View Article Online / Journal Homepage / Table of Contents for this issue

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254. *Studies on the Structure of Emetine. Part III. Stability of Some α-Arylalkyl-trimethylammonium Iodides.*

By Geoffrey Norcross and H. T. Openshaw.

In view of the instability of *N*-methylemetinetetrahydromethine dimethiodide (I), the behaviour of a number of model methiodides containing the α-alkylbenzylamine structure has been studied. Ready decomposition with fission to yield trimethylamine hydriodide occurs only when a methoxy-group is present in the *p*-position of the benzene ring, and is further facilitated by alkylation of the β-carbon atom of the side-chain. These results accord with current theories of the mechanisms of such elimination reactions. In contrast, 2-*p*-methoxyphenyl-1-methylpiperidine methiodide (VII), in which the nitrogen atom is cyclically linked, is stable at 100°.

The decomposition of *N*-methylemetinetetrahydromethine dimethiodide (I), in solution at 100°, to give trimethylamine hydriodide and an unsaturated monomethiodide (II), represents an unusual type of Hofmann degradation. By analogy with the similar reactions of the methiodides of gramine and of pavinemethine, the decomposition has been ascribed to the presence in (I) of a suitably substituted benzylamine structure (Battersby and Openshaw,

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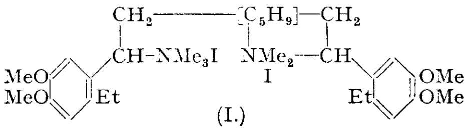
Part I, this vol., p. S 59). In order to determine more fully the structural features required, a qualitative study has been made of the stability of some α-arylalkyl-trimethylammonium iodides.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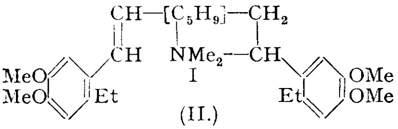
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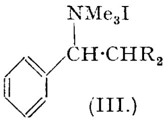
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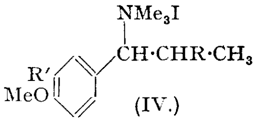
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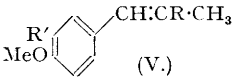
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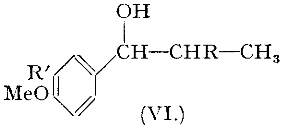
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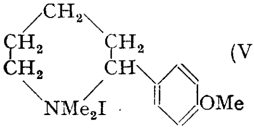
(VII.)

Trimethyl-1-*phenylethylammonium iodide* (III; R = H) and *trimethyl*-1-*phenyl*iso*butylammonium iodide* (III; R = Me) were unaffected by prolonged heating in aqueous solution at 100°. On similar treatment, *trimethyl*-1-3′ : 4′-*dimethoxyphenyl*-n-*propylammonium iodide* (IV; R = H, R′ = OMe) underwent slow decomposition with the formation of trimethylamine hydriodide and a neutral, water-insoluble oil. The yield of the latter was *ca.* 13% after 10 hours and *ca.* 70% after 48 hours, and this oil appeared to be a mixture of *O*-methyl*iso*eugenol (V; R = H, R′ = OMe) and α-3 : 4-dimethoxyphenyl-*n*-propyl alcohol (VI; R = H, R′ = OMe); after treatment of a specimen with dilute acid, the known dimer of *O*-methyl*iso*eugenol was obtained. *Trimethyl*-1-p-*methoxyphenyl*iso*butyl*- (IV; R = Me, R′ = H) and -1-3 : 4-*dimethoxyphenyl*iso*butylammonium iodides* (IV; R = Me, R′ = OMe) were very much less stable, decomposition being virtually complete after one hour at 100°. The crystalline, neutral product obtained from the latter salt was shown to be 1-3′ : 4′-*dimethoxyphenyl*iso*butyl alcohol* (VI; R = Me, R′ = OMe) by comparison with a specimen synthesised from veratraldehyde and *iso*propylmagnesium bromide. The neutral product from (IV; R = Me, R′ = H) was an oil, which gave a rather unsatisfactory analysis for the corresponding alcohol, but comparison with the behaviour of a synthetic specimen indicated it to be essentially 1-*p*-methoxyphenyl-*iso*butyl alcohol (VI; R = Me, R′ = H). Decomposition of (IV; R = Me, R′ = OMe) in diethyl ketone solution at 100°, however, proceeded in a manner analogous to that of (I) under similar conditions, giving trimethylamine hydriodide and the unsaturated compound 1-3′ : 4′-*dimethoxyphenyl*iso*but*-1-*ene* (V; R = Me, R′ = OMe).

The methiodides used in this investigation were prepared by treatment of the corresponding primary amines with methyl iodide and aqueous sodium carbonate at 45°. In order to avoid possible decomposition of the methiodides during their preparation, an alternative method was investigated, in which the primary amines were methylated by formaldehyde and formic acid (Icke, Wisegarver, and Alles, *Org. Synth.*, 1945, **25**, 89) and the resulting tertiary amines treated with methyl iodide in ethereal solution at room temperature. Although 1-phenyl-*iso*butylamine was satisfactorily converted into its *NN*-dimethyl derivative, 1-p-*methoxyphenyl*iso*butylamine* gave none of the desired tertiary amine, but largely decomposed to trimethylamine and an unsaturated, neutral oil which had a powerful odour of aniseed and appeared to be impure β-methylanethole (V; R = Me, R′ = H). Similar treatment of 1-3′ : 4′-*dimethoxyphenyl*iso*butylamine* gave a 30% yield of the *NN*-dimethyl derivative together with a considerable amount of 1-3′ : 4′-dimethoxyphenyl*iso*butyl alcohol. Thus, on heating with formaldehyde and formic acid these amines undergo a decomposition similar to that shown by their methiodides.

The thermal decomposition of the dimethiodide (I) involves only one of the two quaternary nitrogen atoms present, although both are linked to 3 : 4-dimethoxybenzyl groups. The environment of the stable nitrogen atom differs mainly in that this atom forms part of a ring. In order to determine the influence of such a structure on the stability, 2-*p*-methoxyphenyl-piperidine was converted into its *methiodide* (VII). This substance proved to be completely stable in aqueous solution at 100°.

From the experimental results obtained, it is clear that the decomposition of the quaternary iodides is induced by the presence of a methoxy-group in the *p*-position of the benzene ring

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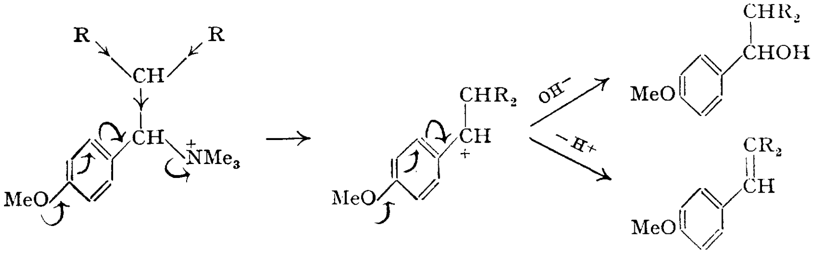
and assisted by alkylation of the β-carbon atom. The effect can be correlated with the influence of a *p*-methoxy-group on the ease of hydrolysis of the benzyl halides (Lapworth and Shoesmith, *J.*, 1922, **121**, 1391). In the latter case, the methoxy-group facilitates the ionisation of the halide and thus increases its reactivity by the S_N1 mechanism. The decomposition of the methiodides can be supposed to occur by an analogous process involving separation of a carbonium ion as the initial step, that is, by the mechanism (*B*1) of Hughes, Ingold, and Patel (*J.*, 1933, 526).

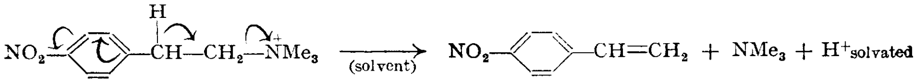
In the present case, the ion is stabilised by the mesomeric effect of the *p*-methoxy-group, and its separation is also facilitated by the inductive effects of the alkyl substituents on the β-carbon atom.



In the second stage the ion either loses a proton from the β-carbon atom, to give an unsaturated product, or combines with an anion. In aqueous solution, the substances described in this paper appear to follow principally the latter course, a hydroxyl ion being taken up to produce an alcohol. In diethyl ketone, the principal reaction is probably loss of a proton, but the liberation of iodine which occurred when the crude reaction product from (IV; R = Me, R′ = OMe) was distilled suggested that some of the unstable benzyl iodide was also produced by interaction of the carbonium ion with iodide ion. Although no alcohol was isolated from the decomposition of (I) in aqueous solution, such a substance may be formed to some extent, since the yield of pure product is much lower than results from its decomposition in diethyl ketone.

The stability of the cyclic compound (VII) may perhaps be ascribed to the reversibility of the C–N fission process. In the case of an open-chain compound, it is possible for the two fission products to separate quickly to a distance sufficient to prevent recombination, but with the cyclic compound such rapid separation of the carbonium ion and the nitrogen atom may be prevented by the restraint of the carbon chain connecting them.

The instability of the methiodides described in this paper provides an interesting comparison with the instability of trimethyl-*p*-nitrophenylethylammonium iodide (VIII) (Hughes and Ingold, *J.*, 1933, 523). This compound also decomposes in aqueous solution at 100° to give trimethylamine hydriodide and the unsaturated substance, *p*-nitrostyrene, but the decomposition proceeds by an entirely different mechanism [mechanism (*A*1) of Hughes, Ingold, and Patel, *loc. cit.*] which is initiated by the tendency to ionisation of a hydrogen atom attached to the β-carbon atom. Such an ionisation is facilitated by polarisation effects exactly opposite to those which cause the instability of the methiodides we have described, the two reactions standing at opposite ends of the " mechanistic series ".



(VIII.)

Independently of our work (Part I, *loc. cit.*), Späth and Pailer (*Monatsh.*, 1948, **78**, 348) also observed that *N*-methylemetinetetrahydromethine is converted into (II) and trimethylamine hydriodide when heated with methyl iodide in methanol. Since the work described in our present paper was completed, Pailer and Bilek (*ibid.*, 1948, **79**, 135) have described a similar degradation of two synthetic dimethyl-1-3′ : 4′-dimethoxy-6′-ethylphenylalkylamines.

EXPERIMENTAL.

(All m. p.s are corrected.)

Trimethyl-1-*phenylethylammonium Iodide* (III; R = H).—A mixture of 1-phenylethylamine (3·5 g.), methyl iodide (28 g.) and aqueous sodium carbonate (6 g. in 40 ml.) was warmed under reflux on the water-bath for 7 hours. After evaporation of excess of methyl iodide, the cooled solution was extracted

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thrice with chloroform. The extract was dried (K_2CO_3) and evaporated, leaving a residue which crystallised on trituration with ether. On crystallisation from anhydrous alcohol, the *methiodide* formed deliquescent, colourless plates (4·65 g., 55·2%), which after recrystallisation had m. p. 144·5—145·5° (Found: N, 4·8; I, 43·5. $C_{11}H_{18}NI$ requires N, 4·8; I, 43·6%). A solution of the methiodide (1·07 g.) in water (30 ml.) was boiled under reflux for 6 hours. There was no evidence of decomposition, and the methiodide was recovered unchanged.

1-*Phenyl*iso*butylamine.*—*iso*Butyrophenone (71 g.) was treated with anhydrous ammonium formate (100 g.) essentially as described by Ingersoll (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 503); a final reaction temperature of 200—210° was employed. Hydrolysis of the crude formamide with boiling hydrochloric acid was continued for 1½ hours, and on cooling the solution deposited crystals of the amine hydrochloride which were redissolved by the addition of water. The aqueous solution was washed with benzene, made alkaline with sodium hydroxide (65 g.), and steam-distilled, the distillate separating into two layers. The upper layer of amine was removed and the aqueous layer extracted with benzene, the extract being added to the amine. After drying (KOH) and distillation, 1-phenyl*iso*butylamine (54·7 g., 77%), was obtained as a colourless liquid, b. p. 102—104°/20 mm. The neutral oxalate separated as rosettes of colourless needles, m. p. 177—178°, from anhydrous alcohol [Found: C, 68·0; H, 8·1. Calc. for $(C_{10}H_{15}N)_2,C_2H_2O_4$: C, 68·0; H, 8·3%]; Konowalow (*Ber.*, 1895, **28**, 1852) gives m. p. 120·5—122° (decomp.) for this salt. The hydrochloride crystallised from water in colourless, prismatic needles, m. p. 276—277°; Billon (*Ann. Chim.*, 1927, **7**, 314) gives m. p. 275°, and Konowalow (*loc. cit.*) gives m. p. 275—277°.

Trimethyl-1-*phenyl*iso*butylammonium Iodide* (III; R = Me).—1-Phenyl*iso*butylamine (6 g.) was heated under reflux for 13 hours with methyl iodide (32 g.) and aqueous sodium carbonate (8 g. in 50 ml.), and the product isolated as described above. The *methiodide* (5·39 g., 42%) formed needles, m. p. 147·5—148·5°, from alcohol–ether (Found: I, 39·9. $C_{13}H_{22}NI$ requires I, 39·8%). No decomposition occurred when an aqueous solution of the methiodide was boiled under reflux for 10 hours.

1-3′ : 4′-*Dimethoxyphenyl*-n-*propylamine.*—This amine was prepared from propioveratrone (17·5 g.) (Adams, Geissman, Baker, and Teeter, *J. Amer. Chem. Soc.*, 1941, **63**, 528) and ammonium formate (18 g.) essentially as described above for 1-phenyl*iso*butylamine. It was obtained as a colourless liquid (5·2 g., 30%), b. p. 120°/0·2 mm., and formed a *picrate*, rosettes of yellow needles, m. p. 182—183°, from alcohol (Found: C, 48·1; H, 4·8; N, 12·9. $C_{11}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 48·1; H, 4·7; N, 13·2%).

Trimethyl-1-3′ : 4′-*dimethoxyphenyl*-n-*propylammonium Iodide* (IV; R = H, R′ = OMe).—A mixture of the above amine (2·51 g.), methyl iodide (9·5 g.), and aqueous sodium carbonate (3 g. in 45 ml.) was heated gently for ½ hour, and the colourless, flocculent precipitate was collected. On crystallisation from anhydrous alcohol, the *methiodide* formed colourless, lozenge-shaped plates, m. p. *ca.* 258° (decomp.) after sintering from 204° (Found: C, 46·2; H, 6·4; N, 4·2. $C_{14}H_{24}O_2NI$ requires C, 46·0; H, 6·6; N, 3·8%).

Thermal Decomposition of the Methiodide (IV; R = H, R′ = OMe).—(*a*) A solution of the methiodide (1·16 g.) in water (25 ml.) was boiled under reflux for 10 hours. Extraction of the cooled, turbid solution with ether gave an oil (0·14 g.), which was redissolved in ether and shaken with dilute (1 : 1) hydrochloric acid (5 ml.). Evaporation of the solvent left an oil (0·075 g.) which rapidly solidified. Crystallisation from light petroleum gave bis-*O*-methyl*iso*eugenol, m. p. 104—106·5° (Szeki, *Ber.*, 1906, **39**, 2422, gives m. p. 106°), which did not react with bromine in carbon tetrachloride (Found: C, 74·1; H, 8·0; OMe, 34·7. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9; OMe, 34·8%). Evaporation of the aqueous liquor left a pale brown solid (0·87 g.), which liberated trimethylamine (picrate, m. p. 217°) on treatment with alkali.

(*b*) A solution of the methiodide (1·895 g.) in water (25 ml.) was boiled under reflux for 48 hours. Extraction with ether gave a light brown, viscous oil (0·709 g., *ca.* 70%). After distillation at 9 mm. from a bath at 150°, the material analysed as a mixture of *O*-methyl*iso*eugenol and 1-3′ : 4′-dimethoxyphenyl-*n*-propyl alcohol (Found: C, 69·9; H, 8·2; OMe, 32·4. Calc. for $C_{11}H_{14}O_2$: C, 74·1; H, 7·9; OMe, 34·9. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2; OMe, 31·7%). It decolorised bromine in carbon tetrachloride solution. [Interaction of ethylmagnesium bromide and veratraldehyde gave a product which after distillation at 10^{-3} mm., consisted of a similar mixture of the alcohol and *O*-methyl*iso*eugenol, containing about 30% of the latter as shown by bromine titration (cf. Béhal and Tiffeneau, *Bull. Soc. chim.*, 1908, [iv], **3**, 309; Müller, Raltschewa, and Papp, *Ber.*, 1942, **75**, 700).] The aqueous liquor remaining after the ether extraction contained trimethylamine hydriodide and a little unchanged methiodide.

p-*Methoxy*iso*butyrophenone.*—Prepared by a method similar to that used for propioveratrone (Adams *et al.*, *loc. cit.*), this ketone distilled at 82—87°/4 × 10^{-2} mm. as a colourless oil, giving a semicarbazone in felted needles, m. p. 183·5—184·5°, from methyl alcohol (Found: C, 61·2; H, 7·0. Calc. for $C_{12}H_{17}O_2N_3$: C, 61·2; H, 7·3%). Tiffeneau and Levy (*Bull. Soc. chim.*, 1926, [iv], **39**, 763) claim to have prepared this ketone, but give the m. p. of the semicarbazone as 212—213°. Sosa (*Ann. Chim.*, 1940, **14**, 5) gives m. p. 193—194° (block) and 205—206° (capillary).

Trimethyl-1-p-*methoxyphenyl*iso*butylammonium Iodide* (IV; R = Me, R′ = H).—*p*-Methoxy*iso*butyrophenone (14·3 g.) was treated with ammonium formate (16·3 g.) as described above. The amine (7·1 g., 50%) was a colourless liquid, b. p. 83°/0·1 mm., and formed a *picrate* which crystallised from alcohol as yellow prisms, which melted at 183·5—184°, immediately resolidified, and then melted with decomposition at 271—273° (Found: N, 13·5. $C_{11}H_{17}ON,C_6H_3O_7N_3$ requires N, 13·7%). The amine (1·2 g.) was treated with aqueous sodium carbonate (1·5 g. in 25 ml.) and boiling methyl iodide (9·5 g.) for 30 minutes. When the mixture had been kept in the cold, *trimethyl*-1-p-*methoxyphenyl*iso*butylammonium iodide* (1·83 g., 78%) separated as a white, flocculent precipitate. It was purified by shaking it with cold anhydrous alcohol for 5 hours and concentrating the filtered and seeded solution by evaporation in a partly evacuated desiccator over calcium chloride; it formed octahedra which began to decompose at *ca.* 165° and finally melted at 269—271° (Found: C, 48·3; H, 7·1; N, 3·9. $C_{14}H_{24}ONI$ requires C, 48·15; H, 6·9; N, 4·0%).

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Thermal Decomposition of the Methiodide (IV; R = Me, R′ = H).—A solution of the methiodide (1·043 g.) in water (100 ml.) was shaken with peroxide-free ether to ensure the absence of ether-soluble materials, separated, and boiled under reflux. A steam-volatile oil appeared in the condensate after 5 minutes. After 40 minutes the solution was cooled and extracted with ether, giving a colourless, odourless oil (0·348 g.) which did not react with bromine in carbon tetrachloride; this distilled at 0·5 mm. from a bath at 90°, but gave unsatisfactory analytical results (Found : C, 72·6; H, 8·6. Calc. for $C_{11}H_{16}O_2$: C, 73·3; H, 8·9%). When boiled under atmospheric pressure, it developed a strong aniseed odour and became unsaturated.

Anisaldehyde was treated with *iso*propylmagnesium bromide in the usual manner, and the intermediate complex decomposed with ice and ammonium chloride (Sosa, *loc. cit.*). After removal of unchanged anisaldehyde with sodium bisulphite, a light brown oil (21% yield) was obtained, which did not smell of aniseed. Bromine titration indicated the presence of about 5% of the related unsaturated compound. The substance distilled at 125—140°/16 mm., and the distillate contained 54% of unsaturated material and had a strong odour of aniseed. Perkin (*J.*, 1879, **35**, 145) describes β-methylanethole (V; R = Me, R′ = H) as possessing an odour of aniseed.

iso*Butyroveratrone*.—A solution of *iso*butyryl chloride (31 g.) in pure benzene (50 ml.) was added during 1½ hours to a cooled and stirred mixture of veratrole (25 g.), aluminium chloride (28 g.), and benzene (100 ml.). The mixture was heated under reflux for 1 hour with stirring and decomposed in the usual manner. The benzene solution of the product was shaken with aqueous sodium hydroxide, and the phenolic material thus extracted was remethylated by shaking the alkaline solution with methyl sulphate and extracting it with benzene. The combined benzene solutions were distilled through a short column. *iso*Butyroveratrone (32·1 g., 85%) was obtained as a colourless liquid, b. p. 116—117°/0·2 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in short, orange needles, m. p. 189—189·5° (Found : C, 55·9; H, 5·3; N, 14·4. $C_{18}H_{20}O_6N_4$ requires C, 55·7; H, 5·2; N, 14·4%). The *semicarbazone* formed colourless, rectangular tablets, m. p. 149—150°, from methyl alcohol (Found : N, 15·6. $C_{13}H_{19}O_3N_3$ requires N, 15·9%).

Trimethyl-1-3′ : 4′-*dimethoxyphenyl*iso*butylammonium Iodide* (IV; R = Me, R′ = OMe).—The foregoing ketone (31·2 g.) was treated with ammonium formate (32·3 g.) in the usual manner. 1-3′ : 4′-Dimethoxyphenyl*iso*butylamine (23·5 g., 75%) distilled at 101—105°/0·2 mm. as a colourless oil, and formed a *picrate*, yellow plates (from alcohol), which melted on rapid heating at 188·5—190·5°, and on slow heating at 255° (decomp.) after softening at 175° (Found : C, 49·7; H, 5·1; N, 13·0. $C_{12}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 49·3; H, 5·1; N, 12·8%). The amine (5 g.) was methylated in the usual manner for 1 hour. Excess of methyl iodide was removed by distillation, and the aqueous solution was extracted twice with ether to remove a little water-insoluble material. The *methiodide* was isolated by extraction with chloroform. It crystallised in contact with alcohol as colourless plates (6·4 g., 95%). The salt was recrystallised by evaporating its cold solution in anhydrous alcohol under reduced pressure; when rapidly heated, it had m. p. 214—215° (decomp.) (Found : C, 46·8; H, 6·7; N, 4·2; OMe, 16·4. $C_{15}H_{26}O_2NI$ requires C, 47·5; H, 6·9; N, 3·7; OMe, 16·35%). Repeated crystallisation from hot alcohol caused almost complete decomposition to yield trimethylamine hydriodide, m. p. 253—256° (decomp.) (Found : C, 20·0; H, 5·6; N, 7·4. Calc. for $C_3H_{10}NI$: C, 19·2; H, 5·4; N, 7·5%).

Thermal Decomposition of the Methiodide (IV; R = Me, R′ = OMe).—(a) *In water*. A solution of the methiodide (0·57 g.) in water (30 ml.) was boiled under reflux. After 3 minutes the condensate became milky and an oil separated from the solution. After 1 hour the solution was cooled and extracted with ether, yielding, after evaporation of the ether, a brown oil which largely solidified on standing. Crystallisation from water and from light petroleum gave long, colourless needles of 1-3′ : 4′-*dimethoxyphenyl*iso*butyl alcohol*, m. p. 66—67° (Found : C, 69·0; H, 8·6. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%). Trimethylamine was liberated when the aqueous solution from the decomposition was made alkaline, and was identified as the picrate, m. p. 215°.

(b) *In diethyl ketone*. The methiodide (3 g.) was suspended in diethyl ketone (50 ml.), and the mixture heated at 100° under reflux for 2 hours. There was a noticeable odour of trimethylamine, and the evolved vapours were alkaline to litmus. At no time was a homogeneous solution obtained. The cooled mixture was filtered, and the precipitate (1·37 g.; 93%), which was washed with a little acetone, was identified as trimethylamine hydriodide. The filtrate was evaporated under reduced pressure, and the residue dissolved in peroxide-free ether. A trace of insoluble material (mainly trimethylamine hydriodide) was removed and the solution was evaporated, leaving an orange mobile oil (1·61 g.). Distillation gave a fraction (1·425 g.), b. p. 150—151°/13 mm., which was strongly coloured with iodine. It was dissolved in ether and shaken with sodium thiosulphate solution; the recovered oil had a pale straw colour, and on distillation at 147—148°/10 mm. the first portion of the distillate again contained free iodine, which was removed as before. A third distillation gave 1-3′ : 4′-*dimethoxyphenyl*iso*but*-1-*ene* (0·74 g.) as a colourles,s liquid $n_D^{17°}$ 1·5565 (Found : C, 75·0; H, 8·4. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

Synthesis of 1-3′ : 4′-*Dimethoxyphenyl*iso*butyl Alcohol* (VI; R = Me, R′ = OMe).—A solution of veratraldehyde (16·45 g.) in anhydrous ether (30 ml.) was added during 30 minutes to the Grignard reagent prepared from *iso*propyl bromide (15·5 g.), magnesium (3·8 g.), and anhydrous ether (25 ml.). The reaction mixture was decomposed with ice and ammonium chloride, and the ethereal extract of the product was shaken with sodium hydrogen sulphite solution, dried, and evaporated, leaving a brown oil (6·79 g.) which partly crystallised when seeded with the alcohol (VI; R = Me, R′ = OMe). The crystalline material was separated from the oil by filtration, and after crystallisation from light petroleum formed colourless needles, m. p. 65·5—67° (undepressed on admixture with the material obtained from decomposition of the methiodide). The filtered oil distilled at 151—152°/15 mm., the distillate being colourless and having $n_D^{17°}$ 1·5565. It immediately decolorised a solution of bromine in carbon tetrachloride.

Methylation of 1-3′ : 4′-*Dimethoxy- and* 1-p-*Methoxy-phenyl*iso*butylamine*.—A mixture of 1-3 : 4-dimethoxyphenyl*iso*butylamine (7·16 g.), 85% formic acid (15 ml.), and paraformaldehyde (4·1 g.) was

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heated under reflux in an oil bath at 120—140°. After a few hours, an oil was seen floating on the aqueous solution. After 17 hours, the cooled mixture was acidified (Congo-red) with hydrochloric acid and extracted with ether. Evaporation of the aqueous solution under reduced pressure left a white solid together with a little brown oil; the latter was removed by washing with ether, the washings being added to the ethereal extract. The solid was dissolved in water and treated with sodium hydroxide, whereupon a strong odour of trimethylamine was observed. Ether extraction afforded a brown oil (3·24 g.), which on distillation at 141°/11 mm. gave a colourless liquid (2·43 g., 30%) which crystallised on standing in short, colourless needles, m. p. 18—19°. The product did not react with toluene-*p*-sulphonyl chloride and aqueous sodium hydroxide, and on treatment with ethereal methyl iodide at room temperature was converted into the methiodide, identical with that described above. Evaporation of the original ethereal extract gave a pale brown oil, with an odour of formic acid. After removal of this contaminant by washing with water, the oil partly crystallised when kept. The solid was collected and crystallised from water and then from light petroleum, giving colourless needles, m. p. 66—67°, identified as 1-3′ : 4′-dimethoxyphenyl*iso*butyl alcohol.

Similar treatment of 1-*p*-methoxyphenyl*iso*butylamine (5·9 g.) also gave trimethylamine, together with a small amount of an impure, oily base. The main product (2·4 g.) was a neutral oil, b. p. 130—140°/12 mm., which was unsaturated and had a strong odour of aniseed. Analytical results were unsatisfactory.

2-p-*Methoxyphenylpiperidine*.—A solution of 2-*p*-methoxyphenylpyridine (5·29 g.) (Haworth, Heilbron, and Hey, *J.*, 1940, 360) in anhydrous alcohol (40 ml.) was heated under reflux, and sodium (12·5 g.) was added in portions during 30 minutes. Three additional 20-ml. portions of alcohol were also added at intervals during this process to maintain a vigorous reaction. Finally, unchanged sodium was destroyed by the gradual addition of 50% aqueous alcohol (30 ml.) and then water (10 ml.). Alcohol was removed by evaporation under reduced pressure, the base separating from the residual aqueous solution as an oil which solidified on cooling. It was extracted with ether, and the moist ethereal extract was treated with a slow stream of carbon dioxide for two hours. The white, flocculent precipitate of amine carbonate (4·96 g.) was collected and washed with anhydrous ether. The ethereal filtrate and washings were concentrated to about 30 ml., saturated with water, and again treated with carbon dioxide until precipitation was complete; the total yield of carbonate was 5·85 g. The carbonate was dissolved in excess of 2N-hydrochloric acid, and the solution evaporated to dryness, leaving a residue of 2-p-*methoxyphenylpiperidine hydrochloride* (5·57 g., 86%), m. p. 203—205°. After recrystallisation from water, the salt formed colourless prismatic needles, m. p. 204—206° (Found : C, 63·0; H, 7·9; N, 5·9. $C_{12}H_{17}ON,HCl$ requires C, 63·3; H, 8·0; N, 6·1%). Treatment of an aqueous solution of the hydrochloride with sodium hydroxide precipitated the base as an oil which soon solidified. Isolated by means of ether and purified by distillation at 155—158°/13 mm., followed by crystallisation from light petroleum (b. p. 40—60°), it formed rosettes of colourless needles, m. p. 35·5—36·5°. Crystallisation from aqueous methanol gave the hydrate, m. p. 57°, as described by van der Zanden (*Rec. Trav. chim.*, 1942, **61**, 365).

2-p-*Methoxyphenyl*-1-*methylpiperidine Methiodide*.—A mixture of the above base (1·44 g.), aqueous sodium carbonate (0·675 g. in 10 ml.), and methyl iodide (1 ml.) was warmed under reflux for 15 minutes, and the methyl iodide was then distilled off. Unchanged base was removed by ether extraction, and the aqueous phase was extracted with three 10-ml. portions of chloroform. The recovered base (0·5 g.) was remethylated for ½ hour and worked up as before. The combined chloroform extracts were dried and evaporated, leaving a brown syrup (2·34 g., 89%) which crystallised to a cream-coloured solid, m. p. 156—161°, on trituration with ether. On recrystallisation from anhydrous acetone the *methiodide* formed deliquescent, colourless, rectangular plates, m. p. 160—161° (Found : C, 48·5; H, 6·6; N, 3·7. $C_{14}H_{22}ONI$ requires C, 48·4; H, 6·4; N, 4·0%). The quaternary nature of the salt was confirmed by its failure to liberate any ether-soluble base on treatment with cold aqueous sodium hydroxide; the methiodide was recovered unchanged by extraction of the alkaline solution with chloroform. An aqueous solution of the methiodide (236 mg. in 15 ml.) was heated under reflux for 48 hours, cooled, made alkaline with aqueous sodium hydroxide and extracted with ether; evaporation of the ethereal extract left a negligible residue (0·8 mg.); the original methiodide was recovered from the aqueous solution as a light brown solid (235 mg.), m. p. 149—153°, and crystallisation from acetone gave the pure substance (149 mg.), m. p. 159—161°.

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