SYNTHESIS OF ALKYL SUBSTITUTED 1-(ALKYLOXY-PHENYL)ETHYLAMINES

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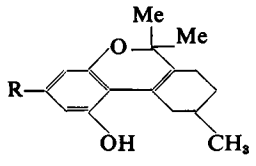
THE ability of synthetic tetrahydrocannabinols (I) to induce ataxia in dogs was markedly influenced by the nature of the alkyl side chain R[1]. A vague resemblance both in structure and pharmacology between morphine and tetrahydrocannabinol suggested that suitable alkyl substituents might favourably influence the analgesic activity of 1-(*p-cyclo*hexyloxyphenyl)-ethylamine[2]. Methyl, ethyl and *n*-propyl derivatives (III; R = Me, Et, Pr, IV; R = Pr) were readily obtained but attempts to synthesise III (R = *n*-amyl or *n*-hexyl) by various routes were unsuccessful. Among various failures it was noteworthy that the bromine



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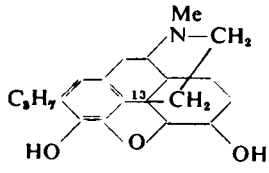

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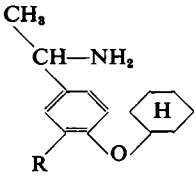

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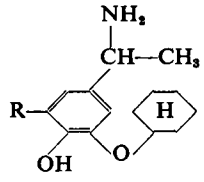
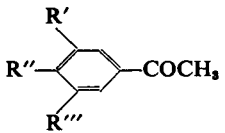


IV

of 4-bromo-2-*n*-hexylphenol was not replaceable by lithium, and its *cyclo*hexyl ether, unlike the 2-ethyl analogue, gave only traces of a Grignard reagent. *o-n*-Amylphenol, again unlike the ethyl analogue, could not be acetylated or chloracetylated in workable yield, apparently due to polymerisation.

III (R = Me, Et, or Pr) had increasing toxicity in mice as the alkyl chain was lengthened (LD50 approximately 80, 56 and 48 mg./kg. respectively) and while there was a noticeable increase in depressant activity, the analgesic action of the parent amine had disappeared. Conversely IV (R = Pr) had a short lived analgesic action at 3–5 mg./kg. intraperitoneally, a considerable increase in activity compared to the amine (IV; R = H). It was very toxic (LD50, 26 $\pm$ 2 mg./kg. intraperitoneally in mice). The corresponding *n*-hexyl ether was inactive. 2-*n*-propyldihydromorphine (II), like other morphine derivatives substituted in the benzene ring, was completely inactive.

TABLE I

OXIMES and 1-PHENYLETHYLAMINES DERIVED FROM SUBSTITUTED ACETOPHENONES 

			Oxime				1-Phenylethylamine hydrochloride								
									Found per cent.			Required per cent.		
R′	R″	R‴	Formula	M.pt. °C.	Found per cent. N	Required per cent. N	Formula	M.pt. °C.	C	H	N	C	H	N
OC_6H_{11}(i)	OH	C_3H_5(iii)	$C_{17}H_{23}O_2N$	107	4·7	4·8	$C_{17}H_{24}O_2NCl$(v)	175	65·1	8·4	4·4	65·1	8·9	4·5
OC_6H_{13}(ii)	OH	C_3H_5(iii)	$C_{17}H_{25}O_2N$	85	—(iv)	—	$C_{17}H_{26}O_2NCl$(v)	148	64·5	9·3	4·3	64·7	9·5	4·4
H	OC_6H_{11}(i)	Me	$C_{15}H_{21}O_2N$	100	5·7	5·7	$C_{15}H_{24}ONCl$(vi)	202	66·8	8·8	5·5	66·9	8·9	5·2
H	OC_6H_{11}(i)	Et	$C_{16}H_{23}O_2N$	121	5·6	5·4	$C_{16}H_{26}ONCl$(vii)	226	67·3	9·2	5·0	67·7	9·2	4·9
H	OC_6H_{11}(i)	Pr^n	$C_{17}H_{25}O_2N$	114	5·2	5·1	$C_{17}H_{28}ONCl$	169	69·1	9·5	4·5	68·6	9·4	4·7

(i) C_6H_{11} = *cyclo*hexyl. (ii) C_6H_{13} = *n*-hexyl. (iii) C_3H_5 = allyl. (iv) Found: C, 70·1; H, 8·6. Required, C, 70·1; H, 8·6 per cent. (v) R‴ = *n*-propyl.
(vi) B.pt. of base, 140–145° C./1 mm. (vii) B. pt. of base, 150–160° C./2 mm.

EXPERIMENTAL

Amines (Table I) were all prepared by reduction of the corresponding acetophenone oximes by sodium amalgam and acetic acid in methanol. Cyclohexylations were by the method previously described[3]. Hydrogenations were at room temperature and pressure. Boiling ranges refer to air bath temperatures.

2-n-*Propyldihydromorphine.*—Morphine hydrochloride was hydrogenated on palladised charcoal in methanol to dihydromorphine (89 per cent.). The *allyl ether* crystallised from light petroleum (b.pt. 60–80° C.) in prisms, m.pt. 77–78° C.(48 per cent). Found: C, 73·3; H, 7·5; N, 4·2. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·6; N, 4·3 per cent. Rearrangement of this ether (1·1 g.) in boiling diethylaniline (45 minutes) gave an alkali soluble material (0·7 g.) which did not crystallise. It was hydrogenated on Raney nickel in methanol to 2-n-*propyldihydromorphine* (structure assigned from method of synthesis), prisms from light petroleum (b.pt. 60–80° C.) m.pt. 99° C. (95 per cent.). Found: C, 72·7; H, 8·3; N, 4·1. $C_{20}H_{27}O_3N$ requires C, 73·0; H, 8·2; N, 4·3 per cent.

4-Cyclo*hexyloxy*-3-*methylacetophenone.*—4-Hydroxy-3-methylacetophenone gave the *cyclo*hexyl ether, b.pt. 145–150° C./0·4 mm. (16 per cent.), characterised as the 2:4-*dinitrophenylhydrazone*, red needles from ethyl acetate-ethanol, m.pt. 181° C. Found: N, 13·4. $C_{21}H_{24}O_5N_4$ requires N, 13·6 per cent.

4-Cyclo*hexyloxy*-3-*ethylacetophenone.*—Reduction of 5-bromo-2-hydroxyacetophenone by the Huang-Minlon method[4] gave 4-bromo-2-ethylphenol, b.pt. 160–170° C./22 mm. (75 per cent.), characterised as the α-*naphthylurethane*, needles from benzene, m.pt. 140° C. (Found: C, 61·8; H, 4·4; N, 3·7. $C_{19}H_{16}O_2NBr$ requires C, 61·6; H, 4·3; N, 3·8 per cent.). The *cyclo*hexyl ether, b.pt. 210–212° C./16 mm. (3 per cent.). (Found: Br, 28·1. $C_{14}H_{19}OBr$ requires Br, 28·3 per cent.) was converted to the Grignard reagent and added to acetic anhydride at − 70° C. to give 4-*cyclo*hexyloxy-3-ethylacetophenone, b.pt. 190–192° C./3 mm. The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m.pt. 152° C. Found: C, 61·6; H, 6·2; N, 13·2. $C_{22}H_{26}O_5N_4$ requires C, 62·0; H, 6·1; N, 13·2 per cent. The same ketone was obtained more conveniently by acetylation of *o*-ethylphenol. The product on fractional distillation gave 3-*ethyl*-4-*hydroxyacetophenone*, b.pt. 170–180° C./1 mm., m.pt. 95° C. (60 per cent., calc. on phenol reacting). Found: C, 73·1; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3 per cent. The *cyclo*hexyl ether gave the same 2:4-dinitrophenylhydrazone (mixed m.pt.) as the product from the first method.

4-Cyclo*hexyloxy*-3-n-*propylacetophenone.*—Hydrogenation of 3-allyl-4-hydroxyacetophenone[5] on palladised charcoal in ethanol gave 4-*hydroxy*-3-n-*propylacetophenone*, prisms from benzene-ethanol, m.pt. 89–90° C. (100 per cent.). Found: C, 73·8; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9 per cent. The *cyclo*hexyl ether, b.pt. 145–150° C./0·3 mm. (14 per cent.) was characterised as the 2:4-*dinitrophenylhydrazone*, red needles from ethyl acetate-ethanol, m.pt. 141° C. Found: C, 62·6; H, 6·1. $C_{23}H_{28}O_5N_4$ requires C, 62·7; H, 6·4 per cent.

3 - *Allyl*-5-cyclo*hexyloxy*-4-*hydroxyacetophenone*.—3-*cyclo*-Hexyloxy-4-hydroxyacetophenone[6] (2·3 g.) gave an allyl ether (not purified) which rearranged in boiling diethylaniline (1 hour) to the above *product*, b.pt. 170–180° C./0·6 mm. (1·85 g., 69 per cent.). It crystallised from light petroleum (b.pt. 80–100° C.) in needles m.pt. 58° C. Found: C, 74·3; H, 8·5. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·3 per cent.

3-*Allyl*-5-n-*hexyloxy*-4-*hydroxyacetophenone*.—4-Benzyloxy-3-hydroxy-acetophenone[6] gave the n-*hexyl ether*, plates from light petroleum (b.pt. 60–80° C.) m.pt. 74° C. (77 per cent.). Found: C, 77·3; H, 8·1. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0 per cent. Catalytic debenzylation on palladised charcoal gave 3-n-*hexyloxy*-4-*hydroxyacetophenone*, needles from light petroleum (b.pt. 60–80° C.), m.pt. 48° C. (89 per cent.). Found: C, 71·4; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5 per cent. The allyl ether (not purified) at 200° C. for 35 minutes gave the above *product*, b.pt. 175–180° C./0·9 mm. It crystallised from light petroleum (b.pt. 80–100° C.) and finally from ethanol, in needles, m.pt. 83° C. (47 per cent.). Found: C, 73·8; H, 8·8. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7 per cent.

2-*Bromo*-4-n-*hexylphenyl* cyclo*hexyl ether*.—*p*-Bromophenyl caproate, b.pt. 125–130° C./2 mm., in 5 g. quantities was treated with an equal weight of aluminium chloride in tetrachlorethane and then heated at 120°C. for 30 minutes to give 4-*bromo*-2-caproylphenol, b.pt. 145–150° C./1 mm. (86 per cent.). It crystallised from light petroleum (b.pt. 60–80° C.) in plates, m.pt.58–59° C. Found: C, 53·3; H, 5·6; Br, 29·1. $C_{12}H_{15}O_2$ Br requires C, 53·2; H, 5·5; Br, 29·5 per cent. The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange needles, m.pt. 206° C. Found: N, 12·1; Br, 17·2. $C_{18}H_{19}O_5N_4Br$ requires N, 12·4; Br, 17·7 per cent. Reduction with hydrazine gave 4-*bromo*-2-n-*hexylphenol*, b.pt. 125–145° C./1 mm. (86 per cent.), crystallised from light petroleum (b.pt. 80–100° C.) in needles m.pt. 52° C. Found: C, 56·3; H, 6·7; Br. 31·6. $C_{12}H_{17}OBr$ requires C, 56·0; H, 6·6; Br, 31·2 per cent. Carbonation of the product of reaction with lithium butyl (3 equivalents) gave only valeric acid and unchanged material. The *cyclo*hexyl ether, b.pt. 195–200° C./0·5 mm. (16 per cent.). Found: C, 63·9; H, 7·8; Br. 23·6. $C_{18}H_{27}OBr$ requires C, 63·7; H, 8·0; Br, 23·6 per cent.) slowly reacted with magnesium in boiling ether (dibutyl ether or phenetole had no advantage) whence reaction with acetic anhydride at — 70° C. gave a trace of ketone, isolated as the 2:4-dinitrophenylhydrazone. It could not be purified.

2-n-*Amyl*-4-*bromophenol*.—*p*-Bromophenyl valerate by similar methods to the above gave 4-bromo-2-valeroylphenol, b.pt. 120–121° C./1 mm. (45 per cent.). Found: C, 51·6; H, 5·0; Br, 31·3. $C_{11}H_{13}O_2Br$ requires C, 51·4; H, 5·1; Br, 31·1 per cent. The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red plates m.pt. 231° C. Found: N, 13·0; Br, 18·6. $C_{17}H_{17}O_5N_4Br$ requires N, 12·8; Br, 18·3 per cent. The above *product* crystallised from light petroleum (b.pt. 60–80° C.) in needles m.pt. 30° C. Found: C, 54·4; H, 6·0; Br, 32·7. $C_{11}H_{15}OBr$ requires C, 54·3; H, 6·2; Br, 32·9 per cent.

SUMMARY

1. The synthesis of alkyl substituted 1-(alkyloxyphenyl)ethylamines is described.

2. Introduction of alkyl groups into the benzene ring of 1-(*p-cyclo*-hexyloxyphenyl)ethylamine or dihydromorphine abolished their analgesic activity.

3. 1-(3-*cyclo*Hexyloxy-4-hydroxy-5-*n*-propylphenyl)ethylamine had analgesic activity in rats but was very toxic.

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