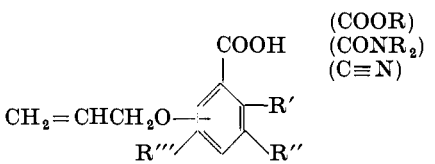
Journal of Medicinal and Pharmaceutical Chemistry

VOL. 2, No. 2 (1960)

Central Nervous System Depressants—IV. 4-Allyloxy-3,5-dialkyl-benzyl Amines*

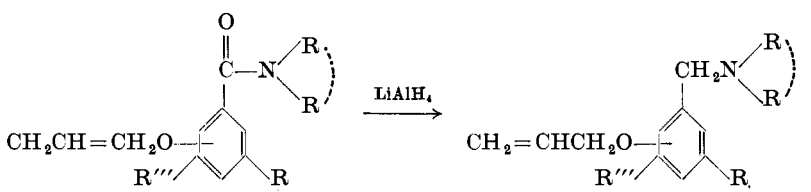
ROBERT BRUCE MOFFETT and PATRICK H. SEAY, *Research Laboratories of The Upjohn Company, Kalamazoo, Michigan*

In preceding articles of this series[1, 2, 3] a considerable number of compounds were disclosed which greatly increase the sleeping time of mice given small doses of hexobarbital. These were, for the most part, 2- or 4-allyloxy-3,5-dialkylbenzoic acids or their functional derivatives (esters, amides or nitriles) (I).



(I)

We have now prepared a series of benzyl amines (II) by lithium aluminum hydride reduction of the corresponding amides (III).



(III) (II)

Surprisingly, in spite of the great difference in the functional group, these amines increased the hexobarbital sleeping time of mice similarly to the corresponding carboxyl derivatives. However, in general they seemed to be less depressive in the motor

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

activity test than the corresponding non-basic analogues and at certain doses some of them were slightly stimulating.

A few 4-hydroxy-3,5-dialkyl amines were prepared by the Mannich reaction on the corresponding phenols. These proved to be less active than the allyloxy amines. All these benzyl amines are listed in Table I with some of their pharmacological properties, and their preparation is described in the experimental part. Infrared spectra* were obtained on all pure products and in all cases were consistent with the proposed structures.

Experimental†

4-Allyloxy-3,5-dipropylbenzyl-1-pyrrolidine. To lithium aluminium hydride (3·8 g, 0·1 mole) in absolute ether (50 ml) was slowly added 4-allyloxy-3,5-dipropylbenzoyl-1-pyrrolidine[1] (15·1 g, 0·048 mole) in absolute ether (50 ml). The mixture was heated under reflux with stirring for 3 h and allowed to stand overnight. Then were cautiously added in succession with stirring, ethyl acetate (12 ml) in ether (100 ml), water (4 ml), 20 per cent aqueous sodium hydroxide (3 ml) and water (14 ml). After thorough stirring the mixture was filtered and the precipitate was extracted with more ether. The ether solutions were washed with water and extracted with dilute hydrochloric acid. An oily hydrochloride separated, insoluble in both layers. The aqueous and the hydrochloride layers were combined and made basic with sodium hydroxide. The free base was extracted with ether, washed with water and dried over potassium carbonate. After filtration and removal of the solvent the product was distilled giving a nearly colourless liquid (13·2 g, 91 per cent), b.p. 120°/0·005 mm, n_D^{25} 1·5122.

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79·68; H, 10·37; N, 4·65. Found: C, 80·16; H, 10·68; N, 5·11.

A solution of the above free base (11·84 g, 0·039 mole) in ether (300 ml) was acidified with ethanolic hydrogen chloride giving nearly white crystals (13·22 g, 99·5 per cent) of the hydrochloride

* 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 are by Mr. Wm. Struck and staff of our Analytical Chemistry Laboratory.

(No. 5), m.p. 156–159°. These were recrystallized from ethyl acetate giving colourless platelets (10·81 g, 92·5 per cent), m.p. 160–161·5°.

Anal. Calcd. for $C_{20}H_{32}ClNO$: C, 71·08; H, 9·55; Cl, 10·49. Found: C, 71·28; H, 9·15; Cl, 10·63.

4-Allyloxy-3,5-dipropylbenzylamine. This was prepared in a similar way from 4-allyloxy-3,5-dipropylbenzamide[1] (39·2 g, 0·15 mole). The free base was distilled giving a colourless liquid (16·8 g, 42 per cent), b.p. 110°/0·025 mm, n_D^{25} 1·5150.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77·68; H, 10·17; N, 5·66. Found: C, 77·90; H, 10·22; N, 5·62.

To a solution of this free base (16·5 g, 0·062 mole) in ether was added an ethanolic solution of a slight excess of citric acid. On cooling, the citrate salt (No. 1) crystallized and was collected, washed with ether and dried giving a white solid (25·7 g, 94·6 per cent), m.p. 139–140°.

Anal. Calcd. for $C_{22}H_{33}NO_8$: C, 60·12; H, 7·57; N, 3·19. Found: C, 60·14; H, 7·60; N, 3·25.

*4-Allyloxy-3,5-dipropyl-*N*-methylbenzylamine.* This was prepared in a similar way from 4-allyloxy-3,5-dipropyl-*N*-methylbenzamide[1] (40·9 g, 0·162 mole). The base was distilled giving a nearly colourless liquid (31·1 g, 73·5 per cent), b.p. 115°/0·025 mm.

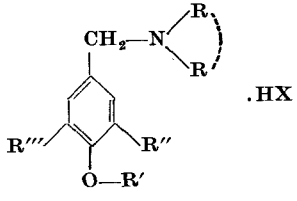
Anal. Calcd. for $C_{17}H_{27}NO$: N, 5·36. Found: N, 5·40.

An ethyl acetate solution of the above free base (30·25 g, 0·115 mole) was converted to the hydrochloride (No. 2) with ethanolic hydrogen chloride. The solution was concentrated, diluted with benzene and pentane giving 30·6 g (90 per cent) of crystals, m.p. 132–140°. This hydrochloride was remarkably soluble in organic solvents and was recrystallized with difficulty from ether, then from benzene–hexane and finally from benzene–ether giving 7·4 g of crystals, m.p. 157–158°.

Anal. Calcd. for $C_{17}H_{28}ClNO$: C, 68·55; H, 9·47; Cl, 11·91. N, 4·70; Found: C, 68·85; H, 9·47; Cl, 10·89; N, 4·46.

*4-Allyloxy-3,5-dipropyl-*N,N*-dimethylbenzylamine.* This was prepared in a similar way from 4-allyloxy-3,5-dipropyl-*N,N*-dimethylbenzamide[1] (43·5 g, 0·15 mole). The free base was distilled through a short column giving a nearly colourless liquid (37 g, 89·5 per cent), b.p. 107°/0·05 mm, n_D^{25} 1·4996.

Table I. Pharmacological properties



No.	—N(R)(R)	R′	R″	R‴	.HX (or base)	Toxicity LD50[a]	% Increase in hexobarbital sleeping time[b]	% Decrease in motor activity[c] at 40% LD50	% Decrease in motor activity[c] at 20% LD50
1	—NH_2	$CH_2CH=CH_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	Citric acid	200	>2530[d]	—	91
2	—$NHCH_3$	$CH_2CH=CH_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	.HCl	100	450	35	−7
3	—$N(CH_3)_2$	$CH_2CH=CH_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	.HCl	80	>760[e]	26	20
4	—$N(CH_2CH_3)_2$	$CH_2CH=CH_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	.HCl	60	240	—	—
5	—$NCH_2CH_2CH_2CH_2$	$CH_2CH=CH_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	.HCl	60	320	29	−52

6	$-N(CH_3)_2$	H	$CH_2CH_2CH_2$	$CH_2CH_2CH_3$	.HCl	200	200	87	23
7	$-NH_2$	$CH_2CH=CH_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	.HCl	60	1640	73	27
8[5]	$-N(CH_3)_2$	H	$CH(CH_3)_2$	$CH(CH_3)_2$	base	200	300	93	41
9	$-N(CH_2CH_3)_2$	$CH_2CH=CH_2$	C_2H_5	C_2H_5	.HCl	100	170	51	4
10	$-N(CH_3)_2$	H	CH_3	CH_3	base	100	110	3	1
11	$-N(CH_3)_2$	H	CH_3	$CH_2CH_2CH_3$	.HCl	80	110	1	−4
12	$-N(CH_3)_2$	H	CH_3	Cl	base	80	−40	−20	−7
13	$-NH_2$	$CH_2CH=CH_2$[f]	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	.HCl	100	500	84	55
14	$-NH_2$	H[f]	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	.HCl	60	400	53	7

[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, dissolved or suspended in aqueous carboxymethylcellulose in doses representing 20% of their LD50's, were 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 the indicated percentage of their LD50's and injected intraperitoneally into mice. Thirty minutes later the effect on motor activity was determined using the technique of Dews.[4] 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] 1030% increase at 10% of LD50; 1170% at 5%; 890% at 2·5%.

[e] 650% increase at 10% of LD50; 620% at 5%; 380% at 2·5%.

[f] The oxygen substituent is in the *ortho* position of this compound instead of the *para* position.

Anal. Calcd. for $C_{18}H_{29}NO$: C, 78·49; H, 10·61; N, 5·09. Found: C, 78·68; H, 10·34; N, 5·01.

A solution of the base (36 g, 0·13 mole) in ethyl acetate (100 ml) was acidified with ethanolic hydrogen chloride and the solution was diluted with absolute ether (500 ml). On cooling waxy crystals of hydrochloride (No. 3) (16·9 g) were obtained. An additional 13·4 g was obtained by concentrating the filtrate and diluting with ether. The total yield was 74·6 per cent, m.p. 138–140°.

Anal. Calcd. for $C_{18}H_{30}ClNO$: C, 69·32; H, 9·70; Cl, 11·37. Found: C, 68·80; H, 9·38; Cl, 11·40.

4-Allyloxy-3,5-dipropyl-N,N-*diethylbenzylamine.* This was prepared in a similar way from 4-allyloxy-3,5-dipropyl-*N*,*N*-diethylbenzamide[1] (35·26 g, 0·105 mole). The product was distilled giving a nearly colourless liquid (37·2 g, 85 per cent), b.p. 130°/0·1 mm, n_D^{25} 1·4951.

Anal. Calcd. for $C_{20}H_{33}NO$: C, 79·15; H, 10·96; N, 4·62. Found: C, 79·17; H, 10·79; N, 4·41.

The hydrochloride (No. 4) was prepared as described for No. 3 from the base (26·5 g, 0·87 mole) yielding waxy crystals (15·9 g, 51 per cent), m.p. 149–150°.

Anal. Calcd. for $C_{20}H_{34}ClNO$: C, 70·87; H, 9·81; Cl, 10·46; N, 4·13. Found: C, 70·22; H, 9·86; Cl, 10·57; N, 3·91.

4-Allyloxy-3,5-diisopropylbenzylamine. This was prepared in a similar way from 4-allyloxy-3,5-diisopropylbenzamide[2] (28·5 g, 0·109 mole). The base was a waxy solid, yield 12·6 g, m.p. 35–40°. Recrystallization from petroleum hexane gave 4·0 g of light yellow crystals, m.p. 46–48°.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77·68; H, 10·19; N, 5·66. Found: C, 76·26; H, 9·89; N, 5·95.

An ether solution of the base was made acidic with ethanolic hydrogen chloride. A gelatineous precipitate separated. By standing, boiling, adding a little ethanol and scratching, the precipitated hydrochloride (No. 7) was obtained as silky needles which, after cooling, were collected, washed with absolute ether and dried giving 5·5 g of white solid, m.p. 210–213° (d.). The total yield (pure free base plus hydrochloride) was 33 per cent.

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67·70; H, 9·23; Cl, 12·49. N, 4·94; Found: C, 67·60; H, 9·51; Cl, 12·3; N, 5·23.

4-Allyloxy-3,5-diethyl-N,N-*diethylbenzylamine.* This was prepared in a similar way from 4-allyloxy-3,5-diethyl-*N*,*N*-diethylbenzamide[2] (28·0 g, 0·0965 mole). The product was distilled giving a liquid (23·5 g, 88·4 per cent), b.p. 105°/0·025 mm, n_D^{25} 1·5010.

Anal. Calcd. for $C_{18}H_{29}NO$: C, 78·49; H, 10·61; N, 5·81. Found: C, 78·82; H, 10·84; N, 5·01.

The free base was dissolved in absolute ether and acidified with alcoholic hydrogen chloride, giving hydrochloride (No. 9) (24·13 g), m.p. 158–159·5°. This was recrystallized from ethyl acetate giving colourless crystals (20·48 g, 86 per cent), m.p. 161–162°.

Anal. Calcd. for $C_{18}H_{30}ClNO$: C, 69·31; H, 9·70; Cl, 11·37; N, 4·49. Found: C, 69·32; H, 9·41; Cl, 11·43; N, 4·77.

2-Allyloxy-3,5-dipropylbenzylamine hydrochloride (*No. 13*) *and 2-hydroxy-3,5-dipropylbenzylamine hydrochloride* (*No. 14*). 2-Allyloxy-3,5-dipropylbenzamide[3] (26 g, 0·1 mole) was reduced with lithium aluminum hydride as described above. The ether solution of the free base was shaken with dilute hydrochloric acid and the aqueous layer was separated and made basic. Very little amine precipitated. The ether solution was extracted with water and this, when made basic, yielded most of the product. The base was extracted with ether which was washed with water, saturated salt solution, and dried over sodium sulphate. After filtration and removal of the solvent the residue was distilled giving a colourless liquid (13·14 g, 51·23 per cent), b.p. 103°/0·05 mm, n_D^{25} 1·5178.

Anal. Calcd. for $C_{16}H_{25}NO$: N, 6·52. Found: N, 5·58.

The amine was converted to the hydrochloride in ether by the addition of ethanolic hydrogen chloride. Fractional crystallization of this hydrochloride mixture from ethyl acetate gave silky needles (3·3 g), m.p. 160–161°, which were found by infrared spectrum and analysis to be the 2-hydroxy compound (No. 14).

Anal. Calcd. for $C_{13}H_{22}ClNO$: C, 64·05; H, 9·10; Cl, 14·54; N, 5·75. Found: C, 63·90; H, 9·10; Cl, 14·49; N, 6·01.

The more soluble 2-allyloxy compound (No. 13) (2·9 g) was obtained from the filtrates as waxy crystals, m.p. 168–171° (with some sintering from 160° up).

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67·70; H, 9·23; Cl, 12·49. Found: C, 67·55; H, 8·99; Cl, 12·40.

4-Hydroxy-3,5-dimethyl-N,N-*dimethylbenzylamine* (*No. 10*). A solution of 2,6-dimethylphenol (61·08 g, 0·5 mole), ethanol (500 ml) and 25 per cent aqueous dimethylamine (248 g, 1·38 moles) was cooled to 0° and 37 per cent aqueous formaldehyde (75 g, 0·93 mole) was added with stirring during 30 min. The mixture was allowed to warm to room temperature, stirred for ½ h and then heated under reflux for 3 h. It was poured into ice-water giving white crystals which were collected, washed with water and dried in a vacuum desiccator yielding 69·69 g (77·7 per cent) of material, m.p. 112–113°. This was recrystallized from benzene–hexane giving a white product (66·83 g), m.p. 115–117°.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73·70; H, 9·56; N, 7·82; neut. equiv., 179·26. Found; C, 73·77; H, 9·80; N, 7·94; neut. equiv., 180.

3-Chloro-4-hydroxy-5-methyl-N,N-*dimethylbenzylamine* (*No. 12*). This was prepared in a similar way from 2-chloro-6-methylphenol (71 g, 0·5 mole). The product was recrystallized first from petroleum hexane and then from ethyl acetate giving crystals (13·2 g, 13 per cent), m.p. 110·5–112°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: C, 60·15; H, 7·07; Cl, 17·76, N, 7·02. Found: C, 60·38; H, 7·18; Cl, 17·70; N, 7·19.

4-Hydroxy-3,5-dipropyl-N,N-*dimethylbenzylamine hydrochloride* (*No. 6*). In a similar way the free base of this compound was prepared from 2,6-dipropylphenol (89 g, 0·5 mole). The oily free base was extracted with pentane, washed with water and dried over sodium sulphate. After filtration the solution was acidified with ethanolic hydrogen chloride and diluted with absolute ether. The hydrochloride was fractionally crystallized from ethyl acetate giving colourless crystals (9 g, 7 per cent), m.p. 95–98°.

Anal. Calcd. for $C_{15}H_{26}ClNO$: C, 66·27; H, 9·64; Cl, 13·05; N, 6·15. Found: C, 65·38; H, 8·77; Cl, 13·25; N, 5·46.

4-Hydroxy-3-methyl-5-propyl-N,N-*dimethylbenzylamine hydrochloride* (*No. 11*). This was prepared in a similar way from 2-methyl-6-propylphenol (75 g, 0·5 mole). The oily free base was extracted with ether, dried and converted to the hydrochloride with ethanolic hydrogen chloride. The product was crystallized from chloroform and recrystallized from methanol–ether yielding colourless crystals (10·58 g, 8·7 per cent), m.p. 153·5–154·5°.

Anal. Calcd. for $C_{13}H_{22}ClNO$: C, 64·05; H, 9·10; Cl, 14·55; N, 5·75. Found: C, 63·78; H, 9·02; Cl, 14·6; N, 5·84.

Summary. Substituted benzylamines (II) were prepared by lithium aluminum hydride reduction of previously reported amides (III). Surprisingly these amines retained a considerable degree of the biological activity of the parent amides.

Acknowledgements. The authors wish to thank Dr. Richard V. Heinzelman for guidance in this work; and Mr. Raymond F. Tripp, Mr. H. J. Triezenberg and Mr. R. R. Russell for technical assistance.

(*Received 12 November, 1959*)

References

[1] Moffett, R. B., Seay, P. H. and Reid, W. B. This Journal, **2**, 179 (1960)
[2] Moffett, R. B. and Seay, P. H. This Journal, **2**, 201 (1960)
[3] Moffett, R. B. and Seay, P. H. This Journal, **2**, 213 (1960)
[4] Dews, P. B. *Brit. J. Pharmacol.*, **8**, 46 (1953)
[5] Coffield, T. H., Filbey, A. H., Eche and Kolka, A. J. *J. Amer. chem. Soc.*, **79**, 5019 (1957)