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SYNTHESIS OF SOME SUBSTITUTED 2- AND 4-[2'-(5"-NITRO-2"-FURYL)VINYL]-QUINOLINES

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A series of 2- and 4-[2'-(5"-nitro-2"-furyl)vinyl]quinolines were synthesized by catalytic condensation of 5-nitrofurfural with 2- and 4-methylquinolines. 2-Methylquinoline (quinaldine) and its substituted derivatives also react when the starting reagents are fused directly.

5-Nitrofurylvinylquinolines seem of interest as a promising new class of antibacterial and antitumorogenic substances [1-3]. In a search for new potential chemotherapeutic preparations in this series we investigated the condensation of alkylquinolines with 5-nitrofurfural and synthesized a series of 2- and 4-substituted [2'-(5"-nitro-2"-furyl) vinyl]quinolines (I-IX).

Despite the apparent simplicity of condensation via this scheme, satisfactory preparative variants of it have not been available up until now, and the desired product was obtained in only 30-40% yield [5-8].

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*Deceased.

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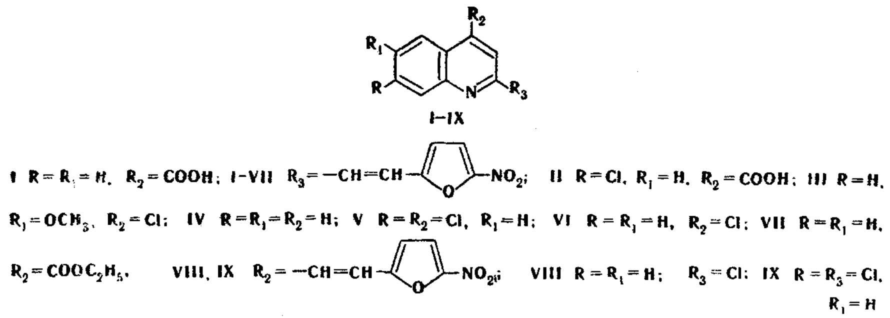

To solve the problem of the suitability of this reaction for preparative purposes we made a more detailed study of the condensation of 5-nitrofurfural with 2-methylquinoline (quinaldine), 2-methyl-4,7-dichloro- and -4-chloro-6-methoxyquinolines, and ethyl 2-methylquinoline-4-carboxylate as model systems.

Some of the experiments were carried out by heating a mixture of equimolecular amounts of the starting reagents in acetic acid, acetic anhydride, or acetic acid—acetic anhydride at an optimum temperature of 130-135°. The formation of a crystalline phase in the reaction mixture served as a criterion for completion of the reaction. It was found that such prolonged heating periods (up to 2-6 h) as were used in [5-8] are not necessary for successful reaction, and the corresponding condensation products were isolated in crystalline form after a few minutes. The effect of acetic acid, acetic anhydride, and acetic acid—acetic anhydride on the yields of the desired product was followed. The best results were obtained when the reaction was carried out in minimum amounts of acetic anhydride (Fig. 1). It should be noted that we were unable to realize the reaction of 5-nitrofurfural with chloro derivatives of 4-methylquinoline under the conditions indicated above.

For the first time we tested anhydrous zinc chloride as a condensing agent. A violent reaction takes place at 140-145° and is complete in a few minutes to give the corresponding 2- and 4-[2'-(5"-nitro'2"-furyl)vinyl]quinolines in relatively high yields (55-99%, Table 1).

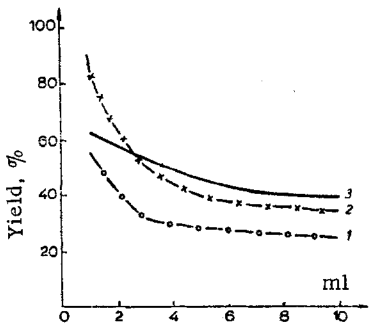

Fig. 1. Yield of V as a function of the amounts of AcOH (1), Ac₂O (2), and AcOH—Ac₂O (3) in the reaction of 2-methyl-4,7-dichloroquinoline (0.01 mole) with 5-nitrofurfural (0.01 mole) at 130-135°C.

TABLE 1. Substituted 2-[2'-(5"-Nitro-2"-furyl)vinyl]quinolines (with anhydrous zinc chloride as the condensing agent)

Compound	mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
I	303—304† (dec.)	$C_{16}H_{10}N_2O_5$	61,8	3,0		9,0	61,9	3,2		9,0	89
II	298—302 (dec.)	$C_{16}H_9ClN_2O_5$	55,8	3,0	10,1	8,0	55,7	2,6	10,3	8,1	76
III	221	$C_{16}H_{11}ClN_2O_4$	57,7	3,5	10,8	8,6	58,1	3,3	10,7	8,5	90
IV	179—180‡	$C_{15}H_{10}N_2O_3$	68,0	3,4	—	10,6	67,7	3,8	—	10,5	96
V	239—240	$C_{15}H_8Cl_2N_2O_3$	53,5	2,3	21,1	8,6	53,8	2,4	21,2	8,4	97
VI	205	$C_{15}H_9ClN_2O_3$	60,1	3,1	12,1	9,4	59,9	3,0	11,8	9,3	99
VII	187 **	$C_{18}H_{14}N_2O_5$	63,6	4,2	—	8,1	63,9	4,2	—	8,3	99
VIII	164—165	$C_{15}H_9ClN_2O_3$	59,6	3,1	11,5	9,2	59,9	3,0	11,8	9,3	73
IX	185—186	$C_{15}H_8Cl_2N_2O_3$	53,4	2,9	20,9	8,2	53,8	2,4	21,2	8,4	55

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*From dimethylformamide.
†With mp 290° [3].
‡With mp 180° [4].
**With mp 187° [3].

The reaction proceeds similarly in the presence of catalytic amounts of concentrated hydrochloric acid, but the yields of the desired products are considerably lower.

It was found that the reaction of quinaldine and 2-methyl-4,7-dichloroquinoline can also be carried out without any solvents or condensing agents. A violent reaction begins when the starting reagents are heated directly at 175-180°, and the temperature of the mixture rises to 190-195°. After a few minutes, the reaction terminates with the formation of the corresponding 2-[2'-(5"-nitro-2"-furyl)vinyl]quinolines. However, the condensation products require repeated recrystallization, and their yields are low.

The 2- and 4-[2'-(5"-nitro-2"-furyl)vinyl]quinolines are orange to yellow crystalline substances that are soluble in DMF, only slightly in alcohol, and practically insoluble in water.

EXPERIMENTAL

2-[2'-(5"-Nitro-2"-furyl)vinyl]quinoline (IV). A) An 0.07-g (0.5 mmole) sample of anhydrous zinc chloride was added to a mixture of 1.43 g (0.01 mole) of 2-methylquinoline and 1.41 g (0.01 mole) of 5-nitrofurfural, and the temperature of the stirred mixture was gradually raised to 130-135°, at which point an exothermic reaction began and the temperature of the reaction mixture rose to 140-145°. Stirring was continued for 1-3 min, after which the mixture was cooled to 60-80°, and 5 ml of water and 15-20 ml of alcohol were added to it. The mixture was then stirred, and the resulting solid was removed by filtration, washed with alcohol, and dried at 100° to give 2.56 g (96%) of IV with mp 179-180°.

Quinolines III and V-IX were similarly obtained. Because of the extremely high melting point of the quinoline component, 0.02-0.03 mole of 5-nitrofurfural per 0.01 mole of 2-methylquinoline-4-carboxylic acid (or 2-methyl-7-chloroquinoline-4-carboxylic acid) was used for the preparation of I and II.

Equimolecular amounts of starting reagents in the presence of catalytic amounts of concentrated hydrochloric acid were used for reactions by the method described above. The yields in this case were 69% for IV, 38% for III, 73% for V, and 41% for VIII.

B) A mixture of 1.43 g (0.01 mole) of 2-methylquinoline and 1.41 g (0.01 mole) of 5-nitrofurfural was stirred and gradually heated. A violent reaction began at 175-180°, and the temperature of the mixture rose spontaneously to 190-195°. The reaction was complete in a few minutes, and workup gave 1.49 g (56%) of IV with mp 179-180°.

Compounds III and V were similarly obtained in 55 and 75% yields, respectively.

2-[2'-(5"-Nitro-2"-furyl)vinyl]quinoline-4-carboxylic Acid (I). A 15-ml sample of acetic anhydride was added to a mixture of 1.87 g (0.01 mole) of 2-methylquinoline-4-carboxylic acid and 1.41 g (0.01 mole) of 5-nitrofurfural, after which the mixture was heated at 130-135° for 15-20 min. It was then cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and recrystallized to give 1.12 g (36%) of I with mp 303-304° (decomp.). Compound II was similarly obtained in 54% yield.

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