

Synthesis and Some Reactions of 4-(3,4-Dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one



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**ABSTRACT**

4-(3,4-Dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one (3) was prepared by the base-catalysed reaction of 4,5-dihydro-6-phenylpyridazin-3(2H)-one (1) with 3,4-dimethoxybenzaldehyde. The reaction of (3) with dimethyl sulphate, acrylonitrile and the formation of the Mannich base proceeded smoothly at the 2-position to give compounds (5), (7) and (8) respectively. 3-Chloro-4-(3,4-dimethoxybenzyl)-6-phenylpyridazine (8) was prepared by the action of phosphorus oxychloride on (3). The reaction of (8) with aniline gave the 3-phenylaminopyridazine derivative (9). 4-(3,4-Dimethoxybenzyl)-6-phenylpyridazin-3(2H)-thione (11) was prepared by the action of thiourea on (8).

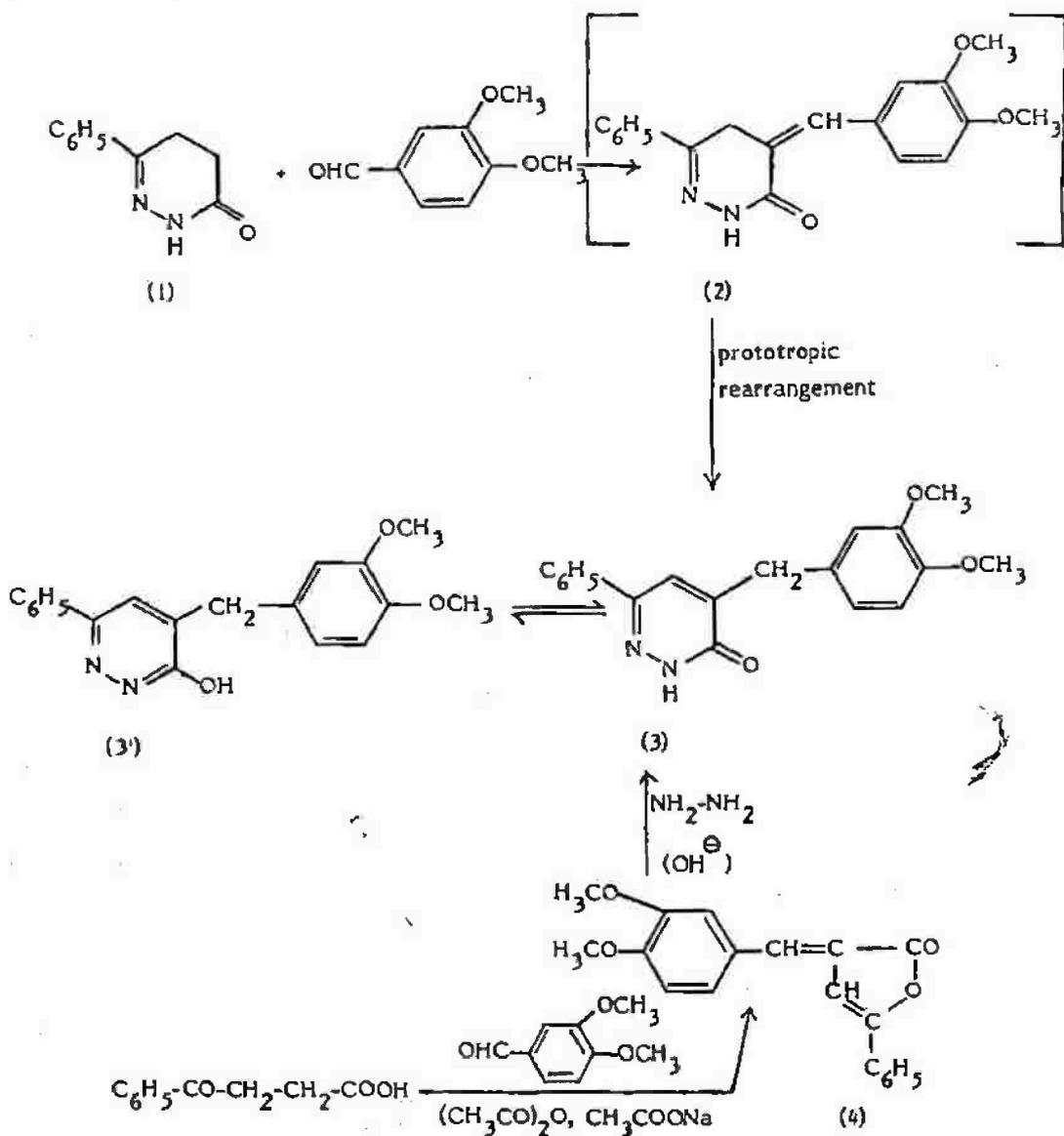
The present investigation deals with the synthesis of 4-(3,4-dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one (3) by base-catalysed condensation of 3,4-dimethoxybenzaldehyde with 4,5-dihydro-6-phenylpyridazin-3(2H)-one (1). The reaction proceeded via the intermediate formation of 4,5-dihydro-4-(3,4-dimethoxybenzylmethylene)-6-phenylpyridazin-3(2H)-one (2), which underwent prototropic rearrangement to give (3).

The structure of (3) was inferred from: (i) Microanalytical and spectral data. Its infrared spectrum shows close similarity to the spectra of other pyridazin-3(2H)-ones<sup>1,2</sup> ( $\nu_{C=O}$  of cyclic

(2)

amides at  $1650 \text{ cm}^{-1}$  and the broad spectrum at  $3035-3320 \text{ cm}^{-1}$  characteristic of  $-\text{C}-\text{NH}- \rightleftharpoons -\overset{\text{OH}}{\text{C}}=\text{N}$  grouping). (ii) It is stable towards alkalis and acids. It dissolves easily in aqueous sodium hydroxide solution and precipitates upon addition of mineral acids. This fact excludes structure (2), since compounds of this nature are readily cleaved by acids or alkalis<sup>3</sup>. (iii) The structure was rigidly established by an independent synthesis of (3) by the action of hydrazine hydrate in the presence of alkali<sup>4</sup> on 3-(3,4-dimethoxyphenylmethylene)-5-phenylfuran-2(3H)-one (4). The latter compound was synthesised easily by the Perkin reaction of 3,4-dimethoxybenzaldehyde with  $\beta$ -benzoylpropionic acid (scheme 1). The structure of the orange lactone (4) was substantiated, other than from analytical data, from the fact that its infrared spectrum shows the intense carbonyl stretching frequency of five-membered lactones at  $1753 \text{ cm}^{-1}$ .

(3)



Scheme 1

The reaction of (3) with dimethyl sulphate proceeded easily to afford 4-(3,4-dimethoxybenzyl)-2-methyl-6-phenylpyridazin-3(2H)-one (5) whose infrared spectrum shows strong absorption of carbonyl group at  $1645\text{ cm}^{-1}$  and lacks any significant absorption in the region characteristic of NH and OH groups. (Scheme 2).

The reaction of 4-(3,4-dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one (3) with formaldehyde in the presence of morpholine, proceeded normally to give the Mannich base (6). (Scheme 2).

The reaction of an alcoholic solution of (3) with acrylonitrile in the presence of catalytic amount of aqueous sodium hydroxide involved Michael-type addition to supply 2-(2'-cyanoethyl)-4-(3,4-dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one (7). (Scheme 2).

The structure of (6) and (7) were substantiated from: (i) Analytical data (ii) Their infrared spectra lack any significant absorption in the region characteristic of  $\text{NH}$ , a fact indicating that these reactions involved the NH group at position 2, while they show strong carbonyl stretching frequencies, of pyridazinones at  $1650$  and  $1660\text{ cm}^{-1}$ , respectively. The spectrum of (7) shows in addition a sharp absorption at  $2240\text{ cm}^{-1}$  characteristic of the cyano group.

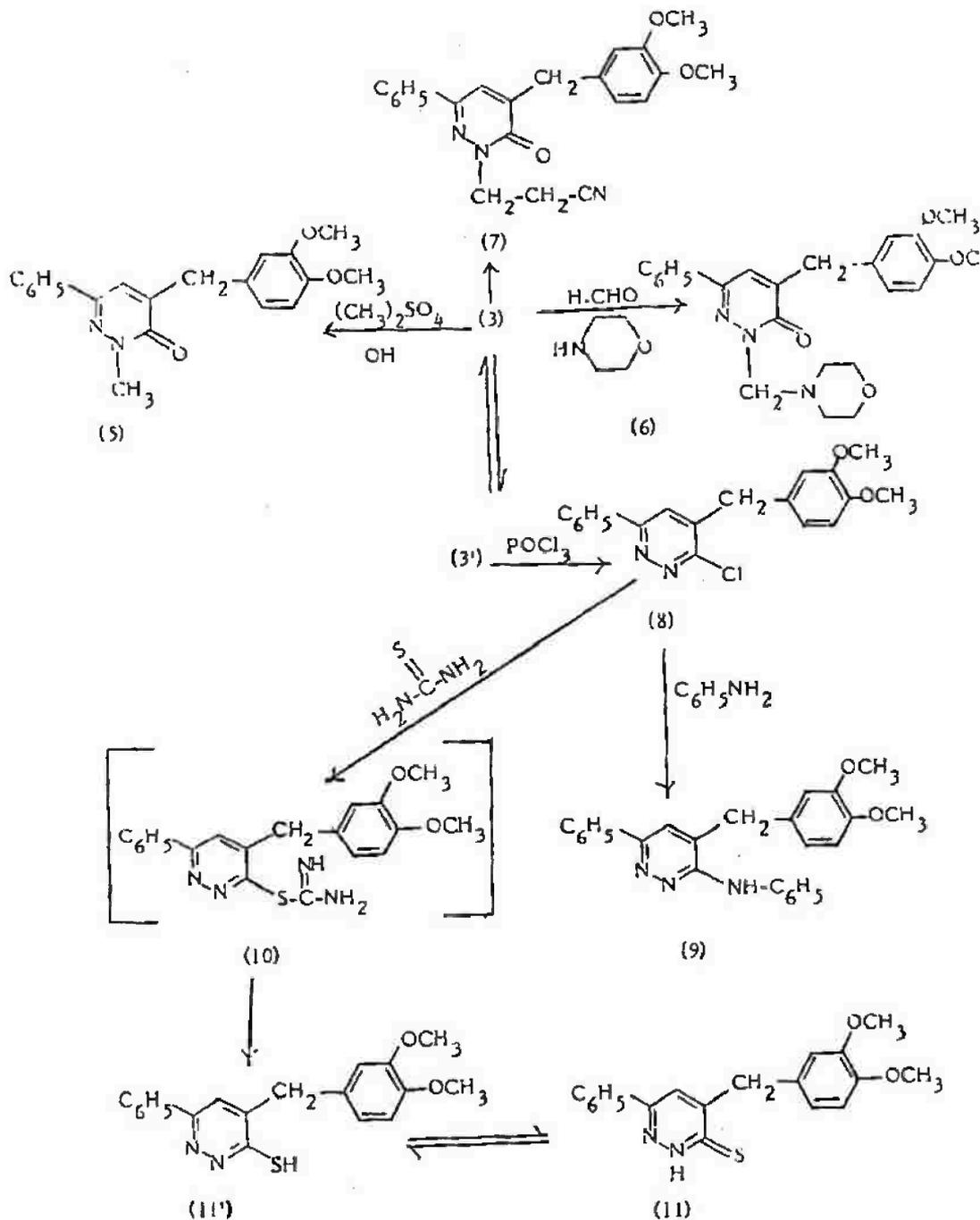
The reaction of (3), in the enol form (3'), with phosphorus oxychloride yielded 3-chloro-4-(3,4-dimethoxybenzyl)-6-phenylpyridazine (8). The structure of (8) was established from analytical data and the fact that its infrared spectrum is devoid of the significant

(5)

absorptions of NH, OH and C=O groups. When (8) was treated with aniline, the corresponding 3-phenylamino derivative (9) was formed. This reaction clearly involved the nucleophilic displacement of the chlorine atom by the amino group. The structure of (9) was substantiated, other than from analytical data from the fact that its infrared spectrum shows significant NH absorption at  $3120\text{ cm}^{-1}$  and by the similarity with previously reported cases<sup>5</sup>.

The reaction of (8) with alcoholic thiourea yielded 4-(3,4-dimethoxybenzyl)-6-phenylpyridazin-3(2H)-thione (11) or its tautomeric thiol (11'). The reaction, evidently, involved the intermediate formation of thioronium derivative (10), which was not isolated. The structure of the thione (11) was confirmed by analytical and spectral data. Its infrared spectrum shows close similarity to that previously reported for pyridazin-3(2H)-thiones<sup>6</sup>, namely, a broad absorption at  $3300 - 3545\text{ cm}^{-1}$  and  $\nu_{\text{C=S}}$  at  $1270\text{ cm}^{-1}$ .

(6)



Scheme 2

### Experimental

All melting points are uncorrected. Analyses were carried out in the Research Microanalytical laboratory of Cairo University. Infrared spectra were carried out on Pye - Unicam SP 1200 spectrophotometer using KBr wafer technique.

#### 4-(3,4-Dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one (3) :

A mixture of 4,5-dihydro-6-phenylpyridazin-3(2H)-one (1) (0.01 mol) and 3,4-dimethoxybenzaldehyde (0.01 mol) in ethanol (10 ml) was treated with 4 % ethanolic KOH solution (25 ml). The reaction mixture was heated under reflux for 3h, cooled, poured over ice - cold water and rendered just acidic with conc. HCl. The resultant solid was filtered off and crystallised from ethanol to give (3) as colourless crystals. (Table).

#### 3-(3,4-Dimethoxyphenylmethylene)-5-phenylfuran-2(3H)-one (4) :

A mixture of  $\beta$ -benzoylpropionic acid (1.8 g, 0.01 mol), 3,4-dimethoxybenzaldehyde (1.7 g, 0.01 mol) and freshly prepared sodium acetate (0.5 g) in acetic anhydride (5 ml) was heated until a clear solution was obtained. The reaction mixture was then transferred to a steam bath and heating was continued until crystals separated. The reaction mixture was poured into water. The solid product formed was filtered off and crystallised from ethanol to give (4) as orange crystals. (Table).

**Action of hydrazine hydrate on 3-(3,4-dimethoxyphenylmethylene)-5-phenylfuran-2(3H)-one (4) :**

A mixture of (4), (1 g) and hydrazine hydrate (1 ml) in ethanol was heated under reflux for 1h. The reaction mixture was treated with few drops of aqueous sodium hydroxide solution (10 %) and heating was continued for further 3h. The mixture was cooled and made just acidic by the addition of conc. HCl. The solid formed was filtered off and crystallised from ethanol to give (3) m.p. 148-50°C, yield 60%. The product was found to be identical with the product obtained by the base - catalysed condensation of 3,4-dimethoxybenzaldehyde with (1) by m.p., m.m.p. and superimposable IR spectra.

**Action of dimethyl sulphate on (3); Formation of 4-(3,4-dimethoxybenzyl)-2-methyl-6-phenylpyridazin-3(2H)-one (5) :**

Dimethylsulphate (1 ml) was added to a solution of (3) (1 g) in 20% aq. NaOH (25 ml). The reaction mixture was heated on a boiling water bath for 1 h. The solid product formed was filtered off and crystallised from benzene to give (5) as colourless crystals. (Table).

**Reaction of (3) with a mixture of formaldehyde and morpholine; Formation of Mannich base (6) :**

A mixture of the pyridazone (3) (2 g, 0.01 mol), formaldehyde solution (3 ml) and morpholine (1 g, 0.01 mol) in ethanol (25 ml) was heated under reflux for 4h. The solid formed after the removal of most of the solvent was crystallised from ethanol

to give the Mannich base (6) as colourless crystals. (Table).

Action of acrylonitrile on (3); Formation of 2-(2'-cyanoethyl)-4-(3,4-dimethoxybenzyl)-6-phenylpyridazin-3(2H)-one (7) :

The solution of (3) (0.01 mol) in ethanol (20 ml) was treated with acrylonitrile (0.01 mol) and few drops of 10% aqueous NaOH solution. The reaction mixture was heated under reflux for 6 h and left to cool. The solid formed was filtered off and crystallised from ethanol to give (7) as colourless crystals. (Table).

Action of phosphorus oxychloride on (3); Formation of 3-chloro-4-(3,4-dimethoxybenzyl)-6-phenylpyridazine (8) :

A mixture of (3), (5 g) and phosphorus oxychloride (15 ml), was heated on a boiling water bath for 1 h, cooled, poured over crushed ice and the solution made alkaline with cold sodium hydroxide solution (20%). The solid thus formed was filtered, washed with water and crystallised from benzene to give (8) as colourless crystals. (Table).

4-(3,4-dimethoxybenzyl)-3-phenylamino-6-phenylpyridazine (9) :

An equimolar, mixture of the 3-chloropyridazine (8) and aniline was heated at 140°C in a sand bath for 3h. The solid product was boiled with water for few minutes, filtered off and crystallised from ethanol to give (9) as colourless crystals. (Table).

Action of thiourea on (8); Formation of 4-(3,4-dimethoxybenzyl)-6-phenylpyridazin-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 5h. The yellow solid obtained after cooling was crystallised from ethanol to give (II) as yellow crystals. (Table).

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(11)

Table

Compd.	M.p.°C	Yield %	Molecular formula	Analysis % Found / Calc.				
				C	H	N	Cl	S
3	148-50	75	$C_{19}H_{18}O_3N_2$	71.80 70.80	5.30 5.59	7.96 8.69		
4	120-22	80	$C_{19}H_{16}O_4$	74.40 74.02	5.50 5.19			
5	107-9	80	$C_{20}H_{20}O_3N_2$	71.65 71.92	5.60 5.95	8.40 8.31		
6	115-17	75	$C_{24}H_{27}O_4N_3$	68.90 68.90	6.20 6.41	9.60 9.97		
7	110-12	70	$C_{22}H_{21}O_3N_3$	70.00 70.90	5.50 5.60	11.30 11.20		
8	130-32	70	$C_{19}H_{17}O_4N_2Cl$	67.22 66.96	5.17 4.99	- -	11.10 10.42	
9	163-65	80	$C_{25}H_{23}O_2N_3$	74.90 75.56	5.50 5.79	10.60 10.57		
11	172-74	85	$C_{19}H_{18}O_2N_2S$	67.90 67.45	5.20 5.32	7.80 8.78		9.30 9.46

ملخص البحث

تخليق ومعض تفاعلات ٤ - ( ٤٣ - ثنائي ميثوكسي بنزويل )

٦ - فنيل بيريدازين - ٣ ( ٢ يد ) - أون

أمنية عز الدين عبد العزيز مصطفى

قسم الكيمياء - كلية العلوم - جامعة عين شمس

تم في هذا البحث تخليق مركب ٤ - ( ٤٣ - ثنائي ميثوكسي بنزويل ) - ٦ - فنيل بيريدازين - ٣ ( ٢ يد ) - أون عن طريق تكاثف ٤ ر ٥ - ثنائي هيدرو - ٦ - فنيل بيريدازين - ٣ ( ٢ يد ) - أون مع ٤ ر ٣ - ثنائي ميثوكسي البنزالدهيد في وجود هيدروكسيد البوتاسيوم الكحولية .

وقد تم دراسة تفاعل ذلك المركب مع ثنائي كبريتات الحثيل والاكربونيتربيل والنفورمالدهيد في وجود المورفولين ، وكذلك تفاعله مع أوكس كلوريد الثيوفور حيث نتج من التفاعل الأخير مركب ٣ - كلورو - ٤ - ( ٤٣ ثنائي ميثوكسي بنزويل ) - ٦ - فنيل بيريدازين والذي تم تفاعله مع الانيلين وكذلك انثيوبوريا .