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-chlorophenyl-maleimide with 5-arylidene-3-phenyl-4-thiohydantoins is reported. The reaction of acrylonitrile with hydantoins and 2-thiohydantoins 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-thiohydantoins.

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 epilepsy[6] and as anticonvalsant.[7,8]

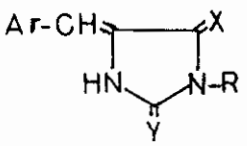
The 5-arylidene-3-phenyl-4-thiohydantoins (1d-f) needed for this investigation were prepared by refluxing 5-arylidene-3-phenylhydantoins[9] (1a-c, 0.1 mole) and phosphorus pentasulphide (9 g) in anhydrous dioxane (100 ml) for 45 min, followed by filtration while hot and then cooling to room temperature.

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 (2a-e). The structure 2 was assigned for the reaction products based on elemental analysis and IR spectra. The IR spectrum of each of 2a,b showed absorption peaks characteristic for NH and CN groups. The IR spectrum of 2c, as a typical example of 6-ethoxycarbonyl derivatives 2c-e, showed absorption peaks related to NH and ester carbonyl stretching.

Refluxing 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 (3a-c). The structure 3 was assigned based on elemental analysis and IR spectra.

We investigated previously[10] the behaviour of acrylonitrile toward 5-arylidene-2-thiohydantoins (1g,h) and proved that the active center for cyanoethylation is position 3 only based on the fact that the 3-phenyl derivative 1i failed to react with acrylonitrile. In continuation of this work, we extended our study to the action of acrylonitrile on hydantoins (4a-c) and 2-thiohydantoins (4d-f). A mixture of acrylonitrile (3 ml) and each of 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 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 5a gave a band characteristic for NH, but in case of 5d this band was entirely absent.



1a, Ar = R = Ph; X = Y = O

b, Ar = $C_6H_4OCH_3$-p; R = Ph; X = Y = O

c, Ar = C_6H_4Cl-p; R = Ph; X = Y = O

d, Ar = R = Ph; X = S; Y = O

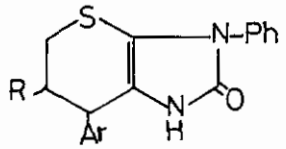
e, Ar = $C_6H_4OCH_3$-p; R = Ph; X = S; Y = O

f, Ar = C_6H_4Cl-p; R = Ph; X = S; Y = O

g, Ar = Ph; R = H; X = O; Y = S

h, Ar = $C_6H_4OCH_3$-p; R = H; X = O; Y = S

i, Ar = R = Ph; X = O; Y = S



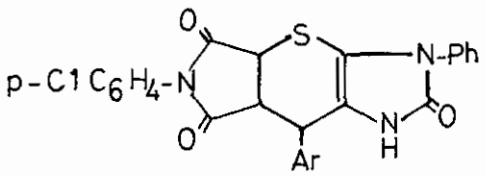
2a, Ar = Ph; R = CN

b, Ar = $C_6H_4OCH_3$-p; R = CN

c, Ar = Ph; R = $COOC_2H_5$

d, Ar = $C_6H_4OCH_3$-p; R = $COOC_2H_5$

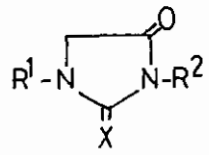
e, Ar = C_6H_4Cl-p; R = $COOC_2H_5$



3a, Ar = Ph

b, Ar = $C_6H_4OCH_3$-p

c, Ar = C_6H_4Cl-p



4a, $R^1 = R^2 = H$; X = O

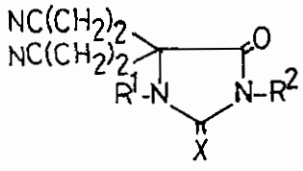
b, $R^1 = H$; $R^2 = Ph$; X = O

c, $R^1 = Ph$; $R^2 = H$; X = O

d, $R^1 = R^2 = H$; X = S

e, $R^1 = H$; $R^2 = Ph$; X = S

f, $R^1 = Ph$; $R^2 = H$; X = S



5a, $R^1 = H$; $R^2 = (CH_2)_2CN$; X = O

b, $R^1 = H$; $R^2 = Ph$; X = O

c, $R^1 = Ph$; $R^2 = (CH_2)_2CN$; X = O

d, $R^1 = R^2 = (CH_2)_2CN$; X = S

e, $R^1 = (CH_2)_2CN$; $R^2 = Ph$; X = S

f, $R^1 = Ph$; $R^2 = (CH_2)_2CN$; X = S

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

Comp.*	Solvent of cryst.**	M.p. (°C)	Yield (%)	Formula	Comp.*	Solvent of cryst.**	M.p. (°C)	Yield (%)	Formula
1d	A	268	90	$C_{16}H_{12}ON_2S$	3b	E	230	70	$C_{27}H_{20}O_4N_3SCl$
1e	A	288	88	$C_{17}H_{14}O_2N_2S$	3c	A	135	75	$C_{26}H_{17}O_3N_3SCl_2$
1f	A	300	90	$C_{16}H_{11}ON_2SCl$	5a	E	205	80	$C_{12}H_{13}O_2N_5$
2a	E	233	70	$C_{19}H_{15}ON_3S$	5b	E	120	82	$C_{15}H_{14}O_2N_4$
2b	E	255	65	$C_{20}H_{17}O_2N_3S$	5c	E	175	85	$C_{18}H_{17}O_2N_5$
2c	E	220	70	$C_{21}H_{20}O_3N_2S$	5d	E	110	90	$C_{15}H_{16}ON_6S$
2d	E	258	73	$C_{22}H_{22}O_4N_2S$	5e	E	145	85	$C_{18}H_{17}ON_5S$
2e	E	115	70	$C_{21}H_{19}O_3N_2SCl$	5f	A	120	80	$C_{18}H_{17}ON_5S$
3a	A	251	72	$C_{26}H_{18}O_3N_3SCl$					

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

**A=Acetic acid; E=Ethanol

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