2,4-DIHYDROXYQUINOLINE DERIVATIVES

VI.* SYNTHESIS AND SOME TRANSFORMATIONS OF 2,4-DIHYDROXY-3-(3-CHLOROCROTYL)QUINOLINE

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Instead of the expected 2,4-dihydroxy-3-quinolyl-3-butanol, the product of its cyclization in the form of the angular isomer – 2-methyl-5-hydroxypyrano[3,2-c]quinoline – is obtained in the reduction of 2,4-dihydroxy-3-quinolyl-3-butanone with aluminum isopropoxide. Some transformations of 2,4-dihydroxy-3-(3-chlorocrotyl)quinoline were investigated.

In connection with the search for routes to the synthesis of pyranoquinolines – the skeleton of a number of alkaloids – we carried out the reaction of 3-chlorocrotylmalonic ester with aniline and obtained 2,4-dihydroxy-3-(3-chlorocrotyl)quinoline (I) in 50% yield. Simultaneously formed in 22% yield is 3-chlorocrotylmalonic acid dianilide (II), heating of which with $AlCl_3$ + NaCl at 220°C brings about cyclization to give I in 76% yield.

The acid hydrolysis of I leads to 2,4-dihydroxy-3-(3-oxobutyl)quinoline (III). Reaction of I with phosphorus oxychloride converts it to 2,4-dichloro-3-(3-chlorocrotyl)quinoline (IV), which on acid hydrolysis forms 2,4-dichloro-3-(3-oxobutyl)quinoline (V). It is interesting that, as we have previously pointed out [1], the chlorine atoms in the 2 and 4 positions remain unchanged during acid hydrolysis, while when the compound is refluxed with acetic acid [2] or with alcoholic HCl [3] one observes hydrolysis, as a consequence of which the chlorine atom attached to C_2 is replaced by a hydroxyl group, and 2-hydroxy-4-chloro-3-(3-chlorocrotyl)quinoline (VI) is obtained from I. Under more severe hydrolysis conditions, the halogen in the side chain of VI is saponified to give 2-hydroxy-4-chloro-3-(3-oxobutyl)quinoline (VII).

The IR spectrum of V contains the characteristic absorption of a carbonyl group at 1714 cm^{-1}.

In the spectrum of ketone VII this band is partially shifted to 1650 cm^{-1} and is superimposed on the absorption bands of the N–C=O amide carbonyl group. The intensity of the band at 1714 cm^{-1} is sharply diminished.

In the case of 2,4-dihydroxy-3-quinolyl-3-butanone (III), in which there are two groupings that form a hydrogen bond, strong absorption disappears almost completely at 1714 cm^{-1} and appears at 1641 cm^{-1}.

In the reduction of the ketone with aluminum isopropoxide, the aliphatic ketone group is selectively reduced to an alcohol group with simultaneous cyclization of the 4-hydroxy group and the formation of 2-methyl-5-hydroxypyrano[3,2-c]quinoline (VIII), which does not dissolve in alkali (this is characteristic for compounds of the VIII type [4]) and reacts with $POCl_3$ to give 2-methyl-5-chloropyrano[3,2-c]quinoline (IX). The IR spectrum of cyclization product VIII contains absorption bands at 1090, 1275, and 1645 cm^{-1}; this is characteristic for –C–O–, =C–O–, and N–C=O groups.

For comparison, ketone VII was reduced to the corresponding 2-hydroxy-4-chloro-3-quinolyl-3-butanol (X) and then, by heating in 17% hydrochloric acid, was cyclized to 2-methyl-5-chloro-3,4-dihydropyrano[2,3-b]quinoline (XI), which is isomerized to IX. This confirms that ring formation in the synthesis of VIII proceeds precisely through the hydroxyl group in the 4 position rather than through that in the 2 position.

*See [1] for communication V.

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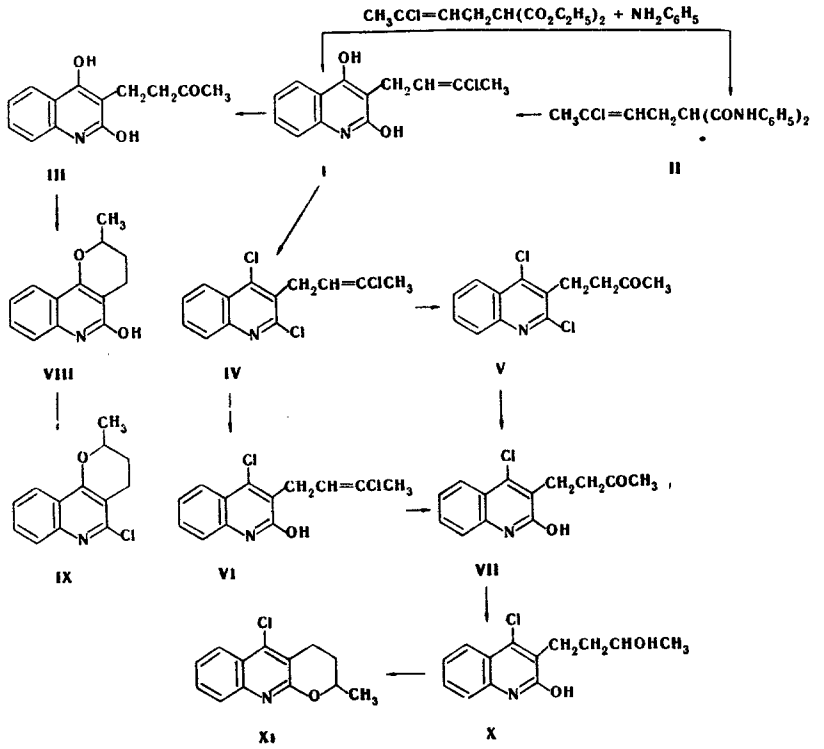
According to thin-layer chromatography (TLC), the linear isomer is not formed at all in this case.



EXPERIMENTAL

Thin-layer chromatography was carried out on activity-II Al_2O_3 with benzene–chloroform (1 : 1).

2,4-Dihydroxy-3-(3-chlorocrotyl)quinoline (I). This compound was synthesized by the method in [1] from 74.5 g (0.3 mole) of 3-chlorocrotylmalonic ester [5] and 23.3 g (0.25 mole) of aniline to give 28 g (48%) of colorless crystals of I with mp 218°. Found: Cl 15.4; N 5.7%. $C_{13}H_{12}ClNO_2$. Calculated: Cl 15.0; N 5.6%. Simultaneously obtained was 7.5 g (21%) of 3-chlorocrotylmalonic acid dianilide with mp 230-231°. Found: Cl 10.7; N 7.9%. $C_{19}H_{19}ClN_2O_2$. Calculated: Cl 10.4; N 8.2%.

The method in [1] was used to obtain 3.8 g (76%) of I from 6.8 g (20 mmole) of anilide II.

2,4-Dihydroxy-3-quinolyl-3-butanone (III). A mixture of 5 g (21 mmole) of 2,4-dihydroxy-3-(3-chlorocrotyl)quiniline and 20 ml of 85% sulfuric acid was heated at 50-60° for 10-15 min, after which it was cooled and poured into 50 g of ice. The precipitate was removed by filtration and dissolved in alkali, and the alkali solution was treated with charcoal and neutralized with hydrochloric acid. The resulting precipitate was recrystallized from 50% alcohol to give 4.3 g (86%) of colorless crystals with mp 182-183°. Found: N 6.2%. $C_{13}H_{13}NO_3$. Calculated: N 6.0%. The semicarbazone had mp 236° (from alcohol). Found: N 20.8%. $C_{14}H_{16}N_4O_3$. Calculated: N 20.4%.

2,4-Dichloro-3-(3-chlorocrotyl)quinoline (IV). The method in [1] was used to obtain 8.4 g (93%) of 2,4-dichloro-3-(3-chlorocrotyl)quinoline (IV) with mp 59-60° (from 50% alcohol) from 9 g of 2,4-dihydroxy-3-(3-chlorocrotyl)quinoline. Found: Cl 36.8; N 4.6%. $C_{14}H_{10}Cl_3N$. Calculated: Cl 37.2; N 4.9%.

2,4-Dichloro-3-quinolyl-3-butanone (V). This compound was prepared by the method used to synthesize III: 3.5 g (13 mmole) of 2,4-dichloro-3-(3-chlorocrotyl)quinoline was subjected to hydrolysis with sulfuric acid to give 3.36 g (96%) of V with mp 110-111°. Found: Cl 26.8; N 5.1%. $C_{13}H_{11}Cl_2NO$. Calculated: Cl 26.5; N 5.2%. The semicarbazone had mp 159-160° (from alcohol). Found: Cl 21.6; N 14.2%. $C_{14}H_{14}Cl_2N_4O$. Calculated: Cl 21.8; N 14.1%.

2-Hydroxy-3-(3-chlorocrotyl)-4-chloroquinoline (VI). A mixture of 5.7 g (0.02 mole of 2,4-dichloro-3-(3-chlorocrotyl)quinoline and 50 ml of acetic acid was refluxed for 2 h, after which it was cooled, and the precipitate was removed by filtration. Removal of a portion of the solvent by distillation precipitated another certain amount of substance. The overall yield of product with mp 222° was 4.6 g (84.5%). Found: Cl 26.9; N 5.3%. $C_{13}H_{11}Cl_2NO$. Calculated: Cl 26.5; N 5.2%.

2-Hydroxy-4-chloro-3-quinolyl-3-butanone (VII). A. As in the preparation of III and V, 2.6 g (0.01 mole) of 2-hydroxy-4-chloro-3-(3-chlorocrotyl)quinoline was subjected to hydrolysis with sulfuric acid to give 2.3 g (83%) of a white crystalline substance with mp 199-200°. Found: Cl 14.1; N 5.4%. $C_{13}H_{12}ClNO_2$. Calculated: Cl 14.2; N 5.6%.

B. As in the preparation of VI, refluxing V in acetic acid gave 2.3 g (81%) of VII from 2.6 g (0.01 mole) of V. The semicarbazone had mp 238-239° (from alcohol). Found: Cl 11.2; N 18.7%. $C_{13}H_{15}ClN_4O_2$. Calculated Cl 11.8; N 19.2%.

2-Methyl-5-oxo-3,4,5,6-tetrahydro-2H-pyrano[3,2-c]quinoline (VIII). A mixture of 2.6 g (11 mmole) of 2,4-dihydroxy-3-quinolyl-3-butanone, 30 ml of 1 M aluminum isopropoxide, and 50 ml of absolute isopropyl alcohol was refluxed with constant removal of isopropyl alcohol by distillation. When the test for acetone was negative, the isopropyl alcohol was removed completely by distillation, and water was added to the residue. The resulting precipitate was removed by filtration and refluxed in alcohol. Cooling of the alcohol solution precipitated 2.3 g (89%) of yellow needles with mp 221°. The product was insoluble in acids and bases. IR spectrum: 1645 HN−C=O), 1075 (−C−O−), and 1270 cm^{-1} (=C−O−). Found: N 6.4%. $C_{13}H_{13}NO_2$. Calculated N 6.5%.

2-Methyl-5-chloro-3,4-dihydro-2H-pyrano[3,2-c]quinoline (IX). As in the preparation of IV, 1.5 g (7 mmole) of VIII was treated with phosphorus oxychloride to give 1.1 g (73%) of IX with mp 210°. Found: Cl 15.4; N 5.8%. $C_{13}H_{12}ClNO$. Calculated: Cl 15.2; N 6.0%.

2-Hydroxy-4-chloro-3-quinolyl-3-butanol (X). As in the preparation of VIII (except that the precipitate was treated with 10% sulfuric acid) 2 g (72 mmole) of VII was reduced to give 1.76 g (88%) of X with mp 185° (50% alcohol). Found: Cl 24.5; N 5.3%. $C_{13}H_{14}ClNO_2$. Calculated: Cl 14.1; N 5.5%.

2-Methyl-5-chloro-3,4-dihydro-2H-pyrano[2,3-b]quinoline (XI). A mixture of 1.5 g (6 mmole) of X and 30 ml of 20% hydrochloric acid was refluxed for 2 h, filtered, and diluted to three times its volume with water, and neutralized with ammonia. The precipitate was removed by filtration and recrystallized from 50% alcohol to give 1.5 g (92%) of a substance with mp 108-109°. Found: C 67.3; H 5.0; Cl 15.0; N 5.7%. $C_{13}H_{12}ClNO$. Calculated: C 66.7; H 5.1; Cl 15.2; N 5.9%.

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