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SYNTHESIS OF CHALCONE ANALOGS – 4- AND 5-NITROPYRROLE DERIVATIVES

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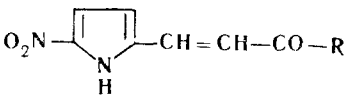
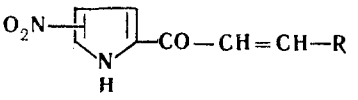
Nitropyrrole analogs of chalcone have been synthesized by aldol condensation in basic medium from 5-nitropyrrole-2-carboxaldehyde, 4- and 5-nitro-2-acetylpyrrole, and the corresponding aromatic aldehydes and methyl ketones; their 2,4-dinitrophenylhydrazones have been obtained. Some considerations are expressed concerning the reactivity of pyrrole-2-carboxaldehyde, 2-acetylpyrrole, and their nitro derivatives.

In a previous communication [1], we described the synthesis of chalcone analogs containing a pyrrole nucleus. It was of interest to synthesize some of their derivatives with a nitro group in the 4- and 5-positions of the pyrrole ring in order to investigate their properties. There are reports in the patent literature that some compounds of the nitropyrrole series possess interesting physiological activity [2]. The synthesis of some nitropyrrole analogs of chalcone by the aldol condensation of 4- and 5-nitropyrrole-2-carboxaldehyde with 2-acetylpyrrole, 2-acetylthiophene, and 2-hydroxyacetophenone has recently been described [3].

We condensed 5-nitropyrrole-2-carboxaldehyde and 4- and 5-nitro-2-acetylpyrrole with aromatic methyl ketones and aldehydes and obtained the nitropyrrole chalcone analogs (I–X) (see table).





R = phenyl (I-III), 4-methoxyphenyl (IV-VI), 4-nitrophenyl (VII-IX), and 2-pyrryl (X).

It has previously been shown that the 5-nitro derivatives of furfural, 2-acetylfuran [4], thiophene-2-carboxaldehyde, and 2-acetothienone [5] are easily resinified under the influence of base, and it is difficult to carry out an aldol condensation with them in the presence of a basic catalyst. The analogous nitro compounds of the pyrrole series have proved to be insensitive to bases, and one can bring about the aldol condensation in the presence of a 15% sodium hydroxide solution at 100°C for 2–10 hr.

The hypothesis has been expressed [3] that 2-acetylpyrrole and pyrrole-2-carboxaldehyde are less reactive in condensation reactions than are their furan and thiophene analogs because of the greater electron-donating character of the pyrrole nucleus. If this were in accord with reality, the introduction of such a powerful electron-accepting substituent as the nitro group into these carbonyl compounds would lead to a pronounced increase in reactivity. In reality, however, 5-nitropyrrole-2-carboxaldehyde and 4- and 5-nitro-2-acetylpyrrole enter into condensation with more difficulty than do the compounds not containing a nitro group. For example, 1-(2-pyrryl)-3-phenyl-3-propenone is obtained in good yield on condensation of pyrrole-2-carboxaldehyde with acetophenone for 1.5 hr at room temperature in the presence of 10% sodium hydroxide solution [1]. The analogous condensation with 5-nitropyrrole-2-carboxaldehyde proceeds only when the reagents are boiled 4 hr on a water bath with a more concentrated solution of base.

It may probably be supposed that one of the factors leading to the decrease in reactivity of pyrrole-2-carboxaldehyde and 2-acetylpyrrole in comparison with their furan and thiophene analogs is the presence in the former of a hydrogen bond [6] blocking the carbonyl group. The introduction of a nitro group into the pyrrole nucleus increases the acidic properties of the imino hydrogen, thereby increasing the energy of the hydrogen bond and leading to a still greater depression of the reactivity.

It is interesting that the majority of the nitropyrrole chalcone analogs which we have obtained, with the exception of VII, VIII, and IX, are fairly soluble in 10% aqueous sodium hydroxide solution with the formation of colored organic anions (see table), as a result of the enhanced acidic properties of the imino hydrogen. To isolate the condensation products, therefore, we acidified the solutions with acetic acid in all cases.

The nitropyrrole chalcone analogs which we have obtained (see table) are solid, well-crystallized substances, soluble in alcohol, acetone, and benzene, with the exception of VII, VIII, and IX, and insoluble in water. In concentrated sulfuric acid, they all form stable halochromic solutions with colors from bright yellow to violet.

Most of the nitropyrrole chalcones have been characterized in the form of 2,4-dinitrophenylhydrazones, which were obtained in the usual way [7].

Nitropyrrole Analogs of Chalcone and Their 2, 4-Dinitrophenylhydrazones

Ketone no.	Name of ketone	Starting substances	Yield, %	mp, °C (from alcohol), appearance	Color in 10% NaOH	Formula	N, % found	N, % calc.	2, 4-Dinitrophenylhydrazones mp, °C	2, 4-Dinitrophenylhydrazones formula	2, 4-Dinitrophenylhydrazones N, % found	2, 4-Dinitrophenylhydrazones N, % calc.
I	1-(5-Nitro-2-pyrryl)-3-phenyl-1-propenone	5-Nitro-2-acetylpyrrole and benzaldehyde	36	223.5 Light green needles	Yellow-green	$C_{13}H_{10}N_2O_3$	11.72 11.50	11.57	231	$C_{19}H_{14}N_6O_6$	20.11 19.89	19.90
II	1-(4-Nitro-2-pyrryl)-3-phenyl-1-propenone	4-Nitro-2-acetylpyrrole and benzaldehyde	31	259 White needles	Yellow-green	$C_{13}H_{10}N_2O_3$	11.86 11.76	11.57	244—245	$C_{19}H_{14}N_6O_6$	19.82 19.70	19.90
III	1-(5-Nitro-2-pyrryl)-3-phenyl-3-propenone	5-Nitropyrrole-2-carboxaldehyde and acetophenone	50	233 Yellow-green needles	Bright yellow	$C_{13}H_{10}N_2O_3$	11.66 11.45	11.57	237	$C_{19}H_{14}N_6O_6$	20.03 19.84	19.90
IV	1-(5-Nitro-2-pyrryl)-3-(4-methoxyphenyl)-1-propenone	5-Nitro-2-acetylpyrrole and anisaldehyde	74	250* Yellow needles	Yellow-green	$C_{14}H_{12}N_2O_4$	10.20 10.13	10.29	230	$C_{20}H_{16}N_6O_7$	18.79 18.68	18.58
V	1-(4-Nitro-2-pyrryl)-3-(4-methoxyphenyl)-1-propenone	4-Nitro-2-acetylpyrrole and anisaldehyde	35	265 Yellow-green needles	Yellow	$C_{14}H_{12}N_2O_4$	10.42 10.35	10.29	224—225	$C_{20}H_{16}N_6O_7$	18.82 18.70	18.58
VI	1-(5-Nitro-2-pyrryl)-3-(4-methoxyphenyl)-3-propenone	5-Nitropyrrole-2-carboxaldehyde and 4-methoxyacetophenone	67	245 Yellow-green needles	Orange-red	$C_{14}H_{12}N_2O_4$	10.49 10.38	10.29	217—218	$C_{20}H_{16}N_6O_7$	18.60 18.45	18.58
VII	1-(5-Nitro-2-pyrryl)-3-(4-nitrophenyl)-1-propenone	5-Nitro-2-acetylpyrrole and 4-nitrobenzaldehyde	37	305** Yellow-green needles		$C_{13}H_9N_3O_5$	14.92 14.63	14.63	249,5	$C_{19}H_{13}N_7O_8$	21.13 20.81	20.98
VIII	1-(4-Nitro-2-pyrryl)-3-(4-nitrophenyl)-1-propenone	4-Nitro-2-acetylpyrrole and 4-nitrobenzaldehyde	27	312 Light brown parallelepipeds		$C_{13}H_9N_3O_5$	14.85 14.78	14.63	—	—	—	—
IX	1-(5-Nitro-2-pyrryl)-3-(4-nitrophenyl)-3-propenone	5-Nitropyrrole-2-carboxaldehyde and 4-nitroacetophenone	30	260 Yellow prisms		$C_{13}H_9N_3O_5$	14.71 14.59	14.63	—	—	—	—
X	1-(5-Nitro-2-pyrryl)-3-(2-pyrryl)-1-propenone	5-Nitro-2-acetylpyrrole and pyrrole -2-carboxaldehyde	29	226 Red-violet needles	Red	$C_{11}H_9N_3O_3$	18.25 18.13	18.18	—	—	—	—

* From a benzene-alcohol mixture.

** From acetic acid.

Experimental

5-Nitropyrrole-2-carboxaldehyde, mp 185° C, was obtained according to [8]; 4-nitro-2-acetylpyrrole (mp 197° C) and 5-nitro-2-acetylpyrrole (mp 156° C) were obtained according to [9].

Aldol condensation. Equimolar amounts (0.01 mole) of the appropriate aldehyde and methyl ketone (see table) were dissolved in the minimum quantity of alcohol (20–30 ml), 3–4 ml of 15% sodium hydroxide solution was added dropwise with stirring, and the mixture was heated on a water bath under reflux for 2–10 hr. The solution was acidified with acetic acid and the resulting crystalline precipitate was filtered, washed with aqueous alcohol (50%), and recrystallized from a suitable solvent with the addition of acetic acid.

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