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STUDIES ON SOME PYRAZOLONE DERIVATIVES

Presented By

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بسم الله الرحمن الرحيم

STUDIES ON SOME PYRAZOLOBENZIMIDAZOLES

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DISCUSSION ....

SUMMARY

PART I

The condensation of ethyl benzoylacetate or ethyl acetoacetate with phenyl hydrazine gave 3-methyl/phenyl-1-phenyl-2-pyrazoline-5-ones (Ia and b).

Michael addition of 1,3-diphenyl-2-pyrazolin-5-one (Ia) to some chalcones (II a - c) gave the Michael adducts 4-[α-(phenacyl) benzyl] -1,3-diphenyl-2-pyrazolin-5-one derivatives (III a-c).

Condensation of the Michael adducts (III a-c) with hydrazine hydrate or phenyl hydrazine, in boiling ethanol, gave the corresponding hydrazones (IV a-f), while in boiling acetic acid it gave decomposition products of (Ia) and 1-acetyl/phenyl-3,5-diaryl-2-pyrazolines (V a-f) which were prepared authentically by treatment of hydrazines with chalcones (II a-c) in boiling acetic acid.

Condensation of adducts (III a-c) with hydroxylamine in boiling ethanol gave the corresponding oximes (VI a-c) .

Reduction of adducts (III a-c) with zinc dust in acetic acid gave 4-[α-(β-hydroxyphenethyl) benzyl] -1,3-diphenyl-2-pyrazolin-5-one derivatives (VII a-c) .

Treatment of the adducts (III a-c) with Grignard reagents, gave the corresponding tertiary alcohols 4-[α-(β-aralkyl-β-hydroxyphenethyl) benzyl] -1,3-diphenyl-2-pyrazolin-5one derivatives (VIII a-i) .

PART II:

Formylation of 1,3-diphenyl-2-pyrazolin-5-one (Ia) by dimethyl formamide and phosphoryl chloride mixture gave 5-chloro-1,3-diphenyl-1H-pyrazol-4-carboxaldehyde (IX), and 1,3-diphenyl-4-formyl-2-pyrazolin-5-one (X).

Knoevenagel condensation of the aldehyde (IX) with acetophenone or p-methylacetophenone gave 3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl/p-tolyl-prop-2-en-1-ones (XIa and b) and aldehyde (X).

Condensation of chalcones (XIa and b) with hydrazine hydrate in boiling ethanol or acetic acid gave 4-(3-phenyl/p-tolyl-2-pyrazolin-5-yl)-5-chloro/oxo-1,3-diphenyl-1H-pyrazoles (XIIa and b), and 4-(1-acetyl-3-phenyl/p-tolyl-2-pyrazolin-5-yl)-5-chloro-1,3-diphenyl-1H-pyrazoles (XIIc and d), but with phenylhydrazine at the same conditions gave 4-(1-phenyl-3-phenyl/p-tolyl-2-pyrazolin-5-yl)-5-chloro-1,3-diphenyl-1H-pyrazoles (XIIIa and b). However, with hydroxylamine in boiling ethanol gave β-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-β-hydroxylaminopropiophenone oximes (XIVa and b), while in acetic acid alone gave 3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-3-oxo-propionitrile (XV), and 3-(1,3-diphenyl-5-oxo-1H-pyrazol-4-yl)-p-tolyl-prop-2-enoxime (XVI) respectively.

On the other hand, reaction of the chalcones (XIa and b) with sodium methoxide, in boiling methanol, gave 3-(1,3-diphenyl-5-methoxy-1H-pyrazol-4-yl)-1-phenyl/p-tolyl-prop-2-en-1-ones (XVIIa and b).

Chalcones (XIa and b) were easily cleaved on treatment with aqueous ethanolic potassium hydroxide solution to give a mixture of aldehyde (X) and acetophenone or p-methylacetophenone.

Treatment of chalcones (XIa and b) with Grignard reagents at 25°C, gave 3-(5-chloro-1,3-diphenyl-1<u>H</u>-pyrazol-4-yl)-1-aralkyl-prop-2-en-1-ols (XVIIIa-c).

However, chalcone (XIa) with methyl magnesium iodide in boiling dry ether gave 1,3-diphenyl-6-methyl pyrazolopyran (XIX) which is authentically obtained by treatment of propenol (XVIIIa) with boiling ethanol containing few drops of piperidine.

Friedel-Crafts reaction of chalcones (XIa and b) with aromatic hydrocarbons, underwent fission of the exocyclic double bond to give the chloroaldehyde (IX).

Fusion of chalcones (XIa and b) with p-toluidine at 130°C gave a mixture of 1,3-diphenyl-5-p-tolyl amino pyrazole (XX) and the corresponding Schiff's base (XXIa and b).

Bromination of the chalcones (XIa and b) with bromine in acetic acid gave 2,3-dibromo-3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl/p-tolyl propan-1-ones (XXIIa and b) which were dehydrobrominated by ethanolic potassium hydroxide to give 3-(4,5-dihydro-1,3-diphenyl-5-oxo-1H-pyrazol-4-yl)-1-phenyl/p-tolyl-prop-2-yn-1-ones (XXIIIa and b).

Condensation of the dibromides (XXIIa and b) with hydrazine hydrate or phenyl hydrazine in acetic acid gave 5-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-1-acetyl/phenyl-3-phenyl/p-tolyl-1H-pyrazoles (XXIVa and b). However, with hydroxylamine in acetic acid the dibromides gave 3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl/p-tolyl-prop-2-enoximes (XXVa and b), but they underwent debromination under Friedel-Crafts conditions to give the corresponding chalcones (XIa and b).

Epoxidation of the chalcones (XIa and b) with hydrogen peroxide, sodium hydroxide mixture in methanol gave 3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl/p-tolyl-2,3-epoxypropan-1-ones (XXVIa and b).

The epoxides (XXVIa and b) gave the aldehyde (X) and β-(4,5-dihydro-1,3-diphenyl-5-oxo-1H-pyrazol-4-yl)-α-hydroxy-α-p-tolyl propionic acid (XXVII), respectively, under the action of aqueous ethanolic sodium hydroxide.

Unexpectedly, the Grignard reagents, added to the epoxides (XXVIa and b) to give 1-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-propan-2-ol (XXVIII) or α-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl) acetic acid (XXIX) respectively.

Base-catalyzed cycloaddition of some active methylene compounds to chalcones (XIa and b) in presence of sodium ethoxide at 25°C gave the expected Michael adducts:

With ethyl acetoacetate it gave ethyl 3-phenyl/p-tolyl-5-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-oxo-cyclohex-2-en-6-carboxylate (XXXa and b), while with ethyl cyanoacetate it gave 2-cyano-3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-prop-2-enoic acid (XXXI); however, chalcone (XIa) with ethyl cyanoacetate in ethanol containing few drops of piperidine gave α-(5-cyano-1,3-diphenyl-6-ethoxy-1H-pyrazolopyran)-acetophenone (XXXII). Acetylacetone cyclized with the chalcone (XIa) to give 2-methyl-3,6,6a-trihydro-5,7,9-triphenyl-6H-(1)-benzopyrano (3,4-c)-1H-pyrazol-3-one (XXXIII).

On the other hand, chalcones (XIa and b) with cyclohexanone gave 3-aroyl-2,4-bis-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-2,3,4,5,6,7,8 -heptahydrobenzopyran (XXXIVa and b).

Base-catalyzed cycloaddition of some active methylene compounds to chalcones (XIa and b) in presence of ammonium acetate at 130°C gave many interesting unexpected products:

With ethyl cyanoacetate it gave 6-phenyl/p-tolyl-2-oxo-1,2,3,4-tetrahydro-4-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-nicotinonitriles (XXXVa and b), while, with ethyl acetoacetate it gave α-(1,3-diphenyl-5-carbethoxy-6-methyl-1H-pyrazolo-(3,4-c)-pyridin-4-yl)-acetophenone derivatives (XXXVIa and b).

However, with diethylmalonate it gave α-(4,5,6,7-tetrahydro-1,3-diphenyl-5-carbethoxy-6-oxo-1H-pyrazolo(3,4-c)-pyridin-4-yl)-acetophenone or p-methylacetophenone (XXXVIIa and b).

With cyclohexanone 1,3-diphenyl-4-(2-oxocyclohexyl)-1*H*-pyrazolo (3,4-c)-pyridine (XXXVIII) was obtained. Condensation with 1,3-diphenyl-2-pyrazolin-5-one gave 1,3-diphenyl-4-(4,5-dihydro-1,3-diphenyl-5-oxo-1*H*-pyrazol-4-1*H*-pyrazolo-(3,4-c)-4,7dihydro pyridine (XXXIX).

All new products were established by correct elemental analysis, and IR, ^{1}H-NMR and ^{13}C-NMR spectral data.

* INTRODUCTION

CHEMISTRY OF 2-PYRAZOLIN-5-ONES

Structure:

The structure of pyrazolinones has been very extensively studied using ultraviolet and infrared absorption spectra.

The stretching frequency of carbonyl group in pyrazolinones is expected to be influenced both by its presence as a part of the 5-membered ring, as well as by its conjugation with the adjacent nitrogen. There is no simple way of predicting exactly in which region it will absorb. However, Gagnon *et al*(1) studied the I.R. spectra of a series of 4-alkyl-1,3-diphenyl-5-pyrazolones and observed a characteristic absorption at (1710-1705 cm^{-1}), which they attributed to the carbonyl stretching frequency and from which they concluded the existance of these pyrazolones in the ketonic form. Carbonyl absorption was absent, however, in 3-phenyl-5-pyrazolones investigated by the same authors(2) they assigned the enolic structure to these pyrazolones. Furthermore, they noted the existance of absorption bands at (1600-1590 cm^{-1}), which they attributed to the cyclic C=N group by analogy to an assignment reported by Randal *et al*(3), who observed the presence of such a band at about 1610 cm^{-1} for 3-methyl-5-pyrazolone.