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SYNTHESIS OF FURAN ANALOGS OF 1, 3, 5-TRIPHENYLPYRAZOLINE DERIVATIVES

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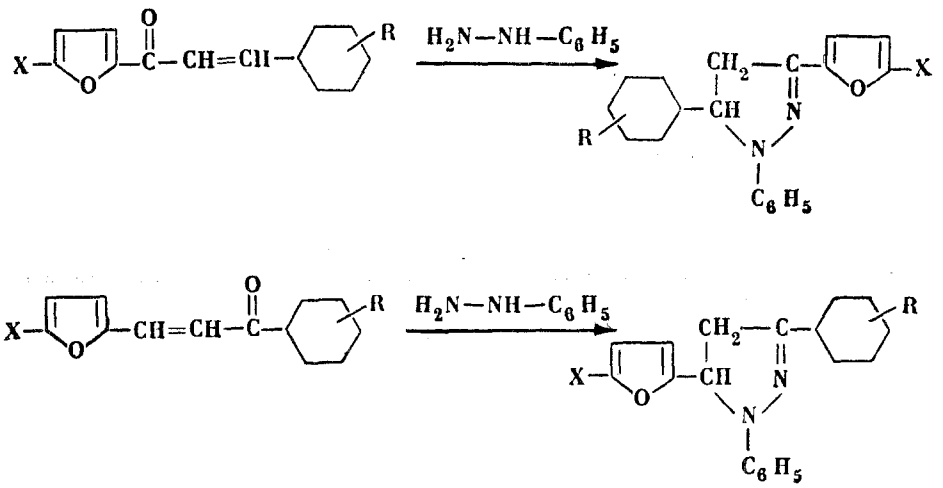
Furan analogs of chalcones are condensed with phenylhydrazine to give a number of Δ^2-pyrazolines hitherto not described in the literature. It is shown that in α,β-unsaturated ketones, a nitro-group in the nucleus and remote from the carbonyl group makes cyclization to the corresponding Δ^2-pyrazolines more difficult than does one adjacent to the carbonyl.

1,3,5-Triphenyl-Δ^2-pyrazoline and its derivatives have interesting optical properties, and some of them have found application as luminophores and scintillation materials [1].

It was decided to prepare certain new Δ^2-pyrazolines with 2-furyl at positions 3 and 5, with a view to future study of their spectroscopic properties.

The literature contains only a few papers dealing with synthesizing pyrazolones containing the furyl group. In 1929 Kizhner [2] reported preparing 3-methyl-4-furyl-Δ^2-pyrazoline and converting it to a cyclopropane derivative. A paper [3] describes synthesis of 1,5-diphenyl-3-(furyl-2)-; 1,3-diphenyl-5-(furyl-2)- and 1-phenyl-3,5-di(furyl-2)-Δ^2 pyrazolines from heterocyclic analogs of chalcone plus phenylhydrazine in the presence of acetic acid, and also of two pyrazolines containing not only the furan, but also the thiophene ring. A. N. Kost and coworkers [4] have synthesized a series of substituted 5-(furyl-2)-Δ^2-pyrazolines from α,β-unsaturated ketones of the furan series plus hydrazine hydrate or alkylhydrazines. Other papers [5-8] describe a number of 5-(furyl-2)-Δ^2-pyrazolines and their derivatives.

It was decided to synthesize the pyrazolines of interest by reacting isomeric furan analogs of chalcones with phenylhydrazine in aqueous alcohol in the presence of acid



X = H, NO_2, R = H, 4-CH_3O, 2,4-di(CH_3O)
2,4,6-tri(CH_3O), 4-Cl, 4-NO_2, 4-$(CH_3)_2N$

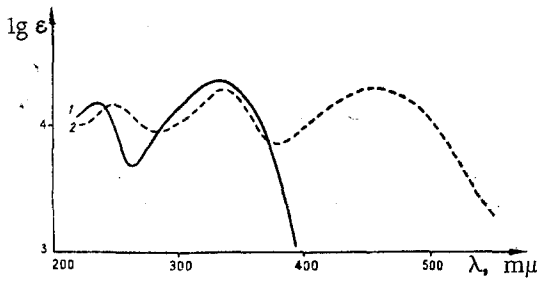
This reaction is complicated by the fact that it does not occur in neutral medium, while in an acid one these chalcones readily resinify due to the acidophobic nature of the furyl group. Optimum conditions were chosen to secure satisfactory yields of the pyrazolines, those of basic importance being the time for which the reactants were boiled together, and certain other factors (see table).

The literature [9] indicates that ease of cyclization of α,β-unsaturated ketones to pyrazolines largely depends on the chemical nature and structures of the reacting molecules. It is known that electron-accepting groups, e.g., nitro or halogen, hinder cyclization [10]. We have now found that 1-(furyl-2)-3-(4-nitrophenyl)-propenone-3 can be converted to the pyrazoline IX by heating with phenylhydrazine for 2 hr 30 min, (see table), while the corresponding isomeric propenone-1 cannot be converted to pyrazoline, this furan ketone resinifying during reaction. It was previously found [11] that of the two isomeric furan chalcones the more stable to attack by acid is 1-(furyl-2)-3-(4-nitrophenyl)-propenone-1,

from which a pyrazoline cannot be prepared. Hence a nuclear nitro-group remote from the carbonyl one hinders cyclization of α, β unsaturated ketones to pyrazolines more than one adjacent to the carbonyl. This is supported by the fact that 1-(5-nitrofuryl-2)-3-phenylpropenone-1 could be converted to the pyrazoline IV, whereas the isomeric propenone-3 gave only the corresponding phenylhydrazone XI.

Introduction of the methoxy group at the p-position in the aromatic ring facilitates formation of pyrazolines, particularly when introduced into the ring remote from the carbonyl. Thus the pyrazoline I is formed in good yield when the reactants are refluxed for only 20 min, while the isomeric pyrazoline V is formed more slowly. However, build-up of methoxyl groups at the o-positions in the benzene ring has a negative effect on the reaction, and from the isomeric 1-(furyl-2)-3-(2,4-dimethoxyphenyl)propenones only pyrazoline VI could be prepared, while despite repeated attempts, 1-(furyl-2)-3-(2,4,6-trimethoxyphenyl) propenones could, generally, not be converted to pyrazolines. Evidently this is due on the one hand to steric hindrances hindering cyclization, and on the other to piling-up of methoxy groups increasing the acidophobic nature of the furyl group, the latter readily resinifying in acid medium as was shown in [12].

The literature contains some indications making it possible to differentiate between pyrazolines and the hydrazones from which they are formed by cyclization. First and foremost there is the Knorr reaction [13], then the fluorescence characteristic of pyrazolines [14], or the stability of pyrazolines on prolonged boiling with acetic acid [3], and others [15, 16]. These factors are not objective enough (see Table). The pyrazolines here prepared differ from the phenylhydrazones in not having hydrogen at one of the nitrogen atoms, so their structure was confirmed by their not having the IR absorption band characteristic of valence vibrations of the N-H group at 3200-3500 cm^{-1} (LiF prism). For example the product of reaction of 1-(5-nitrofuryl-2)-3-phenylpropenone-3 with phenylhydrazine was hydrazone XI, as it has a medium intensity absorption band at 3320 cm^{-1}, although it does not give a blue color in the Knorr reaction and is unchanged on prolonged refluxing with acetic acid. A hydrazone structure can also readily be differentiated from a pyrazoline one by the electronic spectra. The Figure shows the absorption curves for hydrazone XI and 1-phenyl-3-phenyl-5-(5-nitrofuryl-2)-Δ^2-pyrazoline*, whence it is evident that XI is more deeply colored than the corresponding thiophene analog of the pyrazoline, and has three characteristic absorption bands.



Absorption plots for hydrazone XI and 1, 3-diphenyl-5-(5-nitrofuryl-2)-Δ^2-pyrazoline in alcohol: 1) 1, 3-diphenyl-5-(5-nitrofuryl-2)-Δ^2-pyrazoline; 2) hydrazone XI.

EXPERIMENTAL

Preparation of Δ^2-pyrazolines

a) 0.01 mole α, β-unsaturated ketone and 0.015 mole phenylhydrazine hydrochloride were dissolved in a minimum amount of hot alcohol, and the solution refluxed for the time given in the table. The crystals which precipitated on the following day were filtered off, washed with cold alcohol, and recrystallized (II, III, V, VI, VIII, IX, from 1:1 alcohol-acetone; VII from 1:3 alcohol-acetone; IV from methanol).

b) 0.01 mole α, β-unsaturated ketone was dissolved in the minimum amount of hot alcohol, and 0.015 mole phenylhydrazine hydrochloride in 20 ml water with 2 ml 50% acetic acid was added. The oil precipitated on refluxing was immediately rubbed until crystals appeared, and next day the crystals were filtered off, washed with cold alcohol, and recrystallized from methanol.

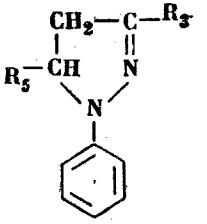
c) A mixture of 0.01 mole α, β-unsaturated ketone and 0.015 mole 4-nitrophenylhydrazine was dissolved in a minimum amount of hot alcohol, 10 ml concentrated hydrochloric acid added, and the whole refluxed for 3 hr 30 min. The next day the crystals were filtered off, washed with cold alcohol, and recrystallized from 1:1 alcohol-acetone.

1-(5-Nitrofuryl-2)-3-phenylpropenone-3 phenylhydrazone (XI)

A mixture of 0.01 mole 1-(5-nitrofuryl-2)-3-phenylpropenone-3 and 0.015 mole phenylhydrazine was dissolved in a minimum amount of alcohol, 5 ml glacial acetic acid added, and the whole refluxed for 1 hr. The next day the crystals which had separated were filtered off, washed with cold alcohol, and recrystallized from 1:1 alcohol-acetone.

*The synthesis of this compound and of the starting α, β-unsaturated furan ketones have already been described [17].

1-Phenyl-3-R_3-5-R_5-Δ^2-pyrazolines



Compound no.	R_3	R_5	Method of preparation	Boiling time hr	mp, °C	Crystal form	Fluorescence (in n-hexane)	Knorr reaction	Formula	N, % Found	N, % Calc.	Yield, %
I	2-furyl	4-methoxyphenyl	b	0.3	121.5—122	Slightly yellow polyhedra	Violet	—	$C_{20}H_{18}N_2O_2$	8.95 8.75	8.80	80
II	2-furyl	4-dimethylaminophenyl	a	2	177—177.5	Pale green needles	Violet	—	$C_{21}H_{21}N_3O$	12.70 12.86	12.68	37
III	2-furyl	4-chlorophenyl	a	1	127	Colorless plates	Violet	—	$C_{19}H_{15}ClN_2O$	8.60 8.86	8.68	78
IV	5-nitro-1-furyl	Phenyl	a	1.5	166.5	Bright red plates	Green	+	$C_{19}H_{15}N_3O_3$	12.76 12.58	12.60	60
V	4-methoxyphenyl	2-furyl	a	2.5	134—134.5*	Colorless plates	Violet	+	$C_{20}H_{18}N_2O_2$	—	—	78
VI	2,4-dimethoxyphenyl	2-furyl	a	1.5	130—130.5	Colorless cubes	Violet	+	$C_{21}H_{20}N_2O_3$	8.15 8.25	8.40	54
VII	4-dimethylaminophenyl	2-furyl	a	2	219—219.5	White needles	Violet	+	$C_{21}H_{21}N_3O$	12.82 12.87	12.68	76
VIII	4-chlorophenyl	2-furyl	a	0.6	130—131	Colorless parallelepipeds	Violet	+	$C_{19}H_{15}ClN_2O$	8.76 8.85	8.60	77
XI	4-nitrophenyl	2-furyl	a	2.5	164.5	Orange needles	Green	+	$C_{19}H_{15}N_3O_3$	12.60 12.59	12.60	60
X**	phenyl	2-furyl	c	3.5	182	Bright yellow plates	None	—	$C_{19}H_{15}N_3O_3$	12.80 12.64	12.60	40

* Mp 135° given in [6].

** In compound X, 4-nitrophenyl occupies position 1.

Dark red needles, mp 176.5-177° (decomp.); yield 70%. Found: N 12.53; 12.71%. Calculated for $C_{19}H_{15}N_3O_3$ N 12.60%. λ_{max} 460 mμ in alcohol.

Attempts to prepare the corresponding Δ^2-pyrazoline under various conditions failed.

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