Streptonigrin and Related Compounds. II (1). Synthesis of the C-Ring Precursors

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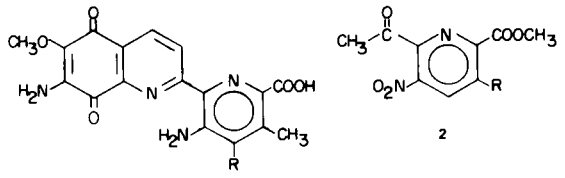
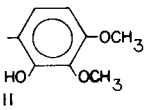
Synthesis of the tricyclic analogue **1b** of the antitumor antibiotic streptonigrin **1a** by the application of Friedlander condensation required a substituted 2-acetylpyridine (**2**) as the precursor for the C-ring. A practical, 8-step sequence was devised for its synthesis starting from 2,5-lutidine.

In Part I, methods based on the Friedlander condensation for the synthesis of simpler tricyclic analogues of the autitumor antibiotic, streptonigrin (**1a**) were described with emphasis on the generation of the aminoquinone system. Synthesis of the destrioxyphenylstreptonigrin (**1b**) by the same general scheme would require the ketone **2** (R = CH_3) as the precursor for ring C. This paper describes the synthesis of **2** and related compounds.

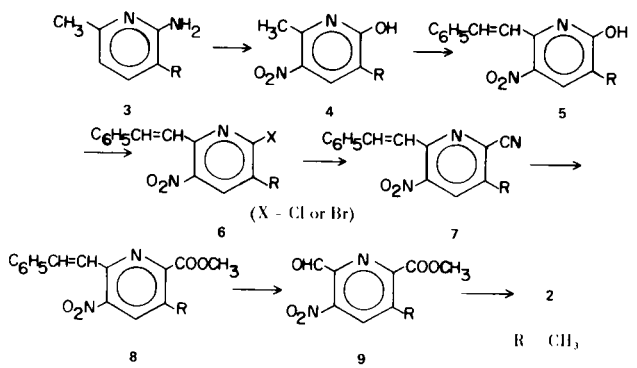


1a, R = 

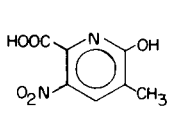
1b, R = H

The following scheme was developed for the synthesis of the ketone **2**.

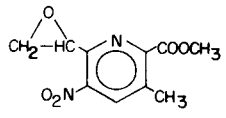
Scheme I



The scheme started with 6-amino-2,5-lutidine (**3**, 3a,b) which on treatment with nitrous acid followed by nitration gave, in one step, 6-hydroxy-3-nitro-2,5-lutidine (**4**). The objective was to selectively oxidize **4** to the acid **10** and convert the carboxyl to a methyl keto function. However, selective oxidation of **4** was not successful and even the styryl derivative **5** gave only **4** as the major product with alkaline permanganate (4). Hence, **5** was converted to the bromo derivative (**6**, X = Br, 5) which gave the nitrile **7** on reaction with cuprous cyanide (6). The chloro derivative (**6**, X = Cl, 7) was unreactive. Reaction of **7** with methanolic sulfuric acid gave the 6-carbomethoxy-5-methyl-3-nitro-2-styrylpyridine **8**. Oxonolysis of **8** followed by reduction of the oxonide gave the picolinaldehyde **9**. When **9** was treated with diazomethane (8) a 3:1 mixture of the ketone **2** and the epoxide **11** was formed which were separated by chromatography.

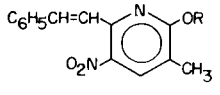


10

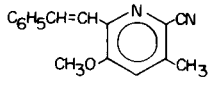


11

Attempted saponification of **7** with aqueous ethanolic base gave **12a** by the displacement of the nitrile function by an ethoxyl. This was confirmed by the formation of **12b** from **7** by the action of aqueous methanolic base and from **5** by methylation. In the reaction **7** → **12b**, a second product, **13** was also formed in which a nitro group was displaced by a methoxyl. These two represent examples of unusual displacements in the pyridine series (9).



12a, R = C_2H_5
12b, R = CH_3

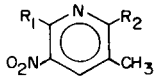


13

For the ozonolysis of 2-vinylpyridine, Callighan and Wilt (10) postulated cleavage to picolinaldehyde and methylene peroxide zwitterion. We observed that, in the present case, the picolinaldehyde component retained the peroxidic function since an unstable peroxide could be separated by chromatography, and it gave **9** on reduction. We also observed that ascorbic acid was a satisfactory reagent for the oxonolytic preparation of aldehydes, especially if they were readily solvent-extractable.

For the success of the reaction **9** → **2** with diazomethane, two factors must be considered. The aldehyde readily formed a hydrate which either failed to react with diazomethane or gave unexpected by-products. The reaction was also solvent-dependent; in chloroform, a complex mixture, in which **2** was only 20%, was formed while in methanol a 3:1 mixture of **2** and **11** resulted.

Using the same general approach, four analogues of the ketone **2** (R = CH_3) which would serve to generate corresponding analogues of **1b** were also prepared. These are the 6-bromoketone **15**, the 6-cyanoketone **18**, the 6-methoxyketone **21** and the ketone **2** (R = H).

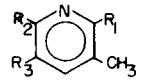


14, R_1 = CHO, R_2 = Br; **15**, R_1 = $COCH_3$, R_2 = Br; **16**, R_1 = CH_2—CH, R_2 = Br;
O

17, R_1 = CHO, R_2 = CN; **18**, R_1 = $COCH_3$, R_2 = CN; **19**, R_1 = CH_2—CH, R_2 = CN;
O

20, R_1 = CHO, R_2 = OCH_3; **21**, R_1 = $COCH_3$, R_2 = OCH_3.

As an alternative to Scheme 1, conversion of ethyl-6-hydroxy-2,5-dimethylnicotinate (**22**, 11) to the amide followed by the Hofmann degradation to the amine **23** was studied. With methanolic ammonia **22** gave not the amide but the methyl ester. Although **22** could be converted to the amine **23** *via* the hydrazide **24** and the azide **25**, subsequent efforts at oxidation were hampered by the instability of **23**. Finally, **22** was saponified and the acid **26** converted to the chloroamide **27**. Hofmann degradation and acetylation gave **28** which on selective oxidation gave **29**. The methyl ester **30**, however, could not be made to undergo Claisen condensation with ethyl acetate and sodium to form the desired β-keto ester.



22, R_1 = OH, R_2 = CH_3, R_3 = COOEt; **23**, R_1 = OH, R_2 = CH_3, R_3 = NH_2;
24, R_1 = OH, R_2 = CH_3, R_3 = $CONHNH_2$; **25**, R_1 = OH, R_2 = CH_3, R_3 = N_3;
26, R_1 = OH, R_2 = CH_3, R_3 = COOH; **27**, R_1 = Cl, R_2 = CH_3, R_3 = $CONH_2$;
28, R_1 = Cl, R_2 = CH_3, R_3 = $NHCOCH_3$; **29**, R_1 = Cl, R_2 = COOH, R_3 = $NHCOCH_3$;
30, R_1 = Cl, R_2 = $COOCH_3$, R_3 = $NHCOCH_3$.

EXPERIMENTAL

Melting points were taken using a Thomas-Hoover apparatus and were uncorrected. Spectra were obtained using the following instruments: Beckman Model 25 (uv), Beckman Acculab 3 (ir), Varian A 60A (nmr) and Hitachi-Perkin Elmer SMU-6E (mass spectra). Thin layer chromatography (tlc) was performed using Merck silica gel (HF 254 + 366) without a binder. Column chromatography was carried out using a 1:1 mixture of silicic acid (Mallinckrodt, 275-325 mesh) and cellulose powder (Brown & Co.), using benzene as the solvent with increasing concentrations of acetone in benzene as eluant, or alternatively, starting with 1:1 benzene-hexane and gradually changing to benzene.

6-Amino-2,5-lutidine (3).

The following is an improved procedure based on that of Albert and Willet (3): A mixture of sodium amide (24 g., Apache Chem. Co.) dimethylaniline (90 ml.) and 2,5-lutidine (45 ml.) was stirred at 140-145° for 4 hours and then at 165-175° for 24 hours. If tlc showed the reaction to be incomplete, another 10 g. of sodium amide was added and the heating continued for another 24 hours. The cooled reaction mixture was treated with ice (200 g.) and 2 *N* sodium hydroxide (200 ml.) and the mixture stirred until all the lumps were digested. Sodium hydroxide (50 g.) and benzene (300 ml.) were added and, after the pellets dissolved, the mixture was filtered through a bed of Hyflo Supercel (Johns Manville Co.). The tarry solid was washed with 2 x 100 ml. portions of hot benzene and the combined clear benzene filtrate and washes were concentrated to about half the original volume. It was then extracted with 100 ml. portions of 5% aqueous acetic acid until the tlc of the extracts showed the absence of aminolutidine. The combined extracts were freed from tarry solids and concentrated to dryness. The crystalline acetate salt was recrystallized from benzene; yield 60 g. (80%); m.p. 85-87°.

Anal. Calcd. for $C_7H_{10}N_2 \cdot C_2H_4O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.01; H, 8.05; N, 15.65.

6-Hydroxy-3-nitro-2,5-lutidine (4).

To a slurry of **3** (40 g.) in dilute sulfuric acid (80 ml. of acid and 60 ml. of water) was added, dropwise, aqueous sodium nitrite (19 g. in 40 ml. of water) with stirring at 30-35° during 2 hours. The mixture was heated at 70° for 30 minutes and cooled. Concentrated nitric acid (28 ml.) was added and the temperature cautiously raised to 55°. After this, a vigorous reaction ensued with much fuming and foaming and with the temperature rising to 110°. During this period, the flask was shaken by hand and held over an ice-water bath for immediate chilling, if necessary. As the temperature dropped below 80°, ice was added and the crystalline solid filtered. It was recrystallized from ethanol; yield, 18 g. (53%); m.p. 232-233°; nmr (deuteriochloroform): τ 1.70, s, 1H; τ 7.15, s, 3H; τ 7.75, s, 3H.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.76; N, 16.66. Found: C, 49.76; H, 4.70; N, 16.38.

6-Hydroxy-5-methyl-3-nitro-2-styrylpyridine (5).

A mixture of **4** (50 g.) and benzaldehyde (50 ml.) in 2 *N* aqueous potassium hydroxide (250 ml.) was boiled under reflux for 16-20 hours. During this period, a yellow crystalline solid began to separate. The cooled mixture was diluted with water (250 ml.) and acidified to *p*H 12. The yellow solid was filtered and washed with 25% aqueous ethanol. It was crystallized from pyridine; yield, 51 g. (70%); m.p. 290-292°; nmr (trifluoroacetic acid): τ 1.65, s, 1H; τ 2.30 and 2.35, d, 2H; τ 2.40-2.80, m, 5H; τ 7.71, s, 3H.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.87; H, 4.70; N, 10.92.

6-Chloro-5-methyl-3-nitro-2-styrylpyridine (**6**, X = Cl).

One g. of **5** was mixed with phosphorus pentachloride (1 g.) and phosphorus oxychloride (0.5 ml.) and the mixture heated at 110° for 3 hours. Addition of ice and filtration gave the product which was crystallized from ether; yield, 0.75 g. (70%); m.p. 102-103°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.03; Cl, 12.81; N, 10.92. Found: C, 16.51; H, 4.23; Cl, 13.11; N, 10.67.

6-Bromo-5-methyl-3-nitro-2-styrylpyridine (**6**, X = Br).

To 50 g. of **5** in nitrobenzene (100 ml.) was added phosphorus tribromide (30 ml.) and the mixture stirred at 140-145° for 90 minutes. After cooling, ice was added and the product, together with nitrobenzene was extracted with chloroform. The solvent extract was steam-distilled to remove nitrobenzene and the residue taken up in hot benzene and filtered. Concentration of the filtrate to dryness and crystallization from ether gave **6** as a yellow crystalline solid, yield, 44 g. (70%); m.p. 95-97°.

Anal. Calcd. for $C_{14}H_{11}BrN_2O_2$: C, 52.68; H, 3.47; Br, 25.04; N, 8.78. Found: C, 52.90; H, 3.52; Br, 25.36; N, 8.98.

6-Cyano-5-methyl-3-nitro-2-styrylpyridine (**7**).

A solution of **6** (X = Br, 25 g.) in nitrobenzene (100 ml.) was boiled under reflux with cuprous cyanide (12 g.) for 3-4 hours. It was filtered, washed with hot chloroform and the filtrate steam-distilled to remove nitrobenzene. The residue was extracted with hot chloroform, filtered, the filtrate concentrated to dryness and the solid crystallized from ethanol, yield, 17 g. (80%); m.p. 168-170°.

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 68.21; H, 4.05; N, 15.63.

6-Carbomethoxy-5-methyl-3-nitro-2-styrylpyridine (**8**).

To 25 g. of **7** was added methanolic sulfuric acid (2:1, 150 ml.) and the mixture heated at 140-145° in an oil bath for 3 hours. After cooling and addition of ice it was extracted twice with ethyl acetate. To the extract was added ethereal diazomethane until tlc showed the absence of the acid formed as a byproduct. Concentration of the extract and crystallization from ethanol gave **8**; yield, 19 g. (85%); m.p. 132-133°; m.p. (deuteriochloroform): τ 1.75, 2.02; half of a quartet, J = 16 Hz, 1H; τ 1.90, s, 1H; τ 2.22-2.70, m, 6H; τ 5.94, s, 3H; τ 7.44, s, 3H.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.69; N, 9.39. Found: C, 64.20; H, 4.69; N, 19.17.

6-Carbomethoxy-5-methyl-3-nitropicolinaldehyde (**9**).

Ozonized oxygen was bubbled into a suspension of **8** (10 g.) in chloroform (100 ml.) at -40° until tlc showed the absence of **8**. The ozone was displaced by nitrogen and a solution of ascorbic acid (8 g.) in methanol (50 ml.) was added. After 15 minutes (negative starch-iodide test) the mixture was diluted with water (200 ml.) and the chloroform layer concentrated and washed with hexane twice. The residue was crystallized from ether, yield, 5.5 g. (73%); m.p. 80-82°; M^+ 224.

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.21; H, 3.57; N, 12.50. Found: C, 47.95; H, 3.25; N, 12.66.

2-Carbomethoxy-5-methyl-3-nitro-2-acetylpyridine **2** and 6-Carbomethoxy-5-methyl-3-nitro-2,2-pyridyloxirane (**11**).

Ethereal diazomethane was added in small portions to a solution of **9** (5 g.) in 1:1 methanol-chloroform (50 ml.) until tlc showed the absence of starting material. After concentration to near dryness, the oily residue was subjected to chromatography on a silicic acid column (15 g.) in 1:1 benzene-hexane. The first and major band gave **2** as a crystalline solid, recrystallized from ether-hexane, yield, 3.3 g. (60%); m.p. 65-66°; nmr (deuteriochloroform): τ 2.0, s, 1H; τ 5.95, s, 3H; τ 7.31; s, 3H, ir: 1730, 1700, 1540, 1380 cm^{-1}; M^+238.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.26; H, 4.20; N, 11.53.

The second band, eluted with benzene, gave a solid, crystallized from ether, yield 1.1 g. (20%); m.p. 87-88°; nmr (deuteriochloroform): τ 1.80, s, 1H; τ 5.44, 5.49, 5.54, t, J = 3 Hz; τ 6.02, s, 3H; τ 6.75, 6.80, d, J = 3 Hz, 2H; τ 7.39, s, 3H; ir: 1720, 1560, 1380 cm^{-1}; M^+ 238.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.08; H, 4.20; N, 11.66.

6-Ethoxy-5-methyl-3-nitro-2-styrylpyridine (**12a**).

A solution of **7** (1 g.) in ethanol (20 ml.) was stirred with 2 *N* aqueous potassium hydroxide (20 ml.) for 4 hours at room temperature. Dilution with water, extraction with chloroform and concentration of the extract gave a yellow solid crystallized from ethanol, yield, 0.92 g. (90%); m.p. 98-100°; nmr (deuteriochloroform): τ 1.92, s, 1H; τ 2.04, s, 2H; τ 2.16-2.70, m, 5H; τ 5.19, 5.30, 5.42, 5.53, q, 2H; τ 7.70, s, 3H; τ 8.35, 8.47, 8.59, t, 3H.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.84; H, 5.65; N, 9.89.

6-Methoxy-5-methyl-3-nitro-2-styrylpyridine (**12b**).

The above experiment was repeated with methanol instead of ethanol and the product crystallized twice from methanol-ether, yield, 0.82 g. (80%); m.p. 127-129°; nmr (deuteriochloroform): τ 1.99, s, 2H; τ 2.04, s, 2H; τ 2.14-2.87, m, 5H; τ 5.90, s, 3H; τ 7.77, s, 3H.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.61; H, 5.34; N, 10.10.

Alternatively, a solution of **5** (2 g.) in DMF (100 ml.) was treated with a slight excess of diazomethane. Concentration to dryness and crystallization from methanol-ether gave **12b**, yield, 1.6 g. (76%). It was identical with **12b**.

6-Cyano-3-methoxy-5-methyl-2-styrylpyridine (**13**).

In the conversion of **7** to **12b**, the mother liquor from crystallization of **12b** was concentrated to dryness and chromatographed on a silicic acid column in benzene. The first band gave **12b** and the second band gave a colorless crystalline solid, yield, 0.1 g. (10%), m.p. 144-146°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.51; H, 5.65; N, 11.04.

6-Bromo-5-methyl-3-nitropicolinaldehyde (**14**).

Ozonolysis of **6** (X = Br, 3 g.) was carried out as described under **9**. The aldehyde was crystallized from ether, yield, 1.9 g. (83%), m.p. 94-96°.

Anal. Calcd. for $C_7H_5BrN_2O_3$: C, 34.31; H, 2.06; Br, 32.61; N, 11.43. Found: C, 34.56; H, 2.39; Br, 32.28; N, 11.09.

6-Bromo-5-methyl-3-nitro-2-acetylpyridine **15** and 6-Bromo-5-methyl-3-nitro-2,2-pyridyloxirane (**16**).

Reaction of **14** (2 g.) with diazomethane followed by chromatographic separation was as described under **2** and **11**. The ketone **15** was crystallized from ether-hexane, yield, 1.26 g. (60%), m.p. 98-100°.

Anal. Calcd. for $C_8H_7BrN_2O_3$: C, 37.09; H, 2.72; Br, 30.85;

N, 10.80. Found: C, 37.19; H, 2.69; Br, 31.06; N, 10.86.

The epoxide **16** was crystallized from ether, yield, 0.22 g. (10%); m.p. 78-80°.

Anal. Calcd. for $C_8H_7BrN_2O_3$: C, 37.09; H, 2.72; Br, 30.85; N, 10.80. Found: C, 36.87; H, 2.69; Br, 30.64; N, 10.71.

6-Cyano-5-methyl-3-nitropicolinaldehyde (**17**).

Ozonolysis of **7** (10 g.) was carried out as described under **9**. The product crystallized from ether as colorless needles, yield, 5 g. (70%); m.p. 101-103°; nmr (deuteriochloroform): τ -0.05, s, 1H; τ 1.82, s, 1H; τ 7.20, s, 3H; ir: Peaks at 2240, 1720, 1540, 1380 cm^{-1}; M^+ 191.

Anal. Calcd. for $C_8H_5N_3O_3$: C, 50.26; H, 2.64; N, 21.99. Found: C, 49.99; H, 2.71; N, 21.94.

6-Cyano-5-methyl-3-nitro-2-acetylpyridine (**18**) and 6-Cyano-5-methyl-3-nitro-2,2-pyridyloxirane (**19**).

To a solution of **17** (2 g.) in 1:1 chloroform-methanol (50 ml.) was added ethereal diazomethane until tlc showed the absence of starting material. Concentration and chromatography on silicic acid as given under **2** gave the first band as a colorless crystalline solid, yield, 1.28 g. (60%), m.p. 112-113°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.41; N, 20.48. Found: C, 52.60; H, 3.37; N, 20.20.

The second band gave a crystalline solid (ether-hexane), yield, 0.32 g. (15%), m.p. 117-119°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.41; N, 20.48. Found: C, 52.45; H, 3.49; N, 20.56.

6-Methoxy-5-methyl-3-nitropicolinaldehyde (**20**).

Ozonolysis of **12b** (2 g.) in chloroform (25 ml.) was carried out as described under **9**. The aldehyde was crystallized from ether-hexane, yield, 0.55 g., m.p. 105-107°; nmr (deuteriochloroform): τ -0.70, s, 1H; τ 1.97, s, 1H; τ 5.90, s, 3H; τ 7.70, s, 3H.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.01; H, 4.56; N, 15.82.

6-Methoxy-5-methyl-3-nitro-2-acetylpyridine (**21**).

Reaction of **20** (2 g.) with diazomethane was carried out as under **2**. After chromatography, the ketone **21** was crystallized from hexane, yield, 1.3 g. (65%), m.p. 88-90°.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.32. Found: C, 51.49; H, 5.02; N, 13.55.

2-Methyl-3-nitro-6-pyridinol (**4**, R = H).

Nitration of 6-amino-2-picoline (50 g.) was carried out as described by Parker and Shive (12). To the reaction mixture was added aqueous sodium nitrite (39 g. in 100 ml.) dropwise with stirring at 30-35°. After heating for 30 minutes at 70°, ice was added and the solid filtered. This was a mixture of **4**, R = H (75%) and the isomeric 5-nitro compound (25%), yield, 42 g. After two crystallizations from methanol-chloroform **4**, R = H was obtained as a cream-colored crystalline solid, m.p. 230-232° (lit. 230-231°, 12).

6-Hydroxy-3-nitro-2-styrylpyridine (**5**, R = H).

To the mixed nitro compounds from the preceeding experiment (25 g.) was added 2 *N* aqueous potassium hydroxide (250 ml.) and benzaldehyde (25 ml.) and the mixture boiled under reflux for 20 hours. It was cooled, acidified to *p*H 12 and the solid filtered. It was crystallized from pyridine, yield 25 g. (66%); m.p. 255-257°. It was essentially pure 3-nitro isomer.

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.78; H, 4.25; N, 11.22.

6-Bromo-3-nitro-2-styrylpyridine (**6**, R = H, X = Br).

Prepared from **5**, (R = H) by the procedure given under **6** (X = Br), yield, 70%; m.p. 101-102°.

Anal. Calcd. for $C_{13}H_9BrN_2O_2$: C, 51.17; H, 2.97; Br, 26.19; N, 9.17; Found: C, 51.50; H, 3.21; Br, 25.85; N, 9.42.

6-Cyano-3-nitro-2-styrylpyridine (**7**, R = H).

Prepared from **6**, (R = H, X = Br) by the procedure given under **7**, yield, 80%; m.p. 123-124°.

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.92; H, 3.61; N, 16.73. Found: C, 67.11; H, 3.72; N, 16.98.

6-Carbomethoxy-3-nitro-2-styrylpyridine (**8**, R = H).

This was prepared from **7**, (R = H) by the procedure described under **8**, yield, 82%, m.p. 129-130°.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.51; H, 4.43; N, 10.12.

6-Carbomethoxy-3-nitropicolinaldehyde (**9**, R = H).

Prepared by the ozonolysis of **8** (R = H) as described under **9**, yield, 71%, m.p. 203-205°.

Anal. Calcd. for $C_8H_6N_2O_5$: C, 45.72; H, 2.88; N, 13.33. Found: C, 45.95; H, 3.12; N, 13.01.

6-Carbomethoxy-3-nitro-2-acetylpyridine (**2**, R = H).

Reaction of **9**, (R = H) with diazomethane and chromatography as described under **2** gave the ketone as a colorless crystalline solid, yield, 70%, m.p. 67-69°.

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 31.60; N, 12.50. Found: C, 48.41; H, 3.56; N, 12.68.

3-Amino-2,5-dimethyl-6-pyridinol (**23**).

A mixture of **22**, (11, 1 g.) and hydrazine hydrate (2 ml.) was heated at 100° for 16 hours. Addition of water gave the acylhydrazine **24** which was crystallized from ethanol, yield, 0.85 g. (90%), m.p. 272-277°.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.07; N, 23.21. Found: C, 52.84; H, 6.06; N, 22.98.

To a solution of **24** (0.54 g.) in 2 *N* hydrochloric acid (10 ml.) was added, dropwise, aqueous sodium nitrite (0.25 g. in 3 ml.) with cooling (5°). After 30 minutes the solid, **25**, was filtered and crystallized from ethyl acetate, yield, 0.45 g. (85%), m.p. >310°.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.10; H, 4.12; N, 29.50.

The azide **25** 0.4 g.) was heated under reflux with trifluoroacetic acid (2 ml.) for 1 hour. The mixture was concentrated to dryness and the residue shaken with ether and aqueous sodium bicarbonate. The solvent layer gave **23** which was recrystallized from ether-hexane, yield, 0.22 g. (80%), m.p. 227-229°.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 61.01; H, 7.21; N, 20.58.

6-Chloro-2,5-dimethylnicotinamide (**27**).

A mixture of **26** (11, 4 g.) and phosphorus oxychloride (10 ml.) was boiled under reflux for 90 minutes and then concentrated to near dryness. It was taken up in a mixture of chloroform and *t*-butyl alcohol (100 ml. 1:1) and added to *t*-butyl alcohol saturated with ammonia. After 1 hour, concentration to dryness and addition of water gave a solid which was filtered and crystallized from ethyl acetate, yield, 3.7 g. (84%), m.p. 173-175°.

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.32; H, 4.87; Cl, 19.12; N, 15.17. Found: C, 51.98; H, 4.86; Cl, 19.50; N, 15.26.

3-Acetylamino-6-chloro-2,5-lutidine (**28**).

The amide **27** (3 g.) was dissolved in aqueous potassium hypobromite (0.5 g. bromine and 2.67 g. potassium hydroxide in 48 ml. of water) and the solution stirred at 25° for 1 hour and at 70° for 3 hours. It was cooled, acidified with acetic acid and extracted with ether once. The aqueous layer was basified and extracted with ether four times. Concentration of the extract and crystallization from ether-hexane gave **28**, yield, 1.9 g. (76%), m.p. 120-122°; nmr (deuteriochloroform): τ 3.15, s, 1H; τ 6.45, broad, 2H; τ 7.65, s, 3H; τ 7.75, s, 3H; M^+ 184.

Anal. Calcd. for $C_7H_9ClN_2$: C, 53.67; H, 5.65; N, 17.80. Found: C, 53.42; H, 5.89; N, 17.63.

Acetylation of the above amine (1 g.) by heating in acetic anhydride (2 ml.) and triethylamine (0.2 ml.) for 3 hours at 100° gave the *N*-acetyl derivative (**28**) which was crystallized from benzene, yield, 1.05 g. (83%); m.p. 144-146°; nmr (deuteriochloroform): τ 0.90, s, 1H; τ 1.20, s, 1H; τ 7.50, s, 3H; τ 7.68, s, 3H.

Anal. Calcd. for $C_9H_{11}N_2ClO$: C, 54.40; H, 5.54; N, 14.10. Found: C, 54.21; H, 5.41; N, 14.32.

3-Acetylamino-6-chloro-5-methylpicolinic Acid (**29**).

A solution of **28** (0.25 g.) in pyridine (5 ml.) was heated under reflux with 5% aqueous potassium permanganate (20 ml.) added in small portions. The cooled mixture was acidified in presence of sodium bisulfite (2 g.) and extracted with ether. The extract was washed with aqueous sodium bicarbonate and the acidified aqueous layer reextracted with ether. Concentration of the extract gave **29** which was recrystallized from ether, yield, 0.1 g. (60%), m.p. 155-156°; nmr (deuteriochloroform): τ 0.90, s, 1H; τ 1.20, s, 1H; τ 7.50, s, 3H; τ 7.68, s, 3H.

Anal. Calcd. for $C_9H_9ClN_2O_3$: C, 47.28; H, 3.96; N, 12.24. Found: C, 47.42; H, 4.10; N, 12.51.

Esterification of **29** with diazomethane gave **30** which was crystallized from ether, m.p. 133-135°; nmr (deuteriochloroform): τ 0.95, s, 1H; τ 5.95, s, 3H; τ 7.50, s, 3H; τ 7.75, s, 3H.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3$: C, 49.48; H, 4.53; N, 11.54. Found: C, 49.28; H, 4.49; N, 11.41.

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