NEW DERIVATIVES OF QUINALDIN-4-OL

XIX.* 3-(3,3-DICHLOROALLYL)-4-HYDROXY-2-METHYLQUINOLIN-6-CARBOXYLIC ACID AND ITS REACTIONS

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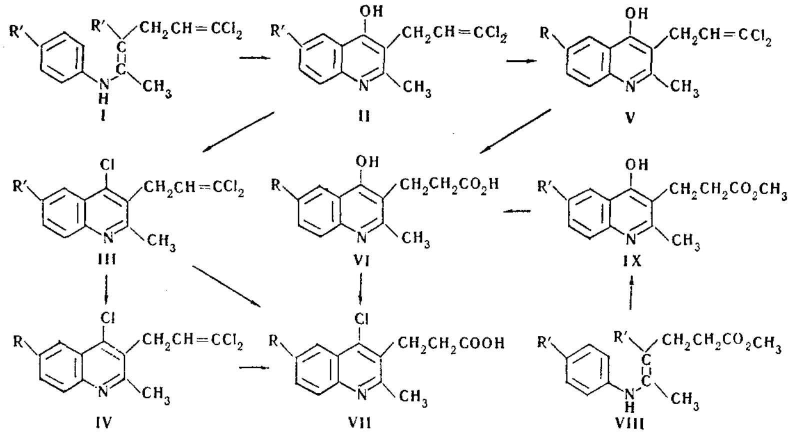
The synthesis and chemical reactions of 3-(3,3-dichloroallyl)-4-hydroxy-2-methylquinoline-6-carboxylic acid, 3-(2-carboxyethyl)-4-hydroxy-2-methylquinoline-6-carboxylic acid, and of derivatives of these acids are described.

In continuation of previous work [1-3] on the synthesis and the study of the chemical behavior of derivatives of quinolin-4-ol, we have carried out the synthesis of 3-(3,3-dichloroallyl)-4-hydroxy-2-methylquinoline-6-carboxylic acid and its ethyl ester and their 4-chloro analogs using the Conrad–Limpach thermal method [4]. 1,1-Dichloro-4-ethoxycarbonyl-5-(p-ethoxycarbonylphenylamino)hexa-1,4-diene (I) which is formed by the reaction of benzocaine with 6,6-dichloro-3-ethoxycarbonylhex-5-en-2-one, was subjected to cyclization. The hexenone was obtained by alkylating acetoacetic ester with 1,1,3-trichloroprop-1-ene, which is formed by the dehydrochlorination of 1,1,1,3-tetrachloropropane [5,6]. On cyclization, the ester of 3-(3,3-dichloroallyl)-4-hydroxy-2-methylquinoline-6-carboxylic acid (II) was first obtained, and this was converted by saponification into the acid V.

By reaction with phosphorus oxychloride, II was converted into its 4-chloro analog III, which was then saponified to give the acid IV.



R = COOH; R′ = COOC$_2$H$_5$

As is well known, on reaction with sulfuric acid, a γ,γ-dichloroallyl group is converted into a carboxy group [2,7,8]. Compound II was converted in this way into 3-(2-carboxyethyl)-4-hydroxy-2-methoquinoline-6-carboxylic acid (VI). We obtained the same acid by saponifying its mixed ethyl-methyl ester IX, synthesized independently. First the reaction of methyl 3-ethoxycarbonyl-2-oxopentanecarboxylate and ethyl p-

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*For Communication XVIII, see [1].

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aminobenzoate gave methyl 3-ethoxycarbonyl-2-(p-ethoxycarbonylphenylamino)pent-2-enecarboxylate (VIII), which was then converted by thermal cyclization into the ethyl-methyl ester IX of the acid VI.

Compounds III and IV were converted by sulfuric acid hydrolysis into 4-chloro-3-(2-carboxyethyl)-2-methylquinolin-6-carboxylic acid (VII), the latter also being obtained by the reaction of VI with phosphorus oxychloride. It was found by tritration that the acids VI and VII are dibasic.

EXPERIMENTAL

Ethyl 3-(3,3-dichloroallyl)-4-hydroxy-2-methylquinoline-6-carboxylate was obtained by the thermal cyclization [2] in paraffin oil of 1,1-dichloro-4-ethoxycarbonyl-5-(p-ethoxycarbonylphenylamino)hexa-1,4-diene (I). 38.6 g (0.1 mole) of I yielded 29 g (85.3%) of II, with mp 251°C (from ethanol). Found %: Cl 20.76; N 4.13. $C_{15}H_{15}Cl_2NO_3$. Calculated %: Cl 20.85; N 4.11.

3-(3,3-Dichloroallyl)-4-hydroxy-2-methylquinoline-6-carboxylic Acid. A solution of 1 g of II in 50 ml of a 1% ethanolic solution of NaOH was boiled for approximately 1 h. Then, after the ethanol had been distilled off, the residue was dissolved in water and the aqueous solution, after filtration, was acidified with acetic acid. The precipitate that formed was separated off by filtration and was washed with water and hot ethanol. White crystals, mp 332°C. Yield quantitative. Found %: Cl 22.83; N 4.54. $C_{14}H_{11}Cl_2NO_3$. Calculated %: Cl 22.72; N 4.49. Heating the ester II with 17% hydrochloric acid led to the same result.

Ethyl 4-chloro-3-(3,3-dichloroallyl)-2-methylquinoline-6-carboxylate (III). A mixture of 1 g (about 3 mmoles) of II and 4 ml (43.5 mmoles) of $POCl_3$ was heated in the water bath until the evolution of HCl ceased (about 2 h). The excess of $POCl_3$ was distilled off under reduced pressure, ice was added to the residue, and the mixture was left overnight. Then the solution was neutralized with sodium carbonate and filtered. The product obtained was recrystallized from 50% ethanol. White acicular crystals, mp 85°C. Yield 0.8 g (76.2%). Found %: Cl 29.82; N 4.11. $C_{16}H_{14}ClNO_2$. Calculated %: Cl 29.65; N 3.90.

4-Chloro-3-(3,3-dichloroallyl)-2-methylquinoline-6-carboxylic Acid (IV). A mixture of 0.5 g of III and 20 ml of 17% HCl was boiled. The III dissolved in 2-3 min and then, after some time, the hydrolyzate precipitated. Heating was continued for another 15 min and, after cooling, the product was filtered off and recrystallized from 50% ethanol. White crystals, mp 220°C, yield 0.4 g (86.9%). Found %: Cl 31.93; N 4.16. $C_{14}H_{10}Cl_3NO_2$. Calculated %: Cl 32.15; N 4.24.

3-(2-Carboxyethyl)-4-hydroxy-2-methylquinoline-6-carboxylic Acid (VI). a. A solution of 1 g of II or V in 5 ml of conc. H_2SO_4 was heated in the water bath until the evolution of HCl ceased. Then the mixture was poured onto ice, and the precipitate that separated out was filtered off, washed with water, and dissolved in 5% NaOH solution. After filtration, the solution was neutralized with hydrochloric acid. The precipitate obtained was filtered off again and was washed with hot ethanol. White crystals, mp 332°C (decomp.), yield 0.55 g (70%). Found %: N 5.18. $C_{14}H_{13}NO_5$. Calculated %: N 5.09.

b. A solution of 3.17 g (0.1 mole) of IX in 100 ml of 1% ethanolic NaOH solution was boiled for approximately 1 h 30 min. Then the ethanol was distilled off and the precipitate was dissolved in water. The resulting solution was filtered and acidified wth acetic acid. The precipitate formed was filtered off and washed with hot ethanol, mp 332°C (decomp.). The ester IX can also be hydrolyzed by being heated with 17% HCl. A mixture of the acids obtained by the hydrolysis of IX, II, and V gave no depression of melting point.

Determination of the Basicity of VI. 0.0163 g of the substance obtained by the sulfuric acid hydrolysis of II was dissolved in 6 ml of 0.05 N KOH. The excess of alkali was back-titrated, 3.6 ml of 0.05 N HCl being consumed. Hence 1 mole of VI (mol. wt. = 275.26) corresponds to 2.02 g-eq. Similarly, 0.0186 g of the acid VI obtained by the hydrolysis of IX consumed 2.7 ml of 0.05 N KOH. This shows that a gram-molecule of the acid corresponds to 2.01 g-eq.

3-(2-Carboxyethyl)-4-chloro-2-methylquinoline-6-carboxylic Acid (VII). a. In a similar manner to the conversion of II, the hydrolysis of 1 g of III or IV in conc. H_2SO_4 gave a 75-85% yield of white crystals, mp 305°C (decomp., from 60% ethanol). Found %: Cl 11.89. $C_{14}H_{12}ClNO_4$. Calculated %: Cl 12.08.

b. A mixture of 1 g (about 3.9 mmoles) of VI and 10 ml (about 0.1 mole) of $POCl_3$ was heated in a water bath for 2.5-3 h. Then the excess of $POCl_3$ was distilled off under reduced pressure, ice was added to the residue, and the mixture was left overnight. On the following day the product was filtered off and recrystallized from 50% ethanol. White flocculant crystals, mp 305°C. The substances obtained by methods a and b were identical, a mixture giving no depression of the melting point.

Determination of Basicity of VII. The neutralization of 0.013 g of VII obtained by the sulfuric acid hydrolysis of III consumed 1.8 ml of 0.05 N KOH. According to this, a gram-molecule of VII (mol. wt. = 293.7) represents 1.97 g-eq.

Ethyl 4-Hydroxy-3-(2-methoxycarbonylethyl)-2-methylquinoline-6-carboxylate (IX). A mixture of 21.6 g (0.1 mole) of methyl 3-ethoxycarbonyl-2-oxopentanecarboxylate and 16.5 g (0.1 mole) of ethyl p-aminobenzoate was left for several days in a closed desiccator over sulfuric acid. Then the mixture was washed with 3% hydrochloric acid and the residue was extracted with ether. The ethereal solution was dried with $MgSO_4$. After the elimination of the ether, the residue, consisting of methyl 3-ethoxycarbonyl-2-(p-ethoxycarbonylphenylamino)pent-2-enecarboxylate (VIII) was subjected to thermal cyclization in a similar manner to I. This gave white flocculant crystals of IX, mp 272-272°C (from ethanol). Yield 20.13 g (63.5%), calculated on the initial acetoacetic ester or benzocaine. Found %: C 64.28; H 6.17; N 4.51. $C_{17}H_{19}NO_5$. Calculated %: C 64.34; H 6.03; N 4.44.

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