Synthetic Studies of the Antitumor Antibiotic Streptonigrin. II. Synthesis of the C-D Ring Portion of Streptonigrin

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Partial methylation of gallopropiophenone (**4**) followed by benzylation and base-catalyzed condensation with ethyl acetate yielded 3-(2-benzyloxy-3,4-dimethoxy)benzoyl-2-butanone (**6**). Amination of the latter and subsequent base-catalyzed cyclization with ethyl cyanoacetate gave 4-(2-benzyloxy-3,4-dimethoxy)phenyl-5,6-dimethyl-2-oxo-1,2-dihydropyridine (**8**). Removal of the 2-oxo group of **8** through chlorination and dechlorination and stepwise conversion of the 5-cyano and 2-methyl groups into the 5-amino and 2-carboxylic acid groups, respectively, with introduction and removal of protecting groups at proper stages, yielded the C-D ring moiety of the antitumor antibiotic streptonigrin.

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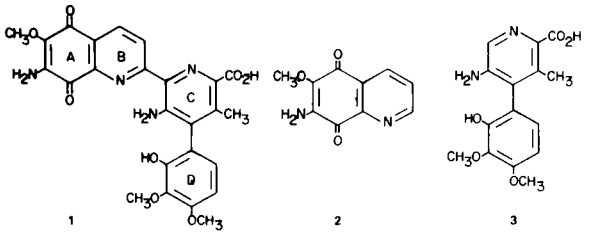
In connection with the structure-activity relationship study of the antitumor antibiotic streptonigrin (**1**) (1-7), a program to synthesize both the A-B ring and the C-D ring portions was initiated in this laboratory. The synthesis of the A-B ring portion (**2**) was completed in 1967 (8). The present paper accounts for the first synthesis of the C-D ring moiety: 5-amino-4-(3,4-dimethoxy-2-hydroxy)-phenyl-2-pyridinecarboxylic acid (**3**).



1 2 3

In contrast to the coplanarity of the AB ring of streptonigrin, the presence of many substituents located *ortho* to the pyridine-benzene linkage should not only cause nonplanarity of rings C and D but should also restrict rotation between these two rings. This is substantiated by the fact that a recent X-ray diffraction study of the molecular and crystal structure of streptonigrin (8) revealed that rings A, B, and C are very nearly coplanar and that ring D is virtually perpendicular to ring C. Our synthetic route to the C-D ring was so designed as to avoid such steric hindrance that might otherwise be encountered during the course of synthesis. The present preparative method is also suitable for scale-up preparation of the C-D ring and related compounds despite the lengthy operations, which involve successive functionalization of the built-in substituents.

Gallopropiophenone (ethyl 2,3,4-trihydroxyphenyl ketone, **4**) was prepared in 59% yield from pyrogallol by a Friedel-Crafts reaction with propionic anhydride, based on a similar procedure for the synthesis of galloacetophenone (9). Partial methylation of **4** with methyl iodide and potassium carbonate in acetone (10) gave a quantitative yield of 3′,4′-dimethoxy-2′-hydroxypropiophenone (**5a**). The structural assignment of **5a** was supported by its ir spectrum which gave no OH band and a carbonyl band at 1635 cm^{-1}, indicating the presence of an aromatic hydrogen bonded carbonyl. Conversion of **5a** to the benzylated derivative **5b** was achieved with benzyl chloride and sodium ethoxide. Here the expected carbonyl absorption in the ir spectrum was found at 1675 cm^{-1} because of the absence of hydrogen bonding.

Introduction of an acetyl function to **5b** was realized by stirring **5b** in a large excess of ethyl acetate in the presence of sodium hydride in ether. The α,γ-diketone **6** thus obtained was treated with ethanolic ammonia (11) to give 2-amino-3-(2-benzyloxy-3,4-dimethoxy)benzoyl-2-butene **7**. Condensation of the β-ketoenamine **7** with ethyl cyanoacetate in the presence of sodium ethoxide, according to a similar procedure of a well-defined pyridine synthesis (12), gave 4-(2-benzyloxy-3,4-dimethoxy)phenyl-3-cyano-5,6-dimethyl-2-oxo-1,2-dihydropyridine (**8**) as the sole cyclization product. It should be noted that a yield of 68% of **8** from **7** was obtained when a large excess of both

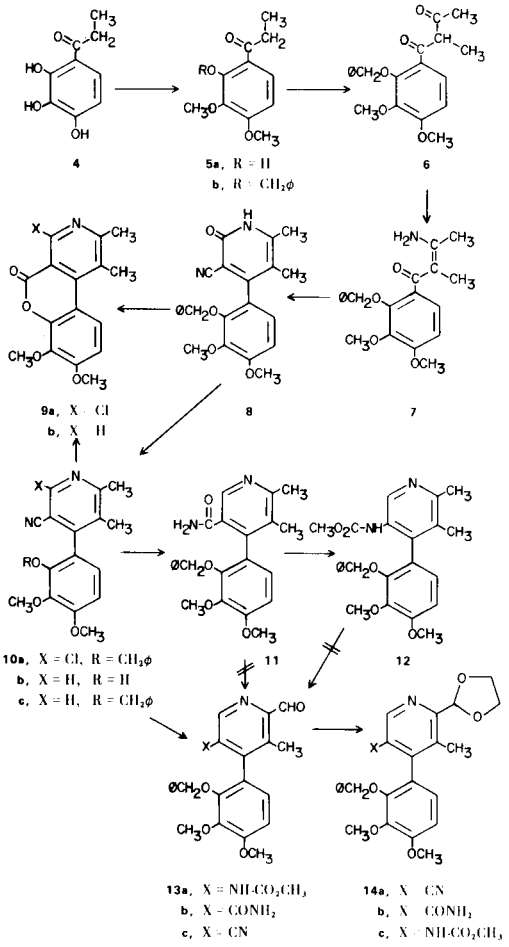
sodium ethoxide and ethyl cyanoacetate was used in the condensation reaction. Compound **8** was synthesized previously by a different synthetic route in low yield (13).

Halogenation of **8** to **10a** initially presented considerable difficulty. Treatment of **8** with the conventional halogenating agents such as phosphorus oxychloride, phosphorus pentachloride or phosphorus tribromide under a variety of reaction conditions either resulted in the recovery of starting material or the formation of decomposed, intractable material. The difficulty was overcome by heating a mixture of **8** and dichlorophenylphosphine oxide at 140-150° to give the chloro compound **10a** in 73% yield. Overheating of this reaction mixture resulted in debenzylation of **10a** with the formation of a large amount of polymeric substance as well as lactone **9a**, m.p. 215-216°. The structure of **9a** was substantiated by comparison of its infrared absorption spectrum with that of lactone **9b**. The latter was obtained by treatment of **10b** (*vide infra*) with polyphosphoric acid.

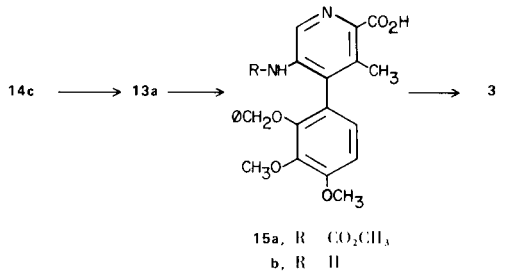
Catalytic dehalogenation of **10a** with either 5% palladium-on-calcium carbonate or 10% palladium-on-charcoal in the presence of aqueous ammonia resulted in the simultaneous loss of the protecting benzyl group, to give 4-(3,4-dimethoxy-2-hydroxy)phenyl-5,6-dimethylnicotinonitrile (**10b**) in 95% yield. Rebenzylation of **10b** followed by hydrolysis of the intermediate **10c** with dilute sodium hydroxide in aqueous ethanol gave the carboxamide **11** in 65% overall yield.

The amide **11** was readily converted to the corresponding urethane **12** by the action of bromine in a large excess of sodium methoxide in methanol (14). However, attempts to oxidize the 6-methyl group of **12** with selenium dioxide failed to yield the desired pyridinecarboxaldehyde **13a**. Attempted oxidation of **11** with selenium dioxide gave only a trace of the corresponding aldehyde **13b** with the recovery of most of the starting material. On the other hand, the cyano compound **10c** was smoothly oxidized by selenium dioxide in glacial acetic acid (15) to give an 80% yield of the 5-cyano-2-pyridinecarboxaldehyde **13c**. The readiness of such a selective oxidation is evidently facilitated by the *para*-substituted electron-withdrawing cyano group. Compound **13c** was subsequently converted to the corresponding acetal **14a** in 88% yield.

The base-catalyzed hydrolysis of the cyano group of **14a** was carried out in a refluxing aqueous methanol solution containing sodium hydroxide and the amide **14b** was obtained in 66% yield. Compound **14b** readily underwent a Hofmann reaction to give 67% yield of the urethane **14c**. The result of this conversion was quite satisfactory in view of the involvement of the highly hindered amide function as well as the fact that the highly activated phenyl ring remained intact under the Hofmann reaction conditions. A low temperature (-40°) technique for the Hofmann reaction described in the literature (16) appears to be unnecessary as long as a large excess of sodium methoxide is present throughout the entire reaction. In a repeated experiment, it was found that the crude hydrolysis product **14b** could be used without purification for the Hofmann reaction and a 72% overall yield was obtained in the two-step reaction.



Acid hydrolysis of compound **14c** gave a 91% yield of the desired pyridinecarboxaldehyde **13a**, the compound which could not be prepared by the direct oxidation of **11**. Treatment of **13a** with silver oxide in dilute base (17, 18) gave an 88% yield of the 2-pyridinecarboxylic acid **15a**, which possesses all the required functionality of the



C-D ring. Removal of the methoxycarbonyl protecting group of **15a** was carried out by a base-catalyzed hydrolysis, and the resulting amino compound **15b**, which was obtained in 87% yield, upon catalytic hydrogenation gave a near quantitative yield of **3**, the C-D ring portion of streptonigrin, m.p. 213-215° dec.

EXPERIMENTAL

Gallopropiophenone (Ethyl 2,3,4-Trihydroxyphenyl Ketone, **4**).

In a 5-liter round-bottomed flask connected to a water aspirator was placed 560 g. of zinc chloride. Under reduced pressure, the flask was gently heated with a small flame until complete fusion of zinc chloride took place, while the moisture present in the zinc salt was constantly removed from the flask. The contents were cooled to room temperature and 850 ml. of propionic acid was added. The reaction mixture was slowly heated (heating mantle) under reflux with intermittent swirling until a clear reddish brown solution was formed. To this was added 1 kg. (8 moles) of pyrogallol and the mixture was again gradually heated until an almost clear solution was formed. During this time the reaction temperature was always kept below 100°. The resulting brown and slight viscous solution was then cooled to 40-60° and to it was carefully added 1 kg. of propionic anhydride. The rate of addition was such that a sudden rise of reaction temperature could be avoided. The temperature of the solution eventually rose to 120°. It was then heated, with exclusion of moisture, at 135-140° for 40 minutes and was allowed to stand at room temperature overnight whereupon a crystalline product gradually formed. The semisolid was triturated with water and the solid collected by filtration. It was washed repeatedly with water until the wash was almost colorless. The solid was transferred into a 4-liter beaker and vigorously stirred with 175 ml. of water presaturated with sulfur dioxide. The resulting solid product was collected by filtration, washed repeatedly with water and finally dried at 85° under reduced pressure to give 850 g. (59% yield) of **4**, m.p. 125-127°. An analytical sample was prepared by recrystallization from water, m.p. 125-127°; ir (nujol): 3350 (OH) and 1635 cm^{-1} (C=O); nmr (deuteriochloroform-DMSO-d_6): δ 1.17 (3H, t, J = 7 Hz; CH_3), 2.95 (2H, q, J = 7 Hz, CH_2), 6.44 (1H, d, J = 9 Hz, aromatic) and 7.27 ppm (1H, d, J = 9 Hz, aromatic).

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.00; H, 5.50.

3′,4′-Dimethoxy-2′-hydroxypropiophenone (**5a**).

A mixture of 364 g. (2 moles) of **4**, 560 g. of anhydrous potassium carbonate, 650 g. (4.58 moles) of methyl iodide and 3.5 liters of reagent grade acetone was stirred at room temperature for 20 hours. (The mixture initially became a semisolid mass, which was difficult to stir, but soon turned into a stirrable mixture). It was then heated gently with stirring under an efficient reflux condenser for 8 hours. After cooling to room temperature, most of the acetone solution was decanted, the remaining reaction mixture was filtered, and the combined acetone solutions evaporated under reduced pressure to a yellow mass. This was triturated with water and the solid collected by filtration. It was repeatedly washed with water and subsequently with 50% aqueous ethanol to afford 395 g. (94% yield) of **5a** as a white crystalline solid, m.p. 93-95°. The product was pure enough for subsequent reaction. An analytical sample was prepared by recrystallization from 95% ethanol, m.p. 94-96°; ir: 1635 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.20 (3H, t, J = 7 Hz, CH_3), 2.94 (2H, q, J = 7 Hz, CH_2), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.51 (1H, s, J = 9 Hz, aromatic), and 7.55 ppm (1H, s, J = 9 Hz, aromatic).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.50; H, 6.68.

2′-Benzyloxy-3′,4′-dimethoxypropiophenone (**5b**).

To a solution of 69 g. (3 g.-atoms) of sodium dissolved in 2.5 liters of absolute ethanol was added 630 g. (3 moles) of **5a** with stirring. The mixture gradually thickened and, when stirring finally became impossible, 400 g. (3.15 moles) of benzyl chloride was slowly added to the mixture. The resulting solution was refluxed with stirring for 18 hours and cooled to room temperature. It was then evaporated to dryness under reduced pressure. The residue was triturated with water and the resulting solid collected by filtration. Recrystallization of the crude product from ethanol gave 700 g. (78% yield) of the desired compound, m.p. 83.5-85°; ir (nujol): 1675 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.88 (6H, s, OCH_3), 5.14 (2H, s, OCH_2), 6.75 (1H, d, J = 9 Hz, aromatic), and 7.20-7.60 ppm (6H, m, aromatic).

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.10; H, 6.77.

3-(2-Benzyloxy-3,4-dimethoxy)benzoyl-2-butanone (**6**).

To a partial solution of 330 g. (1.1 mole) of **5b** and 500 ml. of ethyl acetate in 2.5 liters of anhydrous ether was added positionwise, with stirring, 75 g. of 57% sodium hydride in mineral oil at 0-5°. The mixture was stirred at room temperature for 48 hours. The viscous slurry was neutralized with dilute hydrochloric acid. The ether solution was separated, washed with water, and dried. Evaporation of the solvent gave a brown oily residue. This was washed with hexane to remove mineral oil. It was then added to 150 ml. of absolute ethanol and chilled overnight. The resulting solid product was collected by filtration, washed with ethanol and hexane, and dried under reduced pressure to give 130 g. of product. The mother liquor was distilled *in vacuo* and the fraction boiling between 170-210°/0.5 mm (60 g.) was collected. The distillate was found to be the same product as the solid obtained from the chilled ethanol solution. The combined yield was 51%. The product was used for the subsequent reaction without further purification. For analytical purposes, a small portion was recrystallized from ethanol and hexane, m.p. 79.5-80°; ir (nujol): 1675 (C=O) and 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.20 (3H, d, J = 7 Hz, CH_3), 1.93 (3H, s, CH_2), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.37 (1H, q, J = 7 Hz, CH), 5.04 (2H, s, OCH_2), 6.57 (1H, d, J = 9 Hz, aromatic), and 7.03-7.35 ppm (6H, m, aromatic).

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.30; H, 6.61.

2-Amino-3-(2-benzyloxy-3,4-dimethoxy)benzoyl-2-butene (**7**).

A partial solution of 400 g. (1.17 moles) of **6** in 2 liters of absolute ethanol presaturated with ammonia was allowed to stand at room temperature with occasional agitation while a stream of dry ammonia was slowly passed through the mixture. The starting material **6** gradually dissolved in 3 days and the desired product started to precipitate from the solution. At the end of the 4th day, the white crystalline solid (140 g.) was collected by filtration and washed with ethanol and ether. The combined filtrate and the washings were concentrated at 60° to a slurry and, upon chilling, yielded another 120 g. of crude product. The latter was recrystallized from absolute ethanol to give 105 g. of crystalline

product. The total yield was 245 g. (61%), m.p. 113-115°; ir (nujol): 3250 (NH_2) and 1620 cm^{-1} (sh, C=O); nmr (deuteriochloroform): δ 1.57 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.91 (2H, s, OCH_2), 6.51 (1H, d, J = 9 Hz, aromatic), 6.76 (1H, d, J = 9 Hz, aromatic), and 6.95-7.34 ppm (5H, m, aromatic).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.49; H, 6.85; N, 4.16.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-3-cyano-5,6-dimethyl-2-oxo-1,2-dihydropyridine (**8**).

To a solution of ethanolic sodium ethoxide (prepared from 18 g. of sodium and 500 ml. of absolute ethanol) cooled in an ice-water bath was added, with stirring, 80 ml. of ethyl cyanoacetate. The solution was heated to boiling, then cooled in an ice-water bath. To this solution was added 100 g. (0.3 mole) of **7** in one portion. The mixture was protected from moisture and refluxed for 48 hours. It was cooled in an ice-bath and neutralized with 60 ml. of glacial acetic acid. The resulting mixture was diluted with 1.5 liters of water and kept at 5° overnight. The precipitated product was collected by filtration, washed successively with water, ethanol, and ether. After drying at 90-100° in a vacuum oven, 78 g. (68% yield) of **8**, m.p. 235-238° was obtained. An analytical sample was prepared by recrystallization from *p*-dioxane to give a white crystalline solid, m.p. 236-238°; ir (nujol): 2230 (C≡N) and 1640 cm^{-1} (C=O); nmr (TFA-deuteriochloroform): 1.90 (3H, s, CH_3), 2.52 (3H, s, CH_3), 4.03 (3H, s, OCH_3), 4.14 (3H, s, OCH_3), 4.97 (1H, d, J = 12 Hz, OCH_2), 5.21 (1H, d, J = 12 Hz, OCH_2) and 6.95-7.47 ppm (7H, m, aromatic).

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.98; H, 5.82; N, 7.28.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-2-chloro-5,6-dimethylnicotinonitrile (**10a**).

A mixture of 10 g. (0.026 mole) of **8** in 20 ml. of dichlorophenylphosphine oxide protected from moisture was heated under reflux in an oil bath from room temperature to 160° in 25 minutes. The dark reaction solution was cooled to 40° and poured, with vigorous stirring, into 200 g. of crushed ice. The resulting cold, viscous mixture was then made basic with 28% aqueous ammonia at 0-5° with constant stirring to break up the dark green semi-solid mass. It was extracted with ether (3 x 150 ml.). The combined ether extract was dried (magnesium sulfate) and evaporated under reduced pressure to yield a solid residue. This was purified through a silica gel column eluting with chloroform to give 7.6 g. (73% yield) of **10a**, m.p. 110-112°; ir (nujol): 2230 cm^{-1} (C≡N); nmr (deuteriochloroform): δ 1.93 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.94 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.87 (1H, d, J = 12 Hz, OCH_2), 5.13 (1H, d, J = 12 Hz, OCH_2) and 6.78-7.36 ppm (7H, m, aromatic).

Anal. Calcd. for $C_{23}H_{21}ClN_2O_3$: C, 67.56; H, 5.18; N, 6.85. Found: C, 67.77; H, 5.51; N, 6.71.

4-(3,4-Dimethoxy-2-hydroxy)phenyl-5,6-dimethylnicotinonitrile (**10b**).

A mixture of 23.5 g. (0.058 mole) of **10a**, 3 g. of 5% palladium-on-calcium carbonate in 300 ml. of methanol was hydrogenated at 4.2 kg/cm^2 at room temperature for 6 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The remaining solid residue was purified through a silica gel column eluting with chloroform to give 15.5 g. (95% yield) of **10b** as a white powder, m.p. 154-156°. An analytical sample was prepared by recrystallization from aqueous ethanol, m.p. 154-156°; ir (nujol): 3450 (OH) and 2280 cm^{-1} (C≡N); nmr (deuteriochloroform): δ 2.17 (3H, s, CH_3), 2.65 (3H, s, CH_3), 3.94 (6H, s, OCH_3), 6.61 (1H, d, J = 9 Hz, aromatic), and 6.87 ppm (1H, d, J = 9 Hz, aromatic).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.35; H, 5.69; N, 9.61.

7,8-Dimethoxy-1,2-dimethyl-5*H*-benzopyrano[3,4-*c*]pyridin-5-one (**9b**).

A mixture of 1.0 g. (0.0035 mole) of **10b** and 10 ml. of polyphosphoric acid was heated at 110-120° for 75 minutes. The reaction solution was cooled and poured onto 200 g. of crushed ice. The cold acid mixture was neutralized with aqueous ammonia and the resulting precipitate collected by filtration. It was recrystallized from aqueous dioxane to give 0.8 g. (80% yield) of **9b** as white needles, m.p. 188-189°; ir (nujol): 1730, 1600, 1540, 1125, 1100, 1000 and 775 cm^{-1}. The infrared absorption spectrum was almost superimposible with that of the corresponding chloro compound **9a**, m.p. 215-216°.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.40; H, 5.56; N, 4.64.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5,6-dimethylnicotinonitrile (**10c**).

A stirred mixture of 28.4 g. (0.1 mole) of **10b**, 15 g. (0.12 mole) of benzyl chloride and ethanolic sodium ethoxide (prepared from 2.5 g. of sodium and 200 ml. of absolute ethanol) protected from moisture was refluxed for 8 hours. The reaction mixture was cooled, neutralized with glacial acetic acid, and evaporated to dryness under reduced pressure. The residual solid was triturated with 100 ml. of water and the mixture was extracted with chloroform (3 x 100 ml.). Evaporation of the chloroform extract yielded a semi-solid residue. This was chromatographed through a silica gel column eluting with chloroform to give 27.8 g. (74% yield) of pure **10c**, m.p. 113-115°; ir (nujol): 2235 cm^{-1} (C≡N); nmr (deuteriochloroform): δ 1.95 (3H, s, CH_3), 2.54 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.81 (1H, d, J = 12 Hz, OCH_2), 5.06 (1H, d, J = 12 Hz, OCH_2), 6.75-7.25 (7H, m, aromatic) and 8.57 ppm (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 74.26; H, 5.84; N, 7.53.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5,6-dimethylnicotinamide (**11**).

To a solution of 20 g. of sodium hydroxide, 100 ml. of water and 150 ml. of ethanol was added 5.0 g. (0.0134 mole) of **10c**. The mixture was refluxed, with stirring, for 4 hours. It was cooled, poured into 800 ml. of water, and acidified with 30 ml. of glacial acetic acid. The resulting milky mixture was kept at room temperature for 20 hours to allow precipitation of the product as a white crystalline solid. The product was collected by filtration, washed repeatedly with water, and purified through a silica gel column. Chloroform was initially used to remove the impurity and the product was collected by eluting with acetone to give 4.6 g. (88% yield) of the amide **11**, m.p. 163-165°. Recrystallization from a mixture of ethanol and hexane yielded analytically pure sample, m.p. 164-165°; ir (nujol): 3460 (NH_2) and 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.80 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.80 (6H, s, OCH_3), 4.69 (1H, d, J = 12 Hz, OCH_2), 4.94 (1H, d, J = 12 Hz, OCH_2), 5.45-5.80 (2H, broad, NH_2) and 6.50-7.15 ppm (7H, m, aromatic).

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.13; H, 6.38; N, 7.10.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-2,3-dimethyl-5(methoxycarbonylamino)pyridine (**12**).

To a methanol solution of sodium methoxide (prepared from 0.5 g. of sodium and 40 ml. of methanol) was added 1 g. (0.0026 mole) of **11**. The resulting solution was cooled in an ice-water bath. To the cooled solution was added, with stirring and exclusion from moisture, 1 g. of bromine in one portion. The solution was stirred for 30 minutes with continuous external cooling followed by refluxing on a steam bath for 30 minutes. It was again cooled, neutralized with glacial acetic acid, and evaporated to dryness under reduced pressure. The residual solid was triturated with water and collected by filtration. Recrystallization from ethanol gave 0.7 g. (65% yield) of the urethane **12**, m.p. 109-110.5°; ir (nujol): 3340 (NH) and 1750 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.85 (3H, s, CH_3), 2.47 (3H, s, CH_3), 3.63 (3H, s, CO_2CH_3), 3.94 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.89 (2H, s, OCH_2), 6.24 (1H, s, NH), 6.75-7.39 (7H, m, aromatic) and 8.97 ppm (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.10; H, 6.34; N, 6.35.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5-cyano-3-methyl-2-pyridinecarboxaldehyde (**13c**).

A stirred mixture of 12 g. (0.032 mole) of **10c** and 12 g. of selenium dioxide in 150 ml. of glacial acetic acid was refluxed for 3 hours. The hot reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was taken up with a small amount of chloroform, washed with water, dried (magnesium sulfate), chromatographed through a silica gel column and eluted with chloroform. The chloroform solution was evaporated and the residue was triturated with water to remove the remaining acetic acid. The solid was collected by filtration and dried at room temperature to give 10 g. (80% yield) of **13c**. This material was adequate for the preparation of **14a** without further purification. An analytical sample was prepared by recrystallization from a mixture of methanol and hexane, m.p. 113-115°; ir (nujol): 2250 (C≡N) and 1725 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.33 (3H, s, CH_3), 3.98 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.96 (1H, d, J = 12 Hz, OCH_2), 4.98 (1H, d, J = 12 Hz, OCH_2), 6.60-7.40 (7H, m, aromatic), 8.74 (1H, s, pyridine aromatic) and 10.18 ppm (1H, s, CHO).

Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.22; H, 5.45; N, 7.08.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5-cyano-3-methyl-2-pyridinecarboxaldehyde Ethylene Glycol Acetal (**14a**).

To a solution of 10 g. (0.0258 mole) of **13c** in 175 ml. of benzene was added 2.5 g. (0.0403 mole) of ethylene glycol and 0.5 g. of *p*-toluenesulfonic acid monohydrate. The solution was refluxed and the water removed by means of a Dean-Stark trap. After water formation had ceased (*ca.* 4 hours) the benzene solution was washed with aqueous sodium bicarbonate. The benzene layer was separated, dried (magnesium sulfate), and evaporated *in vacuo* to yield an oil. Crystallization from ether gave 9.8 g. (88% yield) of the acetal **14a** as pale yellow prisms, m.p. 111-113°. An analytical sample was prepared by column chromatography using petroleum ether (b.p. 62-69°)-ether stepwise elution followed by recrystallization from methylene chloride-ether to give the acetal **14a** as small white prisms, m.p. 113-115°; ir (nujol); 2225 cm^{-1} (C≡N); nmr (deuteriochloroform): δ 2.14 (3H, s, CH_3), 3.94 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.17 (4H, m, C_2H_4), 4.87 (1H, d, J = 12 Hz, OCH_2), 5.07 (1H, d, J = 12 Hz, OCH_2), 6.08 (1H, s, acetal), 6.74-7.39 (7H, m, aromatic), and 8.67 (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.61; H, 5.64; N, 6.44.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5-carbamoyl-3-methyl-2-pyridinecarboxaldehyde Ethylene Glycol Acetal (**14b**).

To a solution of 2 g. of sodium hydroxide, 10 ml. of water and 15 ml. of ethanol was added 2 g. (0.00463 mole) of **14a**. The mixture was refluxed, with stirring, for 4 hours. The reaction solution was cooled, neutralized with glacial acetic acid, and poured into 150 ml. of water. The resulting mixture was allowed to stand at room temperature overnight to ensure complete precipitation of the product. The solid was collected by filtration and purified through a silica gel column using chloroform as the eluent to give, after recrystallization from ethanol-hexane, 1.4 g. (66% yield) of **14b** as a hemihydrate, m.p. 158-159°; ir (nujol): 3660 (NH_2), 3850 (NH_2), 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.08 (3H, s, CH_3), 3.92 (6H, s, OCH_3), 4.0-4.16 (4H, m, C_2H_4), 4.84 (1H, d, J = 12 Hz, OCH_2), 5.10 (1H, d, J = 12 Hz, OCH_2), 5.57-5.78 (2H, broad, NH_2), 6.10 (1H, s, acetal), 6.75-7.33 (7H, m, aromatic) and 8.71 ppm (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{25}H_{26}N_2O_6 \cdot \frac{1}{2}H_2O$: C, 65.35; H, 5.92; N, 6.10. Found: C, 65.55; H, 6.02; N, 5.87.

4-(2-Benzyloxy-3,4-dimethoxy)-5-methoxycarbonylamino-3-methyl-2-pyridinecarboxaldehyde Ethylene Glycol Acetal (**14c**).

To 1.0 g. (0.0022 mole) of **14b** in methanolic sodium methoxide (prepared from 0.5 g. (0.0217 g.-atom) of sodium and 40 ml. of methanol) cooled in an ice-water bath was added with vigorous stirring, 1.0 g. (0.00625 mole) of bromine in one portion. The resulting solution was stirred for 30 minutes at 0°, then refluxed on a steam bath for another 30 minutes. It was cooled, neutralized with glacial acetic acid, and evaporated to dryness under reduced pressure. The solid residue was purified through a silica gel column using chloroform as the eluent to give, after recrystallization from ethanol, 0.7 g. (67% yield) of **14c**, m.p. 168.5-171°; ir (nujol): 3500 (NH) and 1750 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.03 (3H, s, CH_3), 3.63 (3H, s, CO_2CH_3), 3.93 (6H, s, OCH_3), 4.00-4.30 (4H, m, C_2H_4), 4.88 (2H, s, OCH_2), 6.02 (1H, s, acetal), 6.18 (1H, s, NH), 6.67-7.45 (7H, m, aromatic) and 8.78 ppm (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 65.28; H, 6.03; N, 5.80.

Compound **14c** was also prepared from 10 g. of **14a** without isolation and purification of the intermediate **14b** to give 8 g. (72% yield). The material is pure enough for the preparation of **13a**.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5-methoxycarbonylamino-3-methyl-2-pyridinecarboxaldehyde (**13a**).

To a solution of 50 ml. of acetone and 10 ml. of water was added 4.7 g. (0.0098 mole) of **14c** and 0.5 g. (0.0026 mole) of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 8 hours and allowed to cool. The solution was evaporated *in vacuo* and the residue dissolved in 150 ml. of chloroform. The chloroform solution was washed with aqueous sodium bicarbonate, dried (magnesium sulfate) and decolorized with charcoal. It was then filtered and evaporated *in vacuo* to yield an oil. Crystallization from ether gave 3.9 g. (91% yield) of the aldehyde **13a** as off-white needles, m.p. 123-126°. An analytical sample was prepared by recrystallization from a mixture of methylene chloride and ether after treatment with decolorizing charcoal, m.p. 127-129°; ir (nujol): 3450 (NH), 1750 (C=O), 1715 cm^{-1} (C=O),

nmr (deuteriochloroform): δ 2.23 (3H, s, CH_3), 3.70 (3H, s, CO_2CH_3), 3.97 (6H, s, OCH_3), 4.95 (2H, s, CH_2), 6.37 (1H, s, NH), 6.75-7.25 (7H, *m*, aromatic), 9.42 (1H, s, pyridine aromatic) and 10.16 ppm (1H, s, CHO).

Anal. Calcd. for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.44; H, 5.52; N, 6.59.

4-(2-Benzyloxy-3,4-dimethoxy)phenyl-5-methoxycarbonylamino-3-methyl-2-pyridinecarboxylic Acid (**15a**).

To a stirred slurry of a freshly prepared mixture of silver oxide in water [prepared by combining a solution of 8.94 g. (0.0525 mole) of silver nitrate in 25 ml. of water and a solution of 4.2 g. (0.105 mole) of sodium hydroxide in 50 ml. of water] was added, over a period of 15 minutes, a mixture of 10.7 g. (0.0244 mole) of **13a** in 120 ml. of 95% ethanol. After the mixture was stirred for 1.5 hours, it was filtered and the filter cake washed with a small amount of water. The combined filtrate and washing solution was neutralized by the addition of 4.0 g. (0.067 mole) of glacial acetic acid. The solution was evaporated *in vacuo* and the residue extracted with chloroform (3 x 50 ml.). The chloroform extract was dried (magnesium sulfate) and evaporated to give an oil. Crystallization from ether gave 9.8 g. (88% yield) of the acid **15a** as a white amorphous solid, m.p. 165-167°. An analytical sample was prepared by recrystallization from a mixture of methylene chloride and ether, m.p. 165-167°; ir (nujol): 3340 and 1745 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.33 (3H, s, CH_3), 3.72 (3H, s, CO_2CH_3), 3.97 (6H, s, OCH_3), 4.96 (2H, s, OCH_2), 6.31 (1H, s, NH), 6.71-7.33 (7H, m, aromatic), and 9.20 ppm (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{24}H_{24}N_2O_7$: C, 63.72; H, 5.35; N, 6.19. Found: C, 63.49; H, 5.48; N, 6.13.

5-Amino-4-(2-benzyloxy-3,4-dimethoxy)phenyl-3-methyl-2-pyridinecarboxylic Acid (**15b**).

To 50 ml. of 50% aqueous ethanol containing 2.5 g. (0.0625 mole) of sodium hydroxide was added 2.5 g. (0.00553 mole) of **15a**. The solution was refluxed on a steam bath for 30 minutes, allowed to cool, and filtered. The dark solution was diluted with 100 ml. of water and acidified with 4 g. of glacial acetic acid. The white amorphous precipitate was collected by filtration, washed with water, and air dried to give 1.9 g. (87% yield) of the amino acid **15b**, m.p. 196-197°. An analytical sample was prepared by recrystallization from a mixture of methylene chloride and methanol to yield **15b** as a white granular solid, m.p. 198-200°; ir (nujol): 3550, 1655 and 1645 cm^{-1}, nmr (deteriochloroform-DMSO-d_6): δ 2.25 (3H, s, CH_3), 3.92 (6H, s, OCH_3), 4.86 (2H, s, OCH_2), 6.63-7.43 (7H, m, aromatic), and 8.10 ppm (1H, s, pyridine aromatic).

Compound **15b** can also be prepared in two steps from **13a** in 93% yield without isolation of the intermediate.

Anal. Calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.18; H, 5.72; N, 7.00.

5-Amino-4-(3,4-dimethoxy-2-hydroxy)phenyl-3-methyl-2-pyridinecarboxylic Acid (**3**).

A mixture of 4.4 g. (0.0112 mole) of **15b** in 250 ml. of absolute ethanol was hydrogenated at 3.5 kg/cm^2 in the presence of 0.5 g. of 10% palladium-on-charcoal. The mixture was filtered. The filter cake was slurried with 200 ml. of methanol-methylene chloride (1:1) and filtered again. The combined filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from aqueous methanol to give 3.3 g. (97% of yield) of **3** as beige prisms, m.p. 210-215° dec. An analytical sample was prepared by recrystallization from aqueous ethanol, m.p. 213-215° dec; ir (nujol): 3500, 3400, 3300, 2600 (broad), 1650 (sh) and 1615 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): δ 2.33 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.44 (broad, deuterium oxide exchangeable), 6.64 (2H, m, aromatic), and 8.01 ppm (1H, s, pyridine aromatic).

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.20. Found: C, 59.01; H, 5.50; N, 9.14.

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