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Synthesis and reactions of 4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one

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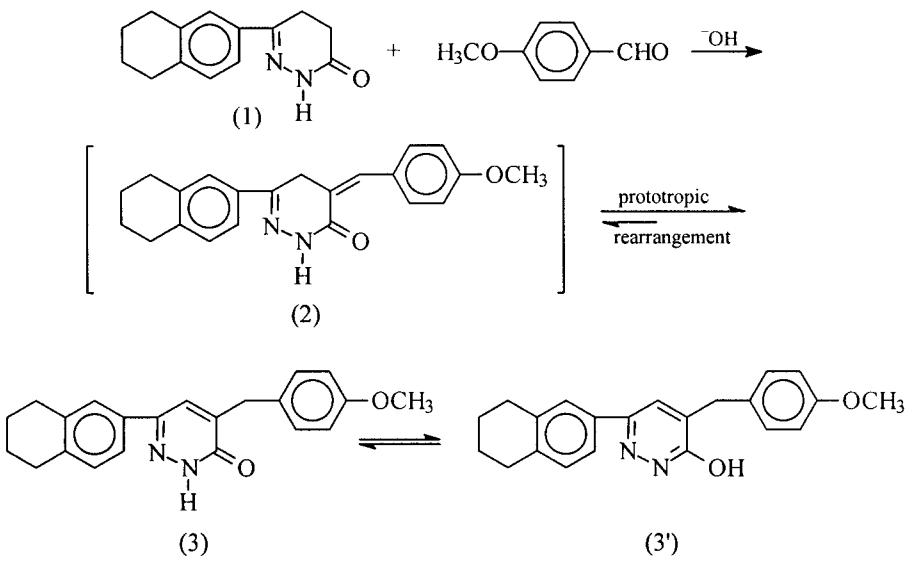
The condensation of 4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**3**), prepared by the reaction of 6-[5,6,7,8-tetrahydro-2-naphthyl]-4,5-dihydropyridazin-3(2*H*)-one (**1**) and anisaldehyde, with dimethyl sulphate, formaldehyde and acrylonitrile, and also the formation of the Mannich base, proceeded smoothly at the 2-position to give compounds **4,5,6,7**, respectively. 4-*p*-Methoxybenzyl-3-chloro-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazine (**9**) was prepared in law yield by the action of phosphorus oxychloride on **3**. The reaction of **9** with benzylamine, aniline and piperidine gave **10a,b,c**, respectively. 4-*p*-Methoxybenzyl-6-[5,6,7,8-tetrahydro-2-napthyl]pyridazine-3(2*H*)-thione (**12**) was prepared either by the action of thiourea on **9**, or by the reaction of **3** with phosphorus pentasulphide. The reaction of these thiones with acrylonitrile, morpholine and piperidine to give **13** and **14 a,b**, respectively, were also investigated.

Key words: pyridazin-3(2*H*)-one, dimethyl sulphate, formaldehyde, acrylonitrile, chloropyridazine, benzylamine, aniline, piperidine, pyridazinthione, morpholine.

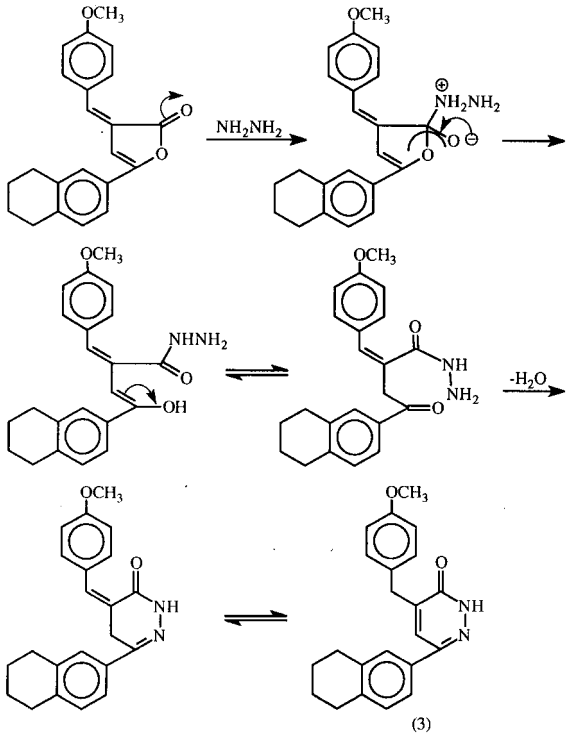
The present work deals with synthesis of 4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**3**) and some of its reactions. Compound **3** was prepared by the base-catalyzed condensation of *p*-methoxybenzaldehyde with 6-[5,6,7,8-tetrahydro-2-naphthyl]-4,5-dihydropyridazin-3(2*H*)-one (**1**). The reaction proceeded smoothly *via* the intermediate **2**, which underwent prototropic rearrangement to give **3**.

The structure of **3** was inferred from analytical data and its solubility in aqueous sodium hydroxide solution.[1] Its structure was further confirmed by its ^{1}H-NMR spectrum which displayed a singlet at δ 4.33, characteristic of benzyl methylene protons. Its IR spectrum is similar to those of previously prepared 6-arylpyridazin-3(2*H*)-ones.[2,3] The electronic spectrum shows a strong absorption at wavelengths characteristic of pyridazin-3(2*H*)-ones (*cf.* Table I).

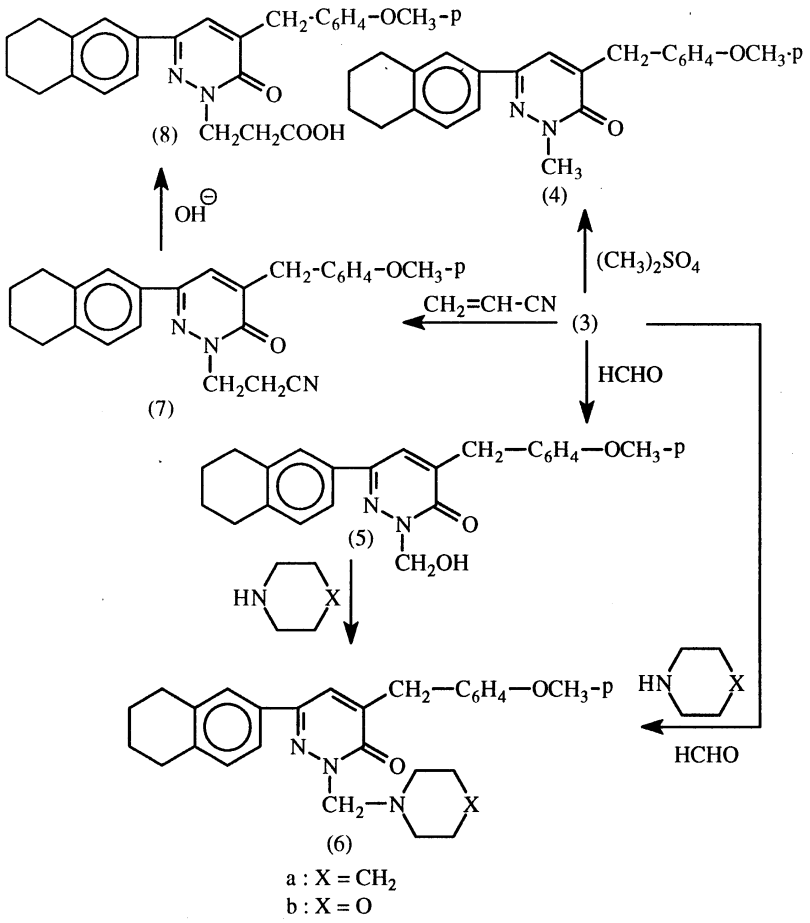
The structure was further established by an independent synthesis of **3** *via* the reaction of 3-*p*-methoxy-benzylidene-5-[5,6,7,8-tetrahydro-2-napthyl]-3(3*H*)-furanone[4] with hydrazine hydrate in boiling ethanol.



Scheme 1.



Scheme 2.

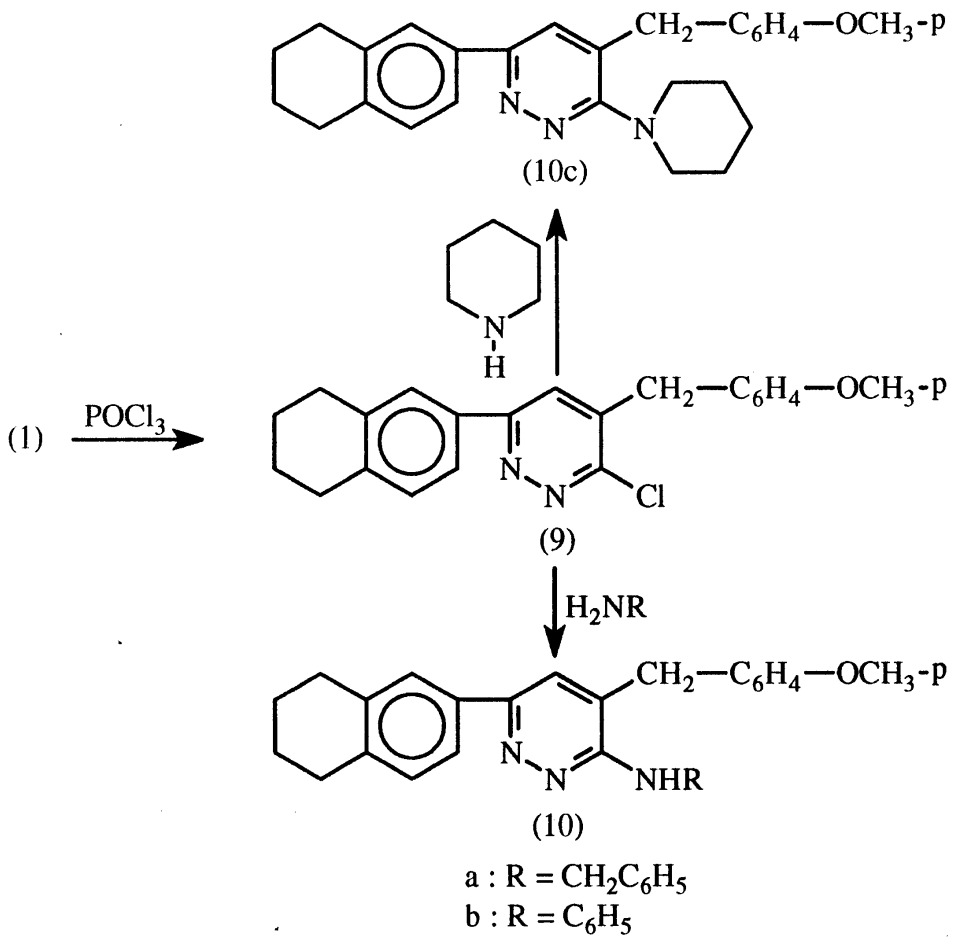


Scheme 3.

The reaction of **3** with dimethyl sulphate proceeds easily to afford 2-methyl-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**4**) whose IR spectrum shows a lack of any significant absorption the region characteristic for NH and OH groups.

When **3** was treated with formaldehyde, hydroxymethylation took place to give 2-(hydroxymethyl)-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]pyridazin-3(2*H*)-one[3] (**5**). Alternatively, the reaction of **3** with formaldehyde in the presence of secondary amines yielded the Mannich bases **6a,b**. These bases could also be obtained by the condensation of **5** with secondary amines.

Compound **3** underwent a Michael type addition with acrylonitrile in the presence of a catalytic amount of aqueous sodium hydroxide to yield 2(2'-cyanoethyl)-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-napthyl]-pyridazin-3(2*H*)-one (**7**). This compound could be hydrolyzed to the corresponding acid **8** (*cf.* Table

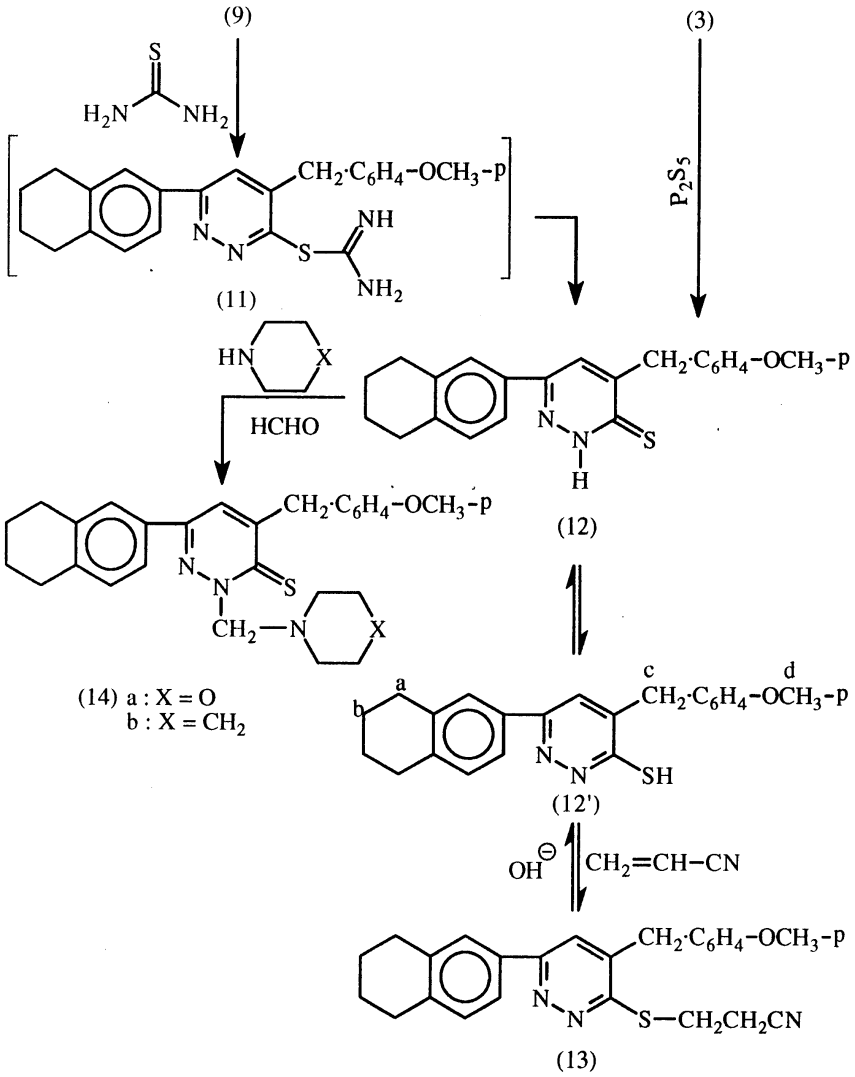


Scheme 4.

I). To extend this study to some reactions involving the 3-position of 4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-napthyl]-pyridazine derivatives, the reactivity of 3-chloro-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazine (**9**) towards some nucleophilic reagents was also investigated. Compound **9** was prepared by the action of phosphorus oxychloride on **3**.

When **9** was treated with benzylamine or aniline, the 3-benzylamino and 3-anilino pyridazine derivatives **10a** and **10b** were formed, respectively. Similarly the reaction of piperidine with **9** afforded **10c** (*cf.* Table I).

The reaction of **9** with alcoholic thiourea provided 4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyradizin-3(2*H*)-thione (**12**) *via* the intermediate formation of the thioronium salt **11** which was difficult to isolate. The structure of **12** was established by elemental analysis and spectral data.[5]



Scheme 5.

Its structure was further confirmed by the independent synthesis of **12** by the action of phosphorus pentasulphide on **3**. However, in basic medium, this compound reacts in the mercaptopyridazine form **12** as indicated by its reaction with acrylonitrile to give the *S*-cyanoethyl derivative **13**.

The structure of the latter compound was established through the observation of its infrared spectrum and also by its hydrolysis to the parent thione **12**. This excludes the *N*-cyanoethyl derivative since compounds of similar nature are easily hydrolyzed to the corresponding acid.[3] The reaction of **12** with formaldehyde in the presence of morpholine and piperidine yielded the Mannich bases **14a.b.**

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were obtained on a Pye Unicam SP 200 G spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian T-60, a Varian FT-90 and/or a Brucker AC-200 spectrometer. The chemical shifts are expressed in ppm (δ) relative to the internal standard Me_4Si.

*4-(*p*-Methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**3**)*

Method (a): A mixture of 6-[5,6,7,8-tetrahydro-2-napthyl]-4,5-dihydropyridazin-3(2*H*)-one (**1**) (0.01 mol) and *p*-methyoxybenzaldehyde (0.01 mol) in ethanol (10 ml) was treated with 4% ethanolic KOH solution (25 ml). The reaction mixture was refluxed for 3 h, cooled, poured over ice-cold water and rendered just acidic with conc. HCl. The resultant solid was filtered and crystallised from ethanol to give **3** as pale yellow crystals (Table I).

Method (b): A solution of the appropriate 3-*p*-methoxybenzylidene-5-[5,6,7,8-tetrahydro-2-naphthyl]-2(3*H*)-furanone (1 g) in ethanol (10 ml) was refluxed for 3 h with hydrazine hydrate (0.5 ml), cooled and diluted with water. The solid product was filtered and recrystallised from ethanol to give **3**.

Action of dimethylsulphate on **3**; *Formation of 2-methyl-4-(*p*-methyoxy-benzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**4**)*

Dimethylsulphate (1 ml) was added to a solution of **3** (1 g) in aq. NaOH (20%) (25 ml). The reaction mixture was warmed on a water bath for a few minutes and left to cool. The solid product formed was filtered and crystallised from methanol containing a few drops of benzene to give **4** as colorless crystals (Table I).

Action of formaldehyde on **3**; *Formation of 2-(hydroxymethyl)-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-napthyl]-pyridazin-3(2*H*)-one (**5**)*

A mixture of **3** (1 g), formaldehyde (1 ml) and a few drops of water in ethanol (20 ml) was refluxed for 6 h, and left to cool. The solid product formed was crystallised from benzene to give **5** as colorless crystals (Table I).

Reaction of **3** *with formaldehyde and secondary amines; Formation of the Mannich base* **6a,b**

A mixture of **3** (0.01 mol), formaldehyde solution (5 ml) and a secondary amine (0.02 mol) in ethanol (25 ml) was refluxed for 6 h. The reaction mixture was concentrated and the solid which fromed after cooling was filtered and crystallised from ethanol containing a few drops of benzene to give **6a,b** as colorless crystals (Table I).

Action of acrylonitrile on **3**; *Formation of 2-(2'-cyanoethyl)-4-*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**7**)*

A mixture of **3** (0.01 mol) and acrylonitrile (0.01 mol) in ethanol (20 ml) was treated with a few drops of 10% aq. NaOH solution and the mixture heated under reflux for 10 h. The solid which formed after cooling was crystallised form methanol to give **7** as colorless crystals (Table I).

*2-(2'-Carboxyethyl)-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazin-3(2*H*)-one (**8**)*

A suspension of **7** (0.01 mol) in 20% aq. NaOH solution (25 ml) was heated under reflux till no ammonia could be detected (10 h). The reaction mixture was cooled and acidified with conc. HCl. The solid which formed was purified by dissolving in 10% sodium carbonate solution and subsequent acidification with conc. HCl. The product was crystallised from benzene to give **8** as a colorless solid. (Table I).

Action of phosphorus oxychloride on **3**; *Formation of 3-chloro-4-(*p*-methoxybenzyl)-6-[5,6,7,8-tetrahydro-2-naphthyl]-pyridazine (**9**)*

A mixture of **3** (1 g) and phosphorus oxychloride (5 ml) was heated on a boiling water bath for 3 h, cooled, treated with crushed ice and made alkaline with aq. sodium hydroxide. The resulting solid product was filtered and crystallised from benezne to give **9** as colorless crystals (Table I).

*3-Benzylamino-4-(*p-*methoxybenzyl)-6-*[*5,6,7,8-tetrahydro-2-naphthyl*]*-pyridazine (***10a***)*

An equimolar mixture of the 3-chloropyridazine and benzylamine was heated on a sand bath at 120–130 °C for 10 h. The solid product which formed was boiled with water for few minutes, filtered off and crystallised from ethanol to give **10a** as colorless crystals. (Table I).

*3-Anilino-4-(*p-*methoxybenzyl)-6-*[*5,6,7,8-tetrahydro-2-naphthyl*]*-pyridazine (***10b***)*

The reaction was carried out as described for the synthesis of **10a** using aniline. The resulting solid product was crystallised from ethanol to give **10b** as colorless crystals (Table I).

*3-Piperidino-4-(*p-*methoxybenzyl)-6-*[*5,6,7,8-tetrahydro-2-naphthyl*]*-pyridazine (***10c***)*

The reaction was carried out as described for **10a** using morpholine. The solid product formed was crystallised from ethanol to give **10c** as colorless crystals (*cf.* Table I).

Action of thiourea on **9***; Formation of 4-(*p-*methoxybenzyl)-6-(5,6,7,8-tetrahydro-2-naphthyl*]*-pyridazine-3(*2H*)-thione (***12***)*

Method (a): Thiourea (0.01 mol) was added to a solution of **9** (0.01 mol) in ethanol (30 ml) and the reaction mixture was heated under reflux for 10 h. The yellow solid obtained was crystallised from benzene to give **12** as yellow crystals (Table I).

Method (b): To a solution of **3** (0.01 mol) in xylene (20 ml), phosphorus pentasulphide (0.01 mol) was added and the mixture was heated under reflux for 6 h. The solid which formed after cooling was filtered off and identified as **12** by m.p. and mixed m.p. experiments with the corresponding product obtained in the previous experiment.

Aciton of acrylonitrile on **12;** *Formation of 2,5,2'-cyanoethyl-4-(*p-*methoxybenzyl)-6-*[*5,6,7,8-tetrahydro-2-naphthyl*]*-pyridazine (***13***)*

The reaction was carried out as described for **3**. The solid product was crystallised from ethanol to give **13** as yellow crystals (Table I).

Attempted hydrolysis of **13**

A suspension of **13** (1 g) in 10% aqueous sodium hydroxide solution (30 ml) was heated under reflux for 10 h. The clear reaction mixture was cooled and acidified by the addition of conc. HCl. The yellow solid obtained was filtered and crystallised from ethanol to give **12** as yellow crysals m.p. 169 °C, yield 80%. The product showed no melting point depression when admixed with an authentic specimen.

Reaction of **12** *with formaldehyde and secondary amines: Formation of the Mannich bases* **10a,b**

A mixture of **12** (0.01 mol), formaldehyde solution (5 ml) and a secondary amine (0.02 mol) in ethanol (25 ml) was refluxed for 3 h. The reaction mixture was concentrated and the solid formed after cooling was filtered and crystallised from methanol containing a few drops of benzene to give **14a,b** as colorless crystals (Table I).

ИЗВОД

СИНТЕЗА И РЕАКЦИЈЕ 4-(*p*-МЕТОКСИБЕНЗИЛ)-6-[5,6,7,8-ТЕТРАХИДРО-2-НАФТИЛ]-ПИРИДИАЗИН-3(2*H*)-она

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Кондензација 4-(*p*-метоксибензил)-6-[5,6,7,8-тетрахидро-2-нафтил]пиридазин-3(2*H*)-она (**3**), добивеног реакцијом 6-[5,6,7,8-тетрахидро-2-нафтил]-4,5-дихидропири-

дазин-3(2*H*)-она (**1**) и анизалдехида, са диметил-сулфатом, формалдехидом и акрилонитрилом, као и грађење Mannich-ове базе, врши се лако у положају 2, при чему се добијају једињења **4, 5, 6** и **7**. 4-*p*-Метоксибензил-3-хлоро-6-[5,6,7,8-тетрахидро-2-нафтил]-пиперазин (**9**) добијен је у ниском приносу дејством фосфор-оксихлорида на једињење **3**. Реакцијом производа **9** са бензиламином, анилином и пиперидином добијена су једињења **10a,b,c**. 4-*p*-Метоксибензил-6-[5,6,7,8-тетрахидро-2-нафтил]пиперазин-3(2*H*)-тион (**12**) награђен је дејством тиокарбамида на једињење **9**, као и реакцијом производа **3** са фосфор-пентасулфидом. Такође је проучавана реакција ових тиона са акрилонитрилом, морфолином и пиперидином, која је дала деривате **13**, односно **14a,b**.

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