

SYNTHESIS OF SOME NEW 4-SUBSTITUTED ANTIPIRINES OF ANTICIPATED BIOLOGICAL ACTIVITY

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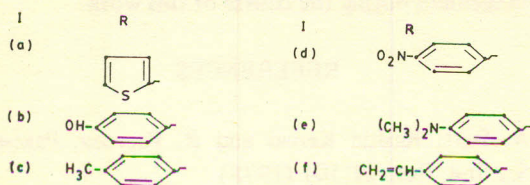
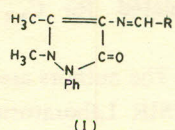
Schiff's bases of 4-amino-antipyrine were obtained. POCl_3/DMF treatment of base (Id) gave imidine salt which with alkaline solutions gave the imidine base and the aldehyde respectively.

INTRODUCTION

The analgesic, antipyretic and anti-inflammatory effects of pyrazolone derivatives are well known [1-4]. Antipyrine, 1-phenyl-2,3-dimethyl-5-pyrazolone, has been replaced by its more potent and less toxic structural analogues.

The aim of the present work is to explore this class of compounds by synthesising some new-4-substituted antipyrine derivatives for bioevaluation.

Thus, 4-substituted antipyrines (Ia-f) were synthesised by the condensation of 4-amino-antipyrine with heterocyclic or aromatic aldehydes in ethanol and characterized on the basis of correct analytical and spectral data [5].

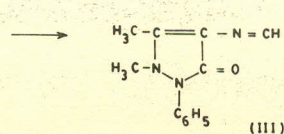
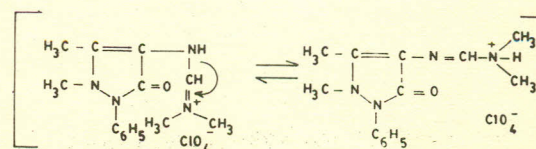
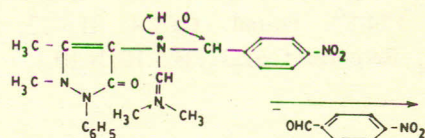
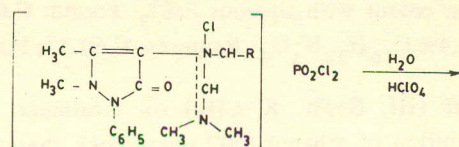
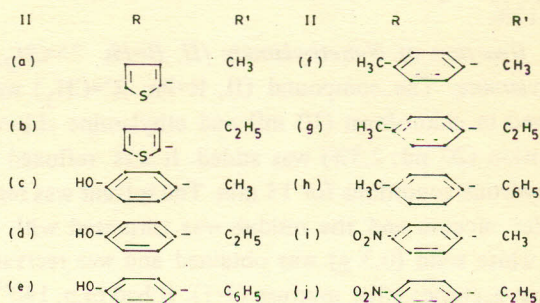
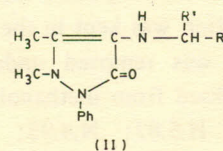


The addition of Grignard reagents onto Schiff's bases (Ia-d) adds on the C=N bond yielding colourless products of the type (II) in good yield.

Reaction of Id with one mole of phosphorous oxychloride under the Vilsmeier-Haeke conditions [6] gave the corresponding perchlorate salt of the imidine (III) in almost quantitative yield. IR spectrum of the latter showed the absorption of CH=N- grouping at 1690 cm^{-1} together with the perchlorate absorption band at 1100 cm^{-1} .

The reaction has obviously taken place by an attack by

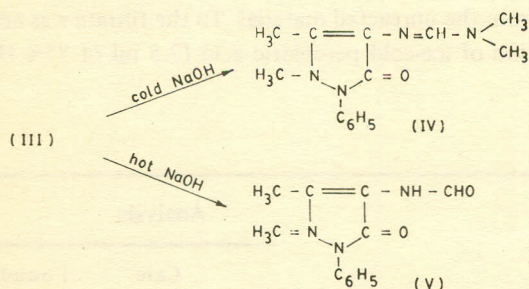
the acid chloride-amide, carbonium ion at the unshared pair of electrons of the phenyl nitrogen.



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The mechanism of this reaction can be rationalised according to the following scheme:

Moreover, alkaline hydrolysis of the salt (III) with cold 5% aqueous sodium hydroxide (7) solution gave the corresponding imidine base (IV). The IR spectrum of base (IV) showed the absence of the perchlorate absorption band at 1100 cm^{-1} . Meanwhile, hydrolysis with boiling 5% aqueous sodium hydroxide solution gave the corresponding aldehyde derivative (V). The aldehyde (V) showed a broad absorption band at 2800 cm^{-1} , which indicates its existence in the enolic chelated form.



An authentic sample was prepared by the formylation of (Ia) to give the perchlorate salt of amidine (III) which in

turn was hydrolysed by cold and hot aqueous sodium hydroxide solution to give the corresponding imidine base (IV) and aldehyde (V) respectively. The products in this case were found to be exactly identical with the formulation products of (Id) as shown by melting and mixed melting points as well as IR measurements.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were determined in potassium bromide on Unicam S.P. 1100 infra red spectrophotometer.

Preparation of Schiff's bases (Ia-f) (general procedure).

A solution of 4-aminoantipyridine (0.01 mole) and the appropriate aldehyde (0.01 mole) in ethyl alcohol (50 ml), was heated under reflux for 2-5 hr. The reaction mixture was allowed to cool, poured into crushed ice and the precipitated solid was collected by filtration and washed several times with cold water. The solid obtained was then crystallised from ethanol to give the corresponding hydrazones (Ia-f) (cf. Table 1).

Table 1

Compd	M.P.°C	Yield %	Formula (M. Wt)	Analysis	
				Calc.	Found
Ia	168	82	$\text{C}_{16}\text{H}_{15}\text{N}_3\text{OS}$ (297)	C H	64.64 5.55 64.80 5.55
Ib	236	92	$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$ (307)	C H	70.35 5.53 70.47 5.74
Ic	140	79	$\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$ (305)	C H	74.75 6.23 75.19 6.48
Id	248	91	$\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_3$ (336)	C H	64.29 47.60 64.65 5.03
Ie	215	81	$\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}$ (334)	C H	71.85 6.58 71.86 6.86
If	196	93	$\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}$ (317)	C H	75.70 5.99 76.20 6.38

(*) All products (Ia-f) are crystallised for purification from ethanol.

Action of organo-magnesium halides on schiff's bases (Ia-f): Preparation of products (II) (general procedure). An ethereal solution of alkylmagnesium halide (prepared from 0.15 mole of magnesium turning; 0.01 mole of alkyl halide and 50 ml of dry ether), was added to a suspension of (I) (0.01 mole) in dry benzene (100 ml).

The material dissolved rapidly with discharge of colour. The reaction mixture was heated under reflux for 3 hr, set aside at room temperature overnight, then treated with a cold saturated aqueous ammonium chloride solution and extracted with an ether-benzene mixture.

The ether-benzene extract was dried over anhydrous magnesium sulphate and on evaporation it deposited colour-

less crystals. Recrystallization from ethanol gave the corresponding addition products (II) (cf. Table 2).

Reaction of POCl₃-DMF with Schiff's Bases: Preparation of the perchlorate salt of the imidine (III): Freshly distilled POCl₃ (10 ml, 0.11 mole) was added dropwise with stirring to DMF (20 ml; 0.2 mole) at 0-5°. A solution of 0.1 mole of the aldehyde Schiff's base, in 20 ml of DMF was added dropwise at 5-10°. The reaction mixture was kept at room temperature for ½ hr, then at 60-70° for about 6 hr.

After cooling, it was poured into crushed ice, then filtered from the unreacted material. To the filtrate was added a solution of ice-cold perchloric acid (7.5 ml of 75% HC10₄

Table 2

Compd	M.P. °C	Yield %	Formula (M. Wt)	Analysis	
				Calc.	Found
Ila	174	62	C ₁₇ H ₁₉ N ₃ OS (313)	C H	65.17 6.07 64.80 5.95
b	164	59	C ₁₈ H ₂₁ N ₃ OS (327)	C H	66.05 6.42 65.76 6.81
c	236	55	C ₁₉ H ₂₁ N ₃ O ₂ (323)	C H	70.57 6.50 70.66 5.91
d	224	63	C ₂₀ H ₂₃ N ₃ O ₂ (337)	C H	71.21 6.82 71.10 5.49
e	236	59	C ₂₄ H ₂₃ N ₃ O ₂ (385)	C H	74.80 5.97 74.62 5.45
f	140	64	C ₂₀ H ₂₃ N ₃ O (321)	C H	74.76 7.16 74.72 7.11
g	164	68	(C ₂₅ H ₂₅ N ₃ O (335)	C H	75.22 7.46 75.12 7.60
h	184	65	C ₂₅ H ₂₅ N ₃ O (383)	C H	78.08 6.52 78.08 6.91
i	248	69	C ₁₉ H ₂₀ N ₄ O ₃ (352)	C H	64.77 5.68 65.04 5.08
j	288	66	C ₂₀ H ₂₂ N ₄ O ₃ (366)	C H	65.57 6.01 65.55 5.92

in 20 ml H₂O), and the separated perchlorate salt (III) was filtered off and washed several times with cold water.

Analysis for: C₁₄H₁₉N₄O₅Cl (358.5); Calc.: C 47.06 H 5.04; Found: C 46.46 H 4.56.

Hydrolysis of Perchlorate salt (III) with sodium hydroxide: Preparation of the imidine (IV):

1. *On cold:* To a cold sodium hydroxide solution 5% (100 ml) in a beaker, perchlorate salt solution (0.01 mol in 25 ml ethanol) was added portionwise.

After complete addition the reaction mixture was left in the refrigerator for 3 days; then the formed solid was filtered off, washed several times with cold water to give the expected imidine base (IV), m.p. 250°

Analysis for: C₁₄H₁₈N₄O (258); Calc.: C 65.12 H 6.97% Found: C 65.27 H 6.83%.

2. *On hot.* To a boiling sodium hydroxide solution 5% (100 ml) in a beaker, perchlorate salt (0.01 mol) was added portionwise while shaking over a period of 30 min.

After complete addition, the reaction mixture was set aside to cool, then extracted with ether; the excess ether was distilled off and the aldehyde derivative (V) was recrystallised from ethanol, m.p. over 250°.

Analysis for: C₁₂H₁₃N₃O₂ (231); Calc.: C 62.33 H 5.62%; Found: C 62.35 H 5.52%.

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