

## Synthesis of New Proline Derivatives

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### الخلاصة:

في هذا البحث تحت مفاعلة الحامض الاميني البرولين مع انهريد الخليك للحصول على مشتق اللاكتون الحلقي A1 ثم حضر مشتق اللاكتام الحلقي A2 من مفاعل الهيدرازين المائي مع اللاكتون الحلقي حيث استفيد من مجموعة الامين الحرة في مركب اللاكتام للحصول على ملح الديازونيوم والذي ادخل في نوعين من التفاعلات اولاً امينات ثانوية للحصول على مشتقات النترازين A3 – A5 ثانياً مع مركبات تحتوي على هيدروجين فعال ثم اجراء الغلق الحلقي باستخدام الهيدرازين والفنيل هيدرازين A7 A8 – تم الحصول على قواعد شيف A9 – A13 بتفاعل مجموعة الامين الحرة في المركب اللاكتام مع الديهايدات مختلفة. شخّصت المركبات المحضرة بأستخدام الطرائق الطيفية ( IR, UV, C.H.N ) analysis

### Abstract:

Reaction of Proline with acetic anhydride gave compound (A<sub>1</sub>), which upon treatment with hydrazine afforded The lactame (A<sub>2</sub>). The reaction of (A<sub>2</sub>) with sodium nitrite and hydrochloric acid, obtained diazonium Salt in good Yield. Then, diazonium Salt has been treated with secondary amines and with ethylacetoacetate to give compounds (A<sub>3</sub>-A<sub>5</sub>) and compound (A<sub>6</sub>) respectively Compound A<sub>6</sub> could be cyclised by hydrazine and phenyl hydrazine to give A<sub>7</sub> and A<sub>8</sub> Upon The reaction of A<sub>2</sub> with aldehyde, Schiff's bases were obtained in a good yield (A<sub>9</sub>-

A<sub>13</sub>).The structure of the synthesized compounds have been elucidated by physical and spectroscopic methods (IR, UV, C.H.N. analysis

## **Introduction:**

Proline and its derivatives represent very important heterocyclic compounds for their biological activity and pharmacological activity. Aminoazo derivatives or tetrazenes represent a stable diazonium ion source, in a well known classical synthesis the Diaz amino system is formed in the reaction between a diazonium cation and the nucleophilic nitrogen atom of an amine<sup>(1)</sup>. In addition, tetrazenes are of considerable interest antitumor<sup>(2)</sup>, anti-inflammatory<sup>(3)</sup> and other important properties. A series of compounds containing a pyrazolinone and pyrazol ring have been reported to possess significant activity as antihypertensive<sup>(4)</sup>, antifibrillatory<sup>(5)</sup>, antifungal<sup>(6)</sup>, anticonvulsant agents<sup>(7)</sup>, anticancer<sup>(8)</sup> and anti-inflammatory<sup>(9)</sup>. Schiff's bases have also been widely reported to be biologically versatile compounds having antifungal, herbicidal and plant growth regulating properties<sup>(10)</sup>.

## **Experimental:**

Melting points were determined in open capillary tubes on a Galle Kamp melting point apparatus and are uncorrected. The IR spectra( KBr discs) were recorded with a pye- Unicom SP- 300 spectrometer. UV spectra were recorded on Hitachi- 2000 spectrophotometer using absolute ethanol a solvent.

### **Synthesis of 3-methyl tetrahydro-1-H-pyrrolo[1,2-c][1,3]oxazole-1-one (A1)**

A mixture of Proline (5gm) and acetic anhydride (15ml) was refluxed for 3 hours. Excess of acetic anhydride was evaporated

and the residue was purified by column on silica gel. 75% yield; IR( $\nu$ ,  $\text{cm}^{-1}$ ): 1740(C=O), 2975-2880(C-H<sub>aliph.</sub>), 1210(c-o); UV( $\lambda_{\text{max}}$ ) 294 nm; calculated for C<sub>7</sub>H<sub>11</sub>NO<sub>3</sub> (157): 53.49%C, 7.05%H, 8.91%N Found: 52.21 %C, 7.33%H, 8.25%N.

**Synthesis of 2-amino-3-methyl hexahydro -1H pyrrol[1,2-c] imidazol-1-one (A2)**

To a solution of compound A<sub>1</sub>(0.01 mole) in dry benzene (10 ml), hydrazine(10 ml) was added. The mixture was refluxed for 7 hour. The solvent was removed in vacuum and the solid product was collected and crystallized from methanol, mp. 175-177C°; 65% Yield; IR( $\nu$ ,  $\text{cm}^{-1}$ ):1695(C=O),1230(C-N),2990-2850 (C-H Aliph), 3300-3250 (NH<sub>2</sub>); UV( $\lambda_{\text{max}}$ ): 328nm; calculated for C<sub>7</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> (155): 49.11%C, 7.65%H, 24.54%N found 48.16%C 7.12%H, 25.31%N.

**Synthesis of: 3-methyl-2-(pyrrolidin-1-yl diazenyl)hexahydro-1-H-pyrrol[1,2-c] imidazol-1-one(A3-A5)**

A mixture of A<sub>2</sub> (0.01 mole) in concentrated HCl (3ml) was cooled to 0-5C° under ice and cooled sodium nitrite solution (1.5gm in 10 ml of water) added to it drop wise during 10 minutes. The reaction mixture was the stirred for 30 minutes, then the appropriate amine (0.05 mole) was added at room temperature and stirring was continued for 10 minutes. The reaction temperature was then gradually raised to 50C° and after 10 minutes the solution was treated with KOH (0.1 mole) in methanol (20 ml), this mixture was heated to reflux and cooled. The precipitate was filtered and crystallized from ethanol-Water.

**A3** Yield 63% mp 253-255C°; Calculated for C<sub>11</sub>H<sub>12</sub>N<sub>5</sub>O<sub>2</sub> (253): 52.16%C, 7.56%H, 27.65%N found: 52.84%C, 7.86%H, 27.10%N; I.R ( $\nu$ ,  $\text{cm}^{-1}$ ) 1660(C=O), 2980-2850(C-H<sub>aliph.</sub>) 1430 (N=N); UV ( $\lambda_{\text{max}}$ ) 343nm.

**A4** Yield 53% mp 270-272C°; IR ( $\nu$ ,  $\text{cm}^{-1}$ ) 1690 (C=O),2930-2810(C-H<sub>aliph.</sub>),1450 (N=N);UV ( $\lambda_{\text{max}}$ ) 305nm.

**A5** Yield 58% mp 232-235C°; IR(v,cm<sup>-1</sup>) 1668 (C=O), 2960-2890 (C-H<sub>alph.</sub>), 1425 (N=N); UV(λ<sub>max</sub>) 328nm.

**Synthesis of: ethyl-2-[2-(3-hydroxy-3-methyl-1-oxo tetrahydro-1-pyrrolo[1,2-c]imidiazol-2-(3H)-yl)hydrazine]-3oxo butanoate(A6)**

To an ice-cold mixture of ethylacetoacetate (0.01 mole) and sodium acetate (4.10 gm, 0.05mole) in ethanol (50 ml), was added drop wise with stirring a solution of diazonium salt compound (A2) over 15 minutes. The Stirring was continued for 30 minutes and the reaction mixture then left for 2 hours at room temperature, the solid product was collected and recrystallized from methanol. Yield 65%; mp 151-153C°; Calculated for C<sub>13</sub>H<sub>22</sub>ON<sub>4</sub>O<sub>5</sub> (330): 50.90%C, 7.93%H, 16.96%N, found: 51.51%C, 7.13%H, 16.45%N. IR(v,cm<sup>-1</sup>) 1620(C=O,lactame), 1710 (C=Oester), 2960-2880 (C-H<sub>alph.</sub>) 1220(C-O), 3110(NH); U.V(λ<sub>max</sub>) 364nm.

**Synthesis of 3-mthyl-2-[2-(3-methyl-5-oxo-1-(phenyl) or(H)-4,4-dihydro)-1-H-pyrazol-4-yl) hydrazine] hexahydro-1-H-pyrrol[1,2-c] imidazol-1-one(A7,A8)**

A mixture of (A<sub>6</sub>) (0.005 mole) and hydrazine (99%) or phenyl hydrazine (0.01 mole) in ethanol (25ml) was heated under refluxed for 6 hours. The solvent was concentrated and the reaction product was allowed to cool, the separated product was filtered off, washed with water and recrystallized from methanol.

**A7** Yield 61%; mp 183-185C°; Calculated for (C<sub>17</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>) (360) 56.65%C, 6.71%H, 23.32%N, found: 55.33%C, 6.18%H, 24.60%N IR(v,cm<sup>-1</sup>) 1620(C=O,lactame), 1650 (C=N), 2990-2890(C-H<sub>alph.</sub>) 3230 (NH); UV(λ<sub>max</sub>) 315nm.

**A8** Yield 55%; mp 278-281C°; Calculated for (C<sub>11</sub>H<sub>20</sub>N<sub>6</sub>O<sub>3</sub>) (284) 46.47%C, 7.09%H, 29.56%N, found: 45.90%C, 6.43%H, 28.51%N; IR(v,cm<sup>-1</sup>) 1680 (C=O), 1660 (C=N), 3080(Ar-H), 3180(NH), 2960-2880 (C-H<sub>alph.</sub>), UV (λ<sub>max</sub>) 352nm.

**Synthesis of Schiff's bases (A<sub>9</sub>-A<sub>13</sub>)**

The corresponding aryl aldehyde (0.05 mole) was added to a stirred solution of compound (A<sub>2</sub>) (0.05 mole) in absolute ethanol

(30 ml) and the mixture was refluxed for 2 hours. After cooling the mixture was filtered and the solid recrystallized for methanol.

(A<sub>10</sub>): purified by column on silica gel)

**A9:** Yield 83%; mp 263-265°C<sup>o</sup>; Calculated for C<sub>14</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>2</sub> (338): 49.72%C, 4.77%H, 12.42%N, found: 49.51%C, 4.41%H, 12.18%N; IR (v,cm<sup>-1</sup>) 1680 (C=O), 1630 (C=N), 3050 (Ar-H), 2980-2850 (C-H<sub>alph</sub>), 1580-1490 (C=C<sub>aro</sub>); UV: 324nm, 246nm.

**A10:** Yield 85%; Calculated for C<sub>14</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub> (293): 57.24%C, 5.49%H, 14.30%N, found: 56.23%C, 4.67%H, 13.18%N; IR: (v,cm<sup>-1</sup>) 1700(C=O), 1620(C=N), 3100(Ar-H), 3400 (O-H), 2970-2850(C-H<sub>alph</sub>); UV: 362nm, 253nm.

**A11:** Yield 63%; mp 125-127°C<sup>o</sup>; 1680(C=O), 1650(C=N); 3090(Ar-H), 1050(C-Cl), 1600-1480(C=C<sub>aro</sub>); UV: 385nm, 273nm.

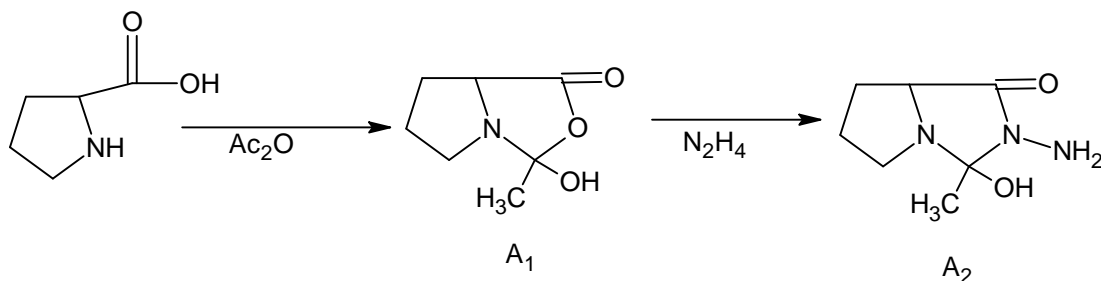
**A12:** Yield 54%, mp 163-165°C<sup>o</sup>; IR: (Cm<sup>-1</sup>) 1670(C=O), 1620(C=N) 3080(Ar-H), 2980-2895(C-H<sub>alph</sub>), 1600-1500(C=C<sub>aro</sub>); UV: 348 nm, 286nm.

**A13:** Yield 72%; mp 238-240°C<sup>o</sup>; Calculated for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> (304): 55.26%C, 5.30%H, 18.41%N, found: 54.11%C, 5.22%H, 18.63%N, IR: 1690(C=O), 1640(C=N) 3010(Ar-H), 2910-2830 (C-H<sub>alph</sub>), 1590-1480(C=C); UV: 355nm, 2

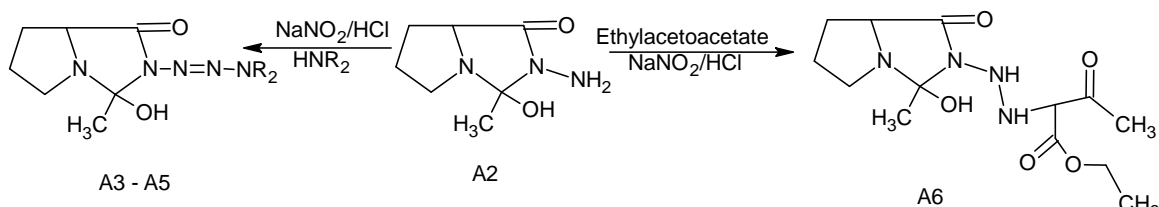
## Result and Discussion:

Compound 3-methyl tetrahydro-1-H-pyrrolo\_\_[1,2-c][1,3]oxazole-1-one (A1) was obtained by reaction Proline with acetic anhydride, compound was confirmed by presence bands at 1740 Cm<sup>-1</sup> for (C=O) and at 2975-2880 Cm<sup>-1</sup> due to (C-H<sub>alph</sub>), When 3-methyl tetrahydro-1-H-pyrrolo\_[1,2-c][1,3]oxazole-1-one (A1) treated with hydrazine hydrate (99%) (Scheme 1) 2-amino-3-methyl hexahydro -1H pyrrol[1,2-c] imidazol-1-one (A2) (Lactame) was obtained in good Yield. The IR Spectra showed the NH<sub>2</sub>. stretching absorption near 3300-3250 cm<sup>-1</sup> and C=O stretching one at 1695 cm<sup>-1</sup>. The data of (C.H.N.)analysis show the found data was so close from calculated data for above compounds.

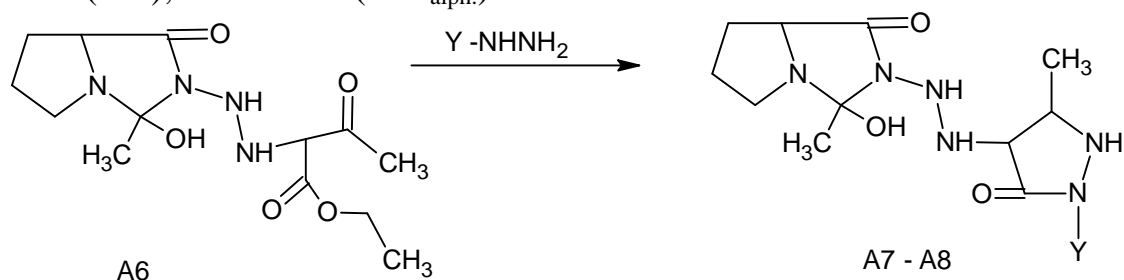
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Treating compound  $A_2$  with ( $\text{NaNO}_2, \text{HCl}$ ) and then with secondary amines afforded 3-hydroxy-3-methyl-2-(pyrrolidin-1-yl diazenyl)hexahydro-1H-pyrrolo[1,2-c]imidazol-1-one ( $A_3$ ), 3-hydroxy-3-methyl-2-(piperidin-1-yl diazenyl)hexahydro-1H-pyrrolo[1,2-c]imidazol-1-one ( $A_4$ ) and 2-(3,3-dimethyltriaz-1-en-1-yl)-3-hydroxy-3-methylhexahydro-1H-pyrrolo[1,2-c]imidazol-1-one ( $A_5$ ) which displayed two bands at  $3300$  and  $3250 \text{ cm}^{-1}$  for  $\text{NH}_2$  stretching. The data of (C.H.N.) analysis show the found data was so close from calculated data for above. Moreover, compound ethyl-2-[2-(3-hydroxy-3-methyl-1-oxo tetrahydro-1-pyrrolo[1,2-c]imidazol-2-(3H)-yl)hydrazine]-3-oxo butanoate  $A_6$  was obtained in 65% Yield from the reaction of  $A_2$  with ethylacetoacetate the absorption band at  $1710 \text{ cm}^{-1}$  in the IR spectrum of  $A_6$  is due to  $\text{C}=\text{O}$  stretching of ester and at  $1620 \text{ cm}^{-1}$  for  $\text{C}=\text{O}$  stretching of amid (lactame), The data of (C.H.N.) analysis show the found data was so close from calculated data for above.

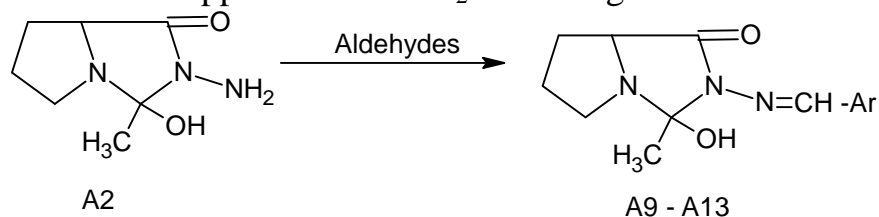


Ring closure with hydrazine and phenyl hydrazine gave compounds 3-hydroxy-3-methyl-2-[2-(3-methyl-5-oxo-1-phenyl-4,4-dihydro-1-H-pyrazol-4-yl) hydrazine] hexahydro-1-H-pyrrol[1,2-c] imidazol-1-one A<sub>7</sub> and 3-hydroxy-3-methyl-2-[2-(3-methyl-5-oxo-1-H-pyrazol-4-yl) hydrazine] hexahydro-1-H-pyrrol[1,2-c] imidazol-1-one A<sub>8</sub> respectively. The IR Spectra A<sub>7</sub> showed the 1620(C=O,lactame), 1650 (C=N), 2990-2890(C-H<sub>alph.</sub>) 3230 (NH); (A<sub>8</sub>) 1680 (C=O lactame), 1660 (C=N), 3080(Ar-H), 3180(NH), 2960-2880 (C-H<sub>alph.</sub>).



Y = H, Ph

On the other hand the reaction of A<sub>2</sub> with different aldehydes in absolute ethanol afforded Schiff's bases (A<sub>9</sub> – A<sub>13</sub>), the formation of these Schiff bases were indicated by presence in their IR spectra of the azomethine (CH=N) stretching band at 1650 cm<sup>-1</sup>, combined with the disappearance of NH<sub>2</sub> stretching band.



Ar = p-Br-C<sub>6</sub>H<sub>5</sub>, p-Cl-C<sub>6</sub>H<sub>5</sub>, p-NO<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>, o-Cl-C<sub>6</sub>H<sub>5</sub>, o-NO-C<sub>6</sub>H<sub>5</sub>

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