anal. Calcd. for $C_{14}H_{17}I_2NO_2$: C, 34·66; H, 3·53; I, 52·32; N, 2·89. Found: C, 34·93; H, 3·56; I, 52·22; N, 3·43.

3,5-Di-t-butyl-4-hydroxybenzaldoxime (*No. 12*). To a solution of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde[7] (No. 11) (82·1 g, 0·351 mole) in ethanol (2·3 l.) was added hydroxylamine hydrochloride (36 g, 0·52 mole) in water (60 ml). Then 52 ml of 50 per cent aqueous sodium hydroxide was slowly added and the mixture allowed to stand overnight. Enough water was added to dissolve a small amount of crystals and the solution was neutralized with acetic acid. After filtration the solution was distilled under reduced pressure until a considerable amount of precipitate had separated. After dilution with water and cooling the solid was collected, washed with water and dried giving a light yellow solid (85·54 g), m.p. 130–133°. This was recrystallized from methanol containing a little water yielding nearly white crystals (70·6 g, 80 per cent), m.p. 134–135·5°.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72·25; H, 9·30; N, 5·62. Found: C, 72·32; H, 9·20; N, 5·61.

3,5-Di-t-butyl-4-hydroxybenzonitrile (*No. 13*). A mixture of the above oxime (No. 12) (50 g, 0·2 mole) and acetic anhydride (95 ml, 1 mole) was heated under reflux with stirring for ½ h. After cooling it was poured onto about 200 g of ice giving a crystalline solid. To this was added 50 per cent aqueous sodium hydroxide (200 ml) and enough ethanol to dissolve the solid at 75°. The green solution was heated on a steam bath for 15 min, cooled and acidified, giving a brown crystalline solid. This was collected, washed with water and dried yielding 45·3 g of crystals, m.p. 134–137·5°. Recrystallization from ethanol gave tan crystals (31 g), m.p. 142·5–144°. A second recrystallization gave nearly white needles, m.p. 143–144·5°.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77·88; H, 9·15; N, 6·06. Found: C, 77·70; H, 9·14; N, 5·99.

Ethyl 4-hydroxy-3-ethyl-2-methylbenzoate (*IV*, *No. 14*). A mixture of 4-carbethoxy-2-ethyl-3-methyl-2-cyclohexenone[3] (V) (103·5 g, 0·488 mole), 10 per cent palladium on charcoal (5·55 g) and Dowtherm (200 ml) was heated with stirring at 190–200° for 8 h. The mixture was filtered, diluted with ether and extracted three times with ice cold 20 per cent aqueous sodium hydroxide and then with water. The basic solutions were acidified and the resulting solid was collected, washed with water and dried giving a tan solid (49·15 g). This was recrystallized from

petroleum heptane giving tan crystals (46·48 g, 47 per cent), m.p. 86–90·5°.

Further recrystallization from petroleum heptane raised the melting point to 94–96°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 69·21; H, 7·74. Found: C, 69·17; H, 7·80.

Ethyl 3-ethyl-2-methyl-4-propoxybenzoate (*No. 15*). A mixture of phenolic ester No. 14 (41·4 g, 0·197 mole), propyl bromide (28 g, 0·23 mole), and potassium carbonate (24 g, 0·21 mole) in acetone (200 ml) was heated under reflux for 14 h. The mixture was filtered and the solid was extracted with acetone. The acetone solutions were distilled to dryness. The residue was dissolved in ether, washed with cold dilute sodium hydroxide, twice with water, and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled giving a colourless liquid (31·3 g, 63·5 per cent), b.p. 105°/0·025 mm; n_D^{25} 1·5128.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71·96; H, 8·86. Found: C, 71·64; H, 8·68.

3-Ethyl-2-methyl-4-propoxybenzoic acid (*No. 16*). A solution of the propoxy ester No. 15 (25 g, 0·1 mole) and 85 per cent potassium hydroxide (36 g) in ethanol (100 ml) and water (70 ml) was heated under reflux for 8 h. After distilling most of the solvent, water was added. The solution was washed with ether and acidified giving a crystalline acid (21·5 g, 96·7 per cent), m.p. 141–143°. This was recrystallized from petroleum hexane giving colourless crystals (18·8 g), m.p. 143–146°.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70·24; H, 8·16. Found: C, 70·03; H, 8·33.

Ethyl 4-allyloxy-3-ethyl-2-methylbenzoate (*No. 17*). This was prepared as described above for 4-allyloxy-3,5-diiodobenzoic acid (No. 6) using ethyl 4-hydroxy-3-ethyl-2-methylbenzoate (324 g, 1·56 mole), sodium methoxide* from sodium (69 g, 3 moles), and allyl bromide (390 g, 3·24 moles). The ester was not hydrolyzed. After distillation of most of the methanol, water was added and the product was extracted with ether. The ether solution was washed with cold 10 per cent aqueous sodium hydroxide, twice with water, then with saturated salt solution and dried over

* Sodium ethoxide would have been preferable because of the possibility of some ester interchange.

odium sulphate. After filtration and removal of the solvent the ester was distilled giving a nearly colourless liquid (372 g, 96 per cent). This was carefully redistilled through a glass helices-packed column. A middle fraction of colourless liquid, b.p. 107°/0·05 mm, n_D^{25} 1·5260, was taken for analysis.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72·26; H, 8·49. Found: C, 72·04; H, 8·18.

Ethyl 5-allyl-3-ethyl-2-methyl-4-hydroxybenzoate (*No. 18*). A sample of the above allyl ether No. 17 (367 g, 1·48 mole) was heated under nitrogen at 230–250° for ½ h. The product was distilled giving a white solid (286 g, 78 per cent), m.p. 66–74°. Several recrystallizations from petroleum hexane gave colourless crystals, m.p. 79–80°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12. Found: C, 72·60; H, 8·18.

Ethyl 3-ethyl-4-hydroxy-2-methyl-5-propylbenzoate (*No. 19*). A solution of ethyl 5-allyl-3-ethyl-2-methyl-4-hydroxybenzoate (136·4 g, 0·55 mole) in enough ethanol to make 250 ml was hydrogenated with platinum oxide (0·2 g) at 60 lb pressure and room temperature. After about 3½ h the theoretical amount of hydrogen had been absorbed. Two runs were combined, filtered and the solvent removed. The product was distilled giving white crystals (234·2 g, 94 per cent), m.p. 63·5–67·5°. This was recrystallized from petroleum hexane giving a white solid (183·4 g), m.p. 65·5–69°. An additional 12·92 g was obtained from the filtrate.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86. Found: C, 71·98; H, 8·94.

4-Allyloxy-3-ethyl-2-methyl-5-propylbenzoic acid (*No. 20*). Crude ethyl 4-allyloxy-3-ethyl-2-methyl-5-propylbenzoic acid was prepared as described above for 4-allyloxy-3,5-diiodobenzoic acid (No. 6) using the above ethyl 3-ethyl-4-hydroxy-2-methyl-5-propylbenzoate (No. 19) (181·3 g, 0·72 mole), and sodium methoxide from sodium (34·5 g, 1·5 moles), and allyl bromide (242 g, 2 moles). The product was distilled giving a colourless liquid (133·3 g). The infrared spectrum and titration indicated that this still contained a considerable amount of 4-hydroxy ester which was not removed by washing an ether solution of the mixture with cold 10 per cent aqueous sodium hydroxide. Therefore, the allylation was repeated on the entire mixture. The product

was distilled giving 174·5 g of ester which contained practically no phenolic material.

This was saponified with sodium hydroxide (160 g, 4 moles) in water (2 l.) and ethanol (700 ml) by heating under reflux for 6 h. After distilling most of the solvent and adding water the solution was washed with ether and acidified giving a waxy solid. This was extracted with ether which was washed with water and dried over sodium sulphate. After filtration and removal of the solvent the residue was crystallized from petroleum hexane giving colourless crystals (87·6 g, 47·6 per cent), m.p. 81–82°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73·25; H, 8·45. Found: C, 73·08; H, 8·77.

Methyl 4-allyloxy-3-ethyl-2-methyl-5-propylbenzoate (*No. 21*). Crude acid chloride was prepared from the above acid No. 20 (19·3 g, 0·073 mole), thionyl chloride (25 ml) and benzene (25 ml). After heating under reflux until evolution of gas ceased the excess thionyl chloride and benzene were distilled under reduced pressure and the crude acid chloride was dissolved in absolute ether (50 ml). To this was added methanol (100 ml) and dry pyridine (10 mg). After heating under reflux for 2 h, the solvent was distilled and the residue was diluted with ether. The ether solution was washed with cold dilute hydrochloric acid, water, cold dilute sodium hydroxide, twice again with water, and dried over sodium sulphate. After filtration and removal of the solvent, the product was distilled, giving a nearly colourless liquid (11·55 g, 52·5 per cent), b.p. 114°/0·05 mm; n_D^{25} 1·5160.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75. Found: C, 74·07; H, 8·61.

4-Allyloxy-3-ethyl-2-methyl-5-propylbenzamide (*No. 22*). Ammonia was passed with stirring into an ether solution of acid chloride prepared as above. A white solid separated. When the mixture seemed saturated with ammonia, it was well mixed with water. Part of the solid remained insoluble and was collected, washed with water and dried, giving a white material (20·88 g), m.p. 174·5–176°. This was recrystallized from ethanol giving colourless crystals (17·8 g, 93 per cent), m.p. 177–178°.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73·55; H, 8·87; N, 5·36. Found: C, 73·62; H, 8·87; N, 5·11.

4-Allyloxy-3-ethyl-2-methyl-5-propyl-N,N-*diethylbenzamide* (No. *23*). Acid chloride solution was prepared as above from the acid No. 20 (38·6 g, 0·147 mole). To this diethylamine (33 g, 0·45 mole) was slowly added. After thorough mixing, dilute hydrochloric acid was added. The ether solution was washed with water, cold dilute sodium hydroxide, twice with water and finally with saturated salt solution. After drying over sodium sulphate, filtering and removing the solvent, the product was distilled giving a light yellow liquid (29·5 g, 63·5 per cent), b.p. 139°/0·05 mm; n_D^{25} 1·5190.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 75·67; H, 9·84; N, 4·44. Found: C, 75·67; H, 9·70; N, 4·34.

Methyl 2-hydroxy-3,5-dipropylbenzoate (*No. 28*). A solution of methyl 3,5-diallyl-2-hydroxybenzoate[4] (58 g, 0·25 mole) in methanol (100 ml) was hydrogenated with platinum oxide (0·2 g) at room temperature and 50 lb pressure. The theoretical amount of hydrogen was absorbed in ½ h. The solution was filtered from the catalyst, combined with two more similar runs (total 0·894 mole) and the solvent was removed. The product was distilled through a short column giving a colourless liquid (207·8 g, 98·5 per cent), b.p. 127°/1·5 mm; n_D^{25} 1·5139.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71·16; H, 8·53. Found: C, 71·34; H, 8·78.

2-Hydroxy-3,5-dipropylbenzoic acid[8] (*No. 29*). A solution of the above ester No. 28 (23·6 g, 0·1 mole) in methanol (50 ml) was saponified by refluxing for 7½ h with 20 per cent aqueous sodium hydroxide (100 ml). The solution was diluted with water, washed with ether and acidified giving a white solid (22·1 g, 99·4 per cent) m.p. 100–101·5°. Recrystallization from pentane gave acid with the same melting point.

Methyl 2-allyloxy-3,5-dipropylbenzoate (*No. 30*). This was prepared by the method used for 4-allyloxy-3,5-diiodobenzoic acid (No. 6) from the above 2-hydroxy methyl ester No. 28 (178·5 g, 0·75 mole). The infrared spectrum and titration indicated the product contained some starting material. This was removed by careful distillation through a 12 in. column packed with ⅛ in.-glass helices. The last fractions were pure alloxy ester, b.p. 118°/0·45 mm; n_D^{25} 1·5051. The yield of pure material was 64 g (31 per cent).

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75. Found: C, 74·35; H, 8·93.

2-Allyloxy-3,5-dipropylbenzoic acid (*No. 31*). A solution of methyl 2-allyloxy-3,5-dipropyl-benzoate (No. 30) (114·1 g, 0·413 mole), 20 per cent aqueous sodium hydroxide (500 ml) and methanol (400 ml) was heated under reflux for 6 h. Part of the solvent was distilled under reduced pressure and 1·5 l. of water was added. The addition of ether caused all the material to dissolve in the two layers. The aqueous layer was removed and acidified, but only very little acid precipitated. The ether solution was extracted with 1 l. of water in two portions. These aqueous extracts were acidified causing the separation of a large amount of oil which crystallized on bubbling in nitrogen to remove the remaining ether. The solid was collected, washed with water and dried giving a white solid (104·5 g, 96·5 per cent), m.p. 42–47°. This was recrystallized from pentane giving colourless crystals (80·2 g), m.p. 47–49°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73·25; H, 8·46; neut. equiv., 262·34. Found: C, 73·07; H, 8·75; neut. equiv., 264.

2-Allyloxy-3,5-dipropylbenzamide (*No. 32*). A solution of 2-allyloxy-3,5-dipropylbenzoic acid (87·5 g, 0·334 mole) in benzene (50 ml) and thionyl chloride (72·6 ml., 1 mole) was heated under reflux for 1¾ h. Excess thionyl chloride and benzene were distilled under reduced pressure, the oily acid chloride was dissolved in absolute ether and ammonia was passed in with stirring and cooling in an ice bath until the solution appeared saturated. After standing for another ½ h the mixture was washed twice with water, twice with dilute hydrochloric acid, twice with water and finally with saturated salt solution. After drying over sodium sulphate, filtering and distilling the solvent, a brown oil was obtained which crystallized on standing. This was recrystallized from petroleum hexane giving nearly white crystals (65·4 g, 74·9 per cent), m.p. 86–88°. A second recrystallization did not raise the melting point.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73·53; H, 8·87; N, 5·36. Found: C, 73·63; H, 9·09; N, 5·14.

2-Hydroxy-3,5-dipropylbenzamide (*XII, No. 33*). A solution of 2-allyloxy-3,5-dipropylbenzamide (XI, No. 32) (18·25 g, 0·07 mole) in ethanol (150 ml) was hydrogenated with platinum oxide (0·2 g) at room temperature and 50 lb pressure. About 0·07 mole of hydrogen was absorbed in ½ h. The solution was filtered

and distilled to dryness under reduced pressure giving a crystalline solid. This was recrystallized from petroleum hexane (80 ml) giving white crystals (7·66 g, 50 per cent), m.p. 120–121·5°, which gave a very strong ferric chloride test (dark purple colour) and whose analysis checked for the 2-hydroxy compound. The infrared spectrum could not distinguish with certainty between the 2-hydroxy and 2-propoxy compounds due to the chelate nature of the hydroxyl and the presence of an NH group. However, a nuclear magnetic resonance spectrum* unequivocally supported the 2-hydroxy-3,5-dipropylbenzamide structure.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70·56; H, 8·65; N, 6·33. Found: C, 70·69; H, 8·54; N, 6·30.

Allyl 5-allyl-2-hydroxy-3-isopropyl-6-methylbenzoate (*No. 36*). Crude allyl 2-allyloxy-3-isopropyl-6-methylbenzoate was prepared as described for No. 6 from *o*-thymotinic acid,[9] (461 g, 2·65 moles), sodium methoxide from sodium (230 g, 10 moles), allyl bromide (1 l.), and methanol (4 l.). After completion of the reaction most of the solvent was distilled and cold dilute sodium carbonate solution was added. The allyl ester was extracted three times with ether. The ether solutions were washed with dilute sodium carbonate, water, saturated salt solution and dried over sodium sulphate. After filtration and removal of the solvent an attempt was made to distill the 2-allyloxy ester through a 30 cm fractionating column. However, during this distillation much of the product rearranged to the 5-allyl-2-hydroxy ester (No. 36). The entire material was then heated to 250° to complete the rearrangement and again distilled through the column giving the ester No. 36 (131·7 g, 18 per cent), b.p. 109°/0·06 mm; n_D^{25} 1·5300. The structure of this rearranged product was confirmed by both infrared and nuclear magnetic resonance spectra.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74·42; H, 8·08. Found: C, 74·17; H, 8·11.

5-Allyl-2-hydroxy-3-isopropyl-6-methylbenzoic acid (*No. 37*). This was prepared by saponification of the ester No. 36 (108·59 g, 0·432 mole) in ethanol (250 ml) with 50 per cent aqueous sodium hydroxide (50 ml). After heating under reflux for 1¼ h and standing overnight more water was added and most of the ethanol was

* Nuclear magnetic resonance spectra are by Dr. George Slomp of our Department of Physical and Analytical Chemistry.

distilled. The aqueous solution was washed with ether and acidified giving an oil which crystallized on standing. This was collected and dried yielding 85·8 g of acid, m.p. 85–92°. Recrystallization from petroleum hexane gave colourless crystals (68 g, 67 per cent), m.p. 94–95°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71·77; H, 7·74. Found; C, 71·75; H, 7·71.

Summary. Replacing the propyl groups of 4-allyloxy-3,5-dipropylbenzoic acid and derivatives (I, R=propyl) with chlorine or iodine gave compounds with less central nervous system depressant activity. 4-Allyloxy-3-ethyl-2-methyl-5-propylbenzoic acid (II), prepared via an aromatization reaction from 2-ethyl-3-methyl-4-carbethoxy-2-cyclohexenone (V) also gave less active derivatives. Compounds isomeric with (I) but with the allyloxy group in the 2-position were prepared from methyl salicylate by methods analogous to those previously described for (I) (R=propyl). These were nearly as active as the corresponding 4-allyloxy derivatives.

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