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Analgesics—I. 4-Acyloxy-3,4-Diphenyl-1-Methylpiperidines

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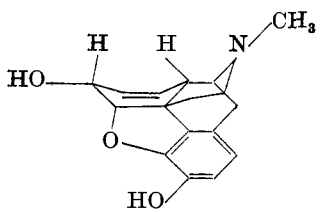
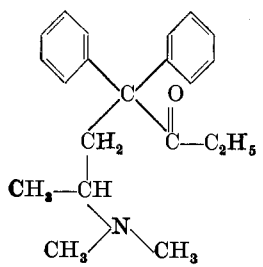
In morphine (I) there is a phenyl ring attached axially to the 4-position of a piperidine ring. A receptor site for analgesia has been proposed in which this structural element was used to map the receptor surface.[1] A diversity of strong analgesics are considered to be able to fit this receptor site including some, such as methadone (II), which have no piperidine ring. Beckett[2,3] and Gero[4] believe that methadone is positioned on the receptor surface through nitrogen–carbonyl interaction. There is some infrared and dissociation-constant evidence for this interaction in solution.[2]



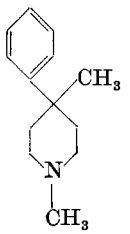
(I)



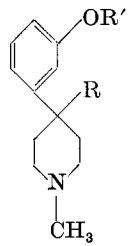
(II)

According to an older view, the carbonyl in methadone indirectly assists placement of the tertiary nitrogen by increasing binding at the quaternary centre. This is an extension of the observation that a carbonyl near the quaternary centre generally increases analgesia in structures which already contain a piperidine ring. For example, (III) has slight activity[5] whereas replacement of its quaternary methyl by $-\overset{\overset{O}{\|}}{C}-C_2H_5$, $-O-\overset{\overset{O}{\|}}{C}-C_2H_5$ and $-\overset{\overset{O}{\|}}{C}-O-C_2H_5$ leads to highly active and medically important

analgesics. It is true that the activity of (III) may be increased by modifications at positions other than the quaternary methyl. McElvain[6] prepared a series of compounds of class (IV) in which



(III)

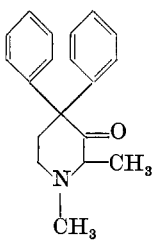


(IV)

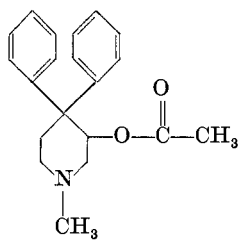
excellent analgesic potency could be obtained with aliphatic side chains in the order propyl > ethyl > methyl *provided that* a *meta*-hydroxyl or *meta*-methoxy was substituted in the phenyl ring.

We had occasion to review these speculations since we desired to cyclize analgesics of the methadone family with the hope of increasing potency and specificity. In one theory the carbonyl and nitrogen should be brought into close proximity by reducing some rotational possibilities, and in the other a piperidine ring should be constructed with provision for a carbonyl directed toward a secondary binding site. Both ideas were used in turn. In this paper, the latter speculation was used as guide, i.e. we shall describe the construction of a substituted piperidine ring from the elements of a methadone-related analgesic.

Some cyclizations of methadone (II) to form piperidine rings have already been accomplished. V was inactive[7] as was the acetylmethadol analogue (VI).[7] However, in these compounds the ketone arm of methadone has been incorporated into the

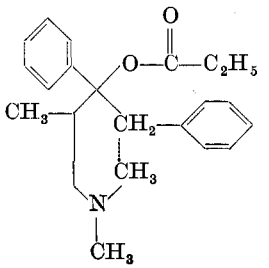


(V)

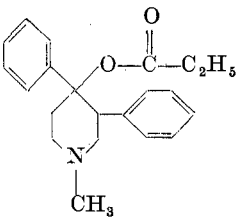


(VI)

piperidine ring. In fact, formation of a piperidine ring from methadone is impossible with retention of the ketone function at 4- and with the phenyl rings as substituents. This requirement can, however, be fulfilled with propoxyphene (VII)[8] by formation of the dotted bond as indicated. We were attracted by this possibility since propoxyphene has a low addiction liability.[9] If analgesia were obtained in such a meperidine 'reversed ester' skeleton, then potency and side effects might be easily altered by appropriate *N*-substitution on the piperidine ring.[10] For synthetic simplicity, we chose to make the reversed meperidine ester (VIII).



(VII)



(VIII)

Such compounds as (VIII) are made from 3-substituted-4-piperidones and these have been prepared many times previously.[11–14] Our flow sheet is given in Fig. 1. Literature procedures were used for the preparation of the starting materials, ethyl α-phenylacrylate[15] and ethyl β-methylaminopropionate.[16]

The addition of ethyl β-methylaminopropionate to ethyl α-phenylacrylate was possible at room temperature but not at elevated temperatures or pressures. A similar observation has been made by others[14] in the synthesis of prodine analogues. Phenyllithium added normally to 1-methyl-3-phenyl-4-piperidone without appreciable enolization of the carbonyl. The intermediate 4-piperidinols were not isolated since their acylations were accomplished most simply by direct reaction of the lithium salts with the anhydride. Alumina chromatography afforded two isomers of (VIII), α- and β-, in a ratio of roughly 7:1.

The stereochemical course of phenyllithium addition to 3-methyl-4-piperidone has been the subject of considerable

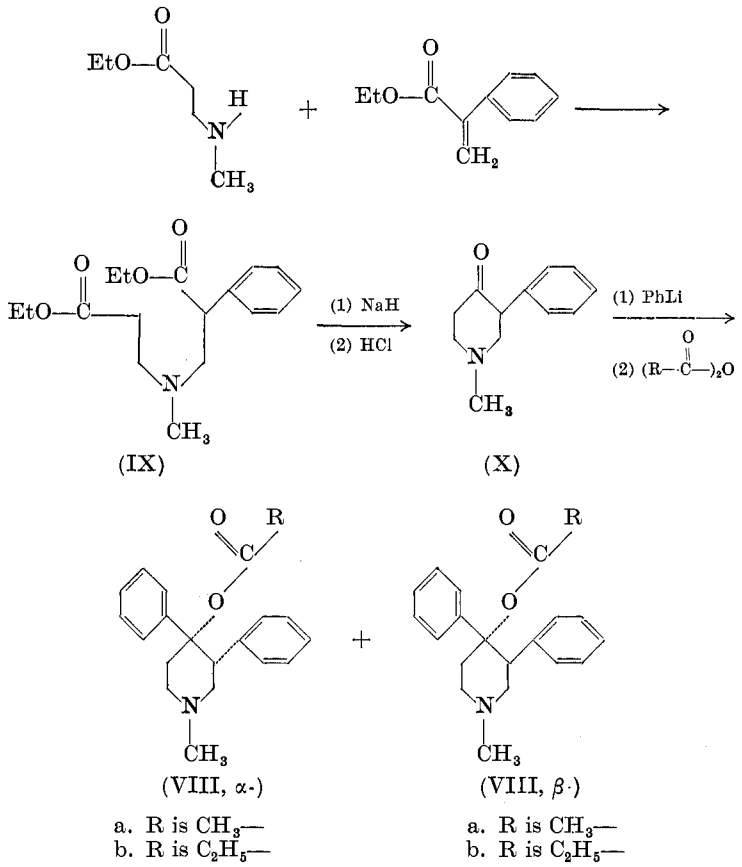
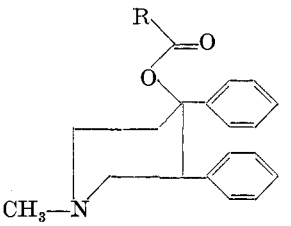


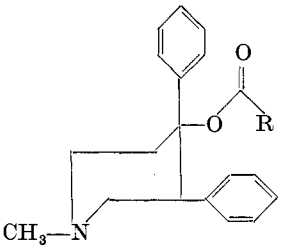
Fig. 1

discussion.[17] Finally, Ahmed *et al.*[18] used X-ray crystallography to show that in the dominant α-isomer, the 4-phenyl and 3-methyl are *trans*-diequatorial substituents on a chair conformation of the piperidine ring. The conformations of (VIII, α-) and (VIII, β-) are suggested below in analogy with these results.

A rat tail-flick test[22] was used for evaluation of (VIII, α-) and (VIII, β-) as acetates and propionates. *All of these compounds were inactive as analgesics.* These results strongly suggest that propoxyphene does not have a comparable geometry to either (VIII,



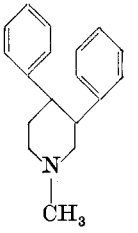
(VIII, α-)



(VIII, β-)

α-) or (VIII, β-) on the receptor surface. It is true that (VIII) lacks a methyl at position 5- of the piperidine ring. Thus, (VIII) is an analogue of a des-methyl propoxyphene whose analgesic potency may be rather low. Presumably the unsubstituted arm of the piperidine (VIII) must enter the 'analgesic trough'[1] and binding on this arm might benefit from methyl substitution in analogy with the prodines. However, the inactivity of (VIII) does not indicate that 5-methyl substitution will be profitable since the addition of a 5- or 6-methyl in the reversed esters of meperidine only increases potency by 3–8 times.[19]

A compound related to (VIII) is 1-methyl-3,4-diphenylpiperidine (XI). Like (VIII), this compound is devoid of analgesic properties and is a 'stimulant'.[20,21]



(XI)

In addition to phenyl, the list of 3-substituents in the reversed esters of meperidine includes methyl, ethyl, propyl, allyl, crotyl, butyl, hexyl and benzyl. Good activity has been reported through allyl, but reversed esters of meperidine with the higher substituents (including now phenyl) are either inactive or unreported.

Experimental

Methyl-(β-carboethoxyethyl)-(β-carboethoxy-β-phenethyl)-amine (IX). Ethyl α-phenylacrylate[15] (164 g, 0·928 moles) and ethyl β-methylaminopropionate[16] (134 g, 1·02 moles) were slowly combined with magnetic stirring and left at room temperature overnight. The heat of reaction produced an internal temperature of 36° for 5 h.

The crude reaction product was partitioned between ether and iced 2·5N HCl. The aqueous layer was separated and the ether was washed once again with dilute acid. The combined acid layers were made alkaline in the cold with 20 per cent sodium hydroxide. Several extractions with ether afforded the product, after drying and removal of solvent, as a mobile oil weighing 102 g. This was suitable for the next step without further purification. However, a portion was converted to an analytical sample, b.p. 120–123°/0·05 mm. Nuclear magnetic resonance, infrared and ultraviolet spectra were in agreement with the assigned structure (IX).

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66·42; H, 8·20; N, 4·56. Found: C, 66·49; H, 7·97; N, 4·54.

1-Methyl-3-phenyl-4-piperidone (X). A 52 per cent NaH emulsion in mineral oil (37 g) was carefully added to methyl-(β-carboethoxyethyl)-(β-carboethoxy-β-phenethyl)-amine (IX) (129 g, 0·42 moles) in azeotropically dried benzene (3600 ml). This mixture was stirred and refluxed for 7 h. It was then cooled and carefully extracted with a total of 3100 ml of 6N HCl. The combined acid extracts were then refluxed for 2·5 h, cooled, treated with excess sodium carbonate and extracted with ether. The dried ether layers were removed and the residue was fractionally distilled. Product weighing 40 g was collected, b.p. 98–99·5°/0·05 mm.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76·15; H, 7·99; N, 7·40. Found: C, 76·28; H, 7·80; N, 7·33.

3,4-Diphenyl-1-methyl-4-propionyloxypiperidine (VIIIb, α- and β-). Phenyllithium was prepared under nitrogen by the addition of bromobenzene (50 g, 0·32 moles) to lithium wire (4·42 g, 0·64 moles) in dry ether (150 ml). 1-Methyl-3-phenyl-4-piperidone (20 g, 0·11 moles) was then added in dry ether (150 ml) at a

rate sufficient to effect a gentle reflux. Upon complete addition, the solution was refluxed for an additional 2 h.

The reaction mixture was allowed to come to room temperature and propionic anhydride (104 g, 0·793 moles) was added dropwise with stirring. After 16 h at room temperature, the acylation was terminated by extraction with 2·5N NaOH. The ether layer was then extracted several times with 2·5N HCl and the product was liberated from this aqueous acid into ether with 20 per cent NaOH in the cold. Removal of the ether left a mixture of the α- and β-isomers of (VIII) which were separable on Merck alumina (slightly basic). The β-isomer was eluted first with benzene–ether (2:1) while the α-isomer was eluted with benzene-ether (1:1). The β-isomer from benzene had m.p. 75–76°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77·98; H, 7·79. Found: C, 78·18; H, 7·60.

Its hydrochloride from water had m.p. 118–122°.

The α-isomer as free base from benzene had m.p. 72·5–73·5°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77·98; H, 7·79. Found: C, 77·83; H, 8·02.

A hydrochloride was prepared which had m.p. 208–209° after several crystallizations from methyl ethyl ketone.

4-Acetoxy-3,4-diphenyl-1-methylpiperidine (VIIIa, α- and β-). The acetoxy derivatives of (VIII) were prepared in the same manner as the propionyloxy compounds except for the use of acetic anhydride in place of propionic anhydride. Once again a chromatographic separation of α- and β-isomers was possible on alumina. The β-isomer was eluted with benzene–ether (2:1) and the α-isomer with benzene–ether (1:2).

The α-isomer was crystallized from benzene as the free base, m.p. 119–119·5°.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77·64; H, 7·49. Found: C, 77·67; H, 7·40.

The β-isomer analysed as the hemihydrate of its hydrochloride salt, m.p. 143–144°. The recrystallization solvent was methyl ethyl ketone.

Anal. Calcd. for $C_{20}H_{24}ClNO_2 \cdot \frac{1}{2}H_2O$: C, 67·69; H, 6·82. Found: C, 67·62; H, 6·57.

Summary. The acetates and propionates of the *cis*- and *trans*-isomers

of 3,4-diphenyl-1-methyl-4-piperidinol are described. They are inactive as analgesics.

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