

## SYNTHESIS OF NEW CONDENSED PYRIMIDINES: I

M. Ebeid, S. Lashine, A. El Shanawany, M. Abou Kull and  
N. Abou Taleb

Pharmaceutical Chemistry Department, Faculty of Pharmacy, University  
of Cairo and Faculty of Pharmacy, University of Zagazig, Egypt .

### ABSTRACT

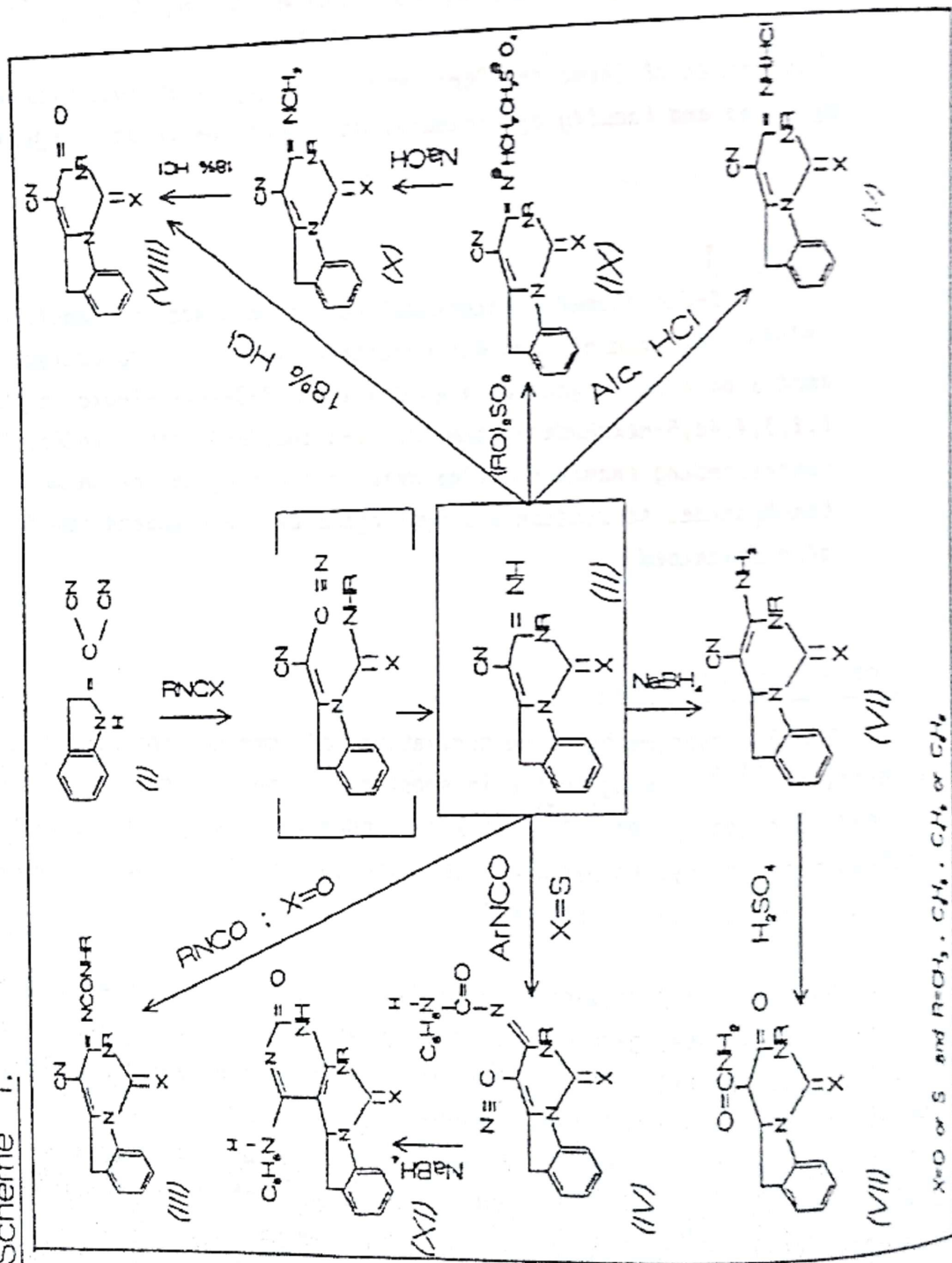
*2-Dicyanomethylidinoindoline (I) obtained from lactime ether of oxindole and malononitrile, when added to various isocyanates or isothiocyanates afforded 2-alkyl-3-imino-1-oxo or thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile. The corresponding enamionitriles were obtained by reduction with sodium borohydride. Alkylation and hydrolysis of the prepared compounds are also described .*

### INTRODUCTION AND DISCUSSION

The 2-dicyanomethylidene derivatives of some heterocyclic compounds were described (1-5). Owing to the interesting pharmacological features of the bridgehead nitrogen system (6,7), it was planned in this work to obtain the bridgehead nitrogen system pyrimido[1,6-a]indole. The route for obtaining these compounds is shown in scheme 1.

Reaction of 2-dicyanomethylidinoindoline (I) with different isocyanates or isothiocyanates gave an intermediate which give iminonitriles via nucleophilic addition (II a-g). The i.r. spectra of (II) revealed a strong and sharp absorption band at  $2220\text{ cm}^{-1}$ , corresponding to one cyano group, instead of the characteristic absorption bands of the geminal dicyano groups present in (I) which appeared at  $2225$  and  $2185\text{ cm}^{-1}$ . Moreover a sharp stretching band appeared at  $3320\text{ cm}^{-1}$  attributed to the 3-imino group.

Scheme 1:



The 1,4- addition<sup>(8)</sup> of one molecule of hydrogen was achieved by the reaction of sodium borohydride<sup>(9)</sup> with the 3-imino compounds(II) to give the 3-amino derivatives(VI a-c). The ir spectra of the reduced compounds showed two bands at 3200 and 3400  $\text{cm}^{-1}$  attributed to an amino group. It is also worth mentioning that a lower absorption at 2180  $\text{cm}^{-1}$  of the cyano group was observed, this lowering of the nitrile frequency is attributed to conjugation<sup>(10)</sup>.

The nmr spectra and the microanalytical data of compounds(IIa) and (IIIa) confirm the conclusion that the obtained compounds are 3-imino-2-methyl-1-oxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile and 2-methyl-3-methylureido-1-oxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile, respectively. These compounds were obtained by addition of (I) to methylisocyanate followed by intermolecular additive cyclization to give the 3-iminopyrimido[1,6-a]indole derivatives (IIa). The latter addition of another molecule of methylisocyanate gave (IIIa). Similar results were obtained with other alkyl and aryl isocyanates to give the corresponding 2-alkyl and 2-aryl derivatives(IIIb&IIIc). These had their support from the fact that, the 2-alkyl-3-imino-1-oxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile derivatives were obtained using equimolecular amounts of (I) and the alkyl or aryl isocyanates.

Reaction of alkyl and arylisothiocyanates with (I) was found to give 2-alkyl-3-imino-1-thioxo-pyrimido[1,6-a]indole-4-carbonitrile (II d-g). These obtained thio compounds didn't react with excess isothiocyanates used and no alkyl or arylthioureido derivatives were separated. However, these compounds remain reactive towards aryl but not alkylisocyanates, thus (II d) when reacted with phenylisocyanate afforded 3-phenylureido derivative (IV), which upon treatment with sodium borohydride underwent intermolecular addition to give the tricyclic compound (XI). The vanishing of the nitrile absorption band at 2220  $\text{cm}^{-1}$  in the ir spectrum of (XI), was taken as a confirmation for the tricyclic structure pyrimido[4,5:4,5]pyrimido[1,6-a]indole, which confirm Dimorth rearrangement<sup>(11)</sup>.

Alkylation of O-iminonitriles using alkyl halides was unsuccessful, while heating the 3-imino derivatives with dimethyl sulphate in benzene afforded the corresponding 3-methylmonium methyl sulphate salts (IXa,b), and the 3-methylimino derivatives were obtained from the aqueous solution of these salts by the action of sodium hydroxide<sup>(2)</sup> (Xa-e).

Hydrolysis of the 3-imino (II) or the 3-methylimino (X) to the corresponding 3-oxo derivatives (VIII) was accomplished by the action of 18% hydrochloric acid<sup>(1,2)</sup>. However, the 4-carboxamide derivatives (VII) were obtained from the reduced compounds (VI) via hydrolysis of the nitrile group by the action of concentrated sulphuric acid. This was confirmed by the ir spectrum in which the nitrile absorption band was replaced by multiple absorption band in the NH stretching region together with C=O stretching strongly absorbed at  $1680\text{ cm}^{-1}$ .

It was interesting to find that, while tautomerization was not observed in 2-alkyl-3-oxo-1-thioxo-4-carbonitrile derivatives, the 1,3-dioxo analogues were found to exhibit such tautomeric phenomena, as two nitrile absorption at  $2260$  and  $2220\text{ cm}^{-1}$  were observed in the ir spectrum of 2-methyl-1,3-dioxo-pyrimido[1,6-a]indole-4-carbonitrile (VIIIId).

The hydrochlorides (Va-d) were prepared by passing HCl gas in the alcoholic solutions of the corresponding 3-imino compounds (IIa,d,e,f).

## EXPERIMENTAL

All melting points are uncorrected and were determined by open capillary method. IR spectra were performed using Perkin-Elmer PE-298 spectrophotometer. Microanalysis was performed at the Microanalytical Center, Cairo University.  $^1\text{H NMR}$  were recorded on Varian-T-60 spectrophotometer using  $\text{CDCl}_3$  as solvent. Oxindole is available from Sigma Chemical Company.

2-Alkyl or aryl-3-imino-1-oxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (IIa-c)

A mixture of (I) (0.02 mole), methylisocyanate or ethylisocyanate or phenylisocyanate (0.02 mole), 15 ml of methylene chloride and two drops of triethylamine was stirred for one hour and left to stand for 8 hours at room temperature, the solvent was removed under vacuum and the residue was dissolved in dilute HCl filtered, the filtrate was rendered alkaline with ammonia, the separated crystals were filtered and recrystallized.

2-methyl-3-methylcarbonylimino-1-oxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (IIIa)

A mixture of (I) 1.8 g (0.01 mole), 2 ml (excess) of methylisocyanate, 15 ml of methylene chloride and two drops of triethylamine was stirred for one hour and left to stand for 8 hours at room temperature, filtered and recrystallized from methanol .

2-Ethyl-3-ethylcarbonylimino and 2-phenyl-3-phenylcarbonylimino derivatives IIIf and IIIf were prepared similarly using ethyl and phenylisocyanate, respectively.

3-Imino-2-alkyl or aryl-1-thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (IIId-g)

A mixture of (I) (0.02 mole), alkylisothiocyanate or phenylisothiocyanate (0.04 mole), 15 ml of methylene chloride and 1 ml of triethylamine was refluxed for 6 hours, the solvent was removed under vacuum and the residue was triturated with ethanol , filtered and recrystallized.

2-Methyl-3-phenylcarbonylimino-1-thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (IV)

A mixture of (IIId) 1.3 g (0.005 mole), 0.5 ml (0.005 mole) of phenylisothiocyanate, 10 ml of methylene chloride and few drops of triethylamine was refluxed for 2 hours, the separated crystals was filtered while hot, washed to give 1.6 g of IV and recrystallized from ethanol.

The hydrochlorides (Va-d) were prepared by passing HCl gas in the ethanolic solution of the corresponding 3-imino derivatives (IIa,d-f) .

2-Alkyl-3-oxo-1-(oxo or thioxo)-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (VIIIa-d)

A mixture of (IIa,d-f) 2 g and 18% hydrochloric acid (20 ml) was refluxed for 3 hours. The reaction mixture was concentrated under vacuum, cooled , the separated crystals were filtered and recrystallized from ethanol.

2-Alkyl-3-amino-1-oxo-1,2,4a,5-tetrahydro-pyrimido[1,6-a]indole-4-carbonitrile (VIa-c)

To a stirred mixture of (IIa-c) (0.1 mole) in absolute ethanol (20 ml), sodium borohydride (0.05 mole) was added in portions, and stirring was continued for one hour. The reaction mixture was left to stand overnight at room temperature, the separated crystals were filtered, washed with water and recrystallized from ethanol .

2-Alkyl-1,3-dioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carboxamide (VIIa,b)

A mixture of (VIa,b) (0.01 mole), sulphuric acid (10 ml) was stirred until complete dissolution, left overnight at room temperature and then poured onto ice cooled ammonia solution. The separated crystals were filtered, washed with water and recrystallized from ethanol .

2-Alkyl-3-methylmonium sulphate-1-thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (IXa,b)

A mixture of (II d,e) (0.01 mole) and dimethyl sulphate 1.3 ml (0.011 mole) were refluxed in benzene (20 ml) for 5 hours. The separated crystals were filtered while hot and recrystallized from ethanol .

2-Alkyl-3-methylimino-1-thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (Xa,b)

The solution of (IXa,b) 1 g in water (10 ml) was rendered alkaline to pH 10 using 5N sodium hydroxide solution. The separated crystals were filtered, washed with water and recrystallized from ethanol .

2-Alkyl-3-methylimino-1-thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile (Xc-e)

To compounds (II f,a,b) (0.01 mole) in benzene (20 ml), dimethyl sulphate 1.3 ml (0.011 mole) was added, the reaction mixture was refluxed for 5 hours , cooled, extracted with water (25 ml). The aqueous extract was rendered alkaline with 5N sodium hydroxide solution. The separated crystals were filtered, washed with water and recrystallized from ethanol.

5-methyl-1-phenylamino-3-oxo-6-thio-12,12a-dihydropyrimido[4,5 : 4,5] pyrimido-[1,6-a]-2H,5H-indole XI

A mixture of VI (0.01 mole), 20 ml ethanol and sodium borohydride (0.005 mole) added in portions was left to stand over night. The separated crystals was filtered, washed with water and recrystallized from ethanol.  
m.p 234°C , yield 88.2%

Microanalysis for  $C_{20}H_{17}N_5OS$

	C%	H%	N%
Calcd	64.00	4.53	18.67
Found	64.4	4.67	18.82

$^1H$  nmr (ppm) for compound IIIa

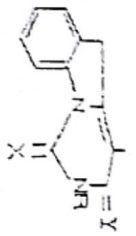
3.82 (s, 2H,  $CH_2$ ); 2.75 (d, 3H,  $NH-CH_3$ ); 3.45 (s, 3H,  $CH_3$ ); 5.2 (m, br, 1H, NH); 7.8 (m, 4H, aromatic protons).

After deuteration, 2.75 (s, 3H,  $ND-CH_3$ ); 5.2 disappeared.

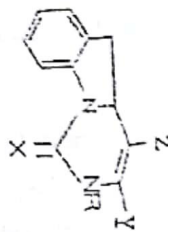
$^1H$  nmr (ppm) for compound XI

3.30 (s, 3H,  $CH_3$ ); 2.8 (d, 2H,  $CH_2$ ); 3.7 (t, 1H, CH); 9.8 (s, br,  $NH+NH$ ); 7.6 (m, 9H, aromatic protons)

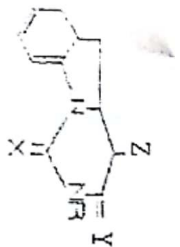
After deuteration, 9.8 disappeared.



II, III, IV, V, VIII, IX and X



VI



VII

No	R	X	Y	Z	M.P. <sup>o</sup> C	M.F. & M.wt.	Microanalysis		
							Calcd	Found	
IIa	CH <sub>3</sub>	O	NH	CN	165-6	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O 238	C	65.55	65.7
							H	4.20	4.1
IIb	C <sub>2</sub> H <sub>5</sub>	O	NH	CN	98-9	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O 252	N	23.53	23.7
							C	66.67	66.8
IIc	C <sub>6</sub> H <sub>5</sub>	O	NH	CN	124-5	C <sub>18</sub> H <sub>12</sub> N <sub>4</sub> O 300	H	4.76	4.6
							N	22.22	22.4
IId	CH <sub>3</sub>	S	NH	CN	152-3	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> S 254	C	72.00	72.3
							H	4.00	4.4
IId	CH <sub>3</sub>	S	NH	CN	152-3	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> S 254	N	18.60	18.2
							C	61.42	61.6
IId	CH <sub>3</sub>	S	NH	CN	152-3	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> S 254	H	3.94	3.8
							N	22.05	22.3
IIe	C <sub>2</sub> H <sub>5</sub>	S	NH	CN	114-5	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> S 268	C	62.69	62.8
							H	4.48	4.3
IIe	C <sub>2</sub> H <sub>5</sub>	S	NH	CN	114-5	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> S 268	N	20.90	21.1
							C	64.86	64.9
IIe	C <sub>2</sub> H <sub>5</sub>	S	NH	CN	114-5	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> S 268	H	5.41	5.6
							N	18.92	19.1
IIe	C <sub>2</sub> H <sub>5</sub>	S	NH	CN	114-5	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> S 268	C	68.35	68.5
							H	3.80	3.6
IIe	C <sub>2</sub> H <sub>5</sub>	S	NH	CN	114-5	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> S 268	N	17.72	17.9



No	R	X	Y	Z	M.P. <sup>o</sup> C	M.F & M.wt.	Microanalysis		
							Calcd	Found	
IIIa	CH <sub>3</sub>	O	NCONHCH <sub>3</sub>	CN	211-2	C <sub>15</sub> H <sub>13</sub> N <sub>5</sub> O <sub>2</sub> 295	C	61.02	61.3
							H	4.41	4.3
IIIb	C <sub>2</sub> H <sub>5</sub>	O	NCONHC <sub>2</sub> H <sub>5</sub>	CN	195-6	C <sub>17</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> 323	N	23.73	23.9
							C	63.16	63.3
IIIc	C <sub>6</sub> H <sub>5</sub>	O	NCONHC <sub>6</sub> H <sub>5</sub>	CN	202-3	C <sub>25</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> 419	H	5.26	5.4
							N	21.67	21.9
IV	CH <sub>3</sub>	S	NCONHC <sub>6</sub> H <sub>5</sub>	CN	188-9	C <sub>20</sub> H <sub>15</sub> N <sub>5</sub> OS 373	C	71.60	71.8
							H	4.06	3.9
Va	CH <sub>3</sub>	O	NH.HCl	CN	228-9	C <sub>13</sub> H <sub>11</sub> ClN <sub>4</sub> O 274.5	N	16.71	16.9
							C	64.34	64.5
Vb	CH <sub>3</sub>	S	NH.HCl	CN	175-6	C <sub>13</sub> H <sub>11</sub> ClN <sub>4</sub> S 290.5	H	4.02	3.9
							N	18.77	18.9
Vc	C <sub>2</sub> H <sub>5</sub>	S	NH.HCl	CN	207-8	C <sub>14</sub> H <sub>13</sub> ClN <sub>4</sub> S 304.5	C	56.83	57.0
							H	4.00	4.2
Vd	C <sub>11</sub> H <sub>9</sub>	S	NH.HCl	CN	133-4	C <sub>16</sub> H <sub>17</sub> ClN <sub>4</sub> S 332.5	N	20.40	20.6
							C	53.70	54.1
							H	3.79	3.9
							N	19.28	19.4
							C	55.17	55.3
							H	4.27	4.0
							N	18.39	18.5
							C	57.74	58.1
							H	5.11	5.0
							N	16.84	17.1

No	R	X	Y	Z	M.P. <sup>o</sup> C	M.F. & M.wt.	Microanalysis		
							Calcd	Found	
VIA	CH <sub>3</sub>	O	NH <sub>2</sub>	CN	183-4	C <sub>13</sub> H <sub>12</sub> N <sub>4</sub> O 240	C	65.00	65.3
							H	5.00	4.8
							N	23.33	23.5
VIB	C <sub>2</sub> H <sub>5</sub>	O	NH <sub>2</sub>	CN	161-2	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O 254	C	66.14	66.4
							H	5.51	5.3
							N	22.04	22.2
VIC	C <sub>6</sub> H <sub>5</sub>	O	NH <sub>2</sub>	CN	110-1	C <sub>18</sub> H <sub>14</sub> N <sub>4</sub> O 302	C	71.52	71.7
							H	4.64	4.5
							N	18.54	18.5
VIIa	CH <sub>3</sub>	O	O	CONH <sub>2</sub>	125-6	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> 259	C	60.23	60.4
							H	5.02	4.9
							N	16.22	16.3
VIIb	C <sub>2</sub> H <sub>5</sub>	O	O	CONH <sub>2</sub>	105-6	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> 273	C	61.54	61.7
							H	4.49	4.4
							N	15.38	15.5
VIIIa	CH <sub>3</sub>	S	O	CN	117-8	C <sub>13</sub> H <sub>9</sub> N <sub>3</sub> OS 255	C	61.18	61.3
							H	3.53	3.6
							N	16.47	16.5
VIIIb	C <sub>2</sub> H <sub>5</sub>	S	O	CN	106-7	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> OS 269	C	62.45	62.6
							H	4.09	4.2
							N	15.61	15.7
VIIIc	C <sub>4</sub> H <sub>9</sub>	S	O	CN	98-9	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> OS 297	C	64.65	64.8
							H	5.05	5.2
							N	14.14	14.3

No	R	X	Y	Z	M.P. °C	M.F. & M.Wt.	Microanalysis		
							Calcd	Found	
VIII d	CH <sub>3</sub>	O	O	CN	128-9	C <sub>13</sub> H <sub>9</sub> N <sub>3</sub> O <sub>2</sub> 239	C H	65.27 3.77	65.4 3.5
IXa	CH <sub>3</sub>	S	NHCH <sub>3</sub> -CH <sub>3</sub> SO <sub>4</sub> <sup>-</sup>	CN	135-6	C <sub>15</sub> H <sub>16</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub> 380	N C H	17.57 47.37 4.21	17.7 47.5 4.0
IXD	C <sub>2</sub> H <sub>5</sub>	S	NHCH <sub>3</sub> -CH <sub>3</sub> SO <sub>4</sub> <sup>-</sup>	CN	166-7	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub> 394	N C H	14.21 48.73 4.57	14.5 48.9 4.4
Xa	CH <sub>3</sub>	S	NCH <sub>3</sub>	CN	99-100	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> S 268	N C H	20.90 62.69 4.48	21.1 62.8 4.4
Xb	C <sub>2</sub> H <sub>5</sub>	S	NCH <sub>3</sub>	CN	83-4	C <sub>15</sub> H <sub>14</sub> N <sub>4</sub> S 282	N C H	20.90 63.83 4.96	21.1 63.9 4.7
Xc	C <sub>4</sub> H <sub>9</sub>	S	NCH <sub>3</sub>	CN	72-3	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> S 310	N C H	19.86 65.81 5.81	19.8 65.9 5.6
Xd	CH <sub>3</sub>	O	NCH <sub>3</sub>	CN	144-5	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O 252	N C H	18.06 66.67 4.76	18.2 66.8 4.6
X	C <sub>2</sub> H <sub>5</sub>	O	NCH <sub>3</sub>	CN	123-4	C <sub>15</sub> H <sub>14</sub> N <sub>4</sub> O 266	N C H	22.22 66.67 5.26	22.4 66.8 5.1

REFERENCES

- 1) Ebeid, M. and Bitter, I.; Proceedings of XIV Egypt. Conference of Pharm. Sci., p.99 (1975)
- 2) Lashine, S.; M.Sc. Pharm. Thesis, Zagazig Univ. (1980).
- 3) Ebeid, M. and Bitter, I.; Egypt. J. Pharm. Sci., 19, 349-54 (1978).
- 4) Ebeid, M. and Bitter, I.; ibid, 19, 355-60 (1978).
- 5) Ebeid, M., El Sayed, N. and Ahmed, El-S.; Proceedings of XXI Conference of Pharm. Sci., p. 105-12 (1990).
- 6) Ebeid, M. Y., Hassanein, H. H., Obidan, N. N. and Hassan, A. B.; Egypt. J. Pharm. Sci., 29, 533-43 (1988).
- 7) Ebeid, M. Y., Hassanein, H. H., Obidan, N. N. and Hassan, A. B.; ibid, 30, 194 (1989).
- 8) Reutov, O. A.; "Fundamentals of Theoretical Organic Chemistry", 2nd Ed., Scripta Technica Inc., Applenton Century-Crofts, New York, p. 216 (1967).
- 9) Mayers, A. I. and Nazarenko, N.; J. Am. Chem. Soc., 94, 3243 (1972).
- 10) Dyke, S. F., Floyd, A. J., Sainsbury, M. and Theobald, R. S.; "Organic Spectroscopy", 2nd Ed, London and New York, p. 86-7 (1978).
- 11) Brown, D. J. and England, B. T.; J. Chem. Soc., 250 (1971)

تخليق مشتقات جديدة للبيريميدينيات المكثفة-١  
\* محمد عبيد - السيد لاشين - عبد الله الشنواني  
منصور أبوكل - ناجح أبو طالب  
قسم الكيمياء الصيدلية - كلية الصيدلة - \* جامعة القاهرة  
وكلية الصيدلة - جامعة الزقازيق

في هذا البحث تم الحصول من الأوكس أندول على ٢ - ثنائي السينانوميثيليد نواندولين وقد تم الحصول من هذا المركب على ٢ - (الكيل أولاريل) ٣ - أمينو - ١ - (أكسواويثواكسو) ١،٢،٣،٤،٥،٦ - سداسي أيدرو-بيريميديدو (١ و ٦ - أ) أندول - ٤ سكاربيونستريل وكذلك إلى أيزوثيوسيانات الألكيل أو الأريل -  
وقد تم دراسة إدخال مجموعة الألكيل والإختزال والتحليل لهذه المركبات حقق التركيب الكيماوى للمركبات المختلفة بالوسائل الطيفية كالرنين النووي المغناطيسى وكذلك الأشعة دون الحمراء بالإضافة إلى التحليل .