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

The Synthesis of 2- and 3-Substituted Naphth[1,2]imidazoles

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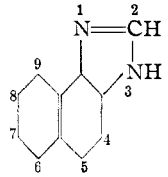
Many of the compounds which have been synthesized in this Laboratory because of possible interest as antimalarial agents have included the benzoquinoline nucleus as part of the structure.[2] The syntheses of a number of similar compounds which are based on the naphth[1,2]imidazole nucleus (I) have been studied and are reported in the



I

present investigation. The antimalarial screening of one derivative of the proposed nucleus, 2-aminonaphth[1,2]-imidazole, was reported after the inception of this work; the quinine equivalent was less than 0.08.[3]

The Phillips reaction[4] was used in the preparation of the 2,3-disubstituted naphth[1,2]imidazoles. The parent diamine in the disubstituted series is 1-amino-2-methylaminonaphthalene. The most promising synthesis for this unreported diamine was by reduction of 1-nitroso-2-methylaminonaphthalene. The necessary aminonitroso compound was prepared very simply according to the method of Fischer, Dietrich, and Weiss.[5] Methods usually employed for the reduction of nitroso compounds failed because of the formation of extremely insoluble complexes between the aminonitroso compound and various metallic ions. Reduction with molecular hydrogen and Raney nickel catalyst proceeded very smoothly and in excellent yields.

Literature reports[6] and preliminary experiments with ethyl ε-diethylaminocaproate indicated that amino acids do not undergo the Phillips reaction, and so the tertiary amine groups which were desired in the final structure were introduced into the molecule after the ring closure; the secondary hydroxyl group could be present in the molecule of the carboxylic acid. The desired intermediates were therefore prepared from the acids listed below, chloroacetic acid and β-chlorolactic acid. The respective products, 2-chloromethyl-3-methylnaphth[1,2]imidazole and 2-(α-hydroxy-β-choroethyl)-3-methylnapth[1,2]imidazole, were then treated with morpholine and piperidine to give products of the desired structure.

The naphth[1,2]imidazoles which are substituted only in the 2-position can be regarded as derived from 1,2-diaminonaphthalene. However, the Phillips reaction could not be successfully applied to this diamine because of the insolubility of the amine salt in acid of the required strength. Attempts to prepare the desired intermediate by fusion of the diamine and chloro acids were also unsuccessful. Hydroxy compounds have been converted to chloro derivatives in the benzimidazole series quite readily[6,7] and therefore 2-hydroxymethylnaphth[1,2]imidazole was prepared by fusion of the diamine with glycolic acid, the method used by Sachs for the preparation of a perimidine.[8] However, preliminary experiments on the conversion of 2-hydroxymethylnaphth[1,2]imidazole to the desired chloromethyl compound by means of thionyl chloride showed no promise of success because of the insolubility of the hydroxy compound and therefore a third and successful approach was made. 1-Nitro-2-aminonaphthalene was converted to N-(1-nitro-2-naphthyl)-α-chloroacetamide by treatment with chloroacetyl chloride; the halogen on the acetyl group of this compound is active and readily reacted with an amine such as morpholine. The product of this reaction, N-(1-nitro-2-naphthyl)-α-morpholinoacetamide, was converted to the desired compound, 2-morpholinomethylnaphth[1,2]imidazole, by two different methods. Reductive ring closure,[9] refluxing the nitro amide in alcohol with zinc and hydrochloric acid, accomplished the transformation in one step. A somewhat longer but more satisfactory synthesis was through the catalytic reduction of the nitro compound to N-(1-amino-2-naphthyl)-α-morpholinoacetamide; the ring closure was then accomplished by the method of Kelly and Day.[9] In this series the placement of the hydrogen on either nitrogen of the ring is immaterial since the tautomeric nature of the structure has been demonstrated.[9] The compounds of the series with hydrogen on the heterocyclic nitrogen rather than a methyl group were characterized by a very high melting point, very low solubility in organic solvents, and solubility in both aqueous alkali and acid.

Experimental[10]

1-Nitrosonaphthol-2.—This nitroso compound was prepared by the direct nitrosation of naphthol-2.[11] For best results in the subsequent catalytic reduction it was

(1) Parke, Davis and Company Fellow.

(2) Benson and Hamilton, THIS JOURNAL, **68**, 2644 (1946).

(3) "A Survey of Antimalarial Drugs 1941–1945," ed. by F. Y. Wiselogle, J. W. Edwards, Ann Arbor, Mich., 1946, SN. 13,406.

(4) Phillips, *J. Chem. Soc.*, 2820 (1929).

(5) Fischer, Dietrich and Weiss, *J. prakt. Chem.*, **100**, 167 (1920).

(6) Hughes and Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 209 (1938).

(7) Skolnik, Miller and Day, THIS JOURNAL, **65**, 1854 (1943).

(8) Sachs, *Ann.*, **365**, 108 (1909).

(9) Kelly and Day, THIS JOURNAL, **67**, 1074 (1945).

(10) All melting points are corrected for stem emergence. We wish to thank Mr. Anton Kashas for the performance of a number of the carbon and hydrogen analyses.

(11) Marvel and Porter, "Organic Syntheses," Coll. Vol. I, ed. 2, John Wiley and Sons, New York, N. Y., 1941, p. 411.

necessary to recrystallize the crude yield from 88–100° ligroin.

1-Nitroso-2-methylaminonaphthalene (II).—A mixture of 100 ml. of water and 127 ml. of aqueous methylamine (25% methylamine by weight, 0.94 mole) was cooled to 15° and 34.6 g. (0.2 mole) of recrystallized 1-nitroso-naphthol-2 was slowly added. The mixture was warmed to 35° to complete solution of the salt. The mixture was allowed to stand at room temperature for twenty-four hours, during which time the product crystallized out in black platelets. Purification by solution in dilute hydrochloric acid, filtration, and precipitation with dilute ammonium hydroxide was sufficient for excellent results with the subsequent catalytic reduction. The product weighed 33.5 g. (90%). A sample which was recrystallized from methanol melted at 145–146°; literature values vary from 141–142° to 148–149°.[5]

1-Amino-2-methylaminonaphthalene Dihydrochloride (III).—A suspension of 18.6 g. of II in 115 ml. of absolute ethanol was reduced at room temperature with Raney nickel catalyst and molecular hydrogen at 50 lb. pressure. The calculated quantity of hydrogen was absorbed in twenty to twenty-five minutes and the pressure was constant thereafter. After removal of the catalyst, dry hydrogen chloride was passed into the cooled alcoholic solution and the product isolated as the dihydrochloride; yield, 23.3 g. (95%).

This new diamine was found to be an unstable oil with a blue fluorescence; it was always isolated and used as the dihydrochloride. The dihydrochloride salt, after solution in hot water and treatment with charcoal and recrystallization from dilute hydrochloric acid melted with decomposition at 194–196°. The diamine was characterized by the conversion to a known derivative and to three new compounds which are described in the following four procedures; the Phillips reaction with acetic, chloroacetic, lactic and β-chlorolactic acid was used in these conversions. A known compound, 2,3-dimethylnaph[1,2]imidazole,[12] was formed with acetic acid; the identities of the other three products were confirmed by the elementary analysis and by the results of succeeding reactions.

2,3-Dimethylnaphth[1,2]imidazole (IV).—A mixture of 1.0 g. of III, 1.6 ml. of acetic anhydride, and 8 ml. of 4 *N* hydrochloric acid was heated under reflux for one hour. The cooled solution was neutralized with solid sodium bicarbonate, whereupon a quantitative yield of 2,3-dimethylnaphth[1,2]imidazole was obtained in crystalline form. When recrystallized from dilute alcohol and from benzene, the product melted at 142–143°, the same value as reported in the literature.[12]

2-(α-Hydroxyethyl)-3-methylnaphth[1,2]imidazole (V).—A mixture of 1.8 g. (0.02 mole) of lactic acid and 2.45 g. (0.01 mole) of III was refluxed in 24 ml. of 4 *N* hydrochloric acid for six hours. The reaction mixture was cooled in ice and neutralized carefully with solid sodium bicarbonate. The crude yield of crystalline product weighed 2.2 g. (96%). A sample which was recrystallized from benzene and from alcohol melted at 184.1–184.6°.

Anal. Calcd. for $C_{14}H_{14}ON_2$: C, 74.31; H, 6.24. Found: C, 74.22; H, 6.37.

2-Chloromethyl-3-methylnaphth[1,2]imidazole (VI).—Technical chloroacetic acid (5.64 g., 0.06 mole) was dissolved in 72 ml. of 4 *N* hydrochloric acid and the mixture was heated on a steam-bath. Three 1.23-g. portions of III (total of 3.69 g., 0.015 mole) was added at thirty-minute intervals during the first hour of heating. The mixture was heated a total of four hours, after which it was cooled in ice, a layer of ether added, and the mixture carefully neutralized with sodium bicarbonate. The tar which formed during the addition of the first half of the total amount of base was skimmed off before the product began to precipitate. The dried crude yield was extracted with 75 ml. of 2:1 benzene–ligroin, the extract was treated with charcoal, filtered, and the product crystallized from the cooled solution; yield 1.2 g. (34%).

(12) Meldola and Lane, *J. Chem. Soc.*, **85**, 1602 (1904).

VI, similar to an analogous compound in the benzimidazole series,[13] is a powerful skin irritant. The compound was crystallized from benzene–ligroin mixtures and from absolute alcohol. The substance turns yellow at 150–155° and melts with decomposition at 160–162°.

Anal. Calcd. for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.81. Found: C, 67.70; H, 4.93.

2-(α-Hydroxy-β-chloroethyl)-3-methylnaphth[1,2]imidazole (VII).—A mixture of β-chlorolactic acid (7.46 g., 0.16 mole) and III (9.8 g., 0.04 mole) in 96 ml. of 3 *N* hydrochloric acid was heated on a steam-bath for seven hours. The subsequent procedure was the same as in the preparation of VI except that 135 ml. of benzene–ligroin was used for the extraction. A yield of 2.96 g. (29%) was obtained from experiments in which two of three separate lots of β-chlorolactic acid were used. With a third lot, identical with the other two as far as physical tests indicated, a yield of only 8–10% could be obtained. The product was recrystallized from benzene and from alcohol; m. p., 168.9–169.0°.

Anal. Calcd. for $C_{14}H_{13}ON_2Cl$: C, 64.49; H, 5.03. Found: C, 64.48; H, 5.11.

β-Chlorolactic Acid.—This acid was prepared by the oxidation of glycerol α-monochlorohydrin.[14] The chlorohydrin was made by the procedure of "Organic Syntheses" and redistilled before use[15]; the fraction which was collected between 117 and 120° at 13 mm. was used in the oxidation. The time required for the oxidation with nitric acid was considerably longer than that reported by Koelsch, but it was also noted that just a few degrees of variation in room temperature had a marked effect on the rate of this exothermic reaction.

A modified method of isolating the desired product was used. The oily crystalline mass of crude product was subjected to prolonged suction on a filter until practically all the oil was removed. The melting point of this product, 77–78°, was excellent, comparable to the values reported for recrystallized material, 77°[14] and 78.5–79.0°.[16]

2-Piperidinomethyl-3-methylnaphth[1,2]imidazole (VIII).—A solution of VI and a three-fold excess of piperidine in benzene was refluxed in benzene for two hours. The piperidine hydrochloride was removed by washing and the product isolated in 97% yield by evaporation of the benzene solution. The product was recrystallized from dilute alcohol and from ligroin; m. p., 134.8–135.0°.

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58. Found: C, 77.46; H, 7.63.

2-Morpholinomethyl-3-methylnaphth[1,2]imidazole (IX).—The same procedure was used as in the preparation of VIII, with morpholine in place of the piperidine. This very similar product melted at 134.0–134.4°.

Anal. Calcd. for $C_{17}H_{19}ON_3$: C, 72.58; H, 6.81; N, 14.94. Found: C, 72.67; H, 6.82; N, 14.92.

2-(α-Hydroxy-β-piperidinoethyl)-3-methylnaphth[1,2]imidazole (X).—A solution of VII in piperidine was heated on a steam-bath for three hours. The resulting mixture was poured into water and the product allowed to crystallize; the crude yield was 95%. The product was recrystallized from dilute alcohol and from benzene–ligroin. The crystals which were obtained from anhydrous solvents or which were very carefully dried melted at 149.2–149.6°.

Anal. Calcd. for $C_{19}H_{23}ON_3$: C, 73.76; H, 7.49. Found: C, 73.83; H, 7.61.

2-(α-Hydroxy-β-morpholinoethyl)-3-methylnaphth[1,2]imidazole (XI).—This compound was prepared from VII and morpholine by the same procedure as for the preparation of X. The product possessed the same properties as X, with respect to solubility, etc.; the melting point was 168.4–169.0°.

(13) Bloom and Day, *J. Org. Chem.*, **4**, 14 (1939).

(14) Koelsch, THIS JOURNAL, **52**, 1105 (1930).

(15) Conant and Quayle, "Organic Syntheses," Coll. Vol. I, ed. 2, John Wiley, New York, N. Y., 1941, p. 294.

(16) Smith, *Z. physik. Chem.*, **81**, 366 (1913).

Anal. Calcd. for $C_{18}H_{21}O_2N_3$: C, 69.43; H, 6.80. Found: C, 69.27; H, 6.87.

N-(1-Nitro-2-naphthyl)-α-chloroacetamide (XII).—Seven grams (0.07 mole) of precipitated chalk was suspended in a solution of 12.1 g. (0.064 mole) of 1-nitro-2-aminonaphthalene in 32 ml. of dry dioxane, and to this mixture a solution of 9.6 g. (0.085 mole) of redistilled chloroacetyl chloride in 18.6 ml. of dry dioxane was slowly added. The mixture was stirred and kept between 20 to 25° during the addition and then allowed to stand at room temperature for several days. The product was precipitated by the slow addition of 200 ml. of water, and after acidification the product was collected by filtration. The crude product was purified by crystallization from ligroin. By use of a Soxhlet extractor a yield of 88% of the purified product was obtained. A sample which was crystallized from benzene and from alcohol melted at 119.8–120.6°.

Anal. Calcd. for $C_{12}H_9O_3N_2Cl$: C, 54.33; H, 3.42. Found: C, 54.39; H, 3.50.

N-(1-Nitro-2-naphthyl)-α-morpholinoacetamide (XIII).—A solution of 18.0 g. (0.075 mole) of XII and 16.3 g. (0.1875 mole) of morpholine in 120 ml. of 80% ethanol was refluxed for one hour. The resulting mixture was cooled slowly, finally to −10°, and 19.3 g. (82%) of very pure product crystallized. A sample which was recrystallized from benzene–ligroin and from absolute alcohol melted at 131.9–132.5°.

Anal. Calcd. for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.44. Found: C, 61.04; H, 5.50.

N-(1-Amino-2-naphthyl)-α-morpholinoacetamide (XIV).—Fifteen grams of XIII was dissolved in 100 ml. of warm absolute alcohol, Raney nickel catalyst was added, and hydrogen under 50 pounds pressure admitted. The calculated quantity of hydrogen was slowly absorbed and the pressure subsequently remained constant. The final solution was warmed to dissolve the product which crystallized during the reaction, filtered, and upon cooling 8.0 g. of pure product (58%) was obtained. By precipitating the product as the dihydrochloride a yield of 82% was obtained. A sample which was recrystallized from benzene–ligroin, acetone, and absolute ethanol melted at 163.9–164.4°.

Anal. Calcd. for $C_{16}H_{19}O_2N_3$: C, 67.34; H, 6.71. Found: C, 67.36; H, 6.76.

2-Morpholinomethylnaphth[1,2]imidazole Dihydrochloride (XV): Reductive Ring Closure.—One gram of XIII was dissolved in 100 ml. of warm alcohol, 1.0 g. of granulated zinc was placed in the flask, and the solution was refluxed for seven hours. During this time 10 ml. of concentrated hydrochloric acid was added very slowly. The salt of the ring closure product precipitated during the reaction. This salt was freed from inorganic impurities by solution in water and the free base was obtained as an amorphous white solid upon neutralization of the solution with sodium bicarbonate. The dihydrochloride salt was prepared by addition of hydrogen chloride to an ethereal solution of the free base; the characteristics of this salt are described in the following section.

Ring Closure of XIV in Xylene.—One gram of XIV was refluxed in 80 ml. of xylene for one hour. The product was extracted with acid, the solution treated with charcoal, neutralized, and finally the amorphous free base was again isolated as the dihydrochloride salt. The amorphous free base was soluble in dilute acid and alkali and in organic solvents. The dihydrochloride was purified by recrystallization from ethanol which contained 3 to 4% of water; m. p. 241–243°.

Anal. Calcd. for $C_{16}H_{17}ON_3 \cdot 2HCl$: C, 56.47; H, 5.63; Cl, 20.84. Found: C, 56.24; H, 5.73; Cl, 20.74.

N-(1-Nitro-2-naphthyl)-α-anilinoacetamide.—A solution of 1.2 g. (0.0045 mole) of XII and 1.9 g. (0.02 mole) of aniline in 25 ml. of absolute ethanol were heated on a steam-bath for six hours. During this time the volume of solvent was allowed to decrease to 15 ml., and upon cooling the final mixture a precipitate of pure crystalline product was obtained which weighed 1.3 g. (87%). This compound was insoluble in dilute acid, but could be recrystallized from benzene–ligroin and alcohol; m. p. 171–172°.

Anal. Calcd. for $C_{18}H_{15}O_3N_3$: C, 67.28; H, 4.71. Found: C, 67.44; H, 4.84.

1,2-Diaminonaphthalene (XVI).—1-Nitro-2-aminonaphthalene in alcoholic solution was reduced at room temperature with Raney nickel catalyst and molecular hydrogen at 50 lb. pressure. The solvent was evaporated to a small volume and the product precipitated by the careful addition of water; yield, 71%. The crude product melted at 91–92°; literature values vary from 90–96°.[17]

2-Hydroxymethylnaphth[1,2]imidazole (XVII).—A mixture of XVI (3.6 g., 0.023 mole) and glycolic acid (1.8 g., 0.024 mole) was heated slowly up to 150°. The initially fluid mixture became viscous after a considerable amount of water had been lost, and after twenty minutes of heating 10 ml. of glycerol was added. Heating was continued for a total of two hours, and then the mixture was poured into 100 ml. of water. Ten milliliters of 6 *N* hydrochloric acid was added to the mixture, the solution was heated to boiling, treated with charcoal, and filtered while hot. The hydrochloride of XVII crystallized from the filtrate upon cooling; yield, 45%.

The free base is soluble in dilute acid, dilute alkali, and alcohol; it is very sparingly soluble in other organic solvents, but it can be recrystallized from acetone; m. p. 253–255° (dec.).

Anal. Calcd. for $C_{12}H_{10}ON_2$: C, 72.71; H, 5.09. Found: C, 72.78; H, 5.18.

Summary

A new diamine, 1-amino-2-methylaminonaphthalene, was prepared by reduction of 1-nitroso-2-methylaminonaphthalene. Naphth[1,2]imidazoles which are substituted in the 2- and 3-positions were prepared by the Phillips reaction between this diamine and acetic, lactic, chloroacetic, and β-chlorolactic acids. The products from the latter two acids were treated with piperidine and morpholine to give compounds of the desired structures, 2-piperidinomethyl-3-methylnaphth[1,2]-imidazole, 2-morpholinomethyl-3-methylnaphth-[1,2]imidazole, 2-(α-hydroxy-β-piperidinoethyl)-3-methylnaphth[1,2]imidazole, and 2-(α-hydroxy-β-morpholinoethyl)-3-methylnaphth[1,2]imidazole.

Naphth[1,2]imidazoles which are substituted only in the 2-position were prepared by the chloroacetylation of 1-nitro-2-aminonaphthalene, reaction of the chloro compound with morpholine to give N-(1-nitro-2-naphthyl)-α-morpholinoacetamide, and conversion of this compound to 2-morpholinomethylnaphth[1,2]imidazole by two different methods.

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(17) Bamberger and Schieffelin, *Ber.*, **22**, 1376 (1889).