

removal of the liquids, the residue was heated with 150 cc. of a 1% aqueous solution of potassium hydroxide and the solution was filtered and acidified. A solution of the precipitate in acetone was boiled with Norit, filtered and evaporated, and the product recrystallized from dilute alcohol; yield, 0.15 g.; m. p. 149–150°. From the filtrate an additional 0.05 g. of slightly less pure material was obtained. After two more recrystallizations the α -form formed colorless prisms; m. p. 150–150.5°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 80.1, 80.8; H, 8.2, 8.3.

When the β -methyl ether was heated with the acid mixture for one-half hour or longer and then cooled, about 10% of a crystalline product precipitated, which melted at 203.5–204° (vac.) and crystallized in fine colorless needles

from dilute alcohol. Analysis showed that it was not the desired compound (Found: C, 85.1; H, 8.0). From the acid filtrate only an uncrystallizable oil was obtained.

Summary

5,6,7,8-Tetrahydro-1-methoxynaphthalene reacts with succinic anhydride in the 4-position. The keto acid was reduced by the Clemmensen method and the reduced acid was cyclized to 1-keto-9-methoxy-*s*-octahydrophenanthrene. From the latter compound 6-hydroxy-1,2,3,4-tetrahydro-17-equilenone was synthesized.

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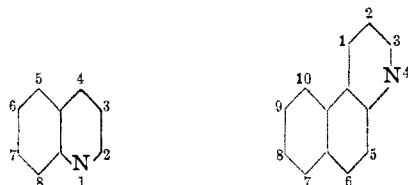
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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

5-Amino- and 1-Aminobenzo(f)quinolines and Derivatives

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Since a number of the 8-dialkylaminoalkylaminoquinolines, including Plasmoquin, have been found to possess strong antimalarial action,² it was believed that the synthesis of benzo(f)quinolines with dialkylaminoalkylamino- or other side chains in the 5-position, analogous to the 8-position in quinoline, should be investigated.



5-Aminobenzo(f)quinoline, obtained from the 5-carboxy- derivative by the Curtius reaction, exhibited reactions similar to those of 8-aminoquinoline. It was diazotized and coupled with 2-naphthol and with R-acid. In addition the amine was condensed with various dialkylaminoalkyl bromides and with 2-bromopyridine to produce the corresponding substituted aminobenzo(f)quinolines. 5-(γ -Diethylaminopropylamino)-benzo(f)quinoline was isolated as the dihydrochloride because the free base was an oil at room temperature.

In order to compare the reactivity of amino groups in the three rings of benzo(f)quinoline, 1-aminobenzo(f)quinoline was synthesized from 5,6-benzocinchoninic acid³ by the Curtius reac-

tion. The amine was similar to 4-aminoquinoline in that it could not be diazotized and coupled with R-acid and 2-naphthol and like the 7,8 and 10-aminobenzo(f)quinolines⁴ could not be alkylated.

Experimental

5-Carboxybenzo(f)quinoline (I).—Sulfuric acid (106 g.) was carefully added to a mixture of 2-amino-3-naphthoic acid (70 g.), arsenic acid (54 g.) and glycerol (115 g.) and the temperature was slowly raised to 120°. With stirring, the temperature was gradually increased to 135° during a period of four hours, and then to 145–150°, where it was maintained for an additional four hours. The mixture was poured into water (1 liter), allowed to stand overnight, heated to boiling, filtered, and the filtrate made basic with ammonium hydroxide. This mixture was filtered, the filtrate acidified with acetic acid and the very viscous material which formed was separated by filtration. Repeated treatments of the gum-like material with ammonium hydroxide finally gave a solution which, upon filtration, acidification with acetic acid, and concentration produced crude (I). The crude product was recrystallized from cellosolve and then from ethanol; white needles; yield, 26 g. (32%); m. p. 204–205°.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.31; H, 4.07; N, 6.26. Found: C, 75.11; H, 4.09; N, 6.29.

Application of the same reaction to 3-carbomethoxy-2-naphthylamine gave (I) in about the same yield.

5-Carbomethoxybenzo(f)quinoline (II).—Esterification of (I) with absolute methanol in the presence of dry hydrogen chloride gave (II) as white plates; yield, 54%; m. p. 86°.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.96; H, 4.68. Found: C, 75.86; H, 4.87.

(1) Parke, Davis and Company Fellow.

(2) Von Oettingen, *Am. Chem. Soc. Mono.*, **64**, 108 (1933).

(3) Robinson and Bogert, *J. Org. Chem.*, **1**, 65 (1936).

(4) Clem and Hamilton, *This Journal*, **62**, 2350 (1940).

5-Carbamylbenzo(f)quinoline (III).—Made by the action of ammoniacal methanol on (II) for twenty-four hours at 40°; white plates; yield, 66%; m. p. 205–206°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.61; H, 4.52. Found: C, 76.02; H, 4.69.

5,6-Dihydro-(5,6-dichloro-5-carbomethoxybenzo(f)-quinoline (IV).—To 18 g. of (I) was added thionyl chloride (75 ml.) and the mixture was heated on a water-bath for forty-five minutes. After removal of the excess thionyl chloride under reduced pressure, the residue was refluxed with absolute methanol (400 ml.) for one hour and the mixture was cooled and made alkaline with sodium bicarbonate solution. Recrystallization of the separated product from methanol gave a white powder; 19 g. (76%); m. p., 134–135°.

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_2$: C, 58.42; H, 3.66; Cl, 23.01. Found: C, 58.56; H, 3.61; Cl, 22.84.

The chlorine atoms were assumed to be in the 5,6 positions because of the similarity in structures of benzo(f)-quinoline and phenanthrene. The 9,10 double bond of phenanthrene has been shown to be more olefinic in character than the other double bonds.^{6,7} By analogy it was expected that the 5,6 double bond of benzo(f)quinoline would be more susceptible to addition reactions. Since the elucidation of the structure of the dichloro addition product was not considered pertinent to the investigation, no rigorous proof of its structure was attempted.

6-Chloro-5-carbomethoxybenzo(f)quinoline (V).—After compound (IV) was dissolved in a saturated methanol-ammonia solution (150 ml.), the solution was heated at 40–50° for six hours and then cooled. The precipitate which separated was filtered, washed with water and finally recrystallized from methanol as white rods; yield, 3.7 g. (84%); m. p., 187–189°.

Anal. Calcd. for $C_{15}H_{10}ClNO_2$: C, 66.25; H, 3.72; Cl, 13.06. Found: C, 66.00; H, 3.78; Cl, 12.60.

Hydrazide of 5-Carboxybenzo(f)quinoline (VI).—Nineteen grams of (IV), dissolved in methanol (300 ml.) by warming, was treated with 85% hydrazine hydrate (40 ml.), the mixture was refluxed for four hours, cooled, filtered, and the separated solid was recrystallized from methanol; white needles; yield, 13.5 g. (82%); m. p., 203–204°.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.90; H, 4.68; N, 17.71. Found: C, 70.86; H, 4.71; N, 17.60.

The hydrazide may also be prepared from (II) by the same procedure.

Azide of (I).—The hydrazide (13.5 g.) was dissolved in an excess of hydrochloric acid (15%), the solution was cooled to 10°, and sodium nitrite (7.8 g.) dissolved in water (15 ml.) was slowly added with stirring. Upon addition of sodium bicarbonate solution, the azide was precipitated, filtered and dried; yellow powder; yield, 14 g. (almost theoretical); m. p. 65–67°. The azide was unstable so no attempt was made to analyze it.

5-Acetaminobenzo(f)quinoline (VII).—The azide (14 g.) was added to a mixture of acetic acid (40 ml.) and acetic anhydride (28 ml.), and after the evolution of nitrogen ceased, the mixture was heated on a water-bath for an

hour. It was then cooled, diluted with water (150 ml.) and warmed for an additional hour. Acetic acid was added until the red gum dissolved, the solution was decolorized (activated charcoal), filtered, and then was allowed to stand overnight in a refrigerator. Ammonium hydroxide was added to the solution until alkaline and the crude product, which separated, was recrystallized from a water-methanol solution as white plates; yield 10 g. (78%); m. p. 126–127°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.23; H, 5.12. Found: C, 76.11; H, 5.16.

5-Aminobenzo(f)quinoline (VIII).—Sulfuric acid (80 ml.), cooled in an ice-bath was slowly added to 10 g. of (VII), and the mixture was allowed to stand for two hours. Water (150 ml.) was then slowly added, the solution was heated on a water-bath for two hours, cooled, and the crude amine was precipitated with ammonium hydroxide. It was recrystallized, first, from methanol and then from petroleum ether (b. p. 85–100°); yellow needles; yield, 6.2 g. (76%); m. p. 137–138°.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19. Found: C, 80.29; H, 5.32.

5-(β -Diethylaminoethylamino)-benzo(f)quinoline (IX).—A mixture of (VIII) (1 g.), β -diethylaminoethyl bromide hydrobromide (2.7 g.), sodium acetate (1.5 g.), and absolute ethanol (30 ml.) was refluxed for twenty-four hours, the alcohol was removed by distillation, and water (100 ml.) was added to the residue. The solution was then made basic with ammonium hydroxide, and the yellow oil, which formed upon cooling in the refrigerator, was first recrystallized from a water-methanol solution and then from an acetone-water mixture; yellow needles; yield, 1.2 g. (80%); m. p. 85°.

Anal. Calcd. for $C_{19}H_{23}N_3$: C, 77.77; H, 7.90. Found: C, 77.73; H, 7.92.

5-(γ -Diethylaminopropylamino)-benzo(f)quinoline Dihydrochloride (X).—By following the procedure for (IX), the free base of (X) was obtained as an oil. The oil was dissolved in dry acetone and (X) was precipitated by hydrogen chloride. Recrystallization first from *n*-butyl alcohol-ether solution and then from *n*-butyl alcohol gave orange needles (hygroscopic); yield, 50%; m. p. 235–240°.

Anal. Calcd. for $C_{20}H_{27}Cl_2N_3$: Cl, 18.68. Found: Cl, 18.83.

5-(2'-Pyridylamino)-benzo(f)quinoline (XI).—A mixture of (VIII) (1.5 g.), 2-bromopyridine (1.5 g.), sodium acetate (1 g.), a trace of copper bronze, and butanol-1 (25 ml.) was refluxed for twenty-four hours. After the mixture cooled, ether (60 ml.) was added and the contents were extracted with dilute hydrochloric acid. A brown gum was formed by making the acid extract basic with ammonium hydroxide, and recrystallization of the gum from ethanol gave yellow crystals; yield, 0.8 g. (40%); m. p. 142–144°.

Anal. Calcd. for $C_{18}H_{18}N_3$: C, 79.68; H, 4.83. Found: C, 79.46; H, 4.86.

5-Hydroxybenzo(f)quinoline (XII).—Following a procedure somewhat similar to that for (I), the above compound was prepared in a poor yield from 3-hydroxy-2-naphthylamine sulfate, sulfuric acid, glycerol, and nitrobenzene as starting materials; white plates; m. p. 104–106°.

(3) Fieser, Jacobsen and Price, *THIS JOURNAL*, **58**, 2136 (1936).

(6) Hayduck, *Ann.*, **167**, 181 (1873).

(7) Price, *THIS JOURNAL*, **58**, 1834 (1936).

Anal. Calcd. for $C_{12}H_8NO$: C, 79.98; H, 4.66; N, 7.18. Found: C, 80.03; H, 4.82; N, 7.20.

1-Carbamylbenzo(f)quinoline (XIII).—5,6-Benzocinchonic acid (15 g.) was refluxed for thirty minutes with thionyl chloride (70 ml.) and the excess thionyl chloride was removed by distillation under reduced pressure. The crude acid chloride was then treated with concentrated ammonium hydroxide (150 ml.) and the product formed was recrystallized from ethanol; white needles; yield, 6 g. (40%), m. p. 253–255°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.71; H, 4.52. Found: C, 75.48; H, 4.62.

1-Carbomethoxybenzo(f)quinoline (XIV).—Crude 5,6-benzocinchoninoyl chloride, prepared as above, was refluxed for thirty minutes with absolute methanol, and the ester was precipitated by the addition of sodium bicarbonate solution. Recrystallization from methanol gave white needles; yield, 80%; m. p. 104–105°.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.68. Found: C, 76.00; H, 4.62.

1-Carboethoxybenzo(f)quinoline (XV).—(XV) was prepared by the same procedure as outlined for (XIV); white pyramids; yield, 71%; m. p. 56°.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.22. Found: C, 76.37; H, 5.42.

Hydrazide of 5,6-Benzocinchonic Acid (XVI).—A mixture of (XIV) (64 g.), methanol (170 ml.), and hydrazine hydrate (40 ml.) was heated on a water-bath for thirty hours and the crude hydrazide (16 g.) thus produced was recrystallized from methanol; white needles; yield 13 g. (23%); m. p. 224–225°.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.90; H, 4.68; N, 17.71. Found: C, 70.81; H, 4.74; N, 17.70.

1-Aminobenzo(f)quinoline (XVII).—Dilute acetic acid (excess) was slowly added with stirring to a mixture of (XVI) (14.5 g.), water (300 ml.), and sodium nitrite (7 g.). After stirring for four hours, the azide was separated by filtration, and was added immediately to dioxane (150 ml.). The mixture was then heated on a water-bath for five hours, decolorized (activated charcoal), filtered, and the dioxane was removed by distillation. Hydrochloric acid (200 ml.) was added to the viscous residue, the solution was refluxed for five hours, and the amine hydrochloride, which separated upon cooling the solution in an ice-bath, was removed by filtration. It was dissolved in water and the free amine was precipitated by the addition of ammonium hydroxide. Recrystallization from ethanol gave white needles; yield, 10 g. (85%); m. p. 149–150°.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.38. Found: C, 80.20; H, 5.15; N, 14.14.

1-Acetaminobenzo(f)quinoline (XVIII).—This compound was prepared, in the usual manner, from (XVII), acetic acid and acetic anhydride. The product was recrystallized from aqueous alcohol solution; white needles; yield, 85%; m. p. 192°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: N, 11.86. Found: N, 11.65.

1-(*p*-Diethylaminobenzalmino)-benzo(f)quinoline (XIX).—*p*-Dimethylaminobenzaldehyde (1 g.) and (XVII) (1 g.) were dissolved in cellosolve (15 ml.), the solution was refluxed for four hours, and then poured into water (50 ml.). The oil, which separated, was crystallized from aqueous ethanol solution; yellow powder; yield, 0.4 g. (22%); m. p. 136–138°.

Anal. Calcd. for $C_{24}H_{24}N_3$: N, 11.86. Found: N, 11.85.

N-(5,6-Benzocinchoninoyl)-N'-(diethylaminobenzal)hydrazine (XX).—A mixture of (XVII) (1.8 g.), *p*-dimethylaminobenzaldehyde (1.4 g.) and 95% ethanol (60 ml.) was refluxed for two hours, and the yellow product, which separated on cooling, was recrystallized from ethanol; yellow needles; yield, 2.2 g. (72%); m. p. 216–218°.

Anal. Calcd. for $C_{26}H_{24}N_4O$: C, 75.74; H, 6.10. Found: C, 75.53; H, 6.20.

Summary

5-Aminobenzo(f)quinoline was prepared from 5-carboxybenzo(f)quinoline by the Curtius reaction. The amine was condensed with a number of dialkylaminoalkyl halides and with 2-bromopyridine to give the corresponding substituted aminobenzo(f)quinolines. 5-Aminobenzo(f)quinoline exhibited reactions similar to those of 8-aminoquinoline.

5-Carboxybenzo(f)quinoline was obtained in yields of 35% by the Skraup reaction, but 5-hydroxybenzo(f)quinoline was prepared in poor yields by the same reaction.

1-Aminobenzo(f)quinoline prepared by the Curtius reaction was found analogous to 4-aminoquinoline in chemical behavior.

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