[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Syntheses of Papaverine, Papaverinol and Papaveraldine from Reissert Compounds

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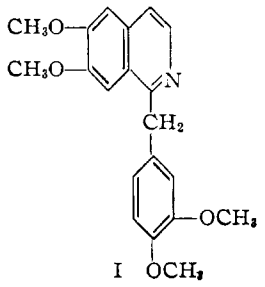
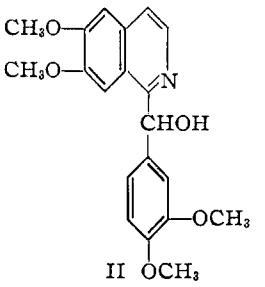
Papaverine (I), papaverinol (II) and papaveraldine (III) have been synthesized from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) as the key starting material. Improved methods for the preparation of 6,7-dimethoxyisoquinoline (V) have been developed. Several new Reissert compounds have been prepared and subjected to characteristic acid-catalyzed hydrolysis and base-catalyzed condensation, displacement or rearrangement reactions.

Papaverine (I) has been synthesized in a number of different ways, all of the reported methods requiring application of a ring-closure reaction as one of the last steps of a relatively long sequence of reactions.[1] There are several known industrial



I



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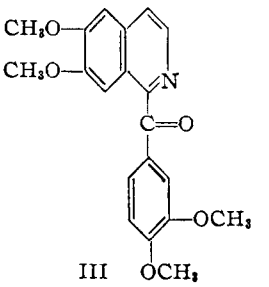
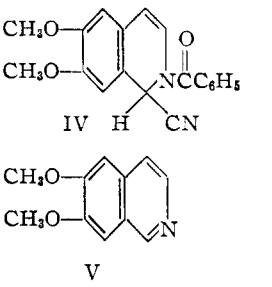


III



IV

V

methods for the preparation of papaverine (I), and these methods have been reviewed by Burger,[2] Dickenson[3] and Wahl.[4] Since procedures are known[5-15] for the interconversion of papaverine (I), papaverinol (II) and papaveraldine (III), syntheses of the latter two compounds may also be considered equivalent to syntheses of papaverine (I).[16,17]

Owing to a number of recently discovered reactions of Reissert compounds,[18] it appeared likely that papaverine (I), papaverinol (II) and papaveraldine (III) could all be synthesized quite readily from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV)[19] as the key starting material. The first requirement, however, was to develop a convenient method of synthesis of 6,7-dimethoxyisoquinoline (V), from which the Reissert compound IV may be prepared.[19]

On the basis of reports in the literature it appeared that 6,7-dimethoxyisoquinoline (V) could be prepared from homoveratrylamine (VI) in about 35% yield by a Bischler–Napieralski reaction of the N-formyl derivative of VI, followed by catalytic dehydrogenation of the resulting dihydro derivative of V.[20-24] 6,7-Dimethoxyisoquinoline (V) also has been prepared in 19% yield by oxidative cyclization of veratrylaminoacetal (VII) with arsenic pentoxide and sulfuric acid.[25,26] It was stated[25] that veratrylideneaminoacetal (VIII) would not undergo a normal Pomeranz–Fritsch reaction. By appropriate modifications of the previously reported[20-24] procedures it has now been found that 6,7-dimethoxyisoquinoline (V) may be prepared in about 70% yield by the Bischler–Napieralski ring-closure and catalytic dehydrogenation route. Also, by use of a mixture of polyphosphoric acid and phosphorus oxychloride as the cyclizing agent, veratrylideneaminoacetal (VIII) has been converted to 6,7-dimethoxyisoquinoline (V) in about 55% yield. Other workers have found that Pomeranz–Fritsch ring-closure reactions may sometimes be effected by use of polyphosphoric acid when the usual sulfuric acid method fails.[27]

By reaction of 6,7-dimethoxyisoquinoline (V), benzoyl chloride and aqueous potassium cyanide, Haworth and Perkin[19] obtained a 35% yield of

(1) A review of these syntheses has been given by D. Elad and D. Ginsburg, *Bull. Narcotics*, **4**, 27 (1952).

(2) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 405–413.

(3) H. G. Dickenson, "The Manufacture of Papaverine in the French and American Zones of Germany," British Intelligence Objectives Sub-Committee Final Report No. 1774, Item No. 24, H. M. Stationery Office, London, England, pp. 1–45. See also, B.I.O.S. Final Report No. 755, 119 (1945).

(4) H. Wahl, *Bull. soc. chim. France*, [5] **18**, D1 (1951).

(5) G. Goldschmiedt, *Monatsh.*, **6**, 954 (1885).

(6) G. Goldschmiedt, *ibid.*, **7**, 485 (1886).

(7) M. I. Kobachnik and A. I. Zitser, *J. Gen. Chem. U.S.S.R.*, **7**, 162 (1937); *C. A.*, **31**, 4320 (1937).

(8) G. Tsatsas, *Ann. pharm. franc.*, **10**, 61 (1952).

(9) E. P. Taylor, *J. Pharm. Pharmacol.*, **2**, 324 (1950).

(10) K. N. Menon, *Proc. Indian Acad. Sci.*, **19A**, 21 (1944); *C. A.*, **39**, 390 (1945).

(11) A. S. Labensky, *J. Gen. Chem. U.S.S.R.*, English Translation, **22**, 945 (1952).

(12) L. Stuchlik, *Monatsh.*, **21**, 813 (1900).

(13) J. Gadamer and H. Schulemann, *Arch. Pharm.*, **253**, 284 (1915).

(14) J. S. Buck, W. H. Perkin, Jr., and T. S. Stevens, *J. Chem. Soc.*, **127**, 1462 (1925).

(15) G. I. Braz and A. K. Chizhov, *J. Applied Chem. U.S.S.R.*, English Translation, **26**, 301 (1953).

(16) J. S. Buck, R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 2176 (1924).

(17) D. Guthrie, A. W. Frank and C. B. Purves, *Canadian J. Chem.*, **33**, 729 (1955).

(18) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(19) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1434 (1925).

(20) E. Spath and H. Epstein, *Ber.*, **59**, 2791 (1926).

(21) E. Spath and N. Polgar, *Monatsh.*, **51**, 190 (1929).

(22) G. A. Swan and D. Wright, *J. Chem. Soc.*, 1549 (1956).

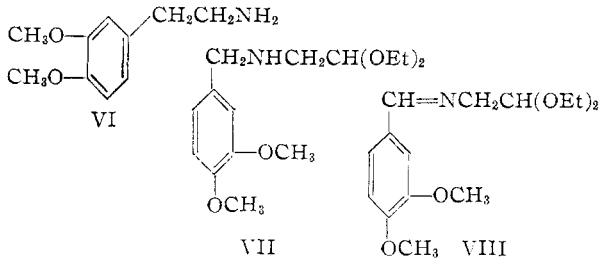
(23) J. S. Buck and W. Ide, THIS JOURNAL, **60**, 2101 (1938).

(24) W. M. Whaley and M. Meadow, *J. Chem. Soc.*, 1067 (1953).

(25) L. Rugheimer and P. Schon, *Ber.*, **42**, 2374 (1909).

(26) R. Forsyth, C. Kelly and F. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

(27) W. Herz and L. Tsai, THIS JOURNAL, **75**, 5122 (1953).



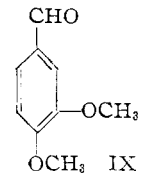
VI VII VIII

crude 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV). We have found that crude material can be obtained in as high as 90% yield, but that purification of the product by recrystallization from ethanol leads to a marked diminution of the yield. Furthermore, no Reissert compound can be obtained by concentration of the mother liquor; 6,7-dimethoxyisoquinoline (V) is recovered instead of IV. The implication that even gentle heating of IV brings about its decomposition was confirmed when it was found that 6,7-dimethoxyisoquinoline picrate could be obtained in high yield by warming pure IV in an alcohol solution containing picric acid. The thermal instability of IV must be due in large measure to the presence of the methoxyl groups because neither 2-benzoyl-1,2-dihydroisoquinaldonitrile nor 1-benzoyl-1,2-dihydroquinaldonitrile gave a picrate of the heterocyclic base upon being warmed in an alcohol solution containing picric acid. The lithium salt of IV, prepared by a metal–hydrogen exchange reaction of IV and phenyllithium, proved to be even less stable than the Reissert compound itself. Even at −10°, the characteristic red color of the lithium salt in ether–dioxane solution rapidly disappeared. However, at a temperature of −20°, the red color persisted for an appreciable period of time.

In view of the thermal instability of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) and its lithium salt, it was felt that a synthesis of papaverine (I) or one of its derivatives could best be effected by use of reactions which occur at low temperatures. A recent finding,[28] namely, that the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile would react with benzaldehyde at an initial temperature of −20° to give eventually the benzoate of phenyl-1-isoquinolylcarbinol, suggested a method for the synthesis of papaverinol (II). The lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile, prepared by metalation of IV with phenyllithium in ether–dioxane solution, was caused to condense with one equivalent of veratraldehyde (IX) at an initial temperature of −20°. Alkaline hydrolysis of the resultant product afforded papaverinol (II) in 67% yield. When the lithium salt of IV was treated with an excess of veratraldehyde (IX) and the reaction mixture later refluxed with aqueous alcoholic potassium hydroxide solution, papaveraldine (III) rather than papaverinol (II) was obtained in 67% yield. Evidently the excess veratraldehyde (IX) functions as an oxidizing agent for the conversion of II to III in a strongly alkaline medium.

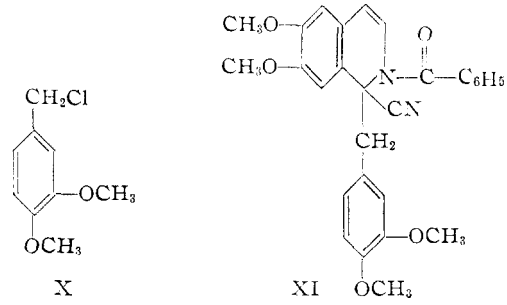
Owing to the fact that 3,4-dimethoxybenzyl-

(28) I. R. Walters and W. E. McEwen, unpublished results.



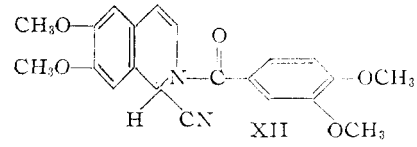
IX

chloride (X) is highly reactive in nucleophilic displacement reactions, it was felt that an alkylation reaction similar to that reported by Boekelheide and co-workers[29–31] might be carried out at a low temperature. Treatment of the lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) with X at an initial temperature of −20° gave the condensation product, XI, which was not purified; alkaline cleavage of crude XI afforded papaverine (I) in 22% yield.



X XI

Due to the relatively high temperature required to bring about the base-catalyzed rearrangement of a Reissert compound to the α-acyl derivative,[29,32,33] it did not seem likely that papaveraldine (III) could be synthesized by application of such a method. This proved to be the case. 2-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII) was prepared in 73% yield by the Grosheintz and Fischer method,[34] but no papaveraldine (III) was obtained on treatment of XII with sodium hydride in refluxing xylene.



XII

During the course of these studies, a number of new Reissert compounds were prepared and some of their characteristic reactions investigated. In addition to XII, the new compounds included 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile, 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile and 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile. Papaverinol (II) could be obtained from the latter two compounds in the same manner as described earlier for the preparation of II from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV). All four Reissert compounds gave aldehydes in high yield upon acid-

(29) V. Boekelheide and J. Weinstock, THIS JOURNAL, **74**, 66 (1952).

(30) V. Boekelheide and J. Godfrey, *ibid.*, **75**, 3679 (1953).

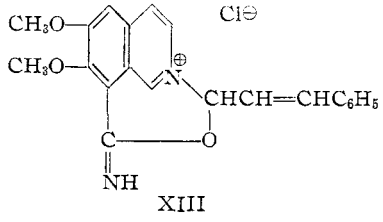
(31) V. Boekelheide and A. Seig, *J. Org. Chem.*, **19**, 587 (1954).

(32) W. E. McEwen, J. V. Kindall, R. N. Hazlett and R. H. Glazier THIS JOURNAL, **73**, 4591 (1951).

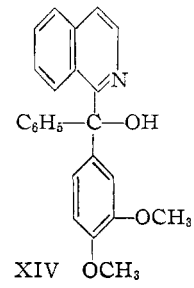
(33) A. P. Wolf, W. E. McEwen and R. H. Glazier, *ibid.*, **78**, 861 (1956).

(34) J. M. Grosheintz and H. O. L. Fischer, *ibid.*, **63**, 2021 (1941).

catalyzed hydrolysis. By reaction of 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with anhydrous hydrogen chloride, there was obtained a red solid of molecular formula $C_{21}H_{21}N_2O_4Cl$. This corresponds to the monohydrate of the salt of structure XIII (or a tautomer), the type of intermediate anticipated on the basis of the mechanism recently proposed[35] for the acid-catalyzed hydrolysis of Reissert compounds. Although 2-(3,4-dimethoxybenzoyl) - 1,2 - dihydroisoquinaldonitrile would not undergo reaction with sodium hydride to form 1-(3,4-dimethoxybenzoyl)-quinoline, reaction with phenyllithium gave phenyl-3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XIV), proving that a rearrangement reaction could be effected under the right conditions.



XIII



XIV

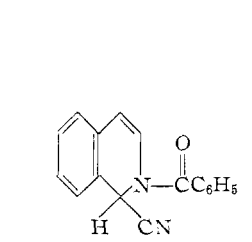
Prior to the reactions cited earlier, those leading to the preparation of papaverine (I), papaverinol (II) and papaveraldine (III), some model reactions were carried out with the readily available[36] Reissert compound, 2-benzoyl-1,2-dihydroisoquinaldonitrile (XV). Reaction of the lithium salt of XV with one equivalent of veratraldehyde (IX) gave the benzoate XVI of 3,4-dimethoxyphenyl-1-isoquinolylcarbinol XVII in 86% yield, whereas reaction of the lithium salt of XV with an excess of veratraldehyde (IX), with subsequent alkaline hydrolysis of the crude product, gave a mixture of XVII and 1-(3,4-dimethoxybenzoyl)-quinoline (XVIII). Alkylation of the lithium salt of XV with 3,4-dimethoxybenzyl chloride (X), with subsequent alkaline cleavage of the initially formed product, gave 1-(3,4-dimethoxybenzyl)-isoquinoline (XIX) in 53% yield.

Acknowledgment.—This investigation was supported by a research grant, H-2155, from the National Heart Institute of the National Institutes of Health, Public Health Service.

Experimental[37]

6,7-Dimethoxy-3,4-dihydroisoquinoline.—This compound was prepared in 97% yield from homoveratrylamine (VI) by the same procedure used by Haworth[38] to prepare 5,6-dimethoxy-3,4-dihydroisoquinoline from β-(2,3-dimethoxyphenyl)-ethylamine. Its picrate melted at 207–208° (reported[39] m.p. 206–208°).

6,7-Dimethoxyisoquinoline (V).—To a solution of 10.3 g. (0.054 mole) of crude 6,7-dimethoxy-3,4-dihydroisoquinoline in 31.5 cc. of decalin was added 5.7 g. of 10% palladium-on-charcoal catalyst, and the mixture was refluxed for 1.5 hr. The suspension was extracted with 15% hydrochloric acid, the acid solution filtered, made alkaline and extracted with ether. Distillation of the ether afforded 8.34 g. (82%) of crude 6,7-dimethoxyisoquinoline (V); picrate, m.p. 222–224° (reported m.p. 218–220°,[25] 226–227°[21]). Distillation of 37.3 g. of crude material gave 33 g. of purified 6,7-dimethoxyisoquinoline (V), b.p. 152–158° (0.8–0.9 mm.).



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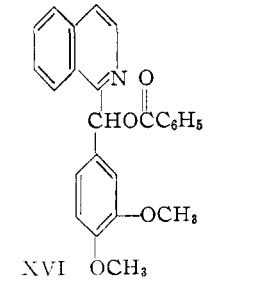
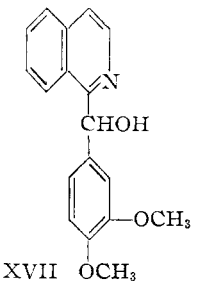
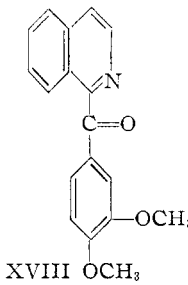


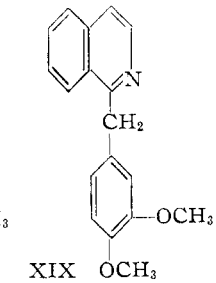
XVI



XVII



XVIII



XIX

Preparation of 6,7-Dimethoxyisoquinoline (V) by the Pomeranz–Fritsch Method.—Veratrylideneaminoacetal (VIII) was prepared in quantitative yield from veratraldehyde (IX) and aminoacetal by the method of Forsyth, Kelly and Pyman.[26] To a solution of 25 g. of phosphorus oxychloride in 160 g. of polyphosphoric acid maintained at 23–26° was added with stirring during a 10-minute period 25 g. (0.087 mole) of veratrylideneaminoacetal (VIII). The mixture was stirred for an additional 2 hr. at 23–26°, then added to ice-water. The acid solution was washed with ether, made alkaline and extracted with chloroform. Distillation of the chloroform left a dark, viscous oil, which was extracted with ether. Distillation of the ether afforded 8.25 g. (53%) of crude 6,7-dimethoxyisoquinoline (V); picrate, m.p. 220–221°.

2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV).—To an ice-cold mixture of 5.3 g. (0.081 mole) of potassium cyanide, 30 cc. of water and 5.1 g. (0.027 mole) of 6,7-dimethoxyisoquinoline (V) was added with stirring 7.6 g. (0.054 mole) of benzoyl chloride during a period of seven minutes. The mixture was stirred for an additional 1.7 hr. at room temperature, then the aqueous solution was decanted from an orange solid. After having been washed with water, 10% hydrochloric acid, water again and ether, and dried, the solid weighed 8.0 g. and had a m.p. of 130–135°. One crystallization from absolute ethanol gave 2.66 g. (31%) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV), m.p. 153–155° (reported[19] m.p. 164°). This material was sufficiently pure to be used in the reactions to be described below.

In another run, the anhydrous method of Grosheintz and Fischer[34] was employed. From a mixture of 37.84 g. (0.20 mole) of 6,7-dimethoxyisoquinoline (V), 10 cc. of liquid hydrogen cyanide and 14.06 g. (0.10 mole) of benzoyl chloride in anhydrous benzene there was obtained 27.0 g. of gummy material. One crystallization from absolute ethanol gave 6.05 g. (19%) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV), m.p. 156–157°.

Reaction of the Lithium Salt of 2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with 1.16 Equivalents of Veratraldehyde (IX).—To a solution of 2.00 g. (0.0062 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) in 15 cc. of anhydrous ether and 25 cc. of anhydrous dioxane was added slowly an ether solution of phenyllithium prepared from 1.62 g. of bromobenzene, the solution being stirred and maintained at a temperature of −20° and under a nitrogen atmosphere during this and the subsequent operation. To the deep red solution was added slowly 1.20 g. (0.0072 mole) of veratraldehyde (IX). The mixture was stirred for 1 hr. at −20° and then for 12 hr. at room tem-

(35) R. L. Cobb and W. E. McEwen, THIS JOURNAL, **77**, 5042 (1955).

(36) J. Padbury and H. Lindwall, *ibid.*, **67**, 1268 (1945).

(37) Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. All m.p.'s are corrected.

(38) R. D. Haworth, *J. Chem. Soc.*, 2281 (1927).

(39) F. Pyman, *ibid.*, **95**, 1610 (1909).

perature. The mixture was extracted with 20-cc. portions of water, 2% hydrochloric acid solution and water once again.

The aqueous acid solution was made alkaline and extracted with chloroform. Distillation of the chloroform left a residue of 0.77 g. of papaverinol (II), m.p. 137–138° (reported[13] m.p. 137°), which did not depress the m.p. of an authentic sample of papaverinol (II), prepared by the action of mercuric acetate on papaverine (I).[13] The infrared spectrum of the material was taken in chloroform solution and found to be identical with that of the authentic papaverinol (II).

After distillation of the solvents from the original ether–dioxane solution, there remained 2.80 g. of a gummy material. Most of this material readily dissolved in ethanol, but 0.30 g. of crystalline material, m.p. 209.5–211.0°, remained undissolved. Further purification by crystallization from a relatively large amount of ethanol gave material of m.p. 211.0–211.8°. This was not papaveraldine (III) since the m.p. of authentic papaveraldine (III), prepared by oxidation of papaverine (I) with potassium dichromate in acetic acid,[7] was depressed on admixture with the compound. Also, the infrared spectra of the two compounds, taken in chloroform solution, were not identical. However, the compound, m.p. 211.0–211.8°, had an absorption peak at 1650 cm.$^{-1}$, indicating the presence of a keto group.

Anal. Found: C, 68.80; H, 5.39; N, 8.37.

A solution of 0.88 g. of potassium hydroxide in 50 cc. of water was added to the ethanol solution of the gummy material cited above and the mixture was refluxed for 1.7 hr. The ethanol was distilled *in vacuo* and the aqueous solution extracted with chloroform. Evaporation of the chloroform gave 0.72 g. of papaverinol (II), m.p. 133–135°. The total yield of papaverinol (II) was 1.49 g. (67%).

Reaction of the Lithium Salt of 2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with an Excess of Veratraldenyde (IX).—A reaction was carried out with the lithium salt prepared from 2.70 g. (0.0084 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) and 6.50 g. (0.039 mole) of veratraldehyde (IX) in the same manner as described above. After the washing operation with water and 2% hydrochloric acid (no organic material obtained on making the acid wash alkaline), the solvent was distilled from the organic layer. The residual oil was added to a solution of 1.17 g. of potassium hydroxide in 60 cc. of 33% ethanol, and the resulting mixture was refluxed for 1 hr. Most of the alcohol was removed by distillation *in vacuo*, and the residual mixture was extracted with chloroform. The chloroform solution was extracted with 10% hydrochloric acid, then the aqueous acid solution was made alkaline and extracted with fresh chloroform. Removal of the chloroform by distillation gave 1.99 g. (67%) of papaveraldine (III), m.p. 195–200° (reported[8,9] m.p. 210°). Recrystallization from absolute ethanol gave material of m.p. 208–209°, which did not depress the m.p. of authentic papaveraldine (III).[7] The infrared spectrum of the compound was taken in chloroform solution and found to be identical with that of the authentic material.

3,4-Dimethoxybenzyl Chloride (X).—This compound, m.p. 49–51°, was prepared in 73% yield by the method of Kindler and Gehlhaar.[40]

Synthesis of Papaverine (I).—To a solution of 3.20 g. (0.01 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) in 25 cc. of anhydrous ether and 30 cc. of anhydrous dioxane maintained at −20° was added with stirring an ether solution of phenyllithium prepared from 1.93 g. of bromobenzene. The solution was maintained under an atmosphere of pure nitrogen during this and the subsequent operation. To the exchange mixture was added a solution 2.33 g. (0.0125 mole) of 3,4-dimethoxybenzyl chloride in 5 cc. of ether. The reaction mixture was stirred at −20° for 2 hr., then at room temperature for 12 hr. The mixture was washed with 25-cc. portions of water, 0.5 *M* hydrochloric acid and water once again. Distillation of the solvent gave 5.63 g. of gummy material. Upon addition of ethanol to this material, 0.33 g. of starting material, 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV), m.p. 159.5–161.0°, crystallized and was collected by filtration. To the filtrate was added a solution of 1.40 g. of potassium hydroxide in 60 cc. of water, and the resulting mixture was refluxed for 1.5 hr. Most of the alcohol was removed by distillation *in vacuo*, and the residue was extracted with ether. Distillation of the ether gave 3.62 g. of gummy solid. This was dissolved in chloroform, extracted with 10% hydrochloric acid and the acid solution made alkaline by addition of sodium bicarbonate. Extraction of the alkaline mixture with benzene afforded 2.06 g. of gummy material. Trituration of this material with absolute ethanol gave as the residue 0.68 g. (22%) of papaverine (I), m.p. 140–144°, reported[15] m.p. 146–147°. Recrystallization from ethanol gave material of m.p. 145–147° which did not depress the m.p. of an authentic sample of papaverine (I). The infrared spectrum of the material was taken in chloroform solution and found to be identical with that of authentic papaverine (I).

Addition of picric acid to the alcohol solution from the trituration step caused 0.46 g. of the picrate of 6,7-dimethoxyisoquinoline (V) to precipitate. The m.p. was found to be 225–226°, also in admixture with authentic V.

2-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII).—The compound was prepared in 73% yield from 6,7-dimethoxyisoquinoline, 3,4-dimethoxybenzoyl chloride[41] and liquid hydrogen cyanide by the Grosheintz and Fischer method.[34] After recrystallization from 95% ethanol the compound had a m.p. of 152.0–152.4°.

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.49; H, 5.53; N, 7.21.

Attempted Rearrangement of 2-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII).—Attempted rearrangement of XII by use of sodium hydride in boiling xylene according to the procedure of Boekelheide and Weinstock[29] led only to partial recovery of XII and decomposition with formation of 6,7-dimethoxyisoquinoline (V).

2-(3,4-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile.—To a mixture of 13.5 g. (0.207 mole) of potassium cyanide, 80 cc. of water and 8.90 g. (0.069 mole) of isoquinoline was added with stirring 26.2 g. (0.138 mole) of freshly prepared 3,4-dimethoxybenzoyl chloride[41] during a period of 15 minutes. The mixture was stirred for an additional 50 minutes. A solid material which had formed was collected by filtration and washed with water, 10% hydrochloric acid and ether. This treatment provided 16.16 g. (73%) of crystalline 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile, m.p. 193.5–196.5°. Recrystallization from glacial acetic acid, then absolute ethanol gave pure material, m.p. 202.3–202.6°.

Anal. Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.24; H, 5.04; N, 8.75. Found: C, 71.02; H, 5.26; N, 8.80.

2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—The compound was prepared in 68% yield from 6,7-dimethoxyisoquinoline (V), cinnamoyl chloride and liquid hydrogen cyanide by the Grosheintz and Fischer method.[34] Upon recrystallization from absolute ethanol there was obtained yellow crystalline material of m.p. 164.8–165.4°.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 73.05; H, 5.21; N, 7.91.

2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—Prepared in 78% yield by the Grosheintz and Fischer method,[34] the compound was crystallized from absolute ethanol, giving material of m.p. 156.4–157.2°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.69; H, 4.95; N, 8.16.

Acid-catalyzed Hydrolysis of the Reissert Compounds.—Each of the Reissert compounds was subjected to acid catalyzed hydrolysis in a hydrochloric acid solution of 2,4-dinitrophenylhydrazine as previously described.[42] From 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) there was obtained an 84% yield of benzaldehyde 2,4-dinitrophenylhydrazone; from 2-(3,4-dimethoxybenzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII), 87% of veratraldehyde 2,4-dinitrophenylhydrazone; from 2-(3,4-dimethoxybenzoyl-1,2-dihydroisoquinaldonitrile, 91% of veratraldehyde 2,4-dinitrophenylhydrazone; from 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile, 98% of cinnamaldehyde 2,4-dinitrophenylhydrazone; and from 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile, 89% of anisaldehyde 2,4-dinitrophenylhydrazone.

(40) K. Kindler and E. Gehlhaar, *Arch. Pharm.*, **274**, 377 (1936).

(41) H. Ryan and M. Walsch, *Sci. Proc. Roy. Dublin Soc.* (*N.S.*), **15**, 113 (1916).

(42) W. E. McEwen, R. H. Terss and I. W. Elliott, THIS JOURNAL, **74**, 3605 (1952).

Reaction of 2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with Anhydrous Hydrogen Chloride.—When anhydrous hydrogen chloride was passed into a pure chloroform solution of 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile at 0° and in an atmosphere of pure nitrogen, the solution first turned yellow, then orange and finally a red solid precipitated. This was washed with ether and dried over calcium chloride *in vacuo*. It is thought that the substance is a monohydrate of XIII or its tautomer. The substance decomposed at 190–192°.

Anal. Calcd. for $C_{21}H_{21}N_2O_4Cl$: C, 62.92; H, 5.28; N, 6.99; Cl, 8.85. Found: C, 61.92; H, 5.18; N, 6.84; Cl, 9.53.

Preparation of Papaverinol (I) from 2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile and from 2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—The condensation reactions with veratraldehyde (IX) were carried out in the same manner as described above for the reaction of the lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) with 1.16 equivalents of veratraldehyde (IX). The yields of papaverinol (I) were about the same as when IV was employed.

Base-catalyzed Rearrangement of 2-(3,4-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile.—Only starting material was recovered after an attempt to prepare 1-(3,4-dimethoxybenzoyl)-isoquinoline by treatment of 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile with sodium hydride in boiling xylene according to the procedure of Boekelheide and Weinstock.[29]

To a solution of 5.12 g. (0.016 mole) of 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile in 18 cc. of anhydrous dioxane and 5 cc. of anhydrous ether maintained at −10° and in an atmosphere of nitrogen, there was slowly added with stirring an ether solution of phenyllithium prepared from 3.70 g. of bromobenzene. The deep red reaction mixture was stirred for an additional 15 minutes at −10°, for 3.5 hr. at room temperature, for 15 minutes at 100°, then allowed to stand at room temperature for 12 hr. The mixture was washed with water, then extracted with 10% hydrochloric acid. The acid solution was made alkaline, and ether extraction provided 1.76 g. of very crude phenyl-3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XIV). This material was converted to the picrate, m.p. 172.5–173.5° after several recrystallizations from ethanol.

Anal. Calcd. for $C_{30}H_{24}N_4O_{10}$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.25; H, 4.02; N, 9.25.

The picrate was decomposed with lithium hydroxide solution and extracted with chloroform. From the chloroform extract there was obtained phenyl-3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XIV), m.p. 135–136° after recrystallization from ethanol.

Anal. Calcd. for $C_{24}N_{21}NO_3$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.73; H, 5.82; N, 3.84.

Concentration of the organic layer remaining after the extraction with hydrochloric acid gave 2.27 g. of a viscous oil. Sublimation at 0.4 mm. afforded 0.5 g. of isoquinaldonitrile, m.p. 86–87° after recrystallization from petroleum ether (reported[30] for isoquinaldonitrile, m.p. 89.0–89.5°). This product did not depress the m.p. of a sample of authentic isoquinaldonitrile. The infrared spectrum of the material was taken in chloroform solution and found to be identical with that of authentic isoquinaldonitrile.

Condensation of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (XV) with Veratraldehyde (IX).—To a solution of 10.41 g. (0.04 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XV) in 60 cc. of anhydrous dioxane and 20 cc. of anhydrous ether, maintained at −15° and under an atmosphere of nitrogen, was added slowly with stirring an ether solution of phenyllithium prepared from 7.22 g. of bromobenzene. To the deep red exchange mixture there was added slowly 6.65 g. (0.04 mole) of veratraldehyde (IX). The mixture was stirred at −15° for 2 hr., then at room temperature for 12 hr. The reaction mixture was washed with successive 25-cc. portions of water, 0.5 *M* hydrochloric acid and water. Distillation of the solvent left a residue of viscous oil. Addition of ethanol caused 13.76 g. (86%) of 3,4-dimethoxyphenyl-1-isoquinolylcarbinyl benzoate (XVI) to precipitate, m.p. 121–130°. Recrystallization from ethanol gave material of m.p. 134–135°.

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.06; H, 5.07; N, 3.77.

In a second run, a fourfold excess of veratraldehyde (IX) was employed. The benzoate XVI was isolated in 45% yield upon addition of ethanol to the residual oil as described above. The alcohol mother liquor was diluted to 40 cc. by addition of fresh ethanol, and then a solution of 3.2 g. of potassium hydroxide in 75 cc. of water was added. The mixture was refluxed for 5.5 hr. Ether extraction provided an oil, which was dissolved in chloroform and extracted with 10% hydrochloric acid. The acid solution was made alkaline and extracted with chloroform. Distillation of the chloroform gave an oil which was probably a mixture of 3,4-dimethoxy-1-isoquinolylcarbinol (XVII) and 1-(3,4-dimethoxybenzoyl)-isoquinoline (XVIII), since the infrared spectrum showed a characteristic carbinol peak at 3335 cm.$^{-1}$ and a characteristic ketone peak at 1685 cm.$^{-1}$.

Saponification of 3,4-Dimethoxyphenyl-1-isoquinolylcarbinyl Benzoate (XVI).—To a solution of 5.00 g. of the benzoate XVI in 50 cc. of ethanol was added a solution of 1.75 g. of potassium hydroxide in 100 cc. of water, and the mixture was refluxed for 6 hr. Ether extraction, followed by removal of the solvent gave 3.32 g. (90%) of 3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XVII), m.p. 89–90°. The m.p. was not changed by recrystallization of the solid from ethanol or petroleum ether.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.00; H, 5.91; N, 4.86.

The picrate, m.p. 100–101°, was crystallized from ethanol.

Anal. Calcd. for $C_{24}H_{20}N_4O_{10}$: C, 54.96; H, 3.84; N, 10.68. Found: C, 54.77; H, 3.99; N, 10.45.

Acidification of the alkaline solution remaining from the ether extraction gave benzoic acid in quantitative yield.

When the benzoate XVI was mixed with an equal weight of veratraldehyde, then saponified, there was obtained a mixture of carbinol XVII and ketone XVIII, as indicated by the presence of absorption peaks at 3335 and 1680 cm.$^{-1}$ in the infrared spectrum.

Preparation of 1-(3,4-Dimethoxybenzyl)-isoquinoline (XIX).—When the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XV) was treated with 3,4-dimethoxybenzyl chloride (X) and the reaction mixture worked up in the same manner as described for the preparation of papaverine (I), there was obtained crude 1-(3,4-dimethoxybenzyl)-isoquinoline (XIX), an oil, in 53% yield. **The picrate** melted at 165.0–165.5° after crystallization from ethanol.

Anal. Calcd. for $C_{24}H_{20}N_4O_9$: C, 56.69; H, 3.97; N, 11.02. Found: C, 56.92; H, 3.89; N, 10.93.

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