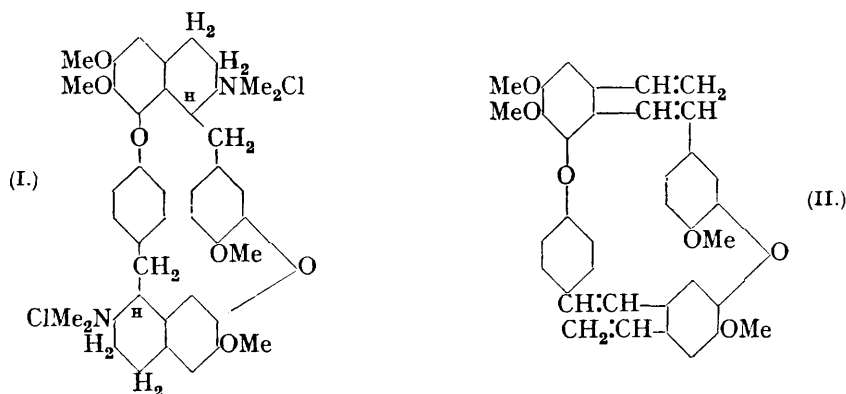


273. Curare Alkaloids. Part II. Tubocurarine and Bebeerine.

By HAROLD KING.

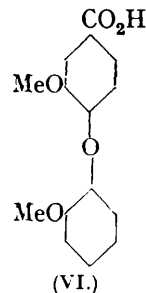
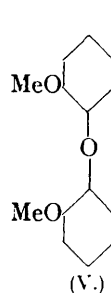
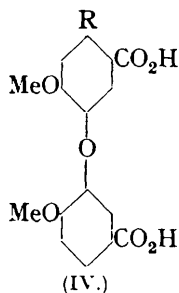
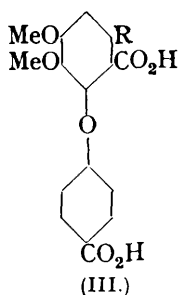
IN Part I (J., 1935, 1381) it was shown that the *O*-methyl ether of the active principle of tubocurare, namely, *O*-methyltubocurarine chloride, and *O*-methylbebeerine methochloride were diastereoisomerides, and that both after a two-stage Hofmann degradation gave the same nitrogen-free substance, $C_{36}H_{32}O_6$, named *O*-methylbebeerilene. On the basis of the structure (I) proposed by Späth and Kuffner (*Ber.*, 1934, 67, 55) for *O*-methylbebeerine methochloride, *O*-methylbebeerilene should have the structure (II) and on oxidation should



yield a mixture of two isomeric dimethoxytricarboxydiphenyl ethers (III) and (IV) where $R = CO_2H$. Späth and Kuffner have already announced the isolation of the former acid (III, $R = CO_2H$) by oxidation of the final product of a two-stage Hofmann degradation of *O*-methylbebeerine and the characterisation of it by a direct comparison of the m. p. of its trimethyl ester with a specimen of this ester isolated by Faltis and Neumann (*Monatsh.*, 1921, 42, 321) by degradation and oxidation of *isobebeerine* (*isochondrodendrine*). No experimental details have however been published.

Since a knowledge of the constitution of tubocurarine chloride, which is a rare and inaccessible substance, is dependent on that of the readily accessible bebeerine, the author has submitted the nitrogen-free substance *O*-methylbebeerilene (II) derived from bebeerine

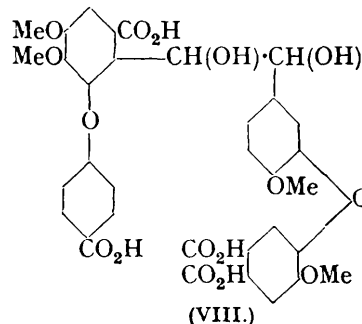
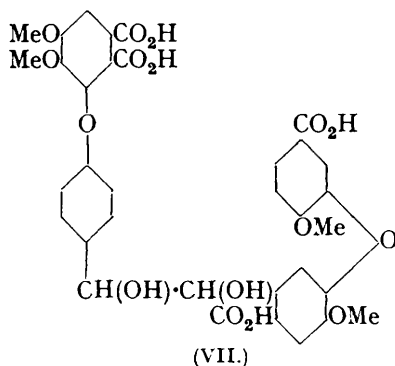
to permanganate oxidation. The product is a complex mixture of acids from which two isomeric acids, $C_{17}H_{14}O_9$, each crystallising with 2 molecules of water, and a third acid,



$C_{34}H_{30}O_{16}$, have been isolated in a pure condition. The first of the isomeric acids melted at 207° with effervescence, forming an anhydride, m. p. 245° . It contained two methoxy-groups and on demethylation lost carbon dioxide and gave a diphenolic dicarboxylic acid, $C_{17}H_{14}O_9 \cdot 4H_2O$, m. p. $262-263^\circ$, in which the phenolic groups are adjacent to each other since the substance gave a typical catechol reaction. To the parent acid must be ascribed the constitution 5 : 6 : 4'-tricarboxy-2 : 3-dimethoxydiphenyl ether (III, $R = CO_2H$). It is evidently a different *hydrate* of the monohydrated acid obtained by Faltis and Neumann (*loc. cit.*) from *O*-methylisochondrodendrine, which melted at 178° and then formed an anhydride, m. p. 245° . Slightly different data for the synthetic acid are given by Faltis and Frauendorfer (*Ber.*, 1930, **63**, 814), *viz.*, m. p. 188° ; anhydride, m. p. 245° . On demethylation of the natural and the synthetic acid, Faltis and co-workers also obtained a diphenolic dicarboxylic acid, m. p. $238-240^\circ$ and $246-249^\circ$ respectively, somewhat lower than that now found. Although there are these differences in detail, there can be no doubt that the parent acid in question has the constitution (III).

The second isomeric acid, $C_{17}H_{14}O_9 \cdot 2H_2O$, m. p. $262-264^\circ$, has not hitherto been described. On demethylation it lost two methyl groups and formed a crystalline acid (or mixture of acids) which did not give a catechol reaction. Furthermore, on decarboxylation the parent acid gave 2 : 2'-dimethoxydiphenyl ether (V), identified by comparison with a synthetic specimen. *O*-Methylbebeerine being accepted as a bisbenzylisoquinoline, this second acid must in all probability have the structure (IV, $R = CO_2H$), and *O*-methylbebeerine methochloride, and consequently *O*-methyltubocurarine chloride, must be represented by (I). The last link in the proof of the structure (I) will be the synthesis of the acid (IV, $R = CO_2H$).

The third acid, $C_{34}H_{30}O_{16}$, characterised by its sparing solubility in boiling water, is clearly an intermediate product of permanganate oxidation and should have one of the structures shown by (VII) and (VIII) which are based on (II).



When the work now described was complete, an important paper appeared by Faltis, Kadiera and Doblhammer (*Ber.*, 1936, **69**, 1269), in which essentially the same conclusions

with regard to bebeerine are arrived at by a different route. After ozonolysis of inactive *O*-methylbebeerinemethine (a product of a one-stage Hofmann degradation), the products of ozonolysis after re-methylation were oxidised to carboxylic acids, freed from nitrogen by a second Hofmann degradation, and thus gave a mixture of two acids to which are assigned the constitutions (III) and (IV), where $R = CH:CH_2$. The former acid was identical with an acid obtained by Faltis and Dieterich (*Ber.*, 1934, 67, 234) from *O*-methylisochondrodendrine (*O*-methylisobebeerine) by a similar method. The latter acid was new, and on decarboxylation gave a dimethoxyvinylidiphenyl ether which on oxidation gave 4-carboxy-2 : 2'-dimethoxydiphenyl ether (VI), identical with a synthetic specimen. The important point was thus established that the methoxy-groups are ortho to the ether linkage and are on different phenyl nuclei, as is required by formula (I) for *O*-methylbebeerine methochloride.

EXPERIMENTAL.

Preparation of *O*-Methylbebeerilene.—Bebeerine (59.4 g.) was completely methylated as previously described (King, *loc. cit.*, p. 1389). The iodide was converted into the chloride and then boiled with 2*N*-sodium hydroxide (700 c.c.) for 90 minutes. The ether-soluble portion of the methine was extracted, and remethylated by boiling the methyl-alcoholic solution with methyl iodide. After conversion into methochloride, the latter was again boiled with 2*N*-sodium hydroxide (700 c.c.) and the nitrogen-free *O*-methylbebeerilene extracted with chloroform. On removal of the solvent, the residue (48 g.) readily crystallised and was used in the oxidation experiment without further purification.

Permanganate Oxidation of *O*-Methylbebeerilene.—Crude *O*-methylbebeerilene (10 g.) in pure acetone (500 c.c.) was mechanically stirred, and finely powdered potassium permanganate (34 g.) added until a permanent pink colour resulted. On filtration the whole of the oxidation products were found in the precipitated manganese oxides. The latter were extracted repeatedly with hot water until the filtrate was colourless and gave no precipitate on acidification. The combined aqueous filtrates were concentrated (250 c.c.), and treated on the water-bath with aqueous 5% potassium permanganate (1000 c.c.) until consumption was very slow.

In similar portions, the whole of the *O*-methylbebeerilene was oxidised, and the combined aqueous filtrates from the final oxidation were concentrated and acidified. The crude amorphous acids, 56.95 g. (*O*-Me = 14.1%), were collected, and the aqueous filtrate extracted thoroughly with ether, which gave a fraction (A, 2.05 g.) which gradually solidified.

Isolation of 5 : 6 : 4'-Tricarboxy-2 : 3-dimethoxydiphenyl Ether (III).—Fraction A was recrystallised three times from water (successively 10, 20, and 30 c.c.). The acid had a great tendency to separate as an oil (cf. Faltis and Frauendorfer, *loc. cit.*), but on long standing became transformed into very fine white silky needles; yield 0.91 g. It melts at 207° (efferv.), forming an opalescent melt which clears at 230°, then resolidifies and melts at 245° (Found: loss at 100°, 9.0; C, 51.1; H, 4.3; MeO, 15.3. $C_{11}H_{14}O_9 \cdot 2H_2O$ requires C, 51.2; H, 4.6; $2H_2O$, 9.1; 2MeO, 15.6%). The product from the Zeisel determination, on 118 mg. of acid, crystallised from the hydriodic acid solution; it was taken up in ether, and decolorised with sulphurous acid. Recrystallised from a few c.c. of hot water, it separated in flattened leaflets, yield 71.4 mg., m. p. 258° (Found: C, 46.4; H, 5.2. Calc. for $C_{11}H_{10}O_7 \cdot 4H_2O$: C, 46.4; H, 5.0%), raised by further crystallisation to 262—263°. The ferric chloride colour reaction was very sensitive, a minute drop of the reagent in a dilute solution of the acid giving a pure blue colour, changed by a trace of sodium carbonate solution to a magenta-red. According to Faltis and Troller (*Ber.*, 1928, 61, 352) this acid is 2 : 3-dihydroxy-5 : 4'-dicarboxydiphenyl ether.

The parent acid, 5 : 6 : 4'-tricarboxy-2 : 3-dimethoxydiphenyl ether, was converted into its dimethyl ester by diazomethane, but the neutral product has so far resisted all attempts to crystallise it.

Isolation of 4 : 5 : 5'-Tricarboxy-2 : 2'-dimethoxydiphenyl Ether (IV) and an Acid $C_{34}H_{30}O_{16} \cdot 2H_2O$ (VII or VIII).—The main crop of crude amorphous acids (56.95 g.) was thoroughly extracted with ether in a Soxhlet apparatus and gave 16.2 g. of ether-soluble acids, which were converted into neutral sodium salts by addition of *N*-sodium hydroxide (107.1 c.c.). The solution was now fractionally acidified with 13 successive portions of *N*-hydrochloric acid, each of 10 c.c., and extracted, after each addition, with ether. Fractions 1—6 averaged 0.2 g. each, and consisted of complex amorphous hydroxy-acids very sparingly soluble in boiling water. Fractions 7—13 were larger, rising to a maximum at fraction 10 (4.6 g.), and were more readily soluble in boiling water, fractions 9—13 readily depositing crystals, the main constituent of

which was the required *ether*. Thus, fraction 12 (0.8 g.) in water (5 c.c.) gave a microcrystalline powder (0.7 g.). Recrystallised from water (20 c.c.) it again separated as a microcrystalline powder which under a microscope ($\frac{1}{8}$ " objective) consisted of aggregates of minute plates. The behaviour on melting shows some variation. It may effervesce at 257—258° and form a clear liquid which solidifies on cooling; when the m. p. is retaken at the same rate as previously, it is now 262—264°, presumably that of the anhydride. In some instances the original crystalline acid may only show a sintering between 250° and 260°, then rapidly solidify, and melt at 262—264° (Found: loss at 100°, 9.4; C, 50.9; H, 4.6. $C_{17}H_{14}O_9 \cdot 2H_2O$, requires C, 51.2; H, 4.6; $2H_2O$, 9.1%. Found, for dried material: MeO, 16.9. $C_{17}H_{14}O_9$ requires 2MeO, 17.1%). On long standing of aqueous solutions of this acid, a different *hydrate* (plates) with $2\frac{1}{2}H_2O$ is deposited. (Found: loss at 100°, 11.2. $C_{17}H_{14}O_9 \cdot 2\frac{1}{2}H_2O$ requires $2\frac{1}{2}H_2O$, 11.1%). This acid effervesces to a clear melt between 145° and 150°, then solidifies as the temperature is raised and melts at 262—264°. On dilution of the hydriodic acid liquors from the Zeisel determination and extraction with ether, a crystalline mass was obtained which showed no catechol reaction with ferric chloride but gave a turbid yellow solution.

Fraction 11 (2.5 g.), dissolved in water (10 c.c.), deposited a micro-crystalline powder (1.8 g.) which now required 40 c.c. of water for solution. A crystalline powder (1.77 g.) separated which was boiled with water (90 c.c.) and filtered from a sparingly soluble acid (43 mg., m. p. 200°). The latter acid now required 170 c.c. of boiling water to dissolve it, and separated in minute needles, m. p. 283—284° (yield 24 mg.) (Found: loss at 100° in a high vacuum 4.2, 4.3. Found, for dried solid: C, 58.9, 58.7; H, 4.3, 4.2. $C_{34}H_{30}O_{16}$ requires C, 58.8; H, 4.3%. $C_{34}H_{30}O_{16} \cdot 2H_2O$ requires $2H_2O$, 4.9%).

Decarboxylation of 4 : 5 : 5'-Tricarboxy-2 : 2'-dimethoxydiphenyl Ether.—A solution of the acid (0.8 g.) in pure quinoline (40 c.c.) and copper-bronze (4 g.) were boiled vigorously for 30 minutes. The ethereal extract was treated with 3*N*-hydrochloric acid, followed by 2*N*-sodium hydroxide, and then distilled. The residue (0.4 g.) readily crystallised on seeding with 2 : 2'-dimethoxydiphenyl ether. It was crystallised for analysis by solution in heptane, yield 0.09 g., m. p. 77—78° (Found: C, 73.1; H, 6.3. Calc. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1%). A synthetic specimen prepared from guaiacol and *o*-bromoanisole by the method of Ullmann and Stein (*Ber.*, 1906, **39**, 624) melted at 79—80°, and a mixture taken simultaneously in the same bath melted intermediately at 78—79°.

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