375. *The Synthesis of* dl-*Homolaudanosoline and its Dehydrogenation.*

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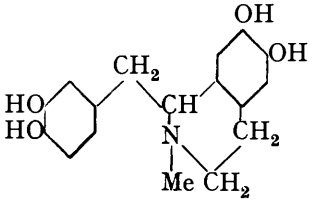
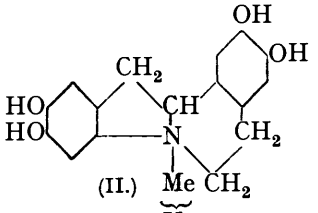
ROBINSON and SUGASAWA have studied the behaviour of laudanosoline (I) towards oxidising agents and found that smooth oxidation could be brought about by means of chloranil in alcoholic suspension with formation of the corresponding dehydro-compound, a tetrahydroxydibenzotetrahydropyrrocolinium salt (II), the constitution of which was elucidated chiefly by studying its behaviour in the Hofmann and Emde degradations (J., 1932, 789). A little later, the work of Schoepf and Thielfelder (*Annalen*, 1932, **497**, 22) covered almost the same ground.

We have now applied this method of oxidation to *dl*-homolaudanosoline (III), and conclude from analogy that the reaction proceeded in the same manner as with (I), giving rise to a new type of ring-system, the constitution of the methylation product being (IV).



(I.)



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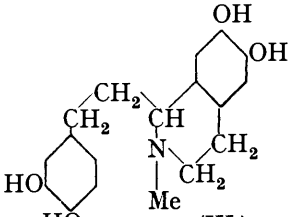

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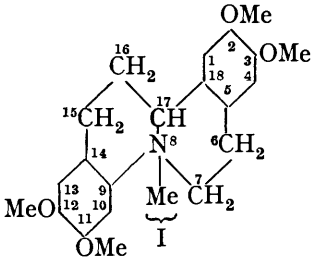

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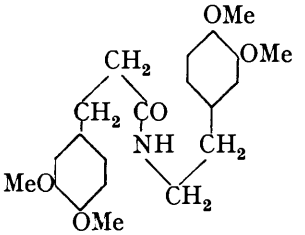

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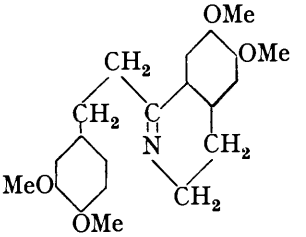
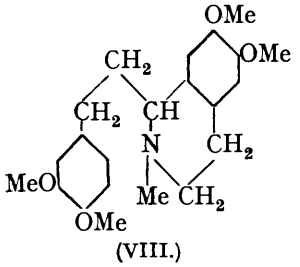
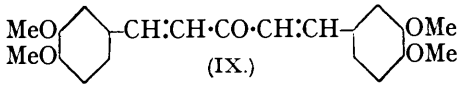


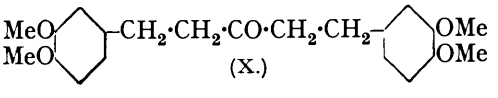
(VII.)



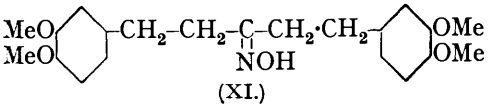
(VIII.)



(IX.)



(X.)



(XI.)

dl-Homolaudanosoline was synthesised in two ways from veratraldehyde. The first method is essentially the same as that of Narang, Rây, and Silooja, published (J., 1932, 2510) during the course of our work; it depends on the dehydration of the *amide* (VI) to the methochloride of 6 : 7-dimethoxy-1-β-3′ : 4′-dimethoxyphenylethyl-3 : 4-dihydro*iso*-quinoline (VII), which was catalytically reduced to *dl*-homolaudanosine (VIII).

The second and better of the two methods consists in condensing veratraldehyde and acetone by means of alkali (Stobbe and Haertel, *Annalen*, 1909, **307**, 104); the diveratrylideneacetone (IX) thus obtained was partially reduced to di-(β-3 : 4-dimethoxyphenyl)ethyl ketone (X). When treated with phosphoryl chloride in dry toluene, the related oxime (XI) readily underwent the Beckmann rearrangement and the amide (VI) thus formed

suffered ring-closure in the same operation. The yield at each stage is satisfactory and the initial materials are readily accessible.

Hydriodic acid was found to be the best reagent for the demethylation of *dl*-homolaudanosine; aluminium chloride, used advantageously in the former case (Robinson and Sugasawa, J., 1932, 795), did not give good results, chiefly because the homolaudanosoline hydrochloride is too freely soluble in water.

The dehydrogenation of homolaudanosoline was first tried under the same conditions as in the previous case (Robinson and Sugasawa, *loc. cit.*), alcohol being used as solvent, without satisfactory outcome; but when acetic acid was used (compare Schoepf and Thielfelder, *loc. cit.*), the corresponding dehydro-derivative could be isolated. This on methylation gave (IV). The corresponding methochloride appears to suffer normal decomposition at 220—230° under diminished pressure, but the results of analysis of the crystalline product were ambiguous, and this compound is being further investigated.

Experimental.

β-3 : 4-*Dimethoxyphenylpropiono*-β-3' : 4'-*dimethoxyphenylethylamide* (VI).—Homoveratrylamine (17·5 g.) in ether (100 c.c.) was mixed with aqueous sodium hydroxide (200 c.c. of 5%), and the acid chloride (from 21·5 g. of veratrylpropionic acid in 100 c.c. of chloroform) was introduced with vigorous shaking and cooling in melting ice. After 30 minutes, the organic solvents were removed in a current of air and the semi-solid *acid amide* which separated was taken up in ethyl acetate, and the extract washed with dilute hydrochloric acid, dried, and evaporated. The residue crystallised from ethyl acetate in colourless needles, m. p. 99—100° (yield, about 70%) (Found : C, 67·9; H, 7·7. $C_{21}H_{27}O_5N$ requires C, 67·7; H, 7·2%).

6 : 7-*Dimethoxy*-1-β-3' : 4'-*dimethoxyphenylethyl*-3 : 4-*dihydro*isoquinoline (VII).—(A) A mixture of the foregoing amide (15 g.), dry toluene (80 c.c.), and phosphoryl chloride (60 g.) was heated (oil-bath at 120—130°) for 1·5—2 hours; the amide soon disappeared and after some time a yellow crystalline substance separated. After cooling, this was collected and washed with light petroleum; the washings were added to the mother-liquor, causing some pasty material to be precipitated. The crystalline substance, the hydrochloride of the base (VII), was dissolved in water, and the filtered solution was basified and thoroughly extracted with ether. When the concentrated ethereal solution was allowed to evaporate slowly, the base (VII) separated in long colourless needles, m. p. 96—97°, already analytically pure (m. p. 94° according to the Indian authors, *loc. cit.*). Once obtained in solid form, the base is very sparingly soluble in ether and can then be crystallised from aqueous alcohol. By working up the pasty mass obtained from the mother-liquor, a further quantity of the base was isolated (total yield, 13 g.) (Found : C, 71·2; H, 7·3; N, 3·5. Calc. for $C_{21}H_{25}O_4N$: C, 71·0; H, 7·1; N, 3·9%).

(B) The preparation of diveratrylideneacetone (IX) was shortened as follows. Aqueous sodium hydroxide (10 g. of 10%) was added to veratraldehyde (20 g.) and acetone (3·2 g.) dissolved in alcohol (160 c.c.), and the mixture was cooled in running water and stirred mechanically. The colourless solution became yellow and an oil, which became crystalline after 2—3 hours, separated. After 10 hours, the solid was collected, washed with water, and crystallised from alcohol, forming bright yellow needles, m. p. 84° (yield, 16·5 g. or 85%).

When this unsaturated ketone, dissolved in ethyl acetate, was partly reduced by means of hydrogen and the Adams platinum oxide catalyst, di-β-3 : 4-dimethoxyphenylethyl ketone was obtained in theoretical yield. After $2H_2$ were absorbed, the reduction suddenly slackened and the solution was colourless. The filtrate from the catalyst was concentrated; the colourless residue crystallised from aqueous methyl alcohol in needles, m. p. 84° (compare Nomura and Hotta, *C.*, 1925, II, 1745). The oxime, prepared by the usual method, crystallised from alcohol in needles, m. p. 138—139° (compare Nomura and Hotta, *loc. cit.*) (yield, exceeds 90%).

The foregoing oxime (5 g.) was suspended in dry toluene (25 c.c.), and phosphoryl chloride (20 g.) added. The light brown solution obtained was heated (oil-bath at 120—130°) for 2 hours, the evolution of hydrogen chloride then ceasing. Sufficient light petroleum was added to produce a thick brown precipitate and after some time the supernatant liquid was decanted. The residue was repeatedly extracted with warm water and the combined filtrates were basified. The base was extracted and dried in ether, recovered, and crystallised from aqueous alcohol, forming colourless needles, m. p. 96—97°, not depressed on admixture with an authentic specimen of the base (VII) (yield, 4 g. or 85%).

dl-*Homolaudanosine* (VIII).—The foregoing base (11·8 g.), dissolved in methyl alcohol

(25 c.c.), was heated with methyl iodide (6·5 g.) on a steam-bath for several hours. On cooling, the methiodide separated in aggregates of yellow crystals (17·1 g.). Recrystallised from methyl alcohol containing a little water, it formed yellow prismatic needles decomposing at 132·5—133·5°.

The corresponding methochloride was prepared by the usual method and catalytically reduced in alcoholic solution, exactly 1 mol. of hydrogen being absorbed smoothly. The filtrate from the catalyst was basified, and the free base isolated by means of ether as a light yellow, viscous oil, which would not crystallise. The *perchlorate* crystallised from hot water, containing a small amount of perchloric acid, in colourless pillars, decomposing at 183—185° (Found : C, 55·3; H, 6·7; N, 2·7. $C_{22}H_{29}O_4N,HClO_4$ requires C, 55·9; H, 6·4; N, 3·0%).

dl-*Homolaudanosoline.*—A mixture of homolaudanosine (10 g. of crude substance), hydriodic acid (150 g., *d* 1·7), and a little acetic anhydride was heated (oil-bath at 150°) for 1·5—2 hours. Hydriodic acid was then removed by distillation in a vacuum, and water added to the residue, which was evaporated again; *dl*-homolaudanosoline hydriodide was then obtained as an amorphous hygroscopic powder. In order to show that homolaudanosine suffered no structural change during demethylation, the demethylated compound, which was proved to be methoxyl-free, was dissolved in an excess of 33% potassium hydroxide solution in an atmosphere of hydrogen and was methylated by means of methyl sulphate. Potassium iodide was added to the reaction product, but since the methiodide of the methylated base is readily soluble in water, no precipitate was obtained. The whole was, therefore, concentrated in a vacuum and heated at 250° for about 20 minutes, and the residue was then extracted with ether. After removal of the solvent, the perchlorate of the base was prepared, m. p. 183—185° (decomp.), and proved to be identical with the perchlorate of *dl*-homolaudanosine.

Dehydrogenation of Homolaudanosoline.—Crude homolaudanosoline hydriodide (3·7 g.) was dissolved in glacial acetic acid (100 c.c.), a solution of chloranil (2·1 g.) in acetic acid (80 c.c.) added gradually, and the whole heated on a steam-bath for 30 minutes and kept over-night. The acetic acid was evaporated in a vacuum, and the residue freed by means of ether from tetrachloroquinol and crystallised from dilute hydriodic acid, forming yellowish-brown, sandy crystals decomposing at 252—253° (yield, *ca.* 3 g. or 80%) (Found : C, 49·4; H, 4·4; N, 3·7. $C_{18}H_{20}O_4NI$ requires C, 49·0; H, 4·5; N, 3·2%). From the analytical results and by analogy with the former investigation, we are of the opinion that the substance is 2 : 3 : 11 : 12-*tetrahydroxy*-8-*methyl*-6 : 7 : 15 : 16-*tetrahydro*-5 : 18 : 9 : 14-*dibenzpyridocolinium iodide* (compare IV).

2 : 3 : 11 : 12-*Tetramethoxy*-6 : 7 : 15 : 16-*tetrahydro*-5 : 18 : 9 : 14-*dibenzpyridocoline.*—The foregoing iodide (2 g.) was suspended in water (5 c.c.) in an atmosphere of hydrogen, and 33% potassium hydroxide solution (20 c.c.) and methyl sulphate (12 c.c.) added with shaking. The methylation was completed by adding further similar portions of alkali and methyl sulphate and, after the evolution of heat subsided, an excess of alkali was introduced. On cooling, the corresponding methosulphate separated; this was collected, and potassium iodide added to the filtrate; the corresponding *methiodide* then separated. The methosulphate was also converted into the methiodide, and both portions of the latter salt were together crystallised from aqueous methyl alcohol, forming yellow pillars (2·1 g.), decomposing at 237—238° (Found : C, 53·1; H, 5·6; N, 2·9. $C_{22}H_{28}O_4NI$ requires C, 52·6; H, 5·7; N, 2·9%).

The methiodide was converted into the corresponding methochloride, and a colourless solid, decomposing at 204—205° (crude substance), which was obtained was heated at 220—230° (oil-bath) until effervescence had ceased and then for a further 10 minutes. On cooling, the residue was extracted with hot dry benzene, the solvent evaporated, and the residue crystallised from alcohol, forming colourless leaflets, m. p. 153·5—154·5°, which soon turned yellow on exposure to light, although without change of m. p. Though the m. p. was not raised by further purification, the results of several analyses were indefinite, and the substance is still under investigation.

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