STRUCTURAL REQUIREMENTS FOR ANALGESIC ACTIVITY IN ALKYLOXY-l-PHENYLETHYLAMINES AND SOME VIEWS ON ANALGESIC MECHANISM

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The complex pharmacological pattern characteristic of morphine, methadone and pethidine and their derivatives, suggests that these drugs have some common property when in contact with living tissues. The only readily discernible chemical similarity is possession of a phenylalkylamine unit of structure, a feature of a large number of drugs devoid of morphine-like properties. An attempt to trace the postulated common factor has been made by considering the structural requirements for morphine-like activity in 1-(*p-cyclo*hexyloxyphenyl)ethylamine[1], a substance more adaptable to systematic chemical studies than the better known therapeutic agents mentioned.

Experimental

Synthesis of materials.—New materials were prepared by conventional methods as follows. Boiling ranges refer to air bath temperatures.

p-cyclo*Hexyloxybenzylamine.*—*p-cyclo*Hexyloxybenzoic acid[2], converted to the acid chloride and treated with aqueous ammonia gave the *amide*, that crystallised from benzene m.pt. 148° C. (77 per cent.). Found: C, 72·2; H, 7·7; N, 5·9. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·8; N, 6·4 per cent. It was reduced by lithium aluminium hydride in boiling ether to give the above amine, b.pt. 130–140° C./2 mm. (80 per cent.). The *hydrochloride* crystallised from benzene-ethanol in prisms m.pt. 239° C. Found: C, 64·6; H, 8·5; N, 5·8. $C_{13}H_{19}ON$, HCl requires C, 64·6; H, 8·3; N, 5·8 per cent.

N - *Ethyl* - 1 - (p - cyclo*hexyloxyphenyl)ethylamine.*—1-(*p-cyclo*Hexyloxyphenyl)ethylamine gave the *acetamido derivative*, crystallised from light petroleum, m.pt. 85° C. (95 per cent.). Found: C, 73·3; H, 8·9; N, 5·4. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·9; N, 5·4 per cent. It was reduced by lithium aluminium hydride in ether to the above amine. The *hydrochloride* crystallised from benzene-light petroleum in prisms, m.pt. 161° C. (88 per cent.). Found: C, 68·0; H, 9·1; N, 5·1. $C_{16}H_{25}ON$, HCl requires C, 67·7; H, 9·2; N, 4·9 per cent.

1-(p-cyclo*Hexyloxyphenyl*) - n - *propylamine.*—Cyclohexylation[3] of *p* - hydroxypropiophenone gave p-cyclo*hexyloxypropiophenone*, needles from light petroleum, m.pt. 63° C. (19 per cent.). Found: C, 77·5; H, 8·5. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6 per cent. The *oxime*, needles from ethanol, m.pt. 115° C. (88 per cent. found: N, 5·8. $C_{15}H_{21}O_2N$ requires N, 5·7 per cent.) was reduced by sodium amalgam and acetic acid in methanol to the above amine, b.pt. 140–150° C./23 mm. (60 per cent.).

The *hydrochloride* crystallised from benzene-light petroleum in plates that fell to a powder when dried, m.pt. 167° C. Found: C, 66·5; H, 8·7; N, 5·2. $C_{15}H_{23}ON$, HCl requires C, 66·8; H, 8·9; N, 5·2 per cent.

NN-*Dimethyl*-1-(p-cyclo*hexyloxyphenyl*)*ethylamine*.—Prepared from 1-*p-cyclo*hexyloxyphenylethanol by treatment with phosphorus tribromide and reaction with dimethylamine. The amine b.pt. 180–185° C./16 mm. (48 per cent.) was converted to the *hydrochloride* and crystallised from benzene in prisms m.pt. 178° C. Found: C, 68·0; H, 9·2; N, 5·1. $C_{16}H_{25}ON$, HCl requires C, 67·7; H, 9·2; N, 4·9 per cent. The corresponding diethylamine could not be obtained as a crystalline derivative.

Assay.—Analgesic activity, taken as a measure of morphine-likeness, was sought by the method of D'Amour and Smith[4]. Groups of six albino rats, serving as their own controls received 1/10 to 1/5 of the approximate lethal dose for mice, and usually 20 mg./kg., intraperitoneally. The blacked tail tip was exposed to radiant heat and reaction times were measured before and at ten minute intervals for thirty minutes after the dose.

Results

The amines described above caused only small changes in reaction times, within $\pm$ 10 per cent. of the control values, e.g., after the propylamine (10 mg./kg.; approximate lethal dose in mice, 105 mg./kg.), the mean control value of 9·8 $\pm$ 1·2 seconds fell to 9·3 $\pm$ 2 seconds at ten minutes and returned to 9·8 $\pm$ 2 seconds at twenty minutes after the dose.

The molecule of 1-(*p-cyclo*hexyloxyphenyl)ethylamine can be considered in four sections (I). The above and previous results have shown that

(*a*) Mono or dialkylation (Me, Et) of the amino group, or acetylation, gave inactive materials.

(*b*) Replacement of the methyl group by hydrogen or ethyl abolished activity.

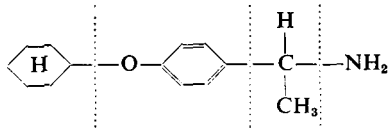
(*c*) Hydroxyl at position 3 reduced activity. Alkyl groups (Me, Et, Pr^n) at the same position abolished activity though depressant activity and toxicity increased.

(*d*) Only *cyclo*hexyl ethers were active. It had been shown however that moving the *cyclo*hexyl ether group to the 3 position had no influence on activity[1]. In summary, every feature of the molecule so far as examined, was essential for activity.

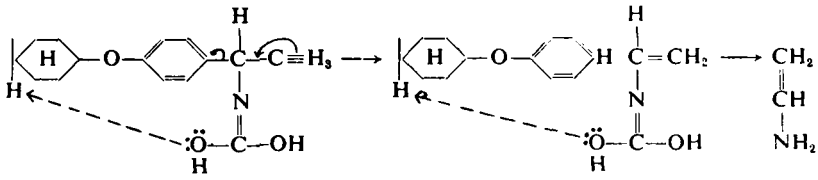
Discussion

Evidence had been obtained[5] that the carbamic acid derived from (I) in the presence of carbon dioxide or bicarbonate could enolise. Formation of this species (II) appeared to require a *cyclo*hexyl group and a primary amino group. Since both these groups have been found to be essential for analgesic activity in the series, it seems justifiable to assume that II may be an intermediate active molecular species. Enolisation could not be linked to the essential methyl group.

Both II and methadone (III) have a carbon atom, adjacent to a benzene



I



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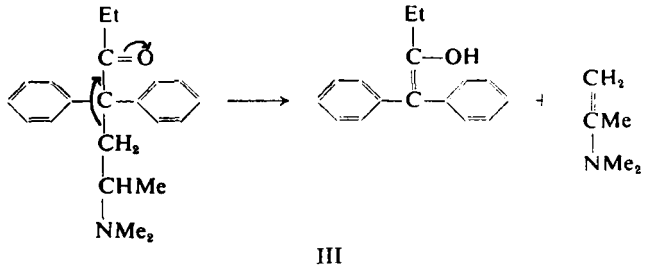
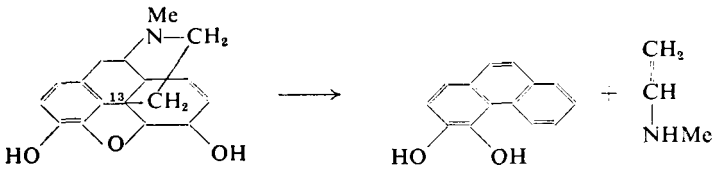
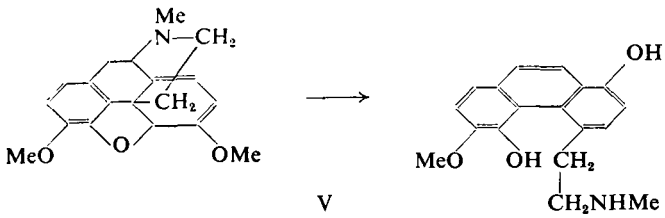


III



IV



V

nucleus, that occupies a central position in a system of unconjugated double bonds. In methadone a crossed conjugation can result if the alkamine chain be extruded as indicated. II can achieve a partial conjugation by similar electron transfer that cleaves the molecule to give a vinylamine, a process that requires both benzene nucleus and the methyl group. Removal of an ethanamine group from a benzene ring is known to occur during the oxidation of diiodotyrosine to thyroxine.

In morphine (IV), C(13) is probably under strain due to its position at the junction of four rings. The alkaloid is well known to extrude its

ethanamine chain under certain conditions, e.g., by heating with acetic anhydride, a process thought to be promoted by the drive towards conjugation (aromatisation) in the phenanthrene nucleus. Morphine can be regarded as a *gem*-substituted tetralin and extrusion of blocking groups during aromatisation can occur in this class of compound[6].

These three molecules appear to have a similarity in that an electron transfer around a carbon atom adjacent to a benzene nucleus can lead to extrusion of an ethanamine fragment to allow a fuller degree of conjugation in a system of double bonds. A similar consideration can apply to pethidine, e.g., if as seems likely, the piperidine ring is first cleaved to give products bearing analogy with methadone. Oxidative scission of piperidine derivatives is known to occur in animals[7]. The concept is difficult to apply to certain analgesics e.g., the dithienylbutenylamines, but it does offer a possible explanation for the inactivity of thebaine. Here, a major pathway of degradation (V), leads to thebenine. The initial process is probably the same as occurs with morphine, i.e., scission of the C(13)–C(15) bond, but the subsequent rearrangement gives a product that still retains the ethanamine chain.

The suggested degradations of II and III, perhaps foreign to concepts of organic chemistry, would be less surprising than some enzymically induced reactions. The stereospecificity of analgesic drugs and the proposals of Beckett[8] on overall shape of their molecules strongly suggest that an enzymic step is involved at some stage of analgesic mechanism.

Summary

1. Modification of the structure of 1-(*p-cyclo*hexyloxyphenyl)ethylamine resulted in considerable loss of analgesic activity.

2. It is suggested that analgesic activity is a property of molecules that are capable under biological conditions, of extruding a vinylamine. This can be derived from an ethanamine structure associated with a strained carbon atom adjacent to a benzene nucleus.

References

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6. Linstead and Thomas, *J. chem. Soc.*, 1940, 1127.
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DISCUSSION

The paper was presented by THE AUTHOR.

DR. A. H. BECKETT (London) criticised the author's hypotheses of the reaction at the "analgesic receptor surface" for the following reasons: (1) Consideration of molecular models showed that hydrogen bonding between the enol oxygen and the 4-axial hydrogen of the *cyclo*hexane ring could not occur as shown in structure II. (2) The theory stated that

the driving mechanism for extrusion of the ethanamine group was derived from increase in conjugation effected thereby, but that was not true for compound II. In compound III the enol form would not be stable, the carbonyl group would not attract electrons from the amine-ethyl chain as shown, and the chemical evidence always showed cleavage between the carbonyl group and the quaternary carbon atom. It was illogical to use chemical arguments and then state that the degradations under biological conditions were foreign to concepts of organic chemistry.

DR. W. MITCHELL (London) asked the author whether he was suggesting that the analgesic action of morphine and the other compounds he had discussed was caused, directly or indirectly, by the ethanamine. If that were so, he was presumably suggesting that the rest of the molecule, acted simply as a carrier of the fragment.

DR. N. J. HARPER (London) said that Dr. McCoubrey found it difficult to explain the activity of the dithienyl type of analgesic. If the postulate concerning the degradation of methadone were correct, how did he explain the activity of acetylmethadols and also other analgesics such as the reversed esters of pethidine? The author offered an explanation of the inactivity of thebaine, but he suggested that the unsaturation in thebaine compared with morphine or diamorphine, was such that the nitrogen ring was labelised, e.g., the reaction of cyanogen bromide on morphine resulted in demethylation while in thebaine there was cleavage of the nitrogen ring with addition of the elements of cyanogen bromide. It seemed possible that in the metabolic process there was cleavage of the nitrogen ring with the result that the cleaved product might not fit the receptor site thought to be involved in the analgesic process.

DR. G. BROWNLEE (London) said that thebaine has, in an exaggerated degree the same excitatory actions as morphine and maybe the same receptor. One liked to think that morphine fitted an analgesic receptor site rather well but this was only one of the actions of morphine.

DR. MCCOUBREY in reply said that models could only be regarded as an approximation and should not be taken too seriously. He agreed that the apparent enolisation arises by some obscure mechanism and he would have preferred to avoid mention of hydrogen bonds, the last ditch of the organic chemist in difficulties. He admitted a seeming inconsistancy in using chemical concepts while at the same time disowning them. There is no exact knowledge of the mechanism of enzyme degradation and analogies based on chemical principles serve only as guides. The main hypotheses refers to electron redistribution by an unknown mechanism around a benzyl carbon atom with associated bond cleavage. He had suggested a possible driving force for certain examples. Dr. Mitchell had anticipated him in mentioning a carrier molecule concept and he was studying the theoretical probabilities of this.