traction. All of the carbinols were purified by recrystallization from ethanol except the following: phenyl-2-quinolylcarbinol was recrystallized from low boiling petroleum ether; *n*-propyl-2-quinolylcarbinol was recrystallized from water–acetone; isopropyl-2-quinolylcarbinol, *n*-propyl-1-isoquinolylcarbinol and isopropyl-1-isoquinolylcarbinol were purified by distillation *in vacuo*.

Conversion of *n*-Propyl-2-quinolylcarbinol (XI) to 2-*n*-Butylquinoline.—A solution of 2.00 g. of *n*-propyl-2-quinolylcarbinol in 20 cc. of glacial acetic acid was chilled in an ice-bath, and then anhydrous hydrogen bromide was passed into the solution for a period of an hour. The solution was allowed to stand at 0° for 12 hours, and then it was warmed to room temperature. Over a period of 45 minutes and with mechanical stirring, a total of 1.29 g. (20-fold excess) of zinc dust was added. The resulting clear solution was made alkaline by addition of ammonium hydroxide solution and extracted with ether. After removal of the ether there remained a brown liquid. Distillation gave about 1.5 cc. of 2-*n*-butylquinoline, b.p. 103–108° (0.9–1.0 mm.), reported[9] b.p. 94–98° (0.7 mm.) and 153° (14 mm.). A portion of this material was converted to the picrate by treatment with an ethanol solution of picric acid. After recrystallization from ethanol, the m.p. was 161.5–164.0°, reported[9] m.p. 162°.

Conversion of *n*-Propyl-1-isoquinolylcarbinol (XIV) to 1-*n*-Butylisoquinoline.—The reduction was carried out as described above. The picrate had a m.p. of 183–186° after recrystallization from ethanol; reported[7] for 1-*n*-butylisoquinoline picrate, m.p. 183–185°.

Qualitative Rate Studies.—The condensation reaction between the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) and benzaldehyde was carried out exactly as described in the general procedure, but with the exception that the reaction was quenched by addition of 25 cc. of water just as soon as the red color had been discharged. The total time of reaction at −10° from the start of the addition of benzaldehyde to the quenching operation was six minutes. Phenyl-2-quinolylcarbinyl benzoate (VII) was obtained in 97% yield. Phenyl-1-isoquinolylcarbinyl benzoate (XV) was obtained in 88% yield in an identical experiment with the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) and benzaldehyde. In the reaction between the lithium salt of II (R = C_6H_5) and anisaldehyde, however, the red color was not completely discharged even after several hours. Hydrolysis of the reaction mixture at any time during this interval led to the isolation of both *p*-anisyl-1-isoquinolylcarbinyl benzoate and unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Reaction of the Lithium Salt of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) with Ethylene Oxide.—The reaction was carried out in the same manner as described above for the condensation of the lithium salts of Reissert compounds with aldehydes or ketones. In the work-up of the reaction mixture, the organic layer was extracted with three 50-cc. portions of 10% hydrochloric acid, rather than with 12 cc. of 0.5 *N* hydrochloric acid, as described for the aldehyde reactions. Only an intractable material was obtained after removal of the solvents from the organic layer. However, after the hydrochloric acid extract had been made alkaline by addition of sodium hydroxide solution, ether extraction provided a colorless solid, m.p. 79–80°, after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 77.95; H, 5.60; N, 4.84.

LAWRENCE, KANSAS

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

Approaches to the Synthesis of Emetine from Reissert Compounds[1]

BY FRANK D. POPP AND WILLIAM E. MCEWEN

RECEIVED OCTOBER 11, 1957

Reasonably convenient syntheses of 3-ethylpyridine-4-carboxaldehyde (III) and 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV) have been developed. Condensation of these aldehydes with the lithium salt of 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II), followed by alkaline hydrolysis of the initially formed anisate esters, gave 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinol (XIII) and 1-(6,7-dimethoxyisoquinolyl)-4-(2-methyl-5-ethylpyridyl)-carbinol (XV), respectively. 1-(3,4-Dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-pyridinium bromide (XIX) has been prepared, and oxidation of this compound with alkaline potassium ferricyanide solution gave either 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-2-pyridone (XXII) or 1-(3,4-dimethoxyphenethyl)-4-carboxaldehyde diethylacetal)-5-ethyl-2-pyridone (XXIII). Compounds XIII, XV and XXIII are considered to be attractive intermediates for the synthesis of ipecac alkaloids.

Although syntheses of emetine (I)[2] and its dehydrogenation product the rubremetinium cation[3] have been reported, it was of interest to us to attempt the synthesis of the alkaloid or one of its diastereoisomers from 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II), a compound previously used in the synthesis of papaverine,[4] as a starting material. It was thought that the condensation of the lithium salt of II with an appropriate aldehyde, a recently discovered reaction of Reissert compounds,[5] would serve as a key step in the proposed synthesis. The stereochemistry of emetine, shown in structure I, recently has been determined.[6]

Efforts were first directed toward the development of convenient syntheses of 3-ethylpyridine-4-carboxaldehyde (III) and 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV), the aldehydes which were to be used in the condensation reaction with the lithium salt of II. Inasmuch as Ginsburg and Wilson[7] were able to convert 2,3-dimethylpyridine to 3-methylpyridine-2-carboxaldehyde by a suitable adaptation of a reaction discovered by Boekelheide and Linn,[8] it was thought that the

(1) Abstracted from a portion of the dissertation submitted by Frank D. Popp in partial fulfillment of the requirements for the Ph.D. degree, Kansas University, 1957.

(2) R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova and N. A. Preobrazhenskii, *Doklady Akad. Nauk S.S.S.R.*, **75**, 539 (1950); *C. A.*, **45**, 7577 (1951); N. A. Preobrazhenskii, R. P. Evstigneeva, T. S. Levchenko and K. M. Fedyushkina, *Doklady Akad. Nauk S.S.S.R.*, **81**, 421 (1951); *C. A.*, **46**, 8130 (1952).

(3) A. R. Battersby and H. T. Openshaw, *Experientia*, **6**, 378 (1950); A. R. Battersby, H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953); Y. Ban, *Pharm. Bull. (Japan)*, **3**, 53 (1955); *C. A.*, **50**, 1854 (1956).

(4) F. D. Popp and W. E. McEwen, THIS JOURNAL, **79**, 3773 (1957).

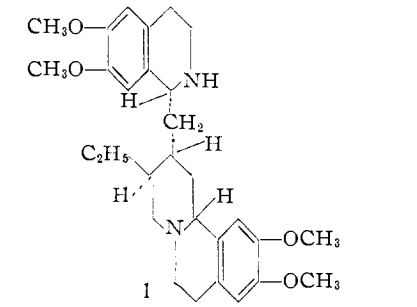
(5) L. R. Walters, T. Iyer and W. E. McEwen, *ibid.*, **80**, 1177 (1958).

(6) A. R. Battersby R. Binks, D. Davidson, G. C. Davidson and T. P. Edwards, *Chemistry & Industry*, 982 (1957). See also E. E. van Tamelen, P. E. Aldrich and J. B. Hester, Jr., THIS JOURNAL, **79**, 4817 (1957).

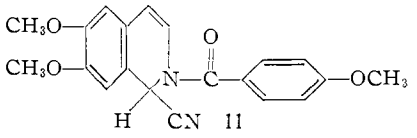
(7) S. Ginsburg and I. B. Wilson, *ibid.*, **79**, 481 (1957).

(8) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954).

same approach could be used to convert 3-ethyl-4-methylpyridine (V), a commercially available compound, to III. Treatment of V with hydrogen

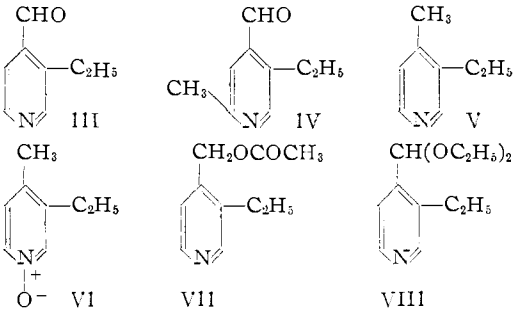


I



II

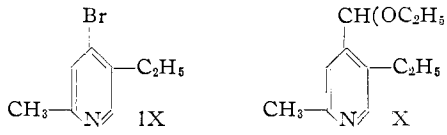
peroxide in acetic acid gave 3-ethyl-4-methylpyridine-1-oxide (VI) in 69% yield. 3-Ethylpyridine-4-methanol acetate (VII) was obtained in 64% yield by reaction of VI with acetic anhydride. In a repetition of the hydrogen peroxide–acetic anhydride reactions, followed by acid hydrolysis, III was obtained from VII in 30% yield. 3-Ethylpyridine-4-carboxaldehyde diethylacetal (VIII) was also prepared from III in 54% yield.



III IV V

VI VII VIII

The known preparations of pyridine-3-carboxaldehyde diethylacetal[9] and pyridine-2-carboxaldehyde diethylacetal[10] from 3-bromopyridine and 2-bromopyridine, respectively, by reaction of ethyl orthoformate with each pyridylmagnesium bromide, suggested the method of synthesis of the second of the desired aldehydes, 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV). 2-Methyl-4-bromo-5-ethylpyridine (IX) was prepared from 2-methyl-5-ethylpyridine by the method of Lee and Swan[11] and converted to the Grignard reagent by the entrainment method. This was treated with ethyl orthoformate to give 2-methyl-5-ethylpyridine-4-carboxaldehyde diethylacetal (X) in 37% yield. Acid-catalyzed hydrolysis of X provided IV in 87% yield.



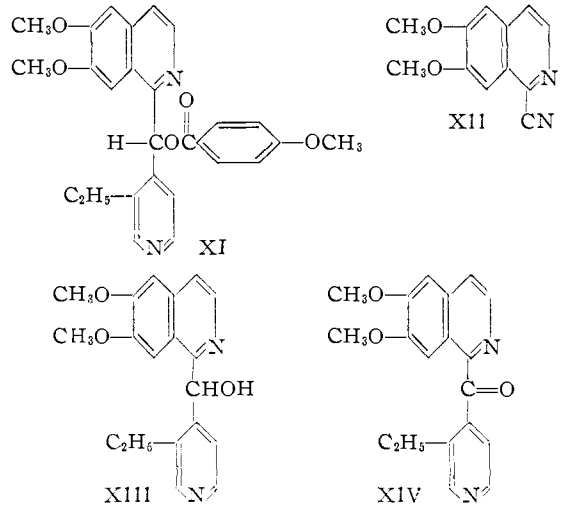
IX X

(9) J. P. Wibaut and H. G. P. van der Voort, *Rec. trav. chim.*, **71**, 798 (1952).

(10) J. P. Wibaut and R. Huls, *ibid.*, **71**, 1021 (1952).

(11) T. B. Lee and G. A. Swan, *J. Chem. Soc.*, 771 (1956).

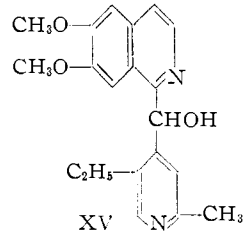
Condensation of 3-ethylpyridine-4-carboxaldehyde (III) with the lithium salt of 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II) proceeded as expected[5] and gave 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinyl anisate (XI) in about 50% yield. 6,7-Dimethoxyisoquinaldonitrile (XII) also was isolated from the reaction mixture in 4% yield. It was characterized by synthesis and by conversion to 6,7-dimethoxyisoquinaldamide, a known compound,[12] by treatment with polyphosphoric acid. Saponification of XI gave anisic acid and 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinol (XIII) in 95% yield. The latter compound was oxidized to 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl) ketone (XIV) by sodium dichromate and acetic acid.



XI XII

XIII XIV

The reaction of 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV) with the lithium salt of II gave a gum which, after saponification, afforded 1-(6,7-dimethoxyisoquinolyl)-4-(2-methyl-5-ethylpyridyl)-carbinol (XV). Experiments are currently being carried out in an attempt to build up the remainder of the emetine skeleton from compounds XIII, XIV and XV.

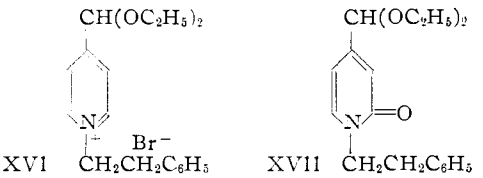


XV

As an alternative approach to the synthesis of emetine or one of its diastereoisomers, it was thought that it might prove advantageous first to prepare the quinolizidine system, then add the 6,7-dimethoxyisoquinolyl group by means of the reaction with the Reissert compound II. In a series of model experiments, pyridine-4-carboxaldehyde diethylacetal was prepared and heated with 2-bromoethylbenzene to form 1-(β-phenethyl)-4-(carboxaldehyde diethylacetal)-pyridinium bromide (XVI). Attempts to convert XVI to a pyridone by treatment with sodium hydroxide solution, fol-

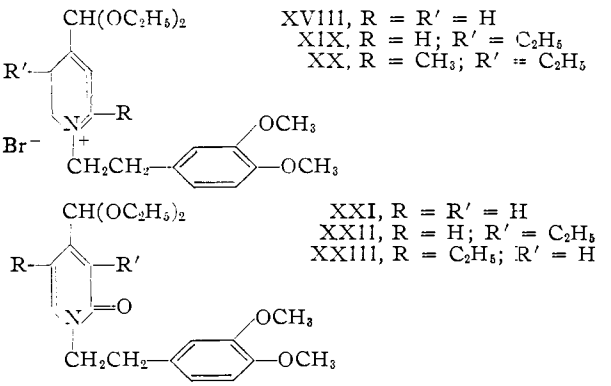
(12) R. D. Haworth and W. H. Perkin, Jr., *ibid.*, **127**, 1434 (1925).

lowed by addition of potassium ferricyanide, gave only a tarry product. A modification of the oxidation reaction, suggested by some recent publications of Sugasawa and co-workers,[13] was carried



out in which an aqueous solution of XVI was treated with an excess of potassium ferricyanide, followed, several hours later, by the addition of benzene and a very large excess of sodium hydroxide solution. From the benzene solution there was obtained 1-(β-phenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XVII) in 53% yield.

When pyridine-4-carboxaldehyde diethylacetal, 3-ethylpyridine-4-carboxaldehyde diethylacetal (VIII) and 2-methyl-5-ethylpyridine-4-carboxaldehyde diethylacetal (X) were heated with 3,4-dimethoxyphenylethyl bromide, the expected quaternary ammonium salts XVIII-XX were obtained. Oxidation of the bromides XVIII and XIX by the method cited above gave, in each case, a gummy material which could not be induced to crystallize. However, treatment of each of the gums with acid, then 2,4-dinitrophenylhydrazine solution, provided crystalline 2,4-dinitrophenylhydrazones. Analyses of the latter derivatives showed that the desired pyridones had been formed. There can be little doubt that the product from XVIII was 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XXI). The product from XIX, however, might have been either 1-(3,4-dimethoxyphenethyl) - 3 - ethyl - 4 - (carboxaldehyde diethylacetal)-2-pyridone (XXII) or 1-(3,4-dimethoxyphenethyl) - 4 - (carboxaldehyde diethylacetal)-5-ethyl-2-pyridone (XXIII). Although data in the literature[14] show that 3-alkyl-2-pyridones usually are obtained from quaternary salts of 3-alkylpyridines, there is no information available concerning oxidation of quaternary salts of 3,4-disubstituted pyridines. It was hoped that, owing to a steric effect of the 3-ethyl group buttressed by the acetal group in the 4-position, the desired pyridone XXIII would be obtained rather than XXII as a result of the potassium ferricyanide oxidation of XIX. In an attempt to prove the structure of the oxidation product of XIX, the pyridinium bromide XX was treated with an iodine solution of pyridine, followed by sodium hydroxide solution, according to the scheme developed by Berson and Cohen[14] for the preparation of pyridones. Unfortunately, no pure pyridone and no satisfactory derivative could be obtained from the reaction mixture. It was found, however, that the infrared spectrum of the crude oxidation product, taken in chloroform solution, was virtually identical with that of a chloroform solution of the gum obtained by the potassium ferricyanide oxidation of XIX. Further studies are being carried out to prove the structure of the pyridone obtained from XIX and to convert it, if it is indeed XXIII, to a quinolizidine derivative suitable for eventual conversion to emetine or one of its diastereoisomers.



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

Experimental[15]

2-Methyl-4-bromo-5-ethylpyridine (IX), b.p. 55–57° (0.9 mm.), was prepared in 53% yield from 94 g. of 2-methyl-4-nitro-5-ethylpyridine-1-oxide and 325 cc. of phosphorus tribromide by the method of Lee and Swan.[11]

2-Methyl-5-ethylpyridine-4-carboxaldehyde Diethylacetal (X).—To 36.48 g. (1.5 g. atom) of magnesium turnings and 75 cc. of anhydrous ether was added slowly with mechanical stirring 5.0 g. of ethyl bromide. After the initial reaction had subsided, a solution of 108.5 g. (0.542 mole) of 2-methyl-4-bromo-5-ethylpyridine (IX) and 99.4 g. (0.9 mole) of ethyl bromide in 300 cc. of anhydrous ether was added at such a rate as just to maintain reflux. The solution was heated under reflux for an additional two hours, the ether distilled and 375 cc. of anhydrous benzene added to the residue. To the cooled solution was added 222.3 g. (1.5 mole) of ethyl orthoformate. The solution was then heated to the reflux temperature, maintained under reflux for two hours, and finally allowed to stand at room temperature for 15 hours. After having been hydrolyzed by addition of 500 cc. of ammonium chloride solution, the reaction mixture was extracted with ether, and the ether solution, in turn, was extracted with one liter of 1 *N* sulfuric acid in portions. The acid extract was made basic by addition of sodium bicarbonate solution, then extracted with ether. The ether solution was dried over anhydrous potassium carbonate, then distilled. After removal of the ether and collection of a small amount of 2-methyl-5-ethylpyridine as a forerun, there was obtained 44.36 g. (37%) of 2-methyl-5-ethylpyridine-4-carboxaldehyde diethylacetal (X), b.p. 109–114° (3 mm.). The compound was characterized as the picrate, m.p. 139–140° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{24}N_4O_9$: C, 50.44; H, 5.35; N, 12.38. Found: C, 50.73; H, 5.59; N, 12.50.

2-Methyl-5-ethylpyridine-4-carboxaldehyde (IV).—A solution of 11.15 g. (0.05 mole) of 2-methyl-5-ethylpyridine-4-carboxaldehyde diethylacetal (X) in 90 cc. of 10% hydrochloric acid was refluxed under a nitrogen atmosphere for two hours. After having been permitted to stand at room temperature for 16 hours under nitrogen, the solution was made alkaline by addition of sodium carbonate solution and extracted five times with 20-cc. portions of chloroform. The chloroform solution was dried over anhydrous potassium carbonate and distilled. There was obtained 6.47 g. (87%) of 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV), b.p. 64–68° (1 mm.). The compound was characterized

(13) S. Sugasawa and T. Tatsuno, *Pharm. Bull. (Japan)*, **2**, 193 (1954); *C. A.*, **50**, 1017 (1956); S. Sugasawa, S. Akahoshi and M. Suzuki, *J. Pharm. Soc. Japan*, **72**, 1273 (1952); *C. A.*, **47**, 10539 (1953).

(14) For leading references see J. A. Berson and T. Cohen, THIS JOURNAL, **78**, 416 (1957), and numerous papers by S. Sugasawa and co-workers.

(15) Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. All m.p.'s are corrected but b.p.'s are uncorrected.

as the **oxime**, m.p. 143–144° after recrystallization from ethanol.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.99; H, 7.53; N, 17.17.

3-Ethyl-4-methylpyridine-1-oxide (VI).—This compound, b.p. 142–149° (3 mm.), was prepared in 69% yield from 242.4 g. (2.0 mole) of 3-ethyl-4-methylpyridine (V) by the same method used for the preparation of 2-methyl-5-ethylpyridine-1-oxide.[16] The substance was characterized as the **picrate**, m.p. 141.5–142.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{14}N_4O_8$: C, 45.90; H, 3.85; N, 15.30. Found: C, 45.87; H, 4.11; N, 15.18.

3-Ethylpyridine-4-methanol Acetate (VII).—To 380 cc. of warm acetic anhydride was added slowly 186 g. (1.36 moles) of freshly distilled 3-ethyl-4-methylpyridine-1-oxide (VI). After the initial reaction had subsided, the reaction mixture was heated under reflux for an additional four hours. The solvents were removed *in vacuo* and the residue distilled. There was obtained a small forerun of 3-ethyl-4-methylpyridine (V), then 154 g. (64%) of 3-ethylpyridine-4-methanol acetate (VII), b.p. 108–115° (2.5 mm.). The substance was characterized as the **picrate**, m.p. 137–138° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.95; N, 13.72. Found: C, 47.11; H, 3.93; N, 13.43.

3-Ethylpyridine-4-carboxaldehyde (III).—A mixture of 44.7 g. (0.25 mole) of 3-ethylpyridine-4-methanol acetate (VII), 25 cc. of 30% hydrogen peroxide and 115 cc. of glacial acetic acid was heated on a steam-bath for four hours. Another portion of hydrogen peroxide (21 cc.) was added and the solution heated an additional four hours. After having been allowed to stand at room temperature for 36 hours, the solution was concentrated *in vacuo*, and 125 cc. of acetic anhydride was added. This mixture was heated on the steam-bath for 5.5 hours, then concentrated *in vacuo*. To the residue was added 175 cc. of 6 *N* hydrochloric acid, and the solution was refluxed for two hours. Once again, the solution was concentrated *in vacuo*, then neutralized by addition of sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, then distilled. After removal of ether and a small forerun, there was obtained 10.2 g. (30%) of 3-ethylpyridine-4-carboxaldehyde (III), b.p. 71–75° (2.5 mm.). The compound was characterized as the **oxime**, m.p. 146.5–148.5° after recrystallization from ethanol.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 63.90; H, 6.71; N, 18.55.

3-Ethylpyridine-4-carboxaldehyde Diethylacetal (VIII).—A mixture of 11.25 g. (0.083 mole) of 3-ethylpyridine-4-carboxaldehyde (III) and 52 cc. of a 13.5% solution of hydrogen bromide in ethanol was allowed to stand at room temperature for 88 hours. To this mixture was added a large amount of benzene, and water was removed by azeotropic distillation, the condensate being passed through a thimble containing anhydrous magnesium sulfate in a Soxhlet extractor for a period of 24 hours. Excess alcohol and a portion of the benzene were removed by distillation, the residue made alkaline by addition of potassium carbonate solution, and the resulting mixture was extracted with ether. Distillation of the organic layer, dried over anhydrous potassium carbonate, gave, after removal of ether and recovery of a small forerun of the aldehyde III, 9.47 g. (54%) of 3-ethylpyridine-4-carboxaldehyde diethylacetal (VIII), b.p. 100–102° (1.9 mm.). The product was characterized as the **picrate**, m.p. 115–116° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{22}N_4O_9$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.43; H, 5.28; N, 12.70.

Condensation of 2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II) with 3-Ethylpyridine-4-carboxaldehyde (III).—To a solution of 8.75 g. (0.025 mole) of 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II) in 45 cc. of anhydrous dioxane and 15 cc. of anhydrous ether, maintained at −20° and under an atmosphere of nitrogen, was slowly added with stirring an ether solution of phenyllithium prepared from 4.40 g. of bromobenzene. To the deep red exchange mixture there was added slowly 3.38 g. (0.025 mole) of 3-ethylpyridine-4-carboxaldehyde (III). The mixture was stirred at −20° for 20 minutes, then at room temperature for seven hours. The reaction mixture was washed with successive portions of water, 0.5 *N* hydrochloric acid and water. Distillation of the solvent left a gummy solid. Recrystallization from ethanol gave 0.20 g. (4%) of 6,7-dimethoxyisoquinaldonitrile (XII), m.p. 198.4–199.0° after recrystallization from ethanol. There was no depression of m.p. when this material was mixed with an authentic sample of XII, prepared as described below.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.46; H, 4.93; N, 13.19.

The hydrochloric acid extract was made alkaline with sodium hydroxide solution and extracted with ether. Distillation of the ether left a gummy residue. Addition of ethanol to the gum caused 3.31 g. (29%) of 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinyl anisate (XI) to precipitate. After several recrystallizations from ethanol, the compound had a m.p. of 248.2–248.7°.

Anal. Calcd. for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.96; H, 6.00; N, 6.03.

A solution of 2.8 g. of potassium hydroxide in 20 cc. of water was added to the ethanolic filtrate obtained from the original precipitate of XI. The mixture was refluxed for two hours, and the ethanol was then removed by distillation *in vacuo*. The aqueous residue was extracted with ether. During the extraction process, a solid precipitated and was collected by filtration. More of the same solid was obtained upon evaporation of the ethereal extract. A total of 1.57 g. (19%) of 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinol (XIII) was obtained, m.p. 168–169° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.59; H, 6.39; N, 8.63.

Acidification of the alkaline solution remaining after removal of XIII gave 0.93 g. (25%) of anisic acid.

6,7-Dimethoxyisoquinaldamide.—A mixture of 0.02 g. of the nitrile, m.p. 198.4–199.0°, obtained from the reaction mixture described above, and 4.0 g. of polyphosphoric acid was heated on a steam-bath for one hour. Addition of 10 cc. of ice-water and neutralization of the resulting solution with potassium hydroxide solution caused 0.02 g. of 6,7-dimethoxyisoquinaldamide to precipitate. After recrystallization from ethanol, the material had a m.p. of 169–170° (reported[12] 168–169°).

6,7-Dimethoxyisoquinaldonitrile (XII).—A mixture of 1.45 g. (0.0045 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile[12] and 6 cc. of thionyl chloride was heated on a steam-bath for three hours. After removal of the excess thionyl chloride by distillation *in vacuo*, 35 cc. of water was added to the residue, and the resulting mixture was made alkaline by addition of sodium hydroxide solution. A solid which precipitated was collected by filtration and amounted to 0.8 g. Several recrystallizations from ethanol gave pure 6,7-dimethoxyisoquinaldonitrile (XII), m.p. 198.4–199.0°. Its infrared spectrum was taken in chloroform solution and found to be identical with that of the sample cited previously.

Saponification of 1-(6,7-Dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinyl Anisate (XI).—A mixture of 2.96 g. (0.0065 mole) of XI, 0.95 g. of potassium hydroxide, 25 cc. of ethanol and 55 cc. of water was refluxed for five hours. Upon removal of most of the alcohol by distillation *in vacuo*, 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinol (XIII) precipitated and was collected by filtration. There was obtained 2.01 g. (95%) of XIII. Ether extraction of the aqueous solution did not yield any additional carbinol. Acidification of the aqueous solution gave anisic acid in 98% yield.

1-(6,7-Dimethoxyisoquinolyl) 4-(3-Ethylpyridyl) Ketone (XIV).—A mixture of 0.5 g. of 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinol (XIII), 0.5 g. of sodium dichromate and 10 cc. of 80% acetic acid was stirred for one hour at room temperature. The mixture was made alkaline by addition of sodium bicarbonate solution and extracted with chloroform. Distillation of the chloroform left 0.44 g. (88%) of 1-(6,7-dimethoxyisoquinolyl) 4-(3-ethylpyridyl) ketone (XIV), m.p. 152–153° after recrystallization from ligroin.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.62; H, 5.79; N, 8.86.

(16) J. A. Berson and T. Cohen, *J. Org. Chem.*, **20**, 1461 (1955).

Condensation of 2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II) with 2-Methyl-5-ethylpyridine-4-carboxaldehyde (IV).—To a solution of 13.31 g. (0.038 mole) of 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II) in 70 cc. of anhydrous dioxane and 60 cc. of anhydrous ether, maintained at −25° and under a nitrogen atmosphere, was slowly added with mechanical stirring an ether solution of phenyllithium prepared from 6.60 g. (0.038 mole) of bromobenzene. To the deep red exchange mixture there was added slowly 5.70 g. (0.038 mole) of 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV). The mixture was stirred at −20° for one hour, then at room temperature for 15 hours. The reaction mixture was washed with successive portions of water, 1 *N* hydrochloric acid and water. Removal of the solvent from the organic layer left 4.06 g. of solid material. After several recrystallizations from ethanol there was obtained 6,7-dimethoxyisoquinaldonitrile (XII) as the least soluble component. From the mother liquors there was obtained some starting Reissert compound, II.

The hydrochloric acid extract was made alkaline by addition of sodium hydroxide solution and extracted with ether. Distillation of the ether left 13.1 g. of a gummy residue. To an ethanol solution of this material was added a solution of 4.5 g. of potassium hydroxide in 30 cc. of water, and the resulting mixture was refluxed for 1.5 hours. The ethanol was distilled *in vacuo*, and the aqueous distillation residue was extracted with ether. After distillation of the ether there remained 3.95 g. (31%) of 1-(6,7-dimethoxyisoquinolyl)-4-(2-methyl-5-ethylpyridyl)-carbinol (XV), m.p. 172–174°. Recrystallization from ethanol gave material of m.p. 174–175°.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.56; N, 8.28. Found: C, 70.82; H, 6.88; N, 8.44.

Pyridine-4-carboxaldehyde Diethylacetal.—A mixture of 50.0 g. (0.47 mole) of pyridine-4-carboxaldehyde and 185 cc. of an 11.5% solution of hydrogen chloride in ethanol was allowed to remain at room temperature for 90 hours. To this mixture was then added 450 cc. of anhydrous benzene, and all alcohol and water were removed by azeotropic distillation through a Todd column. The distillation residue was made alkaline by addition of potassium carbonate solution, extracted with ether, and the ether solution dried over anhydrous potassium carbonate. Distillation gave, after removal of the ether and a small forerun, 37.0 g. (44%) of pyridine-4-carboxaldehyde diethylacetal, b.p. 99–100° (6 mm.).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.07; H, 8.23; N, 7.95.

1-(β-Phenethyl)-4-(carboxaldehyde diethylacetal)-pyridinium Bromide (XVI).—A solution of 9.06 g. (0.05 mole) of pyridine-4-carboxaldehyde diethylacetal and 9.25 g. (0.05 mole) of 2-bromoethylbenzene in 35 cc. of anhydrous xylene was heated on a steam-bath for one hour. The xylene solution was decanted from a gum which had formed and, after several days, a solid separated from the xylene solution. Addition of a small amount of ethanol and a large amount of ether to the gum from which the xylene solution had been decanted produced the same solid. The combined yield of crude 1-(β-phenethyl)-4-(carboxaldehyde diethylacetal)-pyridinium bromide (XVI), m.p. 60–69°, amounted to 12.8 g. (70%). Several recrystallizations from ether–ethanol gave a solid, m.p. 65.6–66.5°, which turned to a gum when dried *in vacuo* over sulfuric acid. The solid was therefore washed with ether and dried in air in preparation for analysis.

Anal. Calcd. for $C_{18}H_{24}NO_2Br \cdot 2H_2O$: C, 53.30; H, 7.31; N, 3.66. Found: C, 53.73; H, 7.01; N, 3.48.

A picrate was prepared by treatment of the bromide XVI with ethanolic picric acid. Its m.p. after recrystallization was from 104.6–105.6°.

Anal. Calcd. for $C_{24}H_{26}O_9N_4$: C, 56.03; H, 5.09; N, 10.89. Found: C, 55.84; H, 5.13; N, 10.63.

1-(β-Phenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XVII).—To 2.50 g. (0.006 mole) of the pyridinium bromide dihydrate XVI in 25 cc. of water was added a solution of 8.8 g. (0.027 mole) of potassium ferricyanide in 25 cc. of water. After the solution had been allowed to stand overnight, 25 cc. of benzene was added, and then a solution of 4.0 g. (0.1 mole) of sodium hydroxide in 40 cc. of water was added slowly with stirring at room temperature. After the mixture had been stirred for one hour, the two layers were separated and the aqueous solution extracted with fresh benzene. Distillation of solvent from the combined benzene solution left a residue of 0.95 g. (53%) of crude 1-(β-phenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XVII), m.p. 77.5–80.0°. Several recrystallizations from ligroin gave colorless crystals of m.p. 84.0–84.5°.

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.65; H, 7.72.

3,4-Dimethoxyphenethyl bromide, b.p. 122–129° (1.5 mm.), m.p. 42–48°, was prepared in 63% yield from 3,4-dimethoxyphenethyl alcohol[17] and phosphorus tribromide as described by Sugasawa.[18]

1-(3,4-Dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-pyridinium Bromide (XVIII).—A mixture of 3.62 g. (0.02 mole) of pyridine-4-carboxaldehyde diethylacetal and 4.90 g. (0.02 mole) of 3,4-dimethoxyphenethyl bromide was heated on a steam-bath for 20 minutes. After the mixture had been permitted to stand overnight, a gummy product which had formed was treated with a small amount of alcohol and a large amount of ether. There was obtained 4.90 g. (58%) of crude 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-pyridinium bromide (XVIII), m.p. 79–81.5°.

The bromide XVIII was converted to the **picrate** by treatment with ethanolic picric acid. After recrystallization from ethanol the compound had a m.p. of 115.2–116.0°.

Anal. Calcd. for $C_{26}H_{30}N_4O_{11}$: C, 54.35; H, 5.26; N, 9.75. Found: C, 54.21; H, 5.43; N, 9.51.

1-(3,4-Dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XXI).—From 2.83 g. (0.0066 mole) of crude 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-pyridinium bromide (XVIII) there was obtained 1.35 g. (57%) of crude, gummy XXI by the same procedure used for the preparation of 1-(β-phenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XVII). Treatment of an ethanolic solution of the gum with a few drops of sulfuric acid, followed by addition of 2,4-dinitrophenylhydrazine solution, gave orange, crystalline **1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde 2,4-dinitrophenylhydrazone)-2-pyridone**, m.p. 270.0–270.8° after having been washed with hot ethanol and hot acetone.

Anal. Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.53; H, 4.51; N, 14.98. Found: C, 56.32; H, 4.74; N, 14.94.

1-(3,4-Dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-pyridinium Bromide (XIX).—This compound, m.p. 140–141° after recrystallization from ether–ethanol, was prepared in 90% yield from 5.50 g. (0.026 mole) of 3-ethylpyridine-4-carboxaldehyde diethylacetal (VIII) and 6.44 g. (0.026 mole) of 3,4-dimethoxyphenethyl bromide as described for the preparation of XVIII.

Anal. Calcd. for $C_{22}H_{32}NO_4Br$: C, 58.15; H, 7.10; N, 3.08; Br, 17.59. Found: C, 58.26; H, 7.26; N, 3.04; Br, 17.66.

The picrate was prepared by treatment of the bromide with ethanolic picric acid. Its m.p. was 126.3–127.1° after recrystallization from ethanol.

Anal. Calcd. for $C_{28}H_{34}N_4O_{11}$: C, 55.81; H, 5.69; N, 9.30. Found: C, 56.01; H, 5.74; N, 9.42.

Reaction of 1-(3,4-Dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-pyridinium Bromide (XIX) with Alkaline Potassium Ferricyanide.—Treatment of 4.54 g. (0.01 mole) of XIX as described above for the preparation of 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-2-pyridone (XXI) gave 2.90 g. (75%) of crude pyridone (either XXII or XXIII). Treatment of an ethanolic solution of the gum with a few drops of sulfuric acid, followed by addition of 2,4-dinitrophenylhydrazine solution, gave an orange, crystalline 2,4-dinitrophenylhydrazone, m.p. 268–269° after having been washed with hot ethanol and hot acetone.

Anal. Calcd. for $C_{24}H_{25}N_5O_7$: C, 58.17; H, 5.09; N, 14.14. Found: C, 58.34; H, 5.06; N, 14.19.

1-(3,4-Dimethoxyphenethyl)-2-methyl-4-(carboxaldehyde-diethylacetal)-5-ethylpyridinium bromide (XX), m.p. 150.5–152.0° after recrystallization from ether–ethanol, was pre-

(17) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 4252 (1956).
(18) S. Sugasawa, *J. Pharm. Soc. Japan*, **57**, 1028 (1937).

pared in 43% yield from 3.41 g. (0.0153 mole) of 2-methyl-5-ethylpyridine-4-carboxaldehyde diethylacetal (X) and 3.75 g. (0.0153 mole) of 3,4-dimethoxyphenethyl bromide as described above for the preparation of XVIII.

Anal. Calcd. for $C_{23}H_{34}NO_4Br$: C, 58.97; H, 7.32; N, 2.99; Br, 17.06. Found: C, 59.05; H, 7.27; N, 3.27; Br, 16.94.

LAWRENCE, KANSAS

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

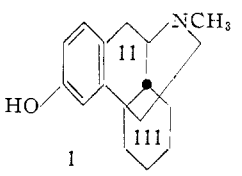
The Synthesis and Resolution of 3-Hydroxy-N-methylisomorphinan[1]

BY MARSHALL GATES AND WILLIAM GATEWOOD WEBB[2]

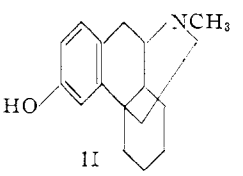
RECEIVED OCTOBER 1, 1957

3-Hydroxy-N-methylisomorphinan and 3-hydroxy-Δ^6-dehydro-N-methylisomorphinan have been synthesized and resolved. The *l*-enantiomorph of each exhibits powerful analgesic activity in animal screening tests.

The marked success of *l*-3-hydroxy-N-methylmorphinan[3] (I) (rings II/III *cis*) as an analgesic and the methyl ether of its enantiomorph as an antitussive[4,5] clearly suggest the desirability of examining the pharmacological properties of the C_{14}-epimers of these substances, and we have synthesized and resolved 3-hydroxy-N-methylisomorphinan (II) (rings II/III *trans*) as well as the corresponding Δ^6-dehydro derivative by the general method reported in earlier papers.[6]

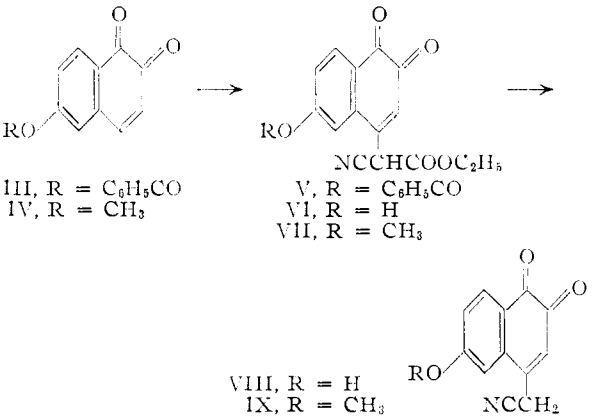


I



II

6-Benzoyloxy-1,2-naphthoquinone (III),[6b] readily prepared in three steps in 55% over-all yield from 2,6-dihydroxynaphthalene, and 6-methoxy-1,2-naphthoquinone (IV)[7] were both used as starting materials. Conversion of these to the 4-cyanomethylquinones VIII and IX through the intermediate cyanoacetates V, VI and VII by the methods developed earlier was successful, over-all yields of 40 and 49%, respectively, being obtained. During the condensation of III with ethyl cyanoacetate, some ethyl 6-hydroxy-1,2-naphthoquinonyl-4-cyanoacetate (VI) is formed by hydrolysis, and although V can readily be obtained, the best yields of VIII are obtained by cleaving the crude condensation product containing both V and VI with strong alkali. An alternative preparation of VII from 6-methoxy-2-naphthol entirely analogous to the preparation of ethyl 1,2-naphthoquinonyl-4-cyanoacetate from 2-naphthol by way of 1-nitroso-2-naphthol and 1-amino-2-naphthol-4-sulfonic acid,[8,9] was also investigated briefly. Comparable over-all yields were obtained. As in earlier examples[6a,b] the point of attachment of the cyanomethyl group in VIII was established by conversion to the known 5-methylbenzo[a]phenazine.[10]



Both quinones VIII and IX condense readily with butadiene and with dimethylbutadiene to give the corresponding enolic diketones X, XI, XII and XIII in approximately 60% yield.

Reductive cyclization[6] of these diketones with copper chromite yielded the ketolactams XIV, XV, XVI and XVII, the yields ranging from 38 to 59%. The phenolic ketolactams XIV and XVI are, of course, easily methylated with dimethyl sulfate and alkali to XV and XVII, and if this methylation is carried out at 50° with a large excess of dimethyl sulfate, the corresponding N-methyketolactams are readily obtained.

The ketonic carbonyl group of XIV, XV, XVI and XVII is easily converted to methylene by Wolff–Kishner–Huang-Minlon reduction, although

(1) Taken in part from the Ph.D. dissertation of William Gatewood Webb, the University of Rochester, 1954.

(2) Sherman Clark Fellow, 1951–1952; Beaunit Mills Fellow, 1952–1953.

(3) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **34**, 2211 (1951); *cf.* R. Grewe, A. Mondon and E. Nollte, *Ann.*, **564**, 161 (1949).

(4) (a) W. M. Benson, P. L. Stafko and L. O. Randall, *J. Pharmacol. Exp. Therap.*, **109**, 189 (1953); (b) R. D. Hunt and F. F. Foldes, *New Engl. J. Med.*, **248**, 803 (1953).

(5) (a) B. Pellmont and H. Bachtold, *Schweiz. Med. Wochschr.*, **84**, 1368 (1954); (b) A. Hottinger, *ibid.*, **84**, 1372 (1954); (c) L. J. Cass and W. S. Frederick, *New Engl. J. Med.*, **249**, 132 (1953); (d) L. J. Cass and W. S. Frederick, *J. Lab. Clin. Med.*, **48**, 879 (1956).

(6) (a) M. Gates and W. F. Newhall, THIS JOURNAL, **70**, 2261 (1948); (b) M. Gates, *ibid.*, **72**, 228 (1950); (c) M. Gates, R. B. Woodward, W. F. Newhall and R. Künzli, *ibid.*, **72**, 1141 (1950); (d) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

(7) H. E. French and K. Sears, *ibid.*, **70**, 1279 (1948). We were able to make substantial improvements (55% compared with 15% over-all from 2-naphthol) in the preparation of this substance by using aqueous alkali and copper-bronze to convert 6-bromo-2-methoxynaphthalene into 6-methoxy-2-naphthol and by using the corresponding nitroso compound rather than the azo compound in the conversion of this naphthol to the quinone.

(8) F. Sachs and M. Craveri, *Ber.*, **38**, 3685 (1905).

(9) E. L. Martin and L. F. Fieser, *Org. Syntheses*, **21**, 91 (1941); L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 42.

(10) L. F. Fieser and C. K. Bradsher, THIS JOURNAL, **61**, 417 (1939).