

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

1-Substituted Benzo(f)quinolines

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Several series of benzoquinolines have been prepared in this Laboratory. The syntheses have been divided into two groups; there are compounds of the plasinochin and atebirin types,^{2,3} and syntheses resulting in compounds somewhat related to quinine.⁴ The present investigation has dealt with a study of the latter type in the benzo(f)quinoline series.

1-Carboxybenzo(f)quinoline (I) was prepared by the method of Robinson and Bogert.⁵ This acid was converted to 1-chlorocarbonylbenzo(f)quinoline hydrochloride³ (II) by treatment with thionyl chloride. The addition of II to an ethereal solution of diazomethane yielded 1-diazoacetylbenzo(f)quinoline (III), by a method similar to that employed by Braz⁶ for the preparation of 9-diazoacetylacridine. 1-Benzo(f)quinolyl bromomethyl ketone (IV) resulted on treatment of III with 48% hydrobromic acid.

Attempts to prepare ethyl 5,6-benzocinchoninyl acetate by means of the Claisen condensation of 1-carbethoxybenzo(f)quinoline³ and ethyl acetate, following the directions of Rabe and Pasternack⁷ for the preparation of ethyl 4-quinolyl acetate, and also by the directions of Chi and Lee⁸ for the preparation of ethyl benzoylacetate, failed. By treatment of ethyl 4-quinolyl acetate with bromine and hydrobromic acid, Rabe, Pasternack and Kindler⁹ prepared 4-quinolyl bromomethyl ketone.

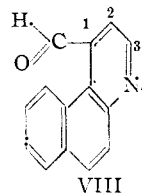
Since the yield in the preparation of 1-diazoacetylbenzo(f)quinoline was low and since the synthesis of ethyl 5,6-benzocinchoninyl acetate had failed, a second method for the preparation of the desired carbinol-type compounds was utilized.

β -Naphthylamine and ethyl acetoacetate were condensed to give β -2-naphthylaminocrotono-2-naphthylamide, following the directions of Knorr.¹⁰ The yield given by Gibson, *et al.*,¹¹ for this reaction could not be duplicated and the original method of Knorr was used.

β -2-Naphthylaminocrotono-2-naphthylamide was hydrolyzed to acetoaceto- β -naphthalide¹¹ and

the product cyclized to 3-hydroxy-1-methylbenzo(f)quinoline (V) by means of concentrated sulfuric acid. The treatment of V with phosphorus pentachloride and phosphorus oxychloride gave 3-chloro-1-methylbenzo(f)quinoline (VI). 1-Methylbenzo(f)quinoline (VII) was prepared by reduction of VI with tin and hydrochloric acid and by the reduction of VI with hydrogen and palladium-on-barium sulfate catalyst. The products obtained were identical and melted at 98–99°. Reed¹² obtained VII by the condensation of β -naphthylamine, methylal and acetone and gives a melting point of 112°, while Knorr and Gibson, *et al.*, who prepared the methyl compound by the distillation of 3-hydroxy-1-methylbenzo(f)quinoline with zinc dust, report a melting point of 91–92°.

1-Formylbenzo(f)quinoline (VIII) was synthe-



sized by the oxidation of VII with selenium dioxide, according to the directions of Kwartler and Lindwall¹³ for the preparation of cinchoninaldehyde. Several condensation products of VIII were synthesized, following the methods of these authors. β -[1-Benzo(f)quinolyl]- β -hydroxy- α -nitroethane (IX) was prepared by the condensation of VIII and nitromethane. The attempts to reduce IX to the corresponding amino derivative in a neutral solution with the use of Raney nickel catalyst resulted in a product that could not be purified. This result agrees with the work of Levitz and Bogert¹⁴ who found that α -(6-methoxyquinolyl-4)- β -nitroethanol could not be reduced to the desired amino compound in neutral solutions. The reduction was attempted by the method of Gakenheimer and Hartung¹⁵ but the yield was so low that an analytical sample was not obtained.

The benzoin type reaction on VIII gave 1'-benzo(f)quinolylglycolyl-1-benzo(f)quinoline (X). The aldehyde (VIII) was condensed with quinaldine to give a few crystals melting at 193–194°. Diphenacyl-1-benzo(f)quinolylmethane (XI) was synthesized by the condensation of VIII and acetophenone. 1-Benzo(f)quinolylcarbinol (XII) resulted from a cross-Cannizzaro reaction with VIII.

- (1) Parke, Davis and Company Fellow.
- (2) Clem and Hamilton, *THIS JOURNAL*, **62**, 2349 (1940); Utermohlen and Hamilton, *ibid.*, **63**, 156 (1941); Mueller and Hamilton, *ibid.*, **65**, 1017 (1943); **66**, 860 (1944); Gerhardt and Hamilton, *ibid.*, **66**, 479 (1944).
- (3) Barnum and Hamilton, *ibid.*, **64**, 540 (1942).
- (4) Gobel and Hamilton, *ibid.*, **67**, 511 (1945).
- (5) Robinson and Bogert, *J. Org. Chem.*, **1**, 65 (1936).
- (6) Braz, *J. Gen. Chem. U. S. S. R.*, **11**, 851 (1941); *C. A.*, **36**, 4122 (1942).
- (7) Rabe and Pasternack, *Ber.*, **46**, 1032 (1913).
- (8) Chi and Lee, *Trans. Science Soc. China*, **8**, 87 (1934); *C. A.*, **29**, 467 (1935).
- (9) Rabe, Pasternack and Kindler, *Ber.*, **50**, 144 (1917).
- (10) Knorr, *ibid.*, **17**, 543 (1884).
- (11) Gibson, *et al.*, *J. Chem. Soc.*, 2255 (1926).

- (12) Reed, *J. prakt. Chem.*, [2] **35**, 298 (1887).
- (13) Kwartler and Lindwall, *THIS JOURNAL*, **59**, 524 (1937).
- (14) Levitz and Bogert, *J. Org. Chem.*, **10**, 341 (1945).
- (15) Gakenheimer and Hartung, *ibid.*, **9**, 85 (1944).

The aldehyde (VIII) was condensed with several amines to yield the corresponding anils. In this manner, 5,6-benzocinchoninal-*p*-hydroxyaniline (XIII), 5,6-benzocinchoninalaniline (XIV), 5,6-benzocinchoninal-*p*-[1-(3,4-dimethyl-1,2,5-triazolyl)]-aniline (XV) and 8-(5,6-benzocinchoninalamino)-6-methoxyquinoline (XVI) were prepared.

1-(*p*-Hydroxyanilinomethyl)-benzo(f)quinoline (XVII) resulted from the reduction of XIII by zinc dust and sodium hydroxide, and by a hydrogen reduction with palladium-on-barium sulfate catalyst. The attempts to reduce the oxime (XVIII) of VIII to 1-aminomethylbenzo(f)quinoline were unsuccessful.

Experimental

1-Chlorocarbonylbenzo(f)quinoline Hydrochloride (II).³—A mixture of 20 g. (0.090 mole) of I and 110 ml. of thionyl chloride was refluxed for thirty minutes and the excess chlorinating agent removed at reduced pressure. The residue was broken up under dry benzene. The product was collected by filtration and dried in a vacuum desiccator over potassium hydroxide; yield 23 g. (92%).

1-Diazoacetylbenzo(f)quinoline (III).—Seven and seven-tenths grams (0.028 mole) of II was added with constant stirring over a period of thirty minutes to an ice cold ethereal solution of diazomethane (approximately 0.1 mole). The diazomethane was prepared from nitrosomethylurea.^{16,17} Stirring and cooling were continued for three hours and the mixture allowed to stand overnight in the refrigerator. Filtration and concentration of the filtrate gave a yellow solid which, on recrystallization from benzene-petroleum ether (b. p. 70–80°), weighed 1.6 g. (23%). The yellow crystals melt at 144.5–145.5° with decomposition. The use of a larger excess of diazomethane (approximately 0.14 mole) gave a 30% yield. The compound decomposed so violently on heating slightly above its melting point that it was not analyzed.

1-Benzo(f)quinolyl Bromomethyl Ketone (IV).—To 20 ml. of 48% hydrobromic acid was added 1.6 g. (0.006 mole) of III in small portions with constant stirring. After twenty minutes the solution was diluted with four times its volume of water, cooled internally and externally with ice and made alkaline with dilute sodium hydroxide. The solid was filtered immediately, dried and crystallized from a small volume of acetone and then from absolute ethanol. The yield was 1.5 g. (77%) of slightly yellow needles; m. p. 132–133°.

Anal. Calcd. for C₁₅H₁₀BrNO: C, 60.02; H, 3.36. Found: C, 60.20, 60.25; H, 3.48, 3.50.

3-Hydroxy-1-methylbenzo(f)quinoline (V).—A mixture of 26 g. (0.115 mole) of acetoaceto- β -naphthalide and 75 ml. of concentrated sulfuric acid was heated on a boiling water-bath for fifteen minutes with constant shaking. The resulting solution was poured with stirring into 200 ml. of water and a white solid immediately separated. The product was filtered, triturated with dilute ammonium hydroxide and washed with water; yield 18 g. (75%), m. p. 285–286°. Knorr¹⁰ and Gibson, *et al.*,¹¹ prepared this compound by cyclization of acetoaceto- β -naphthalide with concentrated hydrochloric acid and give a melting point of 286°.

3-Chloro-1-methylbenzo(f)quinoline (VI).—A solution of 22.5 g. (0.107 mole) of V, 160 ml. of phosphorus oxychloride and 24 g. of phosphorus pentachloride was refluxed for six hours. The chlorides of phosphorus were removed at reduced pressure and the residue broken up with ice and ice water. The solid was filtered, dissolved in 80 ml. of 12 *N* hydrochloric acid and the solution filtered through a glass cloth. The yellow-brown filtrate was added dropwise to 500 ml. of water. The product was collected by

filtration, triturated with dilute ammonium hydroxide and washed with water. The white solid was crystallized from acetone to give white needles of m. p. 155°; yield 14.6 g. (60%). Gibson, *et al.*, give a m. p. of 153–154°.

1-Methylbenzo(f)quinoline (VII).—A mixture of 29.2 g. (0.128 mole) of VI, 200 ml. of water, 150 ml. of 12 *N* hydrochloric acid, 280 ml. of 95% ethanol and 22.5 g. of mossy tin was refluxed for eighteen hours, at the end of which time VI had completely dissolved. The solution was decanted from a small amount of unreacted tin and most of the alcohol removed by distillation. The mixture was made definitely alkaline with sodium hydroxide, warmed to decompose the stannous salt and extracted with ether until the ethereal extracts were colorless. The ether layers were combined, decolorized with carbon, and the ether removed to give an oil that solidified at room temperature. The solid was recrystallized from acetone-water to give white needles of m. p. 98–99°; yield 16 g. (65%).

Reed gives a m. p. of 112°, while Knorr and Gibson, *et al.*, give a m. p. of 91–92° for VII.

The methyl compound (VII) was also prepared by a catalytic reduction. To a solution of 2.26 g. (0.01 mole) of VI in acetone and ethanol was added 20 ml. of 10% alcoholic potassium hydroxide and 4 g. of palladium-on-barium sulfate catalyst. The reduction was begun at a pressure of two pounds. The excess solvent was removed by distillation and VII crystallized on the addition of water to give white needles of m. p. 98–99°; yield 1.7 g. (88%).

Anal. Calcd. for C₁₄H₁₁N: C, 87.01; H, 5.74. Found: C, 87.29, 87.33; H, 5.92, 5.94.

1-Formylbenzo(f)quinoline (VIII).—A solution of 17 g. (0.0882 mole) of VII in 150 ml. of dry xylene was placed in a 3-necked flask and heated by means of an oil-bath maintained at 135°. Sublimed selenium dioxide (14.7 g.) was added in small portions over a period of forty-five minutes with constant stirring. The temperature was maintained at 135° and stirring continued for one hour longer.

The reaction mixture was cooled, filtered and the xylene removed by steam distillation. Extraction of the residue with ether, followed by decolorization with carbon and the addition of petroleum ether (b. p. 70–80°) gave 12.6 g. of light tan crystals of m. p. 74–77°. A second crystallization from ether-petroleum ether gave white needles of m. p. 81.5–82.5°; yield, 11.5 g. (63%). The melting point remains unchanged after recrystallization from ethanol-water.

Anal. Calcd. for C₁₄H₉NO: C, 81.14; H, 4.38. Found: C, 80.92, 81.12; H, 4.58, 4.56.

The fluffy, yellow 2,4-dinitrophenylhydrazone melts at 270–271° with decomposition.

Extraction of the selenium residue with dilute sodium hydroxide, followed by decolorization with carbon and acidification with glacial acetic acid, gave a small amount of 1-carboxybenzo(f)quinoline; m. p. 300–301°.

β -[1-Benzo(f)quinolyl]- β -hydroxy- α -nitroethane (IX).—A solution of 2.5 g. (0.041 mole) of nitromethane, 10 drops of diethylamine and 10 ml. of absolute ethanol was cooled and 2.5 g. (0.0121 mole) of VIII in 30 ml. of absolute ethanol added. The solution was allowed to stand at room temperature for twenty-four hours and then cooled to give yellow crystals that were collected by filtration. Recrystallization from 90% ethanol gave slightly yellow crystals of m. p. 169–170° with decomposition; yield, 2.0 g. (62%).

Anal. Calcd. for C₁₅H₁₂N₂O₃: C, 67.15; H, 4.51. Found: C, 67.43, 67.38; H, 4.67, 4.63.

1-Benzo(f)quinolylglycolyl-1-benzo(f)quinoline (X).—To a solution of 2.07 g. (0.01 mole) of VIII in 20 ml. of 95% ethanol was added a solution of 0.125 g. of sodium cyanide in 10 ml. of water. The resulting solution was refluxed for thirty minutes, the mixture cooled and the solid collected by filtration. The product was washed with water and ethanol. The yellow solid weighed 1.7 g. (82%) and is insoluble in alcohol, benzene, toluene and

(16) Arndt, Loewe and Avan, *Ber.*, **73B**, 606 (1940).

(17) Arndt, "Organic Syntheses," **15**, 3 (1935).

acetone. It was recrystallized from a water-acetic acid mixture to give a yellow powder of m. p. 272–273° with decomposition.

Anal. Calcd. for $C_{28}H_{18}N_2O_2$: C, 81.14; H, 4.38. Found: C, 81.43, 81.40; H, 4.25, 4.29.

Diphenacyl-1-benzo(f)quinolylmethane (XI).—To a mixture of 1.2 g. (0.01 mole) of acetophenone, 21 ml. of 10% sodium hydroxide, 25 ml. of 95% ethanol and a few chips of ice, was added 1.0 g. (0.0048 mole) of VIII in 25 ml. of 95% ethanol. The resulting solution was shaken and allowed to stand overnight at room temperature. After cooling, the solid was collected by filtration and recrystallized from 90% ethanol to give fine, white needles of m. p. 146.5–147.5°; yield, 0.95 g. (46%).

Anal. Calcd. for $C_{30}H_{22}NO_2$: C, 83.89; H, 5.40. Found: C, 84.10, 84.13; H, 5.60, 5.59.

1-Benzo(f)quinolylcarbinol (XII).—A solution of 3.4 g. of potassium hydroxide in 25 ml. of methanol was heated to 60°, and a solution of 5.0 g. (0.025 mole) of VIII and 2.62 ml. of formalin in 50 ml. of methanol added with constant stirring. The stirring was continued and the temperature maintained at 60–70° for three hours. Most of the alcohol was removed by distillation and the residue poured into water. The solid was removed by filtration and crystallized from benzene to give a white powder of m. p. 171–175° after softening at 164°; yield, 2.8 g. (56%).

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30. Found: C, 80.41, 80.04; H, 5.57, 5.57.

5,6-Benzocinchoninal-*p*-hydroxyaniline (XIII).—To a solution of 7.8 g. (0.0377 mole) of VIII in 45 ml. of *n*-butanol and 45 ml. of toluene, was added 4.5 g. (0.0413 mole) of *p*-aminophenol in 45 ml. of *n*-butanol. A few drops of diethylamine were added and the solution refluxed for four hours. After cooling, the solid was collected by filtration and washed with ethanol. The yellow product weighed 9.4 g. (83%); m. p. 241–242° with decomposition. An analytical sample was obtained by recrystallization from methyl alcohol to give yellow needles of m. p. 243–243.5° with decomposition.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73. Found: C, 80.49, 80.64; H, 4.92, 4.95.

5,6-Benzocinchoninalaniline (XIV).—In a manner similar to the preparation of XIII, aniline and VIII were condensed to give XIV. The product was crystallized from benzene-petroleum ether to give a 67% yield of yellow needles of m. p. 202–205°, with decomposition, after softening at 186°.

Anal. Calcd. for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00. Found: C, 85.22, 85.30; H, 5.28, 5.23.

5,6-Benzocinchoninal-*p*-[1-(3,4-dimethyl-1,2,5-triazolyl)]-aniline (XV).—Similar to the preparation of XIII, 1-(*p*-aminophenyl)-3,4-dimethyl-1,2,5-triazole and VIII were condensed to give XV. The yield was 71% of yellow crystals of m. p. 181–182° from 90% ethanol.

Anal. Calcd. for $C_{24}H_{19}N_5$: C, 76.37; H, 5.07. Found: C, 76.52, 76.58; H, 5.21, 5.19.

8-(5,6-Benzocinchoninalamino)-6-methoxyquinoline (XVI).—In a manner similar to the preparation of XIII, 6-methoxy-8-aminoquinoline and VIII reacted to give XVI. After crystallization from absolute ethanol, there

was obtained yellow crystals of m. p. 208.5–209.5°; yield 61%.

Anal. Calcd. for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72. Found: C, 79.38, 79.45; H, 4.87, 4.93.

1-(*p*-Hydroxyanilinomethyl)-benzo(f)quinoline (XVII).—To a dilute sodium hydroxide solution of 3.0 g. (0.01 mole) of XIII was added 2.0 g. of zinc dust and the mixture refluxed for three and one-half hours. The unreacted zinc was removed by filtration and the filtrate made slightly acid to litmus with dilute hydrochloric acid. The solid was filtered, triturated with very dilute alkali, washed with dilute acetic acid and finally washed with water. The product was crystallized from ethanol-water to give a white powder of m. p. 212.5° after softening at 206°; yield, 0.5 g. (17%).

The amine XVII was also prepared by a catalytic reduction. To a hot solution of 1.0 g. of XIII in 95% ethanol was added 2.5 g. of palladium-on-barium sulfate catalyst and the reduction begun at a hydrogen pressure of eight pounds. After two hours, the mixture was reheated, 1.0 g. of catalyst added and the reduction continued for another hour.

The catalyst was removed by filtration and the volume of the filtrate reduced by distillation. On cooling, white crystals separated of m. p. 212°. A mixed melting point with the product from the zinc reduction showed no depression.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37. Found: C, 79.77, 79.85; H, 5.59, 5.63.

1-Formylbenzo(f)quinoline Oxime (XVIII).—The oxime of VIII was prepared in the usual manner in 84% yield. The product was recrystallized from 80% ethanol to give a white solid of m. p. 223–224° after softening at 210°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54. Found: C, 75.78, 75.83; H, 4.49, 4.58.

Summary

The preparation of 1-diazoacetylbenzo(f)quinoline is described. This compound was converted to 1-benzo(f)quinolyl bromomethyl ketone. 1-Methylbenzo(f)quinoline was synthesized and oxidized to 1-formylbenzo(f)quinoline. This aldehyde was condensed with nitromethane to yield β -[1-benzo(f)quinolyl]- β -hydroxy- α -nitroethane and with acetophenone to give diphenacyl-1-benzo(f)quinolylmethane. 1'-Benzo(f)quinolylglycolyl-1-benzo(f)quinoline and 1-benzo(f)quinolylcarbinol were also prepared.

1-Formylbenzo(f)quinoline was condensed with appropriate amines to give 5,6-benzocinchoninal-*p*-hydroxyaniline, 5,6-benzocinchoninalaniline, 5,6-benzocinchoninal-*p*-[1-(3,4-dimethyl-1,2,5-triazolyl)]-aniline and 8-(5,6-benzocinchoninalamino)-6-methoxyquinoline. 5,6-Benzocinchoninal-*p*-hydroxyaniline was reduced to 1-(*p*-hydroxyanilinomethyl)-benzo(f)quinoline.

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