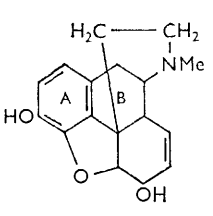
476. *The Synthesis of Alkoxy-1,2,3,4-tetrahydronaphthalene Derivatives. Part I. 2-Amino-, Alkylamino-, and Dialkylamino-derivatives*

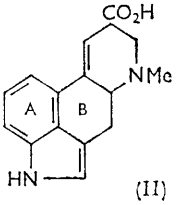
By D. E. Ames, D. Evans, T. F. Grey, P. J. Islip, and K. E. Richards

A series of the title compounds has been prepared for pharmacological testing.

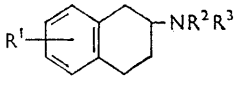
This Paper describes the synthesis of various alkoxy-1,2,3,4-tetrahydro-2-naphthylamines, their *N*-alkyl, and *NN*-dialkyl derivatives, which may be regarded as constituting the structure of rings A and B of morphine (I) and lysergic aid (II) with the amino-group intact.



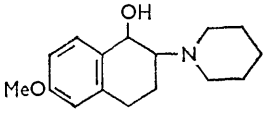
(I)



(II)



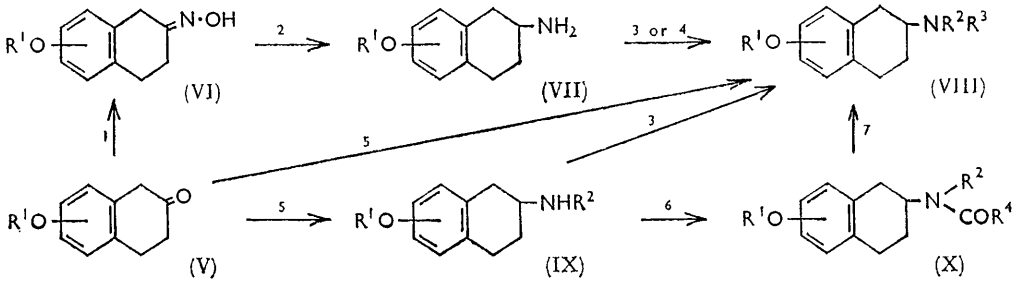
(III)



(IV)

Kraushaar [1] claimed that 1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine (III; R′ = 6-MeO, $R^2 = R^3 = H$) and a few related compounds exhibit oxytocic action and Scheuing and Walach [2] reported that the methoxy-hydroxy-base (IV) possesses distinct analgesic properties. Other related compounds (III; $R^1 = H$, R^2 and $R^3 = H$ to Bu^n) have been synthesised and tested by Chiavarelli *et al.*,[3] Voigtlander,[4] and Cymerman Craig and his co-workers.[5] After a study of many relevant compounds, Marini-Bettolo, Chiavarelli, and Bovet [6] concluded that the 1,2,3,4-tetrahydro-2-naphthylamine element in the structure of ergot alkaloids is more essential for sympatholytic action than the indole portion.

The *N*-alkyl derivatives of the 5-, 7-, and 8-alkoxy-1,2,3,4-tetrahydro-2-naphthylamines prepared during the present investigation were obtained by the routes shown.



Reagents: 1, $NH_2OH,HCl + NaOH$; 2, $NH_3 + H_2$ + Raney Ni; 3, $H{\cdot}CHO + H{\cdot}CO_2H$; 4, $H{\cdot}CHO + H_2$ + Pd/C; 5, R^2R^3NH (or R^2NH_2) + H_2 + PtO_2; 6, $(R^4CO)_2O$ + pyridine; 7, $LiAlH_4$.

The starting tetralones (V; R^1 = 5-, 7-, and 8-Me to 8-Bu^n, Bu^i, and Bu^s) were prepared by Cornforth, Cornforth, and Robinson's [7] method which involved reduction of the appropriate dialkoxynaphthalenes with sodium and ethanol followed by acid hydrolysis. The infrared spectra of the propoxy- and butoxy-2-tetralones showed that the samples were contaminated with about 5% of phenolic material which was not removed by purification *via* the bisulphite complex. However, it was possible to obtain pure 2,4-dinitrophenylhydrazones from this mixture and the impurities did not interfere with later stages of the syntheses.

The methoxy- and ethoxy-2-tetralones gave crystalline oximes which were catalytically hydrogenated, in the presence of ammonia, to the primary amines. *NN*-Dimethylation of the amines was carried out by condensation with formaldehyde and reduction with either formic acid or hydrogen in the presence of palladium–charcoal.

Other alkoxy-1,2,3,4-tetrahydro-2-naphthylamines, (VIII) and (IX), were prepared by reductive amination of the alkoxy-2-tetralones with the appropriate primary or secondary amines. The secondary amines (IX) were either methylated with formaldehyde–formic acid or converted into *N*-acyl-*N*-alkyl derivatives (X) which were reduced by lithium aluminium hydride.

The 6-methoxy-derivatives * were prepared by a different method to the other compounds owing to the inaccessibility of 2,6-dihydroxynaphthalene. Beckmann rearrangement of the oxime of 2-acetyl-6-methoxynaphthalene [8] gave 2-acetamido-6-methoxynaphthalene which was hydrolysed to the amine hydrochloride by treatment with methanolic hydrogen chloride solution. The resulting 2-amino-6-methoxynaphthalene was reduced

* The oxytocic action of these compounds has been reported [1] but we are not aware of any record of their method of preparation.

[1] A. Kraushaar, *Arzneim.-Forsch.*, 1954, **4**, 273.
[2] G. Scheuing and B. Walach, U.S.P. 2,352,020.
[3] S. Chiavarelli, R. L. Vittory, M. Marzadro, and G. Palazzo, *Rend. Ist. Super. Sanita*, 1952, **15**, 862.
[4] W. Voigtlander, *Pharmazie*, 1959, **14**, 318.
[5] J. Cymerman Craig, B. Moore, and E. Ritchie, *Austral. J. Chem.*, 1959, **12**, 447; J. Cymerman Craig, B. Moore, and D. M. Temple, *ibid.*, 1960, **13**, 463.
[6] G. B. Marini-Bettolo, S. Chiavarelli, and D. Bovet, *Gazzetta*, 1950, **80**, 281.
[7] J. W. Cornforth, R. N. Cornforth, and R. Robinson, *J.*, 1942, 689.
[8] R. Robinson and H. N. Rydon, *J.*, 1939, 1394.

with sodium and pentan-1-ol[9] to give the required 1,2,3,4-tetrahydro-6-methoxy-2-naphthyl amine in low yield. Treatment of the product with formaldehyde–formic acid gave the *NN*-dimethyl derivative.

5-Methoxy-1,1-dimethyl-2-tetralone was prepared from 5-methoxy-2-tetralone by methylation with methyl iodide and sodium isopropoxide in propan-2-ol [7] and its crystalline oxime catalytically reduced to the corresponding amine in the presence of ammonia; the corresponding *NN*-dimethyl derivative was obtained by reductive methylation as previously described.

Experimental

All the catalytic hydrogenations were carried out at atmospheric pressure.

Dialkoxynaphthalenes.—These were prepared by one of the following methods. Details of the *products* are given in Table 1.

Table 1

Dialkoxynaphthalenes

Substituents	Reagents	B. p./mm.	Yield (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
1,6-Me_2	Me_2SO_4–KOH	123—126°/0·8 [a,b]	90	—	—	—	—	—
1,7-Me_2	Me_2SO_4–KOH	124—127/0·7 [a,c]	85	—	—	—	—	—
2,7-Me_2	Me_2SO_4–KOH	[d]	86	—	—	—	—	—
1,6-Et_2	Et_2SO_4–KOH	140—144/0·9 [a]	73	77·5	7·6	$C_{14}H_{16}O_2$	77·8	7·5
1,7-Et_2	Et_2SO_4–KOH	[e]	38	77·3	7·5	$C_{14}H_{16}O_2$	77·8	7·5
1,7-Pr^n_2	Pr^nBr–K_2CO_3	147—152/0·7	67	79·2	8·0	$C_{16}H_{20}O_2$	78·7	8·3
1,7-Pr^i_2	Pr^iBr–K_2CO_3	147—153/0·7	63	78·5	7·7	$C_{16}H_{20}O_2$	78·7	8·3
1,7-Bu^n_2	Bu^nBr–K_2CO_3	181—183/1·4	42	78·9	8·9	$C_{18}H_{24}O_2$	79·4	8·9
1,7-Bu^i_2	Bu^iBr–K_2CO_3	158—162/0·5	46	79·2	8·5	$C_{18}H_{24}O_2$	79·4	8·9
1,7-Bu^s_2	Bu^sBr–K_2CO_3	153—155/0·4	55	79·6	8·6	$C_{18}H_{24}O_2$	79·4	8·9

[a] Solid at room temperature. [b] O. Fischer and C. Bauer, *J. prakt. Chem.*, 1916, [2], **94**, 2. [c] P. A. Robins and J. Walker, *J.*, 1958, 409. [d] O. Fischer and W. Kern (*J. prakt. Chem.*, 1916, [2], **94**, 34) give m. p. 136—137° (from ethanol). [e] M. p. 61—62° (from ethanol).

(*a*) Dialkylation of the dihydroxynaphthalene was carried out with dimethyl (or diethyl) sulphate and an excess of potassium hydroxide solution at 60° essentially by the method described in " Organic Syntheses," Coll. Vol. I, p. 58.

(*b*) A mixture of the dihydroxynaphthalene (0·2 mol.), alkyl bromide (0·44 mol.), anhydrous potassium carbonate (0·4 mol.), and ethanol (200 ml.) was stirred on a steam-bath for 20 hr. Solvent was removed by distillation, water was added, and the dialkoxynaphthalene isolated with ether. Distillation *in vacuo* afforded the required products.

Alkoxy-2-tetralones.—A solution (or suspension) of the dialkoxynaphthalene (0·3 mol.) in absolute ethanol (600 ml.) was added, as rapidly as possible, to sodium (2·5 mol.) in a flask fitted with an efficient condenser. The mixture was refluxed until the metal had all disappeared. The cooled solution was diluted with water (500 ml.), and concentrated hydrochloric acid (550 ml.) was added as rapidly as possible. The mixture was stirred on a steam-bath for 30 min., cooled, and extracted with ether. The organic layer was washed with water, concentrated, and the residue added to a stirred saturated sodium hydrogen sulphite solution (200 ml.). After 30 min., the separated solid was filtered off, washed well with ether, and decomposed by addition to a stirred mixture of ether and excess of sodium carbonate solution. The organic layer was separated, washed with water, dried (Na_2SO_4), and distilled to give the required *alkoxy-2-tetralone* (Table 2).

The corresponding *oximes* were prepared by neutralisation of a mixture of the ketone (0·1 mol.) and hydroxylamine hydrochloride (0·11 mol.), in aqueous ethanol, with 2N-sodium hydroxide solution at 60° using Bromothymol Blue as indicator. The cooled solution was diluted with water (500 ml.) and acidified with acetic acid. After 2 hr., the precipitate was filtered off and recrystallised from methanol.

Alkoxy-1,2,3,4-tetrahydro-2-naphthylamines and their N-Alkyl and NN-Dialkyl Derivatives.—The various methods of preparation and details of the above *compounds* are listed in Table 3.

Method A. Ammonium hydroxide solution (*d* 0·88; 5 ml.) and Raney nickel W7 (*ca.* 1 g.) were added to a suspension of the alkoxy-2-oxime (5·0 g.), in ethanol (50 ml.), and the mixture

[9] Cf. A. Windaus, *Ber.*, 1924, **57***B*, 1731.

TABLE 2

Alkoxy-2-tetralones (V)

No.	R^1	B. p./mm.	Yield (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
1	5-Me [a]	118—124°/1·1	65	—	—	—	—	—
2	7-Me [b]	130—136/2·3	46	—	—	—	—	—
3	8-Me [c]	120—123/1·0 [d]	50	—	—	—	—	—
4	5-Et	116—120/0·8	42	75·6	7·4	$C_{12}H_{14}O_2$	75·8	7·4
5	8-Et	122—124/1·1 [d, e]	41	75·9	7·1	$C_{12}H_{14}O_2$	75·8	7·4
6	8-Pr^n	138—143/0·2 [f, g]	51	77·4	8·4	$C_{13}H_{16}O_2$	76·4	7·9
7	8-Pr^i	135—140/0·9 [f, h]	43	77·7	8·2	$C_{13}H_{16}O_2$	76·4	7·9
8	8-Bu^n	133—137/0·3 [d, f, i]	35	77·3	8·6	$C_{14}H_{18}O_2$	77·0	8·3
9	8-Bu^i	144—147/0·3 [f]	29	77·2	8·1	$C_{14}H_{18}O_2$	77·0	8·3
10	8-Bu^s	120—123/0·3 [f]	30	77·0	8·3	$C_{14}H_{18}O_2$	77·0	8·3

Oximes

No.	M. p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
1	134—135°	69·0	7·2	7·4	$C_{11}H_{13}NO_2$	69·1	6·9	7·3
2	134—136	69·0	6·9	7·1	$C_{11}H_{13}NO_2$	69·1	6·9	7·3
3	116—117	68·9	7·0	7·3	$C_{11}H_{13}NO_2$	69·1	6·9	7·3
4	121—122	70·2	6·9	6·9	$C_{12}H_{15}NO_2$	70·2	7·4	6·8
5	112—114	70·2	7·2	6·5	$C_{12}H_{15}NO_2$	70·2	7·4	6·8

[a] Ref. 7. [b] M. D. Soffer, J. C. Cavagnol, and H. E. Gellerson, *J. Amer. Chem. Soc.*, 1949, **71**, 3857. [c] See Table 1, footnote (*c*). [d] Solid at room temperature. [e] 2,4-*Dinitrophenylhydrazone*, m. p. 182—184° (Found: C, 58·2; H, 4·9; N, 15·5. $C_{18}H_{18}N_4O_5$ requires C, 58·4; H, 4·9; N, 15·1%). [f] Product contaminated with *ca.* 5% phenolic material. [g] 2,4-*Dinitrophenylhydrazone*, m. p. 169—170° (Found: C, 59·6; H, 5·3; N, 15·0. $C_{19}H_{20}N_4O_5$ requires C, 59·4; H, 5·2; N, 14·6%). [h] 2,4-*Dinitrophenylhydrazone*, m. p. 161—162° (Found: C, 59·7; H, 5·2; N, 15·0%). [i] 2,4-*Dinitrophenylhydrazone*, m. p. 142—143° (Found: C, 60·5; H, 5·6; N, 13·7. $C_{20}H_{22}N_4O_5$ requires C, 60·3; H, 5·6; N, 14·1%).

TABLE 3

Alkoxy-1,2,3,4-tetrahydro-2-naphthylamines (VIII) and *N*-acyl intermediates

R^1	R^2	R^3	B. p./mm.	Method	M. p. of hydrochloride	Found (%) [a] C	Found (%) [a] H	Found (%) [a] N	Formula	Required (%) C	Required (%) H	Required (%) N
5-Me	H	H	126—128°/2·0	A	258—260° [b]	61·8	7·6	6·1	$C_{11}H_{15}NO$,HCl	61·8	7·5	6·6
5-Me	H	Me	118—123/0·8	D	—	75·1	9·0	7·2	$C_{12}H_{17}NO$	75·3	9·0	7·3
5-Me	Me	Me	110—112/0·4	C	208—210	64·8	8·6	5·9	$C_{13}H_{19}NO$,HCl	64·6	8·3	5·8
5-Me	H	Et	124—127/1·1	D	236—240 [b]	64·4	8·6	6·0	$C_{13}H_{19}NO$,HCl	64·6	8·3	5·8
5-Me	Me	Ac	176—179/0·5	E	—	72·5	8·2	5·6	$C_{14}H_{19}NO_2$	72·1	8·2	6·0
5-Me	Me	Et	126—130/1·0	F	207—209 [b]	65·9	8·9	5·2	$C_{14}H_{21}NO$,HCl	65·8	8·6	5·5
5-Me	Et	Ac	182—188/0·8	E	—	73·0	8·2	5·1	$C_{15}H_{21}NO_2$	72·8	8·6	5·7
5-Me	Et	Et	133—137/0·7	F	200—202 [b]	66·4	8·7	5·1	$C_{15}H_{23}NO$,HCl	66·9	8·9	5·2
5-Me	H	Pr^n	122—125/0·5	D	243—248 [b]	65·5	8·9	5·8	$C_{14}H_{21}NO$,HCl	65·8	8·6	5·5
5-Me	Me	COEt	*c*	E	—	72·9	8·7	5·5	$C_{15}H_{21}NO_2$	72·8	8·6	5·7
5-Me	Me	Pr^n	132—133/0·7	F	144—147	65·5	9·3	5·5	*d*	65·7	8·9	5·1
5-Me	COMe	Pr^n	160—162/0·3	E	—	73·3	8·9	5·4	$C_{16}H_{23}NO_2$	73·5	8·9	5·4
5-Me	Et	Pr^n	130—135/0·5	F	—	77·8	10·6	5·9	$C_{16}H_{25}NO$	77·7	10·2	5·7
5-Me	Pr^n	Pr^n	146—149/0·6	D	—	79·0	10·6	5·6	$C_{17}H_{27}NO$	78·1	10·4	5·4
5-Me	H	Pr^i	124—128/0·3	D	197—205	66·2	8·6	5·5	$C_{14}H_{21}NO$,HCl	65·8	8·6	5·5
5-Me	Me	Pr^i	233—236/0·4	B	—	77·0	9·5	5·5	$C_{15}H_{23}NO$	77·2	9·9	6·0
5-Me	Ac	Pr^i	156—160/0·6	E	—	72·9	8·9	5·7	$C_{16}H_{23}NO_2$	73·5	8·9	5·4
5-Me	Et	Pr^i	132—140/0·6	F	175—180	65·0	9·4	4·5	*e*	64·7	9·3	4·7
5-Me	H	Bu^n	138—144/0·7	D	201—204 [b]	67·2	8·8	5·2	$C_{15}H_{23}NO$,HCl	66·9	8·9	5·2
5-Me	Me	COPr^n	182—186/0·5	E	—	73·7	9·1	5·0	$C_{16}H_{23}NO_2$	73·5	8·9	5·4
5-Me	Pr^i	COEt	180—182/0·6	E	—	73·9	9·0	4·8	$C_{17}H_{25}NO_2$	74·1	9·1	5·1
5-Me	Pr^i	COPr^n	182—190/1·1	E	—	75·2	9·0	4·6	$C_{18}H_{27}NO_2$	74·7	9·4	4·8
5-Me	Pr^i	Bu^n	149—156/0·6	F	173—175	67·8	9·5	4·4	*f*	67·4	9·7	4·4
5-Me	Bu^n	Bu^n	158—164/0·5	D	—	79·2	10·6	4·9	$C_{19}H_{31}NO$	78·8	10·8	4·8
5-Et	H	H	114—116/0·7	A	192—193	62·9	8·1	5·8	$C_{12}H_{17}NO$,HCl	63·3	7·9	6·2
7-Me	H	H	109—113/0·6 [g]	A	213—214 [b]	61·8	7·5	6·7	$C_{11}H_{15}NO$,HCl	61·8	7·5	6·6
8-Me	H	H	110—112/0·8 [g]	A	273—275 [b]	62·1	7·7	6·6	$C_{11}H_{15}NO$,HCl	61·8	7·5	6·6
8-Me	H	Me	115—117/0·9	D	143—144	63·7	8·0	5·8	$C_{12}H_{17}NO$,HCl	63·3	7·9	6·2
8-Me	Me	Me	113—115/0·7	D	242—243	64·2	8·5	5·9	$C_{13}H_{19}NO$,HCl	64·6	8·3	5·8
8-Me	H	Et	112—114/0·6	D	232—233	64·8	8·4	6·2	$C_{13}H_{19}NO$,HCl	64·6	8·3	5·8
8-Me	Me	Ac	158—161/0·2	E	—	72·5	8·4	5·7	$C_{14}H_{19}NO_2$	72·1	8·2	6·0
8-Me	Me	Et	113—115/0·3	F	172—174	65·4	8·6	6·0	$C_{14}H_{21}NO$,HCl	65·8	8·6	5·5

TABLE 3 (*Continued*)

R¹	R²	R³	B. p./mm.	Method	M. p. of hydrochloride	Found (%) [a] C	H	N	Formula	Required (%) C	H	N
8-Me	Et	Et	115—117/0·6	D	—	76·7	9·9	5·7	$C_{15}H_{23}NO$	77·2	9·9	6·0
8-Me	H	Pr^n	112—114/0·2	D	189—190	65·9	8·7	5·5	$C_{14}H_{21}NO,HCl$	65·8	8·6	5·5
8-Me	Me	COEt	153—155/0·1	E	—	72·6	8·6	5·7	$C_{15}H_{21}NO_2$	72·8	8·6	5·7
8-Me	Me	Pr^n	127—128/0·5	F	180—182	66·7	8·8	4·9	$C_{15}H_{23}NO,HCl$	66·8	9·0	5·2
8-Me	Ac	Pr^n	154—158/0·1	E	—	73·3	8·8	5·0	$C_{16}H_{23}NO_2$	73·5	8·9	5·4
8-Me	Et	Pr^n	130—132/0·5	F	—	77·7	10·4	5·9	$C_{16}H_{25}NO$	77·7	10·2	5·7
8-Me	Pr^n	COEt	160—162/0·1	E	—	74·4	9·1	4·5	$C_{17}H_{25}NO_2$	74·1	9·2	5·1
8-Me	Pr^n	Pr^n	128—131/0·3	F	—	78·1	10·3	5·2	$C_{17}H_{27}NO$	78·1	10·4	5·4
8-Me	H	Pr^i	122—126/0·3	D	242—244	65·3	8·4	5·6	$C_{14}H_{21}NO,HCl$	65·8	8·6	5·5
8-Me	Me	Pr^i	126—128/0·4	B	—	76·9	9·8	5·8	$C_{15}H_{23}NO$	77·2	9·9	6·0
8-Me	Ac	Pr^i	182—185/0·8	E	—	73·3	8·8	5·2	$C_{16}H_{23}NO_2$	73·5	8·9	5·4
8-Me	H	Bu^n	128—135/0·5	D	190—192	66·6	8·9	5·2	$C_{15}H_{23}NO,HCl$	66·8	9·0	5·2
8-Me	Me	COPr^n	156—158/0·1	E	—	73·2	8·6	5·0	$C_{16}H_{23}NO_2$	73·5	8·9	5·4
8-Me	Ac	Bu^n	176—178/0·6	E	—	74·4	9·3	5·3	$C_{17}H_{25}NO_2$	74·1	9·2	5·1
8-Me	Et	Bu^n	137—139/0·6	F	—	78·1	10·4	5·4	$C_{17}H_{27}NO$	78·5	10·5	5·1
8-Me	COEt	Bu^n	179—181/0·6	E	—	74·5	9·5	4·8	$C_{18}H_{27}NO_2$	74·7	9·4	4·8
8-Me	Pr^n	Bu^n	141—143/0·6	F	—	78·6	11·0	4·9	$C_{18}H_{29}NO$	78·5	10·6	4·9
8-Me	COPr^n	Bu^n	180—183/0·6	E	—	75·1	9·5	4·4	$C_{19}H_{29}NO_2$	75·2	9·6	4·6
8-Me	Bu^n	Bu^n	136—139/0·2	F	—	78·9	10·4	4·5	$C_{19}H_{31}NO$	78·8	10·8	4·8
8-Et	H	H	116—118/0·5	A	237—239	62·9	8·3	6·1	$C_{12}H_{17}NO,HCl$	63·3	8·0	6·2
8-Et	H	Me	113—115/0·7	D	194—196	63·0	8·6	5·9	*h*	63·5	8·3	5·7
8-Et	Me	Me	132—138/1·5	D	195	66·0	8·5	5·5	$C_{14}H_{21}NO,HCl$	65·8	8·7	5·5
8-Pr^n	H	Me	127—129/0·3	D	199—202	66·0	8·6	5·3	$C_{14}H_{21}NO,HCl$	65·8	8·7	5·5
8-Pr^n	Me	Me	127—128/0·4	D	143—144	66·5	8·8	4·9	$C_{15}H_{23}NO,HCl$	66·8	9·0	5·2
8-Pr^i	H	Me	120—122/0·7	D	198—202	65·4	8·3	5·4	$C_{14}H_{21}NO,HCl$	65·8	8·7	5·5
8-Pr^i	Me	Me	127—129/0·8	D	177—179	66·3	8·9	5·0	$C_{15}H_{23}NO,HCl$	66·8	9·0	5·2
8-Bu^n	H	Me	—	D	168—169	66·3	8·9	5·1	$C_{15}H_{23}NO,HCl$	66·8	8·9	5·2
8-Bu^n	Me	Me	—	D	177—178	68·1	9·4	5·0	$C_{16}H_{25}NO,HCl$	67·7	9·2	4·9
8-Bu^i	H	Me	—	D	200—202	66·5	9·1	5·6	$C_{15}H_{23}NO,HCl$	66·8	8·9	5·2
8-Bu^i	Me	Me	124—126/0·4	D	181—182	66·7	9·2	4·8	$C_{16}H_{25}NO,HCl$	67·7	9·2	4·9
8-Bu^s	H	Me	119—122/0·2	D	181—183	66·7	8·9	5·0	$C_{15}H_{23}NO,HCl$	66·8	8·9	5·2
8-Bu^s	Me	Me	123—126/0·3	D	—	78·0	10·0	5·7	$C_{16}H_{25}NO$	77·7	10·2	5·7

[a] Analyses are given for the hydrochloride if obtained crystalline; otherwise the analytical figures for the free bases are given. [b] Melted with decomposition. [c] M. p. 76—78° (from ethanol). [d] $C_{15}H_{23}NO,HCl,\frac{1}{4}H_2O$. [e] $C_{16}H_{25}NO,HCl,\frac{3}{4}H_2O$. [f] $C_{18}H_{29}NO,HCl,\frac{1}{2}H_2O$. [g] Solid at room temperature. [h] $C_{13}H_{19}NO,HCl,\frac{1}{4}H_2O$.

was hydrogenated at *ca.* 50°. Evaporation of the filtered solution afforded the crude product which was freed from non-basic material in the normal manner. The purified base was distilled *in vacuo* and/or converted into its hydrochloride. Yields ranged from 64 to 75%.

Method B. 5-Ethoxy-1,2,3,4-tetrahydro-2-naphthylamine (4·8 g.) and AnalaR 36% formaldehyde solution (4·2 ml.) were used at 0°. Formic acid (100%; 2·4 g.) was added after 10 min. and the mixture refluxed for 7 hr. The cooled solution was basified with N-sodium hydroxide solution and the amine isolated with ether. Distillation *in vacuo* gave the NN-*dimethylamine* (4·4 g.).

The same procedure was used to *N*-methylate 1,2,3,4-tetrahydro-*N*-isopropyl-5- and 8-methoxynaphthylamines except that only one equivalent of formaldehyde and formic acid was used for these compounds.

Method C. 1,2,3,4-Tetrahydro-5-methoxy-2-naphthylamine (6·0 g.) and 7% formaldehyde solution in ethanol (50 ml.) were hydrogenated at *ca.* 50° over 10% palladium–charcoal (1·0 g.). Filtration and evaporation of the solvent gave an oil which was dissolved in ether (50 ml.). The solution was washed with N-sodium hydroxide solution and then water, and the dried (Na_2SO_4) organic layer was distilled to give NN-*dimethyl*-1,2,3,4-*tetrahydro*-5-*methoxy*-2-*naphthylamine* (5·1 g., 73%).

Method D. A mixture of the alkoxy-2-tetralone (0·5 mol.), primary or secondary amine (1·5 mol.), ethanol (100 ml.), and platinum oxide (0·1 g.) was hydrogenated at *ca.* 50°. The product was isolated as in method A. Yields ranged from *ca.* 80% (with the primary amines) to 20% (with di-n-butylamine).

Method E. The acid anhydride (0·11 mol.) was added to the *N*-alkylated alkoxy-1,2,3,4-tetrahydro-2-naphthylamine (IX) (0·05 mol.), in AnalaR pyridine (30 ml.), and the solution was refluxed gently for 3 hr. The cooled solution was poured on to crushed ice and the crude

product isolated with chloroform. Distillation furnished the required *N*-acyl-*N*-alkylamine in yields of 68—90%.

Method F. The above *N*-acyl compound (0·05 mol.), in benzene (75 ml.) ,was added carefully to a stirred suspension of lithium aluminium hydride (0·1 mol.) in ether (300 ml.). The mixture was stirred under reflux for 12 hr., cooled, and the excess of hydride decomposed by addition of wet ether and then water (200 ml.). The organic layer was separated and the aqueous layer extracted with ether (2 × 100 ml.). The combined organic layers were washed with water, dried (Na_2SO_4), and distilled to give the alkoxy-*NN*-dialkyl-1,2,3,4-tetrahydro-2-naphthylamine in 59—79% yields.

2-*Acetamido*-6-*methoxynaphthalene*.—This was prepared by the method of Robinson and Rydon.[8] 2-Methoxynaphthalene (128 g.) and acetyl chloride (80 g.) gave 2-acetyl-6-methoxynaphthalene (102 g.), b. p. 170—178°/0·7 mm. The oxime (100 g.), m. p. 170—172°, was rearranged, in 20 g. batches, to the required amide (64 g.), m. p. 161—163°.

2-*Amino*-6-*methoxynaphthalene Hydrochloride*.—2-Acetamido-6-methoxynaphthalene (20 g.), methanol (100 ml.), and a saturated solution of methanolic hydrogen chloride (100 ml.) were stirred under nitrogen for 24 hr. at room temperature. Most of the methanol was removed under reduced pressure (bath <35°), and anhydrous ether (100 ml.) was added to precipitate the hydrochloride (12·5 g.) which was recrystallised from methanol–ether. The crystals decomposed above 217° and finally melted at 246—250° (lit.,[9] 181°) (Found: C, 62·9; H, 5·7; Cl, 16·5. Calc. for $C_{11}H_{12}ClNO$: C, 63·0; H, 5·7; Cl, 16·9%).

1,2,3,4-*Tetrahydro*-6-*methoxy*-2-*naphthylamine Hydrochloride*.—The above hydrochloride (12·5 g.) was converted into the free base and the product dissolved in pentan-1-ol (300 ml.). The solution was added to sodium (30 g.) and the mixture refluxed until the metal had all reacted. 6N-Hydrochloric acid (1 l.) was added to the cooled reaction mixture and the pentanol removed by steam-distillation. The residual aqueous solution was basified by the addition of concentrated ammonium hydroxide solution and the products isolated with ether (4 × 250 ml.). The yellow solid, precipitated when carbon dioxide was passed through the concentrated (250 ml.) organic layer,[9] was collected and heated with 2N-hydrochloric acid (100 ml.) at 100° for 15 min. The acid solution was evaporated to dryness under reduced pressure and the residue crystallised from concentrated hydrochloric acid. The *hydrochloride* (1·3 g.) decomposed above 190° and finally melted at 243—246° (Found: C, 62·0; H, 7·6; Cl, 16·9; N, 6·7. $C_{11}H_{16}ClNO$ requires C, 61·8; H, 7·5; Cl, 16·6; N, 6·6%).

1,2,3,4-*Tetrahydro*-6-*methoxy*-NN-*dimethyl*-2-*naphthylamine Hydrochloride*.—The free base was liberated from the above hydrochloride (1·2 g.) in the normal manner. Condensation with formaldehyde and reduction with formic acid as in method C gave the crude *NN*-dimethyl base as a yellow gum. The *hydrochloride* (0·8 g.) had m. p. 210—212° (from methanol–ether) (Found: C, 62·4; H, 8·3; Cl, 14·3; N, 5·4. $C_{13}H_{20}ClNO,\frac{1}{2}H_2O$ requires C, 62·2; H, 8·4; Cl, 14·2; N, 5·6%).

5-*Methoxy*-1,1-*dimethyl*-2-*tetralone*.—5-Methoxy-2-tetralone (27 g.) gave the 1,1-dimethyl compound (19·9 g.), b. p. 87—92°/0·1 mm., by treatment with methyl iodide and sodium isopropoxide in propan-2-ol.[7] The *oxime* was obtained as white crystals, m. p. 111—112° (from methanol) (Found: C, 70·9; H, 8·0; N, 6·0. $C_{13}H_{17}NO_2$ requires C, 71·2; H, 7·8; N, 6·4%).

1,2,3,4-*Tetrahydro*-5-*methoxy*-1,1-*dimethyl*-2-*naphthylamine Hydrochloride*.—Ammonium hydroxide solution (*d* 0·88; 10 ml.) and Raney nickel W7 (*ca.* 1 g.) were added to the above oxime (10·0 g.), in ethanol (120 ml.), and the mixture was hydrogenated at *ca.* 50°. The crude base was isolated as in method A and converted into the *hydrochloride* which separated from methanol–ethyl acetate as cubes (4·4 g.), m. p. 251—253° (Found: C, 64·5; H, 8·7; Cl, 15·1; N, 5·7. $C_{13}H_{20}ClNO$ requires C, 64·6; H, 8·3; Cl, 14·7; N, 5·8%).

1,2,3,4-*Tetrahydro*-5-*methoxy*-NN,1,1,*tetramethyl*-2-*naphthylamine Hydrochloride*.—The free base was liberated from the preceding hydrochloride. The amine (4·1 g.) and 7% formaldehyde in ethanol (50 ml.) were hydrogenated at *ca.* 50° over 10% palladium–charcoal (1·0 g.). The product isolated in the normal manner, was a low-melting solid. The *hydrochloride* (3·3 g.) had m. p. 266—268° (Found: C, 66·7; H, 9·0; Cl, 13·6; N, 4·9. $C_{15}H_{24}ClNO$ requires C, 66·8; H, 8·9; Cl, 13·2; N, 5·2%).

The authors are indebted to Dr. R. E. Bowman for helpful discussions and to Mr. F. H. Oliver for the microanalyses.

RESEARCH DEPARTMENT, PARKE DAVIS AND CO., LTD.,
STAINES ROAD, HOUNSLOW, MIDDLESEX.

[*Received, October 22nd,* 1964.]