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Mannich Reactions in High-boiling Solvents

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Some Mannich bases of potential pharmacological interest have been prepared. In order to obtain the required compounds directly from a Mannich reaction, a high-boiling alcohol had to be used as solvent. The use of dimethylformamide as solvent led to the introduction of a methylene substituent on the α-carbon atom. The structures of the new compounds have been proved by independent synthesis.

BASIC esters of benzilic acid, *e.g.* benactazine (I),[1] have been shown to possess antispasmodic activity. Alkoxy-substituted basic esters derived from various open-chain amino-alcohols have been found to possess useful anti-tussive activity.[2]

$$HO{\cdot}CPh_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$$
(I)

We report the preparation of the ketones (IV) and (IX), which are related to benactazine but have the ester function replaced by a ketonic group. As a result of unexpected side reactions, their branched methyl homologues (VIII) and (XI) were also obtained. In addition, the ketonic groups have been reduced and the resulting alcohols acetylated.

4-Dimethylamino-1-hydroxy-1,1-diphenylbutan-2-one (IV) was prepared by Schlesinger and Gordon[3] by means of a Mannich reaction on 1-hydroxy-1,1-diphenylpropan-2-one (VI) in pentyl alcohol, who reported no yield and quoted m.p. 175° for the hydrochloride. Buehler and his co-workers[4] who performed the same reaction with n-octanol as solvent, claimed a 19% (crude) yield, and gave the m.p. as 163·5—165°.

We investigated the reaction in several solvents. With ethanol a negligible yield of Mannich base was produced. With pentyl alcohol pure material, m.p. 175—176°, was obtained but in very low yield (2%). With n-octanol yields as high as 10% were achieved but on some occasions repeated recrystallisation of the product failed to raise its m.p. above 163—165°. When the reaction product was purified *via* the previously unknown free base two different compounds were obtained. The less soluble base had m.p. 123° and gave the hydrochloride, m.p. 175—176°. Analysis of both base and hydrochloride gave results in agreement with structure (IV). The i.r. carbonyl peak was at the expected position (5·85 μm.). The more soluble base had m.p. 77° and gave a hydrochloride, m.p. 184°. Analysis of these gave results in agreement with the methylene-substituted structure (III) and the carbonyl

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[1] J. Klosa, *Deut. Med. Wochschr.*, 1950, **75**, 870.
[2] F. P. Doyle, M.D. Mehta, R. Ward, J. Bainbridge, and D. M. Brom, *J. Medicin. Chem.*, 1965, **8**, 571.
[3] A. Schlesinger and S. M. Gordon, U.S.P., 2,997,479/1961.
[4] C. A. Buehler, H. A. Smith, K. V. Nayak, and T. A. Magee, *J. Org. Chem.*, 1961, **26**, 1573.

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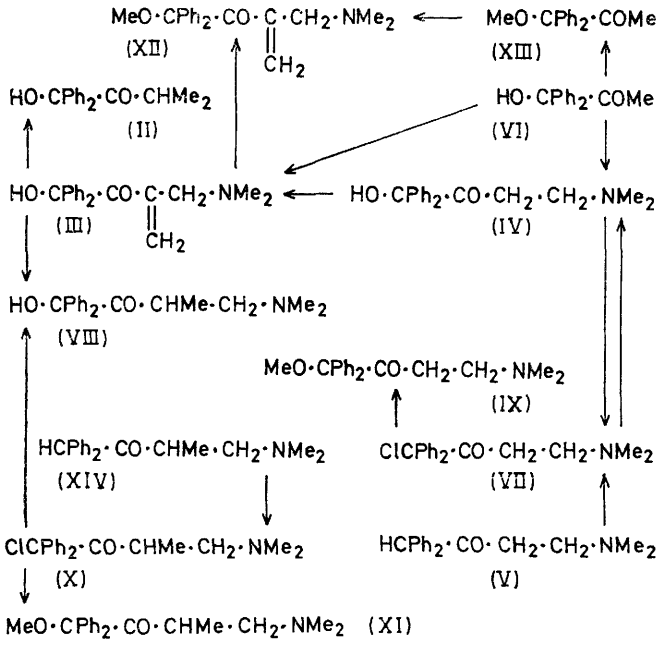
peaks (6·0 μm.) were typical for a conjugated ketone. The product reported by Buehler and his co-workers [4] was probably a mixture of hydrochlorides (III) and (IV). The material m.p. 163—165° which we obtained under the conditions used by those workers was shown by i.r. spectroscopy to be such a mixture. The highest yields



of the normal Mannich base (15%) were obtained when ethylene glycol was used as a solvent. Furthermore, the starting material (VI), preparation of which is a lengthy business, could be recovered in good yield, whereas only polymerised non-basic material was recovered after a reaction in n-octanol. When dimethylformamide or diethyl phthalate was used as solvent the product was exclusively the methylene-substituted compound (III).

To confirm the structures of these products alternative syntheses were sought. Buehler and his co-workers [4] treated 4-dimethylamino-1,1-diphenylbutan-2-one (V) with bromine followed by water to obtain the alcohol (IV), but their yield (12%) and m.p. (163—164°) were again low and the material was probably slightly impure. We have discovered that the ketone (V) reacts with chlorine to give the chloro-compound (VII) which is converted into the alcohol (IV) when left in water overnight. On treatment with thionyl chloride the alcohol (IV) gives back the chloro-compound (VII). This appears the best method for the preparation of the normal Mannich base (IV). Refluxing the hydrochloride of the normal Mannich base (IV) with paraformaldehyde in dimethylformamide gave the methylene-substituted compound (III). The yield was improved if dimethylamine hydrochloride was included in the reaction mixture.

Hydrogenation of the methylene-substituted compound (III) over palladised charcoal gave the branched methyl compound (VIII). When palladium supported on calcium carbonate was used as catalyst, an additional product which proved to be 1-hydroxy-3-methyl-1,1-diphenylbutan-2-one (II) was obtained. The position of the carbonyl absorption band for both these reduction products was normal for unconjugated ketones (5·85 μm). 4-Dimethylamino-3-methyl-1,1-diphenylbutan-2-one (XIV) hydrochloride was treated with chlorine to give the chloro-derivative (X). On treatment with water it gave the alcohol (VIII), confirming the structure of this compound and also providing the best route for its preparation.

Attempts to carry out Mannich reactions on 1-methoxy-1,1-diphenylpropan-2-one (XIII) in any of the alcohols already mentioned resulted in negligible yields of Mannich base. When the solvent was changed to dimethylformamide, the *O*-methyl methylene-substituted compound (XII) was obtained. The same compound was produced by treatment of the methylene-substituted alcohol (III) with thionyl chloride followed by methanol. The normal *O*-methyl Mannich base (IX) could only be obtained by refluxing the chloro-compound (VII) in methanol. Attempts to hydrogenate the *O*-methyl methylene-substituted compound (XII) to the saturated ketone (XI) gave poor yields of products which had un satisfactory analyses. The required product was prepared in good yield by treating the chloro-compound (X) with refluxing methanol.

The straight-chain ketones (IV), (V), and (IX) were easily reduced to the corresponding secondary alcohols by sodium borohydride at room temperature. The branched methyl ketones (VIII), (XI), and (XIV) however, were best reduced by lithium aluminium hydride in refluxing tetrahydrofuran. The alcohols were converted into their acetates by reaction with acetic anhydride or acetyl chloride. 4-Dimethylamino-1,1-diphenylbutane-1,2-diol reacted with acetyl chloride in refluxing ether in the presence of pyridine to give the monoester (XV). When the reaction was carried out with acetic anhydride in refluxing pyridine the corresponding diester (XVI) was obtained. When the diol was refluxed in acetic anhydride alone, the enolic ester (XVII) was obtained.

$$HO{\cdot}CPh_2{\cdot}CH(OAc){\cdot}[CH_2]_2{\cdot}NMe_2$$
(XV)

$$AcO{\cdot}CPh_2{\cdot}CH(OAc){\cdot}[CH_2]_2{\cdot}NMe_2$$
(XVI)

$$Ph_2C{:}C(OAc){\cdot}[CH_2]_2{\cdot}NMe_2$$
(XVII)

EXPERIMENTAL

4-Dimethylamino-1-hydroxy-1,1-diphenylbutan-2-one (IV). —*Method A*. A solution of 1-hydroxy-1,1-diphenylpropan-2-one [5] (200 g.) paraformaldehyde (64 g.), and dimethylamine hydrochloride (100 g.) in ethanediol (1 l.) was refluxed with stirring at 190—195° for 10 min. A suspension of paraformaldehyde (64 g.) in ethanediol (100 ml.) was added during 0·5 hr. Concentrated hydrochloric acid (1

[5] G. F. Hennion and B. R. Fleck, *J. Amer. Chem. Soc.*, 1955, **77**, 3253.

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ml.) was added and refluxing was continued for a further 10 min. to produce a clear solution. The cooled solution was poured into brine (1 l.) and washed with ether (3 × 200 ml.). The aqueous solution was made alkaline (NaOH) and extracted with chloroform (2 × 500 ml.). The chloroform solution was dried ($MgSO_4$) and evaporated to leave the *amino-ketone* (40 g., 16%), m.p. 123—125° [from light petroleum (b.p. 80—100°)] (Found: C, 76·4; H, 7·5; N, 4·8. $C_{18}H_{21}NO_2$ requires C, 76·4; H, 7·4; N, 4·9%). It gave a *hydrochloride*, m.p. 175—176° (from ethanol) (Found: C, 67·9; H, 6·8; Cl, 11·1; N, 4·4. $C_{18}H_{22}ClNO_2$ requires C, 67·6; H, 6·9; Cl, 11·1; N, 4·4).

Method B. A solution of 1-chloro-4-dimethylamino-1,1-diphenylbutan-2-one hydrochloride (0·5 g.) in water (10 ml.) was set aside for 24 hr., then evaporated. The residue was recrystallised to give the amino-ketone hydrochloride (0·4 g., 84%), m.p. and mixed m.p. with sample prepared by method A, 175—176°.

1-*Chloro*-4-*dimethylamino*-1,1-*diphenylbutan*-2-*one* (VII) *Hydrochloride.*—*Method A.* A solution of 4-dimethylamino-1-hydroxy-1,1-diphenylbutan-2-one hydrochloride (2 g.) and thionyl chloride (2 ml.) in chloroform (40 ml.) was refluxed for 3 hr., then evaporated. The residue was refluxed with ethyl acetate, then collected and recrystallised from chloroform–ether to give the *chloro-keto-amine hydrochloride* (1·4 g., 66%), m.p. 132·5—133° (Found: C, 64·3; H, 6·2; Cl, 21·2; N, 4·1. $C_{18}H_{21}Cl_2NO$ requires C, 63·9; H, 6·2; Cl, 21·0; N, 4·1%).

Method B. A solution of 4-dimethylamino-1,1-diphenylbutan-2-one hydrochloride [6] (20 g.) in chloroform (200 ml.) was stirred and heated to 40°. Chlorine was passed in for 15 min. The solvent was removed and the residue was refluxed with ethyl acetate to give the chloro-keto-amine hydrochloride (15 g., 67%), m.p. and mixed m.p. with sample prepared by method A, 132—133°.

3-*Dimethylaminomethyl*-1-*hydroxy*-1,1-*diphenylbut*-3-*en*-2-*one* (III).—*Method A.* A suspension of paraformaldehyde (12·8 g.) in dimethylformamide (20 ml.) was added in portions during 0·75 hr. to a stirred, refluxing solution of 1-hydroxy-1,1-diphenylpropan-2-one (20 g.) and dimethylamine hydrochloride (10 g.) in dimethylformamide (100 ml.) and heating was continued for a further 10 min. The solution was worked up as before and the product was acidified with ethanolic hydrochloric acid to give the *amino-ketone hydrochloride* (8·2 g., 28%), m.p. 182—183° (from ethanol) (Found: C, 68·7; H, 6·9; Cl, 10·7; N, 4·2. $C_{19}H_{22}ClNO_2$ requires C, 68·7; H, 6·6; Cl, 10·7; N, 4·2%), $\nu_{max.}$ 6·0 μm. From the pure hydrochloride was obtained the *free base*, m.p. 76·5—77° [from light petroleum (b.p. 60—80°)] (Found: C, 77·4; H, 7·2; N, 4·7. $C_{19}H_{21}NO_2$ requires C, 77·2; H, 7·1; N, 4·7%).

Method B. A solution of 4-dimethylamino-1-hydroxy-1,1-diphenylbutan-2-one hydrochloride (1·4 g.), paraformaldehyde (0·64 g.), and dimethylamine hydrochloride (0·48 g.) in dimethylformamide (6 ml.) was refluxed for 10 min. More paraformaldehyde (0·64 g.) was added in portions to the refluxing solution during 0·5 hr. Concentrated hydrochloric acid (2 drops) was added and refluxing was continued for a further 5 min. The solution was worked up as before to give the amino-ketone hydrochloride (0·45 g., 31%), m.p. and mixed m.p. with a sample prepared by method A, 182—183°.

4-*Dimethylamino*-3-*methyl*-1,1-*diphenylbutan*-2-*one Hydrochloride* (XIV).—A solution of 1,1-diphenylbutan-2-one [7] (400 g.), paraformaldehyde (150 g.), and dimethylamine hydrochloride (200 g.) in dimethylformamide (2 l.) was refluxed and stirred for 10 min. A suspension of paraformaldehyde (150 g.) in dimethylformamide (200 ml.) was added to the refluxing solution during 40 min. Concentrated hydrochloric acid (5 ml.) was added and refluxing was continued for a further 5 min.

Most of the solvent (1·5 l.) was removed and the residue was poured into water (1 l.) and washed with ether (4 × 500 ml.). The combined ethereal washings were dried ($MgSO_4$) and evaporated to give 3-*methyl*-1,1-*diphenyl but*-3-*en*-2-*one* (339 g., 80%), m.p. 97—98° [from light petroleum (b.p. 80—100°)] (Found: C, 86·6; H, 6·9. $C_{17}H_{16}O$ requires C, 86·5; H, 6·8%), $\nu_{max.}$ 6·0 μm. The aqueous solution was made alkaline (NaOH) and extracted with ether (3 × 200 ml.). The extract was dried ($MgSO_4$) and evaporated and the residue was converted into the *amino-ketone hydrochloride* (55 g., 10%), m.p. 154—155° (from butanone) (Found: C, 71·9; H, 7·7; Cl, 11·0; N, 4·4. $C_{19}H_{24}ClNO$ requires C, 71·8; H, 7·6; Cl, 11·2; N, 4·4%). A solution of the recovered 3-methyl-1,1-diphenylbut-3-en-2-one (339 g.) and dimethylamine (500 ml.) in ether (1 l.) was set aside overnight. The excess of dimethylamine and most of the ether were removed; acid/base extraction of the residue gave the amino-ketone hydrochloride (258 g., 57%), m.p. and mixed m.p. 154—155°.

1-*Chloro*-4-*dimethylamino*-3-*methyl*-1,1-*diphenylbutan*-2-*one* (X) *Hydrochloride.*—Chlorine was passed into a stirred suspension of 4-dimethylamino-3-methyl-1,1-diphenylbutan-2-one hydrochloride (20 g.) in tetrahydrofuran (100 ml.). Refluxing began after 20 min. and the solution cleared after a further 10 min. After a further 10 min. the passage of chlorine was stopped and the solvent was removed to give the *chloro-keto-amine hydrochloride* (15 g., 68%), m.p. 181—182° (from butanone) (Found: C, 64·7; H, 6·5; Cl, 20·0; N, 4·0. $C_{19}H_{23}Cl_2NO$ requires C, 64·8; H, 6·5; Cl, 20·2; N, 4·0%).

4-*Dimethylamino*-1-*hydroxy*-3-*methyl*-1,1-*diphenylbutan*-2-*one* (VIII) *Hydrochloride.*—*Method A.* A solution of 1-chloro-4-dimethylamino-3-methyl-1,1-diphenylbutan-2-one hydrochloride (29 g.) in water (60 ml.) was warmed on a boiling-water-bath for 0·75 hr. The solvent was removed to leave the *hydroxy-keto-amine hydrochloride* (27·3 g., 99%), m.p. 178—179° (from propan-2-ol–ether) (Found: C, 68·4; H, 7·2; Cl, 10·6. $C_{19}H_{24}ClNO_2$ requires C, 68·3; H, 7·2; Cl, 10·6%). It gave the *free base*, m.p. 82—83° (from methanol) (Found: C, 76·6; H, 8·0; N, 4·7. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·8; N, 4·7%).

Method B. A solution of 3-dimethylaminomethyl-1-hydroxy-1,1-diphenylbut-3-en-2-one hydrochloride (2 g.) in methyl alcohol (100 ml.) was hydrogenated over 10% palladised charcoal at room temperature and pressure. The theoretical amount of hydrogen was taken up in 0·75 hr., after which the reaction stopped. The solution was filtered and evaporated to leave the hydroxy-keto-amine hydrochloride (1·3 g., 65%), m.p. and mixed m.p. with a sample prepared by method A, 177—179°, 5·85 μm. When the reaction was repeated with 5% palladised calcium carbonate (2 g.) as catalyst, 1·5 times the theoretical volume of hydrogen had been taken up when the reaction stopped. The yield of the hydroxy-keto-amine hydrochloride was reduced to 36% but from the mother liquors after the

[6] W. Wilson and Zu-Yoong Kyi, *J. Chem. Soc.*, 1952, 1321.
[7] E. Walton, P. Ofner, and R. H. Thorp, *J. Chem. Soc.*, 1949, 648.

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recrystallisation was obtained 1-*hydroxy*-3-*methyl*-1,1-*diphenylbutan*-2-*one* (II) (20%), m.p. 71—72° [from light petroleum (b.p. 40—60°)] (Found: C, 80·7; H, 7·4. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%), $\nu_{max.}$ 5·85 μm.

4-*Dimethylamino*-1-*methoxy*-1,1-*diphenylbutan*-2-*one* (IX) *Hydrochloride*.—A solution of 1-chloro-4-dimethylamino-1,1-diphenylbutan-2-one hydrochloride (2·5 g.) in methanol (50 ml.) was refluxed for 24 hr. The methanol was removed to leave the *methoxy-amino-ketone hydrochloride* (2 g., 80%), m.p. 150—151° (from butanone) (Found: C, 68·3; H, 7·2; Cl, 10·5; N, 4·2; CH_3O, 9·3. $C_{19}H_{24}ClNO_2$ requires C, 68·3; H, 7·2; Cl, 10·6; N, 4·2; CH_3O, 9·3%).

3-*Dimethylaminomethyl*-1-*methoxy*-1,1-*diphenylbut*-3-*en*-2-*one* (XII) *Hydrochloride*.—*Method A*. A solution of 1-methoxy-1,1-diphenylpropan-2-one [8] (80 g.), paraformaldehyde (25 g.), and dimethylamine hydrochloride (80 g.) in dimethylformamide (500 ml.) was stirred under reflux for 10 min. A suspension of paraformaldehyde (25 g.) in dimethylformamide (50 ml.) was added to the refluxing solution during 30 min. Concentrated hydrochloric acid (1 ml.) was added and refluxing was continued for a further 5 min. The solution was worked up as before and the residue was dissolved in ethyl acetate (100 ml.) and added to a solution of picric acid (66 g.) in ethyl acetate (100 ml.) to give the *methoxy-keto-amine picrate* (102 g., 57%), m.p. 152° (from ethanol) (Found: C, 58·1; H, 5·2; N, 10·5. $C_{26}H_{26}N_4O_9$ requires C, 58·0; H, 4·8; N, 10·4%). The picrate (71 g.) was shaken with dilute sodium hydroxide solution (3 l.) and ether (3 × 100 ml.). The combined ethereal extracts were dried ($MgSO_4$) and evaporated. The residue was converted into the *hydrochloride* (36 g., 79%), m.p. 173—174° (from butanone) (Found: C, 69·2; H, 7·2; Cl, 10·2; N, 4·2. $C_{20}H_{24}ClNO_2$ requires C, 69·5; H, 7·0; Cl, 10·3; N, 4·1%).

Method B. A solution of 3-dimethylaminomethyl-1-hydroxy-1,1-diphenylbut-3-en-2-one hydrochloride (6·3 g.) and thionyl chloride (6·3 g.) in chloroform (60 ml.) was refluxed for 3 hr. The solvent was removed and the residue was dissolved in methanol (60 ml.) and refluxed overnight. The excess of methanol was removed to give the methoxy-keto-amine hydrochloride (4 g., 60%), m.p. and mixed m.p. with a sample prepared by method A, 173—174°.

4-*Dimethylamino*-1-*methoxy*-3-*methyl*-1,1-*diphenylbutan*-2-*one* (XI) *Hydrochloride*.—A solution of 1-chloro-4-dimethylamino-3-methyl-1,1-diphenylbutan-2-one hydrochloride (30 g.) in methanol (250 ml.) was refluxed overnight and evaporated to leave the *methoxy-keto-amine hydrochloride* (22 g., 74%), m.p. 165—166° (from butanone) (Found: C, 69·0; H, 7·5; Cl, 10·2; N, 4·1. $C_{20}H_{26}ClNO_2$ requires C, 69·1; H, 7·5; Cl, 10·2; N, 4·0%).

Reduction of Ketones.—*Method A*. A solution of sodium borohydride (1 g.) in water (15 ml.) was added dropwise to a stirred solution of the ketone hydrochloride (3 g.) in methyl alcohol (40 ml.). Stirring was continued for 1 hr. Concentrated hydrochloric acid (3 ml.) was added dropwise and the solution was evaporated. A solution of the residue in water (20 ml.) was made alkaline (NaOH) and extracted with ether (3 × 20 ml.). The combined ethereal layers were dried ($MgSO_4$) and evaporated. The products are listed in Table 1.

Method B. A suspension of the ketone hydrochloride (0·02 mol.) in tetrahydrofuran (100 ml.) was added during

[8] J. V. Greenhill, *J. Chem. Soc.* (*C*), 1970, 1298.

TABLE 1

$R^1CPh_2{\cdot}CH(OH){\cdot}CHR^2{\cdot}CH_2{\cdot}NMe_2$

							Found (%)				Requires (%)			
R^1	R^2	Method	Form	M.p.	Solvent	Yield (%)	C	H	Hal	N	C	H	Hal	N
H	H	A	Base	78—79°	Light petroleum (b.p. 60—80°)	74	80·1	8·7		5·4	80·3	8·6		5·2
HO	H	A	Base	89	Light petroleum (b.p. 80—100°)	77	75·6	8·2		5·0	75·8	8·1		4·9
HO	H	A	HCl	226	Ethanol		66·9	7·6	Cl 10·9	4·7	67·2	7·5	Cl 11·1	4·4
MeO	H	A	Base	89·5—90·5	Light petroleum (b.p. 40—60°)	79	76·3	8·5		4·7	76·2	8·4		4·7
H	Me	B	Base	49—50	Light petroleum (b.p. 40—60°)	67	80·7	8·9		4·8	80·6	8·8		4·9
H	Me	B	HCl	260—261	Methanol–ether		71·5	8·2	Cl 11·1	4·7	71·3	8·1	Cl 11·1	4·4
HO	Me	B	Base	102·5—103·5	Light petroleum (b.p. 60—80°)	51	76·5	8·7		4·7	76·2	8·4		4·7
HO	Me	B	HBr	202—203	Ethanol		60·3	6·9	Br 20·8	3·5	60·0	6·8	Br 21·0	3·7
MeO	Me	B	Base	150—151	Methanol	30	77·1	8·7		4·7	76·7	8·6		4·5

TABLE 2

$R^1CPh_2{\cdot}CHOAc{\cdot}CHR_2{\cdot}CH_2{\cdot}NMe_2$

							Found (%)				Requires (%)			
R^1	R^2	Method	Form	M.p.	Solvent	Yield (%)	C	H	Cl	N	C	H	Cl	N
H	H	A	HCl	193—194°	Ethanol–ether	74	69·1	7·6	10·6	4·0	69·1	7·5	10·2	4·0
HO	H	B	HCl	205·5	Propanol–ether	78	66·0	7·4	9·8	3·5	66·0	7·2	9·8	3·9
HO	H		Base	102·5—103·5	Light petroleum (b.p. 80—100°		73·6	7·9		4·6	73·4	7·6		4·3
AcO	H	C	HCl	193—194	Propan-2-ol–ether	73	65·2	7·3	8·7	3·3	65·1	6·9	8·8	3·5
MeO	H	A	HCl	193—194	Butanone	95	66·6	7·5	9·5	3·6	66·7	7·4	9·4	3·7
H	Me	A	HCl	222—223	Butanone	62	70·0	7·9	9·5	3·9	69·8	7·8	9·8	3·9
HO	Me	D	HCl	196—197	Ethanol–ether	51	66·6	7·6	9·4	3·6	66·7	7·4	9·4	3·7
AcO	Me	C	HCl	199—200	Ethanol–ether	44	66·0	7·6	8·7	3·5	65·8	7·2	8·5	3·3
MeO	Me	A	HCl	192—193	Butanone–ether	73	67·5	7·8	9·1	3·7	67·4	7·7	9·1	3·6

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5 min. to a stirred suspension of lithium aluminium hydride (0·02 mol.) in tetrahydrofuran (100 ml.), and the mixture was refluxed for 0·5 hr., cooled on an ice-bath, and decomposed with water (100 ml.). After acidification with dilute hydrochloric acid, the solution was washed with ether (3 × 200 ml.), made alkaline (NaOH), and extracted with ether (3 × 50 ml.). The combined extracts were dried ($MgSO_4$) and evaporated to give the product (Table 1).

Preparation of Esters. Method A. A solution of the appropriate alcohol hydrochloride (2 g.) in acetic anhydride (30 ml.) was refluxed for 1 hr. The excess of acetic anhydride was removed and the residue was recrystallised from the solvent given in Table 2.

Method B. Acetyl chloride (2 ml.) was carefully added to an ice-cold solution of the appropriate alcohol (2 g.) in pyridine (10 ml.) and ether (20 ml.). The resulting mixture was refluxed with stirring for 3 hr. Sodium carbonate (2 g.) in water (20 ml.) was added to the cooled mixture and the layers were separated. The aqueous layer was washed with ether (2 × 20 ml.). The combined etheral extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in ethanol (10 ml.) and acidified with ice-cold ethanolic hydrochloric acid to give the product (Table 2).

Method C. A solution of the appropriate alcohol (2 g.) in pyridine (3 ml.) and acetic anhydride (3 ml.) was gently refluxed for 0·5 hr. The solvents were removed and the residue was dissolved in ethanol (10 ml.) and acidified with ice-cold ethanolic hydrochloric acid to give the product (Table 2).

Method D. A solution of the appropriate alcohol (1 g.) in pyridine (5 ml.) and acetic anhydride (2 ml.) was set aside overnight. The solvents were removed and the residue was dissolved in ethanol and acidified with ice-cold ethanolic hydrochloric acid to give the product (Table 2).

2-*Acetoxy*-4-*dimethylamino*-1,1-*diphenylbut*-1-*ene* (XVII) *Hydrochloride*.—A solution of 4-dimethylamino-1,1-diphenylbutane-1,2-diol hydrochloride in acetic anhydride (30 ml.) was refluxed for 1 hr. The excess of anhydride was removed to leave the *enol acetate hydrochloride* (1·9 g., 79%), colourless plates, m.p. 218° (from propan-2-ol) (Found: C, 69·5; H, 7·1; Cl, 10·5; N, 4·2. $C_{20}H_{24}ClNO_2$ requires C, 69·5; H, 7·0; Cl, 10·3; N, 4·1%).

[0/027 *Received, January 7th,* 1970]