NEW DERIVATIVES OF 4-QUINALDINOL

XII. 3-(γ, γ-Dichloroallyl)-4-quinaldinol and its Derivatives*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 5, pp. 845–847, 1968

UDC 547.831.4.7:542.944.1

The reactions of 1, 1, 3-trichloro-1-propene and also 1, 1, 1-trichloro-2-propene with acetoacetic ester gave α-(γ,γ-dichlorallyl)acetoacetic ester (I). In the reactions with aniline and o- and p-toluidines, the corresponding α-(γ,γ-dichloroallyl)-β-arylamino-crotonic esters were produced, thermal cyclization of which gave 2-methyl-3-(γ, γ-dichloroallyl)-4-hydroxyquinoline (II) and its $6CH_3$— (III) and $8CH_3$— (IV) homologs. With phosphorus oxychloride, II-IV gave the corresponding 4-chloro-substituted quinolines (V-VII); with concentrated sulfuric acid, II-VII were converted into the corresponding β-quinolinylpropionic acids VIII-XIII.

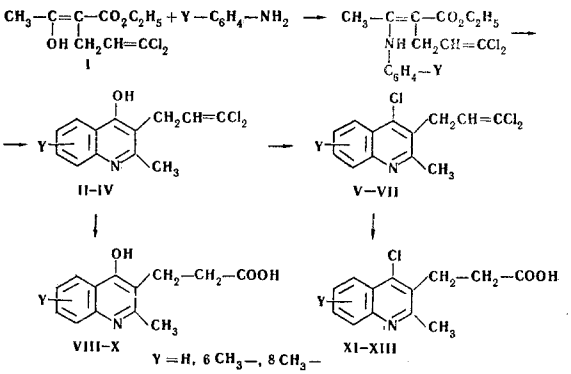
We have previously synthesized derivatives of 4-quinaldinol having a γ-chlorocrotyl group in position 3 [1–3]. Later, 4-quinaldinols which have the γ-chloroallyl group in the same position were synthesized [4]. It was of interest to introduce another chlorine atom into the γ-position of the allyl group while maintaining the β,γ-unsaturated character of the radical, i.e. to synthesize 3-(γ, γ-dichloroallyl)-4-quinaldinols.

The synthesis was carried out using the Conrad-Limpach reaction. The corresponding amines (aniline, o- and p-toluidine) and the ester I were used as starting materials. In the synthesis of I, 1, 1, 3-trichloro-1-propene, which was obtained from the dehydrochlorination of 1, 1, 1, 3-tetrachloropropane, was used. The tetrachloropropane mentioned was one of the products of the telomerization of ethylene and carbon tetrachloride. In the dehydrochlorination of 1, 1, 1, 3-tetrachloropropane, 1, 1, 1-trichloro-2-propene was also obtained; this also gave I in the reaction with sodio-acetoacetic ester. In this way 2-methyl-3-(γ, γ-dichloroallyl)-4-hydroxyquinoline (II) and its $6CH_3$— (III) and $8CH_3$— (VII) homologs were synthesized (see Table 1).

The 4-quinaldinols obtained, were treated with phosporus oxychloride, were converted respectively into 2-methyl-3-(γ, γ-dichloroallyl)-4-chloroquinoline (V), and its $6CH_3$— (VI) and $8CH_3$— (VII) homologs (see Table 2).

Earlier, one of us, by means of the sulfuric acid hydrolysis of 3-(γ-chlorocrotonyl)-4-quinaldinol obtained methyl β-[3-(2-methyl-4-hydroxyquinolinyl)]-ethyl ketone [1]. It was also of interest to subject the newly-synthesized 3-(γ, γ-dichloroallyl)-4-quinaldinols to sulfuric acid hydrolysis in order to obtain the corresponding β-quinolinylpropionic acids. This method turned out to be a convenient way of obtaining the acids, the data for which are given in Table 3.

The work done may be represented by the following equations:



EXPERIMENTAL

Ethyl α-(γ,γ-dichloroallyl)acetoacetate (I). 100 ml of absolute benzene, 6 ml of absolute alcohol, and 61.17 g (0.47 mole) of acetoacetic ester were mixed in a three-necked flask fitted with a mechanical stirrer, dropping funnel and reflux condenser having a calcium chloride tube attached. Then with stirring and slight heating, 10.81 g (0.47 g-at) of metallic sodium was added. After the sodium had dissolved, 69.7 g (0.47 mole) of 1, 1, 3-tri-chloro-1-propene was added through the dropping funnel and the mixture was heated on a water bath until it gave a weakly alkaline reaction. The benzene and alcohol were then evaporated off, and to the residue was added 1% HCl until the deposit had completely dissolved. The product obtained was extracted with ether and dried over magnesium sulfate. After the removal of the ether, the residue was distilled in a vacuum, the fraction with bp 114–116° C (2 mm) being collected; n_D^{20} 1.4780; d_4^{20} 1.2576; yield 52 g (44.7%). Found, %: C 45.34; H 5.23; Cl 29.61; MR_D 53.95. Calculated for $C_9H_{12}Cl_2O_3$, %: C 45.18; H 5.02; Cl 29.79; MR_D 54.69.

Compound I was also obtained by an analogous method from 1, 1, 1-trichloro-2-propene.

2-Methyl-3-(γ,γ-dichloroallyl)-4-hydroxyquinolines (II, III, IV).

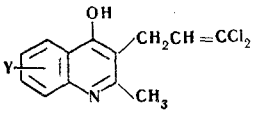
a) In a flask fitted with a water separator and a reflux condenser were mixed 0.1 mole of I, 100 ml of dry benzene, 2–3 drops of glacial acetic acid and 0.1 mole of the aromatic amine. The mixture was heated on a water bath until the required amount of water had been isolated. Then the reaction mixture was heated in a Claisen flask under a vacuum to remove the benzene. The residual liquid was the corresponding ethyl α-(γ,γ-dichloroallyl)-β-arylamino-crotonate.

b) In a three-necked flask, fitted with a mechanical stirrer with a mercury seal, reflux condenser, dropping funnel and a thermometer reaching the bottom of the flask, was placed 300 ml of paraffin oil. To the oil, which was heated to 250° C, was added over a period of 10 min an ethyl α-(γ,γ-dichloroallyl)-4-arylaminocrotonate. After the mixture had been cooled and filtered, the filter was washed with petroleum ether, and the reaction product was recrystallized from alcohol. The products were white lustrous crystals. Data on the quinaldinols obtained are given in Table 1.

2-Methyl-3-(γ,γ-dichloroallyl)-4-chloroquinolines (V, VI, VII). Into a 50 ml round-bottomed flas, fitted with a reflux condenser protected by a calcium chloride tube, were put 0.01 mole of a 3-(γ, γ-dichloroallyl)-4-quinaldinol (II, III or IV) and 15 ml of phosporus oxychloride. The mixture was heated on a water bath for 3–4 hr and then the excess $POCl_3$ was evaporated under reduced pressure, ice was added to the residue, and the mixture was allowed to stand

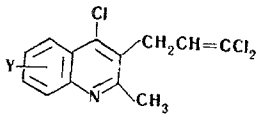
*For part XI, see [5].

Table 1



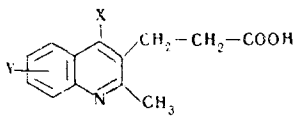
Compound	Y	Mp, °C	Empirical form	Found, %		Calc., %		Yield, %
				Cl	N	Cl	N	
II	H	262	$C_{13}H_{11}Cl_2NO$	26.40	5.39	26.45	5.22	69.0
III	$6CH_3$	270	$C_{14}H_{13}Cl_2NO$	25.00	5.23	25.21	4.99	87.4
IV	$8CH_3$	235	$C_{14}H_{13}Cl_2NO$	24.85	4.82	25.21	4.99	89.2

Table 2



Compound	Y	Mp, °C	Empirical form	C, %		Yield, %
				Found, %	Calc., %	
V	H	102	$C_{13}H_{10}Cl_3N$	37.41	37.17	72.1
VI	$6CH_3$	105	$C_{14}H_{12}Cl_3N$	35.73	35.44	75.4
VII	$8CH_3$	76	$C_{14}H_{12}Cl_3N$	35.80	35.44	69.2

Table 3



Compound	X	Y	Mp, °C	Empirical formula	Mol. wt. (by acid titr.)		Found, %		Calc., %		Yield, %
					found, %	calc., %	Cl	N	Cl	N	
VIII	OH	H	284	$C_{13}H_{13}NO_3$	234.6	231	—	6.23	—	6.06	59.6
IX	OH	$6CH_3$	290	$C_{14}H_{15}NO_3$	242	245	—	5.24	—	5.51	64.1
X	OH	$8CH_3$	256	$C_{14}H_{15}NO_3$	240	245	—	5.17	—	5.51	58.3
XI	Cl	H	267	$C_{13}H_{12}ClNO_2$	250.7	249.5	14.36	—	14.23	—	61.5
XII	Cl	$6CH_3$	275	$C_{14}H_{14}ClNO_2$	272	269.5	13.63	—	13.51	—	70.9
XIII	Cl	$8CH_3$	242	$C_{14}H_{14}ClNO_2$	270	269.5	13.65	—	13.51	—	65.7

overnight. Then it was neutralized with sodium hydroxide and filtered and the product was recrystallized from 50% alcohol solution. Data on the chloroquinolines obtained are given in Table 2.

β-(2-Methyl-4-hydroxyquinolinyl)propionic and β-(2-methyl-4-chloroquinolinyl)propionic acids (VIII–XIII). To a round-bottomed flask fitted with a reflux condenser, containing 0.01 mole of a 2-methyl-3-(γ,γ-dichloroallyl)-4-hydroxyquinoline (II, III, or IV), or 2-methyl-3-(γ, γ-dichloroallyl)-4-chloroquinoline (V, VI or VII), was added 3 ml of 96% sulfuric acid and the mixture heated on a water bath until the evolution of hydrogen chloride ceased. Then the mixture was poured onto ice and neutralized with barium carbonate. The barium sulfate was filtered off and the filtrate carefully reacidified with dilute HCl. White crystals of the respective β-quinolinylpropionic acids (VIII–XIII) separated out (recrystallization from alcohol). The data on the acids are given in Table 3.

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18 August 1966

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