756. α-*Methylbenzylamines. Part II.** 3-cyclo*Hexyloxy*-4-*hydroxy*-α-*methylbenzylamine, Its Deoxy-derivative, and Related Ethers.*

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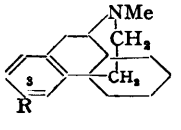
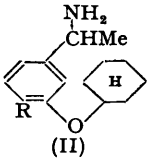
3-*cyclo*Hexyloxy-4-hydroxy-α-methylbenzylamine, 4-*cyclo*hexyloxy-3-hydroxy-α-methylbenzylamine, and ethers of *m*- and *p*-hydroxy-α-methylbenzylamine have been prepared by conventional methods for biological evaluation.

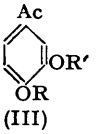
While investigating the influence of chemical structure on biological activity in the morphine group of alkaloids, Small *et al.* (" Studies on Drug Addiction," U.S. Public Health Suppl., 1938, No. 138) found that alkylation (" muzzling ") of the phenolic hydroxyl group in morphine and its derivatives practically always gave the same pharmacological results, irrespective of the nature of other changes in the morphine molecule. These effects were a reduction in most morphine-like activities including the analgesic potency, but usually an increase in toxicity and convulsant activity. Recently it has been found that the analgesic potency (of the order of morphine) of *N*-methylmorphinan (I; R = H) is markedly increased by introduction of hydroxyl at position 3 (Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 376; Zager, Sawtelle, Gross, Nagyfy, and Tidrick, *J. Lab. Clin. Med.*, 1949, **34**, 1530; Gross, Brotman, Nagyfy, Sawtelle, and Zager, *Fed. Proc.*, 1949, **8**, 297). The influence, on analgesic potency, of the position of the hydroxyl group is discussed by Grüssner and Schnider (*Helv. Chim. Acta*, 1949, **32**, 821). It appears that, so far as the morphine ring system is concerned, a suitably located phenolic hydroxyl potentiates the analgesic action. Though there is no reason to suppose that a similar effect would operate in other series of analgesics—thus, inclusion of a *m*-hydroxyl group in pethidine is reported to have no influence on analgesic potency (Macdonald, Woolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, 1946, **1**, 4)—it was desirable nevertheless to determine (*a*) whether demethylation of (II; R = OMe) would enhance the weak analgesic activity which had been detected in this substance (cf. McCoubrey, *J.*, 1951, 2931) and also reduce toxicity, and (*b*) whether the deoxy-derivative would have decreased or increased activity. The synthesis of suitable α-methylbenzylamines was therefore undertaken.



(I)



(II)



(III)

Treatment of 4-acetocatechol (III; R = R′ = H) with *cyclo*hexyl bromide and alkali gave only a poor yield of an easily separable mixture of 3-*cyclo*hexyloxy-4-hydroxy- and 4-*cyclo*hexyloxy-3-hydroxy-acetophenone: the reaction was largely inhibited by precipitation of the sodium salt of 4-acetocatechol. The desired product (III; R = H, R′ = *cyclo*hexyl) was only present in small proportion. The products were distinguished by methylation and comparison with the known 3-*cyclo*hexyloxy-4-methoxyacetophenone. The greater facility with which the *p*-hydroxyl group of 4-acetocatechol is etherified, which is in accordance with the expected electronic displacements, was also evident on monobenzylation since the major product proved to be 4-benzyloxy-3-hydroxyacetophenone (III; R = CH_2Ph, R′ = H), the structure of which was established by conversion into the *cyclo*hexyl ether followed by catalytic debenzylation to give 3-*cyclo*hexyloxy-4-hydroxyacetophenone, identical with that obtained directly from 4-acetocatechol. 3-*cyclo*Hexyloxy-4-hydroxy-α-methylbenzylamine and its 4-*cyclo*hexyloxy-3-hydroxy-isomer were readily obtained by reducing the corresponding acetophenone oximes. The corresponding deoxy-derivatives were similarly synthesised from the *cyclo*hexyl ethers of *m*- and *p*-acetylphenol.

A preliminary pharmacological examination indicated that whereas the phenol (II; R = OH) has approximately the same analgesic potency in rats as the methyl ether (II; R = OMe), the deoxy-derivative is more active. Also, *p*-*cyclo*hexyloxy-α-methylbenzylamine has a somewhat higher activity than its *m*-hydroxy-derivative. It was decided at this point, in view of the relative inaccessibility of *cyclo*hexyl ethers, to investigate the influence of the etherifying alkyl group on activity and to this end the *cyclo*pentyl, ethyl, *iso*propyl,

* Part I, *J.*, 1951, 2931.

n-amyl, *n*-hexyl, and *n*-octyl ethers were prepared from *p*-acetylphenol, and their oximes reduced to the corresponding α-methylbenzylamines. *p*-Phenoxy-α-methylbenzylamine (Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Amer. Chem. Soc.*, 1936, **58**, 1808) was also synthesised for comparison. Noteworthy activity was confined to the higher ethers, but the phenyl analogue proved to be almost inactive.

Most of these amine hydrochlorides show anomalous solubilities similar to those already noted by Ingersoll *et al.* (*loc. cit.*) and examined in 2-amino-*n*-octane by Mann (*J.*, 1944, 456; 1950, 3384).

Solubility in non-ionising solvents increases as the length of the alkyl chain is increased; lower members are easily soluble in benzene. The hydrochlorides of the amyl and hexyl ethers are not precipitated when hydrogen chloride is passed into a dry ethereal solution of the base although the solid hydrochlorides are not appreciably soluble in ether; the octyl ether hydrochloride, however, is easily soluble in ether and is readily soluble in warm light petroleum. The free bases, like α-methylbenzylamine and 2-phenylethylamine, readily absorb atmospheric carbon dioxide.

Experimental.

cyclo*Hexyl Ethers of* 4-*Acetocatechol*.—4-Acetocatechol (Stephen and Weizmann, *J.*, 1914, **105**, 1051) (60 g.) and *cyclo*hexyl bromide (160 g.) were refluxed in alcohol (200 c.c.) while sodium hydroxide (39·5 g.) in methanol (240 c.c.) was added during 50 hours. The sodium derivative of acetocatechol was deposited as a hard cake. The supernatant liquid was decanted and evaporated and the residue acidified. The precipitated oil was extracted with ether, and the extract washed with N-sodium hydroxide. The alkaline washings were acidified with 2N-hydrochloric acid, the phenols were shaken out with ether, and the extract was dried (K_2CO_3) and evaporated. The tarry residue (36·2 g.) was repeatedly extracted with boiling light petroleum (b. p. 80—100°) and the extracts were evaporated. The residual oil (12·8 g.) was dissolved in hot benzene (20 c.c.), and light petroleum (b. p. 80—100°) (15 c.c.) was added. On cooling, 4-cyclo*hexyloxy*-3-*hydroxyacetophenone* (A) (5·6 g.) was obtained which was recrystallised from benzene–light petroleum (b. p. 80—100°) in rosettes of needles, m. p. 103° (Found: C, 71·7; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The mother-liquors were evaporated and dissolved in 70% alcohol. On spontaneous evaporation two types of crystals were distinguished which were separated into (A), and long efflorescent prisms (3-cyclo*hexyloxy*-4-*hydroxyacetophenone*) (B). The latter crystallised from light petroleum (b. p. 80—100°) in long prisms, m. p. 88° (Found: C, 72·3; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The final yields were (A), 7·2 g., and (B), 1·5 g. It was subsequently found that separation of (A) and (B) could be effected by dissolution of the mixed phenols in warm N-sodium hydroxide and addition of an equal volume of 50% sodium hydroxide solution. On cooling, the solution set to a pasty mass which was filtered. The filtrate contained (A) and the residue was the sodium salt of (B).

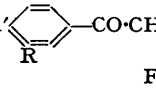
Methylation.—3-*cyclo*Hexyloxy-4-acetophenone (0·8 g.) in 10% sodium hydroxide solution (25 c.c.) at 50° was shaken with methyl sulphate (5 c.c.), added in 0·5-c.c. portions. The methyl ether (0·1 g.) crystallised from light petroleum (b. p. 60—80°) in white crystals, m. p. 60—61°, and gave a 2 : 4-dinitrophenylhydrazone, m. p. 191°. These were respectively identical by mixed m. p. with 3-*cyclo*hexyloxy-4-methoxyacetophenone and its 2 : 4-dinitrophenylhydrazone (McCoubrey, *loc. cit.*). Unchanged starting material (0·5 g.) was recovered.

4-*cyclo*Hexyloxy-3-hydroxyacetophenone (0·5 g.) similarly gave a methyl ether (0·5 g.), m. p. 86—87° [from benzene–light petroleum (b. p. 60—80°)]. Analysis of different samples did not give a satisfactory result (Found: C, 71·7, 71·6, 71·8; H, 7·9, 7·7, 8·2; OMe, 14·3. Calc. for $C_{15}H_{20}O_3$: C, 72·6; H, 8·1; OMe, 12·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m. p. 158° (Found: C, 58·9; H, 6·1; N, 13·3. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6; N, 13·1%).

Benzyl Ethers of 4-*Acetocatechol*.—Potassium hydroxide (7 g.) in aqueous methanol (50%; 50 c.c.) was added during 1 hour to a refluxing solution of 4-acetocatechol (19 g.) and benzyl chloride (15 c.c.) in alcohol (200 c.c.). Alcohols were evaporated and the residue was acidified. The precipitated oil was shaken out with ether, and the extract washed several times with N-sodium hydroxide and dried (K_2CO_3). Evaporation gave 3 : 4-*dibenzyloxyacetophenone* (1·9 g.) which crystallised from alcohol in needles, m. p. 89° (Found: C, 79·5; H, 6·4. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red plates, m. p. 184° (Found: N, 10·8. $C_{28}H_{24}O_6N_4$ requires N, 10·9%). The alkaline washings were acidified and the crystalline precipitate of 4-*benzyloxy*-3-*hydroxyacetophenone* recrystallised from alcohol in prisms (16 g.), m. p. 118° (Found: C, 74·6; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%).

4-*Benzyloxy*-3-cyclo*hexyloxyacetophenone*.—4-Benzyloxy-3-hydroxyacetophenone (23·5 g.) was converted into its *cyclo*hexyl ether as described for 4-acetocatechol. Unchanged material (17·2 g.) was recovered. 4-*Benzyloxy*-3-cyclo*hexyloxyacetophenone*, b. p. 210—215° (bath-temp.)/0·6 mm., crystallised from light petroleum (b. p. 60—80°) in needles (7·8 g.), m. p. 76—77° (Found: C, 77·4; H, 7·4. $C_{21}H_{24}O_3$ requires C, 77·8; H, 7·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m. p. 182° (Found: N, 11·1. $C_{27}H_{28}O_6N_4$ requires N, 11·1%).

4-Benzyloxy-3-*cyclo*hexyloxyacetophenone (13·5 g.) in alcohol (100 c.c.) was shaken with hydrogen in the presence of palladised charcoal (30%; 1 g.) at atmospheric pressure and room temperature, 960 c.c. of hydrogen being absorbed during 8 hours. The solution was filtered and evaporated. The residue crystallised from light petroleum (b. p. 80—100°) in prisms (8·0 g.), m. p. 88°, identical (mixed m. p.) with the product (B) obtained from 4-acetocatechol.

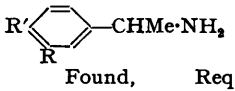
TABLE I. *Acetophenone derivatives* 

No.	R	R′	Yield, %	B. p./mm.	M. p.	Formula	Found, C, %	Found, H, %	Required, C, %	Required, H, %
1	H	O·C_6H_{11} [a]	23	145°/0·6	79°	$C_{14}H_{18}O_2$	76·9	7·9	77·1	8·3
2	OC_6H_{11} [a]	H	27	132—134°/0·8	—	$C_{14}H_{18}O_2$	—	—	—	—
3	H	O·C_5H_9 [c]	52	—	43	$C_{13}H_{16}O_2$	76·2	7·7	76·5	7·8
4	H	O·C_8H_{17}-*n*	64	215—222°/24	—	$C_{16}H_{24}O_2$	—	—	—	—
5	H	O·C_6H_{13}-*n*	48	190—195°/16 [d]	—	$C_{14}H_{20}O_2$	—	—	—	—
6	H	O·C_5H_{11}-*n*	69	181—183°/18	30	$C_{13}H_{18}O_2$	75·3	8·6	75·7	8·7
7	H	OPr^i	—	—	22	$C_{11}H_{14}O_2$	—	—	—	—
8	OPr^i	H	72	150°/13 [d]	—	$C_{11}H_{14}O_2$	—	—	—	—
9	OPr^i	OMe	80	165—166°/15	56	$C_{12}H_{16}O_3$	69·5	7·6	69·2	7·7
10	OPr^i	O·CH_2Ph	84	230—235°/8 [d]	62	$C_{18}H_{20}O_3$	76·1	7·3	76·1	7·0
11	OEt [b]	H	—	—	—	$C_{10}H_{12}O_2$	—	—	—	—

[a] C_6H_{11} = *cyclo*hexyl. [b] From ethylation of *p*-acetylphenol (Gatterman *et al.*, *Ber.*, 1890, **23**, 1199). [c] C_5H_9 = *cyclo*pentyl. [d] Bath-temp.

	Oxime						2 : 4-Dinitrophenylhydrazone		
		Found			Required			Found,	Reqd.,
No.	M. p.	C, %	H, %	N, %	C, %	H, %	N, %	M. p.	N, %	N, %
1	122°	71·6	8·0	6·1	72·1	8·2	6·0	—	—	—
2	84	72·1	8·1	5·8	72·1	8·2	6·0	167°	14·0 [e]	14·1
3	135	—	—	6·3	—	—	6·4	—	—	—
4	67	—	—	5·3	—	—	5·3	135	13·1	13·1
5	79	—	—	6·0	—	—	6·0	141	14·2	14·0
6	78	—	—	6·2	—	—	6·3	—	—	—
7	112	68·4	7·7	7·2	68·4	7·8	7·2	194	15·6	15·6
8	—	—	—	—	—	—	—	143	15·2 [f]	15·6
9	75	—	—	6·4	—	—	6·3	180	14·0	14·4
11	122	—	—	7·7	—	—	7·8	—	—	—

[e] Found: C, 60·7; H, 5·5. Reqd.: C, 60·3; H, 5·5%. Found: C, 56·4; H, 4·8. Reqd.: C, 57·0; H, 5·0%.

TABLE II. *Substituted α-methylbenzylamines* 

R	R′	Yield, %	B. p./mm.[c]	M. p. of hydrochloride	Formula	Found, C, %	Found, H, %	Found, N, %	Required, C, %	Required, H, %	Required, N, %	Solvent [h]
H	O·C_6H_{11} [a]	73	175—180°/16	180°	$C_{14}H_{21}ON$,HCl	65·4	8·5	5·5	65·8	8·6	5·5	B–P
O·C_6H_{11} [a]	H	85	150°/0·5	—	$C_{14}H_{21}ON$	76·1	9·9	6·1	76·7	9·6	6·4	—
H	O·C_5H_9 [b]	50	—	181	$C_{13}H_{19}ON$,HCl	64·9	8·4	5·4	64·6	8·3	5·8	B–E
H	O·C_8H_{17}-*n*	56	—	68—70	$C_{16}H_{27}ON$,HCl	66·9	9·6	4·6	67·2	9·8	4·9	P
H	O·C_6H_{13}-*n*	53	170—175°/20	88—89	$C_{14}H_{23}ON$,HCl	65·0	9·2	5·2	65·2	9·3	5·4	B–P
H	O·C_5H_{11}-*n*	91	170—175°/16	76—78	$C_{13}H_{21}ON$,HCl	64·1	8·8	5·6	64·1	9·2	5·8	B–P
OPr^i	H	78 [g]	145°/13	86	$C_{11}H_{17}ON$,HCl	61·2	8·4	6·5	60·7	8·3	6·6	B–P
OH	O·C_6H_{11} [a]	95	—	111 [d]	$C_{14}H_{21}O_2N$	70·8	9·1	—	71·4	9·0	—	B
				270	$C_{14}H_{21}O_2N$,HCl	62·1	8·3	5·2	61·9	8·1	5·2	A–Ac
OPr^i	OMe	80	—	166	$C_{12}H_{19}O_2N$,HCl	58·4	8·1	—	58·7	8·2	—	A–E
OH	O·C_6H_{11} [a]	76 [g]	—	258 [e]	$C_{14}H_{21}O_2N$,HCl	61·1	8·0	5·9	61·9	8·1	5·2	B–A
H	OPr^i	84	150—170°20	122	$C_{11}H_{17}ON$,HCl	60·7	8·3	6·5	61·2	8·4	6·5	B–P
OH	OPr^i	39 [g]	—	198 [f]	$C_{11}H_{17}O_2N$,HCl	58·0	7·7	5·8	57·0	7·8	6·0	B–A
H	OEt	76	200—205°/33	204	$C_{10}H_{15}ON$,HCl	59·6	8·0	7·0	59·6	7·9	6·9	B–A

[a] C_6H_{11} = *cyclo*hexyl. [b] C_5H_9 = *cyclo*pentyl. [c] Bath-temp. [d] M. p. of base. [e] Dried at 100°/10 mm. to remove benzene of crystallisation. Undried crystals have m. p. 175°, resolidify, and remelt at 252—258° (Found: C, 64·2; H, 7·7; N, 4·7; loss at 100°/10 mm., 8·3. $C_{14}H_{21}O_2N$,HCl,0·33C_6H_6 requires C, 64·5; H, 8·1; N, 4·7; loss, 8·7%). [f] Dried at 140°/10 mm. to remove benzene of crystallisation. Undried crystals have m. p. 198° (Found: C, 63·4; H, 7·7; N, 4·6; loss at 140°/10 mm., 13·4. $C_{11}H_{17}O_2N$,HCl,0·66C_6H_6 requires C, 63·5; H, 7·7; N, 4·9; loss, 13·4%). [g] Calc. on ketone used. [h] A = alcohol; Ac = acetone; B = benzene; E = ether; P = light petroleum (b. p. 60—80°).

p-*Acetylphenol*.—This was prepared in 48% yield from phenol, acetic anhydride, and aluminium chloride (3 mols.) in carbon disulphide. von Auwers and Mauss (*Annalen*, 1928, **460**, 274) report a 70% yield for a similar method using acetyl chloride.

Various Etherifications.—Various *ethers* prepared are shown in Table I. *cyclo*Hexyl ethers were prepared by the method previously described. Other ethers were prepared by refluxing the phenol with two molecular proportions of alkyl bromide and addition of two molecular proportions of methanolic sodium hydroxide during 1 hour.

(±)-α-*Methylbenzylamines*.—The corresponding oximes were reduced in 90% methanol by addition of sodium amalgam (3%) and acetic acid in small portions. The amines, isolated in the usual manner, were converted into the hydrochlorides. The *amines* and *salts* prepared are listed in Table II.

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