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# Analgesics—II. Compounds Related to 1-Acyloxy-1-benzyl-2-dimethylaminomethyl-1,2,3,4-tetrahydronaphthalene

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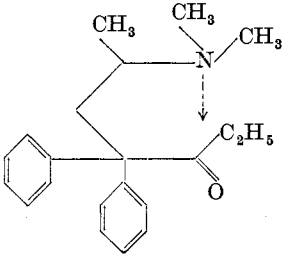
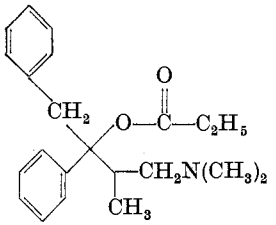
The first paper of this series reported the 'cyclization' of a methadone-related compound to a member of the meperidine-related class of analgesics. In this paper, we report some studies directed at utilization of the Beckett proposal[1, 2] that the analgesically important methadone conformation is characterized by nitrogen–carbonyl interaction. This hypothesis ascribes pseudo-piperidine ring geometry to methadone analgesics on the receptor surfaces through the assistance of the interaction shown in (I). If this idea is correct, then changes that maintain this geometry should



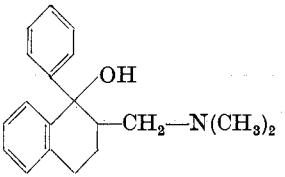

(I)

enhance potency. To fix this spatial relationship, one can imagine the construction of various bridges which one must then evaluate for compatibility with the analgesic site.

Once again we elected to apply these ideas to propoxyphene (II).[3] Some time ago Morrison[4, 5] reported that (III) afforded weak analgesia which was not increased by acylation. We speculated that (III) might be related to (II) and that compounds of class (IV) might be analgesics of the cyclized propoxyphene

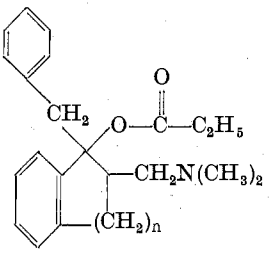


(II)

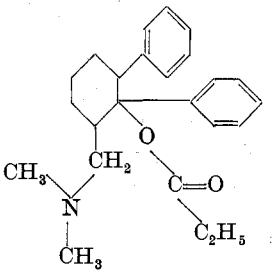


(III)

class. We were not able to examine the pharmacology of compounds such as (V) since we could not acylate the alcohol formed from phenyl Grignard addition to 2-dimethylaminomethyl-6-phenylcyclohexanone. Hori[6] has reported similar findings.



(IV)

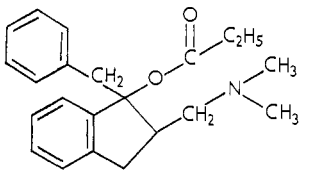


(V)

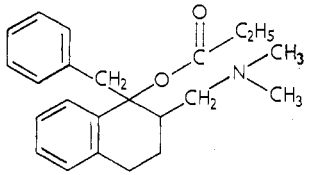
We first investigated the relative analgesic potencies of compounds of class (IV) with variations in the size and nature of the bridging element, as summarized in Fig. 1. Of these, compound (VII) had a subcutaneous potency which approximated α-propoxyphene and (VIII) was about 0·3–0·4 as active as (VII). Ring sizes of 5 and 7 members in compounds (VI) and (IX) reduced analgesic potency to less than 0·3 of (VII). In our tests, (III) was inactive at 128 mg/kg s.c. although (X) gave strong analgesia at this dose, equivalent to 1–2 mg of morphine. (Compound (VII) gave analgesia of this intensity at roughly 32 mg/kg s.c.)

These initial results prompted the synthesis of analogues of (VII) and (VIII) as recorded in Tables I and II respectively. The syntheses generally went quite smoothly and involved Grignard addition to the requisite Mannich ketone followed by direct

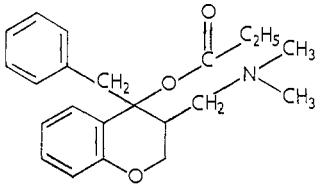
acylation of the magnesium complex. It was also possible to isolate the amino alcohol and acylate it separately either with an acyl chloride in an inert solvent or via the anhydride on the lithium salt.



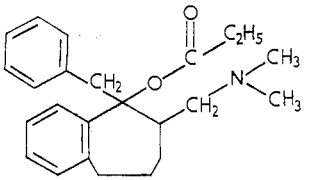
(VI)



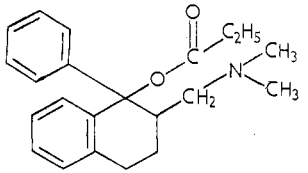
(VII)



(VIII)



(IX)

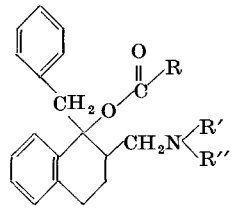


(X)

Fig. 1

The most potent of these compounds was 1-acetoxy-1-benzyl-2-dimethylaminomethyl-1,2,3,4-tetrahydronaphthalene hydrochloride which approached morphine in subcutaneous injection potency. Similar enhancement has also been reported in the propoxyphene series[7] following the replacement of the propionyloxy by the acetoxy group. A further parallel with this series is the lack of utility of morpholino-, methyl-phenethylamino-, or methyl-allylamino-substitution in place of the dimethylamino-function. This statement should be taken with

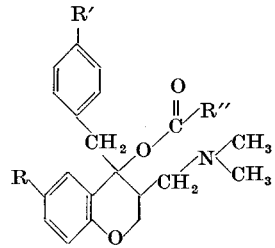
Table I. Esters of 1-benzyl-2-dialkylaminomethyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene



| R | R′ | R″ | m.p., °C HCl | Molecular formula | Analysis, % | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calcd. | | | Found | | |
| | | | | | C | H | N | C | H | N |
| $CH_3$ | $CH_3$ | $CH_3$ | 178–180 | $C_{22}H_{28}ClNO_2$ | 70·66 | 7·55 | 3·75 | 70·94 | 7·74 | 3·97 |
| $C_2H_5$ | $CH_3$ | $CH_3$ | 183–184 | $C_{23}H_{30}ClNO_2$ | 71·21 | 7·80 | 3·61 | 71·12 | 7·65 | 3·56 |
| $C_2H_5$ | $CH_3$ | $CH_2$—CH=$CH_2$ | 114–116 | $C_{25}H_{32}ClNO_2$ | 72·53 | 7·79 | 3·38 | 72·87 | 7·83 | 3·45 |
| $C_2H_5$ | —N(R′)(R″) =N O | | 194 | $C_{25}H_{32}NO_3Cl$ | 69·83 | 7·50 | 3·26 | 70·12 | 7·78 | 3·61 |
| $C_2H_5$ | $CH_3$ | $CH_2CH_2$—$C_6H_5$ | [a] | $C_{30}H_{35}O_2N$ | 81·59 | 7·99 | | 81·35 | 7·92 | |

[a] Analysis as oily free base.

Table II. Derivatives of 4-acyloxy-4-benzyl-3-dimethylamino-chroman




| R | R′ | R″ | m.p., °C HCl | Molecular formula | Analysis, % | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calcd. | | | Found | | |
| | | | | | C | H | N | C | H | N |
| H | H | $CH_3$ | 167–9 | $C_{21}H_{26}ClNO_3$ | 67·10 | 6·97 | | 67·18 | 7·19 | |
| H | H | $C_2H_5$ | 165–6 | $C_{22}H_{28}ClNO_3$ | 67·77 | 7·24 | | 67·77 | 7·07 | |
| $OCH_3$ | H | $C_2H_5$ | 169–170 | $C_{23}H_{30}ClNO_4$ | 65·78 | 7·20 | 3·34 | 65·44 | 7·10 | 3·25 |
| $CH_3$ | H | $C_2H_5$ | 176–7 | $C_{23}H_{30}ClNO_3$ | 68·39 | 7·49 | 3·47 | 68·62 | 7·44 | 3·59 |
| H | $OCH_3$ | $C_2H_5$ | 122–4[a] | $C_{25}H_{31}NO_8$ | 63·41 | 6·60 | | 63·00 | 6·62 | |

[a] m.p. and analysis as the hemioxalate.

slight reservation since only one isomer was isolated in our work and there is no proof of stereochemical unity throughout the series.

Unresolved 1-benzyl-2-dimethylaminomethyl-1-propionyloxy-1,2,3,4-tetrahydronaphthalene hydrochloride was equipotent with its uncyclized, *resolved* analogue, *α-d*-propoxyphene hydrochloride, but onset of tolerance was remarkably fast with the naphthalene derivative. Therefore, this particular fixed geometry raised potency at the expense of a secondary property.

## Experimental

*Mannich ketones.* Most of these ketones have been described previously. The exceptions have been characterized as described in the experimental below. The chroman amino-ketones were reported by Wiley,[8] 2-dimethylaminomethyl-1-indanone by Fry[9] and Hoffman,[10] and 2-dimethylaminomethyl-1-benzosuberone by Tarbell.[11] 2-Dimethylaminomethyl-1-tetralone was prepared by Mannich.[12]

*2-Morpholinomethyl-1-tetralone.* A solution of morpholine hydrochloride (37·6 g), 1-tetralone (46·6 g) and paraformaldehyde (19·5 g) in absolute ethanol (90 ml) was refluxed for 3 h. Several drops of ethanolic hydrogen chloride were used as a catalyst. The mixture was cooled in the refrigerator overnight and the crystalline product was removed by filtration. The yield of 2-morpholinomethyl-1-tetralone hydrochloride was 54 g, m.p. 153–154°. Further crystallization from ethanol raised the m.p. to 156–159°.

*Anal.* Calcd. for $C_{15}H_{20}ClNO_2$: C, 64·13; H, 7·18; N, 4·99. Found: C, 63·84; H, 7·08; N, 4·98.

*2-(N-Methyl-N-allyl)-aminomethyl-1-tetralone.* *N*-Methyl-allylamine hydrochloride was used in place of morpholine hydrochloride in the above procedure. Ether had to be added to the cooled solution to induce the separation of a semi-crystalline hydrochloride. The yield after crystallization from methanol–ethyl acetate was 10 per cent, m.p. 138–141°. Further crystallization raised the m.p. to 141–143°.

*Anal.* Calcd. for $C_{15}H_{20}ClNO$: N, 5·27. Found: N, 5·50.

*2-(N-Methyl-N-phenethyl)-aminomethyl-1-tetralone.* The use of of *N*-methyl-*N*-phenethylamine hydrochloride in the standard

Mannich conditions with 1-tetralone did not lead to a markedly crystalline hydrochloride, and therefore the crude reaction mixture was poured into water and extracted with ether. Removal of the dried solvent left an oil which was of satisfactory purity for use in the Grignard step despite some contamination with unreacted *N*-methyl-*N*-phenethylamine. The hemimaleate salt was crystallized from 2-propanol for analysis; m.p. 103–105°.

*Anal.* Calcd. for $C_{24}H_{27}NO_5$: C, 70·40; H, 6·65; N, 3·42. Found: C, 70·03; H, 6·67; N, 3·33.

*4-Benzyl-3-dimethylaminomethyl-4-propionyloxychroman hydrochloride.* The procedure for the preparation of this compound is representative of those used to prepare most of the compounds reported in Tables I and II. Several compounds were prepared by other routes and are separately recorded.

Benzylmagnesium chloride from benzyl chloride (39·5 g) and magnesium ribbon (10·2 g) was prepared in ether in a 1-litre 3-neck flask equipped with condenser and mechanical stirrer. The ether was then replaced by dry tetrahydrofuran (250 ml). 2-Dimethylaminomethyl-1-chromanone (18·0 g) freshly liberated from the hydrochloride was dissolved in tetrahydrofuran (25 ml). This solution was added dropwise to the stirred Grignard solution at 0°. The ice bath was then removed and stirring was continued at room temperature.

Acylation was accomplished after 4 h by the dropwise addition of propionic anhydride (81 ml) to the stirred Grignard reaction mixture. Sufficient heat was given off during this addition to maintain gentle refluxing. The reaction mixture, after being stirred overnight at room temperature, was poured into iced 2·5N NaOH and ether. The washed organic layer was dried and removed *in vacuo* at room temperature. A hydrochloride salt was precipitated from ether at 0° by the slow addition of HCl gas. The precipitate was rubbed with dry ether to remove excess HCl, and crystallized from acetone. The product was collected after thorough cooling and weighed 12·6 g, m.p. 165–166°.

*Anal.* Calcd. for $C_{22}H_{28}ClNO_3$: C, 67·77; H, 7·24. Found: C, 67·77; H, 7·07.

*5-Benzyl-6-dimethylaminomethyl-5-hydroxy-6,7,8,9-tetrahydro-5H-cycloheptabenzene hydrochloride.* The Grignard addition was conducted as in the preceding example. The Mannich ketone

was liberated from 2-dimethylaminomethyl-1-benzosuberone (21·0 g) and the benzylmagnesium chloride was prepared from magnesium (5·1 g) and benzyl chloride (21·5 g).

After 4 h of stirring at room temperature, the Grignard complex was decomposed with saturated ammonium chloride. Ether was used to wash the inorganic salts and the combined dried solvent was cooled at 0° and carefully treated with HCl gas until there was no more precipitate. After fifteen minutes at 0°, the solvent was decanted and the precipitate was washed several times with dry ether. Crystallization from ethanol–ether yielded 15·2 g of the amino alcohol, m.p. 231–233°. Two more crystallizations from ethanol afforded the analytical sample, m.p. 232–234°.

*Anal.* Calcd. for $C_{21}H_{28}ClNO$: C, 72·91; H, 8·16; N, 4·05. Found: C, 73·12; H, 7·90; N, 3·91.

*5-Benzyl-6-dimethylaminomethyl-5-propionyloxy-6,7,8,9-tetrahydro-5H-cycloheptabenzene hydrochloride.* The above amino alcohol hydrochloride (12 g) was converted to its free base with aqueous potassium carbonate. A dry solution of this base in methylene chloride (175 ml) was treated dropwise at 0° with propionyl chloride (3·52 g) in methylene chloride (25 ml). Stirring was continued at room temperature for 9 h. The solution was then shaken out with dilute iced potassium carbonate, dried, and evaporated at room temperature *in vacuo*. The product was taken up in petroleum ether, filtered, and crystallized by concentration. Several crystallizations from petroleum ether gave the free propionyloxy-amine, m.p. 97°.

*Anal.* Calcd. for $C_{24}H_{31}NO_2$: C, 78·86; H, 8·55; N, 3·84. Found: C, 78·70; H, 8·59; N, 3·79.

The hydrochloride was prepared from an ether solution of the amine at 0° with HCl gas. The yield was 6·2 g, m.p. 195–196°.

*Anal.* Calcd. for $C_{24}H_{32}ClNO_2$: C, 71·71; H, 8·03; N, 3·49. Found: C, 71·78; H, 7·83; N, 3·64.

*1-Benzyl-2-dimethylaminomethyl-1-propionyloxyindane hemioxalate.* The following quantities were used in the Grignard step: benzyl chloride (5·7 g), magnesium ribbon (1·33 g) and an amount of 2-dimethylaminomethyl-1-indanone corresponding to 5·0 g of its hydrochloride. The solvent was a 1:1 mixture of ether and tetrahydrofuran. After 4 h at room temperature, saturated ammonium chloride was slowly added at 0° and then the mixture

was washed with 2N sodium carbonate and dried. Infrared spectra showed the absence of carbonyl absorption in the oily amino alcohol weighing 4·55 g.

A methylene chloride solution of this material (3·96 g) and triethylamine (1·0 ml) was cooled at 0°. Propionyl chloride (1·31 g) was added dropwise in a little methylene chloride. The reaction mixture was extracted with cold 2N sodium carbonate after 8 h at room temperature. The dried solvent was removed *in vacuo* at room temperature. A hemioxalate was prepared at 0° from a small amount of acetone. Several washings with acetone and ether gave an analytically pure material, m.p. 155–156°, weighing 1·88 g.

*Anal.* Calcd. for $C_{24}H_{29}NO_6$: C, 67·43; H, 6·84; N, 3·28. Found: C, 67·29; H, 6·76; N, 3·80.

*2-Dimethylaminomethyl-1-phenyl-1-propionyloxy-1,2,3,4-tetrahydronaphthalene hydrochloride.* A solution of 2-dimethylaminomethyl-1-hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (2·86 g) in ether (10 ml) was treated with 1·4N ethereal butyllithium (11·2 ml). Then propionic anhydride (2·7 ml) was gradually added with stirring. The reaction mixture was stirred and refluxed overnight and was then washed with cold dilute sodium carbonate. A hydrochloride was precipitated with HCl gas, rubbed several times with ether and recrystallized from ethanol–ether. The yield was 1·7 g, m.p. 169–173°. An analytical sample had m.p. 170–171°.

*Anal.* Calcd. for $C_{22}H_{28}ClNO_2$: C, 70·66; H, 7·55; N, 3·75. Found: C, 70·23; H, 7·60; N, 4·01.

## Pharmacology

The compounds were tested as analgesics by the rat tail-flick method.

*Summary.* Good analgesic activity has been found in a series of esters of 1-benzyl-2-dialkylaminomethyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene. Onset of tolerance was relatively rapid, however.

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