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

Some Derivatives of 7-Methoxy- and 10-Methoxybenzo(f)quinoline

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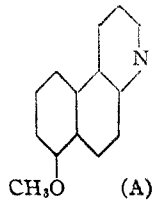
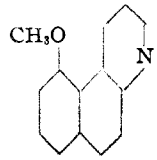
In an earlier paper[2] the preparation of a number of 1-substituted aminobenzo(f)quinolines was described. As a continuation of this work the synthesis of two series of methoxybenzo(f)quinolines with a basic substituent in the 1-position has been undertaken. It was hoped that the presence of the methoxyl would enhance the antimalarial activity of this type of compound. Pharmacological testing of a number of these derivatives is in progress.

The particular isomers chosen for study were 7-methoxybenzo(f)quinoline (A) and 10-methoxybenzo(f)quinoline (B).



(A)



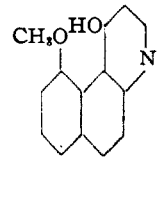
(B)

The starting materials required were 5-methoxy-2-naphthylamine and 8-methoxy-2-naphthylamine. Synthesis of neither of these compounds has been reported in the literature. The aminonaphthols, from which the methyl ethers were prepared, were obtained by the alkali fusion of the appropriate naphthylaminesulfonic acid. To insure efficient conversion of the naphthols to their methyl ethers with dimethyl sulfate, it was necessary to protect the amino groups by acetylation, the acetyl groups being removed by subsequent hydrolysis.

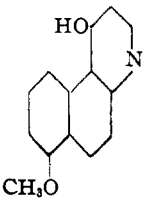
In this investigation the intermediate, 2-acetamido-5-naphthol, was isolated as a stable crystalline hydrate with a melting point higher than that reported by earlier workers.[3,4] Since 8-methoxy-2-naphthylamine was an unstable oil, it was isolated as the hydrochloride.

The conversion of the methoxyamines into the desired methoxybenzo(f)quinolines was accomplished by previously described methods.[2]

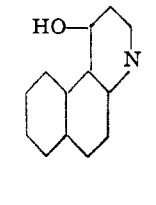
In order to introduce a basic substituent into the 1-position it was necessary to replace the hydroxyl with the more reactive chloro group which, normally, is easily displaced by an amino group. The 7-methoxy isomer reacted smoothly with phosphorus oxychloride to give the desired chloro compound, but all of our attempts to replace the hydroxyl in the 10-methoxy isomer were unsuccessful. It is believed that the group in the 10- or *peri*-position exerts a blocking effect upon the 1-position of the nucleus. Furthermore, IX differed noticeably from XVII and XXI,[2] in other properties, namely, melting point, color and solubility in alkali.



(IX)
m. p. 183°, yellow, insol. in OH^-



(XVII)
m. p. 309°, white, sol. in OH^-



(XXI)
m. p. 288°, white, sol. in OH^-

Two amines, morpholine and piperidine, were condensed with 1-chloro-7-methoxybenzo(f)quinoline yielding the corresponding 1-substituted aminobenzo(f)quinolines.

Experimental

2-Naphthylamine-5-sulfonic acid (I) and 2-naphthylamine-8-sulfonic acid (II) were prepared by the sulfonation of 2-naphthylamine according to the procedure of Green and Vakil.[5]

2-Amino-8-naphthol (III).—A mixture of 83 g. of II and 250 g. of potassium hydroxide was heated in an iron autoclave, equipped with a stirrer, for two and one-half hours at 260°. The fusion melt was cooled and treated with two liters of water. Some insoluble tarry material was removed by filtration and the solution was acidified with concentrated hydrochloric acid. The mixture was filtered again to remove the acid-insoluble portion and the filtrate was neutralized with sodium bicarbonate. The crude product which precipitated was collected on a filter, washed and dried; yield, 44 g. (74%). This was used to prepare the acetyl derivative without further purification. A portion was crystallized from water, then ethanol, yielding pale pink crystals melting at 156–158°; lit.[6] gives 158°.

2-Acetamido-8-naphthol (IV).—Twenty-five grams of III was refluxed briefly in 70 ml. of glacial acetic acid and 30 ml. of acetic anhydride. The mixture was poured into 500 ml. of water and the resulting oil solidified slowly. The crude product was taken up in dilute alkali, filtered and reprecipitated with hydrochloric acid. It was collected by filtration, washed with water and dried; yield, 29 g. (90%). After recrystallization from ethanol it melted at 215–216°. Friedländer and Zinberg reported 210–211°.[7]

2-Acetamido-8-methoxynaphthalene (V).—A solution of 24 g. of IV in 200 ml. of 2 *N* sodium hydroxide was placed in a 500-ml. three-necked flask fitted with a stirrer. Thirty milliliters of dimethyl sulfate was added slowly from a dropping funnel during a period of six hours, the temperature being held at 30°. The product, which precipitated as the reaction proceeded, was collected by filtration, washed with 0.5 *N* alkali and then with water. It was decolorized by charcoal treatment in ethanol and crystallized from ethanol–water solution; yield, 18 g. (70%).

This compound is a white crystalline solid melting at 163–164°. It is soluble in the common organic solvents and sparingly soluble in hot water.

(1) Parke, Davis and Company Fellow.
(2) Mueller and Hamilton, THIS JOURNAL, **65**, 1017 (1943).
(3) Sander, *Ber.*, **58**, 829 (1925).
(4) Bucherer and Wahl, *J. prakt. Chem.*, [2] **108**, 143 (1921).
(5) Green and Vakil, *J. Chem. Soc.*, **113**, 35 (1918).
(6) Newton, English Patent 5148, *J. Soc. Chem. Ind.*, **14**, 264 (1895).
(7) Friedländer and Zinberg, *Ber.*, **29**, 40 (1896).

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09. Found: C, 72.27, 72.40; H, 6.02, 6.15.

8-Methoxy-2-naphthylamine Hydrochloride (VI).—Twenty-three grams of V was refluxed in 200 ml. of ethanol containing 30 ml. of concentrated hydrochloric acid. After three hours the alcohol was removed by distillation and 200 ml. of water was introduced. The resulting solution was treated with charcoal until it was nearly colorless, then concentrated to 100 ml. and cooled slowly. The amine hydrochloride precipitated in long light-pink needles which were collected on a filter. Further concentration of the filtrate yielded additional product; combined yield, 18 g. (81%).

Anal. Calcd. for $C_{11}H_{12}ONCl$: Cl, 16.91. Found: Cl, 16.89, 16.98.

1-Hydroxy-3-carbethoxy-10-methoxybenzo(f)quinoline (VII).—Diethyl sodio-oxalacetate (2 g.) was added to 2 g. of VI in 25 ml. of absolute ethanol. A drop of concentrated hydrochloric acid was introduced and the mixture was shaken intermittently for sixty hours. It was then poured into 70 ml. of water and the alcohol was evaporated. The viscous yellow-brown oil which separated was extracted with ether. The ether was removed *in vacuo*, and the methoxynaphthyliminosuccinate was added slowly to 50 ml. of mineral oil which had been preheated to 260°. After five minutes the mixture was cooled and the crude product separated upon the addition of ether. It was washed with small portions of benzene, decolorized with charcoal and crystallized from ethanol–water mixture yielding 1.7 g. (61%) of pale white crystals; m. p. 181–183°.

Anal. Calcd. for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.09; N, 4.71. Found: C, 68.59; H, 5.15; N, 4.70.

1-Hydroxy-3-carboxy-10-methoxybenzo(f)quinoline (VIII) resulted in quantitative yield when VII was refluxed briefly in 2 *N* alkali and the resulting solution was acidified with dilute hydrochloric acid. The bright-yellow gelatinous product was digested for two hours before it was collected on a filter, washed and dried.

It is a slightly hygroscopic amorphous powder which decomposes at 250–253° with loss of carbon dioxide. It is soluble in basic solutions, but very insoluble in the usual organic solvents.

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12. Found: C, 66.79; H, 3.99.

This acid forms a deep-yellow crystalline hydrochloride from 6 *N* hydrochloric acid solution. The salt hydrolyzes readily in water.

Anal. Calcd. for $C_{15}H_{12}O_4NCl$: C, 59.12; H, 3.97. Found: C, 58.77; H, 3.99.

1-Hydroxy-10-methoxybenzo(f)quinoline (IX).—When 2.5 g. of VIII was heated at its decomposition point (250°) until no more gas was evolved, IX was formed in poor yield. The black residue was pulverized; extracted with 100 ml. of boiling ethanol and filtered free of insoluble material. The extract was clarified with charcoal and concentrated to yield 0.6 g. (28%) of bright yellow crystals which were recrystallized from ethanol–water mixture; m. p. 180–182°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92. Found: C, 74.62, 74.81; H, 4.92, 5.01.

2-Amino-5-naphthol (X) was prepared from I by the same procedure used for making the 2,8 isomer. The product was obtained in yields of 70%; m. p. 198–200°; lit.[4] gives 199.5°.

2-Acetamido-5-naphthol Monohydrate (XI).—Fifty grams of X was treated with 50 ml. of glacial acetic acid and 18 ml. of acetic anhydride. The mixture was refluxed for ten minutes before being poured into 300 ml. of water. The crude product crystallized slowly to yield a gray solid which was reprecipitated from 2 *N* alkali solution with dilute acid. It was decolorized with charcoal and crystallized from ethanol–water solution as nearly white needles; yield (63%); m. p. 117–121°. Sander[3] and Bucherer and Wahl[4] reported 100° and 98–99°, respectively.

This compound contains water of crystallization. Its anhydrous form appeared as an oil and was not obtained in the solid state. It is soluble in alkaline solutions and in the usual organic solvents.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; H_2O, 8.21. Found: C, 65.63, 65.80; H, 5.83, 6.05; H_2O, 8.17.

2-Acetamido-5-methoxynaphthalene (XII) resulted upon treatment of XI with dimethyl sulfate according to the procedure for making the 8-methoxy isomer. Yields up to 61% were obtained. The product crystallized from methanol–water solution as white platelets, m. p. 151–152°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09. Found: C, 72.30, 72.39; H, 6.07, 6.08.

5-Methoxy-2-naphthylamine Hydrochloride (XIII).—A suspension of 8 g. of XII in 250 ml. of 5 *N* hydrochloric acid was refluxed for three hours, during which time the solid dissolved. The hot solution was treated with decolorizing charcoal, filtered and slowly cooled. The sparingly soluble hydrochloride precipitated as tiny gray crystals and was collected by filtration. The filtrate was concentrated to yield more product. When recrystallized from hot water the hydrochloride appeared as long white needles; yield 7 g. (95%).

Anal. Calcd. for $C_{11}H_{12}ONCl$: Cl, 16.91. Found: Cl, 16.99, 16.88.

5-Methoxy-2-naphthylamine (XIV).—When XIII was neutralized with cold alcoholic alkali solution, and the alcohol evaporated, the free amine was liberated quantitatively. It crystallized from ethanol–water solution in pink platelets, m. p. 71–72°. Solutions of this compound darken on standing.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40. Found: C, 75.98, 76.04; H, 6.43, 6.35.

1-Hydroxy-3-carbethoxy-7-methoxybenzo(f)quinoline (XV).—An intimate mixture of XIV (3.5 g.) and diethyl oxalacetate (4 g.) was desiccated over concentrated sulfuric acid for three days with occasional stirring. The viscous brown anil which formed was added with stirring to 100 ml. of preheated (250°) mineral oil. After ten minutes the mixture was cooled, and a light-yellow solid separated. It was removed and washed with benzene, yielding 4 g. (66%) of a light-brown crystalline powder. Repeated crystallizations from ethanol gave nearly white needles, m. p. 256–258°.

Anal. Calcd. for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.09. Found: C, 68.57, 68.75; H, 5.02, 5.07.

1-Hydroxy-3-carboxy-7-methoyxbenzo(f)quinoline (XVI) was formed when XV was heated briefly in 2 *N* alkali and the resulting solution was acidified with dilute hydrochloric acid. The bright-yellow amorphous product was digested on the steam-bath for one hour, collected on a filter, washed and dried. Purification was effected by regenerating the acid from its sodium salt solution after charcoal treatment, m. p. 292–295°, (dec.).

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12 Found: C, 66.84, 66.69; H, 4.29. 4.17.

1-Hydroxy-7-methoxybenzo(f)quinoline (XVII).—By means of a molten potassium–sodium nitrate bath, 0.35 g. of XVI was heated carefully to 295°. When the first sign of decomposition was noticed the temperature was lowered and maintained at 280° until the evolution of carbon dioxide had ceased. The brittle residue was extracted with 200 ml. of ethanol and the extract was decolorized with charcoal. The product precipitated when water was added and the mixture was concentrated. It was taken up in 40 ml. of 2 *N* hydrochloric acid and treated again with charcoal, yielding a bright-yellow solution. When made basic with ammonium hydroxide, a white finely-divided crystalline solid precipitated. This was digested on the steam-bath before being collected, dried and weighed, m. p. 308–311°. The yield was 0.14 g. (55%).

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92. Found: C, 74.31, 74.44; H, 5.08, 5.09.

1-Chloro-7-methoxybenzo(f)quinoline (XVIII).—A mixture of 10 ml. of phosphorus oxychloride and 0.5 g. of

XVII was refluxed for four hours. Most of the excess phosphorus oxychloride was removed by distillation and the residue was poured onto 30 g. of ice. The resulting mixture was heated to boiling, treated with charcoal, filtered and cooled. It was made basic with aqueous sodium hydroxide (10%) yielding a white curdy precipitate. The product was crystallized from ethanol–water mixture from which it formed long silky needles, m. p. 118–119°; lit.[8] gives 119°; yield, 0.4 g. (74%).

Anal. Calcd. for $C_{14}H_{10}ONCl$: C, 69.00; H, 4.30. Found: C, 69.08, 69.23; H, 4.28, 4.41.

1-Morpholino-7-methoxybenzo(f)quinoline (XIX) was formed when 0.3 g. of XVIII and 2 ml. of morpholine was refluxed for eight hours. The mixture was poured into 25 ml. of water and a white precipitate formed. The product was treated with charcoal in dilute hydrochloric acid and regenerated by the addition of alkali. A small amount of gummy impurity was removed at *p*H of 6–7. Two crystallizations from ethanol–water, gave tiny white crystals, m. p. 136–137°.

This compound forms a water soluble yellow hydrochloride and is also soluble in the common organic solvents.

Anal. Calcd. for $C_{16}H_{16}O_2N_2$: C, 73.45; H, 6.16. Found: C, 73.54, 73.23; H, 6.16, 6.23.

1-Piperidino-7-methoxybenzo(f)quinoline (XX) was prepared from XVIII and piperidine, similar to the morpholine analog. The product crystallized from acetone–water mixture as white needles, m. p. 116–117°.

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.06; H, 6.90. Found: C, 78.24; H, 7.13.

(8) Carpmael, English Patent 481,874, *Chem. Zentr.*, **109**, II, 117 (1938).

Summary

1. The preparation of the hydrochlorides of 5-methoxy- and 8-methoxy-2-naphthylamine, respectively, from the corresponding aminonaphthols, has been described.

2. These methoxyamines have been converted to benzo(f)quinoline derivatives by condensation with oxalacetic ester and cyclization of the resulting products.

3. 1-Hydroxy-7-methoxybenzo(f)quinoline yielded 1-chloro-7-methoxybenzo(f)quinoline which gave the 1-substituted amino derivatives with morpholine and piperidine.

4. Apparently steric hindrance by the 10-methoxyl in 1-hydroxy-10-methoxybenzo(f)-quinoline prevented replacement of the hydroxyl group by halogen.

LINCOLN, NEBRASKA RECEIVED JANUARY 31, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

The Carbonation and Carbethoxylation of Certain Ketones Using Sodium Triphenylmethide Reagent: β-Keto Ester Synthesis[1,2,3]

BY ERWIN BAUMGARTEN, ROBERT LEVINE AND CHARLES R. HAUSER

Ketones may be converted to β-keto esters by carbethoxylation by means of an alkyl carbonate or by carbonation followed by esterification of the resulting β-keto-acid. Both reactions are brought about by bases. In the present paper, certain examples of these reactions brought about by sodium triphenylmethide are discussed.

Carbethoxylations.—The carbethoxylation of a number of ketones with diethyl carbonate has been effected by means of sodium ethoxide.[4] The reaction has failed, however, with certain ketones in the presence of this base.[4] One of these ketones, di-isobutyl ketone, has now been carbethoxylated with diethyl carbonate by means of the stronger base, sodium triphenylmethide, to form ethyl α-isovalerylisovalerate. Since certain ketones react

$$[(CH_3)_2CHCH_2]_2CO \xrightarrow[\text{by } CO(OC_2H_5)_2]{(C_6H_5)_3CNa \text{ followed}} (CH_3)_2CHCH_2COCH(COOC_2H_5)CH(CH_3)_2$$

with diethyl carbonate in the presence of sodium ethoxide to give an ethyl vinyl carbonate (the "oxygen derivative" of the ketone),[4] instead of the β-keto ester (the "carbon derivative" of the ketone), the β-keto ester obtained in the present case has been characterized not only by the usual ketonic cleavage but also by acidic cleavage. While the regeneration of the original ketone on ketonic cleavage might result from either the β-keto ester or the "oxygen derivative," the formation of isovaleric acid on acidic cleavage could result only from the β-keto ester.

Previous attempts to carbethoxylate methyl ethyl ketone with diethyl carbonate by means of sodium ethoxide[4] or sodium triphenylmethide[5] have failed, presumably because of the ease with which this ketone self-condenses. We have found that the carbethoxylation fails even in the presence of the more reactive carbethoxylating reagent, ethyl 4-phenyl phenyl carbonate, and sodium triphenylmethide.

Carbonations Followed by Esterification.—The carbonation of ketones to form β-keto acids has been carried out previously apparently only with camphor and a few cyclic ketones,[6] sodium amide being used to effect the reaction.

(1) Paper XXIV on "Condensations"; paper XXIII, THIS JOURNAL, **66**, 345 (1944).

(2) Presented at the Pittsburgh meeting of the A. C. S., Sept., 1943.

(3) Supported in part by a grant from the Duke University Research Council.

(4) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2252 (1941).

(5) Abramovitch and Hauser, *ibid.*, **64**, 2271 (1942).

(6) Bredt, *J. prakt. Chem.*, [2] **104**, 9 (1922); [2] **131**, 132 (1932); Gardner, Perkin and Watson, *J. Chem. Soc.*, **97**, 1756 (1910); Koetz and Grethe, *J. prakt. Chem.*, [2] **80**, 473 (1909).