

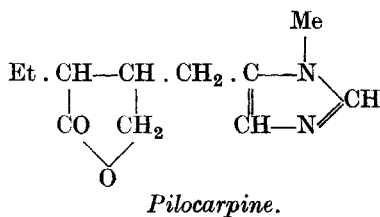
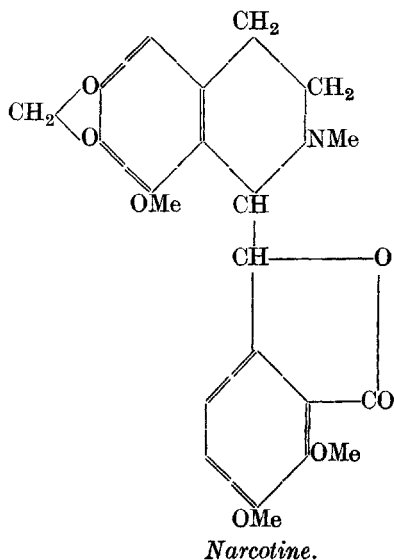
## STUDIES IN THE ISOQUINOLINE SERIES.

### PART V. 4,COUMARO-METHYL, 3,COUMARO-METHYL, AND 3,COUMARYL-1-ISOQUINOLINES.

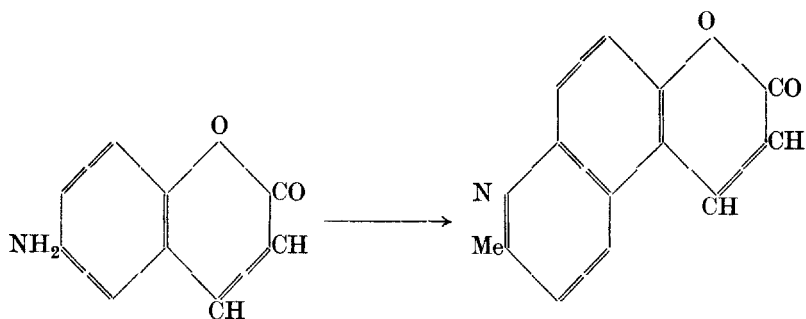
By B. B. DEY and K. SANKARAN.

(Read January 2, 1940.)

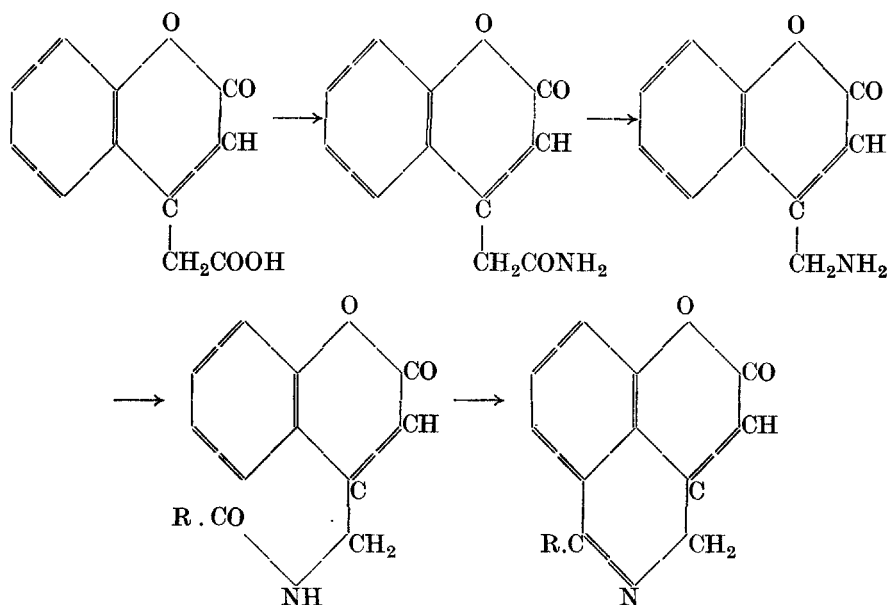
Although the lactone ring has been found to occur so frequently in nature, either as  $\alpha$ - or  $\gamma$ -pyrones, in glucosides and in natural colouring matters, there are only a few instances known of the presence of such ring systems in heterocyclic bases. The two best known examples of natural alkaloids containing the lactone ring are those of narcotine and pilocarpine, having respectively the following constitutions:—



Among the laboratory attempts at syntheses of compounds, containing the combined lactone and heterocyclic basic group, may be mentioned the work of Dey and Goswami (*J. Chem. Soc.*, 1919, 15, 531), on 1 : 8- $\psi$ -isonaphthoxazones by the application of Skraup's reaction to 6-amino coumarins, and its extension to homologues of quinolino-6 : 5- $\alpha$ -pyrones, by the application of the Doebner-Miller reaction to these 6-amino-coumarins (Dey and Seshadri, *J.I.C.S.*, 1926, *Vol. III*, p. 187), thus:



It was hoped in the beginning that isoquinolino-pyrones, like the quinolino-pyrones mentioned above, might be synthesised on similar lines by the route shown below:—

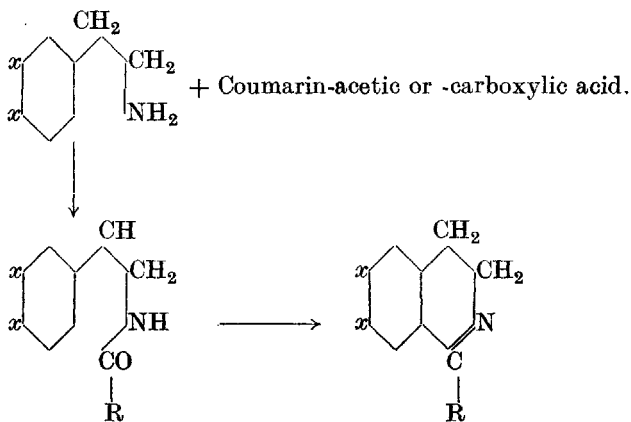


This expectation has unfortunately not been realised by us, all attempts at obtaining the 4-coumaryl methyl amine from the corresponding coumarin-4-acetamide being unsuccessful.

Isoquinolines with a coumaryl group substituted in position 1 were, however, readily obtained from the coumarin-4- and 3-acetic acids, and  $\beta$ -phenyl ethyl amines like homopiperonyl and homoveratryl amines. The reactivity and properties of these coumarin acids (Dey and co-workers, *J.I.C.S.*, 1924, *Vol. I*, 107; *ibid.*, 1931, *Vol. VIII*, 247; *ibid.*, 1931, *Vol. VIII*, 817; *ibid.*, 1934, *Vol. XI*, 381) have been found to be quite similar to those of acetic and phenyl acetic acids. The substitution of these for the usual fatty or aromatic acids in the syntheses of 1-substituted isoquinolines, and a study of

the changes in physiological properties, if any, resulting from the inclusion of the pyrone ring in their molecules, seemed, therefore, to be of considerable importance. The recent patents of E. Merck & Co. [D.R.P. 613-005 (1935); E. Merck & Co., Dalmer and Werder, 612-592 (1937): reference in American Chemical Abstracts, (1937, November)] wherein have been prepared the coumarin 3-carboxylic acid salts of papaverine and of trans-ephedrine, which are claimed to have well-marked sedative and antispasmodic action, lent additional interest to the investigation. Merck's preparations were only salts of the isoquinoline bases with the coumarin carboxylic acids. No syntheses of coumaryl isoquinolines are known and it was therefore considered desirable to undertake a systematic study of the syntheses, properties and possible pharmacological actions of these bodies.

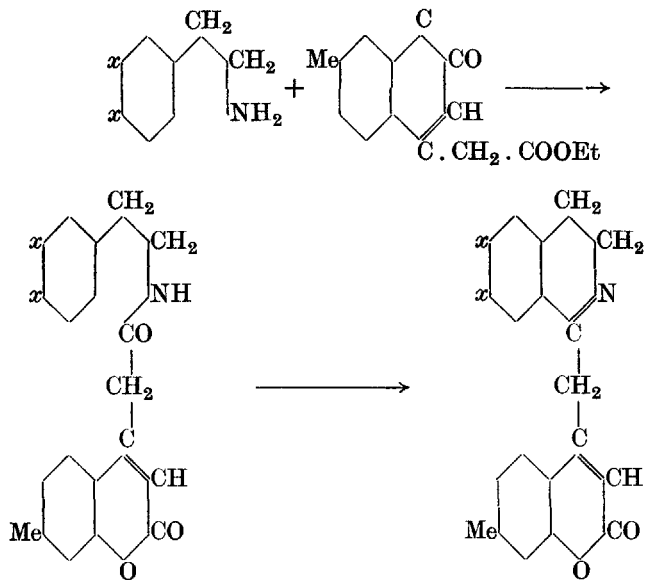
The syntheses of the 1-coumaryl isoquinolines via the  $\beta$ -phenyl ethyl amides of the coumarin acids and cyclisation of the latter into the isoquinolines by the Bischler-Napieralsky method has been found to proceed normally and smoothly according to the following scheme:—



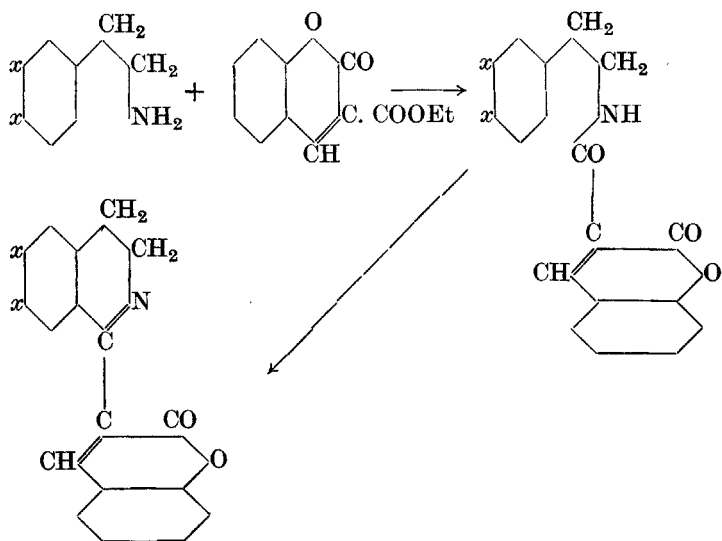
where R = a coumaro-4-methyl or a coumaryl-group. This reaction furnishes a general method of synthesis of 1-coumaryl isoquinolines.

The formation of isoquinolines from homopiperonylamine and homoveratryl amine on the one hand and (a) 7-methyl coumarin 4-acetic acid, (b) coumarin 3-carboxylic acid, and (c) coumarin 3-acetic acid on the other is shown in the schemes A, B and C given below:—

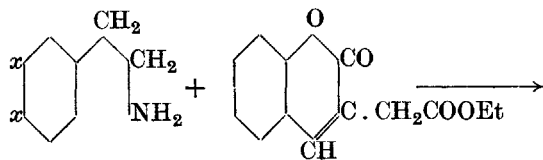
'A'

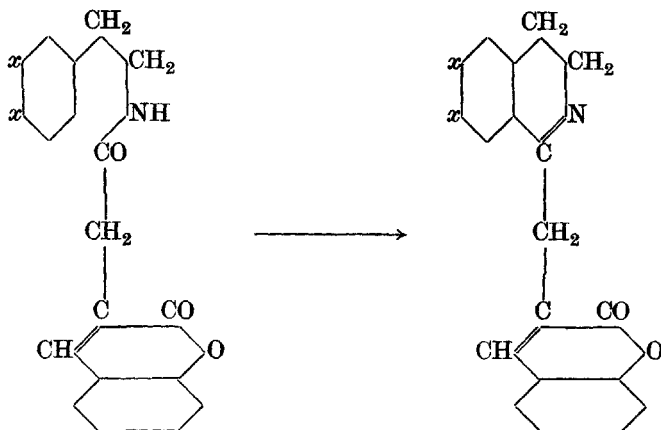


'B'



'C'





*Isoquinolines from coumarin-4,acetic acids: 1, (7-methyl-4-coumaro methyl)-6 : 7,methylene dioxy- or dimethoxy-3 : 4,dihydro-isoquinoline and derivatives.*

7-methyl coumarin 4-acetic acid was prepared by the direct method of Dey and Row (*J.I.C.S.*, 1924, *Vol. I*, 107) from citric acid and meta-cresol. Homopiperonylamine was prepared by the method of Buck and Perkin (*J. Chem. Soc.*, 1924, 125, 1675) and homoveratryl amine by a slightly modified method of Ray (*J.I.C.S.*, 1927, *Vol. IV* 403). The condensation of these to the intermediary amides was effected generally by heating the amine and the ethyl ester (Fries and Volk, *Ann.*, 1911, 379, 107) at 120°, in solvents like toluene or xylene. The difficulty arising from the tendency of the coumarin-4-acetic acid to be decarboxylated was thus avoided. The amides separated in an almost pure condition and the yields were generally good. Cyclisation occurred readily when phosphorus oxychloride was used as the cyclising agent, and the major portion of the reaction product was obtained as the hydrochloride of the base. While the free bases are yellow, the hydrochlorides are colourless crystalline solids. They have a bitter taste. The isoquinolines are not strong bases and are readily precipitated from aqueous solutions of their hydrochlorides by sodium carbonate solution. Reduction to the tetrahydro isoquinolines has been accomplished in most cases, using zinc and sulphuric acid. The hydrochloride of the tetrahydro base from homoveratryl amine and 7-methyl coumarin 4-acetic acid ester has been found to decompose rather rapidly when kept.

*Isoquinolines from coumarin-3,carboxylic acids: 1, (3-coumaryl)-6 : 7,methylene dioxy- or dimethoxy-3 : 4,dihydro-isoquinolines and derivatives.*

The coumarin-3,carboxylic ethyl ester required in these investigations has been prepared in almost quantitative yields by the method of Knoevenagel (*Ber.*, 31, 2593) from salicyl aldehyde and malonic ester. The condensation

to the intermediary amides was carried out according to the method described in Section A. Both the free base and its hydrochloride have been obtained in satisfactory yields under the usual conditions of experimentation. The interesting fact was noticed that the free bases in this case were colourless and their hydrochlorides were yellow while the opposite is the case with the compounds described in Section A. A curious observation to record is that relating to the physical character of the cyclisation product of the amide derived from homoveratryl amine. It invariably set itself to a beautiful fluorescent jelly, which dissolved in hot water, but again formed the jelly on cooling. In this case, the hydrochlorides were obtained by passing dry HCl into benzene solutions of the respective bases. Reduction of the 1, (3-coumaryl)-6 : 7 methylene dioxy-3 : 4, dihydro-isoquinoline was not successful.

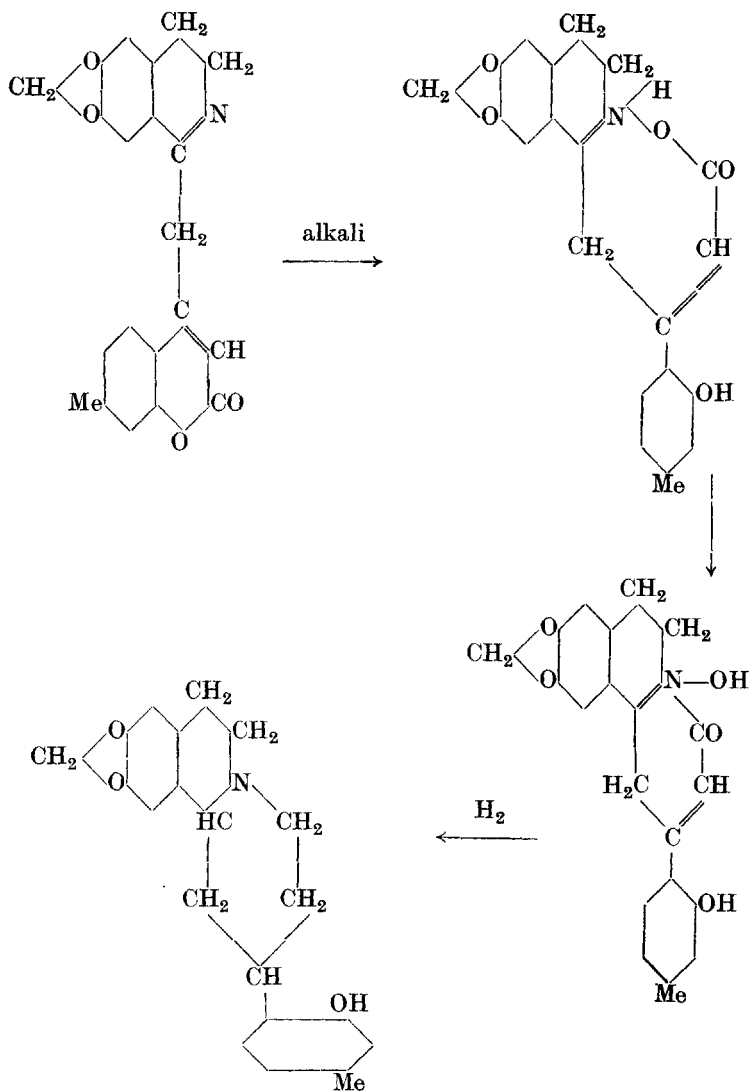
*Isoquinolines from coumarin-3, acetic acids: 1, (3 coumaro-methyl)-6 : 7, methylene dioxy- or dimethoxy-3 : 4-dihydro-isoquinolines and derivatives.*

The coumarin-3, acetic acid was prepared by the method of Dey and Sankaranarayanan (*J.I.C.S.*, 1931, *Vol. VIII*, 817). The condensation to the amide was effected by heating the two components without any solvent. The yields were not as satisfactory as in the former cases, large amounts of by-products being obtained. Cyclisation, too, led to the formation of considerable amounts of tarry products which made it rather difficult to isolate the pure isoquinoline. The free base is yellow in colour but the salt which was first obtained as a solid soon turned into an oil which was only partly soluble in water, showing that partial decomposition had taken place.

*General properties of the coumaryl-isoquinolines.*

All the five 1-coumaryl isoquinolines which have been synthesised have a weak basic character. They dissolve in acids only slowly and can be completely extracted from their acid solutions with chloroform. Salts such as the hydrochloride, hydrobromide, nitrate and picrate have, however, been prepared in the pure state. The methiodides were generally obtained pure on heating the base and methyl iodide under pressure. They begin to decompose on attempting to crystallise them from water or alcohol. The bases, too, decomposed slowly on keeping and were found to be preserved best in the form of their hydrochlorides.

A study of the action of alkali on these bodies should be of interest, as compounds of the pyridocoline type are expected to arise as a result of the opening of the pyrone ring. The following scheme explains the reactions involved:—



Investigations in this direction are in progress.

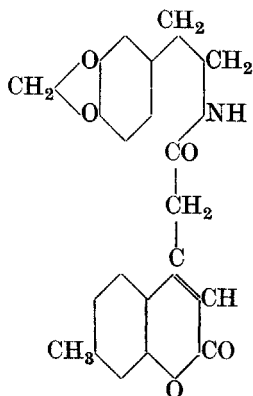
#### EXPERIMENTAL.

The homopiperonylamine required in these investigations was prepared mainly by the method of Buck and Perkin (*J. Chem. Soc.*, 1925, 125, 1675).

7-methylcoumarin-4-acetic acid was prepared by the method of Dey and Row (*J.I.C.S.*, 1924, Vol. I, 197). 9 g. of the coumarin acetic acid crystallising in needles, M.P. 190°, and 4 g. of 4,7-dimethyl coumarin, M.P. 134°, were obtained from 24 g. of citric acid and 10 g. of metal-cresol.

The ethyl ester (Fries and Volk, *Ann.*, 1911, 379, 107) was easily prepared by saturating an absolute alcoholic solution of the acid with dry HCl gas.

*7-methyl, coumarin-4,acet-3 : 4-methylene dioxy-β-phenyl ethyl amide.*



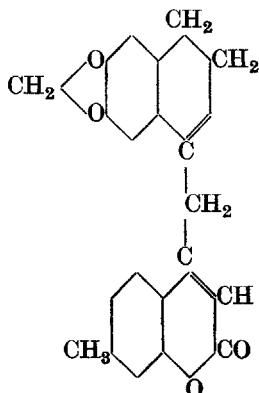
3.30 g. of homopiperonylamine and 4.90 g. of the ester were heated together with 30 c.c. of toluene for a period of 3 to 4 hours at its boiling point, moisture being excluded. On cooling, the amide separated out as a crystalline solid which was filtered, washed with dilute HCl and water alternately, and crystallised from a large quantity of alcohol. Clusters of snow-white needles. M.P. 197°. Yield, 4.5 g.

0.2482 g. gave 8.4 c.c. of nitrogen at 29° and 764 mm.

Found: N, 3.77 per cent.

$C_{21}H_{19}O_5N$  requires N, 3.83 per cent.

*1-(7,methyl-4,coumaromethyl)-6 : 7,methylene dioxy-3 : 4,dihydro-isoquinoline.*



2 g. of the above amide were dissolved in 20 c.c. toluene and refluxed on the sand-bath with 12 c.c. of phosphorus oxychloride for 1½ hours. The contents became dark coloured and a crystalline solid appeared towards the



end of the reaction, the quantity of which increased as the flask cooled down. The deeply coloured fluorescent solution was poured into crushed ice. The thick oil which separated, solidified in about an hour. It was filtered, washed with dilute alcohol and finally crystallised from hot water. Shining plates, M.P. 265° (d.). Yield, 0.9 g. This was found to be the hydrochloride of the base.

The coloured acid filtrate was separated from the toluene layer and then repeatedly exhausted with chloroform and the extract dried over anhydrous potassium carbonate. On removing the solvent, the free base was left behind as a coloured mass which crystallised from benzene or from toluene-petroleum ether mixture in short stout needles, M.P. 184°. Yield, 0.5 g.

0.1696 g. of the base gave 0.4514 g. of CO<sub>2</sub> and 0.0770 g. of water; 2.609 milligrams gave 0.090 c.c. of nitrogen at 22.5° and 767 mm. pressure; 9.276 milligrams of the hydrochloride gave 3.420 milligrams of AgCl.

Found: C, 72.69 per cent; H, 5.04 per cent; N, 4.02 per cent.

C<sub>21</sub>H<sub>17</sub>O<sub>4</sub>N requires C, 72.60 per cent; H, 4.89 per cent; N, 4.03 per cent.

Found: Cl, 9.11 per cent.

C<sub>21</sub>H<sub>17</sub>O<sub>4</sub>NCl requires Cl, 9.25 per cent.

(Analyses by Dr. Ing. A. Schöller of Berlin.)

The free base is yellow in colour and is soluble in all common organic solvents. It can be easily extracted from acid solutions. The aqueous solution of the hydrochloride is strongly fluorescent and is extremely bitter to the taste. The free base is precipitated from aqueous solutions of the hydrochloride by sodium carbonate solution; both the free base and the hydrochloride decompose slowly on keeping.

*The hydrobromide* was obtained as fern-shaped crystals when the free base was rubbed with a few drops of concentrated hydrobromic acid, M.P. 268° (d.).

0.186 g. gave 0.0800 g. of AgBr.

Found: Br, 18.53 per cent.

C<sub>21</sub>H<sub>16</sub>O<sub>4</sub>NBr requires Br, 18.69 per cent.

*The methiodide* was obtained by heating the base and methyl iodide in a sealed tube and washing the dark coloured solid product with a little chloroform. Attempts at crystallisation failed as the compound began to decompose. M.P. 228° (d.).

0.1415 g. gave 0.0675 g. of AgI.

Found: I, 25.79 per cent.

C<sub>22</sub>H<sub>20</sub>O<sub>4</sub>NI requires I, 25.97 per cent.

*The nitrate* was obtained as plates by rubbing the base with dilute nitric acid. M.P. 156°.

*The picrate* was obtained as a yellow precipitate on mixing alcoholic solutions of the base and picric acid; it crystallised from glacial acetic acid as yellow needles. M.P. 248° (d.).

0.1790 g. gave 15.6 c.c. of nitrogen at 28° and 762.7 mm.

Found: N, 9.73 per cent.

$C_{27}H_{20}O_{11}N_4$  requires N, 9.72 per cent.

*1, (7, methyl-4, coumaromethyl)-6, 7, methylenedioxy-1, 2, 3, 4-tetrahydro-isoquinoline.*

1 g. of the dihydro-base, 3 g. of zinc dust and 0.05 g. of copper sulphate were mixed with 30 c.c. of water and warmed on the water-bath. 2.5 c.c. of concentrated sulphuric acid was added during the course of an hour and the mixture was shaken well so that hydrogen was evolved only slowly. As the reaction progressed the yellow solution became gradually colourless. It was filtered after an hour, cooled, basified with sodium carbonate solution and then exhaustively extracted with chloroform and the extract dried over anhydrous potassium carbonate. Removal of this left the tetrahydro compound as an oil. Yield, 0.3 g.

*The hydrochloride* was obtained as plates by rubbing this oil with a few drops of concentrated hydrochloric acid. M.P. 214° (d.). The tetrahydro base was precipitated as a solid by basifying the hydrochloride solution with sodium carbonate. M.P. 175° (decomp.).

0.1386 g. of the base gave 5.1 c.c. of nitrogen at 29° and 759.5 mm.

Found: N, 4.15 per cent.

$C_{21}H_{19}O_4N$  requires N, 4.01 per cent.

0.1935 g. of the hydrochloride gave 0.0745 g. of AgCl.

Found: Cl = 9.50 per cent.

$C_{21}H_{20}O_4NCl$  requires Cl, 9.20 per cent.

*The picrate* was obtained as a yellow precipitate from the aqueous solution of the hydrochloride by the addition of a saturated solution of picric acid. It crystallised from acetic acid as rhombic plates. M.P. 207° (d.).

0.1556 g. gave 13.4 c.c. of nitrogen at 30° and 764.5 mm.

Found: N, 9.56 per cent.

$C_{27}H_{22}O_{11}N_4$  requires N, 9.68 per cent.

*The acetyl derivative* was prepared by treating the tetrahydro base with a few drops of acetic anhydride and crystallising the product from dilute alcohol. M.P. 204° (d.).

0.0694 g. gave 2.2 c.c. of nitrogen at 30° and 767.6 mm.

Found: N, 3.53 per cent.

$C_{28}H_{21}O_5N$  requires N, 3.58 per cent.

Homoveratrylamine was prepared by the method of Buck and Perkin modified by Ray (*J.I.C.S.*, 1927, *Vol. IV*, 403). The yields at each stage were excellent.

*7, methyl-4-coumarin acet-3 : 4-dimethoxy-β-phenyl-ethyl amide.*

1.8 g. of the ester and 2.45 g. of homoveratrylamine were heated under reflux in xylene solution for 3 hours. On cooling, the amide separated

out as a crystalline solid. It was washed with dilute HCl, and crystallised from alcohol. Short rods, M.P. 174°. Yield, 2.6 g.

0.0931 g. gave 3 c.c. nitrogen at 31° and 762.5 mm.

Found: N, 3.63 per cent.

$C_{22}H_{23}O_5N$  requires N, 3.67 per cent.

1, (7-methyl-4-coumaro-methyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline.

The above amide (2 g.) was dissolved in 16 c.c. toluene and gently refluxed on the sand-bath with 11 c.c. of phosphoryl chloride for an hour and a half; the solution which had originally a straw yellow colour acquired a deep reddish tint. On pouring the reaction mixture into ice water, a thick oil separated which solidified after about an hour; this was collected, washed with water and then with the minimum amount of chloroform and crystallised from hot water. The *hydrochloride* separated as thin rhombic crystals. M.P. 108°. Yield, 0.6 g. The toluene layer was carefully removed from the filtrate and extracted five times with chloroform (10 c.c.) and the extract dried over anhydrous potassium carbonate. After removal of the solvent the isoquinoline remained as an oil which rapidly solidified. It crystallised from a mixture of toluene and petroleum ether as short stout needles. M.P. 181°. Yield, 0.5 g. The base is yellow in colour and dissolves readily in the common organic solvents. The hydrochloride is colourless and its aqueous solution has a mild green fluorescence. It affords the rare example of a base melting higher than its salt.

0.1238 g. of the base gave 4.45 c.c. nitrogen at 30° and 764 mm.

Found: N, 3.98 per cent.

$C_{22}H_{21}O_4N$  requires N, 3.85 per cent.

0.1035 g. of the hydrochloride gave 0.0374 g. of AgCl.

Found: Cl, 8.94 per cent.

$C_{22}H_{22}O_4NCl$  requires Cl, 8.88 per cent.

The *hydrobromide* was readily obtained as colourless crystals on mixing the base with aqueous hydrobromic acid. M.P. 207° (d.).

0.1423 g. gave 0.961 g. of AgBr.

Found: Br, 18.24 per cent.

$C_{22}H_{22}O_4NBr$  requires Br, 18.02 per cent.

The *methiodide* was formed on heating the free base with excess of MeI in a stoppered bottle at 100°. M.P. 182° (d.).

0.1201 g. gave 0.056 g. of silver iodide.

Found: I, 25.22 per cent.

$C_{23}H_{24}O_4NI$  requires I, 25.15 per cent.

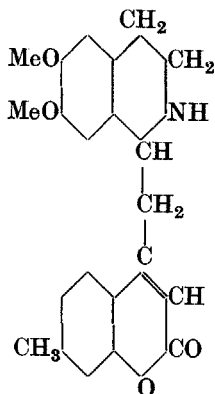
The *picrate* separated from glacial acetic acid as beautiful straw yellow prisms.

0.1904 g. gave 16.1 c.c. nitrogen at 30.3° and 759.8 mm.

Found: N, 9.32 per cent.

$C_{28}H_{24}O_{11}N_4$  requires N, 9.46 per cent.

*Reduction to the 1,2,3,4-tetrahydro-isoquinoline.*



2 g. of the hydrochloride of the dihydro base was dissolved in the minimum amount of water and heated on the boiling water-bath with a tiny crystal of copper sulphate and 6 g. of zinc dust for 3 hours. 5 c.c. of concentrated sulphuric acid was then slowly added during the course of an hour when the solution became practically colourless. It was filtered, cooled, basified with sodium carbonate solution and extracted repeatedly with chloroform. The tetrahydro-base was obtained as an oil. Yield, 0.5 g. The *hydrochloride* separated as crystals on adding a few drops of concentrated hydrochloric acid to the oily base. M.P. 98°. The salt is found to decompose on keeping.

0.1129 g. of the base gave 4.25 c.c. of nitrogen at 30° and 764 mm.

Found: N, 4.16 per cent.

$C_{22}H_{23}O_4N$  requires N, 3.83 per cent.

0.2166 g. of the hydrochloride gave 0.0723 g. of AgCl.

Found: Cl, 8.25 per cent.

$C_{22}H_{24}O_4NCl$  requires Cl, 8.80 per cent.

*The picrate* melted at 165°.

0.2389 g. gave 19.30 c.c. nitrogen at 26.8° and 766.6 mm.

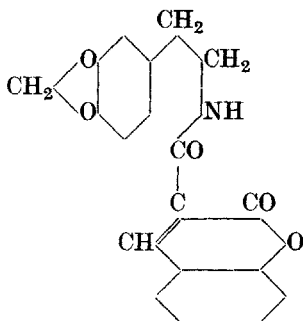
Found: N, 9.12 per cent.

$C_{28}H_{26}O_{11}N_4$  requires N, 9.42 per cent.

*1-(3,coumaryl)-6 : 7-methylene dioxy-3 : 4-dihydro-isoquinoline.*

*Coumarin 3-carboxylic ester*, prepared by Knoevenagel's method (*Ber.*, 31, 2593) from salicyl aldehyde (3 g.), malonic ester (4.5 g.) and a few drops of piperdine, crystallises from alcohol as elongated plates. M.P. 94°. Yield, 3.5 g.

*1-(3 coumaryl)-3 : 4, methylene dioxy-β-phenyl ethyl amide.*

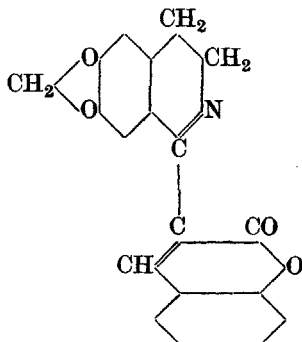


4.36 g. of the ester, 3.30 g. of homopiperonyl amine and 30 c.c. of toluene were heated to boiling for 3 to 4 hours, and the separating solid purified in the usual way. Snow-white needles (from alcohol). M.P. 214°. Yield, 4.8 g. 0.2116 g. gave 7.8 c.c. of nitrogen at 31° and 747.7 mm.

Found: N, 4.07 per cent.

C<sub>19</sub>H<sub>15</sub>O<sub>5</sub>N requires N, 4.10 per cent.

*1, (3-coumaryl)-6 : 7-methylene dioxy-3 : 4-dihydro-isoquinoline.*



2 g. of the amide suspended in 25 c.c. toluene was refluxed on the sand-bath with 12 c.c. of phosphorus oxychloride for an hour and a half. The solution acquired a dark brown colour and a small amount of yellow crystals separated out towards the end of the reaction. The contents were poured into ice water, the yellow solid filtered and the filtrate repeatedly extracted with chloroform. On distilling off the dried solvent the isoquinoline was left behind as a coloured solid which was crystallised from benzene. Fern-shaped crystals. M.P. 253° (d.). The yellow solid that had separated was found to be the impure hydrochloride. It was dissolved in hot water and basified, when the free base was liberated as a colourless solid. Total yield of the base, 1.4 g.

0.1676 g. of the base gave 6.9 c.c. of nitrogen at 30° and 766.3 mm.

Found: N, 4.58 per cent.

C<sub>19</sub>H<sub>13</sub>O<sub>4</sub>N requires N, 4.38 per cent.

*The hydrochloride* was prepared by passing dry HCl gas into a dry benzene solution of the base. M.P. 221° (d.).

0.1895 g. gave 0.0773 g. of AgCl.

Found: Cl, 10.08 per cent.

$C_{19}H_{14}O_4NCl$  requires Cl, 10.09 per cent.

*The hydrobromide* obtained in the usual way melted at 214° (d.).

0.2225 g. gave 0.1037 g. of AgBr.

Found: Br, 19.84 per cent.

$C_{19}H_{14}O_4NBr$  requires Br, 20.00 per cent.

*The methiodide* was obtained by heating the components in a sealed tube. M.P. 218° (d.).

0.1201 g. gave 0.0620 g. of AgI.

Found: I, 27.8 per cent.

$C_{20}H_{16}O_4NI$  requires I, 27.6 per cent.

*The picrate* crystallised from acetic acid as stout yellow prisms. M.P. 213° (d.).

0.1236 g. gave 11.6 c.c. nitrogen at 32° and 766.2 mm.

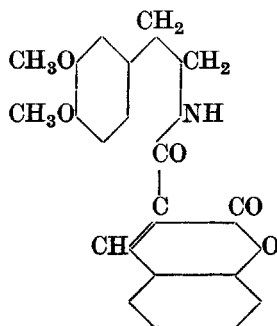
Found: N, 10.30 per cent.

$C_{25}H_{16}O_{11}N_4$  requires N, 10.21 per cent.

*Reduction to the 1,2,3,4-tetrahydro-isoquinoline.* 2.5 g. of the dihydro base was dissolved in the minimum amount of dilute sulphuric acid and refluxed on the boiling water-bath with 7 g. of zinc dust and a small crystal of copper sulphate, and a few c.c. of concentrated sulphuric acid added during the course of the reduction (about one hour). The colourless solution was filtered hot, cooled and basified with sodium carbonate and extracted with chloroform. On evaporating the dried solution the base was left behind as an oil. Yield, 0.9 g.

*The hydrochloride*, prepared by rubbing the above oil with a few drops of concentrated HCl, melted indefinitely between 196° and 205°.

*1, (3 coumaryl)-3 : 4-dimethoxy-β-phenyl ethyl amide.*



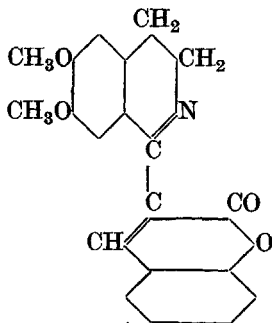
3.62 g. of homoveratryl amine and 4.36 g. of the ester boiled in toluene (20 c.c.) gave nearly 4 g. of the amide, crystallising from alcohol in prisms. M.P. 158°.

0.1347 g. gave 4.96 c.c. of nitrogen at 31° and 758.3 mm.

Found: N, 4.03 per cent.

$C_{20}H_{19}O_5N$  requires N, 3.96 per cent.

*1, (3, coumaryl)-6 : 7-dimethoxy-3 : 4-dihydro-isoquinoline.*



3 g. of the amide, suspended in 20 c.c. toluene and 22 c.c. of phosphorus oxychloride were gently refluxed on the sand-bath for 2 hours. The jelly-like mass which separated on pouring the solution into water was found to be the hydrochloride of the base. It was collected, washed and redissolved in boiling water. On allowing the clear filtrate to cool, the whole of it set to a light fluorescent jelly again. The hot aqueous solution of the jelly was basified, when the isoquinoline separated as a yellowish white solid which crystallised from benzene in short needles. M.P. 194°. Yield, 1.8 g.

0.1263 g. gave 4.45 c.c. nitrogen at 31° and 761.5 mm.

Found: N, 3.93 per cent.

$C_{20}H_{17}C_4N$  requires N, 4.17 per cent.

*The hydrochloride* was obtained as a canary yellow powder on passing dry hydrochloric acid gas into a dry benzene solution of the base. M.P. 204° (d.).

0.1025 g. gave 0.0489 g. of AgCl.

Found: Cl, 9.45 per cent.

$C_{20}H_{18}O_4NCl$  requires Cl, 9.55 per cent.

*The hydrobromide*, obtained in a similar manner, melted at 212° (d.).

0.1587 g. gave 0.450 g. of AgBr.

Found: Br, 19.12 per cent.

$C_{20}H_{18}O_4NBr$  requires Br, 19.23 per cent.

The *picrate* was obtained as a yellow precipitate by mixing alcoholic solutions of the free base and picric acid. It crystallised from glacial acetic acid as golden yellow needles. M.P. 238° (d.).

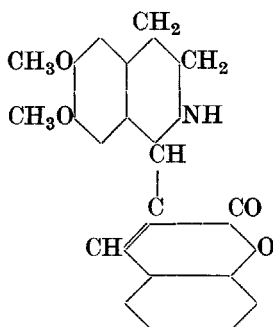
0.1433 g. gave 13.2 c.c. of nitrogen at 31° and 760 mm.

Found: N, 10.20 per cent.

$C_{26}H_{20}O_{11}N_4$  requires N, 9.93 per cent.

The *methiodide* melted at 204° (d.).

1, (3-coumaryl)-6 : 7 dimethoxy-1 : 2 : 3 : 4-tetrahydro-isoquinoline.



1 g. of the dihydro base, 3 g. of zinc dust and 20 c.c. of water were heated on the boiling water-bath and 3 c.c. of concentrated sulphuric acid was added during the course of about 3 hours. The solution, which became colourless when reduction was complete, was filtered, cooled and basified with sodium carbonate solution. The whole was repeatedly exhausted with chloroform, and on removal of the dried solvent the tetrahydro compound was left as an oil. This was rubbed with a few drops of concentrated hydrochloric acid when the hydrochloride separated as a crystalline powder. M.P. 248°. Yield, 0.6 g. On basifying the aqueous solution of the hydrochloride the free base was obtained as shining plates. M.P. 187°.

0.1754 g. of the base gave 6.77 c.c. nitrogen at 30° and 762.4 mm.

Found: N, 4.30 per cent.

$C_{20}H_{19}O_4N$  requires N, 4.16 per cent.

0.1025 g. of the hydrochloride gave 0.0380 g. of AgCl.

Found: Cl, 9.17 per cent.

$C_{20}H_{20}O_4NCl$  requires Cl, 9.50 per cent.

The *picrate* obtained in the usual way melted at 228° (d.).

0.2154 g. gave 19.5 c.c. of nitrogen at 29.5° and 761.25 mm.

Found: N, 9.96 per cent.

$C_{26}H_{22}O_{11}N_4$  requires N, 9.89 per cent.

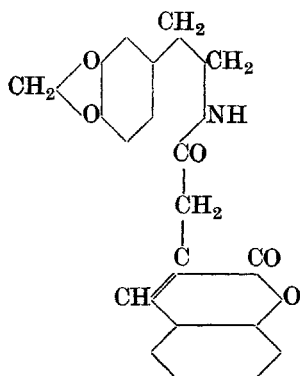


*Synthesis of 1, (3,coumaro-methyl)-6 : 7-methylene dioxy-3 : 4-dihydro-isoquinoline.*

(a) *Preparation of coumarin-3, acetic acid.* Salicylaldehyde (6 g.), sodium succinate dried at 130° for several hours (11 g.) and freshly prepared succinic anhydride (14 g.) were heated in a flask fitted with an air-condenser at 170°-180° for 4 hours. The yellow crystalline mass was transferred on cooling to a mortar with the aid of small amounts of hot water and triturated well with a cold solution of sodium bicarbonate (30 g. in 60 c.c. water). The major portion of the solid dissolved with effervescence and after standing for an hour, the solution was filtered from the insoluble residue of 3,3'-dicoumaryl (M.P. 250°-260°).

The clear filtrate was acidified with dilute HCl and allowed to stand overnight when clusters of beautiful pale yellow plates (2.4 g.) were found to have separated. M.P. 154°-155°. A single crystallisation from boiling absolute alcohol with the addition of animal charcoal gave shining colourless plates, M.P. 158°. Yield, 1.8 g.

The ethyl ester was prepared by suspending the acid in absolute alcohol and saturating with dry hydrochloric acid gas until a clear solution was obtained, and then leaving for 12 hours. Colourless needles, M.P. 88°.

*(b) Preparation of (coumarin 3-acet)-3 : 4 methylene dioxy-β-phenyl ethyl amide.*

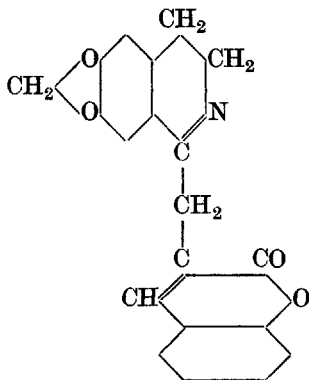
4.72 g. of ethyl ester of the acid and 4 g. of the amine were heated for a period of 3 hours in the oil-bath at 160°-170°, moisture being excluded. The cold mass was washed with dilute alcohol and acid and finally crystallised from alcohol. Colourless needles, M.P. 202°. Yield, 3 g. (1.3 g. of homopiperonyl amine was recovered.)

0.1028 g. gave 3.4 c.c. of nitrogen at 28° and 765 mm.

Found: N, 3.70 per cent.

$C_{20}H_{17}O_5N$  requires N, 3.98 per cent.

## 1, (3 coumaro methyl)-6 : 7-methylene dioxy-3 : 4-dihydro-isoquinoline.



A mixture of 3 g. of the amide, 15 c.c. of toluene and 16 c.c. of phosphorus oxychloride was refluxed on the sand-bath for an hour and a half. On pouring into ice water, the major portion of the reaction product separated as a dark oil. The whole was extracted with chloroform, the extract dried over anhydrous potassium carbonate, and the chloroform removed on the water-bath. The oily residue was treated with warm dilute HCl, filtered and basified with sodium carbonate. The process was repeated twice when a clean solid was obtained. This crystallised from a mixture of benzene and petroleum ether as thin plates. M.P. 175° (d.).

0.1386 g. gave 5.10 c.c. nitrogen at 29° and 759.5 mm.

Found: N, 4.15 per cent.

$C_{20}H_{15}O_4N$  requires N, 4.20 per cent.

*The hydrochloride.* On adding a few drops of concentrated HCl to a suspension of the base in water, it at first turned oily but on keeping overnight in contact with acid, the hydrochloride separated as colourless, stout needles. M.P. 224°.

0.1552 g. gave 0.0604 g. AgCl.

Found: Cl, 9.61 per cent.

$C_{20}H_{16}O_4NCl$  requires Cl, 9.63 per cent.

*The methiodide* was prepared by heating the base and methyl iodide in a sealed tube. M.P. 225° (d.).

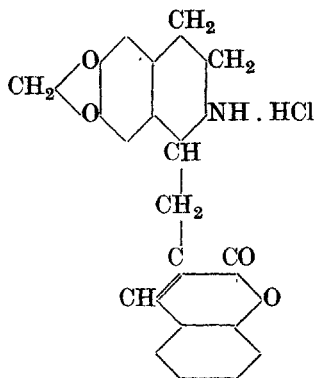
*The picrate* crystallised from glacial acetic acid as clusters of short needles. M.P. 213°.

0.1904 g. gave 16.1 c.c. of nitrogen at 30.3° and 759.8 mm.

Found: N, 9.62 per cent.

$C_{26}H_{18}O_{11}N_4$  requires N, 9.96 per cent.

1, (3,coumaro-methyl)-6 : 7,methylene dioxy-1 : 2 : 3 : 4,tetrahydro-isoquinoline.



The dihydro base (2 g.), zinc dust (6 g.) and a crystal of copper sulphate were heated with 40 c.c. water on the boiling water-bath and 6 c.c. concentrated sulphuric acid added during the course of three hours. The unreacted zinc was removed and the filtrate cooled, basified with sodium carbonate solution, and completely extracted with chloroform. On removal of the dried solvent the tetrahydro compound remained as an oil. Yield, 0.9 g.

The hydrochloride separated as thin plates on the addition of a few drops of concentrated HCl to the oil. M.P. 245° (d.). The free base was obtained as a solid on basifying the aqueous solution of the hydrochloride. M.P. 110°.

0.1536 g. of the hydrochloride gave 0.0582 g. of AgCl.

Found: Cl, 9.38 per cent.

$C_{20}H_{18}O_4NCl$  requires Cl, 9.56 per cent.

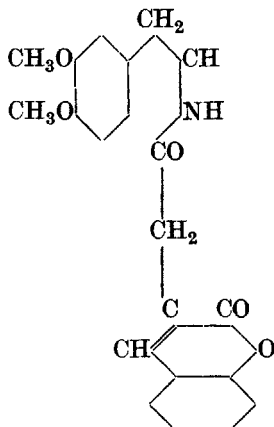
The picrate obtained in the usual way crystallised from dilute acetic acid as plates. M.P. 187° (d.).

0.1593 g. gave 14.6 c.c. of nitrogen at 30° and 748 mm.

Found: N, 10.18 per cent.

$C_{26}H_{20}O_{11}N_4$  requires N, 9.93 per cent.

*Condensation of homo-veratryl amine and coumarin-3,acetic ester. Coumarin-3,acet-3 : 4 dimethoxy-β-phenyl ethyl amide.*



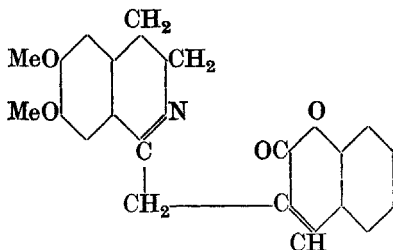
1.81 g. of the homoveratryl amine and 2.36 g. of coumarin 3 ethyl acetate were heated together in an oil-bath at 160°–170° for a period of 4 hours, moisture being excluded. On cooling, the homogeneous semi-solid mass was dissolved in the minimum amount of hot alcohol and filtered. The amide separated from the cold solution as clusters of needles which were recrystallised from alcohol. M.P. 212°. Yield, 2 g. (0.5 g. of the amine hydrochloride was recovered.)

0.1478 g. gave 5.6 c.c. of nitrogen at 31.5° and 762 mm.

Found: N, 4.06 per cent.

C<sub>21</sub>H<sub>21</sub>O<sub>5</sub>N requires N, 3.82 per cent.

*1-(3, coumaro-methyl)-6, 7-dimethoxy-3, 4-dihydro-isoquinoline.*



The amide (3 g.), phosphoryl chloride (22 c.c.) and toluene (20 c.c.) were refluxed for 2 hours on the sand-bath and then poured into excess of ice-water. The hydrochloride of the base separated out. It was washed and crystallised from hot water. Short colourless prisms which do not melt even at 360°. The filtrate was exhaustively extracted with chloroform. The extract dried and

distilled. The base was left behind as a reddish solid. It crystallised from benzene and petroleum ether as orange yellow rhombic plates. M.P. 222° (d.). On rubbing this with a few drops of hydrochloric acid, the colourless hydrochloride melting above 360° was obtained.

0.1990 gm. of the base gave 7 c.c. of nitrogen at 30° and 750.3 mm.

Found: N, 3.91 per cent.

$C_{21}H_{19}O_4N$  requires N, 4.01 per cent.

0.2312 g. of the hydrochloride gave 0.0894 g. of AgCl.

Found: Cl, 9.21 per cent.

$C_{21}H_{20}O_4NCl$  requires Cl, 9.50 per cent.

*The hydrobromide* melted at 240° (d.).

0.116 g. gave 0.0486 g. of AgBr.

Found: Br, 18.52 per cent.

$C_{21}H_{20}O_4NBr$  requires Br, 18.60 per cent.

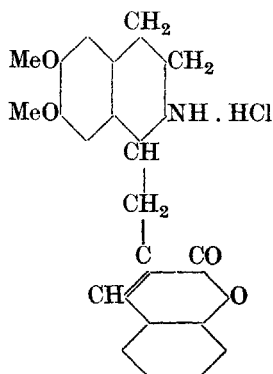
*The picrate* melted at 222° (d.).

0.2334 g. gave 20.1 c.c. of nitrogen at 30° and 748 mm.

Found: N, 9.55 per cent.

$C_{27}H_{22}O_{21}N_4$  requires N, 9.69 per cent.

1, (3,coumaro-methyl)-6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydro-isoquinoline.



The dihydro-isoquinoline (1 g.), zinc dust (3 g.) and a small crystal of copper sulphate were heated with water (30 c.c.) on the boiling water-bath and 2.5 c.c. of concentrated sulphuric acid were added during the course of 2 to 3 hours. The colourless solution was filtered from excess of zinc and the filtrate cooled and basified with sodium carbonate solution. Extraction with chloroform, drying the extract and evaporating the solvent gave the tetrahydro compound as an oil. It was converted into the solid hydrochloride by rubbing with strong HCl. This crystallised from hot water as colourless plates. M.P. 236° (d.).

0.0778 g. of the hydrochloride gave 0.0280 g. of AgCl.

Found: Cl, 8.91 per cent.

$C_{21}H_{22}O_4NCl$  requires Cl, 9.16 per cent.

#### SUMMARY.

1, coumaryl-isoquinolines have been synthesised from homopiperonyl and homoveratryl amines and coumarin-4, and 3, acetic esters and coumarin 3-carboxylic esters, by the Bischler-Napieralsky method.

These dihydro-isoquinolines are feeble bases of a yellow colour, the salts being colourless. The tetrahydro-isoquinolines are stronger bases and are colourless.

PRESIDENCY COLLEGE,  
MADRAS,  
27th November, 1939.