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Central Nervous System Depressants—I. 4-Alkoxy-3,5-dipropylbenzoic Acids and Derivatives.*

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In the course of testing a wide variety of compounds for possible use in mental disease it was found that 4-allyloxy-3,5-dipropylbenzoic acid (I; R = allyl) and a number of its derivatives greatly increased the sleeping time of mice given small doses of hexobarbital. These compounds also had a depressant effect on the motor activity of mice. Consequently a considerable number of derivatives and analogues were prepared. Those in which other ether substituents replace the allyloxy group, and esters, amide or nitrile functions replace the carboxyl group are included in this paper. These compounds are listed in Table I together with a few compounds (obtained from the same intermediates) in which one or both propyl groups are replaced by allyl groups (footnotes *d* and *e*). Table I gives the toxicities of these compounds and their pharmacological activities in the two tests mentioned above. More detailed discussion on the pharmacology is given below.

Ethyl 3,5-diallyl-4-hydroxybenzoate (II) was obtained by repeated allylation and rearrangement from ethyl 4-hydroxybenzoate, as described by Claisen and Eisleb.[1] This was hydrogenated to the 3,5-dipropyl ester (III) which was the starting material for most of these compounds as shown on the next page.

When R = allyl, a satisfactory yield of the allyloxy ester (IV) could be obtained by refluxing a mixture of the phenolic ester and allyl bromide in acetone in the presence of solid potassium carbonate. Allyl chloride was not satisfactory. With some less

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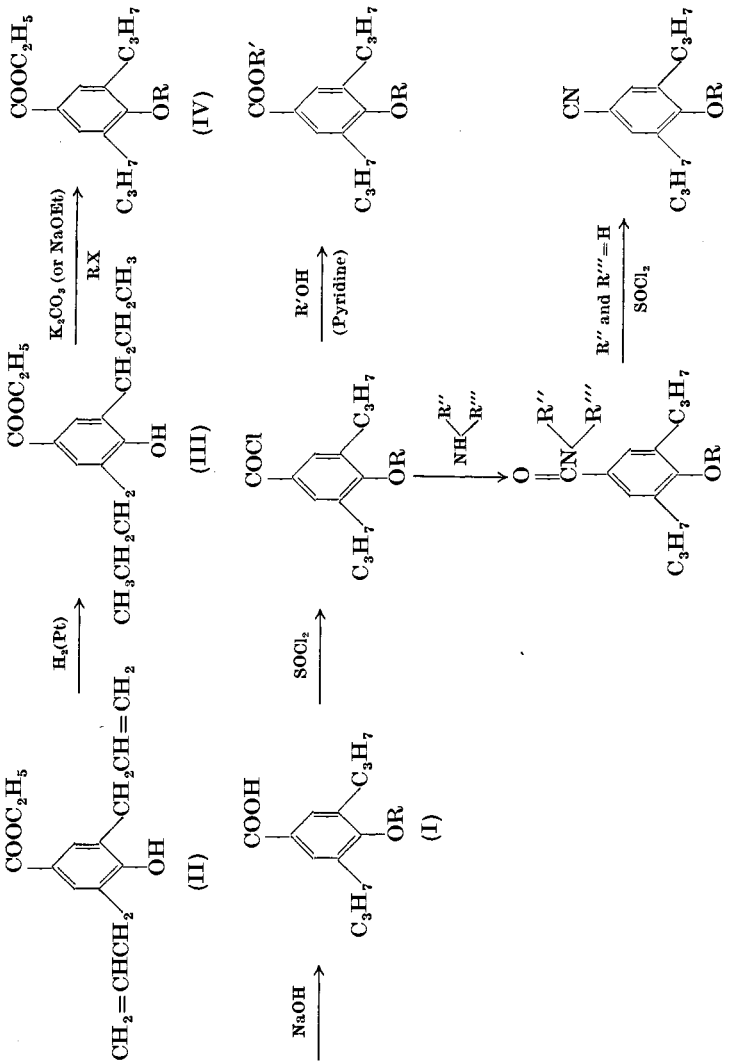
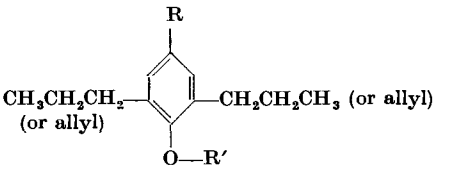
reactive alkyl halides better yields could be obtained by using an excess of sodium ethoxide in ethanol and a slightly larger excess



of the alkyl halide. These were added portionwise and alternatively to the reaction mixture under reflux.

Table I. Pharmacological Properties



No.	R	R′	Toxicity LD50[a]	% Increase in Hexobarbital sleeping time[b]	% Decrease in motor activity[c]
1	COOH	$CH_2CH{=}CH_2$	770	800	25
2	COOH	$CH_2CH_2CH_3$	650	290	
3	COOH	CH_2CH_3	530	40	25
4	COOH	$CH_2C(CH_3){=}CH_2$	650	140	
5	COOH	$CH_2CH{=}CHCH_3$	650	480	
6	COOH	$CH_2C_6H_5$	650	320	71
7	COOH	$CH_2CH_2N(CH_2CH_3)_2.HCl$	200	120	61
8	COOH	CH_2COOH	650	40	19
9	COOH	H	1000	520	50
10[d,i]	COOH	$CH_2CH{=}CH_2$	260	210	8
11[d]	COOH	$CH_2CH_2CH_3$	650	230	
12[d,i]	COOH	H	770	140	16
13[e]	COOH	$CH_2CH{=}CH_2$			
14[e]	COOH	$CH_2CH_2CH_3$			
15	$COOCH_3$	$CH_2CH{=}CH_2$	230	140	38
16	$COOCH_2CH_3$	$CH_2CH{=}CH_2$	650	550	30
17	$COOCH_2CH_3$	$CH_2CH_2CH_3$			
18	$COOCH_2CH_3$	CH_2CH_3	770	90	36
19	$COOCH_2CH_3$	$CH_2C(CH_3){=}CH_2$	530	530	31

Footnotes shown at the end of Table, p. 183

Table I—*cont.*

No.	R	R′	Toxicity LD50[a]	% Increase in Hexobarbital sleeping time[b]	% Decrease in motor activity[c]
20	$COOCH_2CH_3$	$CH_2C_6H_5$	>1000	140	
21	$COOCH_2CH_3$	$CH_2CH_2N(CH_2CH_3)_2.HCl$	200	100	38
22	$COOCH_2CH_3$	$CON(CH_2CH_3)_2$	770	80	26
23	$COOCH_2CH_3$	$CONHCH_2COOCH_2CH_3$	>1000	120	16
24	$COOCH_2CH_3$	H	1000	260	5
25[d,i]	$COOCH_2CH_3$	$CH_2CH{=}CH_2$	770	170	
26[d]	$COOCH_2CH_3$	$CH_2CH_2CH_3$			
27[d,i]	$COOCH_2CH_3$	H	1000	130	
28[e]	$COOCH_2CH_3$	$CH_2CH{=}CH_2$			
29[e]	$COOCH_2CH_3$	$CH_2CH_2CH_3$			
30[e]	$COOCH_2CH_3$	H	1000	390	
31	$COOCH_2CH_2OH$	$CH_2CH{=}CH_2$	230	340	13
32	$COOCH_2CH_2N(CH_2CH_3)_2.HCl$	$CH_2CH{=}CH_2$	150	200	20
33	$COOCH_2CH_2{-}NCH_2CH_2CH_2CH_2$ .HCl	$CH_2CH{=}CH_2$			
34[d]	$COOCH_2CH_2{-}NCH_2CH_2CH_2CH_2$ .HCl	$CH_2CH{=}CH_2$			
35[e]	$COOCH_3CH_2{-}NCH_2CH_2CH_2CH_2$ .HCl	$CH_2CH{=}CH_2$			
36[e]	$COOCH_2CH_2{-}NCH_2CH_2CH_2CH_2$ .HCl	$CH_2CH_2CH_3$			
37	$CONH_2$	$CH_2CH{=}CH_2$	650	>4000[f]	99
38	$CONH_2$	$CH_2CH_2CH_3$	650	610	64
39	$CONH_2$	CH_2CH_3	650	180	43
40	$CONH_2$	$CH_2C(CH_3){=}CH_2$	770	490	76

41	$CONH_2$	$CH_2C_6H_5$	>1000	550	45
42	$CONH_2$	$CH_2CH_2N(CH_2CH_3)_2.HCl$	200	250	16
43	$CONH_2$	CH_2CONH_2	>1000	140	28
44	$CONH_2$	H	770	530	62
45	$CONHCH_3$	$CH_2CH{=}CH_2$	650	>1350[g]	99
46	$CONHCH_2CH(CH_3)_2$	$CH_2CH{=}CH_2$	650	120	75
47	$CON(CH_3)_2$	$CH_2CH{=}CH_2$	200	660	33
48	$CON(CH_2CH_3)_2$	$CH_2CH{=}CH_2$	1000	>1470	92
49	$CONCH_2CH_2CH_2CH_2$	$CH_2CH{=}CH_2$	200	220	
50	$CONHCH_2CH_2{-}NCH_2CH_2CH_2CH_2$ .HCl	$CH_2CH{=}CH_2$	100	40	21
51	$CONCH_2CH_2N(CH_3){-}CH_2CH_2$[h]	$CH_2CH{=}CH_2$	300	270	3
52	$CONHCH_2COOH$	$CH_2CH{=}CH_2$	200	160	22
53	$CONH$*p*-C_6H_4COOH	$CH_2CH{=}CH_2$	650	50	
54	$CONHCONH_2$	$CH_2CH{=}CH_2$	230	180	62
55	$C(=NH)NH_2.HCl$	$CH_2CH{=}CH_2$	65	200	
56	$C{\equiv}N$	$CH_2CH{=}CH_2$	>1000	$\gg$700[i]	83
57	$C{\equiv}N$	$CH_2CH_2CH_3$	>1000	400	
58	$C{\equiv}N$	H	>1000	>400[j]	39
59	Chlorpromazine		160	1100	99

[a] Toxicities were obtained by Mr. Wm. Veldkamp and staff. The compounds were administered to mice intraperitoneally. 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 intraperitoneally 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 per cent 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.[2] Individual mice were put in the actophotometers and the number of breaks in the light beams were determined during a 5-min period. The action of the compounds is expressed as the per cent decrease in activity from the controls.

[d] 3,5-Diallyl instead of 3,5-dipropyl.

[e] 3-Allyl-5-propyl instead of 3,5-dipropyl.

[f] >3750% increase at 10% of LD50; >3000% at 5%; 1310% at 2·5%.

[g] 1000% increase at 10% of LD50.

[h] Citrate salt.

[i] >1020% increase at 10% of LD50; > 960% at 5%; 620% at 2·5 %.

[j] 502% increase at 10% of LD50.

The 3,5-diallyl compounds listed in Table I (footnote *d*) were prepared as above omitting the hydrogenation step. The 3-allyl-5-propyl compounds, Table I (footnote *e*) were prepared by hydrogenating after the first Claisen rearrangement instead of the second.

Infrared spectra were obtained* on all pure products and in all cases were consistent with the proposed structures.

Pharmacology

As can be seen from Table I, the amides and nitriles are in general the most active depressants in both tests although certain of the parent carboxylic acids have high activity. The 4-allyloxy compounds are more active than corresponding compounds with other ether groups in the 4-position. Two compounds, 4-allyloxy-3,5-dipropyl-benzoic acid (No. 1) and the corresponding amide (No. 37), were selected for clinical study. Although they are active in man, side effects would appear to limit their use.

Experimental†

Ethyl 3,5-diallyl-4-hydroxybenzoate (*No. 27; II*). This compound was prepared in an overall yield of 77 per cent by the method of Claisen and Eisleb.[1]

Ethyl 4-hydroxy-3,5-dipropylbenzoate (*No. 24; III*). A mixture of ethyl 3,5-diallyl-4-hydroxybenzoate (1·31 kg, 5·31 moles), platinum oxide (3·52 g) and ethanol (3·5 l. 95 per cent) was hydrogenated in a 20 l. stirred autoclave at 40 lb pressure and room temperature. The theoretical amount of hydrogen was absorbed in about one hour. After filtration from the catalyst the solution was slurried with Nuchar decolourizing charcoal and again filtered. The solvent was removed under reduced pressure leaving an oil which crystallized on cooling to give a quantitative yield of material, m.p. 62·5–66°. Some runs were distilled, b.p. 150°/0·1 mm, but this was usually not necessary. A sample recrystallized from petroleum hexane had the same melting point.

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

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

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71·96; H, 8·86. Found: C, 71·70; H, 8·78.

Ethyl 4-allyloxy-3,5-dipropylbenzoate (*No. 16; IV, R=allyl*). A mixture of ethyl 4-hydroxy-3,5-dipropylbenzoate (1·39 kg, 5·43 moles), anhydrous potassium carbonate (780 g), and acetone (5·6 l.) was heated to reflux with stirring, and allyl bromide (788 g, 6·51 moles) was run in. The mixture was stirred under reflux for 10 h and filtered. The filtrate was slurried with Nuchar decolourizing charcoal (140 g) and again filtered. Removal of the solvent gave 1·44 kg of oil, n_D^{25} 1·5039. This was distilled giving a colourless liquid (1·43 kg, 88 per cent), b.p. 125°/0·05 mm, n_D^{25} 1·5040.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74·44; H, 9·03. Found: C, 74·45; H, 8·77.

4-Allyloxy-3,5-dipropylbenzoic acid (*No. 1; I, R=allyl*). A solution of ethyl 4-allyloxy-3,5-dipropylbenzoate (62·5 g, 0·215 mole), 85 per cent potassium hydroxide (75 g, 1·3 moles) in ethanol (250 ml) (95 per cent) and water (15 ml) was heated under reflux for 7·5 h. Most of the solvent was distilled under reduced pressure and the residue was diluted with water. The basic solution was extracted with ether and acidified giving a yellow oil which soon crystallized. This was collected, washed with water and dried yielding 51·4 g of solid, m.p. 72–74°. Recrystallization from petroleum hexane gave colourless crystals (49·1 g, 87 per cent), m.p. 74–75° (in a capillary tube) or 81·5–82° on a Fisher–Johns block.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73·24; H, 8·46; neut. equiv., 262·34. Found: C, 73·03; H, 8·49; neut. equiv., 262·0.

4-Allyloxy-3,5-dipropylbenzoyl chloride. A solution of 4-allyloxy-3,5-dipropylbenzoic acid (200 g, 0·706 mole) (No. 1) and thionyl chloride (100 ml) in benzene (200 ml) was heated under reflux for 2 h. The solvent and excess thionyl chloride were distilled under reduced pressure and the product was then distilled giving a yellow liquid (186·4 g, 94 per cent), b.p. 127°/0·1 mm; n_D^{25} 1·4281.

Anal. Calcd. for $C_{16}H_{21}ClO_2$: Cl, 12·62. Found: Cl, 12·70.

Methyl 4-allyloxy-3,5-dipropylbenzoate (*No. 15*). A mixture of 4-allyloxy-3,5-dipropylbenzoyl chloride (40·62 g, 0·137 mole), pyridine (12·1 ml, 0·15 mole) and methanol (150 ml) was stirred under reflux until the reaction subsided and was then heated on a

steam bath for ½ h. The excess methanol was distilled under reduced pressure. Water was added and the mixture was extracted three times with ether. The ether solutions were washed twice with water then with saturated salt solution and dried over sodium sulphate. After filtration and removal of the ether, the product was distilled giving a colourless liquid (31·4 g, 78 per cent), b.p. 113°/0·025 mm; n_D^{25} 1·5091.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75. Found: C, 73·75; H, 8·42.

β-*Hydroxyethyl 4-allyloxy-3,5-dipropylbenzoate* (*No. 31*), was prepared as described for No. 15 using the acid chloride (37 g, 0·125 mole), ethylene glycol (160 ml, 2·5 moles) and pyridine (10·5 ml, 0·13 mole). The product was distilled giving a viscous liquid (28·25 g, 70 per cent), b.p. 155°/0·02 mm; n_D^{25} 1·5181.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70·56; H, 8·55. Found: C, 70·31; H, 8·60.

β-*Diethylaminoethyl 4-allyloxy-3,5-dipropylbenzoate.* A mixture of 4-allyloxy-3,5-dipropylbenzoyl chloride (37 g, 0·125 mole), β-diethylaminoethanol (35 g, 0·3 mole), and benzene (100 ml) was heated with stirring under reflux for 1·5 h. After cooling overnight, the mixture was acidified with dilute hydrochloric acid and extracted three times with ether. The aqueous solution was made basic with sodium hydroxide and the product extracted three times with ether. The ether solutions were washed with water and saturated salt solution and dried over sodium sulphate. After filtering, the solvent was removed and the product was distilled giving a light yellow liquid (41·3 g, 91·5 per cent), b.p. 155°/0·025 mm; n_D^{25} 1·5010.

Anal. Calcd. for $C_{22}H_{35}NO_3$: C, 73·09; H, 9·76; N, 3·88. Found: C, 72·82; H, 9·63; N, 4·13.

To a solution of this base in ethyl acetate (500 ml) was added a slight excess of ethanolic hydrogen chloride. The solution was diluted with ether and cooled giving crystals which were collected, washed with ether and dried, yielding a white hydrochloride (No. 32) (34·98 g, 78 per cent), m.p. 105·5–107°.

Anal. Calcd. for $C_{22}H_{36}ClNO_3$: C, 66·39; H, 9·12; Cl, 8·91. Found: C, 66·27; H, 9·06; Cl, 9·00.

β-(*1-Pyrrolidyl*)-*ethyl 4-allyloxy-3,5-dipropylbenzoate hydrochloride* (*No. 33*). A mixture of 4-allyloxy-3,5-dipropylbenzoic acid

(2·88 g, 0·011 mole), β-(1-pyrrolidyl)ethyl chloride hydrochloride (1·70 g, 0·01 mole) and anhydrous potassium carbonate (2·79 g, 0·022 mole) in methyl ethyl ketone (25 ml) was heated under reflux with stirring for 17 h. After filtration the solvent was removed. The residue was mixed with ether and washed with dilute sodium hydroxide then twice with water, and dried over Drierite. Hydrogen chloride was passed in giving a solid hydrochloride which was recrystallized from methyl ethyl ketone, m.p. 117–118°.

Anal. Calcd. for $C_{22}H_{34}ClNO_3$: Cl, 8·95. Found: Cl, 9·08.

N-(*4-Allyloxy-3,5-dipropylbenzoyl*)-p-*aminobenzoic acid* (*No. 53*). To a solution of *p*-aminobenzoic acid (13·7 g, 0·1 mole) in 4·5 per cent sodium hydroxide (90 ml) was added simultaneously and dropwise during ½ h with stirring and cooling, 4-allyloxy-3,5-dipropylbenzoyl chloride (14·1 g, 0·05 mole) and a solution of 6·5 per cent sodium hydroxide (30 ml). After removing the ice bath, the mixture was stirred for 15 min and acidified with hydrochloric acid. The crystalline product was collected and dried giving 24·1 g of crude product. This was dissolved in ethanol (250 ml), treated with Darco, the solution was filtered, concentrated and cooled yielding colourless crystals (12·6 g, 66 per cent), m.p. 204–205°.

Anal. Calcd. for $C_{23}H_{27}NO_4$: C, 72·41; H, 7·14; N, 3·67; neut. equiv., 381·46. Found: C, 72·13; H, 6·94; N, 3·70; neut. equiv., 382.

N-(*4-Allyloxy-3,5-dipropylbenzoyl*)-*glycine* (*No. 52*), was prepared as described for No. 53 using glycine (7·5 g, 0·1 mole) in place of the *p*-aminobenzoic acid. The product was recrystallized from aqueous ethanol giving colourless crystals (3·0 g, 18·8 per cent), m.p. 171–173°.

Anal. Calcd. for $C_{18}H_{25}NO_4$: C, 67·69; H, 7·89; N, 4·39. Found: C, 67·77; H, 7·66; N, 4·36.

4-Allyloxy-3,5-dipropylbenzamide (*No. 37*). To 29 per cent ammonium hydroxide (4 l.) was slowly added 4-allyloxy-3,5-dipropylbenzoyl chloride (647 g, 2·3 moles) with vigorous stirring and cooling while passing in a slow stream of ammonia. After the acid chloride had all been added, the stirring and addition of ammonia was continued at room temperature for 2 h. The product was collected on a filter, washed with water and dried giving a white solid (596 g), m.p. 107–110°. Recrystallization from

petroleum hexane yielded colourless crystals (584 g, 97 per cent), m.p. 109–110°.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73·50; H, 8·87; N, 5·36. Found: C, 73·58; H, 8·53; N, 5·29.

5-Allyloxy-3,5-dipropyl-N-methylbenzamide (*No. 45*). This was prepared as described for No. 37, from the acid chloride (14·1 g, 0·05 mole) using 40 per cent aqueous methylamine (100 ml) in place of the ammonium hydroxide and ammonia gas. The product was dissolved in petroleum hexane, washed with dilute sodium carbonate, then with water and dried over sodium sulphate. Removal of the solvent gave an oil which soon crystallized. This was recrystallized from pentane yielding a white solid (13·4 g, 97 per cent), m.p. 66–68°.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74·14; H, 9·15; N, 5·09. Found: C, 74·41; H, 9·07; N, 5·01.

4-Allyloxy-3,5-diphenyl-N,N-dimethylbenzamide (*No. 47*). To a cold solution of dimethylamine (45 g, 1·0 mole) in benzene (200 ml) 4-allyloxy-3,5-dipropylbenzoyl chloride (92·5 g, 0·35 mole) was slowly added with cooling and stirring. The mixture was stirred for 3 h, washed twice with water and then with saturated salt solution. The aqueous solutions were extracted with ether. The ether and benzene solutions were dried over sodium sulphate, filtered and the solvent removed. The product was distilled giving a light yellow liquid (94·2 g, 98·7 per cent); b.p. 140°/0·2 mm; n_D^{25} 1·6391.

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74·70; H, 9·40; N, 4·84. Found: C, 75·03; H, 9·25; N, 4·94.

4-Allyloxy-3,5-dipropyl-N,N-diethylbenzamide (*No. 48*), was prepared as described for No. 47, using diethylamine in place of dimethylamine. The product was distilled giving an 88 per cent yield of a light yellow liquid, b.p. 128°/0·03 mm: n_D^{25} 1·5112.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 75·66; H, 9·84; N, 4·41. Found: C, 76·03; H, 9·98; N, 4·25.

4-Allyloxy-3,5-dipropylbenzoyl-1-pyrrolidine (*No. 49*), was prepared as described for No. 47, using pyrrolidine in place of dimethylamine. The product was distilled giving a 96 per cent yield of a nearly colourless liquid, b.p. 160°/0·005 mm; n_D^{25} 1·5330.

Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76·15; H, 9·27; N, 4·44. Found: C, 75·87; H, 9·23; N, 4·54.

4-Allyloxy-3,5-dipropyl-N-isobutylbenzamide (*No. 46*), was prepared as described for No. 47 using isobutylamine in place of dimethylamine. After working up the reaction mixture and removing the solvent, crystals were obtained which were recrystallized from aqueous ethanol giving a 72·5 per cent yield of colourless crystals, m.p. 82–84°.

Anal. Calcd. for $C_{20}H_{31}NO_2$: C, 75·66; H, 9·84; N, 4·41. Found: C, 75·80; H, 9·55; N, 4·56.

4-Allyloxy-3,5-dipropyl-N-[β-(1-pyrrolidyl)ethyl]benzamide hydrochloride (*No. 50*). To a solution of β-(1-pyrrolidyl)ethylamine (25·2 g, 0·22 mole) in benzene (50 ml) was slowly added with stirring, 4-allyloxy-3,5-dipropylbenzoyl chloride (28·1 g, 0·1 mole) in benzene (50 ml). The mixture became warm and crystals separated. After refluxing for an additional 10 min, the mixture was cooled and extracted with dilute hydrochloric acid. The aqueous solution was washed with ether and the ether and benzene solutions were extracted with water. The aqueous solutions were made basic with sodium hydroxide giving an oily base which did not crystallize well. This was extracted with ether, washed with water, then with saturated salt solution and dried over sodium sulphate. After removing the ether, the residue was dissolved in ethyl acetate (100 ml) and acidified with ethanolic hydrogen chloride. On dilution with ether and cooling, the crystalline hydrochloride separated, giving colourless crystals (31 g, 78 per cent), m.p. 118–119°.

Anal. Calcd. for $C_{22}H_{35}ClN_2O_2$: C, 66·89; H, 8·93; Cl, 8·98. Found: C, 66·63; H, 8·81; Cl, 9·05.

1-(4-Allyloxy-3,5-dipropylbenzoyl)-4-methylpiperazine citrate (*No. 51*). The base was prepared as described for No. 50 from 4-allyloxy-3,5-dipropylbenzoyl chloride (9·0 g, 0·032 mole) and *N*-methylpiperazine (20 g). It was distilled giving a light yellow oil (10·1 g), b.p. 145°/0·005 mm. This was dissolved in ethanol and a warm ethanolic solution of citric acid hydrate (9·0 g) was added. On cooling crystals separated which were recrystallized from isopropyl alcohol yielding colourless crystals (14·2 g, 83 per cent), m.p. 172–173° (d.).

Anal. Calcd. for $C_{27}H_{40}N_2O_9$: C, 60·43; H, 7·51; N, 5·22. Found: C, 60·15; H, 7·57; N, 5·28.

4-Allyloxy-3,5-dipropylbenzoyl urea (*No. 54*). To dry urea (60

g, 1·0 mole) and benzene (100 ml), 4-allyloxy-3,5-dipropylbenzoyl chloride (28·1 g, 0·1 mole) was added and the mixture was heated under reflux with stirring for 4 h. It was cooled, stirred with dilute sodium carbonate solution and the layers were separated. The aqueous layer was extracted with ether, and the benzene and ether solutions were washed twice with water, then with saturated salt solution and dried over sodium sulphate. Filtration and removal of the solvent gave an oil which partly crystallized on standing. Addition of petroleum hexane dissolved the oil. The crystals were collected, washed with petroleum hexane and dried giving a white solid (1·26 g), m.p. 142–144°. This was recrystallized from ethanol (30 ml) giving colourless crystals (1·13 g, 3·7 per cent), m.p. 147–147·5°.

Anal. Calcd. for $C_{17}H_{24}N_2O_3$: C, 67·08; H, 7·95; N, 9·21. Found: C, 67·03; H, 7·86; N, 9·23.

4-Allyloxy-3,5-dipropylbenzamidine hydrochloride (*No. 55*). Dry hydrogen chloride was passed into a solution of 4-allyloxy-3,5-dipropylbenzonitrile (18·3 g, 0·075 mole) (No. 56 below) in absolute ethanol (4·7 ml). When hydrogen chloride (3·5 g, 0·085 mole) had been added the flask was allowed to stand for 6 days and 7·5 N ethanolic solution of ammonia (35 ml) was added. After standing for 1 week the solution was filtered, concentrated, and acidified with ethanolic hydrogen chloride. Addition of ether caused the separation of more ammonium chloride which was removed. The filtrate was concentrated nearly to dryness when the product crystallized. More ether was added and the product was collected and dried yielding colourless crystals (17·9 g, 32 per cent) m.p. 193–195°.

Anal. Calcd. for $C_{16}H_{25}ClN_2O$: C, 64·74; H, 8·49; Cl, 11·96. Found: C, 64·72; H, 8·40; Cl, 12·17.

Ethyl 4-ethoxy-3,5-dipropylbenzoate (*No. 18*). This ester was prepared as described for No. 16 from ethyl 4-hydroxy-3,5-dipropylbenzoate (75·1 g, 0·3 mole) (No. 24), anhydrous potassium carbonate (44 g), ethyl bromide (38 g, 0·35 mole) and acetone (300 ml). The product was distilled giving a colourless liquid (77·7 g). The infrared spectrum and analyses indicated the presence of unreacted phenolic ester. Extraction of an ether solution of the product with cold 20 per cent aqueous sodium hydroxide failed to remove all of the phenol. A 31 g portion was

dissolved in pentane (300 ml) and chromatographed on alumina (680 g). The column was eluted with pentane containing increasing amounts of acetone (up to 15 per cent). Eleven fractions containing significant amounts of material were obtained. These were combined, the solvent was removed and the residue distilled giving a colourless liquid (27·5 g, 82·3 per cent), b.p. 118°/0·008 mm, n_D^{25} 1·4911. The infrared spectrum showed no phenolic absorption and titration showed no acidic function.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73·34; H, 9·42. Found: C, 73·43; H, 9·43.

4-Ethoxy-dipropylbenzoic acid (*No. 3*). In a 5 l. flask fitted with stirrer, reflux condenser and two dropping funnels was placed a solution of 4-hydroxy-3,5-dipropylbenzoic acid (22·3 g, 1 mole) (No. 9) in absolute ethanol (150 ml). In one of the dropping funnels was placed a solution of sodium ethoxide from sodium (97 g, 4 moles) and absolute ethanol (1·5 l.). In the other dropping funnel was placed ethyl bromide (545 g, 5 moles). One-half of each reagent was added to the flask with stirring and the mixture was heated under reflux until nearly neutral. One-half of the remainder of each reagent was added and refluxed until again nearly neutral. The remainder of the reagents were added and refluxed until a 1 ml sample needed only one drop of 0·1 N acid to bring it to neutrality. The excess ethyl bromide and solvent were distilled and 20 per cent aqueous sodium hydroxide (500 ml) was added. Enough ethanol was added to give a clear solution at the boiling point and the solution was refluxed for 2½ h to hydrolyze the esters formed in the reaction. Most of the solvent was distilled, water was added and the mixture was extracted with ether. The ether layer was extracted twice with water and the aqueous solutions were acidified. Most of the product was in the first aqueous extract and only very little in the original aqueous layer. After removing residual ether the product crystallized and was collected, washed with water and dried. The yield was 240 g, 96 per cent, m.p. 74–77°. A sample recrystallized from pentane had the same melting point.

This compound was also prepared in 90 per cent yield by saponification of its ethyl ester (No. 18).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86. Found: C, 72·12; H, 9·05.

4-Ethoxy-3,5-dipropylbenzamide (*No. 39*). A solution of the acid (8·45 g, 0·0337 mole) (No. 3) and thionyl chloride (8 ml) in benzene (10 ml) was heated under reflux for 2 h. Excess thionyl chloride and benzene were distilled under reduced pressure. The oily acid chloride was added to aqueous ammonium hydroxide (160 ml) with cooling and the mixture was shaken overnight. The crystalline product was collected, washed with water and dried giving a nearly white solid (6·94 g, 82·6 per cent), m.p. 115–118°. This was recrystallized from methylcyclohexane giving colourless crystals, m.p. 118–119·5°.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72·25; H, 9·30; N, 5·62. Found: C, 72·07; H, 9·51; N, 5·55.

Ethyl 4-benzyloxy-3,5-dipropylbenzoate (*No. 20*), was prepared by a modification of the method used for No. 3, using ethyl 4-hydroxy-3,5-dipropylbenzoate (148·7 g, 0·594 mole), sodium methoxide* from sodium (23 g, 1 mole), and benzyl bromide (214 g, 1·25 mole), in methanol (550 ml). The product was distilled giving 179·3 g of oil, b.p. 157°/0·007 mm, which soon crystallized. This was recrystallized from pentane yielding colourless crystals (125 g, 62 per cent), m.p. 43·5–45·5°.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29. Found: C, 77·50; H, 8·55.

4-Benzyloxy-3,5-dipropylbenzoic acid (*No. 6*), was prepared by saponification of the ester No. 20 (114·8 g, 0·362 mole) as described for No. 1. The product was recrystallized from petroleum hexane giving a white solid (102·3 g, 93 per cent), m.p. 94·5–96°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76·89; H, 7·74. Found: C, 77·34; H, 7·91.

4-Benzyloxy-3,5-dipropylbenzamide (*No. 41*). A mixture of 4-benzyloxy-3,5-dipropylbenzoic acid (92·0 g, 0·294 mole), thionyl chloride (150 ml) and benzene (100 ml) was heated under reflux until the evolution of gas ceased. The solvent was removed under reduced pressure leaving crystalline acid chloride. This was dissolved in absolute ether and ammonia was passed in with stirring until saturated. After standing overnight the mixture was diluted with benzene, heated to boiling and filtered from ammonium chloride. On cooling the amide crystallized. Addi-

* Sodium ethoxide would have been preferable due to the possibility of ester interchange.

tional material was obtained from the filtrate by concentration and dilution with pentane giving a total of 65·5 g (72 per cent) of colourless crystals, m.p. 130–131·5°.

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77·13; H, 8·09; N, 4·50. Found: C, 77·13; H, 8·13; N, 4·51.

4-Hydroxy-3,5-dipropylbenzamide (*No. 44*). A mixture of 4-benzyloxy-3,5-dipropylbenzamide (34·2 g, 0·1 mole), methanol (200 ml) and 10 per cent palladium on charcoal (20 g) was hydrogenated at 40 lb pressure and room temperature. The solution was filtered from catalyst, concentrated, diluted with water and cooled giving 21·7 g (98 per cent) of crystals, m.p. 154·5–155°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70·56; H, 8·65; N, 6·33. Found: C, 70·25; H, 8·68; N, 6·29.

4-Hydroxy-3,5-dipropylbenzoic acid (*No. 9*), was prepared by saponification of the ester No. 24 as described for No. 1 giving colourless crystals, m.p. 146–151°, from aqueous methanol.

The same acid was also prepared by simultaneous ester and ether cleavage from ethyl 4-allyloxy-3,5-dipropylbenzoate (580·8 g, 2 moles) (No. 16) by refluxing for 16 h with 48 per cent aqueous hydrobromic acid (1·5 l), acetic acid (1·5 l) and 47 per cent hydriodic acid (100 ml). The solvents were distilled under reduced pressure and the residue was dissolved in dilute sodium hydroxide, washed with ether and acidified giving 275·4 g (62 per cent) of solid, m.p. 144–148°.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70·24; H, 8·16. Found: C, 70·01; H, 7·84.

Ethyl 4-methallyloxy-3,5-dipropylbenzoate (*No. 19*), was prepared as described for No. 20 from No. 24 (150·2 g, 0·6 mole) and methallyl chloride (80 g, 1 mole) giving a mixture of the product and starting material. This was mixed with a cold solution of 85 per cent potassium hydroxide (350 g) in water (250 ml) and methanol (1 l.) and extracted with petroleum hexane. The hexane solution was washed with saturated salt solution and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled through a short helices column giving a colourless liquid (42·8 g, 23 per cent), b.p. 120°/0·025 mm, n_D^{25} 1·5061.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74·96; H, 9·27. Found: C, 74·96; H, 8·81.

4-Methallyloxy-3,5-dipropylbenzoic acid (*No. 4*), was prepared by saponification of the ester No. 19 (30·4 g, 0·1 mole), as described for No. 1. Concentration of an ether solution of the acid nearly to dryness gave crystalline solid (20·7 g, 75 per cent), m.p. 80–83°.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75; neut. equiv., 276·36. Found: C, 74·17; H, 9·29; neut. equiv., 278·0.

4-Methallyloxy-3,5-dipropylbenzamide (*No. 40*), was prepared from the acid No. 4 (12·5 g, 0·045 mole), as described for No. 39. The product was crystallized from methylcyclohexane giving colourless crystals (9·04 g, 73 per cent), m.p. 134·5–136°.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74·14; H, 9·15; N, 5·09. Found: C, 73·98; H, 8·93; N, 5·09.

4-Crotoxy-3,5-dipropylbenzoic acid (*No. 5*). Crude ethyl 4-crotoxy-3,5-dipropylbenzoate was prepared as described for No. 16. It was hydrolyzed as described for No. 1, giving crude acid which crystallized poorly. After several recrystallizations from petroleum hexane a small yield of pure product was obtained, m.p. 50–53°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 73·88; H, 8·75. Found: C, 73·59; H, 8·90.

Ethyl 4-(β-diethylaminoethoxy)-3,5-dipropylbenzoate, was prepared by a modification of the method used for No. 20 from a hexane solution of β-diethylaminoethyl chloride in place of the benzyl bromide. The free base was separated and distilled giving a 35 per cent yield of nearly colourless liquid, b.p. 139°/0·025 mm, n_D^{25} 1·4968.

Anal. Calcd. for $C_{21}H_{35}NO_3$: C, 72·16; H, 10·09; N, 4·01; neut. equiv., 349·50. Found: C, 72·48; H, 9·75; N, 4·24; neut. equiv., 348·0.

The hydrochloride (No. 21) was prepared in ether with ethanolic hydrogen chloride and crystallized from a mixture of benzene and ether giving a 89 per cent yield of white solid, m.p. 86·5–88°.

Anal. Calcd. for $C_{21}H_{36}ClNO_3$: C, 65·32; H, 9·40; Cl, 9·19. Found: C, 65·67; H, 9·26; Cl, 9·60.

4-(β-Diethylaminoethoxy)-3,5-dipropylbenzoic acid hydrochloride (*No. 7*). A solution of ethyl 4-(β-diethylaminoethoxy)-3,5-dipropylbenzoate (25 g, 0·072 mole) in concentrated hydrochloric acid (83 ml, 1 mole) and water (150 ml) was partly slowly distilled through a column. The remaining solution was distilled to dryness under reduced pressure giving a crystalline residue which was

recrystallized from dilute aqueous hydrochloric acid yielding colourless crystals (23·1 g, 90 per cent), m.p. 193–195°. A small sample was recrystallized from ethanol plus benzene, m.p. 195–197°.

Anal. Calcd. for $C_{19}H_{32}ClNO_3$: C, 63·78; H, 9·01; Cl, 9·91. Found: C, 63·51; H, 8·97; Cl, 9·94.

4-(β-Diethylaminoethoxy)-3,5-dipropylbenzamide hydrochloride (*No. 42*). A mixture of the above amino acid hydrochloride (14·4 g, 0·0402 mole) and thionyl chloride (100 ml) was heated under reflux until the evolution of gas ceased. The excess thionyl chloride was distilled under reduced pressure. Addition of ether to the residue caused the acid chloride to crystallize; however it was not isolated but a stream of ammonia was bubbled through the mixture with stirring and cooling. When saturated, the mixture was allowed to stand for 3 days. The mixture was washed with dilute sodium bicarbonate solution, then with water and dried over sodium sulphate. After filtration and concentration the ether solution was acidified with ethanolic hydrogen chloride giving colourless crystals (11·2 g, 78 per cent), m.p. 218–220°.

Anal. Calcd. for $C_{19}H_{33}ClN_2O_2$: C, 63·93; H, 9·32; Cl, 9·93; N, 7·85; neut. equiv., 356·93. Found: C, 63·83; H, 9·04; Cl, 9·97; N, 7·97; neut. equiv., 355.

4-Carboxymethoxy-3,5-dipropylbenzoic acid (*No. 8*). The crude diethyl ester of this acid was prepared as described for No. 16 from ethyl 4-hydroxy-3,5-dipropylbenzoate (75·1 g, 0·3 mole), potassium carbonate (44 g) and ethyl bromoacetate (83·5 g, 0·5 mole). The product was distilled giving a nearly colourless liquid (82·5 g), b.p. 140°/0·02 mm. The infrared spectrum and analysis indicated the presence of some unchanged phenolic ester. The product was hydrolyzed as described for No. 1 and the reaction product was recrystallized first from ethanol and then from toluene giving a 31 per cent overall yield of acid, m.p. 1 55–156°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64·27; H, 7·19; neut. equiv., 140·16. Found: C, 64·64; H, 7·54; neut. equiv., 145·0.

4-(Carboxamidomethoxy)-3,5-dipropylbenzamide (*No. 43*), was prepared from 4-carboxymethoxy-3,5-dipropylbenzoic acid (10 g, 0·0357 mole) by the method described for No. 41. Water was added to the ether reaction mixture leaving a white solid insoluble in both layers. This was collected, washed with water and ether

and dried, yielding the amide (7·47 g), m.p. 169·5–172°. Recrystallization from absolute ethanol gave colourless crystals (7·4 g, 74 per cent), m.p. 170–172°.

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64·72; H, 7·97; N, 10·07. Found: C, 64·81; H, 7·92; N, 9·94.

Ethyl 4-(diethylcarbamoyloxy)-3,5-dipropylbenzoate (*No. 22*). To a suspension of sodium hydride (11·0 g, 0·456 mole) in tetrahydrofuran (800 ml) was slowly added a solution of ethyl 4-hydroxy-3,5-dipropylbenzoate (57·3 g, 0·228 mole) (No. 24) in tetrahydrofuran (200 ml). The mixture was heated under reflux with stirring until no more hydrogen was evolved (about ½ h). Then diethyl-carbamoyl chloride (40·5 g, 0·3 mole) was slowly added and the mixture was refluxed for 5 h. Most of the solvent was distilled, replaced by absolute ether, and water was added. The ether layer was washed with ice-water, cold dilute sodium bicarbonate, water, saturated salt solution and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled giving a light yellow liquid (51·4 g), b.p. 142°/0·005 mm. The infrared spectrum showed some of the starting phenolic ester was still present. By repeated fractional distillations through a short column a sample (23 g, 29 per cent) essentially free of phenolic ester was obtained, b.p. 150°/0·05 mm.

Anal. Calcd. for $C_{20}H_{31}NO_4$: C, 68·74; H, 8·94; N, 4·01. Found: C, 69·40; H, 8·50; N, 4·37.

Ethyl 4-[(carbethoxymethyl)-carbamoyloxy]-3,5-dipropylbenzoate (*No. 23*). A solution of ethyl 4-hydroxy-3,5-dipropylbenzoate (35·2 g, 0·14 mole) (No. 24), carbethoxymethyl isocyanate (26 g, 0·2 mole) and pyridine (1 ml) was heated on a steam bath for 18·5 h. On cooling the product crystallized and was recrystallized from petroleum hexane giving light tan crystals (48·3 g, 91 per cent), m.p. 80–83°.

Anal. Calcd. for $C_{20}H_{29}NO_6$: C, 63·30; H, 7·70; N, 3·69. Found: C, 63·38; H, 7·83; N, 3·66.

4-Allyloxy-3,5-dipropoxybenzonitrile (*No. 56*). A solution of 4-allyloxy-3,5-dipropylbenzamide (44·8 g, 0·171 mole) in thionyl chloride (100 ml) was heated on a steam bath with stirring under reflux until no more gas was evolved. The excess thionyl chloride was distilled under reduced pressure. The residue was dissolved in ether and washed with dilute sodium hydroxide, water, satur-

ated salt solution and dried over sodium sulphate. After filtration, the solvent was removed and the product was distilled giving a light yellow liquid (29·8 g, 71·5 per cent), b.p. 118°/0·005 mm, n_D^{25} 1·5145.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78·97; H, 8·70; N, 5·76. Found: C, 78·66; H, 8·39; N, 5·96.

4-Propoxy-3,5-dipropylbenzonitrile (*No. 57*) *and 4-hydroxy-3,5-dipropylbenzonitrile* (*No. 58*). A solution of 4-allyloxy-3,5-dipropylbenzonitrile (36·4 g, 0·15 mole) in ethanol (150 ml) was hydrogenated with platinum oxide (0·1 g) at room temperature and a starting pressure of 60 lb. About 0·15 moles of hydrogen was absorbed in 15 min. The mixture was filtered, the solvent distilled and the residue was taken up in ether. This solution was washed with dilute hydrochloric acid, water, then with dilute sodium hydroxide, twice again with water and finally with saturated sodium chloride solution. Acidification of the basic wash gave a white solid (5·3 g), m.p. 99–101°, which proved to be the 4-hydroxy compound.

After drying the ether solution over sodium sulphate, filtering and removing the solvent, the residue was distilled from a Claisen flask. After distilling 23·9 g of an oil, b.p. 107–115°/0·06 mm, a white solid distilled, b.p. 115–120°/0·06 mm. When recrystallized from petroleum hexane this solid (2·4 g), m.p. 98–99·5°, was identical with the above 4-hydroxy derivative. The oil was redistilled through a 15 cm column packed with 0·3 cm glass helices giving 16·3 g of liquid, b.p. 96°/0·04 mm, n_D^{25} 1·5073. The infrared spectrum indicated this material contained some 4-allyloxy starting material. It was therefore rehydrogenated and reworked as above giving, after two distillations, a colourless liquid (13·7 g, 37 per cent), b.p. 85°/0·05 mm, n_D^{25} 1·5046.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78·32; H, 9·45; N, 5·71. Found: C, 77·99; H, 9·34; N, 5·85.

An additional 1·76 g of the white solid 4-hydroxynitrile was obtained from the reworking, giving a total of 10·0 g (33 per cent), m.p. 98·5–100·5°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76·81; H, 8·43; N, 6·89. Found: C, 77·08; H, 8·26; N, 6·83.

Ethyl 4-propoxy-3,5-dipropylbenzoate (*No. 17*), was prepared by hydrogenation as described for No. 24 from ethyl 4-allyloxy-3,5-

diallylbenzoate[1] (14·3 g, 0·05 mole) in ethanol (100 ml) with palladium-on-charcoal (2 g). The product was distilled giving 13·1 g (89·7 per cent) of liquid, b.p. 152°/0·7 mm, n_D^{25} 1·4950.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73·93; H, 9·65. Found: C, 74·35; H, 9·73.

4-Propoxy-3,5-dipropylbenzoic acid (*No. 2*), was prepared by saponification of the ester (No. 17) (13·1 g, 0·045 mole) as described for No. 1, giving waxy crystals (11·2 g, 93·8 per cent). A sample recrystallized from petroleum ether had m.p. 52–53°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72·69; H, 9·13; neut. equiv., 264·35. Found: C, 72·58; H, 9·20; neut. equiv., 265·3.

4-Propoxy-3,5-dipropylbenzamide (*No. 38*). A solution of 4-allyloxy-3,5-dipropylbenzamide (13·8 g, 0·0528 mole) in ethanol (125 ml) was hydrogenated with platinum oxide (0·2 g) at 38 lb pressure at room temperature. The calculated amount of hydrogen was absorbed in 5 min. After filtration from the catalyst, the solvent was distilled leaving a white crystalline solid which was recrystallized from aqueous ethanol giving colourless crystals (11·56 g, 83 per cent), m.p. 106–108·5°.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72·96; H, 9·57; N, 5·32. Found: C, 72·67; H, 9·28; N, 5·59.

Ethyl 3,5-diallyl-4-propoxybenzoate (*No. 26*), was prepared as described for No. 16 from ethyl 3,5-diallyl-4-hydroxybenzoate (14·1 g, 0·057 mole), propyl bromide (7·5 g), and potassium carbonate (8·5 g). The product was distilled giving a liquid (9·7 g, 58 per cent), b.p. 157°/0·8 mm, n_D^{25} 1·5143.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74·96; H, 8·39. Found: C, 75·35; H, 8·46.

3,5-Diallyl-4-propoxybenzoic acid (*No. 11*), was prepared by saponification of the ester No. 26 as described for No. 1. A 95 per cent yield of acid was obtained from petroleum hexane, m.p. 107–108·5°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73·82; H, 7·74; neut. equiv. 260·32. Found: C, 73·74; H, 7·81; neut. equiv., 259·5.

β-(*1-Pyrrolidyl*)-*ethyl 4-allyloxy-3,5-diallylbenzoate hydrochloride* (*No. 34*). To sodium ethoxide from sodium (0·25 g, 0·0101 mole) and absolute ethanol (50 ml) was added 4-allyloxy-3,5-diallylbenzoic acid[1] (2·6 g, 0·01 mole) and β-(1-pyrrolidyl)ethyl chloride (1·35 g, 0·01 mole). The mixture was heated under reflux for

8 h, filtered, and the solvent removed. The residue was dissolved in absolute ether and the hydrochloride was precipitated with hydrogen chloride and recrystallized from methyl ethyl ketone, m.p. 118–119°.

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: Cl, 9·04. Found: Cl, 8·80.

Ethyl 4-hydroxy-3-propylbenzoate was prepared as described for No. 24 by hydrogenation of ethyl 3-allyl-4-hydroxybenzoate[1] (20·6 g, 0·1 mole) in ethanol (100 ml) with platinum oxide (0·2 g). The yield of material recrystallized from petroleum hexane was 15·5 g (90·5 per cent), m.p. 78·5–79·5°. A small sample recrystallized from ethanol had m.p. 79–80°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69·21; H, 7·75. Found: C, 68·73; H, 7·35.

Ethyl 4-allyloxy-3-propylbenzoate was prepared as described for No. 16 from ethyl 4-hydroxy-3-propylbenzoate (424·3 g, 20·4 moles). The product was distilled giving a liquid (479·8 g, 96 per cent), b.p. 116°/0·05 mm, n_D^{25} 1·5178.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12. Found: C, 72·59; H, 8·07.

Ethyl 3-allyl-4-hydroxy-5-propylbenzoate (*No. 30*). Ethyl 4-allyloxy-3-propylbenzoate (30 g, 0·136 mole) was heated at 220–290° for 30 min, cooled and triturated with petroleum hexane. The mixture was filtered and the filtrate evaporated, reheated to 260° for 5 min and reworked as above. The total yield from petroleum hexane was 28 g (93 per cent) of solid, m.p. 67–68°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 72·55; H, 8·11. Found: C, 72·40; H, 8·30.

Ethyl 4-allyloxy-3-allyl-5-propylbenzoate (*No. 28*), was prepared as described for No. 16 from the ester No. 30 (12·4 g, 0·05 mole) giving a liquid (9·9 g, 69 per cent), b.p. 149°/0·9 mm; n_D^{25} 1·5130.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74·96; H, 8·39. Found: C, 74·74; H, 8·39.

4-Allyloxy-3-allyl-5-propylbenzoic acid (*No. 13*), was prepared as described for No. 1 from the ester No. 28 (9·5 g, 0·033 mole) giving a solid (8·4 g, 97 per cent), m.p. 39–40°. Recrystallization from petroleum hexane raised the melting point to 40–41°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73·82; H, 7·74; neut. equiv., 260·32. Found: C, 73·69; H, 8·02; neut. equiv., 257·8.

β-(*1-Pyrrolidyl*)-*ethyl 4-allyloxy-3-allyl-5-propylbenzoate* (*No. 35*).

By a procedure similar to that used for No. 33 this was prepared from 4-allyloxy-3-allyl-5-propylbenzoic acid (3·5 g, 0·0135 mole) β-(1-pyrrolidyl)ethyl chloride hydrochloride (1·7 g, 0·1 mole) and potassium carbonate (2·79 g, 0·0202 mole) giving colourless crystals, m.p. 116–117°.

Anal. Calcd. for $C_{22}H_{32}ClNO_3$: Cl, 9·00. Found: Cl, 9·26.

Ethyl 3-allyl-4-propoxy-5-propylbenzoate (*No. 29*), was prepared as described for No. 16 from the ester No. 30 (12·4 g, 0·05 mole), propyl bromide (12·3 g, 0·1 mole), potassium carbonate (8·3 g) and 25 ml of methyl ethyl ketone. The product was distilled giving a colourless liquid (12·0 g, 82·7 per cent), b.p. 155°/0·08 mm, n_D^{25} 1·5098.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74·44; H, 9·03. Found: C, 74·50; H, 8·88.

3-Allyl-4-propoxy-5-propylbenzoic acid (*No. 14*). Prepared by saponification of the ester No. 29 (11·5 g, 0·034 mole) as described for No. 1. A 99 per cent yield of acid was obtained, m.p. 45–47°. Recrystallization from petroleum hexane raised the m.p. to 46–48°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73·24; H, 8·46; neut. equiv., 262·34. Found: C, 73·19; H, 8·37; neut. equiv., 259·0.

β-(*1-Pyrrolidyl*)-*ethyl 3-allyl-4-propoxy-5-propylbenzoate* (*No. 36*). Prepared as described for No. 34, using the acid, No. 14. The product was crystallized from methyl ethyl ketone, m.p. 118–121°.

Anal. Calcd. for $C_{22}H_{24}ClNO_3$: Cl, 8·95. Found: Cl, 9·14.

Summary. 4-Allyloxy-3,5-dipropylbenzoic acid (I), its esters, amides and nitrile have been found to have strong central nervous system depressant activity. Other ether substituents in place of the allyloxy group give compounds of lesser activity. Ethyl 3,5-diallyl-4-hydroxybenzoate (II) was obtained by repeated allylation and rearrangement from ethyl 4-hydroxybenzoate. This was hydrogenated, allylated and hydrolyzed to (I) from which most of the other derivatives were prepared.

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