2-DICHLOROMETHYL-4-METHYL-2,3-DIHYDROFURO[3,2-c]-QUINOLINE DERIVATIVES

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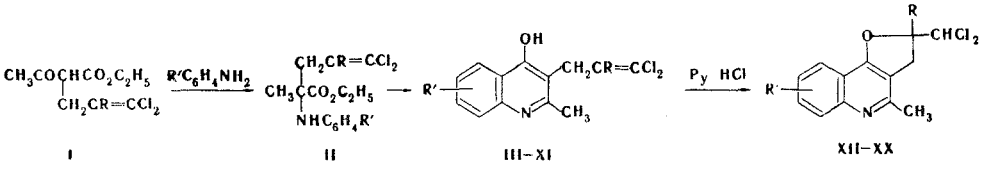
Substituted 2-dichloromethyl-4-methyl-2,3-dihydrofuro[3,2-c]quinolines were obtained by cyclization of substituted 2-methyl-3-(3,3-dichloroallyl)-4-hydroxquinolines, and 2-dichloromethyl-2,4-dimethyl-2,3-dihydrofuro[3,2-c]quinolines were isolated from 2-methyl-3-(2-methyl-3,3,dichloroallyl)-4-hydroxyquinolines.

Natural and synthetic furoquinolines are interesting physiologically active substances that have analgesic, antipyretic, and antiphlogistic action.

Synthetic furoquinolines are obtained from benzofurans [1, 2] or from o-allyl-substituted hydroxyquinolines with subsequent closing of the furan ring [3-5].

We have previously synthesized a number of substituted 2-methyl-3-(3,3-dichloroallyl)-4-hydroxyquinolines [6-9]. In the present paper, 2-methyl-3-(2-methyl-3,3-dichloroallyl)-4-hydroxyquinolines (X, XI) were obtained by the method in [6]. The alkylation of acetoacetic ester with 1,1,3-trichloro-2-methylpropene [11] leads to α-(2-methyl-3,3-dichloroallyl)acetoacetic ester (I). The reaction of I with aniline and p-aminoacetanilide gave the corresponding anils (II), which are cyclized to 2-methyl-3-(2-methyl-3,3-dichloroallyl)-4-hydroxyquinoline (X) and its acetamido derivative (XI).

Substituted 3-(3,3-dichloroallyl)-4-hydroxyquinolines (III-IX) and 2-methyl-3-(2-methyl-3,3-dichloroallyl)-4-hydroxyquinolines (X, XI), like 2-methyl-3-allyl-4-hydroxyquinoline [5], are cyclized to substituted 2-dichloromethyl-4-methyl-2,3-dihydrofuro[3,2-c]quinolines (XII-XVIII) and 2-dichloromethyl-2,4-dimethyl-2,3-dihydrofuro[3,2-c]quinolines (XIX, XX) on heating with pyridine hydrochloride at 200-220°C.



I II III-XI XII-XX

III, XII R=R'=H; IV, XIII R=H, R'=6-CH_3; V, XIV R=H, R'=8-CH_3; VI R=H, R'=6-OCH_3; VII R=H, R'=6-NH_2; VIII R=H, R'=6-Cl; IX R=H, R'=6-$NHCOCH_3$; X, XIX R=CH_3, R'=H; XI R=CH_3, R'=6-$NHCOCH_3$; XV R=H, R'=8-OCH_3; XVI R=H, R'=8-NH_2; XVII R=H, R'=8-Cl; XVIII R=H, R'=8-$NHCOCH_3$; XX R=CH_3, R'=8-$NHCOCH_3$.

Furoquinolines XII-XX melt approximately 150° lower than the starting 2-methyl-3-(3,3-dichloroallyl)-4-hydroxyquinolines and are quite soluble in organic solvents and dilute acids. The IR spectra of the furoquinolines contain clearly expressed absorption bands at 1092 and 1266 cm^{-1}, which is characteristic for an ether group (C–O–C), but the absorption band of an OH group is absent at 3000-3400 cm^{-1}. The furoquinolines do not form a precipitate with alcoholic silver nitrate solution and do not change on heating with sulfuric and hydrochloric acids. Thus the formation of 2,2-dichloro-3,4-dihydro-5-methyl-9-substituted pyrano[3,2-c]quinolines during the cyclization is excluded, since, being α-chloro ethers, they would undergo hydrolysis to form an acid or lactone on heating with acids.

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TABLE 1. 2-Dichloromethyl-4-methyl-2,3-dihydrofuro[3,2-c]-quinoline Derivatives

Compound	R	R′	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			R_f*	Yield, %
					C	H	Cl	C	H	Cl		
XII	H	H	147 (ethyl acetate)	$C_{13}H_{11}Cl_2NO$	58,5	4,1	26,1	58,7	3,7	26,4	0,7	31
XIII	H	6-CH_3	118 (50% ethanol)	$C_{14}H_{13}Cl_2NO$	59,3	4,6	25,5	59,6	4,6	25,3	0,5	33
XIV	H	8-CH_3	181 (light ligroin)	$C_{14}H_{13}Cl_2NO$	60,0	4,3	25,8	59,6	4,6	25,3	0,48	39
XV	H	8-OCH_3	175 (ethanol)	$C_{14}H_{13}Cl_2NO$	56,3	4,0	25,6	56,4	4,4	25,3	0,46	36
XVI	H	8-NH_2	164 (n-nonane)	$C_{13}H_{12}Cl_2N_2O$	54,4	3,9	25,6	54,1	4,2	25,1	0,45	27
XVII	H	8-Cl	138 (methanol)	$C_{13}H_{10}Cl_3NO$	—	—	35,6	—	—	35,8	—	29
XVIII	H	8-$NHCOCH_3$	220 (50% ethanol)	$C_{15}H_{14}Cl_2N_2O$	55,3	4,4	21,5	55,5	4,3	21,8	—	35
XIX	CH_3	H	180 (ethyl acetate)	$C_{14}H_{13}Cl_2NO$	59,7	4,4	25,1	59,6	4,6	25,3	0,6	79
XX	CH_3	8-$NHCOCH_3$	225 (n-nonane)	$C_{14}H_{14}Cl_2N_2O$	56,2	4,4	23,7	56,6	4,7	23,9	0,48	82

*On activity II Al_2O_3 in a benzene–chloroform (1:1) system for XII and XIV, in a CCl_4–petroleum ether (1:1) system for XIII, and in chloroform for the remaining compounds.

The sharp increase in the yield of XIX and XX in comparison with XII-XVIII speaks in favor of the fact that closing of the furan ring proceeds through a carbonium ion formed through the β-carbon atom of the allyl group. When a methyl group is present, the carbonium ion becomes more stable owing to the +I effect of the latter.

EXPERIMENTAL

α-(2-Methyl-3,3-dichloroallyl)acetoacetic Ester (I). This compound was obtained via the method in [6] from 195 g (1.5 mole) of acetoacetic ester, 23 g of sodium, and 159 g (1 mole) of 1,1,3-trichloro-2-methyl-1-propene [11]. The product [159 g (63%)] had bp 128-130° (5 mm), n_D^{20} 1.4886, and d_4^{20} 1.1766. Found: Cl 27.8%. $C_{10}H_{14}Cl_2O_3$. Calculated: Cl 28.1%.

2-Methyl-3-(2-methyl-3,3-dichloroallyl)-4-hydroxyquinoline (X). Ethyl α-(2-methyl-3,3-dichloroallyl)-β-phenylaminocrotonate was obtained from 25.3 g of I and 9.3 g of aniline via the method in [6]. The ester was cyclized in mineral oil [6]. The reaction mass was cooled and filtered, and the filter was washed with petroleum ether to give 20.8 g (76%) of colorless crystals with mp 265° (from alcohol). Found: C 59.9; H 4.9; Cl 25.1%. $C_{14}H_{13}Cl_2NO$. Calculated: C 60.3; H 4.7; Cl 24.7%.

Ethyl α-(2-Methyl-3,3-dichloroallyl)-β-(p-acetamidophenylamino)crotonate (II). A mixture of 25.3 g (0.1 mole) of I, 15 g (0.1 mole) of p-aminoacetanilide, 75 ml of methanol, and two to three drops of hydrochloric acid was refluxed for 6 h. Two-thirds of the solvent was removed, and the precipitated II was removed by filtration to give 35 g (91%) of a product with mp 185° (from methanol). Found: C 56.1; H 5.7; Cl 18.4%. $C_{18}H_{22}Cl_2N_2O_3$. Calculated: C 56.0; H 5.6; Cl 19.0%.

2-Methyl-3-(2-methyl-3,3-dichloroallyl)-4-hydroxy-6-acetamidoquinoline (XI). A 35-g (0.09 mole) sample of III was cyclized via the method in [6] to give 24.6 g (80%) of colorless crystals with mp > 350° (from alcohol). Found: Cl 20.9%. $C_{16}H_{16}Cl_2N_2O_2$. Calculated: Cl 20.6%.

2-Dichloromethyl-4-methyl-2,3-dihydrofuro[3,2-c]quinoline Derivatives (XII-XX). A mixture of 2 g of substituted 2-methyl-3-(3,3-dichloroallyl)-4-hydroxyquinoline or 2-methyl-3-(2-methyl-3,3-dichloroallyl)-4-hydroxyquinoline (X, XI) and 4 g of pyridine hydrochloride was heated on an oil bath at 200-220° for 15 min. The solid mass that formed was treated with water, and the precipitated starting material was removed by filtration. The filtrate was neutralized, and the precipitate was removed by filtration. The properties and results of analysis are presented in Table 1.

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