Napthyridines. IV. Synthesis of Benzo[*f*]-1,7-naphthyridines (1,2)

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Benzo[*f*]-1,7-naphthyridines have been synthesized from 3-nitrolepidine (**3**) by a sequence involving monobromination of the methyl group of **3**, oxidation of the bromomethyl group to the carboxyladehyde group by Franzen's trimethylamine *N*-oxide procedure, and conversion of the resultant 3-nitro-1-quinolinecarboxaldehyde (**6**) to the benzo[*f*]-1,7-naphthyridine by the Borsche modification of the Friedlander cyclization.

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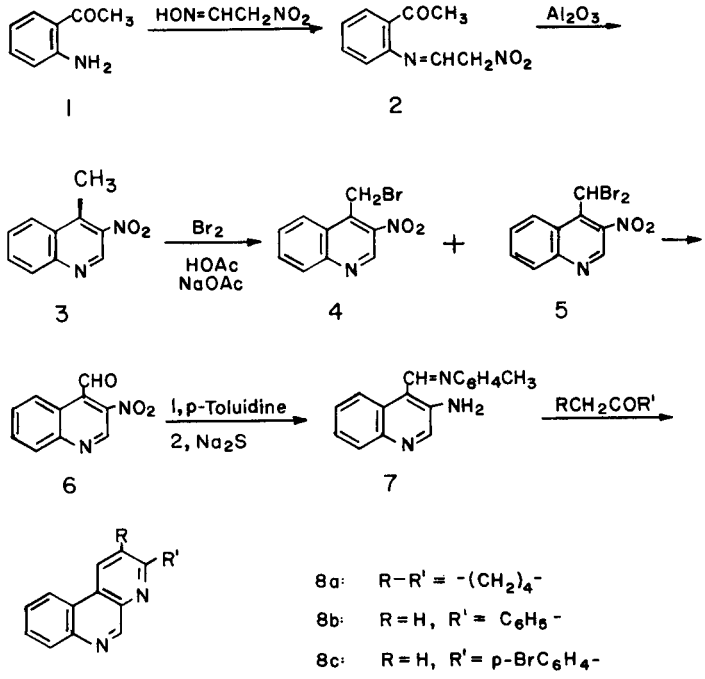
In earlier reports (3) we described a synthetic route to 1,7-naphthyridines from 3-nitro-4-picoline *via* 3-nitro-4-pyridinecarboxaldehyde. Later research (4) showed that this route could be extended to the synthesis of benzo[*f*]-1,7-naphthyridines (**8**) from 3-nitrolepidine (**3**) by the sequence **3** → **4** → **6** → **7** → **8**. Recently the thesis account (4) of this work was cited in a brief report (5) on an apparently similar sequence which utilized the Friedlander synthesis in the final step. This communication describes the details of our work.

The key intermediate in the sequence is 3-nitro-4-quinolinecarboxaldehyde (**6**). Although this compound has not been reported, Ockenden and Schofield (6) have described the synthesis of a compound said to be the *p*-dimethylamino anil of **6**. Following the reaction sequence (**1** → **2** → **3**) of Schofield and Theobald (7,8) we prepared 3-nitrolepidine (**3**) from commercially available 2-aminoacetophenone (**1**) in 47% overall yield (about twice that reported (7)). However, in our hands under a variety of conditions the reaction of **3** with 4-nitrosodimethylaniline yielded only 4,4′-*bis*-dimethylaminoazoxybenzene rather than the desired anil. The reaction of **3** with nitrosobenzene also gave none of the anil of **6**.

Attempts to convert **3** into **6** by the selenium dioxide oxidation (3) used previously with 3-nitropicoline were unsuccessful despite the use of various types of purified selenium dioxide and different solvents such as ethanol, dioxane, and xylene. Chromic acid oxidation (9,10) of **3** also failed to yield **5**. Compound **3** did not react with chloral; thus, the elegant heterocyclic aldehyde synthesis of Clemo and Hoggarth (11) could not be used. These failures may have been due in part to the decreased reactivity of the methyl group in **3** caused by the electronic effect of the adjacent phenyl ring or to steric hindrance of the requisite transition states.

Bromination of **3** with *N*-bromosuccinimide or, preferably, bromine and sodium acetate in acetic acid (12) gave mixtures of 4-bromomethyl-3-nitroquinoine (**4**) and 4-dibromomethyl-3-nitroquinoline (**5**) regardless of the quantities of reagents used (Table I). As expected the formation of **4** was favored by equimolar amounts of **3** and



bromine, and the formation of **5** by use of excess bromine; however, the reaction time and temperature were also important, long reaction times and higher temperatures leading to a higher proportion of **5** relative to **4** even limited amounts of bromine. These observations suggest that there may be some equilibration of the two products, possibly *via* disproportionation (13) on prolonged heating of the reaction mixture. In no instance was any of the 3-nitro-4-tribromomethylquinoline obtained, even when 4 equivalents of bromine were used. These results differ substantially from some of those reported for less hindered quinaldine derivatives (14-17). The mixture of the two bromides was easily analyzed by nmr spectroscopy, the CH_2Br protons of **4** coming at δ 5.15 and the $CHBr_2$ protons of **5** coming at δ 7.67. The bromides were readily separated by thin layer chromatography and with less ease by fractional crystallization. By the latter process yields of up to 68% of **4** were obtained; however, the best yield of **5** was only 39% (18).

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Hydrolysis and oxidation of **4** with silver nitrate in 60% aqueous acetic acid gave only small yields at best of **6**, and application of **5** to Kerfante's procedure (19) for the conversion of dibromides to aldehydes proceeding through the dimorpholine derivative gave only traces of **6**. The best yields (up to 35% based on **4**; 11% based on **1**) of **6** were obtained from **4** by Franzen's method (20), which utilizes the reaction between a halide and trimethylamine *N*-oxide. Even with this reagent the reaction had to be forced toward completion by use of a large excess of trimethylamine *N*-oxide and a small amount of added base, triethylamine, because of the difficulty of separating **6** from unreacted **4**.

Reaction of **6** with 4-toluidine followed by reduction of the nitro group with sodium sulfide gave *N*-(3-amino-4-lepidylidene)-4-toluidine (**7**). Although **7** was obtained in low yield (10-30%) and was not readily freed of inorganic impurities, the crude **7** did react smoothly in the Borsche (3) modification of the Friedlander ring closure with various ketones to give benzo[*f*]-1,7-naphthyridines (**8**), except where the ketone was bulky (*e.g.*, 1-tetralone). Thus, the reaction of **6** with cyclohexanone gave a 90% yield of 5,7-diaza-8,9,10,11-tetrahydro-10-methylbenz[*a*]anthracene (**8a**), with acetophenone a 37% yield of 2-phenylbenzo[*f*]-1,7-naphthyridine (**8b**), and with 4-bromoacetophenone a 54% yield of 2-(2-bromophenyl)-benzo[*f*]-1,7-naphthyridine (**8c**). The reaction of **7** with 1-tetralone proceeded very sluggishly, and even after a protracted reaction period the high resolution mass spectrum of the crude reaction product showed it to consist of the expected product contaminated with substantial amounts of the reactants.

EXPERIMENTAL

Melting points are uncorrected. Nmr spectra were run on a Varian A60 or A60D spectrometer. High resolution mass spectra were run by the Midwest Center for Mass Spectrometry, University of Nebraska-Lincoln. Combustion analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

2-(2-Nitroethylideneamino)acetophenone (**2**) (7).

This compound was prepared in about twice the reported yield (7) by careful control of the conditions in both the preparation of the methazonic acid and its condensation with 2-aminoacetophenone.

To a freshly prepared solution of 60 g. of sodium hydroxide in 120 ml. if water which had cooled to 47°, 60 g. of nitromethane was added dropwise with stirring and with the temperature kept between 47-50°. The color of the solution turned yellow and deepened to orange at the end of the addition. After addition was complete the temperature was allowed to rise freely (to 57°). When it began to drop, the flask was cooled to 5°. The cooled solution was neutralized by slow addition of concentrated hydrochloric acid while the temperature was maintained below 10°. About 130 ml. of acid was used to make the solution just acidic to Congo Red paper.

The light orange methazonic acid was filtered with suction and allowed to dry under suction for 2 hours. The solid turned deep orange in color on contact with air. The solid was further dried by pressing between filter papers. The crude methazonic acid was then used immediately for the following preparation. Crude yield, 39.0 g. (76.5%); in general crude yields ranged from 38-80%.

To a solution of 20.8 g. (0.154 mole) of 2-aminoacetophenone in 400 ml. of water and 28 ml. of concentrated hydrochloric acid 19.5 g. (0.188 mole) of crude methazonic acid was added slowly. Toward the end of the addition, a yellow precipitate formed. An additional 40 ml. of hydrochloric acid was added, and the thick mixture was stirred for 10 minutes and then cooled in the refrigerator overnight.

The precipitate was filtered and washed with water until the filtrate was neutral to litmus. The solids were dried in vacuo over phosphorus pentoxide for 24 hours; crude yield, 27.3 g. (94.5%). Recrystallization from absolute ethanol with gentle warming only (to avoid decomposition) gave 13.2 g. of yellow needles of 2-(2-nitroethylideneamino)acetophenone (**2**), m.p. 124-125° [lit. (8) m.p. 124-125°]; nmr (deuteriochloroform): δ 2.66 (s, 3, CH_3), 6.60 and 7.45 (m, 2, =CH-CH=), 7.13 (s, 1, H-5), 7.22 (s, 1, H-3), 7.40 (s, 1, H-4), 7.80 (s, i, H-6); nmr (acetone): δ 2.66 (s, 3, CH_3), 6.82 and 7.76 (m, 2, =CH-CH=), 7.33 (s, 1, H-5), 7.76 (s, 1, H-3), 7.98 (s, 1, H-4), 8.19 (s, 1, H-6). Another 1.8 g. of product was recovered from the filtrate; total yield, 15.1 g. (52%).

3-Nitro-4-methylquinoline (**3**) (7,21).

To a solution of 2.35 g. (0.0115 mole) of **2** in 230 ml. of warm acetone 21.5 g. (9 times the weight of 2) of alumina (activated by heating at 120° for 2 hr.) was added within 10 minutes with vigorous stirring. Stirring was continued for 20 minutes; then the light yellow mixture was allowed

Table I

Bromination of 4-Methyl-3-nitroquinoline

Mole Ratio		Reaction Times (minutes) (a)	Product Ratio (b)	Final Yield (%) (c)	
3/Br_2	t_a	t_h	**4**/**5**	**4**	**5**
1:1.01	7	10	1:trace	43	-
1:1.02	5	10	1:trace	53	-
1:1.20	5	12	1:0.17	68	-
1:1.28	4	10	1:trace	35	-
1:2.11	30	30	1:1	-	-
1:2.87	13	40	1:1	-	30
1:3.00	20	40	1:5.6	-	20
1:3.11	60	20	1:1	-	39
1:4.35	70	300	1:11	-	-

(a) t_a = addition time; t_h = heating time. (b) Estimated by nmr. (c) Of essentially pure products.

to stand at room temperature for 12 hours. The alumina was removed by filtration and the clear filtrate was evaporated to about 5 ml. Addition of a few drops of water caused precipitation of needle-shaped crystals, 1.94 g. (90%), m.p. 116.5-118.5°. One recrystallization from acetone-water yielded colorless needles, m.p. 116.5-117.5° [lit. (8) m.p. 117-118°]; nmr (deuteriochloroform): δ 2.90 (s, 3, CH_3), 7.99 (m, 4, H-5, 6,7,8), 8.40 (s, 1, H-2).

Anal. Calcd. for $C_{10}H_8NO_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 64.04; H, 4.34; N, 15.07.

3-Nitro-4-bromomethylquinoline (**4**).

A solution of 1.74 g. (0.021 mole) of freshly fused sodium acetate in 5 ml. of glacial acetic acid was stirred and heated to 110°; then a solution of 0.84 g. (0.0045 mole) of **3** in 5 ml. of glacial acetic acid was added rapidly. The temperature of the system was maintained at 114° while a solution of 0.86 g. (0.0054 mole) of bromine in 10 ml. of glacial acetic acid was added dropwise with stirring. The addition was completed in 5 minutes and heating and stirring were continued for another 12 minutes. The hot liquid was poured into a mixture of 400 ml. of cracked ice and water. The mixture was allowed to stand with occasional stirring at room temperature until all the ice had melted. The precipitate was filtered, washed thoroughly with water to remove the last traces of acid, and air-dried; yield, 1.05 g. (85%). Three recrystallizations from 1:1 ethyl acetate and Skellysolve C yielded 0.81 g. (68%) of analytically pure 3-nitro-4-bromomethylquinoline (**4**), m.p. 166.5-167°; nmr (deuteriochloroform): δ 5.15 (s, 2, CH_2Br), 8.10 (m, 4, H-5, 6, 7, 8), 9.35 (s, 1, H-2).

Anal. Calcd. for $C_{10}H_7BrNO_2$: C, 44.97; H, 2.64; N, 10.49; Br, 29.92. Found: C, 44.64; H, 2.66; N, 10.45; Br, 29.90.

3-Nitro-4-dibromomethylquinoline (**5**).

The procedure employed was the same as that described above for **4** except for the quantities of reagents used and the time period allowed for bromine addition and heating after addition: compound **3**, 1.06 g. (0.0056 mole) in 15 ml. of glacial acetic acid; sodium acetate, 2.17 g. (0.023 mole) in 14 ml. of glacial acetic acid; bromine, 2.8 g. (0.018 mole) in 20 ml. of glacial acetic acid. Addition was carried out over one hour (at the approximate rate of discharge of the bromine color). Heating was continued for an additional 20 minutes. The reaction mixture was worked up as described for **4**, crude yield 1.80 g. (91.5%), m.p. 123-130° and 165° (corresponding to a mixture of mono- and dibromo compounds (18). Two recrystallizations from ethanol-water yielded 0.75 g. (39%) of **5**, m.p. 130-131°; nmr (deuteriochloroform): δ 7.67 (s, 1, $CHBr_2$), 8.10 (m, 4, H-5, 6, 7, 8), 9.21 (s, 1, H-2).

Anal. Calcd. for $C_{10}H_6Br_2NO_2$: C, 34.71; H, 1.75; N, 8.10; Br, 46.19. Found: C, 34.56; H, 1.80; N, 8.08; Br, 45.95.

3-Nitroquinoline-4-carboxaldehyde (**6**).

A solution of 3.95 g. (0.0036 mole) of trimethylamine *N*-oxide dihydrate in 12.0 ml. of dimethylformamide was distilled until the temperature of the residue rose to 152°, then the system was connected to the water aspirator to remove the remaining solvent. The anhydrous trimethylamine *N*-oxide was dissolved in 18.0 ml. of chloroform (dried by passage through a column of alumina), and a mixture of 3.00 g. (0.012 mole) of **4** partially dissolved in 70.0 ml. of dried chloroform was added dropwise with vigorous stirring in an apparatus protected from atmospheric moisture. Addition was complete in 20 minutes, and the mixture was heated to the reflux temperature for 30 minutes.

The hot solution was cooled to room temperature and extracted with an equal volume of 2*N* hydrochloric acid. The chloroform layer was washed three times with 20% aqueous sodium bicarbonate, dried (magnesium sulfate), and evaporated to yield a yellow solid, 1.10 g., m.p. 125-131°. Two recrystallizations from ethanol-water gave 0.80 g. (35%) of 3-nitroquinoline-4-carboxaldehyde (**6**), m.p. 134-136°; ir (potassium bromide): 1705 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.05 (m, 4, H-5, 6, 7, 8), 9.68 (s, 1, H-2), 10.68 (s, 1, CHO).

Anal. Calcd. for $C_{10}H_6N_2O_3$: C, 59.41; H, 2.99; N, 13.86. Found: C, 59.78; H, 2.78; N, 13.74.

In another experiment a solution of 0.40 g. (0.0015 mole) of **4** and 0.40 g. (0.00236 mole) of silver nitrate in 10 ml. of 60% acetic acid was heated for 4.5 hours on the steam bath. The silver bromide was removed by gravity filtration, and the filtrate was treated with hydrochloric acid to precipitate any remaining silver ion. The mixture was filtered and the filtrate made alkaline with sodium carbonate. The crude product was recovered by filtration, yield 0.13 g., m.p. 122-128°. Sublimation at 110° (3.5 torr) gave a small amount of fairly pure **6**, m.p 135-136°.

3-Amino-4*N*-(4-tolylformidoyl)quinoline (**7**).

A solution of 0.50 g. (0.0025 mole) of **6** and 0.27 g. (0.0025 mole) of *p*-toluidine in 10 ml. of ethanol was heated under reflux for 1.75 hours. Meanwhile solutions of 1.20 g. (0.05 mole) of sodium sulfide nonahydrate and 0.42 g. (0.05 mole) of sodium bicarbonate, each in the minimum amount of water, were prepared and then diluted with an equal volume of 95% ethanol. The mixtures were allowed to stand at room temperature for 30 minutes and filtered. The filtrates were added to the hot solution of **6** and *p*-toluidine. The red solution which resulted was diluted with 50 ml. of water. The solution (now yellow) was allowed to cool overnight in the refrigerator. The pale yellow solid was collected by filtration, washed with water, and dried, giving 0.23 g. (31%) of crude **7**, m.p. 124-128°. Numerous attempts to purify this material by recrystallization from ethanol-water, benzene-Skellysolve C, and ethyl acetate-Skellysolve C were not successful in giving analytically pure material. The melting point was essentially unchanged on recrystallization, and losses were high. Elemental analysis indicated the principal contaminants to be inorganic. Analysis of the crude material by high resolution mass spectroscopy at several probe temperatures between 75 and 110° gave a very simple spectrum with little or no indication of volatile organic impurities; principal peaks (above 5%): m/e 262.1299 (14.73%), 261.1260 (89.02%, molecular ion (M), calculated for $C_{17}H_{15}N_3$, 261.1266), 260.1184 (100.00%, M—H), 259.1108 (58.22%, M—2H), 258.1036 (8.99%, M—3H), 245.1053 (7.40%, M—NH_2). In other experiments with up to 3.8 g. of the aldehyde, yields of 10-30% of crude **7**, m.p. range 124-129°, were obtained. The crude material was used in subsequent steps of the reaction sequence.

General Procedure for Borsche Cyclization.

A solution of equimolar amounts of crude 3-amino-4*N*-(4-tolylformidoyl)quinoline (**7**) and the ketone in ethanol (sufficient to dissolve the reactants) and 1 ml. of 2*N* sodium hydroxide was heated under reflux on the steam bath for 4-8 hours. Following removal of the ethanol and *p*-toluidine by steam distillation the remaining reaction mixture was chilled overnight in the refrigerator. The solid product was filtered, dried in the desiccator over phosphorus pentoxide, and recrystallized from ethanol-water. The scale of most experiments was in the range of 0.0005-0.0015 mole. Because of the relative simplicity of the mass spectra of the naphthyridines prepared, high resolution mass spectroscopy was used to monitor the purification of the products.

2-Phenylbenzo[*f*]-1,7-naphthyridine (**8c**).

From 0.055 g. (0.0021 mole) of **7** and 0.025 g. (0.00021 mole) of acetophenone in 7 ml. of ethanol 0.020 g. (37%) of crude, yellowish naphthyridine, m.p. 152-156°, was obtained after 4 hours. A second run for 8 hours on the same scale gave 0.032 g. (59%) of crude product, m.p. 154-157°. Two recrystallizations from ethanol-water gave colorless crystals, m.p. 156-158.5° [lit. (5) m.p. 157°]; ms: m/e (% intensity) 257.1031 (18.01%, M + H), 256.0995 (100.00%, molecular ion (M), calcd. for $C_{18}H_{12}N_2$: 256.1000), 255.0922 (42.14%, M - H).

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.15; H, 4.85; N, 10.73.

5,7-Diaza-8,9,10,11-tetrahydro-10-methylbenz[*a*]anthracene (**8a**).

From 0.30 g. (0.0011 mole) of **7** and 0.12 g. (0.0011 mole) of 4-methylcyclohexanone in 6 ml. of ethanol 0.026 g. (90%) of crude naphthyridine, m.p. 118-130°, was obtained after 4 hours. A second run for 8 hours at half the original scale gave 0.012 g. (83%) of crude pro-

duct, m.p. 125-130°. Recrystallization of the crude material from ethanol-water gave colorless crystals, m.p. 134-136°; ms: m/e (% intensity) 249.1344 (18.18%, m + H), 248.1309 (100.00%, molecular ion (M), calcd. for $C_{17}H_{16}N_2$: 248.1349), 247.1237 (16.50%, M - H), 248.1309 (100.00%, molecular ion (M), calcd. for $C_{17}H_{16}N_2$: 248.1349), 247.1237 (16.50%, M - H), 234.1139 (11.77%, M - CH_3), 233.1080 (34.39%, M - CH_3), 231.0914 (10.91%, M - CH_5), 219.0910 (12.46%, M -C_2H_5), 206.0844 (19.16%, M - C_3H_6).

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.01; H, 6.72; N, 11.70.

2-(4-Bromophenyl)benzo[*f*]-1,7-naphthyridine (**8b**).

From 0.20 g. (0.00076 mole) of **7** and 0.15 g. (0.00076 mole) of 4-bromoacetophenone in 15 ml. of ethanol 0.14 g. (54%) of crude, greenish naphthyridine, m.p. 170-187°, was obtained after 4 hours. A second run at the same scale for 8 hours gave 0.16 g, (61%) of product, m.p. 182-190°. Several recrystallizations from ethanol-water gave 0.10 g. (40%) of the naphthyridine, m.p. 225-227°; ms: m/e (% intensity) 337.0105 (10.98%, M + H), 336.0081 (57.50%, one molecular ion (M), calcd. for $C_{18}H_{11}N_2Br$: 336.0085), 335.0109 (14.16%, M + H), 334.0103 (58.67%, one molecular ion (M), calcd. for $C_{18}H_{11}N_2Br$: 334.0105).

Anal. Calcd. for $C_{18}H_{11}N_2Br$: C, 64.50; H, 3.31; N, 8.36; Br, 23.84. Found: C, 64.65; H, 3.09; N, 7.98; Br, 23.46.

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