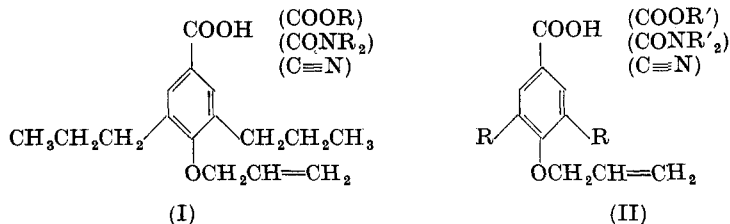


Central Nervous System Depressants—II. 4-Allyloxy-3,5-dialkylbenzoic Acids and Derivatives*

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The high activity of 4-allyloxy-3,5-dipropylbenzoic acid and certain of its derivatives (I) in increasing the sleeping time of mice given small doses of hexobarbital¹ has encouraged us to prepare a number of analogues in which methyl, ethyl, or isopropyl substituents replace the two propyl groups (II). In general these



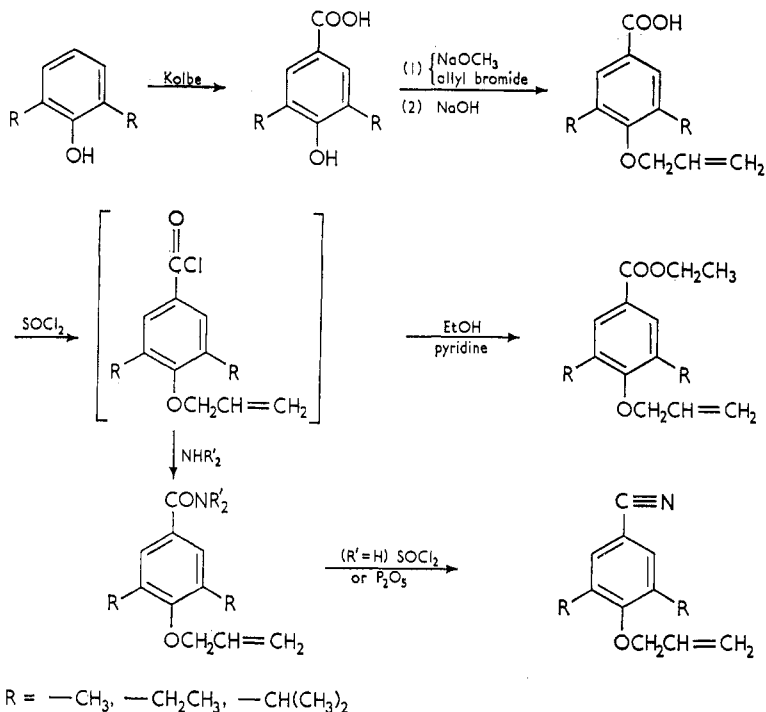
appeared to have about the same order of activity as the 3,5-dipropyl compounds. The acids, esters and amides were slightly less active and the nitriles were slightly more active.

The key 4-allyloxy-3,5-dialkylbenzoic acids were made from the requisite 4-hydroxy acids which in turn were prepared by the Kolbe synthesis from the corresponding phenols. The carboxyl derivatives were prepared through the acid chlorides as shown on the next page.

Table I lists these and a few related compounds with some of their pharmacological properties. The preparation of all new compounds is given in the experimental section. Infrared

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

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



Experimental†

4-Hydroxy-3,5-dimethylbenzoic acid (No. 1). This was prepared by a modification of the method of Wessely *et al.*³ Sodium methoxide was prepared from sodium (57.5 g, 2.5 moles) and methanol (850 ml). To this solid 2,6-dimethylphenol (306 g, 2.5 moles) was added with stirring. The solution was distilled from an oil bath and toluene was added from time to time until

* 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. Wm. Struck and staff of our Analytical Chemistry Laboratory.

the b.p. reached 107° . The toluene suspension of the crystalline sodium salt was transferred to an autoclave and heated at 200° for 6 h with carbon dioxide at 450 lb. The mixture was washed from the autoclave with water, the layers were separated and the toluene layer was extracted with sodium carbonate solution. The aqueous solutions were washed with ether and acidified with hydrochloric acid giving a tan solid which was collected, washed with water and dried. Recrystallization from aqueous ethanol with the aid of Darco yielded colourless crystals (202 g, 48.8 per cent), m.p. $221\text{--}224.5^{\circ}$. Much of the unreacted 2,6-dimethylphenol could be recovered by distillation of the toluene and ether solutions.

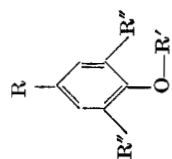
Attempts to prepare this acid without making the sodium salt in advance but using anhydrous potassium carbonate in the carbonation reaction failed to give any appreciable amount of acid.

4-Allyloxy-3,5-dimethylbenzoic acid (No. 2). This was prepared by the method described in the preceding article¹ for 4-ethoxy-3,5-dipropylbenzoic acid using the above acid (No. 1) (223 g, 1.34 moles), and sodium methoxide from sodium (115 g, 5 moles), allyl bromide (475 ml, 5.5 moles), and methanol (2.2 l.). The product was recrystallized from ethanol giving colourless crystals (171.7 g, 62 per cent), m.p. $146\text{--}146.5^{\circ}$. An additional 45 g of slightly less pure acid was obtained from the filtrate.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; neut. equiv., 206.23. Found: C, 69.59; H, 6.72; neut. equiv., 209.

Ethyl 4-allyloxy-3,5-dimethylbenzoate (No. 3). A solution of 4-allyloxy-3,5-dimethylbenzoic acid (45.8 g, 0.22 mole) in thionyl chloride (37 ml, 0.5 mole) and benzene (50 ml) was heated under reflux for one hour. The excess thionyl chloride and benzene were distilled under reduced pressure giving the crude acid chloride. To this were added absolute ethanol (200 ml) and pyridine (25 ml, 0.3 mole). After heating under reflux for $\frac{1}{2}$ h most of the solvent was distilled under reduced pressure. The residue was diluted with ether and washed with dilute hydrochloric acid, with water, then with dilute sodium hydroxide, twice again with water, with saturated salt solution and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled through a short column giving a nearly colourless liquid (46 g, 89 per cent), b.p. $93^{\circ}/0.025$ mm; n_D^{25} 1.5140.

Table I. Pharmacological Properties



No.	R	R'	R''	Toxicity LD50 ^a	% Increase in hexobarbital sleeping time ^b	% Decrease in motor- activity ^c
1	COOH	H	CH ₃	> 1000	140	-16
2	COOH	CH ₂ CH=CH ₂	CH ₃	650	310	27
3	COOCH ₂ CH ₃	CH ₂ CH=CH ₂	CH ₃	650	320	64
4	COOCH ₂ CH ₃	CH ₂ CH ₂ CH ₃	CH ₃	650	170	28
5 ^d	COOCH ₂ CH ₃	H	CH ₃	> 1000	170	17
6	CONH ₂	CH ₂ CH=CH ₂	CH ₃	300	300	41
7	CON(CH ₂ CH ₃) ₂	CH ₂ CH=CH ₂	CH ₃	200	1140	39
8	C≡N	CH ₂ CH=CH ₂	CH ₃	1000	≥ 520 ^d	29
9 ^e	C≡N	CH ₂ CH=CH ₂	CH ₃	650	> 400 ^f	19
10 ^g	Br	H	CH ₃	650	330	
11 ^h	Br	CH ₂ CH=CH ₂	CH ₃	650	> 1400 ^g	35
12	CH ₃	H	CH ₃	> 1000	100	
13	H	H	CH ₃	230	60	8
14	COOH	H	CH ₂ CH ₃	770	440	-1
15	COOH	CH ₂ CH=CH ₂	CH ₂ CH ₃	650		44

16	COOCH ₂ CH ₃	CH ₂ CH=CH ₂	CH ₂ CH ₃	360	1
17	CONH ₂	CH ₂ CH=CH ₂	CH ₂ CH ₃	≥ 600 ^a	99
18	CON(CH ₂ CH ₃) ₂	CH ₂ CH=CH ₂	CH ₂ CH ₃	530	53
19	C≡N	CH ₂ CH=CH ₂	CH ₂ CH ₃	1910	99
20	C≡N	H	CH ₂ CH ₃	> 520 ⁱ	88
21 ⁷	H	H	CH ₂ CH ₃	20	-3
22 ⁸	COOH	H	CH(CH ₃) ₂	50	-12
23	COOH	CH ₂ CH=CH ₂	CH(CH ₃) ₂	≥ 650 ^j	39
24	COOCH ₂ CH ₃	CH ₂ CH=CH ₂	CH(CH ₃) ₂	250	
25	CONH ₂	CH ₂ CH=CH ₂	CH(CH ₃) ₂	≥ 450 ^k	62
26	C≡N	CH ₂ CH=CH ₂	CH(CH ₃) ₂	≥ 570 ^l	25
27	H	H	CH(CH ₃) ₂	40	2
28	H	CONHCH ₂ COOCH ₂ CH ₃	CH(CH ₃) ₂	120	-3

^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 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 Dews². 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 > 1,560% increase at 10% of LD50; 1,340 at 5%.

^e J. Thiele and H. Eichmède, *Ann.*, **311**, 363 (1900).

^f 430% increase at 10% of LD50.

^g 740% increase at 10% of LD50.

^h 940% increase at 10% of LD50.

ⁱ 370% increase at 10% of LD50.

^j 510% increase at 5% of LD50.

^k 97% increase at 10% of LD50.

^l 470% increase at 10% of LD50.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.75; H, 7.75. Found: C, 71.95; H, 8.05.

Ethyl 3,5-dimethyl-4-propoxybenzoate (No. 4) and ethyl 3,5-dimethyl-4-hydroxybenzoate (No. 5). A solution of ethyl 3,5-dimethyl-4-allyloxybenzoate (23.4 g, 0.1 mole) in ethanol (100 ml) was hydrogenated with Adams' catalyst (0.1 g) at 50 lb pressure and room temperature. The theoretical amount of hydrogen was absorbed in 5 min and the uptake practically stopped. After filtration and removal of the solvent the resulting oil was distilled giving 22.72 g of a mixture of oil and crystalline solid, b.p. $90-104^\circ/0.03$ mm. The oil was dissolved in pentane and extracted with cold dilute sodium hydroxide solution. The basic extract was washed with pentane and acidified giving colourless crystals (2.14 g, 11 per cent), m.p. $112-116^\circ$. The melting point and infrared spectrum indicate this is the 4-hydroxy ester (No. 5) produced by hydrogenolysis. Jacobsen⁴ reports m.p. 113° for this compound. The pentane solution was washed twice with water, then with saturated salt solution and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled giving the 4-propoxy ester (No. 4) (20.3 g, 87.3 per cent) as a colourless liquid, b.p. $92^\circ/0.03$ mm; n_D^{25} 1.5020.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.25; H, 8.50.

4-Allyloxy-3,5-dimethylbenzamide (No. 6). Acid chloride, prepared as above from 4-allyloxy-3,5-dimethylbenzoic acid (125 g, 0.7 mole), was diluted to 335 ml with absolute ether and ammonia was passed in with rapid stirring until saturated. A white solid separated immediately. After standing overnight the mixture was diluted with water, the white precipitate was collected, washed with water and ether and dried, giving a colourless solid (109 g, 87.4 per cent), m.p. $139-143^\circ$. The ether layer was separated from the filtrate and on concentration yielded an additional 8.43 g of colourless solid, m.p. $143-145^\circ$. The total yield was 94.3 per cent. Recrystallization raised the m.p. to $144-146^\circ$.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.29; H, 7.55; N, 7.09.

4-Allyloxy-3,5-dimethyl-N,N-diethylbenzamide (No. 7). Acid chloride, prepared as above, from 4-allyloxy-3,5-dimethylbenzoic acid (25 g, 0.12 mole) was diluted to 65 ml with absolute ether.

A solution of diethylamine (22 g, 0.3 mole) in absolute ether (50 ml) was slowly added with stirring at reflux temperature. After standing overnight the mixture was extracted with dilute hydrochloric acid, water, dilute sodium hydroxide, twice more with water, saturated salt solution, and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled under reduced pressure to yield a light yellow liquid (21.0 g, 68 per cent), b.p. $128^{\circ}/0.025$ mm; n_D^{25} 1.5230.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.47; H, 8.90; N, 5.27.

4-Allyloxy-3,5-dimethylbenzonitrile (No. 8). A solution of 4-allyloxy-3,5-dimethylbenzamide (No. 6) (51.4 g, 0.25 mole) in thionyl chloride (130 ml) was heated under reflux for $6\frac{1}{2}$ h and allowed to stand overnight. The excess thionyl chloride was distilled under reduced pressure and the residue was dissolved in the ether. This solution was washed with water, dilute sodium hydroxide, water, saturated salt solution, and dried over sodium sulphate. After filtration and removal of the solvent the product was distilled through a short column giving 20.0 g of crystalline solid, b.p. $93^{\circ}/0.06$ mm; m.p. $54-57^{\circ}$. This was recrystallized from pentane giving colourless crystals (19.8 g, 42.3 per cent), m.p. $53.5-56.5^{\circ}$.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.53; H, 7.16; N, 7.55.

4-Bromo-2,6-dimethylphenol (No. 10), was obtained in 95 per cent yield, m.p. $80-81^{\circ}$, by the method of Kharasch and Winzler.⁵

4-Allyloxy-1-bromo-3,5-dimethylbenzene (No. 11). To a solution of sodium (46 g, 2.0 moles) in methanol (900 ml) was added, with cooling, 4-bromo-2,6-dimethylphenol (402.1 g, 2.0 moles) in methanol (200 ml). Then allyl bromide (363 g, 3.0 moles) was added and the mixture was warmed to boiling. When the mild exothermic reaction subsided the mixture was heated under reflux with stirring for 1.5 h at which point it tested acidic. The solvent was distilled under reduced pressure, and the residue was diluted with ice-water and extracted with benzene and ether. The organic solutions were washed with 10 per cent aqueous sodium hydroxide, twice with water, then with saturated salt solution and dried over sodium sulphate. After filtration and distillation of the solvent, the product was distilled through a short column giving a light

yellow liquid (302.7 g, 62.6 per cent), b.p. $75^{\circ}/0.1$ mm, n_D^{25} 1.5440.

Anal. Calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Br, 33.14. Found: C, 54.48; H, 5.78; Br, 33.12.

This compound was recently reported⁶ but no analysis was given.

2,6-Diethylphenol (No. 21). In a 2-l. beaker, surrounded by an ice bath, were placed 2,6-diethylaniline (101 g, 0.68 moles), and concentrated sulphuric acid (150 ml) in 200 ml of water, and 500 g of ice. Then enough sodium nitrite solution (about 50 g in 125 ml of water) was rapidly added with stirring until the mixture gave a permanent positive test with starch-iodide paper. The temperature was kept at 0 to 5° by adding more ice as necessary. About 3 g of urea was added and stirred for 10 min. The mixture was kept cold while being slowly added to a rapidly steam distilling solution of concentrated sulphuric acid (150 ml) in water (200 ml). The product was distilled as rapidly as possible. Three lots of diazonium salt were added to the flask before it was necessary to replace the contents of the flask by fresh sulphuric acid. A total of eight lots of diazonium salt were made and hydrolyzed in this way.

The combined distillate was extracted twice with ether and the ether solutions were washed with saturated salt solution and dried over sodium sulphate. After filtration and distillation of the solvent the product was distilled through a column giving a colourless liquid (480 g, 59 per cent) which immediately crystallized, b.p. $103^{\circ}/10$ mm; m.p. $42.5-45^{\circ}$. v. Auwers and Wittig⁷ report m.p. $37.5-38^{\circ}$ on material prepared by a different method.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.58; H, 9.39.

3,5-Diethyl-4-hydroxybenzoic acid (No. 14). This was prepared as described for No. 1 from 2,6-diethylphenol (450 g, 3 moles) giving 206.3 g (35.5 per cent) of acid, m.p. $152-154^{\circ}$. Recrystallization from benzene yielded nearly colourless crystals (170 g), m.p. $158-160^{\circ}$.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.31; H, 7.13.

4-Allyloxy-3,5-diethylbenzoic acid (No. 15). This was prepared by the method described in the preceding article¹ for 4-ethoxy-

3,5-dipropylbenzoic acid using the above acid (No. 14) (171.1 g, 0.914 mole), sodium methoxide from sodium (53 g, 2.3 moles), allyl bromide (332 g, 2.7 moles), and methanol (950 ml). A yield of 158.9 g (74.5 per cent) of acid was obtained, m.p. 88–91°. Recrystallization from petroleum hexane and then from ethanol gave white crystals (93 g), m.p. 91–92.5°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; neut. equiv., 234.28. Found: C, 72.16; H, 7.91; neut. equiv., 237.

Ethyl 4-allyloxy-3,5-diethylbenzoate (No. 16). This was prepared as described for the 3,5-dimethyl analogue (No. 3) from the above acid (No. 15) (26.7 g, 0.114 mole). The product was distilled giving a light yellow liquid (26.6 g, 96 per cent), b.p. 110°/0.15 mm; n_D^{25} 1.5101.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.45; H, 8.34.

4-Allyloxy-3,5-diethylbenzamide (No. 17). This was prepared as described for the 3,5-dimethyl analogue (No. 6) from the above acid (No. 15) (53.4 g, 0.228 mole). The product was soluble in the ether solution. This was washed with water, dilute sodium hydroxide, water, saturated salt solution and dried over sodium sulphate. After filtration and distillation of the solvent the product was obtained as a white solid which was recrystallized from ether giving crystals (42.7 g, 80 per cent), m.p. 166–167°.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.01. Found: C, 72.19; H, 8.40; N, 6.05.

4-Allyloxy-3,5-diethyl-N,N-diethylbenzamide (No. 18). This was prepared as described for the corresponding 3,5-dimethyl analogue (No. 7) from the above acid (No. 15) (53.4 g, 0.228 mole). The product was distilled giving a nearly colourless liquid (49.5 g, 77.5 per cent), b.p. 135°/0.05 mm; n_D^{25} 1.5183.

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.41; N, 4.84. Found: C, 74.39; H, 9.44; N, 5.12.

4-Allyloxy-3,5-diethylbenzonitrile (No. 19) and 4-hydroxy-3,5-diethylbenzonitrile (No. 20). A mixture of the above 4-allyloxy-3,5-diethylbenzamide (No. 17) (27.9 g, 0.12 mole) and thionyl chloride (80 ml) was heated under reflux with stirring for 2 h. The excess thionyl chloride was distilled and the residue was dissolved in ether. This was washed with 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 the allyl ether (No. 19) (12 g, 46 per cent) as a light yellow liquid, b.p. $103^{\circ}/0.1$ mm, n_D^{25} 1.5248.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.56. Found: C, 78.18; H, 8.23; N, 6.32.

Continuing the distillation a small intermediate fraction was cut and then a yellow solid distilled, b.p. $120-135^{\circ}/0.1$ mm. This was recrystallized from petroleum heptane giving a white solid (0.65 g, 3.1 per cent), m.p. $92-94^{\circ}$ which was found by infrared spectrum and analysis to be the 4-hydroxynitrile (No. 20), formed by cleavage of the allyl ether.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.86; H, 7.40; N, 7.78.

4-Allyloxy-3,5-diisopropylbenzoic acid (No. 23). This compound was prepared by the method described in the preceding article¹ for 4-ethoxy-3,5-dipropylbenzoic acid using 4-hydroxy-3,5-diisopropylbenzoic acid⁸ (No. 22), (187 g, 0.84 mole) sodium methoxide from sodium (80 g, 3.5 moles), allyl bromide (346 ml, 4 moles), and methanol (1.6 l.). A yield of 168.8 g (76.7 per cent) of acid, m.p. $182-185^{\circ}$, was obtained. This was recrystallized from ethanol giving colourless crystals (149 g, 67.7 per cent), m.p. $185.5-187.5^{\circ}$.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46; neut. equiv. 262.34. Found: C, 73.13; H, 8.60; neut. equiv. 265.

Ethyl 4-allyloxy-3,5-diisopropylbenzoate (No. 24). This material was prepared as described for the 3,5-dimethyl analogue (No. 3) from the above acid (No. 23) (31.9 g, 0.121 mole). The product was distilled through a short column giving a nearly colourless liquid (33.4 g, 94.8 per cent), b.p. $101^{\circ}/0.03$ mm; n_D^{25} 1.5047.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.02. Found: C, 74.10; H, 9.18.

4-Allyloxy-3,5-diisopropylbenzamide (No. 25). This was prepared as described for the 3,5-dimethyl analogue (No. 6) from the above acid (No. 23) (96 g, 0.364 mole). The product was recrystallized from ethanol giving a white solid (85 g, 90 per cent), m.p. $172-173^{\circ}$.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.31; H, 8.79; N, 5.24.

4-Allyloxy-3,5-diisopropylbenzonitrile (No. 26). In a 500-ml Claisen flask were well mixed by shaking 4-allyloxy-3,5-diisopropylbenzamide (26.1 g, 0.1 mole) and phosphorus pentoxide (20 g, 0.14 mole). The flask was heated in an oil bath to 165° and a high vacuum applied to the receiver. The product distilled rapidly at 130°/0.4 mm as a colourless liquid which immediately solidified giving a white solid (13.7 g, 56.4 per cent), m.p. 72–79°. This was recrystallized from pentane yielding colourless crystals (12.26 g), m.p. 75–80°.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.66; H, 8.73; N, 5.80.

Ethyl 2,6-diisopropylphenoxycarbamylglycinate (No. 28). A solution of 2,6-diisopropylphenol (No. 27) (35.66 g, 0.2 mole), carbethoxymethyl isocyanate (32.3 g, 0.25 mole) and dry pyridine (1 ml) was heated on a steam bath for 1½ h and allowed to stand for five days. Addition of a little benzene and scratching caused crystallization. The mixture was dissolved in pentane (400 ml), filtered and cooled in the refrigerator. The resulting crystals were collected, washed with pentane, and dried, giving a light tan solid (36.1 g, 95 per cent), m.p. 70–73°.

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.57. Found: C, 66.36; H, 8.39; N, 4.74.

Summary. The high central nervous system depressant activity found for 4-allyloxy-3,5-dipropylbenzoic acid and derivatives (I) is also present when methyl, ethyl or isopropyl substituents replace the propyl groups.

The 4-allyloxy-3,5-dialkylbenzoic acids were made from the corresponding 4-hydroxy acids which were prepared by the Kolbe synthesis from the 2,6-dialkyl phenols. The acids were also converted to esters, amides, and nitriles through the acid chlorides.

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