Synthesis of 2-Aza Analog of Rosoxacin

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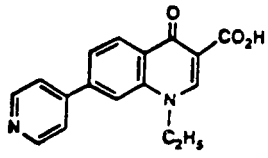
Diazotization of 2-nitro-4-(4-pyridinyl)aniline (**4**) in hydrobromic acid gave the corresponding bromo derivative **5** which was treated with cuprous cyanide to give the benzonitrile derivative **6** which in turn was converted to 2-nitroacetophenone derivative **9**. Reduction of **9** followed by diazotization of the resulting amine **10** gave 7-(4-pyridinyl)cinnolin-4(1*H*)-one (**11**) which was subsequently converted to 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)cinnoline-3-carboxylic acid (**14**) in three steps.



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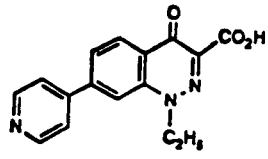

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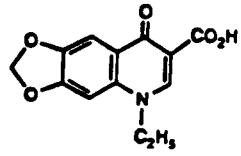

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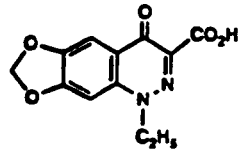

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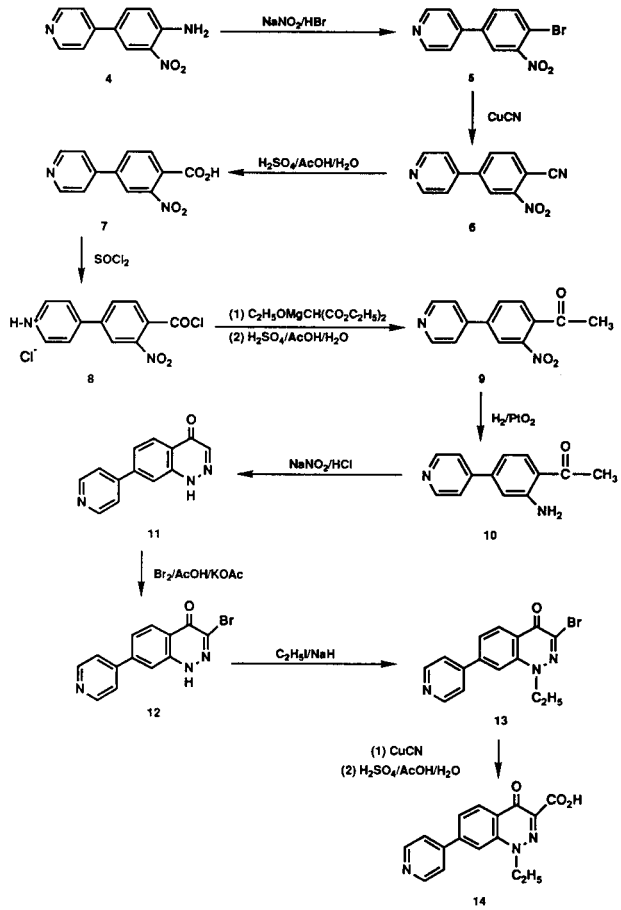
Rosoxacin (**1**) [1] and oxolinic acid (**2**) [2] are both quinolone antibacterial agents. Oxolinic acid (**2**) and its 2-aza analog cinoxacin (**3**) were shown to have similar antibacterial properties [3]. This discovery prompted the synthesis of **14**, the 2-aza analog of rosoxacin.



The cinnolin-4(1*H*)-one ring system has been constructed by the Borsche-Herbert method [4] which involves the intramolecular coupling of the diazonium cation with an acyl enolate anion. The synthesis of **14** was accomplished *via* the ten step sequence depicted in the flow chart, and all the steps except two were accomplished in greater than 75% yield.

Results and Discussion.

Diazotization of amine **4** [5] in aqueous hydrobromic acid gave bromo compound **5**. The activated bromo group of **5** was readily replaced by a cyano group upon treatment with cuprous cyanide to give benzonitrile derivative **6**. The hydrolysis of **6** with aqueous sulphuric acid yielded the corresponding acid **7** which was converted to acid chloride **8** by the reaction of thionyl chloride. The acid chloride **8** was reacted with diethyl ethoxymagnesiummalonate [6] and the resulting crude diethyl acylmalonate was hydrolysed and decarboxylated [7] by heating in a mixture of aqueous sulphuric acid and acetic acid to give 2-nitroacetophenone derivative **9** in 47% yield accompanied by 30% recovered starting acid **7**. Catalytic reduction of **9** gave the corresponding amine **10** which upon diazotization in concentrated aqueous hydrochloric acid led to the formation of cinnolone **11**. The structure of **11** is supported by its ^{1}H nmr spectrum which shows a new aromatic proton in the multiplet at δ 9.10 and the absence of the acetyl group. Bromination of **11** in the presence of potassium acetate in acetic acid yielded bromo compound **12**. The substitution of bromine in 3-position is supported by the ^{1}H nmr spectrum which shows the absence of the 3-H proton. The sodium salt of **12** was alkylated with ethyl iodide to give bromocinnolone **13**. Treatment of **13** with cuprous cyanide, followed by hydrolysis of the resulting

nitrile with aqueous sulphuric acid gave **14** in 33% yield.

In contrast to cinnoxacin (**3**), **14** has no antibacterial activity.

EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The ^1H nmr spectra were obtained in deuteriotrifluoroacetic acid, unless indicated otherwise, on a Varian HA-100 spectrometer using tetramethylsilane as the internal standard, and chemical shifts are reported in parts per million and are given in δ units. Infrared spectra were obtained on a Perkin-Elmer 457 spectrophotometer.

4-(4-Bromo-3-nitrophenyl)pyridine (**5**).

A stirred slurry of amine **4** [5] (34 g, 0.16 mole) and 48% aqueous hydrobromic acid (90 ml) cooled in an ice bath was treated with a solution of sodium nitrite (12.3 g, 0.31 mole) in water (45 ml) over a period of 45 minutes below 5°. The resulting mixture was further stirred in an ice bath for 2.5 hours, left at room temperature overnight and then heated on a steam bath for 1 hour. The orange mixture thus obtained was cooled in an ice bath and neutralized by treating with 10% aqueous potassium carbonate. The resulting orange precipitate was collected, washed with water, and recrystallized from ethanol to give 34 g (77%) of light orange crystals, mp 116-118°; ^1H nmr: δ 8.96 (d, J = 6 Hz, 2H, pyridine 2,6-H), 8.45 (m, 3H), 8.05 (m, 2H).

Anal. Calcd. for $C_{11}H_7N_2O_2Br$: C, 47.34; H, 2.53; N, 10.04. Found: C, 47.61; H, 2.53; N, 10.15.

2-Nitro-4-(4-pyridinyl)benzonitrile (**6**).

A stirred mixture of bromo compound **5** (142 g, 0.51 mole), cuprous cyanide (67 g, 0.77 mole), and DMF (500 ml) was heated under reflux for 3 hours and then poured into water (1 l). The resulting mixture was stirred for 30 minutes. The tan precipitate was collected and added to a stirred solution of concentrated aqueous ammonia (1 l) and ethylenediamine (100 ml). The resulting mixture was stirred for 2 hours and then extracted with chloroform (5 x 500 ml). The combined chloroform extracts were concentrated and the residual solid was recrystallized from ethanol to yield 95.6 g (83%) of a tan solid, mp 206-208°; ir (potassium bromide): ν max 2230 cm^{-1} (CN); ^1H nmr: δ 9.10, 8.55 (A_2B_2, J = 6 Hz, 4H, C_5H_4N), 8.95 (m, 1H), 8.43 (m, 2H).

Anal. Calcd. for $C_{12}H_7N_3O_2$: C, 64.00; H, 3.13; N, 18.66. Found: C, 63.81; H, 3.15; N, 18.60.

2-Nitro-4-(4-pyridinyl)benzoic Acid (**7**).

To a stirred mixture of nitrile **6** (104.8 g, 0.46 mole) and water (500 ml) was added concentrated sulphuric acid (500 ml). The resulting solution was heated in an oil bath at 115-120° for 28 hours, cooled in an ice bath, and neutralized by treating with concentrated aqueous ammonia. The resulting yellow precipitate was collected, washed with water and dried to afford 86.2 g (76%) of **7**, mp 324-327°; ir (potassium bromide): ν max 1730 cm^{-1} (COOH); ^1H nmr: δ 9.05 (d, J = 6 Hz, 2H, pyridine 2,6-H), 8.52 (m, 3H), 8.30 (m, 2H).

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 58.97; H, 3.34; N, 11.48.

2-Nitro-4-(4-pyridinyl)benzoyl Chloride Hydrochloride (**8**).

A stirred mixture of acid **7** (86 g, 0.35 mole) and thionyl chloride (500 ml) was heated under reflux for 5 hours and then cooled to room temperature. The resulting mixture was diluted with methylene chloride (300 ml), and the pale yellow product was collected, washed with methylene chloride and dried to yield 105.2 g (100%) of **8**, mp >225° dec.

Anal. Calcd. for $C_{12}H_7N_2O_3Cl$·HCl: C, 48.19; H, 2.70; N, 9.37. Found: C, 47.89; H, 2.52; N, 9.18.

1-[2-Nitro-4-(4-pyridinyl)phenyl]ethanone (**9**).

To mechanically stirred mixture of diethyl ethoxymagnesiummalonate [6] prepared from [magnesium (22 g, 0.9 mole), diethyl malonate (140 ml, 0.9 mole), ethanol (80 ml) and ether (500 ml)] and ether (500 ml) was added acid chloride **8** (105 g, 0.35 mole) in small portions over 30 minutes. The resulting mixture was heated under reflux overnight. The resulting purple solid product was collected, washed with ether, and added to a stirred mixture of chloroform (1 l) and concentrated aqueous ammonium chloride solution (300 ml). The purple color disappeared and the mixture separated into two layers. The organic layer was separated and concentrated under vacuum to give 135.2 g of a yellow solid. To this solid was added a solution of acetic acid (120 ml), water (80 ml), and concentrated sulphuric acid (15 ml). The resulting mixture was heated under reflux for 6 hours and then most of the acetic acid was removed under reduced pressure. The oily residue was diluted with water (300 ml) and treated with concentrated aqueous ammonia until strongly basic. The oily product was extracted with chloroform (3 x 300 ml). The combined extracts were dried (magnesium sulfate) and concentrated to give a semisolid which was crystallized from 2-propanol to afford 40.2 g (47%) of light brown prisms, mp 122-124°; ^1H nmr (deuteriochloroform): δ 8.80-7.50 (m, 7H), 2.61 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.58; H, 4.36; N, 11.58.

The aqueous layer was acidified with concentrated hydrochloric acid and the resulting yellow precipitate was collected to yield 25.3 g (30%) of the starting acid **7**.

1-[2-Amino-4-(4-pyridinyl)phenyl]ethanone (**10**).

A mixture of nitro compound **9** (37 g, 0.16 mole), ethanol (300 ml), and platinum oxide (500 mg) was reduced on a Parr hydrogenator. The catalyst was removed and the filtrate was concentrated under reduced pressure. The yellow solid residue was crystallized from ethanol to give 27.3 g (80%) of **10**, mp 140-142°; ^1H nmr: δ 9.02 (d, J = 6 Hz, 2H, pyridine 2,6-H), 8.46 (m, 3H), 8.25 (m, 2H), 2.96 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.25; H, 5.73; N, 13.11.

7-(4-Pyridinyl)cinnolin-4(1*H*)-one (**11**).

To a stirred mixture of amine **10** (27 g, 0.13 mole) and concentrated hydrochloric acid (110 ml) cooled in an ice bath was added a solution of sodium nitrite (14 g, 0.2 mole) in water (30 ml) over 45 minutes below 2°. The resulting reaction mixture was further stirred in an ice bath for 2 hours, at room temperature overnight, and finally concentrated under reduced pressure. The residue was neutralized by treating with aqueous sodium acetate. The resulting tan product was collected and recrystallized from DMF

to give 21.8 g (77%) of **11**, mp 281-283°; ^{1}H nmr: δ 9.10 (m, 3H, 3-H and pyridine 2,6-H), 8.82 (m, 2H), 8.60 (m, 2H), 8.36 (m, 1H).

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 70.13; H, 4.21; N, 19.05.

3-Bromo-7-(4-pyridinyl)cinnolin-4(1*H*)-one (**12**).

A stirred mixture of cinnolone **11** (34.7 g, 0.1 mole), potassium acetate (18 g, 0.18 mole), and acetic acid (250 ml) was heated to reflux and then treated with a solution of bromine (24 g, 0.15 mole) in acetic acid (50 ml) over a 2 hour period. The resulting light yellow mixture was concentrated under reduced pressure. The residue was washed with water and recrystallized from DMF to yield 35.8 g (76%) of tan crystals, mp 303-305°; ^{1}H nmr: δ 9.06 (d, J = 6 Hz, 2H, pyridine 2,6-H), 8.60 (m, 4H), 8.12 (m, 1H).

Anal. Calcd. for $C_{13}H_8N_3OBr$: C, 51.68; H, 2.67; N, 13.91. Found: C, 51.86; H, 2.58; N, 14.05.

3-Bromo-1-ethyl-7-(4-pyridinyl)cinnolin-4(1*H*)-one (**13**).

A mixture of bromocinnolone **12** (5.5 g, 18 mmoles), 50% sodium hydride oil dispersion (1 g, 21 mmoles), and DMF (50 ml) was stirred for 30 minutes and then ethyl iodide (1.7 ml, 22 mmoles) was added dropwise. The resulting mixture was further stirred for 2 hours and then concentrated to dryness under reduced pressure . The residue was first washed with hexane to remove oil (from sodium hydride oil dispersion) and then slurried in water. The product was collected and recrystallized from 2-propanol to give 4.5 g (76%) of tan crystals of **13**, mp 193-194°; ^{1}H nmr: δ 9.03 (d, J = 6 Hz, 2H, pyridine 2,6-H), 8.80 (m, 1H), 8.52 (m, 3H), 8.12 (m, 1H), 4.94 (q, J = 7 Hz, 2H, -C*H*$_2$CH$_3$), 1.18 (t, J = 7 Hz, 3H, -CH$_2$C*H*$_3$).

Anal. Calcd. for $C_{15}H_{12}N_3OBr$: C, 54.62; H, 3.64; N, 12.74. Found: C, 54.71; H, 3.72; N, 12.64.

1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)cinnoline-3-carboxylic Acid (**14**).

A stirred mixture of cinnolone **13** (5 g, 15 mmoles), cuprous cyanide (1.5 g, 17 mmoles), and DMF (100 ml) was heated under reflux for 18 hours and then concentrated to dryness under reduced pressure. To the residue were added ethylenediamine (11 ml), water (100 ml), and chloroform (300 ml). The resulting mixture was stirred for 2 hours and then the organic phase was separated. The aqueous phase was extracted once more with chloroform (100 ml). The combined chloroform extracts were evaporated to dryness under vacuum. The residue was dissolved in 50% aqueous sulphuric acid (15 ml) and heated in an oil bath at 110-115° for 12 hours. The resulting brown solution was treated with charcoal and the filtrate was cooled in an ice bath, made slightly basic by treating with aqueous ammonia and then acidified by acetic acid. The yellow solid which precipitated was collected, washed with water, suspended in boiling methanol and filtered off to afford 1.4 g (33%) of **14**, mp 256-258°; ir (potassium bromide): ν max 1735-1715 cm^{-1} (br COOH, C=O); ^{1}H nmr: δ 9.15 (d, J = 6 Hz, 2H, pyridine 2,6-H), 8.94 (m, 1H), 8.64 (m, 3H), 8.42 (m, 1H), 5.29 (q, J = 7 Hz, 2H, -C*H*$_2$CH$_3$), 1.88 (t, J = 7 Hz, 3H, -CH$_2$C*H*$_3$).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.50; H, 4.69; N, 14.18.

Acknowledgement.

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REFERENCES AND NOTES

[1] G. Y. Lesher and P. M. Carabateas, U. S. Patent 3,907,808, September, 1975; *Chem. Abstr.*, **84**, 43880P (1976); B. M. Limson, R. K. Macasaet, J. J. Salem, C. G. Beling and H. A. Burnham, *Curr. Ther. Res.*, **26**, 842 (1979).

[2] D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, **11**, 160 (1968).

[3] T. S. Sisca, R. C. Heel and J. A. Romankiewicz, *Drugs*, **25**, 544 (1983).

[4] W. Borsche and A. Herbert, *Liebigs Ann. Chem.*, **546**, 293 (1941).

[5] P. M. Carabateas and R. P. Brundage, U. S. Patent 3,994,903, November, 1976; *Chem. Abstr.*, **85**, 32854c (1976).

[6] J. A. Price and D. S. Tarbell, *Org. Synth., Coll. Vol.* **4**, 285 (1963).

[7] H. G. Walker and R. C. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).