Synthesis of 8-Amino-6-methoxycinnoline. A Precursor for 2-Azaprimaquine

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4-Methoxy-2-nitroaniline was converted in seven steps to 8-amino-6-methoxycinnoline with an overall yield of 33%. Several attempts to introduce a 5-aminopentan-2-yl side-chain in the amino-group to give 2-azaprimaquine were unsuccessful.

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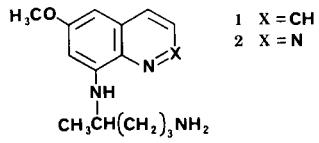
Of the many aminoquinolines which exhibit antiparasitic activity, primaquine (**1**) is well-known as an antimalarial agent (2,3). A large number of aza analogs of these aminoquinolines have been investigated in attempts to discover more effective or less toxic antiparasitic agents (4-7). 2-Azaprimaquine (**2**) is unknown, probably due to the inavailability of 8-amino-6-alkoxycinnolines which arises from the difficulty in introducing the required substituents in a regiospecific manner in a preformed cinnoline. The synthesis of 8-amino-6-methoxycinnoline (**3**) as a precursor for 2-azaprimaquine is described.



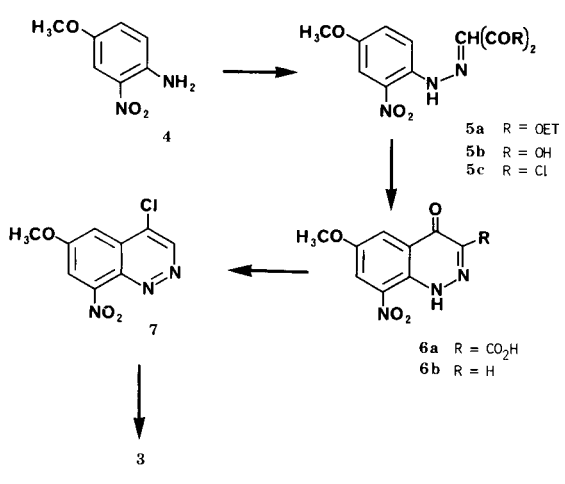
1 X = CH
2 X = N

The synthetic route employed is shown in Scheme I. the use of sulfuric acid in the diazotization of **4** followed by addition of the diazonium salt to diethyl malonate in ethanol containing substantial amounts of sodium acetate gave high yields (97%) of diethyl mesoxalate phenylhydrazone **5a**. The two stage procedure described by Barber, *et al.* (8) for the saponification of **5a** gave diacid **5b** in good yield if the reaction temperature in the second stage was maintained below 45°, otherwise decarboxylation was substantial. The *bis*-acid chloride **5c** was obtained from **5b** by treatment with thionyl chloride in benzene. Cyclization of **5c** to 3-carboxycinnoline-4-one **6a** was achieved in moderate yield (51%) by the use of titanium tetrachloride in nitrobenzene. The best yields in this reaction were obtained when the reaction temperature was in the range of 95-100°. The use of titanium tetrachloride in dichloroethane or aluminum trichloride in nitrobenzene for this cyclization was unsuccessful. Attempted cyclization of diacid **5b** with polyphosphoric acid resulted in only decarboxylation. The use of benzophenone in the decarboxylation of **6a** gave cinnoline **6b** in near quantitative yield. 4-Chlorocinnoline **7** was obtained from **6b** by treatment with phosphorus oxychloride. Although dechlorohydrogenation of **7** to 6-methoxy-8-nitrocinnoline was investigated *via* the 4-*N*-(toluene-*p*-sulfonyl)hydrazide catalytic reduction of **7** using 5% palladium on carbon gave **3** more efficiently in 87% yield.

This synthesis is derived from the report of Barber, *et al.* (8) which indicated that the intramolecular acylation of mesoxalyl chloride phenyl hydrazones to cinnoline-4-ones is feasible despite the de-activating influence of a nitro substituent in the benzenoid ring. Although considerable effort was required to maximize yields in the various steps, the overall yield was 33% and led to no isomerically ambigous products.

A procedure for the alkylation of 6-methoxy-8-aminoquinolines with 4-bromo-1-phthalimidopentane (**8**) and triethylamine, which was reported (9) to be successful with resistant aminoquinoline derivatives, was applied to **3**. This method and others (10-12) involving the use of solvents such as ethanol or dimethylformamide failed to give the desired 6-methoxy-8-(1-methyl-4-phthalimidobutylamino)cinnoline. Elution column chromatography of these reaction mixtures gave fractions whose pmr spectra were indicative of 6-hydroxy-8-(1-methyl-4-phthalimidobutylamino)cinnoline, but neither this material nor its hydrazinolysis product could be obtained analytically pure. These results are analogous to those observed in the attempted demethylation of primaquine with hydrogen bromide (13-15). The use of sodium carbonate in the alkylation reaction did not prevent this apparently facile demethylation.

SCHEME I



The condensations of **3** with 5-diethylamino-2-pentanone, 5-phthalimido-2-pentanone, or their ethylene ketals were investigated. Treatment of **3** with these ketones or ketals in refluxing absolute ethanol or propanol solutions, with or without acid catalyst, gave only recovered starting materials and no evidence of Schiff-base formation. Subjection of the reaction mixture to catalytic hydrogenation during prolonged heating failed to give evidence of Schiff-base formation and reduction. Thus these classical methods for side-chain introduction for 8-aminoquinolines were found to be ineffective when applied to **3**.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns hot stage apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer 727B spectrophotometer and a Nicolet 7199 interferometer. The uv spectra were obtained on a Beckman 25 spectrophotometer. The pmr spectra were recorded on a Varian T-60A spectrometer with tetramethylsilane as an internal reference. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

2-Nitro-4-methoxydiethylmesoxalate Phenylhydrazone (**5a**).

To a stirred, cooled solution (0°) of 2-nitro-4-methoxyaniline (16.8 g, 0.1 mole) and concentrated sulfuric acid (30 ml) in 125 ml of water was added dropwise a solution of sodium nitrite (8.35 g, 0.12 mole) in 20 ml of water. The resulting solution was stored at 0° for 48 hours and was then filtered. The filtrate was divided into three equal parts and each part was added dropwise with stirring to a separate mixture of diethylmalonate (16 ml, 0.105 mole) and anhydrous sodium acetate (16.8 g) in 30 ml of alcohol maintained at 0°. After stirring for 1 hour at 0°, the precipitate was collected and washed with three 25 ml portions of ice-cold water. These washings were added to the filtrate together with sodium acetate (4 g) and stored overnight for further crystallization of product. The combined collections of product were dried under vacuum to give 32 g (97.2%) of **5a** as bright yellow crystals. An analytical sample was recrystallized from absolute ethanol, mp 132-132.5°; ir (potassium bromide): 3175, 1720, and 1660 cm^{-1}; pmr (deuteriochloroform): δ 14.11 (s, 1H), 8.25 (d, J = 8 Hz, 1H), 7.8 (d, J = 8 Hz, 1H), 7.2 (m, 1H), 4.29-4.13 (m, 4H), 4.0 (s, 3H), and 1.46 (t, 6H).

Anal. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.55; H, 5.05; N, 12.38. Found: C, 49.49; H, 5.07; N, 12.45.

2-Nitro-4-methoxymesoxalic Acid Phenylhydrazone (**5b**).

A mixture of **5a** (19.55 g, 69 mmoles) and 28.8 ml of 2*N* sodium hydroxide solution in 380 ml of ethanol was refluxed for 8 hours. To this mixture, cooled to 40°, was added 115 ml of 1*N* sodium hydroxide solution and 130 ml of water. After heating to 40° for 9 hours the solution was cooled to 0°, acidified with concentrated hydrochloric acid, and filtered to give 15.9 g (98.2%) of **5b** as bright yellow crystals. An analytical sample was recrystallized from benzene-petroleum ether, mp 178-180° dec; pmr (DMSO-d_6): δ 15.2 (s, 1H), 8.26 (d, J = 9 Hz, 1H), 7.73-7.90 (m, 2H), and 3.93 (s, 3H).

Anal. Calcd. for $C_{10}H_9N_3O_7$: C, 42.41; H, 3.20; N, 14.84. Found: C, 42.54; H, 3.26; N, 14.95.

2-Nitro-4-methoxymesoxalyl Chloride Phenylhydrazone (**5c**).

A solution of **5b** (5.3 g, 19 mmoles) and thionyl chloride (9 ml, 120 mmoles) in 30 ml of benzene was heated to 40° for 0.5 hours then refluxed for 2.5 hours. The hot reaction mixture was filtered and then cooled. The resulting crystals were collected to give 5.19 g (86%) of **5c**, mp 135-136° dec; ir (potassium bromide): 1775, 1660, and 1510 cm^{-1}.

Anal. Calcd. for $C_{10}H_7Cl_2N_3O_5$: C, 37.52; H, 2.20; Cl, 22.15; N, 13.12. Found: C, 37.60; H, 2.22; Cl, 22.07; N, 13.08.

3-Carboxy-6-methoxy-8-nitrocinnoline-4-one (**6a**).

A solution of **5c** (6.0 g, 1.87 mmoles) in 45 ml of dry nitrobenzene was slowly added at room temperature to a gelatinous mixture of 6 ml of titanium tetrachloride in 12 ml of nitrobenzene. The stirred mixture was heated to 100° for 24 hours. The hot reaction mixture was added to 150 ml of water and the resulting orange slurry was stirred for 3 hours, filtered and the collected residue and nitrobenzene fraction of the filtrate were both extracted with 150 ml of 0.1*N* sodium hydroxide solution. The combined extracts were washed with ether, acidified with concentrated hydrochloric acid, cooled to 5°, and the resultant orange-yellow crystals collected to give 2.52 g (51%) of **6a**. An analytical sample was recrystallized from ethanol; mp 229.5-231° dec; ir (potassium bromide): 3230, 3090, 1750, 1655, and 1405 cm^{-1}; pmr (DMSO-d_6): δ 8.35 (d, H = 4 Hz, 1H), 7.93 (d, J = 4 Hz, 1H), 4.03 (s, 3H).

Anal. Calcd. for $C_{10}H_7N_3O_6$: C, 45.29; H, 2.66; N, 15.85. Found: C, 45.38; H, 2.69; N, 15.76.

6-Methoxy-8-nitrocinnoline-4-one (**6b**).

A mixture of **6a** (1.2 g, 45 mmoles) and 9.6 g of benzophenone was heated at 180-200° for 1.5 hours. The cooled mixture was washed four times with a solution of 3 ml of benzene in 30 ml of petroleum ether (bp 40-60°) and twice with petroleum ether alone to give 1.0 g (99%) of **6b**. Recrystallization from methanol with charcoal treatment or sublimation gave an analytical sample, mp 227-227.5°; ir (potassium bromide): 3240, 1625, and 1525 cm^{-1}; pmr (deuteriochloroform): δ 8.16 (d, J = 3 Hz, 1H), 8.06 (d, J = 3 Hz, 1H), 7.90 (s, 1H), and 3.98 (s, 3H).

Anal. Calcd. for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 18.99. Found: C, 48.85; H, 3.19; N, 18.99.

4-Chloro-6-methoxy-8-nitrocinnoline (**7**).

A mixture of **6b** (0.3 g, 1.35 mmoles) in 9 ml of phosphorus oxychloride was stirred for 12 minutes while heated in an oil bath maintained at 80°. The reaction mixture was poured onto 50 g of crushed ice and the resulting suspension was stirred and cooled while adjusting the *p*H to 12 by addition of 10% sodium hydroxide solution. The resulting precipitate was collected and recrystallized from methylene chloride-petroleum ether (bp 40-60°) to give 0.31 g (95.7%) of **7** as yellow crystals, mp 154-155°; ir (potassium bromide): 1630, 1540, and 1475 cm^{-1}; pmr (deuteriochloroform): δ 9.36 (s, 1H), 7.76 (d, J = 3 Hz, 1H), 7.43 (d, J = 3 Hz, 1H), and 4.41 (s, 3H).

Anal. Calcd. for $C_9H_6ClN_3O_3$: C, 45.11; H, 2.52; Cl, 14.80; N, 17.53. Found: C, 45.04; H, 2.56; Cl, 14.90; N, 17.47.

6-Methoxy-8-aminocinnoline (**3**).

A mixture of **7** (0.3 g, 1.25 mmoles) and 5% palladium on charcoal (0.5 g) which was pre-treated with hydrogen, in 70 ml of absolute ethanol containing 0.05 ml of concentrated hydrochloric acid was stirred under a hydrogen atmosphere at room temperature and pressure. After consumption of 4 molar equivalents of hydrogen, the reaction mixture was filtered and the residue was washed with hot ethanol (20 ml) containing 2 ml of concentrated hydrochloric acid. The residue obtained from evaporation of combined filtrate and washings was dissolved in 60 ml of water. The aqueous solution was filtered, neutralized with saturated sodium carbonate solution, and was extracted with three 60 ml portions of ethyl acetate. The combined extract was concentrated by evaporation to 10 ml which was placed on a column of silica gel. Elution with ethyl acetate gave 0.185 g (84%) of **3** as fluorescent yellow needles, mp 185-186.5°; ir (potassium bromide): 3460, 3250, 1635, and 1460 cm^{-1}; uv (methanol): λ max 398 nm (ϵ, 31,500), 270 (ϵ, 48,400), and 225 (ϵ, 25,100); pmr (deuteriochloroform): δ 9.10 (d, J = 7 Hz, 1H), 7.64 (d, J = 7 Hz, 1H), 6.85 (d, J = 3 Hz, 1H), 6.38 (d, J = 3 Hz, 1H), 5.5 (broad s, 2H), and 3.99 (s, 3H).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.55; H, 5.20; N, 23.91.

Attempted Alkylation of **3**.

A stirred mixture of **3** (0.69 g, 3.9 mmoles) and 4-bromo-1-phthalimidopentane (**8**) (1.5 g, 5 mmoles) (10) was maintained at 150° while triethyl-

amine (0.5 g, 5 mmoles) was added in portions during 1.5 hours. After an additional 1.5 hours at 150°, **8** (0.9 g, 3 mmoles) was added followed by triethylamine (0.3 g, 3 mmoles) in proportions over 1 hour. After an additional 2 hours at 150°, **8** (0.6 g, 2 mmoles) was added followed by triethylamine (0.2 g, 2 mmoles). After stirring for 2 hours at 150° the cooled mixture was diluted with acetone (40 ml) and filtered. The residue obtained by evaporation of filtrate was placed on a column of silica gel. Elution with methanol-triethylamine (15:1) gave 120 mg of a hygroscopic semi-solid assumed to be 6-hydroxy-8-(1-methyl-4-phthalimidobutylamino)cinnoline due to the lack of characteristic methoxy resonance signal; pmr (DMSO-d_6): δ 9.17 (d, J = 7 Hz, 1H), 8.2 (d, J = 7 Hz, 1H), 7.65 (m, 4H), 7.35 (d, J = 3 Hz, 1H), 6.6 (d, J = 3 Hz, 1H), 4.9 (broad s, 1H), 3.1 (m, 3H), 1.8-1.0 (m, 7H).

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