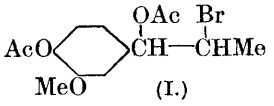
CC.—*Bases derived from Some Substituted Propenylbenzenes, with a Note on the Preparation of Pure Methylamine.*

By THOMAS MARVEL SHARP and WILLIAM SOLOMON.

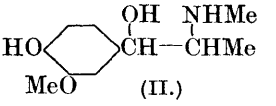
THE interaction of bases with halogenohydrins of the type Ar·CH(OR)·CHXR′, where R and R′ are hydrogen or methyl and X is a halogen, has been the subject of much study, mainly with a view to the synthesis of derivatives of adrenaline and ephedrine (Fourneau, *J. Pharm. Chim.*, 1904, **20**, 481; Barger and Jowett, J., 1905, **87**, 967; Pauly and Neukam, *Ber.*, 1908, **41**, 4159; Böttcher, *Ber.*, 1909, **42**, 259; Mannich, *Arch. Pharm.*, 1910, **248**, 127, etc.). An example is the formation of *p*-methoxyephedrine by the following series of reactions (Koller, *Monatsh.*, 1926, **47**, 397);

$$MeO\cdot C_6H_4\cdot CH{:}CH\cdot CH_3 \longrightarrow MeO\cdot C_6H_4\cdot CHBr\cdot CHBr\cdot CH_3 \longrightarrow MeO\cdot C_6H_4\cdot CH(OMe)\cdot CHBr\cdot CH_3 \longrightarrow MeO\cdot C_6H_4\cdot CH(OMe)\cdot CH(NHMe)\cdot CH_3 \longrightarrow MeO\cdot C_6H_4\cdot CH(OH)\cdot CH(NHMe)\cdot CH_3.$$

In the same paper a series of reactions was described starting from *iso*eugenol, but in this case only amorphous products were obtained. It is noteworthy that in no case has a satisfactory result been obtained when the initial compound has contained a phenolic hydroxyl group. It is well known that dibromides, bromohydrins and methoxybromides of the types under discussion are very unstable substances which rapidly decompose on exposure to air (compare Hell and Portmann, *Ber.*, 1895, **28**, 2089; Auwers and Müller, *Ber.*, 1902, **35**, 114). It appeared to the authors that the process, *e.g.*, with *iso*eugenol, could be improved by starting with acetyl*iso*eugenol dibromide, a colourless, crystalline, comparatively stable compound in which the α-bromine atom might be replaced by an acetoxy-group, by the action of silver acetate. The resulting acetoxybromide (I) is crystalline and is sufficiently stable for the required purpose. This on treatment with methylamine was expected to furnish the desired α-hydroxy-β-methylamino-α-4-hydroxy-3-methoxyphenylpropane (II).



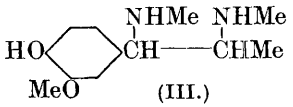
(I.)



(II.)

Actually the compound formed in this reaction was a diamine, *viz.*, αβ-di(methylamino)-α-4-hydroxy-3-methoxyphenylpropane (III),

which was also obtained by the action of methylamine on acetyl-*iso*eugenol dibromide. This unexpected result led to the inves-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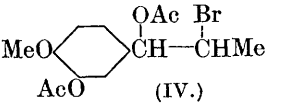
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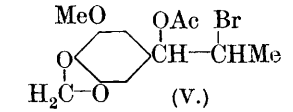
tigation of similarly constituted acetoxybromides. For this purpose the acetoxybromides from acetyl*iso*chavibetol (IV) and *iso*myristicin (V) were chosen. *iso*Chavibetol yields by this process two isomeric monoamino-bases, and *iso*myristicin only one monoamino-base. The acetoxy-group in the side chain is not therefore the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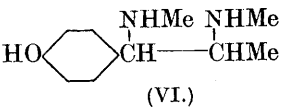
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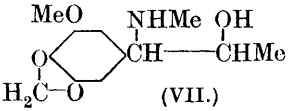
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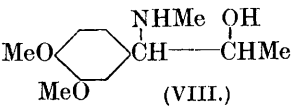
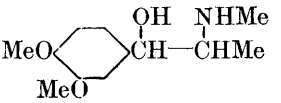

(VIII.)

determining factor in the formation of the diamine, and inspection of the formulæ of the three compounds *iso*eugenol, *iso*chavibetol, and *iso*myristicin shows that the most obvious way in which *iso*-eugenol differs from the other two is in the presence and position of the hydroxyl group. In order to test whether the formation of

(IX.)

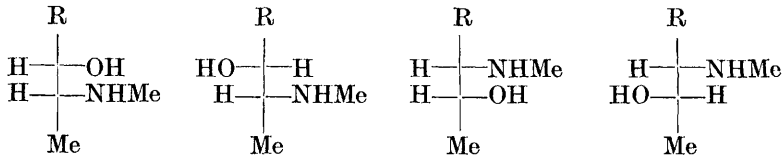


the diamine is due to the influence of a hydroxyl group in the para-position to the side chain, the above series of reactions was performed with *p*-acetoxypropenylbenzene. Here again a diamine was obtained, the compound isolated being αβ-di(methylamino)-α-*p*-hydroxyphenylpropane (VI).

The constitutions of the monoamino-bases obtained from *iso*-chavibetol and from *iso*myristicin do not follow from the method of preparation; for Mannich (*loc. cit.*) has shown that bromohydrins of the type R·CH(OH)·CHBrR′ on treatment with bases first yield internal oxides R·CH—CHR′, which then open to form either R·CH(OH)·CH(N=)·R′ or R·CH(N=)·CH(OH)R′ or both. It was therefore necessary in order to prove the constitutions of these bases to synthesise them by a method which would preclude the formation of intermediate oxides. This was done by the use of

methoxybromides in place of acetoxybromides, and demethylation of the resulting methoxy-bases (compare Koller, *loc. cit.*; Späth, *Ber.*, 1925, **58**, 1268, etc.).

In the case of *iso*myristicin the bases obtained by the two processes were different. Each of these substances, however, contains two asymmetric carbon atoms, so that the α-hydroxy-β-methylamino-compound and the α-methylamino-β-hydroxy-compound can each exist in two diastereoisomeric (racemic) forms (a)(b) and (c)(d).



If the two isomeric bases obtained differed stereochemically only, they should be interconvertible by one of the processes of optical isomerisation; if, however, the difference were structural, the two bases would, on isomerisation, lead to two different diastereoisomerides. Actually it was found that the base from the acetoxybromide gave, by a process of acetylation and hydrolysis, a diastereoisomeric base differing from the base from the methoxybromide. The latter base is (a) or (b) and therefore the bases from the acetoxybromide are the other pair (c) and (d), *viz.*, α-methylamino-β-hydroxy-α-3-methoxy-4 : 5-methylenedioxyphenylpropane (VII).

Acetyl*iso*chavibetol acetoxybromide on treatment with methylamine yields two isomeric bases A and B. The former with diazomethane, which methylates the phenolic hydroxyl group and leaves the alcoholic hydroxyl group and nitrogen intact, gives a methyl ether, m. p. 60—62°, identical with a compound to which Mannich (*Apoth. Ztg.*, 1909, **24**, 60; *loc. cit.*) ascribes the constitution (VIII); the evidence for this, although not conclusive, is strong. B similarly furnishes an isomeric methyl ether, m. p. 95—97°, which may have its methylamino-group on either the α- or the β-carbon atom. The synthesis of one of the possible diastereoisomerides of the constitution (IX) was effected, as in the case of *iso*myristicin, through the methoxybromide. This melts at 130—131° and is thus different from the methyl ethers of A and B. The method of isomerisation which had proved successful in the case of the α-methylamino-derivative of *iso*myristicin led to inconclusive results with the methyl ether of B. The action of phosphorus pentachloride and treatment of the product with alcoholic potassium hydroxide converted this compound into the base (IX), m. p. 130—131°. This result would appear to prove that the methyl ether of B was the

diastereoisomeride of (IX), but subsequent experiments showed that Mannich's base, m. p. 62°, also yields the same base, m. p. 130—131°, by this process. One of these methoxy-bases A and B must have its nitrogen on the α-carbon atom, since neither is identical with the compound derived from the methoxybromide, so that in effect a methylamino-group has passed from an α- to a β-carbon atom. The following mechanism, which it is proposed to submit to experimental verification as soon as sufficient material can be accumulated, would explain the anomaly :

$$R{\cdot}CH(NHMe){\cdot}CH(OH){\cdot}CH_3 \longrightarrow R{\cdot}CH(NHMe){\cdot}CHCl{\cdot}CH_3 \longrightarrow$$

$$R{\cdot}\overset{\displaystyle NMe}{\underset{\displaystyle \diagdown\!\diagup}{CH}}\!\!-\!\!-\!\!-\overset{\displaystyle \diagdown\!\diagup}{CH}{\cdot}CH_3 \longrightarrow R{\cdot}CH(OH){\cdot}CH(NHMe){\cdot}CH_3.$$

The possibility of such a reaction is indicated by the observations of Wolfheim (*Ber.*, 1914, **47**, 1450), who converted β-hydroxy-β-phenylethylamine into the corresponding chloroamine, which with the calculated quantity of sodium hydroxide yielded phenylethyl-

$$\text{eneimine, } Ph\overset{\displaystyle NH}{\underset{\displaystyle \diagdown\!\diagup}{CH}}\!\!-\!\!-\!\!-\overset{\displaystyle \diagdown\!\diagup}{CH_2},$$

and of Gabriel and Colman (*ibid.*, p. 1869), who obtained the same imine from β-hydroxy-α-phenylethylamine. These authors did not study the action of an excess of alkali on their imine but record the formation of β-chloro-β-phenylethylamine by the action of hydrochloric acid.

Experimental.

The general procedure for the preparation of the bases described was the following, (a) *via* acetoxybromides, (b) *via* methoxybromides.

(a) The dibromide from acetyl*iso*eugenol, acetyl*iso*chavibetol, *iso*myristicin, or *p*-acetoxypropenylbenzene was dissolved in a suitable quantity of acetic acid on a warm water-bath and treated gradually with finely powdered silver acetate (1 mol.). The mixture was then heated on a boiling water-bath for 20 minutes with continual agitation, and filtered from the precipitated silver bromide into a large volume of water. This was extracted with benzene, and the benzene extract washed with water, dried, and evaporated, leaving the acetoxybromide either in a crystalline condition or as a pale-coloured oil sufficiently pure for the next process.

(b) The dibromide of *iso*myristicin or *iso*eugenol methyl ether was dissolved in cold methyl alcohol, the calculated quantity of methyl-alcoholic sodium methoxide (15%) added, the solvent removed, water added, and the methoxybromide isolated by extraction with ether. Both the methoxybromides were oils.

In the next stage the acetoxybromide (a) or the methoxybromide (b) was heated in a sealed tube (a) for 9 hours at 110°,

(b) for 24 hours (during 3 days) at 130°, with a considerable excess of a concentrated dry alcoholic solution of methylamine. After removal of the alcohol and excess of methylamine by distillation, the residual oil was treated with an excess of *N*-sulphuric acid and shaken with ether to remove non-basic material, then with chloroform to remove acetylmethylamine (where necessary), and finally made alkaline and either extracted with ether to obtain the base, or, in the case of the bases from *iso*chavibetol, concentrated; the bases then crystallised. Subsequent purification varied with the individual compounds.

iso*Eugenol*.—Acetyl*iso*eugenol dibromide (36·5 g.) (Zincke and Hahn, *Annalen*, 1903, **329**, 1), acetic acid (90 c.c.), and silver acetate (16·7 g.) gave an almost quantitative yield of the *acetoxybromide* (I) as a pale yellow oil, which on the addition of alcohol separated in colourless crystals (Found: Br, 22·8. $C_{14}H_{17}O_5Br$ requires Br, 23·2%). The crude oil (34 g.) with methylamine (25 g.) in dry alcohol (75 c.c.) furnished non-basic material (11·7 g.), which was not examined, and crude base (10·75 g.). The latter was converted into sulphate (9·05 g.), which was almost insoluble in alcohol, and was purified by solution in water (5 vols.) and addition of alcohol (10 vols.); it then separated in rosettes of colourless needles, melting at 254° (corr.) to two layers, the upper red and the lower yellow and cloudy; this behaviour is characteristic (Found: C, 44·6; H, 6·4; N, 8·7; S, 9·5; MeO, 9·7; NMe, 11·6, 12·2, 13·8, 12·7.* $C_{12}H_{20}O_2N_2,H_2SO_4$ requires C, 44·7; H, 6·9; N, 8·7; S, 9·9; MeO, 9·6; 2NMe, 18·0%). The base, prepared from the pure sulphate, rapidly darkened on exposure to air and was not obtained crystalline. The same compound was obtained by the action of methylamine on acetyl*iso*eugenol dibromide. It is therefore αβ-di-(methylamino)-α-4-hydroxy-3-methoxyphenylpropane (III).

iso*Myristicin*.—(a) *iso*Myristicin dibromide (23·5 g.) (Thoms, *Ber.*, 1903, **36**, 3448), acetic acid (100 c.c.), and silver acetate (11·13 g.) yielded the *acetoxybromide* (V) (20·6 g.) as a pale yellow oil which crystallised on the addition of a little alcohol. It separated from petroleum (b. p. 90—120°) in colourless elongated hexagonal plates, m. p. 62—64° (corr.) (Found: C, 46·9; H, 4·8; Br, 24·4. $C_{13}H_{15}O_5Br$ requires C, 47·1; H, 4·6; Br, 24·1%). The crude product (9·6 g.; Br = 23·9%) was heated with methylamine (4·6 g.) in dry alcohol (40 c.c.). Non-basic material from the ethereal

* The analytical figures for the methylimino-groups are neither concordant nor in agreement with the calculated value, and this is true for results obtained either by macro- or by micro-methods of analysis. No explanation of this anomaly can be given at present, but the other evidence provided leaves no doubt of the constitution of the salt.

extract of the acid liquor (0·6 g.) was not examined. The crude base (7·15 g.) was purified through its *hydrochloride*, which crystallised from alcohol in hard, almost colourless prisms (5·9 g.), m. p. 233—235° (corr., decomp.) after previous sintering at 231° (Found : C, 52·3; H, 6·7; N, 5·7; Cl, 12·8; MeO, 10·9; NMe, 9·6. $C_{12}H_{17}O_4N$,HCl requires C, 52·3; H, 6·6; N, 5·1; Cl, 12·9; MeO, 11·3; NMe, 10·5%). The *hydrobromide* forms colourless prisms from alcohol, m. p. 239° (corr., decomp.) after previous sintering at 219° (Found : C, 45·4; H, 5·5; N, 4·3; Br, 24·6. $C_{12}H_{17}O_4N$,HBr requires C, 45·0; H, 5·7; N, 4·4; Br, 25·0%). The *oxalate* separates from alcohol in colourless prisms, m. p. 251° (corr., decomp.) [Found : C, 55·2; H, 6·2; N, 5·5; MeO, 10·9. $(C_{12}H_{17}O_4N)_2,C_2H_2O_4$ requires C, 54·9; H, 6·4; N, 4·9; MeO, 10·9%]. The *picrate* consists of yellow hemispherical aggregates of needles, m. p. 179—182° (corr.) (Found : N, 12·5. $C_{12}H_{17}O_4N,C_6H_3O_7N_3$ requires N, 12·0%). The base (VII), prepared from the pure hydrochloride, is a pale straw-coloured oil.

(b) *iso*Myristicin dibromide (3·16 g.), dry methyl alcohol (30 c.c.), and sodium methoxide yielded β-*bromo*-α-*methoxy*-α-3-*methoxy*-4 : 5-*methylenedioxyphenylpropane* (2·70 g.) as a colourless varnish (Found : Br, 26·2; MeO, 19·3. $C_{12}H_{15}O_4Br$ requires Br, 26·4; MeO, 20·5%). The methoxybromide (12·3 g.) with methylamine (13 g.) in dry alcohol (50 c.c.) furnished non-basic material (5·25 g.) consisting mainly of 3-methoxy-4 : 5-methylenedioxyphenyl ethyl ketone (Scandola, *Atti R. Accad. Lincei*, 1912, **21**, i, 47), and a pale yellow basic oil (4 g.), which afforded crystalline β-*methylamino*-α-*methoxy*-α-3-*methoxy*-4 : 5-*methylenedioxyphenylpropane hydrochloride* (3·6 g.). This salt separates from alcohol in small colourless prisms, m. p. 252° (corr., decomp.) (Found : C, 53·6; H, 7·0; N, 5·3; Cl, 12·1; MeO, 21·0; NMe, 8·0. $C_{13}H_{19}O_4N$,HCl requires C, 53·9; H, 7·0; N, 4·8; Cl, 12·2; 2MeO, 21·4; NMe, 10·0%). Demethylation was effected by allowing the hydrochloride (6·4 g.) to stand in cold hydrochloric acid (*d* 1·19, 65 c.c.) during 21 hours. The partially crystalline base (4·97 g.), which was obtained by extracting the alkaline solution with ether, yielded β-*methylamino*-α-*methoxy*-α-3-*methoxy*-4 : 5-*methylenedioxyphenylpropane* (2·3 g.) as colourless fragile prisms from acetone or from benzene–ether, m. p. 122—124° (corr.) (Found : C, 60·5; H, 7·5; N, 6·1; MeO, 13·0; NMe, 11·2. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2; N, 5·9; MeO, 13·0; NMe, 12·1%). The *hydrochloride* forms colourless prismatic aggregates from alcohol, m. p. 194—198° (corr.) (Found : Cl, 12·8. $C_{12}H_{17}O_4N$,HCl requires Cl, 12·9%).

Isomerisation of α-*Methylamino*-β-*hydroxy*-α-3-*methoxy*-4 : 5-*methylenedioxyphenylpropane* (VII).—The hydrochloride (see above) (10 g.)

was boiled under reflux for 2 hours with a mixture of acetic anhydride (90 c.c.) and acetyl chloride (10 c.c.). After removal of the reagents by distillation, the residual oil was boiled under reflux with 5% alcoholic potassium hydroxide (100 c.c.) for 1½ hours, water (95 c.c.) added, the alcohol removed, and the solution acidified with dilute hydrochloric acid. The non-basic matter (4·2 g.), obtained from the acid liquor by extraction with ether, was again treated with alcoholic potassium hydroxide in the same way. The two acid liquors so obtained were made alkaline and, on extraction with ether, afforded a pale yellow basic oil (8·45 g.), consisting of a mixture of the original base (VII) and its diastereoisomeride. After repeated fractional crystallisation of the hydrochlorides from alcohol, a specimen (0·6 g.) of constant m. p. 212—216° (corr.) was obtained (Found: C, 52·5; H, 6·2; N, 5·0; Cl, 13·0; MeO, 11·5; NMe, 9·0. $C_{12}H_{17}O_4N$,HCl requires C, 52·3; H, 6·6; N, 5·1; Cl, 12·9; MeO, 11·3; NMe, 10·5%). A mixture of this *hydrochloride* with the hydrochloride of the original base (VII) melted indefinitely at 190—210°. The behaviour of this mixture on heating closely resembles that of the crude hydrochloride obtained in this experiment.

iso*Chavibetol*.—(a) *Acetyl*iso*chavibetol* forms colourless platelets from alcohol, m. p. 101° (corr.) (Found: C, 69·6; H, 7·1; MeO, 14·6. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·85; MeO, 15·05%). Treated in dry ethereal solution with the calculated quantity of bromine, it gives a crystalline *dibromide*, m. p. 109—111° (corr.) (Found: C, 39·45; H, 3·9. $C_{12}H_{14}O_3Br_2$ requires C, 39·35; H, 3·85%). The dibromide (167 g.) in acetic acid (320 c.c.) gave with silver acetate (76 g.) an almost quantitative yield of syrupy *acetoxybromide* (IV) (Found: Br, 22·5. $C_{14}H_{17}O_5Br$ requires Br, 23·2%). This was treated with methylamine (115 g.) in dry alcohol (350 c.c.). Non-basic substances, including acetylmethylamine, were removed from the reaction product in the usual manner (54 g.), but the bases were best isolated, not as usual by extraction with ether, but by concentration of the alkaline liquor; they then separated as a brown powder contaminated with potassium sulphate and oily impurity. The former was removed by washing with ice-cold water, and the latter with cold acetone. The crude base thus obtained (43 g.) was distilled, giving a fraction (35·55 g.), b. p. 200—202°/11 mm. (corr.), consisting of a colourless oil which rapidly crystallised on cooling. This consisted of two bases, which were partially separated by fractional crystallisation of the normal oxalates from methyl alcohol. The *oxalate* of *base A* forms hemispherical aggregates of colourless needles, m. p. 222·5° (corr., decomp.), the *oxalate* of *base B*, soft colourless needles, m. p. 222·5° (corr., decomp.), m. p. of mixture about 209° (corr., decomp.); so that in order to effect

a separation it is essential to take a mixed melting point before uniting any two crops. The oxalate of A absorbs moisture, forming a hydrate (Found: loss on drying at 120° in a vacuum, 4·6. $A_2,C_2H_2O_4,1{\cdot}5H_2O$ requires loss 5·0%), the oxalate of B is not hygroscopic [Found for oxalate A: C, 55·8; H, 6·9. Found for oxalate B: C, 56·2; H, 6·9. $(C_{11}H_{17}O_3N)_2,C_2H_2O_4$ requires C, 56·2; H, 7·1%]. *Base A* from the pure oxalate forms colourless prisms from alcohol, m. p. 143—146° (corr.); *base B* is similar, m. p. 166—167° (corr.), mixture m. p. about 140—155° (Found for base A: C, 62·4; H, 8·1; N, 6·4, 6·6; MeO, 14·6, 14·7; NMe, 10·2, 10·0. Found for base B: C, 62·4; H, 8·1; N, 6·6, 6·7; MeO, 14·9, 14·8; NMe, 10·4. $C_{11}H_{17}O_3N$ requires C, 62·5; H, 8·1; N, 6·6; MeO, 14·7; NMe, 13·75%).

Methylation of base A. Base A (7·2 g.) was dissolved in alcohol (120 c.c.) and treated at room temperature with an ethereal solution (150 c.c.) of the diazomethane from nitrosomethylurethane (7 c.c.). After standing over-night, the solution was colourless; the solvents were evaporated, the residue was dissolved in 2% hydrochloric acid and made alkaline with potassium hydroxide, and the base shaken into ether. This gave 6·3 g. of crude base, which was converted into hydrochloride and crystallised from methyl alcohol. It was thus obtained in rosettes of colourless needles (5·5 g.), m. p. 206—207° (corr.) (Found: Cl, 13·5, 13·55; MeO, 23·7, 23·8; NMe, 9·1, 10·0. Calc. for $C_{12}H_{19}O_3N,HCl$: Cl, 13·55; 2MeO, 23·7; NMe, 11·1%). The base (VIII), prepared from the pure hydrochloride, crystallised from ether in minute colourless prisms, m. p. 60—62° (corr.) (Found: C, 63·9; H, 8·15; N, 6·2, 6·1. Calc. for $C_{12}H_{19}O_3N$: C, 63·9; H, 8·5; N, 6·2%). Mannich (*loc. cit.*) records m. p. 63° for the base and 205° for the hydrochloride. The oxalate forms colourless crystals, m. p. 147° (corr., decomp.), from acetone.

Methylation of base B. Base B (8·3 g.) in alcohol (125 c.c.) with the diazomethane from nitrosomethylurethane (7·75 c.c.) in ether (100 c.c.) gave 8·3 g. of crude methyl ether of B. This furnished 7·3 g. of pure *hydrochloride* of the *methyl ether* of *B*, crystallising from dry alcohol in rosettes of colourless needles, m. p. 204—205°, which depress the melting point of the hydrochloride of the methyl ether of A to 184—193° (Found: Cl, 13·5; MeO, 23·7, 23·8; NMe, 11·0, 10·6. $C_{12}H_{19}O_3N,HCl$ requires Cl, 13·55; 2MeO, 23·7; NMe, 11·1%). The oxalate crystallises from acetone in colourless prisms, m. p. 147° (corr., decomp.), which depress the melting point of the corresponding salt of A to 140°. The *base*, prepared from the pure hydrochloride, separates from ether in colourless square plates, m. p. 95—97° (corr.) (Found: C, 64·1, 64·2; H, 8·0, 8·0; N, 6·4, 6·4. $C_{12}H_{19}O_3N$ requires C, 63·9; H, 8·5; N, 6·2%).

(b) Methyl*iso*eugenol dibromide (Mannich, *loc. cit.*) (40 g.) in methyl alcohol (390 c.c.) gave, with the calculated quantity of sodium methoxide in methyl alcohol, the *methoxybromide* in practically quantitative yield as a light brown syrup (Found : Br, 27·4; MeO, 31·2. $C_{12}H_{17}O_3Br$ requires Br, 27·65; 3MeO, 32·2%). This was treated with methylamine (22 g.) in dry alcohol (80 c.c.) and furnished non-basic material (18·6 g.) as an amber-coloured oil, and crude base (10 g.) as a brown oil. The latter was purified as *hydrochloride*, separating from acetone in colourless prismatic aggregates (7·65 g.), m. p. 167° (corr.), to a cloudy liquid clear at 190° (Found : C, 56·1; H, 8·0; N, 5·1; Cl, 12·95; MeO, 34·3; NMe, 9·0. $C_{13}H_{21}O_3N$,HCl requires C, 56·6; H, 8·0; N, 5·1; Cl, 12·9; 3MeO, 33·8; NMe, 10·5%). Demethylation was effected in the manner described for the corresponding derivative of *iso*myristicin (p. 1473). The hydrochloride (8·2 g.) furnished crude base (5·3 g.), from which on addition of acetone crystalline base (3·0 g.) was obtained. The *base* (IX) crystallises in colourless felted needles from acetone, m. p. 130—131° (corr.) (Found : C, 63·7; H, 8·5. $C_{12}H_{19}O_3N$ requires C, 63·95; H, 8·5%). The *oxalate* forms thin colourless prisms from alcohol, m. p. 217—218° (corr., decomp.) [Found : C, 57·9; H, 7·4; N, 5·0; MeO, 22·8; NMe, 10·1. $(C_{12}H_{19}O_3N)_2,C_2H_2O_4$ requires C, 57·7; H, 7·5; N, 5·2; 2MeO, 23·0; NMe, 10·7%].

Isomerisation of the methyl ethers of A and B. The finely powdered methyl ether of base A (VIII) (0·7 g.) was added in small portions to a suspension of phosphorus pentachloride (1·4 g.) in cold dry chloroform (5 c.c.). The phosphorus pentachloride slowly dissolved and after standing for 2 hours with occasional shaking the solvent was evaporated in a desiccator. The residue was boiled under reflux for 30 minutes with alcoholic potassium hydroxide (25 c.c. of 12%), water added, and the alcohol removed by distillation. Acidification of the residue and extraction with ether furnished a brown non-basic oil (0·45 g.), which was not examined; subsequent extraction with ether after the addition of alkali gave a colourless oily base which crystallised on standing. After recrystallisation from ether it was obtained in needles, m. p. 130—131° (corr.), which on admixture did not depress the melting point of β-methylamino-α-hydroxy-α-3 : 4-dimethoxyphenylpropane (IX).

The methyl ether of base B (0·5 g.) similarly gave a non-basic oil (0·15 g.) and a base (0·3 g.) which after crystallisation from ether had m. p. 129—130° (corr.), and was also identical with the above β-methylamino-compound.

p-*Acetoxypropenylbenzene.*—For the preparation of this substance, which was not isolated, the directions given by Béhal and Tiffeneau (*Bull. Soc. chim.*, 1908, **3**, 303) for the preparation of *p*-propenyl-

phenol were adopted, and the crude product (4·85 g.), obtained by the latter method, which probably consists mainly of ethyl-*p*-hydroxyphenylcarbinol, $HO{\cdot}C_6H_4{\cdot}CH(OH){\cdot}C_2H_5$, was heated in a sealed tube at 130° for 3½ hours with a mixture of acetic anhydride (10 c.c.) and acetyl chloride (10 c.c.). The cold solution was then treated with bromine, the absorption, owing to incomplete dehydration, being 0·9 c.c. (calc., 1·6 c.c.). The liquid was poured into water (200 c.c.) and shaken, the precipitate being dissolved in ether and dried over anhydrous sodium sulphate. The dry solid (9·1 g.) so obtained was substantially freed from unbrominated material by one recrystallisation from petroleum (b. p. 90—120°). Yield, 3·3 g.; m. p. 112—122°. This product, which can be used for the next stage, is purified by recrystallisation from petroleum, p-*acetoxypropenylbenzene dibromide* separating in short white needles, m. p. 125—129° (corr.) (Found: C, 39·5; H, 3·6; Br, 47·5. $C_{11}H_{12}O_2Br_2$ requires C, 39·3; H, 3·6; Br, 47·6%). The dibromide (2·64 g.), acetic acid (15 c.c.), and silver acetate (1·31 g.) yielded β-*bromo*-α-*acetoxy*-α-p-*acetoxyphenylpropane* (2·4 g.), which did not crystallise (Found: Br, 25·4. $C_{13}H_{15}O_4Br$ requires Br, 25·4%).

The acetoxybromide (5 g.) with methylamine (4·0 g.) in dry alcohol (20 c.c.) furnished non-basic material (1·0 g.), which was not examined, and crude base (2·35 g.). The latter was converted into sulphate (1·5 g.), which was almost insoluble in alcohol, and was purified by solution in water (1 vol.) and addition of alcohol (15 vols.); the *sulphate* of αβ-*di*(*methylamino*)-α-p-*hydroxyphenylpropane* (VI) then separated in white needles, m. p. 211—213° (corr.) (Found in air-dried salt: loss at 110° in a vacuum, 8·4. $C_{11}H_{18}ON_2,H_2SO_4,1{\cdot}5H_2O$ requires H_2O, 8·5%. Found in salt dried at 110°: C, 45·4; H, 7·1; N, 9·35; S, 10·8; NMe, 20·0. $C_{11}H_{18}ON_2,H_2SO_4$ requires C, 45·2; H, 6·9; N, 9·6; S, 11·0; 2NMe, 19·9%). The anhydrous salt absorbs the equivalent of 1·5 mols. of water on exposure to air.

The Preparation of Pure Methylamine.

Methylamine hydrochloride of commerce usually contains ammonium chloride, which cannot easily be eliminated. As it was desirable to use pure methylamine for the preparation of the bases described above, and since standard methods, for example, that described in "Organic Syntheses," Vol. III, p. 67, gave an impure product, the following process of purification was devised, based on the fact that when a mixture of methylamine and ammonia reacts with an insufficient quantity of hydrochloric acid the methylamine is preferentially neutralised and the ammonia left free.

The most practicable method of applying this principle is one

suggested to us by Mr. J. A. Goodson which is operated as follows. One-tenth of a weighed quantity of the crude methylamine hydrochloride is decomposed by the addition of potassium hydroxide and the liberated bases are absorbed in water in a suitable apparatus. The resulting distillate is added to a cold aqueous solution of the remaining nine-tenths of the material and the gaseous bases are expelled by boiling. The process is repeated, one-tenth of the residual solution of hydrochlorides being decomposed for this purpose. On concentrating the solution a product is obtained which does not respond to the François test for ammonia (*Compt. rend.*, 1907, **144**, 857) and therefore contains less than 0·5% of ammonium chloride. The latter when present in quantities of this order is readily removed from methylamine hydrochloride by recrystallisation from water, as shown by the accumulation of the salt in the resulting mother-liquors, in which it is detectable by the François test.

The proportion of the total hydrochlorides to be decomposed at each stage, as well as the number of stages, depends on the purity of the initial material, the procedure described above being suitable for methylamine hydrochloride containing about 5% of ammonium chloride. A product of this quality is obtainable in commerce and by the usual methods of methylating ammonium chloride.

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