

REACTIONS WITH THIOHYDANTOINS: A NOVEL SYNTHESIS OF THIOPYRANO-
[2,3-d]IMIDAZOLES

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Abstract - A novel synthesis of thiopyrano[2,3-d]imidazoles via reaction of acrylonitrile, ethyl acrylate and *N*-*p*-chlorophenylmaleimide with 5-arylidene-3-phenyl-4-thiohydantoin is reported. The reaction of acrylonitrile with hydantoins and 2-thiohydantoin is also reported and discussed.

In previous work from this laboratory we have reported a new route for the synthesis of pyrano[2,3-d]imidazoles via the reaction of malononitrile with 5-arylidene-1,3-diphenyl-2-thiohydantoin.¹ In the present investigation we report a new procedure for the synthesis of thiopyrano[2,3-d]imidazoles via the reaction of acrylonitrile, ethyl acrylate and *N*-*p*-chlorophenylmaleimide with 5-arylidene-3-phenyl-4-thiohydantoin.

It was previously reported that the α,β -unsaturated thiocarbonyl system of 5-arylidene-2-thiazolidinone-4-thiones and 5-arylidene-2,4-thiazolidinedithiones, when reacted with dienophiles, underwent 1,4-cycloaddition reaction.²⁻⁴ This prompted us to utilise this type of cycloaddition reaction for the synthesis of some fused heterocycles containing the hydantoin moiety of probable pharmacological activities since hydantoin and its derivatives have been recommended for use in cases of anoxia resulting from high altitudes,⁵ in treatment of epilepsy⁶ and as anticonvulsant.^{7,8}

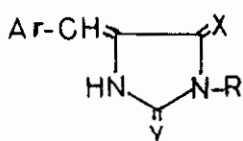
The 5-arylidene-3-phenyl-4-thiohydantoin (*1d-f*) needed for this investigation were prepared by refluxing 5-arylidene-3-phenylhydantoin⁹ (*1a-c*, 0.1 mole) and phosphorus pentasulphide (9 g) in anhydrous dioxane (100 ml) for 45 min, followed by filtration while hot and then cooling to room temperature.

When each of the coloured 5-arylidene derivatives *1d-f* (0.01 mole) was refluxed

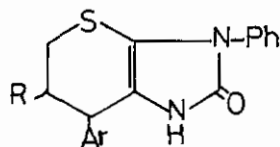
with either acrylonitrile or ethyl acrylate (0.02 mole) in glacial acetic acid (30 ml) for 30 min, the colour discharged. After standing overnight at room temperature the reaction mixture gave, with or without dilution with water, colourless crystals of 6-cyano (or 6-ethoxycarbonyl)-7-aryl-3-phenyltetrahydrothiopyrano-7H-[2,3-d]imidazol-2-ones ($\underline{2a-e}$). The structure $\underline{2}$ was assigned for the reaction products based on elemental analysis and IR spectra. The IR spectrum of each of $\underline{2a,b}$ showed absorption peaks characteristic for NH and CN groups. The IR spectrum of $\underline{2c}$, as a typical example of 6-ethoxycarbonyl derivatives $\underline{2c-e}$, showed absorption peaks related to NH and ester carbonyl stretching.

Refluxing $\underline{1d-f}$ with N-p-chlorophenylmaleimide in acetic acid under similar conditions also affected 1,4-cycloaddition to the α,β -unsaturated thiocarbonyl system of the heterocyclic nucleus with the formation of the colourless adducts 7-aryl-5,6-bishydroxycarbonyl-3-phenyltetrahydrothiopyrano-7H-[2,3-d]imidazol-2-one N-p-chlorophenylimides ($\underline{3a-c}$). The structure $\underline{3}$ was assigned based on elemental analysis and IR spectra.

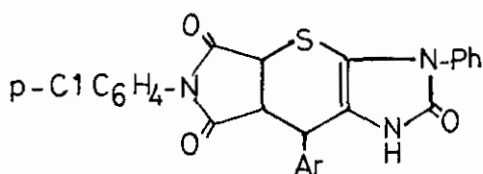
We investigated previously¹⁰ the behaviour of acrylonitrile toward 5-arylidene-2-thiohydantoins ($\underline{1g,h}$) and proved that the active center for cyanoethylation is position 3 only based on the fact that the 3-phenyl derivative $\underline{1i}$ failed to react with acrylonitrile. In continuation of this work, we extended our study to the action of acrylonitrile on hydantoins ($\underline{4a-c}$) and 2-thiohydantoins ($\underline{4d-f}$). A mixture of acrylonitrile (3 ml) and each of $\underline{4a-f}$ (0.01 mole) in pyridine-water (5:1, 60 ml) was refluxed for 5 hr. The solvent was reduced to one half of its volume and then diluted with water to give colourless products $\underline{5a-f}$. In case of hydantoins cyanoethylation takes place in both positions 3 and 5, but in case of 2-thiohydantoins, unexpectedly, cyanoethylation takes place at position 1 in addition to positions 3 and 5. This behaviour was favoured by elemental analysis and IR spectra. The IR spectrum of $\underline{5a}$ gave a band characteristic for NH, but in case of $\underline{5d}$ this band was entirely absent.



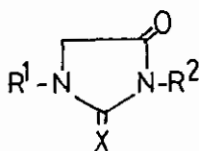
- 1a, Ar = R = Ph; X = Y = O
 b, Ar = C₆H₄OCH₃-p; R = Ph; X = Y = O
 c, Ar = C₆H₄Cl-p; R = Ph; X = Y = O
 d, Ar = R = Ph; X = S; Y = O
 e, Ar = C₆H₄OCH₃-p; R = Ph; X = S; Y = O
 f, Ar = C₆H₄Cl-p; R = Ph; X = S; Y = O
 g, Ar = Ph; R = H; X = O; Y = S
 h, Ar = C₆H₄OCH₃-p; R = H; X = O; Y = S
 i, Ar = R = Ph; X = O; Y = S



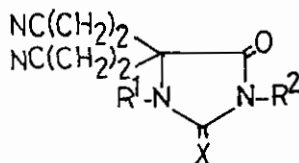
- 2a, Ar = Ph; R = CN
 b, Ar = C₆H₄OCH₃-p; R = CN
 c, Ar = Ph; R = COOC₂H₅
 d, Ar = C₆H₄OCH₃-p; R = COOC₂H₅
 e, Ar = C₆H₄Cl-p; R = COOC₂H₅



- 3a, Ar = Ph
 b, Ar = C₆H₄OCH₃-p
 c, Ar = C₆H₄Cl-p



- 4a, R¹ = R² = H; X = O
 b, R¹ = H; R² = Ph; X = O
 c, R¹ = Ph; R² = H; X = O
 d, R¹ = R² = H; X = S
 e, R¹ = H; R² = Ph; X = S
 f, R¹ = Ph; R² = H; X = S



- 5a, R¹ = H; R² = (CH₂)₂CN; X = O
 b, R¹ = H; R² = Ph; X = O
 c, R¹ = Ph; R² = (CH₂)₂CN; X = O
 d, R¹ = R² = (CH₂)₂CN; X = S
 e, R¹ = (CH₂)₂CN; R² = Ph; X = S
 f, R¹ = Ph; R² = (CH₂)₂CN; X = S

Table 1: List of 5-arylidene-3-phenyl-4-thiohydantoin (1d-f), thiopyrano[2,3-d]-imidazoles (2a-e, 3a-c) and cyanoethylated hydantoin and 2-thiohydantoin (5a-f).

Comp.*	Solvent	M.p.	Yield	Formula	Comp.*	Solvent	M.p.	Yield	Formula
	of	(°C)	(%)			of	(°C)	(%)	
	cryst.**					cryst.**			
1d	A	268	90	C ₁₆ H ₁₂ ON ₂ S	3b	E	230	70	C ₂₇ H ₂₀ O ₄ N ₃ SCl
1e	A	288	88	C ₁₇ H ₁₄ O ₂ N ₂ S	3c	A	135	75	C ₂₆ H ₁₇ O ₃ N ₃ SCl ₂
1f	A	300	90	C ₁₆ H ₁₁ ON ₂ SCl	5a	E	205	80	C ₁₂ H ₁₃ O ₂ N ₅
2a	E	233	70	C ₁₉ H ₁₅ ON ₃ S	5b	E	120	82	C ₁₅ H ₁₄ O ₂ N ₄
2b	E	255	65	C ₂₀ H ₁₇ O ₂ N ₃ S	5c	E	175	85	C ₁₈ H ₁₇ O ₂ N ₅
2c	E	220	70	C ₂₁ H ₂₀ O ₃ N ₂ S	5d	E	110	90	C ₁₅ H ₁₆ ON ₆ S
2d	E	258	73	C ₂₂ H ₂₂ O ₄ N ₂ S	5e	E	145	85	C ₁₈ H ₁₇ ON ₅ S
2e	E	115	70	C ₂₁ H ₁₉ O ₃ N ₂ SCl	5f	A	120	80	C ₁₈ H ₁₇ ON ₅ S
3a	A	251	72	C ₂₆ H ₁₈ O ₃ N ₃ SCl					

*Satisfactory elemental analyses for the newly synthesised compounds were obtained.

**A=Acetic acid; E=Ethanol

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