

Synthesis and Some Reactions of 6-(4-Methoxyphenyl)-4-(3,4-dimethoxyphenyl-
methyl)-pyridazin-3(2H)-one

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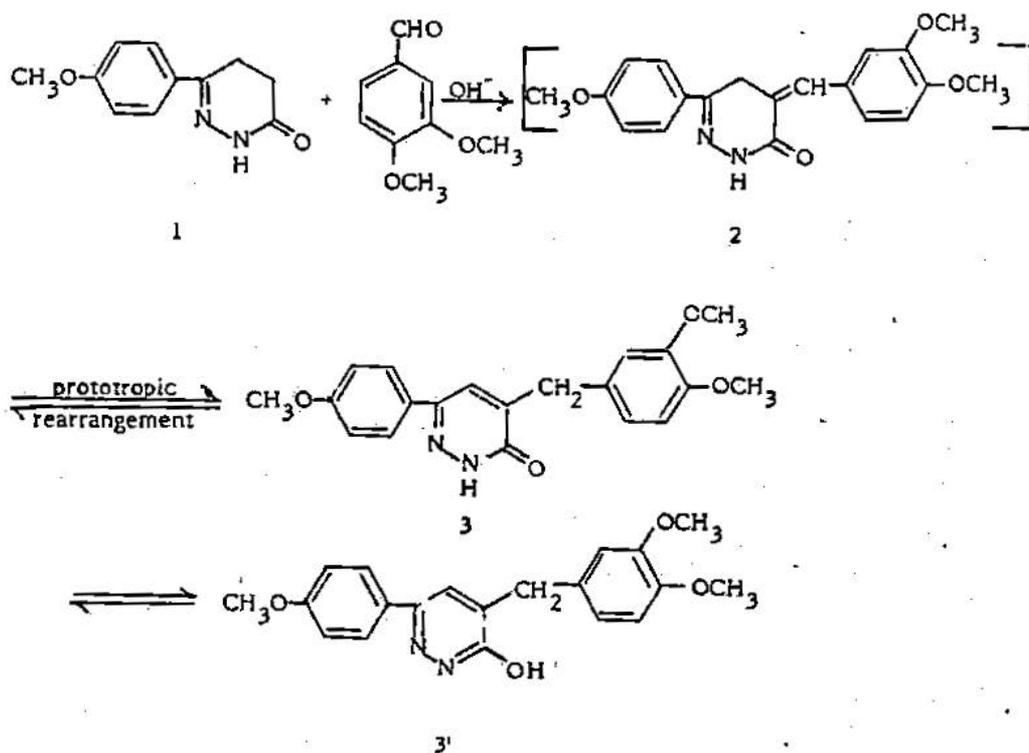


Summary 6-(4-Methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one 3 was prepared by base catalysed reaction of 6-(4-methoxyphenyl)-4,5-dihydropyridazin-3(2H)-one with veratraldehyde. The reaction of 3 with dimethyl sulphate, formaldehyde and acrylonitrile, and the formation of Mannich base proceeded easily at the 2-position to give compounds 4, 5, 7 and 6, respectively. 6-(4-Methoxyphenyl)-3-chloro-4-(3,4-dimethoxyphenylmethyl)-pyridazine 8 was prepared by the action of phosphorus oxychloride on 3. The reaction of 8 with hydrazine hydrate gave 4-hydrazinopyridazine derivative 9. 6-(4-Methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-thione 11 was prepared by the action of thiourea on 8.

Introduction and Results

In a study concerning the steric effect exhibited by bulky groups present in the pyridazine ring, a compound namely: 6-(4-methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one 3 was prepared via base catalysed condensation of veratraldehyde with 6-(4-methoxyphenyl)-4,5-dihydropyridazin-3(2H)-one 1. The formation of 3 might involve the intermediate formation of 6-(4-methoxyphenyl)-4,5-dihydro-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one 2 which underwent prototropic rearrangement to give 3.

(2)



The structure suggested for 3 was established from:

i) Analytical data, ii) stability of the compound towards alkali and acid (it dissolves easily in aqueous sodium hydroxide solution and reprecipitates upon addition of mineral acids. This fact excludes the possibility of structure 2 since compounds of this nature are readily cleaved by acids or bases¹), and iii) independent synthesis of 3 by the reaction of 5-(4-methoxyphenyl)-3-(3,4-dimethoxybenzyl)-2(1H)-furanone with hydrazine hydrate. The infrared spectrum is similar to those of previously prepared 6-arylpyridazin-3(2H)-ones^{2,3}. They show strong carbonyl stretching frequencies near 1660 cm^{-1} , in addition to broad absorption in the region

(3)

characteristic of NH and OH groups.

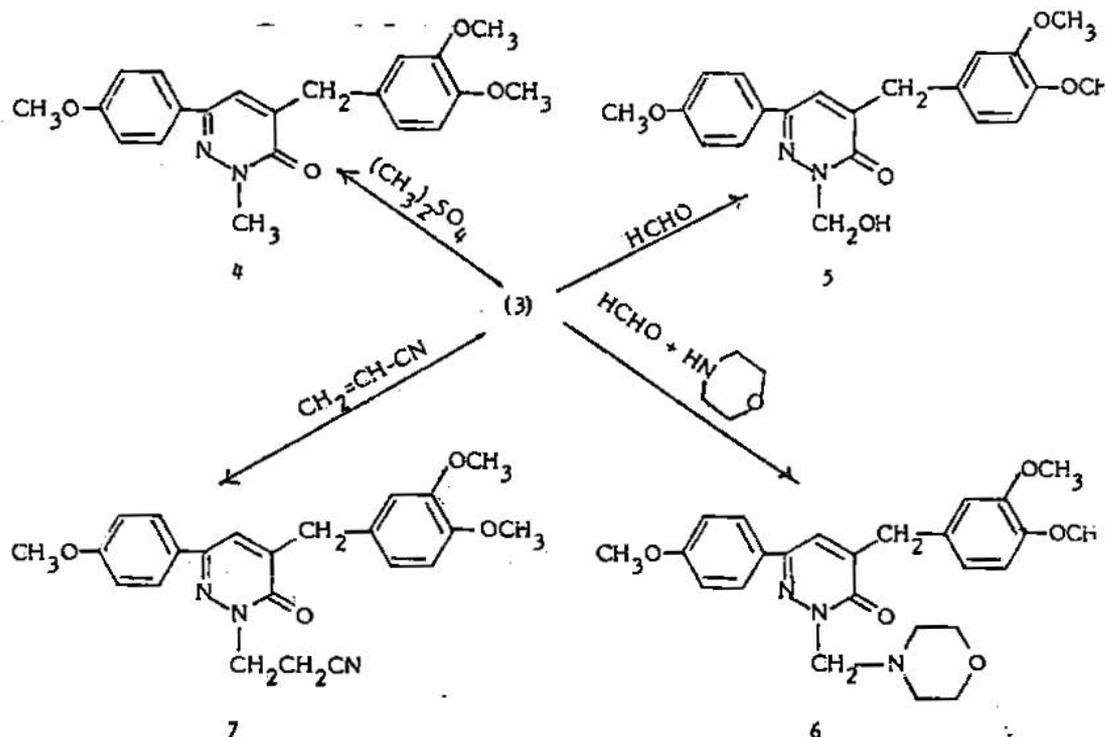
The reaction of 3 with dimethyl sulphate afforded 2-methyl-4-(3,4-dimethoxyphenylmethyl)-6-(4-methoxyphenyl)-pyridazin-3(2H)-one 4 whose infrared spectrum shows $\nu_{C=O}$ at 1650 cm^{-1} and lacks any significant absorption in the region characteristic of NH and OH groups.

When 3 was treated with formaldehyde, hydroxymethylation took place to give 6-(4-methoxyphenyl)-2-hydroxymethyl-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one 5. Similarly, the reaction of 3 with formaldehyde in the presence of a secondary amine, namely morpholine, yielded the Mannich base 6. Compounds 5 and 6 show the carbonyl stretching frequencies of pyridazinones at $1640 - 1650\text{ cm}^{-1}$. Moreover, the hydroxymethyl derivative shows absorption at 3385 cm^{-1} characteristic of ν_{OH} , while that of Mannich base lacks any significant absorption in the region of NH and OH groups.

The reaction of an alcoholic solution of 3 with acrylonitrile in the presence of very small amount of aqueous sodium hydroxide involved a Michael - type addition to supply 2-(2'-cyanoethyl)-4-(3,4-dimethoxyphenylmethyl)-6-(4-methoxyphenyl)-pyridazin-3(2H)-one 7.

It was of interest to extend this study to investigate some reactions involving the 3-position of 6-(4-methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one. For this purpose, the reactivity of 6-(4-methoxyphenyl)-3-chloro-4-(3,4-dimethoxyphenylmethyl)-

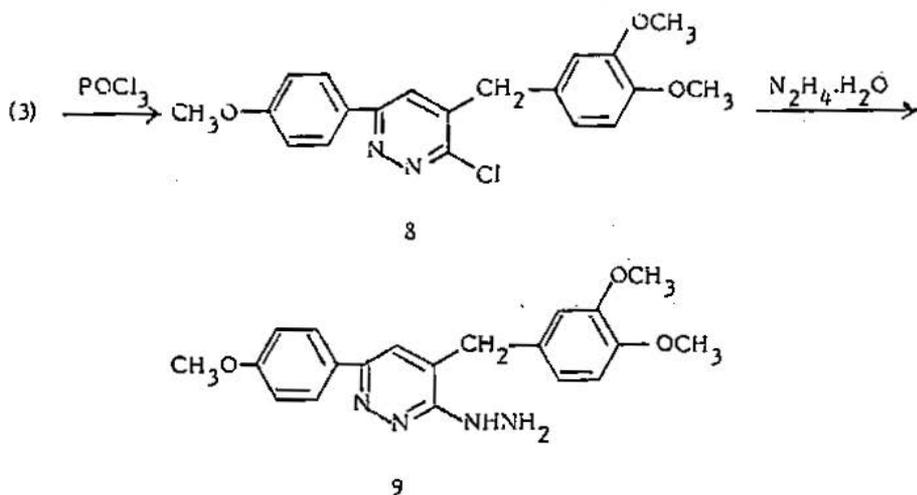
(4)



pyridazine 8 towards some nucleophilic reagents was investigated. Compound 8 was prepared by the action of phosphorus oxychloride on 3. The structure of 8 was established from analytical data and the fact that its infrared spectrum lacks the significant absorptions of NH, OH and C=O groups.

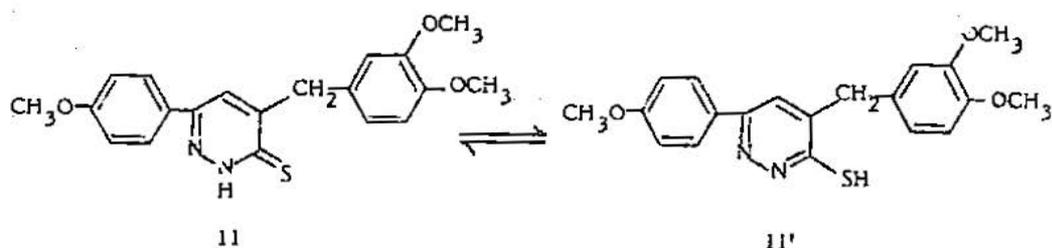
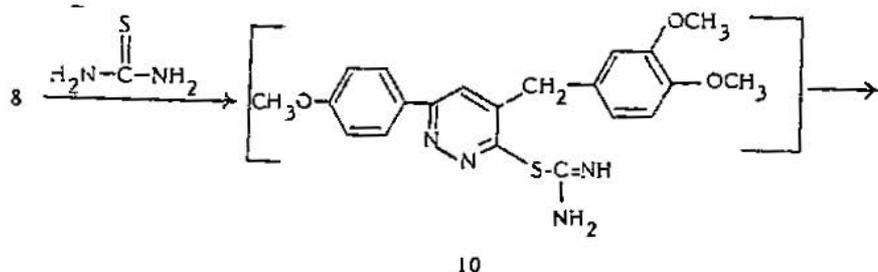
The reaction of hydrazine hydrate with 8 gave the 3-hydrazino derivative 9. This reaction clearly involved the nucleophilic displacement of the chlorine atom by the amino group. The structure of 9 was deduced from analytical data, and from the fact that its infrared spectrum shows significant NH absorption and by the similarity with previously reported cases⁴⁻⁷.

(5)



The reaction of 8 with alcoholic thiourea provided 6-(4-methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-thione 11 via the intermediate formation of thionium salt 10 which was difficult to be isolated. The structure of the thione 11 was confirmed by analytical data and infrared spectrum, which shows $\nu_{\text{C}=\text{S}}$ at 1250 cm^{-1} in addition to a broad band at $3320 - 3500 \text{ cm}^{-1}$ characteristic of the grouping $\begin{array}{c} \text{S} \\ || \\ -\text{C}-\text{NH}- \end{array} \rightleftharpoons \begin{array}{c} \text{SH} \\ | \\ -\text{C}=\text{N}- \end{array}$. Similar results for infrared spectra of pyridazin-3(2H)-thiones were recently reported⁸⁻¹⁰. Therefore, it is evident that this compound exists mainly in the thione form 11.

(6)



Experimental

6-(4-Methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one (3)

A mixture of 6-(4-methoxyphenyl)-4,5-dihydropyridazin-3(2H)-one (0.01 mol) and veratraldehyde (0.01 mol) in ethanol (10 ml) was treated with 4 % ethanolic KOH solution (25 ml). The reaction mixture was heated under reflux for 3 h, cooled, poured over ice - cold water and rendered just acidic with conc. HCl. The formed solid was crystallised from benzene to give (3) as pale yellow crystals (cf. Table 1).

Action of dimethyl sulphate on (3); Formation of 6-(4-methoxyphenyl)-2-methyl-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one (4)

Dimethyl sulphate (1 ml) was added to a solution of (3) (1 gm) in aq. NaOH (25 ml, 20 %). The reaction mixture was heated for 30 minutes and left to cool. The solid product formed

(7)

was crystallised from benzene / light petroleum mixture to give (4) as colourless crystals (cf. Table 1).

Action of formaldehyde on (3); Formation of 6-(4-methoxyphenyl)-2-hydroxymethyl-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one (5)

A mixture of (3) (1 gm), formaldehyde (1 ml) and few drops of water in ethanol (20 ml) was heated under reflux for 2 h, and left to cool. The solid formed was crystallised from benzene to give (5) as colourless crystals (cf. Table 1).

Reaction of (3) with formaldehyde and morpholine; Formation of Mannich base (6)

A mixture of (3) (3 gm, 0.01 mol), formaldehyde solution (5 ml) and morpholine (0.02 mol) in ethanol (25 ml) was heated under reflux for 3 h. After concentration of ethanol, the solid formed was crystallised from benzene to give (6) as colourless crystals.

Action of acrylonitrile on (3); Formation of 2-(2-cyanoethyl)-6-(4-methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one (7)

A mixture of (3) (0.01 mol) and acrylonitrile (0.012 mol) in ethanol (20 ml) and few drops of 10 % aq. NaOH solution was heated under reflux for 4 h. The solid formed was crystallised from benzene to give (7) as colourless crystals (cf. Table 1).

Action of phosphorus oxychloride on (3); Formation of 6-(4-methoxyphenyl)-3-chloro-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-one (8)

A mixture of (3) (1 gm) and phosphorus oxychloride (4 ml) was heated on a boiling water bath for 3 h, cooled, treated

(8)

with crushed ice and made alkaline with aqueous sodium hydroxide. The solid product was filtered and crystallised from benzene.

6-(4-Methoxyphenyl)-3-hydrazino-4-(3,4-dimethoxyphenylmethyl)-pyridazine (9)

A mixture of (8) (1 gm) and hydrazine hydrate (2 ml) in ethanol (25 ml) was heated under reflux for 3 h. The solid product formed after cooling was filtered, and crystallised from benzene to give (9).

Action of thiourea on (8); Formation of 6-(4-methoxyphenyl)-4-(3,4-dimethoxyphenylmethyl)-pyridazin-3(2H)-thione (11)

Thiourea (0.012 mol) was added to a solution of (8) (0.01 mol) in ethanol (30 ml) and the reaction mixture was heated under reflux for 5 h. The solid formed was crystallised from benzene to give (11) (cf. Table I).

N.B. :

All melting points are uncorrected. Analyses were carried out at Chemistry Department, Faculty of Science, Ain Shams University. I.R. spectra were measured on a Unicam SP.1200, Spectrophotometer.

Table 1

Compd. No.	M.p. °C	Yield %	Molecular Formula	Analysis % Found / Calc.				
				C	H	N	Cl	S
3	154-6	85	$C_{20}H_{20}N_2O_4$	67.92	5.60	8.14		
				68.18	5.68	7.95		
4	118-120	70	$C_{21}H_{22}N_2O_4$	69.11	5.86	7.49		
				68.85	6.01	7.65		
5	138	80	$C_{21}H_{22}N_2O_5$	65.49	5.72	7.01		
				65.96	5.75	7.32		
6	110-112	90	$C_{25}H_{29}N_3O_5$	67.00	6.30	9.17		
				66.51	6.43	9.31		
7	149-151	50	$C_{23}H_{23}N_3O_4$	67.80	5.82	10.21		
				68.14	5.67	10.37		
8	133-135	40	$C_{20}H_{19}N_2ClO_3$	65.02	5.00	7.33	9.71	
				64.77	5.12	7.55	9.58	
9	165	60	$C_{20}H_{22}N_4O_3$	65.72	6.11	14.89		
				65.57	6.00	15.30		
11	171-173	30	$C_{20}H_{20}N_2SO_3$	65.12	5.35	7.55		8.7
				65.20	5.43	7.60		8.65

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الملخص العربي

أمكن تحضير ٦ - (٤ - ميثوكسي فينيل) - ٤ - (٤،٣ - ثنائي ميثوكسي فينيل ميثيل) -
- بيريدازين - ٣ (٢ يد) - أون (٣) وذلك بتفاعل ٦ - (٤ - ميثوكسي فينيل) - ٥،٤ - ثنائي
هيدروبيريدازين - ٣ (٢ يد) - أون مع الفيراترالدهيد في وسط قاعدي . ثم تمت مفاعلة
المركب (٢) مع كل من كبريتات ثنائي ميثيل ، فورمالدهيد ، اكريلونيتريل ، والفورمالدهيد
/ مورفولين وامكن فصل المركبات (٤) ، (٥) ، (٦) على التوالي وكانت
جميع التفاعلات السابقة في الوضع ٢ في البيريدازينون (٣) - وعند مفاعلة المركب (٣)
مع أوكسي كلوريد الفوسفور امكن الحصول على ٦ - (٤ - ميثوكسي فينيل) - ٣ - كلورو - ٤ -
(٤ ، ٣ - ثنائي ميثوكسي فينيل ميثيل) - بيريدازين (٨) ، الذي امكن مفاعله مع كل من
هيدرات الهيدرازين والثيوريا ليعطي مشتق ٤ - هيدرازينو بيريدازين (٩) ، ٦ - (٤ -
ميثوكسي فينيل) - ٤ - (٣ ، ٤ - ثنائي ميثوكسي فينيل ميثيل) - بيريدازين - ٣ (٢ يد)
- أون (١١) على التوالي .