SYNTHESIS OF FUSED HETEROCYCLICS: PART I

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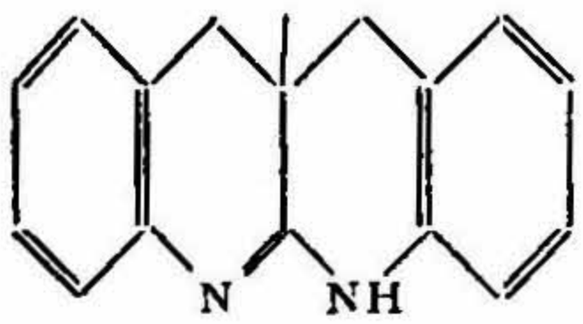
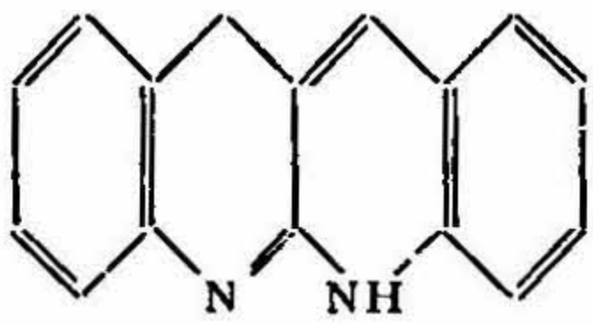
Summary

As a representative of the quinolino (2:3:2′:3′) quinolines, 6:7-dimethoxy-4′-hydroxy-quinolino (2:3:2′:3′) quinoline has been synthesised. This is analogous to the product obtained by the oxidation of dihydronaphthinolin (Reissert, *Ber.*, 1894, **27**, 2244).

As a part of investigations on different quinolinoquinoline derivatives,[1] the synthesis of 4′-hydroxy-6:7-dimethoxyquinolino-(2:3:2′:3′)-quinoline has been achieved. The ring system in the form of its tetrahydro derivative was prepared by Reissert,[2] by the reduction of ethyl bis-*o*-nitrobenzylacetate and called tetrahydronaphthinolin, in analogy with naphthyridine. The tetrahydro compound was oxidised to the dihydro derivative, but attempts to get the fully dehydrogenated naphthinolin, or quinolino (2:3:2′:3′) quinoline failed. Reissert assigned the following structures to the tetrahydro (I) and dihydro (II) derivatives; the naphthinolin being represented as (III).



(I)



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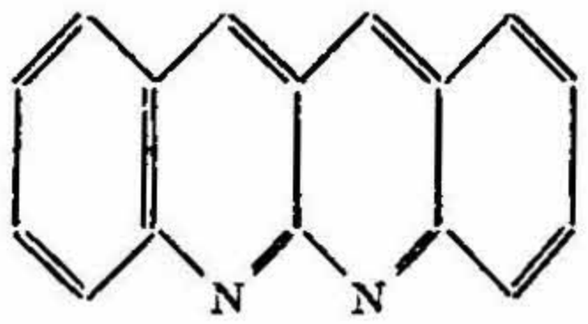


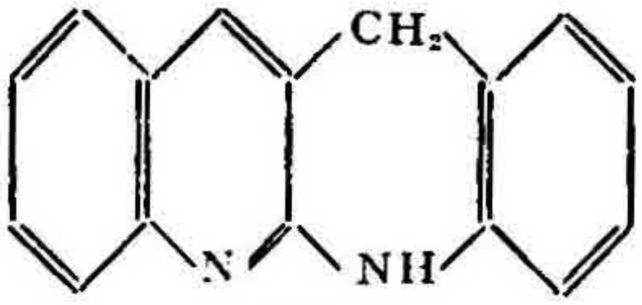
(III)

One of us (R. P.) had occasion to prepare Reissert's compound (I) and found that it did not give the naphthinolin (III) with chloranil, selenium, or palladised charcoal. In all cases, the dihydro derivative (II) was obtained. In an attempt to oxidise the dihydronaphthinolin with potassium dichromate and dilute sulphuric acid, the only product that could be isolated was an acridone-like compound which showed a characteristic green fluorescence changing to red on addition of alkali. Reissert (*loc. cit.*) mentioned that he got an acridone-like substance in one case, but did not isolate it.

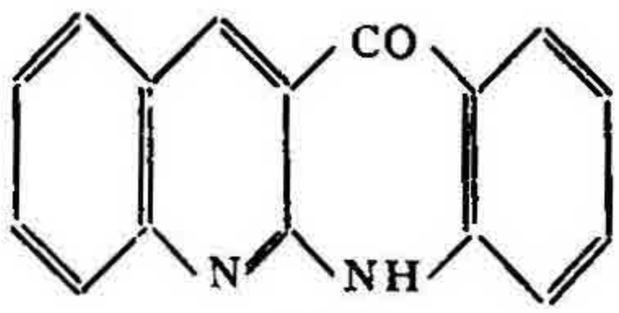
In view of the above results, it was felt that the dihydronaphthinolin was best represented as (II *a*), *i.e.*, as an acridan-like structure. Its resistance to dehydrogenation would not be unusual, as acridans are known to dehydrogenate to acridines in poor yield at temperatures above 300° C.[3] The oxidation with dichromate and sulphuric acid to an acridone-like substance (IV) and not the naphthinolin (III) was unusual as this reagent has been applied successfully in the acridine field.

and is the best method for the conversion of acridans to acridines.[4] The oxidation, therefore, had gone further, the linear naphthinolin, not unlike the hydrocarbon naphthacene, was easily oxidised.

Unfortunately, work had to be stopped at this stage due to unavoidable circumstances. The quinolino - (2 : 3 : 2′ : 3′)-quinoline system was therefore synthesised through the readily available 6-nitroveratraldehyde.



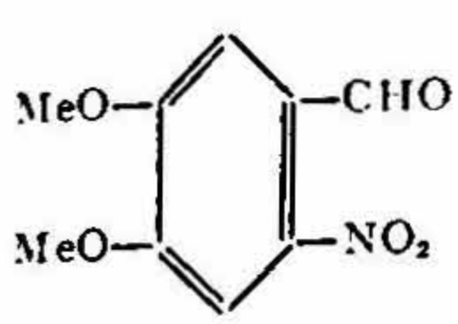
(II *a*)



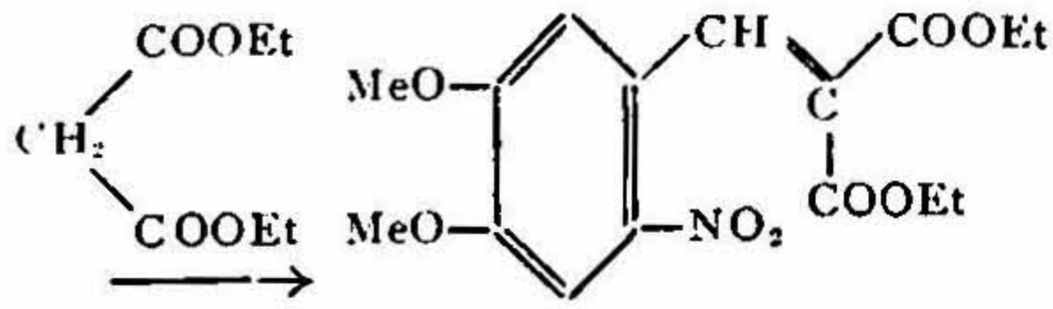
(IV)

During the present investigation 6-nitro-veratraldehyde (V) was prepared by the nitration of veratraldehyde according to Borsche and Barthenheimer,[5] the yield being comparable to that obtained by Fletscher.[6] It was condensed with diethylmalonate in presence of pyridine-piperidine to diethyl *o*-nitroveratrylidene malonate (VI) in 60% yield. The diester was reduced with ammonia and hydrogen sulphide, a method used for the reduction of *o*-nitro-cinnamic acid to carbostyril,[7] to ethyl 6 : 7-dimethoxy 2-hydroxyquinoline-3-carboxylate (VII) in 35–40% yield. Attempts to increase the yield, or use other reducing agents such as zinc and acid, zinc amalgam, iron and dilute mineral acids, ferrous sulphate and ammonia or Raney Nickel were unsuccessful. The reduction was generally incomplete, a mixture of the unreduced ester, the carbostyril ester and the carbostyril acid (resulting from partial hydrolysis) was obtained. This was difficult to separate, as both the carbostyril ester and acid showed similar solubilities in organic solvents as well as aqueous alkali. Furthermore the acid was insoluble in cold sodium carbonate, the unreduced ester, however, could be easily recovered from this mixture. As the yields of the carbostyril-ester and acid were lower than those obtained with ammonia and hydrogen sulphide, the diester was reduced according to this method. The disadvantage of this reduction was that large amounts of the diester could not be reduced at a time, and attempts to recover unreduced diester from the mother liquor resulted in sulphur containing products.

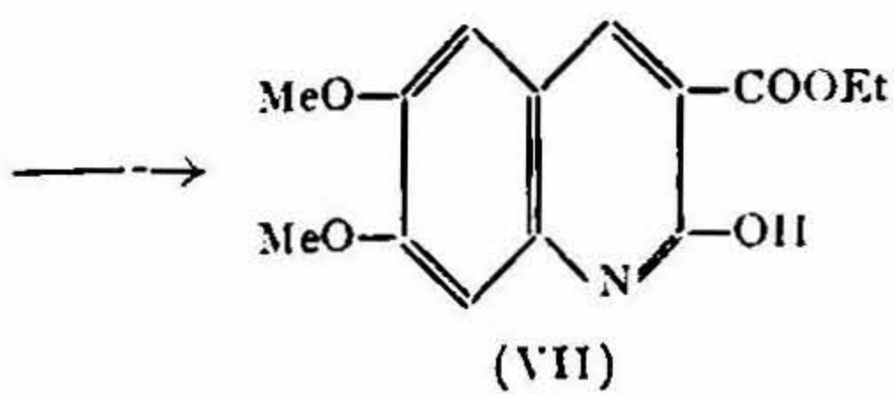
The carbostyril ester (VII) was weakly basic, gave an unstable picrate, and attempts to prepare its hydrochloride resulted in hydrolysis. It was soluble in alkali and could be readily hydrolysed to 6 : 7-dimethoxy-2-hydroxyquinoline-3-carboxylic acid (VIII). The acid could be decarboxylated at high temperatures to 6 : 7-dimethoxy-2-hydroxy-quinoline (IX). The decarboxylation was difficult and resulted in considerable charring, and the yield of the carbostyril was low. This was not unexpected, as pyridine-3-carboxylic acids are known to decarboxylate with difficulty, as compared to the 2- and 4-isomers. The carbostyril (IX) had previously been synthesised by Kefford[8] by reduction of 3 : 4-dimethoxy-6-nitrocinnamic acid. Mixed melting point with a sample prepared by Kefford's method as well as by a slight variation of it (*vide infra*) showed no depression.



(V)



(VI)



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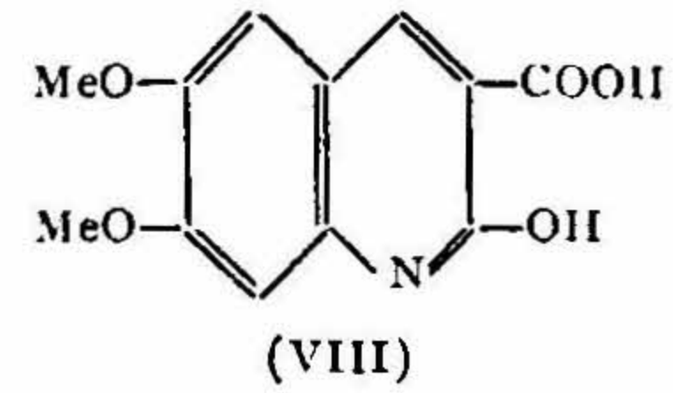
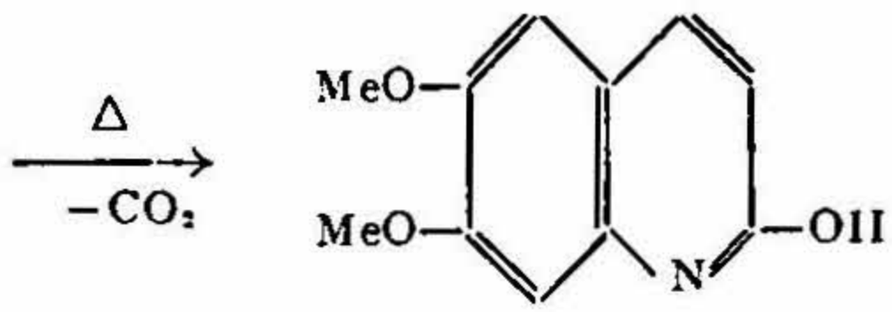


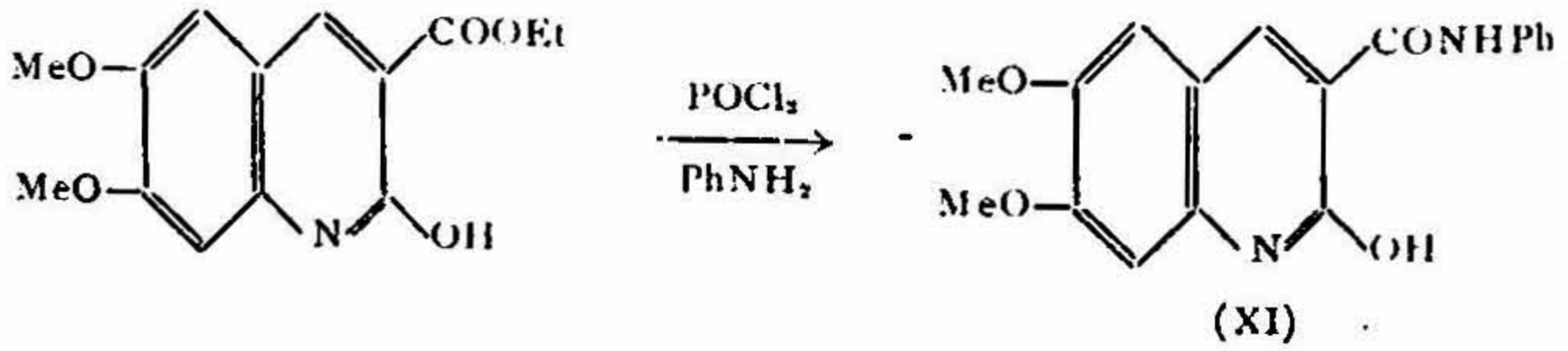
(VIII)



(IX)

The carbostyril ester (VII) was converted to the 2-chloro derivative with phosphorus oxychloride. This was very susceptible to hydrolysis and was therefore directly condensed with aniline. Two products, depending on the reaction conditions, could be obtained. One was the required ethyl-2-anilino-6: 7-dimethoxy-quinoline-3-carboxylate (X) and the other was 2-hydroxy-6: 7-dimethoxy-quinoline-3-carboxylic acid anilide (XI), the latter being obtained in greater proportions if the condensation with aniline took place at elevated temperatures. The anilide was a high melting compound giving blue fluorescent solutions, in presence of alkali, and stable to hydrolysis. The anilino ester (X) on the other hand, was readily hydrolysed to the corresponding 2-anilino-6: 7-dimethoxy-quinoline-3-carboxylic acid (XII). This was cyclised with phosphorus oxychloride, and subsequent hydrolysis to 4′-hydroxy-6: 7-dimethoxyquinolino (2: 3: 2′: 3′)-quinoline (XIII). It may be mentioned that whereas Kermack and Weatherhead[9] were unable to cyclise 2-anilinopyridine-3-carboxylic acid with concentrated sulphuric acid or phosphorus oxychloride, the corresponding 6-amino-derivative cyclised to the pyracridone with sulphuric acid at room temperature.[10] The compound (XIII) like the acridone (IV) gave a yellow solution with a characteristic green fluorescence changing to red on addition of alkali.

Further work on the conversion of the hydroxy derivative to the 6: 7-dimethoxyquinolino (2: 3: 2′: 3′)-quinoline is in progress.



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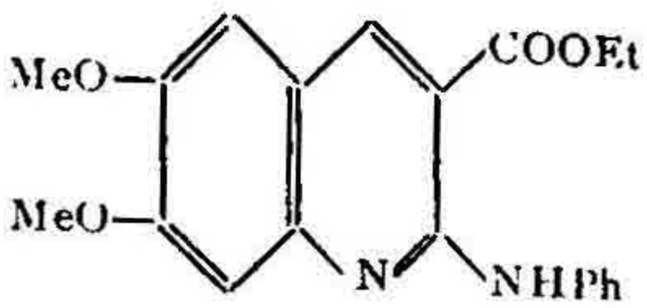

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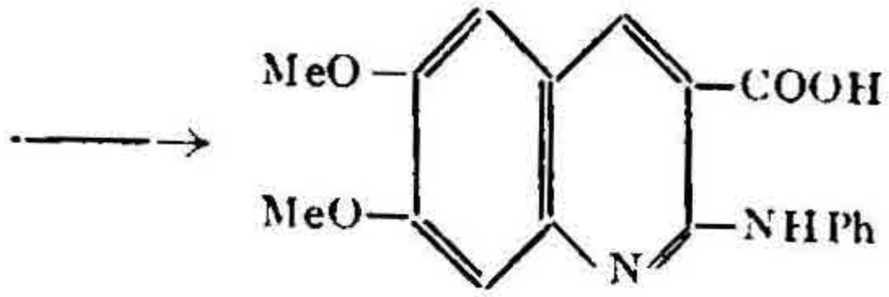

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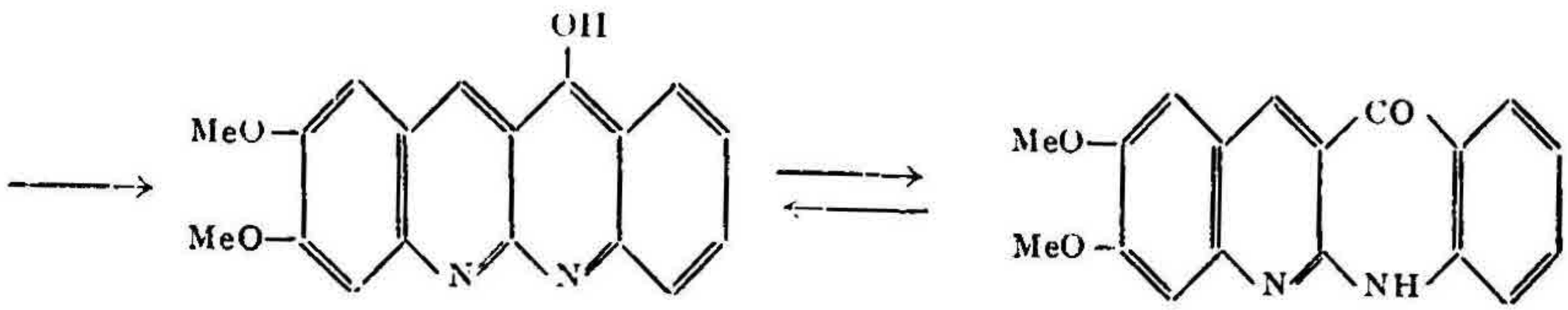
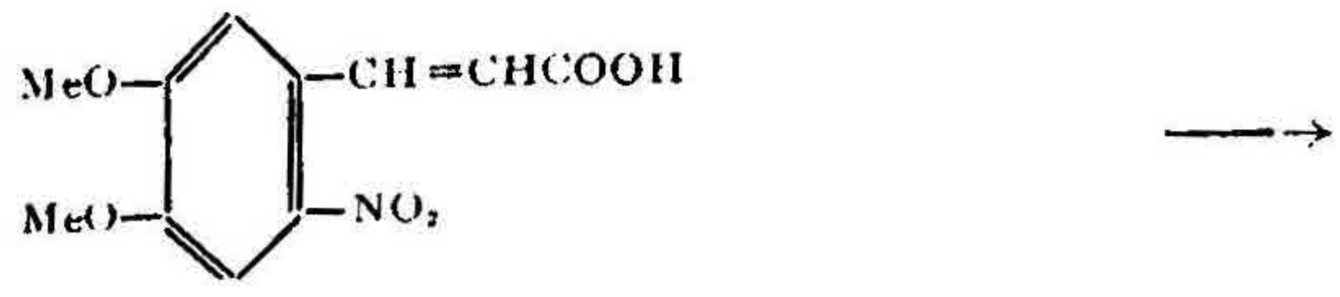


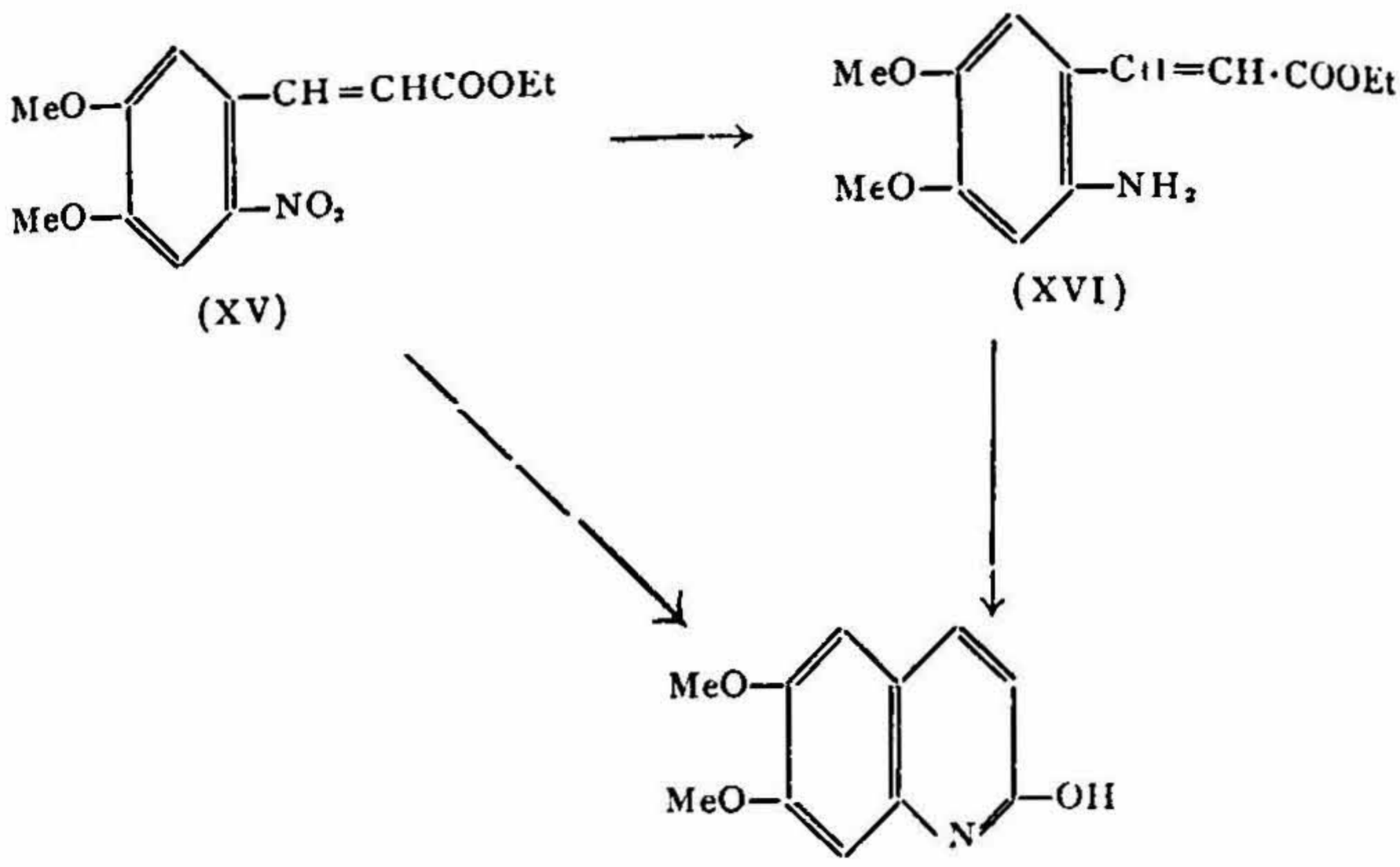
(XIII)

Synthesis of 6 : 7-*dimethoxycarbostyril* (*IX*)

On repeating Kefford's procedure,[8] it was found that the yields of the carbostyril were very poor; the synthesis was therefore modified. 6-Nitro-3 : 4-dimethoxy cinnamic acid (XIV) was prepared in good yield by condensing 6-nitro-veratraldehyde and malonic acid at 100° C. for 4 hours with pyridine piperidine as catalyst. In case the condensation was carried out at room temperature, a low melting solid, presumably the 6-nitro-veratrylidene malonic acid, was obtained which could not be obtained in the pure state as it decarboxylated with great ease. The cinnamic acid was esterified with ethyl alcohol and sulphuric acid to ethyl-6-nitro-3 : 4-dimethoxy cinnamate (XV). The nitro-ester on reduction with ferrous sulphate and ammonia gave the ethyl-6-amino-3 : 4-dimethoxycinnamate (XVI) which could be cyclised with concentrated hydrochloric acid to 6 : 7-dimethoxy-carbostyril (IX). Alternately, it was found that the nitro-ester gave the carbostyril directly with zinc and acetic acid. The nitro-cinnamic ester and acid must therefore be the *trans* derivatives, which were reduced to the *trans* amino compounds, changing to the *cis*-derivatives in presence of acids with instantaneous cyclisation to the carbostyrils.



(XIV)



EXPERIMENTAL

Teterahydronaphthinolin (I)

This was synthesised according to Reissert (*loc. cit.*). *O*-Nitrobenzylchloride (8·6 g.) was condensed with diethylsodiomalonate (from 8 g. diethyl malonate and 2·3 g. sodium) in absolute ethanol at room temperature. The resulting diethyl-bis-*o*-nitrobenzyl-malonate (14 g.) was hydrolysed with concentrated sulphuric acid at 170° C. to bis-*o*-nitrobenzyl acetic acid (6 g.). This was directly esterified with ethanol and hydrochloric acid, and the ethyl bis-*o*-nitrobenzyl acetate purified by crystallisation from alcohol, m.p. 61° C. (Reissert gives the same m.p.).

Hydrochloric acid gas was passed into an alcoholic solution of the above ester, cooled to 0° C. Zinc dust was added gradually until further addition caused vigorous evolution of hydrogen. The alcohol was then distilled off, and the zinc double salt decomposed with excess liquor ammonia. The tetrahydronaphthinolin separated as glistening plates, which, after repeated crystallisation from alcohol, melted at 211–12° C. (Reissert gives the same m.p. Analysis: Found—N=11·8%; $C_{16}H_{14}N_2$ requires N = 11·92%).

Dihydronaphthinolin (II a)

(*a*) Tetrahydronaphthinolin (150 mg.) and chloranil (360 mg.) were refluxed in xylene (about 30 ml.) for four hours. A red precipitate was formed which was filtered off. The xylene solution gave negligible residue on removal of the solvent. The red precipitate was dissolved in ether, and extracted with three successive portions of 10% aqueous sodium hydroxide to remove the tetrachlorohydroquinone, and finally washed with water. The ether layer, after drying over anhydrous sodium sulphate, was passed through a column of alumina, and two bands separated under ultra-violet light. The first gave the unchanged tetrahydronaphthinolin (30 mg.) while the second gave dihydronaphthinolin (70 mg.) which, after crystallisation from alcohol, melted at 200° C. (Reissert, *loc. cit.*,

gives m.p. 201° C.). The picrate melted at 241° C. with decomposition. For analysis the dihydro derivative was repeatedly crystallised from alcohol (Analysis*: Found—N = 11·9%; $C_{16}H_{14}N_2$ requires N = 12·07%).

(*b*) *Selenium dehydrogenation.*—The tetrahydro compound (100 mg.) was thoroughly mixed with powdered selenium (400 mg.) and the mixture heated at 280–300° C. in a metal-bath for 15 hours. The lump formed in the flask on cooling was powdered and extracted with chloroform. The selenium was filtered off, and the chloroform removed under reduced pressure to give dihydronaphthinolin (70 mg.) identical with the sample obtained from the above experiment.

4′-Hydroxyquinolino (2 : 3 : 2′ : 3′)-quinoline (IV)

Tetrahydronaphthinolin (250 mg.), aqueous sodium dichromate (1·2 g. in 50 ml. water) and concentrated sulphuric acid (2 ml.) were refluxed for 8 hours, the solution turning green after the first four hours. The hot solution was filtered and refrigerated overnight. A crystalline precipitate had formed, which was filtered off the next morning. It was suspended in water (100 ml.) and made strongly alkaline with ammonia (20 ml.). Acetic acid was added to neutralise a part of it. The aqueous solution was then extracted with chloroform, the chloroform extract dried, and the solvent removed. A yellow solid was obtained which sublimed easily to give bright yellow needles charring at 280° C., and showing no definite melting point. It was soluble in acetic acid, the alcoholic solution was bright yellow with a green fluorescence, changing to red on addition of alkali. For analysis, the compound was repeatedly sublimed under reduced pressure, and then crystallised from dilute acetic acid. (Analysis*: Found—N = 10·9%; $C_{16}H_{10}N_2O$ requires N = 11·3%).

Diethyl-(6-nitroveratrylidene)-malonate (VI)

6-Nitroveratraldehyde[5] (10 g.) (V), diethyl malonate (12 ml., 1·8 moles), piperidine (6 ml.) and pyridine (8 ml.) were mixed together, and allowed to stand at room temperature for seven days. The dark brown liquid was poured into crushed ice (50 g.) and concentrated hydrochloric acid (10 ml.). A dark gummy mass was obtained, which was filtered and triturated with alcohol (50 ml.) to a crystalline solid (10 g., m.p. 110–15° C.). On repeated crystallisation from alcohol it gave very pale yellow needles, m.p. 118–20° C. It is soluble in acetone, alcohol, ethyl acetate, less so in petroleum ether. (Analysis on a sample dried at 100° C.: Found—C = 54·5, H = 5·8, N = 3·9%. $C_{16}H_{19}NO_8$ requires C = 54·4, H = 5·5, N = 4·0%).

Ethyl-6 : 7-dimethoxy-2-hydroxyquinoline-3-carboxylate (VII)

Diethyl-(6-nitroveratrylidene)-malonate (1 g.) was dissolved in alcohol (50 ml.) and rapidly cooled in ice. To the cold solution, liquor ammonia (20 ml.) was added and hydrogen sulphide passed through it for five hours. During the reaction, a further quantity of liquor ammonia (40 ml.) was added in two instalments. The yellow solid that had separated out was filtered, washed well with

water, and then with alcohol to remove any unreduced starting material. The solid was dried at 100° C. and it melted at 270–71° C. (0·3 g.). The carbostyril ester thus obtained crystallised from alcohol in needles, melting at the same temperature. The ester was soluble in alcohol, ethyl acetate, sparingly so in ether or petrol ether. Its alcoholic solution gave a blue fluorescence. From the alcoholic filtrate, after separating the carbostyril ester, attempts were made to recover unreduced diethyl 6-nitroveratrylidene malonate, but only a material heavily contaminated with sulphur could be obtained. (Analysis on a sample dried in vacuum at room temperature: Found — C = 60·6, H = 5·37, N = 5·1%; $C_{14}H_{15}O_5N$ requires C = 60·6, H = 5·4, N = 5·0%).

6: 7-*Dimethoxy-2-hydroxyquinoline-3-carboxylic acid* (*VIII*)

The above ester (1 g.) was refluxed with 10% aqueous potassium hydroxide (50 ml.) for 2 hours. The hot solution was filtered and the filtrate acidified with acetic acid. On cooling, a yellow solid precipitated out, which was filtered, washed with water and dried (0·8 g., m.p. 310° C. with decomposition). It was crystallised from acetic acid in needles melting at 320° C. with decomposition. Like the ester, the acid gave fluorescent solution in alcohol, was soluble in alkali, but not in sodium carbonate. (Analysis: Found—C = 57·84, H = 4·54, N = 5·70%; $C_{12}H_{11}O_5N$ requires C = 57·8, H = 4·4, N = 5·6%).

6: 7-*Dimethoxy-2-hydroxyquinoline* (*IX*)

The above acid (50 mg.) was sublimed twice in an all-glass apparatus with a cold finger, under reduced pressure (7 mm.). The metal-bath was maintained at 400° C. for twenty minutes. The sublimate was found to melt at 235° C.; it was fractionally crystallised from alcohol. The less soluble 6: 7-dimethoxy-2-hydroxyquinoline-3-carboxylic acid crystallised out first, and from the mother liquor, 6: 7-dimethoxy-2-hydroxyquinoline was obtained as needles, m.p. 230° C. This was identical with the one synthesised from 3: 4-dimethoxy-6-nitrocinnamic acid (*vide infra*), as determined by mixed melting point.

6: 7-*Dimethoxy-2-hydroxyquinoline-3-carboxylic acid anilide* (*X*)

The carbostyril ester (VII) (0·7 g.) was refluxed with phosphorus oxychloride (5 ml.) for 30 minutes with strict exclusion of moisture. After removing the phosphorus oxychloride under reduced pressure, the solid residue was heated with distilled aniline (1·5 ml.) at 140° C. for two hours. A dark coloured solid was obtained which was triturated with alcohol and filtered (0·6 g.). This melted at 280° C. with decomposition and two crystallisations from acetic acid gave yellow needles melting at 350–51° C. The compound was sparingly soluble in most organic solvents but soluble in alcoholic alkali. An alcoholic solution of the compound fluoresced blue on addition of alkali. The anilide was stable to alkaline hydrolysis (Analysis: Found—N = 8·63%; $C_{18}H_{16}N_2O_4$ requires N = 8·64%).

Ethyl-6: 7-*dimethoxy-2-anilinoquinoline-3-carboxylate* (*XI*)

The carbostyril ester (VII) (0·5 g.) was treated with phosphorus oxychloride (1 ml.) and heated gradually to 100° C. The contents of the flask were protected

with a calcium chloride guard tube from moisture. After 30 minutes, the excess of phosphorus oxychloride was removed under reduced pressure and the solid that had separated out was cooled in ice. Aniline (0·5 ml.) was added, and the mixture was gradually heated to 100° C. with occasional shaking and maintained at the temperature for thirty minutes. The solid was taken up in hot acetic acid (5 ml.) and filtered. The filtrate was diluted and partially neutralised with ammonia until a turbidity appeared, which, on cooling, gave a yellow solid (0·5 g., m.p. 145° C.). It was soluble in alcohol to non-fluorescent yellow solutions and was crystallised from dilute acetic acid in needles, m.p. 167° C. (Analysis: Found—N = 8·05%, $C_{20}H_{20}N_2O_4$ requires N = 7·94%).

6: 7-*Dimethoxy-2-anilinoquinoline-3-carboxylic acid* (*XII*)

The above ester (0·5 g.) was refluxed for 3 hours with alcoholic potassium hydroxide (2·5 g. in 50 ml.). After distilling off the alcohol, the residue was acidified with dilute acetic acid, when a yellow solid precipitated out (0·4 g.). It was crystallised from dilute acetic acid in bright yellow needles, m.p. 244–45° C. with decomposition (Analysis: Found—N = 8·53%; $C_{18}H_{16}N_2O_4$ requires N = 8·64%).

4′-*Hydroxy*-6: 7-*Dimethoxyquinolino* (2: 3: 2′: 3′)-*quinoline* (*XIII*)

The above acid (0·2 g.) was treated with phosphorus oxychloride (1·5 ml.) and maintained at 100° C. for thirty minutes under anhydrous conditions. It was cooled, and the excess of the oxychloride destroyed by allowing it to react with cold water (10 ml.). After addition of a few drops of concentrated hydrochloric acid, the aqueous mixture was refluxed for thirty minutes, when a brown solid was obtained (0·16 g.). This was crystallised from dilute acetic acid in golden brown needles, m.p. 290° C. Its alcoholic solution was deep yellow with green fluorescence changing to red on addition of alkali (Analysis: Found—N = 8·77%; $C_{18}H_{14}N_2O_3$ requires N = 9·1%).

6-*Nitro*-3: 4-*dimethoxycinnamic acid* (*XIV*)

6-Nitroveratraldehyde (6 g.), malonic acid (6 g.), piperidine (2 ml.) and pyridine (10 ml.) were heated at 100° C. for four hours. On treating with ice-cold dilute hydrochloric acid, a dark brown solid was obtained, which turned yellow on trituration with alcohol (4·6 g.). The 6-nitro-3: 4-dimethoxycinnamic acid was crystallised from acetic acid in needles, m.p. 285° C. (Kefford reports the same m.p.). The cinnamic acid was sparingly soluble in most organic solvents.

Ethyl-6-*nitro*-3: 4-*dimethoxycinnamate* (*XV*)

The cinnamic acid (4·6 g.), absolute alcohol (350 ml.) and concentrated sulphuric acid (15 ml.) were refluxed on the water-bath for 4 hours. Most of the alcohol was distilled off, and the residue, after washing with dilute ammonia to remove unchanged acid, was crystallised from alcohol in yellow needles, m.p. 148° C. (Found: N = 4·81%; $C_{13}H_{15}NO_6$ requires N = 5·0%).

Ethyl-6-amino-3 : 4-dimethoxycinnamate (XVI)

The above ester (1 g.) was dissolved in a mixture of ethyl alcohol (10 ml.) and ethyl acetate (15 ml.). An aqueous solution of ferrous sulphate (10 g. in 30 ml. water) and liquor ammonia (20 ml.) were added and the mixture refluxed for 30 minutes on the water-bath. The ferric hydroxide that had separated out was filtered off, the filtrate diluted and extracted with ethyl acetate and the extract, after drying over anhydrous magnesium sulphate and removal of the solvent, gave a pale brown solid (0·3 g.). This was very soluble in most organic solvents, and was purified by repeated dissolution in ether and precipitation with petrol ether when it formed a yellow amorphous solid, m.p. 92° C. (Analysis: Found on a sample dried at room temperature in vacuum—N = 5·64%; $C_{13}H_{17}NO_4$ requires N = 5·58%).

6 : 7-*Dimethoxy-2-hydroxyquinoline (IX)*

(*a*) The amino-ester (0·1 g.) was dissolved in boiling concentrated hydrochloric acid (10 ml.). The acid was slowly evaporated off on the water-bath. On treating the residue with aqueous ammonium acetate, the carbostyril was obtained as a pale yellow solid, m.p. 225° C. (Yield = a few milligrams).

(*b*) The nitro-ester (XV) (1 g.) was refluxed gently for 2 hours with zinc dust (5 g.) and 5% acetic acid (100 ml.). It was filtered hot, and the filtrate after cooling extracted with ether. The aqueous solution on standing overnight deposited a pale yellow crystalline solid (0·2 g.). The 6 : 7-dimethoxycarbostyril thus obtained was crystallised from acetone in needles, m.p. 229° C. (Kefford, *loc. cit.*, gives the same m.p.). (Analysis: Found—N = 6·89%; $C_{11}H_{11}NO_3$ requires N = 6·94%).

(*c*) *Kefford's procedure.*—6-Nitro-3 : 4-dimethoxycinnamic acid (0·8 g.) was dissolved in liquor ammonia (8 ml.) and added to a hot solution of ferrous sulphate (8 g. in 20 ml.). The mixture was boiled for some time and allowed to cool. The precipitated ferric hydroxide was filtered off and the filtrate neutralised with dilute sulphuric acid to give a buff-coloured 6-amino-3 : 4-dimethoxycinnamic acid (0·3 g.), m.p. 170° C. (Kefford, *loc. cit.*, gives the same m.p.). The acid was dissolved in boiling concentrated hydrochloric acid and animal charcoal added to it. It was filtered off and the filtrate neutralised with sodium acetate. The 6 : 7-dimethoxycarbostyril could only be obtained in traces.

Analyses marked with an asterisk are by Drs. Weiler and Strauss, Oxford.

The authors wish to thank Prof. D. K. Banerjee for his kind interest.

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