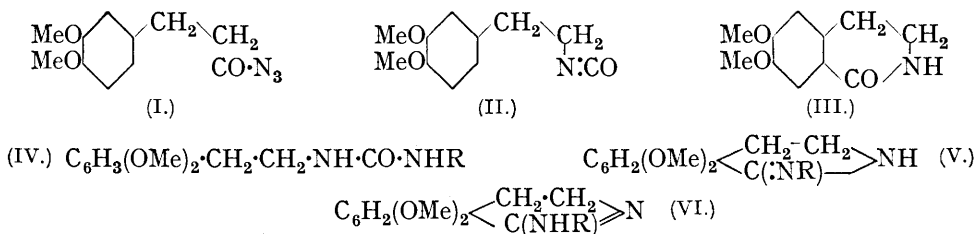


**273. Experiments on the Synthesis of isoQuinoline Derivatives. Part III. A Synthesis of Corydaldine.**

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CORYDALDINE has been prepared in a very poor yield by oxidation of corydaline (cf. Dobbie and Lauder, J., 1899, **75**, 670), but its constitution had not been confirmed by synthesis. Such a synthesis is now described. The azide (I), obtained from the *hydrazide* of  $\beta$ -3 : 4-dimethoxyphenylpropionic acid, on being boiled in toluene solution gave a good yield of the *isocyanate* (II), which was cyclised to corydaldine (III) by phosphoryl chloride. The yield at this stage was not satisfactory; therefore *carbamides* (IV) were prepared by



treating the *isocyanate* (II) with various aromatic amines in the hope that, after a Bischler-Napieralsky condensation to (V), it would be possible to prepare (III) by hydrolysis. This expectation was not realised, for the resultant 1-*arylimino*-6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydroisoquinolines were quite stable, indicating that they can exist as the 1-arylamino-3 : 4-dihydro-tautomerides (VI). Evidence has been obtained that they show virtual tautomerism characteristic of the amidines.

The *hydrazide* of  $\beta$ -3 : 4-dimethoxyphenylpropionic acid was obtained in theoretical yield when methyl  $\beta$ -3 : 4-dimethoxyphenylpropionate (8 g.) in benzene (30 c.c.) was heated with hydrazine hydrate (4.8 g.) for 1 hour under reflux. The product solidified to a hard cake (12 g.) after the removal of the solvent, and was recrystallised from hot benzene; m. p. 132° (Found: N, 12.7.  $\text{C}_{11}\text{H}_{16}\text{O}_3\text{N}_2$  requires N, 12.6%). This hydrazide (1 g.), dissolved in dilute hydrochloric acid (35 c.c. of 10%), was treated with sodium nitrite solution (6 c.c. of 5%) with stirring at 0°, whereupon the azide separated as a granular crystalline mass; m. p. 53—55° (decomp.). The dried azide, dissolved in toluene (60 c.c. at 0°), was dehydrated over calcium chloride (1 hour) and then over sodium sulphate (1½ hours) at 0°, and then decomposed by 5 hours' boiling. The resulting *isocyanate* is volatile in toluene vapour and was not isolated. Phosphoryl chloride (2 c.c.) was introduced into the solution, and the mixture heated at 110° for 2 hours. After decomposition with ice, the toluene layer was repeatedly extracted with dilute hydrochloric acid, and the extracts combined with the original aqueous layer, concentrated to a small bulk, basified with sodium hydroxide (10% solution) at 5°, and extracted repeatedly with much chloroform. The thick viscous mass remaining after the removal of the solvent was repeatedly crystallised from benzene-ether; m. p. 173° (Found: N, 6.8. Calc. for  $\text{C}_{11}\text{H}_{13}\text{O}_3\text{N}$ : N, 6.76%). The substance had all the properties of corydaldine and gave a nitroso-derivative, m. p. 185°. The non-basic substance, m. p. 152°, isolated from the toluene layer is described on p. 1264.

The *isocyanate* (from 1 g. of the hydrazide) when boiled with aniline (in toluene) gave the *carbamide* (1.2 g.) (IV; R = Ph), m. p. 154° (Found : N, 9.5.  $C_{17}H_{20}O_3N_2$  requires N, 9.3%). This (1.2 g.) was treated with phosphoryl chloride (2 c.c.) as above, the acid extract boiled with charcoal, cooled, and basified; the sticky precipitate was crystallised from benzene-ligroin and then twice from boiling ligroin; m. p. 139° (Found : C, 72.4; H, 6.6; N, 9.9.  $C_{17}H_{18}O_2N_2$  requires C, 72.3; H, 6.4; N, 9.9%). The *base* (V or VI; R = Ph) is readily soluble in benzene, chloroform, and alcohol, but sparingly soluble in ether. From a solution of its hydrochloride (m. p. 244°), it was recovered unchanged.

Similarly the *carbamide* (IV; R = *p*-C<sub>6</sub>H<sub>4</sub>Me), m. p. 155° (Found : N, 8.8.  $C_{18}H_{22}O_3N_2$  requires N, 8.9%), was converted into the related *isoquinoline* (V; R = *p*-C<sub>6</sub>H<sub>4</sub>Me), m. p. 126°, after crystallisation from benzene-ligroin (9 : 1) (Found : N, 9.5.  $C_{18}H_{20}O_2N_2$  requires N, 9.46%). The *carbamide* from *m*-toluidine had m. p. 150° (Found : N, 9.1%), and the corresponding *isoquinoline* (70% yield) had m. p. 188° (Found : N, 9.5%). The *carbamide* from *o*-toluidine, m. p. 153° (from toluene) (Found : N, 9.1%), was not smoothly converted into the related *isoquinoline*, which could not be obtained pure; but the *carbamide* from phenetidine (IV; R = *p*-C<sub>6</sub>H<sub>4</sub>•OEt), m. p. 152°, was readily transformed into the *isoquinoline* (V; R = *p*-C<sub>6</sub>H<sub>4</sub>•OEt) (Found : N, 8.8.  $C_{19}H_{22}O_3N_2$  requires N, 8.6%).

In order to establish whether the *isoquinolines* have the structure (V) or (VI), methyl-aniline was condensed with the *isocyanate* (II). The *carbamide* was not isolated, but was directly converted into the related *isoquinoline*, which crystallised from boiling ligroin in thick plates, m. p. 150° (Found : N, 9.8.  $C_{18}H_{20}O_2N_2$  requires N, 9.5%); this substance can only be 1-phenylmethylamino-6 : 7-dimethoxy-3 : 4-dihydroisoquinoline (VI; R = Ph; Me in place of H).

(a) The foregoing base (1 g.) dissolved in moist benzene (50 c.c.) was reduced with aluminium amalgam (1 g. of Al) for 12 hours. The thick viscous oil obtained after the removal of the solvent was purified *via* the hydrochloride, and the resulting *base* was repeatedly crystallised from benzene-ligroin; m. p. 155—158° (Found : N, 9.5.  $C_{18}H_{22}O_2N_2$  requires N, 9.4%).

(b) The dihydroisoquinoline (V; R = Ph) was treated with methyl iodide in methanol (hot), and the crude addition product was reduced with aluminium amalgam; the *base* obtained had m. p. 155—160°; mixed m. p. with substance described under (a), 155—158°.

The *isocyanate* (II) (1 g.), on being boiled with acetic anhydride (5 c.c.) in toluene, lost some carbon dioxide, but diacet-β-3 : 4-dimethoxyphenylethylamide was not detected. After the removal of toluene and acetic anhydride in a vacuum, an oil remained which quickly solidified when stirred with sodium bicarbonate solution. It crystallised from hot benzene in feathery leaflets, m. p. 152° (Found : N, 7.2.  $C_{21}H_{28}O_5N_2$  requires N, 7.2%), and was identical with the neutral product obtained in the synthesis of corydaldine above. It is undoubtedly *s*-bis-(β-3 : 4-dimethoxyphenylethyl)carbamide,  $CO[NH\cdot CH_2\cdot CH_2\cdot C_6H_3(OMe)_2]_2$ , and its original formation was due to traces of water in the toluene.