RESEARCH PAPERS

STUDIES IN SYNTHETIC ANALGESICS

PART I

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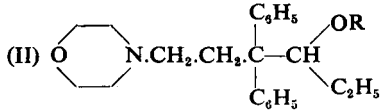
THE reports[1,2] published after the end of the 1939-45 war revealed that German workers had found that compounds of type I possessed pronounced analgesic activity.

(I) $R_2N.CHR'.CH_2.CPh_1.COR''$

R=alkyl; R'=H or methyl; R''= alkyl or −O alkyl.

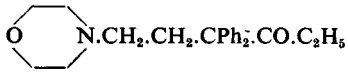
One of the compounds of this class, namely amidone (I; $R=CH_3$, $R'=CH_3$ and $R''=C_2H_5$), was reported to possess 5 to 10 times the analgesic activity of pethidine. These reports led to extensive investigation of related types of compounds. The basic group has been altered; the alkyl chain connecting tertiary nitrogen with quaternary carbon has been varied; the phenyl groups have been reduced, substituted and replaced by other groups; different types of ketones have been investigated. More recently, the ketonic group has been modified to $-CH_2OH$, $-CH_2O.CO.R$, $-CONH_2$, $-C(=NR).C_2H_5$, $-CH(O.CO.R).C_2H_5$, etc. Some of these changes have resulted in producing compounds with increased analgesic activity and reduced side effects.

When this work was commenced, the latter modifications of the ketonic group had not been reported. The present investigation led to the preparation of an alcohol, and a series of esters (II) related to the amidone type of compound, in an attempt to reduce the toxicity of the ketone and provide further information concerning the relationship between structure and analgesic activity.

(II)  R = H or acyl

These changes are attended by the production of an asymmetric centre in the molecule, but attempts to resolve any of the compounds have not been made. After the completion of this portion of the work, Speeter *et al.*[3] reported the preparation and analgesic activity of the above alcohol (II; R = H) and its acetyl ester (II; R = $-CO.CH_3$).

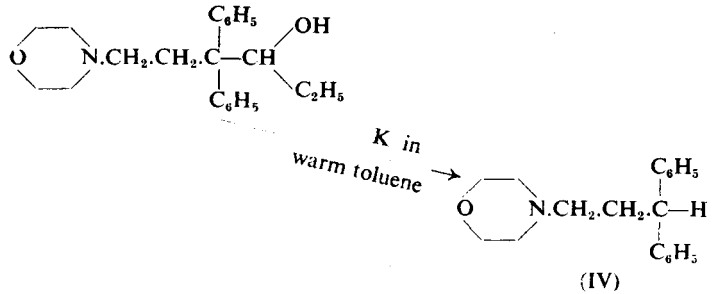
The ketone (III), from which the alcohol (II) was obtained by reduction, was prepared according to the method described by Hems *et al.* (private communication, now published[4]).

(III) 

This reduction did not proceed readily, and it was finally accomplished by aluminium *iso*propoxide, using the method recommended for ketones resistant to reduction[5]. The reaction required 100 hours, and the alcohol (II; R = H) was obtained in 80 to 90 per cent. yields. In the course of this reduction, it was discovered that a solution of sodium nitroprusside, used as described in the experimental section, was a more reliable test for a trace of acetone in solution in toluene than the test using 2:4-dinitrophenylhydrazine described in "Organic Reactions"[6]. May and Mosettig[7] have reported that amidone resisted reduction by aluminium *iso*propoxide, and accomplished their reduction using hydrogenation with platinum oxide as catalyst. More recently, Speeter *et al.* (*loc. cit.*) found that lithium aluminium hydride was very effective for reducing the above type of ketone.

The esters from the alcohol (II; R = H) were prepared by refluxing a toluene solution of the alcohol, under anhydrous conditions, with the appropriate acid chloride for 10 hours, and then diluting with dry ether to produce, upon cooling, the hydrochlorides of the esters on 80 to 90 per cent. yields. The picrates of the esters proved to be very suitable for characterisation. The pharmacological results are reported at the end of this account. Further work to produce related alcohols and esters was discontinued when the publications by May and Mosettig *(loc. cit.)* and Speeter *et al.* (*loc. cit.*) appeared.

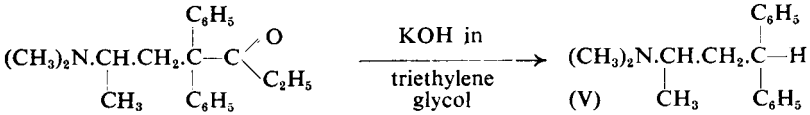
Attempts have been made to prepare a series of ethers from the alcohol (II; R = H) but, up to the present time, these efforts have not met with success. A toluene solution of the alcohol (II; R = H) failed to react with the sodium or sodamide. In some reactions potassium "emulsified" in benzene has been found to be more useful than sodium in the preparation of alcoholates preparatory to reaction with alkyl halides[8]. When a warm solution of the alcohol (II; R = H) was treated with "emulsified" potassium, reaction occurred readily, a gas was evolved, and subsequent treatment with benzyl bromide or ethyl iodide yielded an identical product. This was proved to be 3-morpholino-1:1-diphenylpropane (IV) by analyses, and by the preparation of a hydrochloride and picrate with melting-points and mixed melting-points identical with those of authentic samples. Because of the identity of the product when either benzyl bromide or ethyl iodide was used, the reaction between the alcohol (II; R = H) and potassium was investigated, and the following reaction has been established:—



(IV)

3-Morpholino-1:1-diphenylpropane (IV) was isolated as the picrate in 85 per cent. yields from the reaction. The mechanism involved in the cleavage of this portion of the molecule from the quaternary carbon atom is being investigated further and the results will be communicated later.

A similar type of reaction has recently been reported by May and Mosettig (*loc. cit.*). In attempting to reduce the ketonic group of amidone by the Huang-Minlon[9] modification of the Wolff-Kishner reaction, the entire ketone chain was lost and 3-dimethylamino-1:1-diphenylbutane (V) was produced as follows:—



Small[10] has suggested that this reaction proceeds through the decarboxylation of an intermediate carboxylic acid. This explanation does not appear to be applicable to the production of (IV) from the alcohol (II; R = H), because it is difficult to see how the necessary conditions for oxidation of the alcohol to the intermediate carboxylic acid could obtain in the reaction mixture.

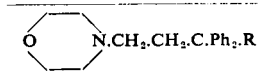
Other attempts to prepare a series of ethers from the alcohol (II, R = H) included the treatment of a toluene solution of the alcohol with lithium-phenyl to produce a white precipitate, which was presumed to be the lithium derivative of the alcohol, but this failed to yield the ether upon treatment with benzyl bromide and only the unchanged alcohol and the benzyl quaternary ammonium bromide of the alcohol were isolated. The replacement of the hydroxyl group by halogen, and then treatment with the sodium salt of benzyl alcohol also proved abortive.

Pharmacological Results

The authors express their thanks to Professor G. A. H. Buttle, Dr. G. F. Somers and Glaxo Laboratories Ltd., for the pharmacological results recorded in Table I. For pharmacological testing the hydrochlorides were used. Analgesic activity was measured in rats against that of

TABLE I

Analgesic activities and toxicities

Compound	Analgesic Activity (pethidine hydrochloride = 1)	LD50(*a*)
		
R = —$CO.C_2H_5$	7 (*b*)	220 mg./kg.
R = —$CH(OH).C_2H_5$	1/2 (*c*)	450 mg./kg.
R = —$CH(O.CO.CH_3).C_2H_5$	3 (*c*)	300 mg./kg.
R = —$CH(O.CO.C_2H_5).C_2H_5$	1/5	800 mg./kg.
R = —$CH(O.CO.C_6H_5).C_2H_5$	0	(*d*)
R = —$CH(O.CO.C_6H_4pNH_2).C_2H_5$	0	800 mg./kg.

(*a*) LD50 was obtained by subcutaneous injection into mice.
(*b*) See Hems *et al* (*loc. cit.*).
(*c*) Compare with Speeter *et al* (*loc. cit.*).
(*d*) The hydrochloride of this substance was not sufficiently soluble in water to give a strong enough solution to kill the mice.

pethidine hydrochloride, two methods being used:—(a) the thermal radiation method described by Thorp[11], and (b) the electric grid method of Dodds *et al.*[12].

EXPERIMENTAL

All melting-points are uncorrected.

6-Morpholino-3 : 3-diphenylhexan-3-one (III). This was prepared according to details supplied by Dr. Hems (now published, Hems *et al.*[4]). The authors are indebted to Glaxo Laboratories Ltd., for supplies of diphenylacetonitrile.

6-Morpholino-3 : 3-diphenylhexan-3-ol (II ; R =H). The ketone III (56 g.) and aluminium *iso*propoxide (135 g.) were heated in dry toluene (250 ml.) in a bath maintained at 140° to 150°C. and slow distillation allowed to occur at intervals. More dry toluene was added as required. When the sodium nitroprusside test for acetone in the distillate gave a negative result (after about 100 hours), the solution was cooled, shaken with hydrochloric acid solution (10 per cent.) to decompose the alcoholates, made alkaline with sodium hydroxide solution (10 per cent.), and extracted with benzene. The combined benzene extracts were dried (anhydrous sodium sulphate) and most of the solvent removed under reduced pressure. Upon cooling, a white crystalline mass separated, and this was recrystallised from ethyl alcohol (97 per cent.) as white crystalline granules of 6-morpholino-3 : 3-diphenylhexan-3-ol (47·5 g., 84 per cent.), m.pt. 129° to 130°C. Speeter *et al. (loc. cit.)* record m.pt. 130° to 131°C. Found: C, 77·8; H, 8·7; N, 4·2 per cent. calc. for $C_{22}H_{29}O_2N$: C, 77·9; H, 8·6; N. 4·1 per cent. The *picrate* crystallised from acetone/ethyl alcohol in yellow prisms, m.pt. 200° to 201°C. Found: C, 59·5; H, 5·7; N, 10·1 per cent. Eq. Wt. (by titration) 565. $C_{22}H_{29}O_2N$, $C_6H_3O_7N_3$ requires C, 59·2; H, 5·6; N, 9·9 per cent. Eq. Wt. 568. The *hydrochloride* crystallised from ether/ethyl alcohol as white clusters, m.pt. 167°C. (with effervescence. Found: C, 69·1; H, 8·0; N, 3·6; Cl, 9·3 per cent. $C_{22}H_{29}O_2N$, HCl requires C, 70·3; H, 8·0; N, 3·7; Cl, 9·4 per cent.

TEST FOR ACETONE IN THE DISTILLATE (where only a very small percentage of acetone is present in solution in toluene).

Acetone test reagent. Sodium nitroprusside solution (4 per cent.) in water. This was discarded if more than 1 week old.

Method. 5 drops of the distillate were collected in a small tube containing 5 drops of water, and a solution of sodium nitroprusside (0·1 ml. of 4 per cent.) added and the mixture shaken. Sodium hydroxide solution (0·1 ml. of 20 per cent.) was added and the mixture shaken again, allowed to stand for 1 minute, and then acidified with acetic acid solution (0·3 ml. of 33 per cent.). The appearance of a cherry-red colour after the addition of the sodium hydroxide solution, followed by a conversion to a much darker red upon acidification with the acetic acid solution, indicated the presence of acetone. The toluene layer did not interfere with this test.

3-Acetoxy-6-morpholino-4 : 4-diphenylhexane hydrochloride (II; R = $-CO.CH_3$).

The alcohol (II; R = H) (2 g.) was dissolved in dry toluene (30 ml.) and acetyl chloride (10 ml.) added. The solution was boiled gently under anhydrous conditions for 10 hours, and then poured into dry ether (250 ml.). Upon cooling, the hydrochloride of the ester separated as rosettes of white crystals (2·27 g., 92 per cent.), m.pt. 250° to 252°C. Recrystallisation from ethyl alcohol gave clusters of colourless prisms, m.pt. 253° to 255°C. (with decomposition). Speeter *et al. (loc. cit.)* record m.pt. 242° to 243°C. Found: C, 69·1; H, 7·7; N, 3·2 per cent. calc. for $C_{24}H_{31}O_3N$, HCl: C, 69·0; H, 7·7; N, 3·4 per cent. The *picrate* (i.e., of the base II; R = $-COCH_3$) was obtained from the hydrochloride, using acetone/ethyl alcohol as solvent, as yellow crystals m.pt. 192° to 193°C. Found: C, 58·9; H, 5·65; N, 9·3 per cent. $C_{24}H_{31}O_3N$, $C_6H_3O_7N_3$ requires C, 58·9; H, 5·6; N, 9·2 per cent.

The following esters of the alcohol (II; R = H) were prepared in a similar manner:—

3-Propionoxy-6-morpholino-4 : 4-diphenylhexane hydrochloride (II; R = $-CO.C_2H_5$).

This was recrystallised from dry ether/ethyl alcohol as rosettes of small white needles, m.pt. 225° to 227°C. (with decomposition). Found: C, 68·7; H, 7·9; N, 3·2; Cl, 8·3 per cent. Eq. Wt. (by titration) 428. $C_{25}H_{33}O_3N$,HCl requires C, 69·5; H, 7·9; N, 3·2; Cl, 8·2 per cent. Eq. Wt. 431·5. The *picrate* (i.e., of the base II, R = $-COC_2H_5$) was obtained from acetone/ethyl alcohol as yellow crystals, m.pt. 181° to 182°C. Found: C, 58·9; H, 5·8; N, 9·0 per cent. Eq. Wt. (by titration) 629. $C_{25}H_{33}O_3N$, $C_6H_3O_7N_3$ requires C, 59·6; H, 5·8; N, 9·0 per cent. Eq. Wt. 624.

3-Benzoxy-6-morpholino-4 : 4-diphenylhexane hydrochloride (II; R = $-CO.C_6H_5$).

This *amino-ester* was recrystallised from dry ether/ethyl alcohol as small white crystals, m.pt. 256° to 258°C. (with decomposition). Found: C, 71·8; H, 7·3; N, 2·9; Cl, 7·4 per cent. Eq. Wt. (by titration) 488. $C_{29}H_{33}O_3N$, HCl requires C, 72·3; H, 7·1; N, 2·9; Cl, 7·4 per cent. Eq. Wt. 479·5. The *picrate* (i.e., of the base II, R = $-COC_6H_5$) was obtained from acetone/ethyl alcohol as yellow crystals, m.pt. 161° to 162°C. Found: C, 61·9; H, 5·5; N, 8·5 per cent. Eq. Wt. (by titration) 667. $C_{29}H_{33}O_3N$, $C_6H_3O_7N_3$ requires C, 62·5; H, 5·4; N, 8·4 per cent. Eq. Wt. 672.

3-p-Nitrobenzoxy-6-morpholino-4 : 4-diphenylhexane (II; R = $-CO.C_6H_4p.NO_2$).

The treatment of the alcohol (II; R = H) (2 g.) in dry toluene (10 ml.) with *p*-nitrobenzoyl chloride (1·5 g.), in the manner described for the acetoxy derivative above, yielded a gum when poured into ether. This gum was separated, decomposed with sodium hydroxide solution (10 per cent.) and the liberated base extracted with benzene. The benzene extracts were dried (anhydrous sodium sulphate) and the solvent removed under reduced pressure. The yellow-coloured solid which

separated on cooling was recrystallised from absolute alcohol as pale yellow needles of the *amino-ester* (2·16 g., 75 per cent.), m.pt. 161° to 162°C. Found: C, 71·7; H, 6·4; N, 5·9 per cent. $C_{29}H_{32}O_5N_2$ requires C, 71·3; H, 6·6; N, 5·7 per cent. The *picrate* was crystallised from acetone/ethyl alcohol as yellow sandy crystals, m.pt. 237° to 238°C. Found: C, 58·4; H, 4·9; N, 9·9 per cent. Eq. Wt. (by titration) 726. $C_{29}H_{32}O_5N_2$, $C_6H_3O_7N_3$ requires C, 58·6; H, 4·9; N, 9·8 per cent. Eq. Wt. 717.

3-p-Aminobenzoxy-6-morpholino-4 : 4-diphenylhexane
(II; R = $-CO.C_6H_4p\text{-}NH_2$).

Finely powdered 3-*p*-nitrobenzoxy-6-morpholino-4 : 4-diphenylhexane (1·5 g.) was added to a solution of stannous chloride (20 g.) in concentrated hydrochloric acid (20 ml.), and the mixture heated in a bath at 100°C. for 3 hours with vigorous stirring. After cooling, the tin complex was filtered off, decomposed with sodium hydroxide solution (10 per cent.) and the liberated base extracted with benzene. The benzene extracts were washed with water, dried (anhydrous sodium sulphate), and the solvent removed under reduced pressure. A little ethyl alcohol was added to the oil which remained, and after standing in the ice-chest overnight, a mass of crystals of the *amino-ester* separated and were recrystallised from ethyl alcohol as glistening white plates (1·26 g., 90 per cent.), m.pt. 110°C. (softening at 106°C.). Repeated recrystallisations did not improve the melting-point of the substance which proved to be the monohydrate of the amino-ester. Found: C, 73·2; H, 7·9; N, 5·8 per cent. $C_{29}H_{34}O_3N_2$, H_2O requires C, 73·1; H, 7·6; N, 5·9 per cent. The loss of weight at 90°C. for 1½ hours under *vacuo* (10 mm.) was 3·6 per cent.; the loss of 1 molecule of water requires a loss of 3·8 per cent. The *dihydrochloride* crystallised from dry ether/ethyl alcohol at small white crystals m.pt. 234° to 237°C. Found: C, 61·8; H, 7·1; N, 4·9 per cent. Eq. Wt. (by titration) 572. $C_{29}H_{34}O_3N_2$, 2HCl, $2H_2O$ requires C, 61·4; H, 7·1; N, 4·9 per cent.. Eq. Wt. 567.

ATTEMPTED PREPARATION OF ETHERS OF 6-MORPHOLINO-4 : 4-DIPHENYLHEXANE-3-OL. (II; R = H).

A. Using the approach ROH→RO Metal, and then reaction with aralkyl or alkyl halides.

(a) *With potassium and benzyl bromide.* Potassium (0·13 g., 0·0033 mole) was emulsified in dry toluene (15 ml.) and the alcohol (II; R = H) (1·13 g., 0·0033 mole) added and the mixture heated under anhydrous conditions for 4 hours at 70°C. The potassium reacted, small bubbles were evolved, and a little yellowish-brown precipitate was produced. The mixture was cooled, benzyl bromide (0·57 g.) dissolved in dry toluene (10 ml.) added, and the contents of the flask heated at 90°C. for 6 hours with vigorous stirring. A white precipitate (0·55 g.), containing chiefly potassium bromide, separated and, after cooling, was filtered off. The filtrate was washed with water, dried (anhydrous sodium sulphate) and the solvent removed under reduced pressure to yield a red oil (1 g.). Distillation under reduced pressure gave a main fraction, b.pt. 135° to

140°C./0·1 to 0·2 mm. (air-bath temperature) $n_D^{22°C.}$ 1·564. Redistillation of this fraction gave a colourless oil (=A, see below), of weight 0·4 g., b.pt. 135° to 140°C./0·1 to 0·2 mm. (air-bath temperature), $n_D^{22°C.}$ 1·565.

(b) *With potassium and ethyl iodide.* The application of the above method using "emulsified" potassium (0·26 g.), the alcohol (II; R = H) (2·2 g.) and ethyl iodide (1·05 g.) yielded a yellow oil (2·2 g.) which was distilled under reduced pressure to give, as the main fraction, a colourless oil (0·95 g.) of b.pt. 128°C./0·04 mm. (air-bath temperature), $n_D^{22°C.}$ 1·561 (=B, see below).

Identification of Oils A and B. These oils were proved to be identical by analysis, by the preparation of their respective hydrochlorides and picrates which possessed identical melting-points and mixed melting-points, and by the equivalent weight of their respective hydrochlorides. These identical products were proved to be 3-*morpholino*-1:1-*diphenylpropane* (IV). Found: C, 80·7; H, 8·2; N, 4·9 per cent. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2; N, 5·0 per cent. The hydrochloride was obtained from dry ether/ethyl alcohol as small white platelets, m.pt. 207° to 208°C. and mixed m.pt of 207° to 208°C. with an authentic sample of the hydrochloride kindly supplied by Glaxo Laboratories Ltd. Adamson[13] records m.pt. 208° to 209°C. Found: C, 71·0; H, 7·8; N, 4·3; Cl, 11·2 per cent. Eq. Wt. (by titration) 316. Calc. for $C_{19}H_{23}ON$, HCl: C, 71·8; H, 7·6; N, 4·4; Cl, 11·2 per cent. Eq. Wt. 317·5. The *picrate* crystallised from acetone/ethyl alcohol as yellow prisms, m.pt. 158° to 159°C. and mixed m.pt. of 158° to 159°C. with a sample of picrate prepared from the authentic sample of 3-morpholino-1:1-diphenylpropane hydrochloride. Found: C, 58·9; H, 5·3; N, 11·1 per cent. Eq. Wt. (by titration) 516. $C_{19}H_{23}ON$, $C_6H_3O_7N_3$ requires C, 58·8; H, 5·1; N, 11·0 per cent. Eq. Wt. 510.

(c) *Quantitative studies of the reaction between potassium, the alcohol* (II; R = H) and benzyl bromide. The reaction was performed as in (a) but on double the scale, and the product treated as follows. The toluene solution, containing a suspension, was extracted with water until free from ionised bromide. The bromide in the aqueous washings was precipitated as silver bromide (1·186 g.), which demonstrates a quantitative conversion of the benzyl bromide to ionised bromide. The toluene solution was dried (anhydrous sodium sulphate), most of the solvent removed under reduced pressure and dry ether (50 ml.) added. A white precipitate separated (0·06 g.) and was filtered off and found to be the *benzyl quaternary ammonium bromide* of the alcohol (II; R=H) with m.pt. and mixed m.pt. with authentic sample of 204° to 205°C. The solvent was removed from the filtrate under reduced pressure to yield a yellow oil (2·58 g.), which was dissolved in absolute alcohol (50 ml.), heated to boiling, and a solution of picric acid (1·48 g.) in boiling absolute alcohol (20 ml.) added. Large rosettes of yellow prisms of 3-morpholino-1:1-diphenylpropane picrate (2·75 g.) m.pt. 158° to 159°C. separated upon cooling, and a further crop (0·1 g.) was obtained after reducing the filtrate to 10 ml. This weight (2·85 g.) corresponds to an 87·6 per cent. conversion of the alcohol (II; R = H) to 3-morpholino-1:1-diphenyl-

propane picrate by the above treatment. The filtrate was poured into water (300 ml.) containing sodium hydroxide solution (5 ml. of 20 per cent) to remove the picric acid, and the non-acidic material extracted with benzene. The benzene extracts were washed with water, dried (anhydrous potassium carbonate) and the solvent removed under reduced pressure to yield a yellow oil (0·9 g.). Fractional distillation gave a colourless oil (0·5 g.), b.pt. 130°C./0·1 mm. which has not yet been identified. Found: C, 81·5; H, 8·1 per cent.

(d) *Reaction between the alcohol (II; R = H) and potassium.* Because of the isolation of identical products from the above experiments using benzyl bromide or ethyl iodide, the following was performed. Potassium (0·26 g.) emulsified in dry toluene (20 ml.) was heated at 60° to 70°C. with the alcohol (II; R = H) under anhydrous conditions, with stirring, for 4 hours. After cooling, a portion (2·5 ml.) of the solution was added to hot absolute alcohol (10 ml.), and a hot solution of picric acid (0·5 g.) in absolute alcohol (10 ml.) added. A yellow precipitate separated immediately, and was filtered off and washed with alcohol and water to remove excess picric acid and potassium picrate to yield a residue (0·395 g.) of m.pt. 155° to 157°C. Recrystallisation from acetone/ethyl alcohol gave yellow prisms (0·322 g.) m.pt. 158° to 159°C. of 3-morpholino-1:1-diphenylpropane picrate. The weight of crude picrate indicates at least an 85 per cent. conversion of the alcohol (II; R = H) to 3-morpholino-1:1-diphenylpropane upon heating with emulsified potassium in toluene.

Other attempts to prepare the ethers of the alcohol (II; R =H) are described briefly as follows: Sodium and benzyl bromide in toluene, or potassium carbonate and benzyl bromide in boiling xylene yielded unchanged alcohol and its benzyl quaternary ammonium bromide. The same products were obtained by the reaction of benzyl bromide upon the white precipitate (presumed to be the lithium derivative of the alcohol) obtained by the treatment of an ethereal solution of the alcohol with lithium-phenyl solution.

(e) *Benzyl quaternary ammonium bromide of the alcohol* (II; R = H).

A solution of the alcohol (0·3 g.) in dry toluene (4 ml.) was refluxed with benzyl bromide for 30 minutes. The resulting white precipitate (0·3 g.) was filtered off, m.pt. 199° to 201° C., and recrystallised from ether/ethyl alcohol as rosettes of white needles, m.pt. 205° to 206°C. Found: C, 67·4; H, 7·2; N, 2·9 per cent. $C_{22}H_{36}O_2NBr$ requires C, 68·2; H, 7·1; N, 2·7 per cent.

B. Using the attempted approach ROH→RX and then treatment with R'ONa.

Thionyl chloride reacted with a chloroform solution of the alcohol (II; R = H) and phosphorus pentachloride reacted with a benzene solution of the alcohol. The analyses of the products indicated that they were mixtures of the desired chloro-compound and the dehydrated alcohol. Attempted distillation under reduced pressure led to decomposition, and attempted separation via the hydrochlorides also failed. The

crude mixture was heated with the sodium derivative of benzyl alcohol, but the desired ether was not obtained.

The attempted preparation of the *p*-toluenesulphonyl ester of the alcohol by the Schotten-Baumann reaction also failed. When the preparation of this ester was attempted by refluxing a solution of the alcohol (1 g.) in dry toluene (10 ml.) with *p*-toluenesulphonyl chloride (1 g.) for 6 hours, and then diluting with dry ether (40 ml.), an oil separated and quickly solidified. This was recrystallised from alcohol/ether to give rosettes of white needles (0·4 g.) of *6-morpholino-4 : 4-diphenylhexan-3-ol p-toluene sulphonate* of m.pt. and mixed m.pt. with authentic sample of 182° to 183°C. Found: C, 68·3; H, 7·4; N, 2·9 per cent. $C_{22}H_{29}O_2N$, $C_7H_8O_3S$ requires C, 68·1; H, 7·2; N, 2·7 per cent.

6-Morpholino-4 : 4-diphenylhexan-3-ol p-*toluene sulphonate.*

To a solution of the alcohol (II; R = H) (0·15 g.) and *p*-toluene sulphonic acid (0·08 g.) in hot absolute alcohol (1 ml.), dry ether (10 ml.) was added. Upon cooling, rosettes of white needles separated, m.pt. 181° to 182°C. Recrystallisation from ether/ethyl alcohol gave rosettes of white needles, m.pt. 182° to 183°C.

References

1. Report No. 981, Office of the Publication Board, Washington, D.C., p. 84.
2. B.I.O.S. Final Report No. 116. Item No. 24, p. 51.
3. Speeter, Byrd, Cheney and Binkley, *J. Amer. chem. Soc.*, 1949, **71**, 57.
4. Dupré, Elks, Hems, Speyer and (in part) Evans, *J. chem. Soc.*, 1949, 501.
5. *Organic Reactions*, John Wiley and Sons, **2**, p. 204.
6. *Organic Reactions*, John Wiley and Sons, **2**, p. 204 footnote.
7. May and Mosettig, *J. org. Chem.*, 1948, **13**, 459.
8. Hickinbottom *Reactions of Organic Compounds*, Longmans, Green and Co., 1936, 70.
9. Huang-Minlon, *J. Amer. chem. Soc.*, 1946, **68**, 2487.
10. Small, *New York Acad. Sci.*, 1948, **51**, 18.
11. Thorp, *Brit. J. Pharmacol.*, 1946, **1**, 113.
12. Dodds, Lawson, Simpson and Williams, *J. Physiol.*, 1945, **104**, 47.
13. Adamson, *J. chem. Soc.*, 1949, S153.

FLUORIMETRIC AND MICROBIOLOGICAL ASSAYS OF RIBOFLAVINE IN MALTED PREPARATIONS

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Correction

Page 928, lines 40-42, *should read:* The low solubility of the blue fluorescent substance in chloroform prevented its efficient removal by the latter, which has been recommended for purifying extracts[10].