STUDIES IN SYNTHETIC ANALGESICS

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Part II

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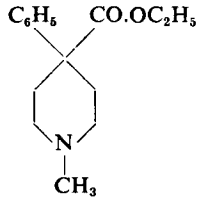
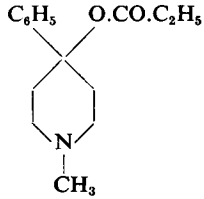
It has been shown by Jensen *et al.*[1] and Foster and Carman[2] that the replacement of the $-CO.R$ or $-CO.OEt$ groups of pethidine-type compounds by the $-O.CO.R$ (" reversed " ester) group was attended with increased analgesic activity. According to the data presented by Foster and Carman (*loc. cit.*) for instance, the compound (II) is about 30 times as active as pethidine (I).

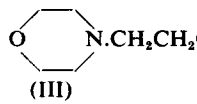


(I)



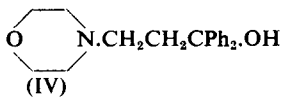
(II)

The authors in the present investigation therefore decided to introduce a similar change in the amidone-type of compounds (i.e. replace the $-CO.R$ group by $-O.CO.R$), to observe the effect upon analgesic activity. A number of compounds of type (III) have been prepared, in order that their activities might be compared with those described in Part I[3] of this work.

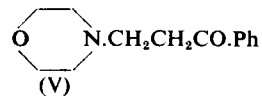


(III) R = alkyl

The reaction of phenylmagnesium bromide upon ethyl β-morpholino propionate produced the tertiary alcohol, 3-morpholino-1:1-diphenyl-propan-1-ol (IV) in 50 per cent. yields, along with the ketone, ω-morpholinopropiophenone (V).



(IV)



(V)

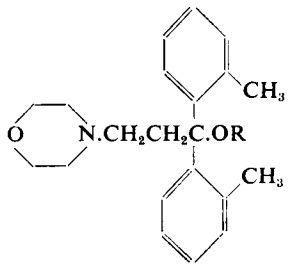
Although it has been shown, in some reactions, that organolithium compounds are more effective than Grignard reagents for the preparation of tertiary alcohols[4], the use of phenyl-lithium in the above reaction did not improve the yield of (IV). This result supports the recently published observation of Adamson[5].

A number of esters (III ; R=CH_3, C_2H_5 and n-C_3H_7) were prepared by the reaction of the alcohol (IV), in ether/benzene solution, with ethylmagnesium bromide to produce the Grignard complex of (IV), and then

stirring this suspension overnight at room temperature with the appropriate acid chloride or anhydride. The esters were obtained in 50 per cent. yields.

The application of the method of preparing esters described in Part I[3], by heating a toluene solution of the amino-alcohol with the acid chloride and then diluting with ether to obtain the hydrochloride of the amino-ester, caused dehydration of the alcohol (IV), and the product consisted of a mixture of the hydrochlorides of unchanged alcohol (IV) and the corresponding unsaturated derivative.

The alcohol (IV) and the esters (III ; R=CH_3, C_2H_5, and n-C_3H_7) proved to be inactive as analgesics. It was conjectured that perhaps the replacement of the $-CO.C_2H_5$ attached to the quaternary carbon atom bearing the two phenyl groups by $-O.CO.R$ had caused increased freedom of movement of these groups in the molecule. Thus the steric compactness which may be associated with analgesic activity had been upset. In order to reduce the freedom of movement of these groups, *ortho* methyl substituents were introduced into the phenyl rings by the preparation of compounds of type (VI).



(R = H or —O alkyl)

(VI)

Steric effects were undoubtedly exhibited, because the reaction of ethyl β-morpholinopropionate with the Grignard reagent prepared from *o*-bromotoluene gave the alcohol (VI ; R=H) in 13·5 per cent. yields, compared with the preparations of the alcohol (IV) in 50 per cent. yields using phenylmagnesium bromide under comparable conditions. After chromatographic separation of the large amount of viscous oil which remained after the isolation of the alcohol (VI ; R=H), a picrate was prepared, which gave the correct analytical figures for β-morpholinoethyl-*o*-tolyl ketone picrate, and the weight obtained indicated at least a 50 per cent. yield of this ketone.

The alcohol (VI ; R=H) proved to be difficult to acylate. The conditions applied with success to produce esters of the alcohol (IV) failed with the alcohol (VI ; R=H). Finally the acylation was accomplished by preparing the Grignard complex of the alcohol in ether/benzene solution, removing the ether by distillation, and then refluxing for 24 hours with the appropriate acid anhydride.

The alcohol (VI ; R=H) and its acetyl and propionyl esters were inactive as analgesics.

The authors thank Professor G. A. H. Buttle, Dr. G. F. Somers and Glaxo Laboratories Ltd. for the pharmacological testing. These tests

were performed according to the methods described by Thorp[6] and by Dodds *et al.*[7]

Conclusions

The replacement of the $-CO.C_2H_5$ group by the $-O.CO.R$ group, in the type of amidone compound tested, leads to a complete loss of analgesic activity. This is completely different from the results of this change in the pethidine type of compound. The introduction of *o*, *o'* methyl groups into the phenyl rings to increase the steric effect in these " reversed " esters of the amidone-type does not lead to substances with analgesic activity.

Experimental

All m.pts. are uncorrected.

Ethyl β-morpholinopropionate. This ester was prepared by the addition of morpholine to acrylonitrile according to the method of Whitmore *et al.*[8], followed by hydrolysis and esterification with ethyl alcohol and sulphuric acid[9]. In some experiments with large batches, this latter process did not go to completion readily. The following method for the preparation of the ester was found to give better results. A mixture of morpholine (218 g.) and ethyl acrylate (250 g.) was refluxed for $6\frac{1}{2}$ hours and then fractionally distilled under reduced pressure to yield ethyl β-morpholinopropionate (428 g., 91 per cent.), b.pt. 112°C./9 mm., $n_D^{24°C.}$ 1.451 (picrate m.pt. 106° to 107°C.). Whitmore *et al.*[9] record b.pt. 138° to 140°C./25 mm., $n_D^{20°C.}$ 1.457 (picrate m.pt. 106° to 107°C.).

3-*Morpholino*-1 : 1-*diphenylpropan*-1-*ol.* (IV).

Method A—A solution of ethyl β-morpholinopropionate (125 g.) in dry toluene (500 ml.) was added slowly with vigorous stirring to the Grignard reagent prepared from bromobenzene (314 g.) and magnesium (48·6 g.) in ether (300 ml.). During this addition, a white precipitate separated. The product was heated at 100°C. for 2 hours, cooled, and then poured slowly with stirring into dilute sulphuric acid solution containing ice. A precipitate of crude 3-morpholino-1 : 1-diphenylpropan-1-ol sulphate separated in the aqueous layer and, after separating the organic layer and further extracting the aqueous layer with ether (organic extracts rejected), the precipitate (=A) was filtered off and washed with water and ether. The aqueous filtrate and washings were retained (=B).

Treatment of Precipitate A.

The base was liberated with aqueous sodium hydroxide, extracted with chloroform, the chloroform extracts dried (anhydrous sodium sulphate), the solvent removed under reduced pressure, and absolute alcohol (50 ml.) added to the oil which remained. Upon cooling, there were obtained white crystals (78 g.) of almost pure 3-morpholino-1 : 1-diphenylpropan-1-ol, m.pt. 103° to 104°C. A brown viscous oil (=C) was obtained from the mother liquor.

Treatment of filtrate and washings (=B).

These were made alkaline with sodium hydroxide solution, extracted

with chloroform, and treated as above to yield almost pure 3-morpholino-1 : 1-diphenylpropan-1-ol (23·5 g.), m.pt. 101° to 103°C. and a brown viscous oil (=D).

The total yield of almost pure 3-morpholino-1 : 1-diphenylpropan-1-ol was thus 101·5 g., 51 per cent. Recrystallisation from ethyl alcohol gave rosettes of white needles, m.pt. 105° to 106°C. Adamson[10] records m.pt. 106°C. Found : C, 76·8 ; H, 7·7 ; N, 4·8 per cent. ; calc. for $C_{19}H_{23}O_2N$: C, 76·8 ; H, 7·7 ; N, 4·7 per cent. The hydrochloride crystallised from ethyl alcohol as white needles, m.pt. 230° to 231°C. (with decomposition). Adamson (*loc. cit.*) records m.pt. 231°C. Found : C, 68·9 ; H, 7·3 ; N, 4·35 ; Cl, 10·3 per cent. Eq. Wt. (by titration) 334 ; calc. for $C_{19}H_{23}O_2N$, HCl : C, 68·4 ; H, 7·2 ; N, 4·2 ; Cl, 10·6 per cent. Eq. Wt. 333·5. The *picrate* crystallised from acetone/ethyl alcohol as rosettes of yellow crystals, m.pt. 138° to 139°C. Found : C, 56·7 ; H, 4·8 ; N, 10·9 per cent. $C_{19}H_{23}O_2N$, $C_6H_3O_7N_3$ requires C, 57·0 ; H, 4·9 ; N, 10·6 per cent.

Treatment of Oils C and D.

The total weight was 56 g. A portion (12 g.) was distilled under reduced pressure to yield *ω-morpholinopropiophenone* (5 g.), b.pt. 84° to 88°C./0·07 mm. The constitution of this compound was proved by the preparation of the following.

(*a*) The hydrochloride, m.pt. 176° to 177°C. (This hydrochloride, m.pt. 177°C. was prepared by Harradence and Lions[11] by the use of the Mannich reaction).

Found : C, 61·0 ; H, 6·9 ; N, 5·8 ; Cl, 14·1 per cent. Eq. Wt. (by titration) 260. Calc. for $C_{13}H_{17}O_2N$,HCl ; C, 61·1 ; H, 7·1 ; N, 5·5 ; Cl, 13·9 per cent. Eq. Wt. 255·5.

(*b*) The picrate, m.pt. 198° to 200°C. (with decomposition). Harradence and Lions (*loc. cit.*) record m.pt. 195° to 196°C. Found : C, 50·2 ; H, 4·4 ; N, 12·2 per cent. Calc. for $C_{13}H_{17}O_2N$,$C_6H_3O_7N_3$; C, 50·9 ; H, 4·5 ; N, 12·5 per cent.

Method B. (using phenyl-lithium and ethyl β-morpholinopropionate). A solution of ethyl β-morpholinopropionate (47 g.) in ether (100 ml.) was added with vigorous stirring, under anhydrous conditions and in an atmosphere of nitrogen, to a solution of phenyl-lithium prepared from freshly distilled bromobenzene (158 g.) and lithium (13·8 g.) in ether (1000 ml.). The mixture was heated at 60°C. for 2 hours, cooled, and worked up as in Method A to yield 3-morpholino-1 : 1-diphenylpropan-1-ol (31·5 g., 42 per cent.) and a brown viscous oil (32 g.) containing ω-morpholinopropiophenone.

3-*Morpholino*-1-*propionoxy*-1 : 1-*diphenylpropane* (III ; R=C_2H_5).

A solution of IV (7 g.) in dry toluene (40 ml.) was added slowly to ethylmagnesium iodide solution prepared from magnesium (1 g.) and ethyl iodide (6·3 g.) in ether (10 ml.), while vigorous stirring was maintained. A grey solid separated. The suspension was heated at 100°C. for 30 minutes, cooled to room temperature, and then addition drop by drop of propionic anhydride (8 ml.) in dry toluene (10 ml.) made with vigorous stirring, and the stirring continued overnight at room temperature. The product was poured into dilute hydrochloric acid solution

containing ice, and the solid (crude hydrochloride of the amino-ester) which separated in the aqueous layer was filtered off and washed with water and ether. From the crude hydrochloride, the base was liberated with sodium carbonate solution, extracted with chloroform, the chloroform extracts dried (anhydrous sodium sulphate) and the solvent removed under reduced pressure to yield a solid which was crystallised from ethyl alcohol as rosettes of colourless prisms (4·6 g., 55 per cent.) of 3-*morpholino*-1-*propionoxy*-1 : 1-*diphenylpropane*, m.pt. 108° to 109°C.

Found : C, 74·8 ; H, 7·5 ; N, 4·2 per cent. $C_{22}H_{27}O_3N$ requires C, 74·8 ; H, 7·65 ; N, 4·0 per cent. The *hydrochloride* crystallised from absolute alcohol as rosettes of white needles, m.pt. 209° to 210°C. (with decomposition). Found : C, 66·7 ; H, 7·5 ; N, 3·6 ; Cl, 9·0 per cent. Eq. Wt. (by titration) 401. $C_{22}H_{27}O_3N$,HCl, $\frac{1}{2}H_2O$ requires C, 66·3 ; H, 7·3 ; N, 3·5 ; Cl, 8·9 per cent. Eq. Wt. 398·5. The *picrate* crystallised from acetone/ethyl alcohol as small yellow prisms, m.pt. 176° to 177°C. Found : C, 58·5 ; H, 5·3 ; N, 9·6 ; $C_{22}H_{27}O_3N$, $C_6H_3O_7N_3$ requires C, 57·7 ; H, 5·2 ; N, 9·6 per cent.

The following esters were prepared in a similar manner and in similar yields :—

1-*Acetoxy*-3-*morpholino*-1 : 1-*diphenylpropane* (III ; R=CH_3) crystallised from ethyl alcohol as colourless prisms, m.pt. 107° to 108°C. Found : C, 74·7 ; H, 7·1 ; N, 4·1 per cent. $C_{21}H_{25}O_3N$ requires : C, 74·3 ; H, 7·4 ; N, 4·1 per cent. The *hydrochloride* was obtained from ethyl alcohol as white needles, m.pt. 205° to 206°C. (with decomposition). Found : C, 65·8 ; H, 7·1 ; N, 3·7 ; Cl, 9·0 per cent. Eq. Wt. (by titration) 389. $C_{21}H_{25}O_3N$, HCl, $\frac{1}{2}H_2O$ requires C, 65·6 ; H, 7·0 ; N, 3·6 ; Cl, 9·2 per cent. Eq. Wt. 384·5. The *picrate* crystallised from acetone/ethyl alcohol as yellow prisms, m.pt. 176° to 177°C. Found : C, 56·6 ; H, 5·0 ; N, 9·9 per cent. $C_{21}H_{25}O_3N$, $C_6H_3O_7N_3$ requires C, 57·0 ; H, 4·9 ; N, 9·9 per cent.

1-*n-Butyroxy*-3-*morpholino*-1 : 1-*diphenylpropane* (III ; R = *n*-C_3H_7) crystallised from ethyl alcohol as colourless prisms, m.pt. 90°C. Found : C, 76·0 ; H, 7·8 ; N, 4·0 per cent. $C_{23}H_{29}O_3N$ requires C, 75·2 ; H, 7·9 ; N, 3·8 per cent. The *hydrochloride* crystallised from ethyl alcohol as white needles, m.pt. 180° to 181°C. (with decomposition). Found : C, 67·6 ; H, 7·6 ; N, 3·4 ; Cl, 8·9 per cent. Eq. Wt. (by titration) 413. $C_{23}H_{29}O_3N$, HCl, $\frac{1}{2}H_2O$ requires C, 67·0 ; H, 7·5 ; N, 3·4 ; Cl, 8·6 per cent. Eq. Wt. 412·5. The *picrate* crystallised from acetone/ethyl alcohol as yellow crystals, m.pt. 160° to 161°C. Found : C, 58·1 ; H, 5·1 ; N, 9·5 per cent. $C_{23}H_{29}O_3N$, $C_6H_3O_7N_3$ requires C, 58·4 ; H, 5·4 ; N, 9·4 per cent.

Attempted preparation of the above esters by other methods.

Propionyl chloride (1 ml.—freshly distilled from a sample to which 10 per cent. of dimethylaniline had been added) was added to a solution of IV (1 g.) in warm dry toluene (10 ml.). A white precipitate was immediately produced. After heating at 100°C. for 30 minutes, dry ether (40 ml.) was added, and the crude product was filtered off (1·09 g.), m.pt. about 185°C. Recrystallisation from ethyl alcohol gave the hydrochloride of IV (0·55 g.), m.pt. and mixed m.pt. with authentic

sample of 230° to 231°C. The analytical figures obtained from the crude product from a subsequent experiment indicated that it was a mixture of the hydrochloride of IV and the corresponding dehydrated alcohol hydrochloride. Found : C, 70·4 ; H, 7·2 ; N, 4·3 per cent. Eq. Wt. (by titration) 327. $C_{19}H_{21}ON$ requires C, 72·5 ; H, 7·0 ; N, 4·4 per cent. Eq. Wt. 315·5. $C_{19}H_{23}O_2N$ requires C, 68·4 ; H, 7·2 ; N, 4·2 per cent. Eq. Wt. 333·5.

The reaction between propionyl chloride and the alcohol in pyridine solution failed to produce the ester.

3-*Morpholino*-1 : 1-*di*-o-*tolylpropan*-1-*ol* (VI : R=H).

From the reaction between ethyl β-morpholinopropionate (120 g.) and the Grignard reagent prepared from magnesium (45·5 g.) and *o*-bromotoluene (318 g.), using the conditions described for the preparation of IV, was isolated 3-*morpholino*-1 : 1-*di*-o-*tolylpropan*-1-*ol* as small white needles (28 g., 13·5 per cent.), m.pt. 162° to 163°C., from ethanol. Found : C, 77·6 ; H, 8·4 ; N, 4·2 per cent. $C_{21}H_{27}O_2N$ requires C, 77·5 ; H, 8·3 ; N, 4·3 per cent. The *hydrochloride* crystallised from ethyl alcohol as colourless prisms, m.pt. 238° to 239°C. (with effervescence). Found : C, 69·3 ; H, 7·5 ; N, 3·8 ; Cl, 9·7 per cent. Eq. Wt. (by titration) 362. $C_{21}H_{27}O_2N$, HCl requires C, 69·7 ; H, 7·8 ; N, 3·9 ; Cl, 9·8 per cent. Eq. Wt. 361·5. The *picrate* crystallised from acetone/ethyl alcohol as yellow prisms, m.pt. 191° to 192°C. Found : C, 57·8 ; H, 5·5 ; N, 10·3 per cent. $C_{21}H_{27}O_2N$, $C_6H_3O_7N_3$ requires C, 58·5 ; H, 5·4 ; N, 10·1 per cent.

A brown viscous oil (95 g.) was the main product from the above reaction. A portion of this oil (4 g.) was dissolved in benzene (200 ml.) completely adsorbed on a column of alumina (2 cm. diameter and 38 cm. long), and benzene used as the eluent. A brown band remained at the top of the column and a yellow band moved down as the development proceeded. The yellow fraction, and subsequent colourless fractions, all gave oils when the solvent was removed (total weight of oil, 1·9 g.), and these oils gave identical picrates, m.pt. 175°C. Recrystallisation of these picrates from acetone/ethyl alcohol gave yellow needles, m.pt. 180° to 181°C. of a substance which, from the analytical figures and by analogy with the production of ω-morpholinopropiophenone by the action of phenylmagnesium bromide upon ethyl β-morpholinopropionate, was considered to be *β-morpholinoethyl-o-tolyl ketone picrate.* Found : C, 52·2 ; H, 4·9 ; N, 11·9 per cent. $C_{14}H_{19}O_2N$, $C_6H_3O_7N_3$ requires C, 51·7 ; H, 5·2 ; N, 11·9 per cent. A yellow oil (1·4 g.), which was not identified, was obtained by the treatment of the column with an eluent of benzene containing 10 per cent. of ethyl alcohol.

The reaction between the lithium derivative derived from *o*-bromotoluene (171 g.), and ethyl β-morpholinopropionate (47 g.), using the conditions described for the reaction of phenyl-lithium with this ester, yielded 3-morpholino-1 : 1-di-*o*-tolylpropan-1-ol (12 g., 14·7 per cent.).

3-*Morpholino*-1-*propionoxy*-1 : 1-*di*-o-*tolylpropane* (VI : R=—COC_2H_5).

A solution of 3-morpholino-1 : 1-di-*o*-tolylpropan-1-ol (4·9 g.) in dry benzene (100 ml.) and dry ether (200 ml.) was added to a 2M solution (30 ml.) of ethylmagnesium bromide in ether, with vigorous stirring.

After refluxing gently for 2 hours, the ether was removed by distillation, and propionic anhydride (30 ml.) added. The resulting suspension was refluxed, with stirring, for 24 hours.

The product was cooled, poured into dilute hydrochloric acid solution containing ice, ether (200 ml.) added and, after stirring well, the precipitate was filtered off, added to sodium carbonate solution, and the liberated base extracted with chloroform. After drying (anhydrous sodium sulphate), the solvent was removed under reduced pressure from the chloroform extracts, and ethyl alcohol (5 ml.) added to the resulting oil. Upon cooling, small rectangular plates of 3-*morpholino*-1-*propionoxy*-1 : 1-*di*-o-*tolylpropane* (1·2 g., 21 per cent.), m.pt. 123° to 126°C. separated. Recrystallisation from ethyl alcohol raised the m.pt. to 127° to 129°C. Found : C, 75·6 ; H, 8·1 ; N, 3·9 per cent. $C_{24}H_{31}O_3N$ requires C, 75·6 ; H, 8·1 ; N, 3·7 per cent. The *hydrochloride* crystallised from ether/ethyl alcohol as colourless prisms, m.pt. 181° to 182°C. (with decomposition). Found : C, 69·0 ; H, 8·0 ; N, 3·5 per cent. $C_{24}H_{31}O_3N$, HCl requires C, 69·0 ; H, 7·7 ; N, 3·3 per cent. The *picrate* was obtained from acetone/ethyl alcohol as yellow crystals, m.pt. 179° to 180°C. Found : C, 59·6 ; H, 5·9 ; N, 9·1 per cent. $C_{24}H_{31}O_3N$, $C_6H_3O_7N_3$ requires C, 59·0 ; H, 5·6 ; N, 9·2 per cent. 1-*Acetoxy*-3-*morpholino*-1 : 1-*di*-o-*tolylpropane* (VI ; R = $-COCH_3$).

This was obtained, by the method used for the corresponding propionoxy compound, as colourless plates, m.pt. 133° to 134°C., from ethyl alcohol. Found : C, 75·2 ; H, 8·0 ; N, 4·0 per cent. $C_{23}H_{29}O_3N$ requires C, 75·2 ; H, 7·9 ; N, 3·8 per cent. The *hydrochloride* crystallised from ethyl alcohol as white needles m.pt 200° to 201°C. Found : C, 68·1 ; H, 7·4 ; N, 3·3 ; Cl, 9·2 per cent. $C_{23}H_{29}O_3N$, HCl requires C, 68·4 ; H, 7·4 ; N, 3·5 ; Cl, 8·8 per cent. The *picrate* crystallised from acetone/ethyl alcohol as yellow needles, m.pt. 164° to 165°C. Found : C, 58·3 ; H, 5·5 ; N, 9·2 per cent. $C_{23}H_{29}O_3N$, $C_6H_3O_7N_3$ requires C, 58·4 ; H, 5·4 ; N, 9·4 per cent.

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