β-(2-HYDROXY-4-CHLORO-3-QUINOLYL)PROPIOLACTONE

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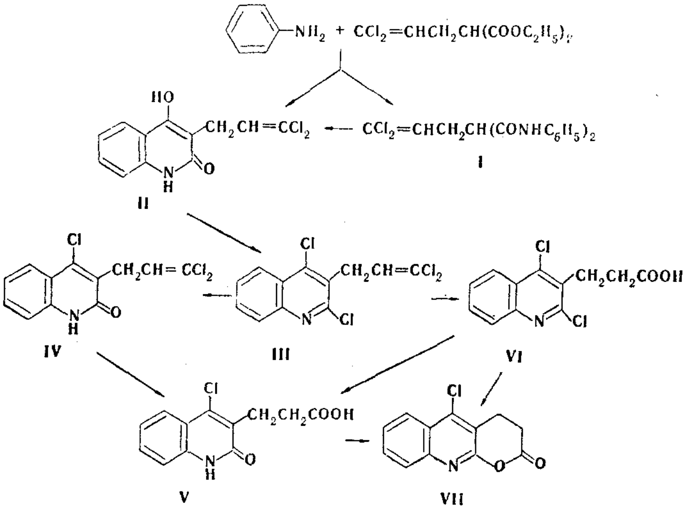
2,4-Dihydroxy-3-(3,3-dichloroallyl)quinoline, the corresponding 4-mono and 2,4-dichloro derivatives, and substituted β-(3-quinolyl)propionic acids were synthesized. β-(2-Hydroxy-4-chloro-3-quinolyl)propiolactone was obtained from the latter.

3-Substituted 2,4-dihydroxyquinolines are obtained by heating substituted malonic ester with primary aromatic amines [1-3]. However, there has been an indication that the reaction does not proceed with allylmalonic ester [2] and is generally hindered with its analogs [4].

We were able to obtain 2,4-dihydroxy-3-(3,3-dichloroallyl)quinoline (II) in 50% yield by the reaction of 3,3-dichloroallylmalonic ester with aniline in a refluxing mixture of diphenyl and diphenyl ether. The reaction also gives 3,3-dichloroallylmalonic acid dianilide (I), which is also converted to II on heating in fused $AlCl_3$ and NaCl [5]. The IR spectrum of II contains absorption bands characteristic for NH (3300 cm^{-1}) and NHCO (1675 cm^{-1}) groups. In fact, II, like 3-substituted 4-hydroxycarbostyril, exists as two tautomeric forms. Compound II is therefore converted to 2,4-dichloro-3-(3,3-dichloroallyl)quinoline (III) on heating with phosphorus oxychloride. When III is heated with 6 N hydrochloric acid [6] or with glacial acetic acid [7], it undergoes partial hydrolysis to give 2-hydroxy-4-chloro-3-(3,3-dichloroallyl)quinoline (IV).

When IV is heated with sulfuric acid, it is hydrolyzed to β-(2-hydroxy-4-chloro-3-quinolyl)propionic acid (V). Under similar conditions, III forms β-(2,4-dichloro-3-quinolyl)propionic acid (VI). It is interesting that in this case the chlorine atoms remain unaffected, while V is formed when VI is refluxed with glacial acetic acid; i.e., nucleophilic substitution of the chlorine in the 2 position occurs.

The protonating action of concentrated sulfuric acid (the –I effect of the ammonium cation formed) should facilitate nucleophilic substitution of chlorine in the 2 position. However, this does not occur; this sort of substitution apparently counteracts the mesomeric effect of chlorine.



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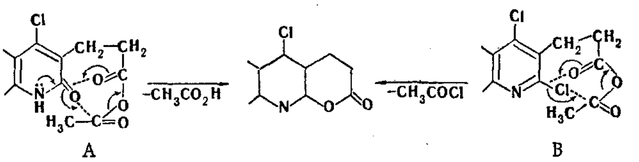
In addition, it was expected that acid V should be converted to lactone VII in concentrated sulfuric acid, but acid V forms a lactone only when it is heated with acetic anhydride. Under the same conditions, acid VI also gives lactone VII. It might have been assumed that the OH group is first acetylated followed by intramolecular transesterification to give the lactone. However, no changes whatsoever occur when quinolines III and IV are heated with acetic anhydride.

In order to ascertain the role of the anhydride in lactone formation, we attempted to obtain the lactone in polar solvents. Thus acids V and VI undergo no change when they are heated in nitrobenzene to 140-150°, but when an equimolecular amount of anhydride is added to this mixture, lactone VII is formed in quantitative yield. Since the amount of anhydride was negligible in comparison with the quantity of nitrobenzene, it must be assumed that it acts as a reagent rather than a medium.

We assume that heating of acids V and VI in acetic anhydride gives mixed anhydrides A and B which, via cyclic transformation, are converted to the same lactone, with splitting out of acetic acid in the case of A and splitting out of acetyl chloride in the case of B.



Lactone VII dissolves when it is heated in alkali. Acidification of the solution precipitates acid V.

EXPERIMENTAL

2,4-Dihydroxy-3-(3,3-dichloroallyl)quinoline (II). A. A total of 9.3 g (0.1 mole) of aniline was added in the course of 1 h to a refluxing mixture of 30 g (0.11 mole) of 3,3-dichloroallylmalonic ester [8], 75 g of diphenyl, and 75 g of diphenyl ether, and the mixture was refluxed for 2 h and cooled. The mixture was diluted with petroleum ether, and the precipitate was removed by filtration and treated with 10% NaOH solution. The insoluble portion was removed by filtration and recrystallized from alcohol to give 20% 3,3-dichloroallylmalonic acid dianilide (I) with mp 209-210°. Found: Cl 19.4; N 7.8%. $C_{18}H_{16}Cl_2NO_2$. Calculated: Cl 19.6; N 7.7%.

The alkaline solution was treated with charcoal and neutralized with hydrochloric acid, and the precipitate was recrystallized from alcohol to give 13.5 g (50%) of a product with mp 218-220°. Found: Cl 26.4; N 5.3%. $C_{12}H_9Cl_2NO_2$. Calculated: Cl 26.3; N 5.2%.

B. A 12-g sample of dianilide I was added with stirring to a mixture of 13.5 g of $AlCl_3$ and 4 g of NaCl heated to 150°, and the mixture was heated to 200-210° in the course of 30 min. The mixture was cooled, acidified with hydrochloric acid, and, after 1 h, filtered. The solid was dissolved in alkali, and the solution was filtered and acidified to give 7.6 g (86%) of II.

2,4-Dichloro-3-(3,3-dichloroallyl)quinoline (III). A mixture of 8.1 g (0.03 mole) of II and 50 ml of phosphorus oxychloride was heated on a water bath for 4 h. The $POCl_3$ was removed by distillation under reduced pressure. Ice water was added to the residue, and the mixture was allowed to stand overnight. The precipitate was removed by filtration, washed with dilute alkali, and recrystallized from 50% alcohol to give 8 g (87%) of a product with mp 54°. Found: Cl 46.1; N 4.7%. $C_{12}H_7Cl_4N$. Calculated: Cl 46.2; N 4.6%.

2-Hydroxy-3-(3,3-dichloroallyl)-4-chloroquinoline (IV). A mixture of 3 g (0.01 mole) of III and 30 ml of glacial acetic acid was refluxed for 3 h and cooled. The precipitate was removed by filtration. Removal of a portion of the solvent from the filtrate precipitated a certain additional amount of product to give a total of 2.6 g (89%) of a product with mp 233°. Found: Cl 36.7; N 4.7%. $C_{12}H_8Cl_3NO$. Calculated: Cl 36.9; N 4.8%.

β-(2-Hydroxy-4-chloro-3-quinolyl)propionic Acid (V). A. A mixture of 1.5 g (0.05 mole) of IV and 10 ml of sulfuric acid (sp. gr. 1.84) was heated on a water bath until HCl evolution ceased (about 4 h). The mixture was cooled and poured over ice, and the precipitate was removed by filtration and dissolved in alkali. The alkaline solution was filtered and acidified, and the precipitate was removed by filtration to give 1.2 g (93%) of a product with mp 242-244°. Found: Cl 14.3; N 5.7%. $C_{12}H_{10}ClNO_3$. Calculated: Cl 14.1; N 5.6%.

B. A mixture of 1.35 g (0.005 mole) of VI and 15 ml of glacial acetic acid was refluxed for 3 h, and the acetic acid was removed by distillation under reduced pressure. The residue was treated in the cold with dilute alkali, and the mixture was filtered. The filtrate was carefully neutralized with dilute hydrochloric acid to precipitate 1.1 g (86%) of acid with mp 244°, which was identical to acid V.

β-(2,4-Dichloro-3-quinolyl)propionic Acid (VI). This compound, with mp 143-144° (from alcohol), was obtained in 81% yield via the method used to prepare acid V (method A). Found: Cl 26.4; N 5.1%. $C_{12}H_9Cl_2NO_2$. Calculated: Cl 26.3; N 5.2%.

β-(2-Hydroxy-4-chloro-3-quinolyl)propiolactone (VII). A. A mixture of 2.7 g (0.01 mole) of VI and 30 ml of acetic anhydride was refluxed for 2 h, and the anhydride was completely removed by distillation under reduced pressure. The residue was cooled and washed with dilute alkali and water and recrystallized from carbon tetrachloride to give 1.9 g (84%) of a product with mp 170-171°. Found: Cl 15.3; N 5.7%. $C_{12}H_{18}ClNO_2$. Calculated: Cl 15.1; N 6.0%.

B. The same method was used to obtain 0.85 g (72%) of lactone VII by heating 1.25 g (0.005 mole) of V with acetic anhydride.

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