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Synthesis and Characterization of New Oxinane Barbituric Acid Derivatives from reaction of Ethylenediamine, Urea and Thiourea (Schiff-Bases) with Malonic Anhydride

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Abstract

The reaction of some new Schiff bases -(2-Amino-ethylimino)-5,5-diethyl-dihydro-pyrimidine-4,6-dione, 2-[2-(5,5-diethyl-4,6-dioxo-pyrimidine-2-ylideneamino)-ethylimino]-5,5-diethyl-dihydro- pyrimidine-4,6-dione. (5,5-Diethyl-4.6-dioxo-tetrahydro-pyrimidin-2-ylidein)-urea, 1,3-Bis(5,5-diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylidein)- urea, (5.5-Diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylidein)-thiourea and1,3-Bis(5,5-diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylidein)- thiourea with malonic anhydride were carried out Subsequent reactions of these products 5-(2-Amino-ethyl)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone.,5-[2-(9,9-Diethyl 2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-yl)-ethyl]- 9,9-diethyl-1-oxa 5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone. , 5,5-Diethyl-4,6-dioxo-tetrahydro-pyrimidin 2-ylidene)-urea ., 5-(9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carbonyl)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone. and 5,5-Diethyl 4,6-dioxo-tetrahydro-pyrimidin-2-ylidene)-thiourea and 5-(9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carbothioyl)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone.

The synthesized compounds were confirmed by their IR,UV specta , C.H.N. analyses data and HNMR spectra.

Key Words: Schiff bases ; Oxazinan ; Synthesis ; Properties.

Introduction

5,5-diethyl barbituric acid derivatives are interesting series of heterocyclic compounds. which have been shown to be diverse pharmacological properties [1] such as antifungal [2], antimicrobial [3] , antipulsive[4] and antibacterial [5,6] . The six –membered heterocyclic ring system: 1,3-oxazine has already been reported and thoroughly reviewed in the literature [7-11]. Maleic. arylmaleic and substituted maleic anhydrides react with trimethylsilyl azide to give 4- and 5-substetuted "oxauraciles": dihydro-1,3-oxazine 2,6-diones [12-13]

Both 2-methoxypyrroline and 2-methoxypiperdinine react with diketene under neutral conditions at 0C° to give the corresponding,2-methoxydihydro 1,3-oxazin-4-ones [14-15]

Diketene reacts with N,N-diphenyl guanidine to give the tranquilizer ketazolam and N- substituted tetrahydro-1,3-oxazin-4-one respectively [16-17].

The reaction of diketene with isocyanic acid ,Cyanamid's and flourosulphinyl isocyanate afforded the corresponding 1,3 oxazin-2,4-diones [18-20].

Ethyl benzimideate,and ethyl butyrimidate react with diketene to give 2-ethoxy-1,3-oxazin 4-ones [21] Imines and N-acyl imines react with diketene to give tetrahydro-1,3-oxazin-4-ones [22-23]

N-acyl imines undergo [4+2] cycloaddition with both-C–C- and hetrodienes. For instance, isolable bis(trifluoromethyl)acyl imine,reacts with 2,2-dimethylethylene to give 1,3-oxazine.

N-acyl immonium ions have been the most commonly used dienes to effect [4+2] cycloaddition as 4π components with substituted 1,3-butadienes. It is found that N-acylimines or immonium ions that are capable of tautomerization undergo intramolecular Diels-alder reaction to give dihydro-1,3-oxazines [24]

Experimental

Melting points were recorded on Gallenkamp melting points Apparatus and were uncorrected . Elemental analysis was carried out in Mutah University on perkin-Elmer 2400 CHN Elemental analyzer .FT-IR spectra were recorded on FT-IR spectrophotometer -8400s Shimadzu (KBr) , UV-Visible spectra were recorded (in ethanol) On Schimadza Reco- 160 Spectrophotometer,and their ^{1}H-NMR spectra were recorded with BRUKER–AC–200MHZFT – NMR spectrophotometer.

Preparation of (Ethylene, Urea and Thiourea Schiff-bases). [25]

To a solution of 0.05 mole of Ethylene or Urea or Thiourea in 30 ml of ethanol (absolute) was added o.o5 mole of 5,5 Diethyl-pyrimidine-2,4,6-trione and refluxed 3hr. Where by a yellow crystalline solid separated out. The solid was filtered and recrystallized from ethanol.

Preparation of Oxinane Barbituric (1,2,3,4,6,8,9,10,11,13,15,16,17,18,20)

To a solution of 0.05 mole of Ethylene or Urea or Thiourea (Schiff-base) in 30 ml of Ethanol (absolute) was added o.o5 mole Malonic anhydride and refluxed 3hr. Where by a crystalline solid separated out. The solid was filtered and recrystallized from ethanol.

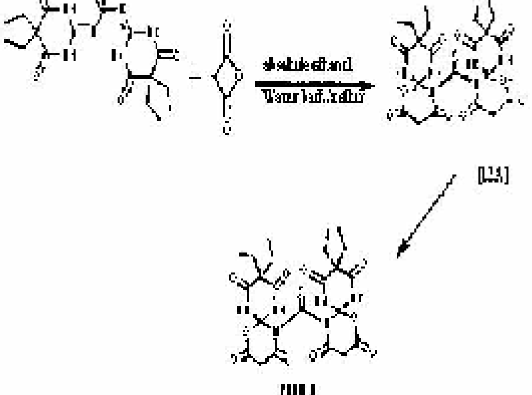
Preparation of Oxinane Barbituric (5,7,12,14,19,21)

To a solution of 0.05 mole of Ethylene or Urea or Thiourea (Schiff-base) in 30 ml.of Ethanol (absolute) was added o.1 mole Malonic anhydride and refluxed 3hr. Where by a crystalline solid separated out. The solid was filtered and recrystallized from ethanol.

Discussion

It is known that Schiff bases react smoothly with acid chlorides and anhydrides to give the corresponding addition products[19-21].

In this paper, the reaction of the 1,3-Bis(5,5-diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylidein)-urea or thiourea give the dipolar intermediate **[11A]** which collapses to the 6- membered heterocyclic ring system.**[11B]** is presented.



5-(n)

Schem (1)

This is indicated by the appearance of the characteristic C=O (lacton-lactam) absorption band at 1700 cm^{-1} in the IR spectra of addition products**[11B]**.

It is impressive to note that the two absorption bands at (1800-1950)cm^{-1} in the IR spectrum of pure malonic (anhydride) have disappeared when the anhydride became part of the 6-membered ring system of the 5-(9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5-7-11-triaza-spiro[5.5]undecane 5-carbonyl)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5] undecane-2,4,8,10-teraone.

The new absorption band of the (C=O) group in the IR spectra of the addition products **[11B]** appear at (1670-1700) cm^{-1}, this is attributed to the fact that the structures of the addition products are combination of the lacton-lactam structure.

The UV spectra of new oxinane barbituric acid derivatives show absorption peak at (240-310)nm due to $(n \longrightarrow \pi^*)$ $(\pi \longrightarrow \pi^*)$ and at (310-445) nm due to charge transfer of the aryl group and cyclic 6- membered structure [11B].

The reaction of malonic anhydride with various Schiff bases is a sort of cyclo addition reaction .Cyclo addition is a ring formation that results from the addition of bonds to either δ or π with formation new δ bonds. This class of reactions and its reverse encompasses a large number of individual types. Huisgen [26] has formulated a useful classification of diverse cycloaddition in terms the number of the new δ bond. The ring size of the product, and the number of atoms in the components taking part in the cycloaddition . This cycloaddition reaction is classified as a 2 + 5-7, and it is the first cycloaddition of this type, although in principle, one would predict that the butadiene cation might add to an olefin through a (4n+2) transition state to yield the cyclohexenyl cation [27].

The new oxinane barbituric acid derivatives are identified by their m.ps, elemental analysis (table 1,2,3) IR spectra (table 4,5,6) , UV spectra (table 7) and ^{1}HNMR spectra (table 8).

Table (1) : physical properties and CHN analysis of compounds (1-7)

Comp.	m.p/C°	Yield%	M.F	Calc.			Found		
				C	H	N	C	H	N
1	179-181	78	C13H20N4O3	49.99	6.45	17.94	50.08	6.57	17.88
2	187-189	68	C15H26N6O4	50.83	7.39	23.71	50.78	7.45	23.56
3	201-203	70	C18H30N6O6	50.69	7.09	19.71	50.65	7.02	19.66
4	170-172	62	C17H32N8O3	51.50	8.13	28.26	51.43	8.21	28.20
5	183-185	70	C20H36N8O5	51.27	7.74	23.92	51.32	7.88	23.78
6	174-176	54	C21H30N6O7	52.71	6.32	17.60	52.65	6.49	17.45
7	150-152	75	C24H32N6O10	51.06	5.71	14.89	51.00	5.89	14.77

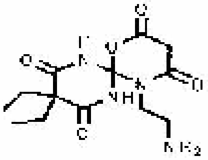
Table (2) : physical properties and CHN analysis of compounds (8-14)

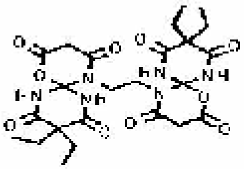
Comp.	m.p/C°	Yield%	M.F	Calc.			Found		
				C	H	N	C	H	N
8	200-202	52	C12H16N4O6	46.15	5.16	17.94	46.11	5.23	17.78
9	210-212	54	C13H18N6O6	44.07	5.12	23.72	44.01	5.25	23.60
10	204-206	62	C16H22N6O8	45.07	5.20	19.71	45.00	5.31	19.63
11	220-222	62	C14H20N8O6	42.42	5.09	28.27	42.33	5.18	28.11
12	240-242	54	C17H24N8O8	43.59	5.16	23.92	43.42	5.24	23.81
13	216-218	63	C20H26N6O8	50.21	5.48	17.56	50.20	5.55	17.43
14	180-182	69	C23H28N6O11	48.94	5.00	14.89	48.90	5.20	14.68

Table (3) : physical properties and CHN analysis of compounds(15-21)

Comp.	m.p/C°	Yield%	M.F	Calc.			Found		
				C	H	N	C	H	N
15	155-157	57	C12H16N4O5S	43.90	4.91	17.06	43.87	5.02	16.98
16	160-162	60	C13H18N6O4S2	40.40	4.69	21.75	40.38	4.76	21.62
17	166-168	62	C16H22N6O6S2	41.91	4.84	18.33	41.82	4.98	18.19
18	215-217	65	C14H20N8O3S3	37.82	4.53	25.21	37.76	4.67	25.15
19	198-200	67	C17H24N8O5S3	39.52	4.68	21.69	39.44	4.80	21.52
20	124-126	66	C20H26N6O7S	48.57	5.30	16.99	48.47	5.47	16.79
21	206-208	58	C23H28N6O10S	47.58	4.86	14.48	47.50	5.02	14.40

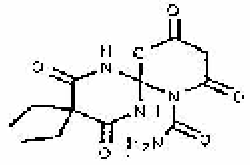
Table (4): IR Spectral data of compounds (1-7)

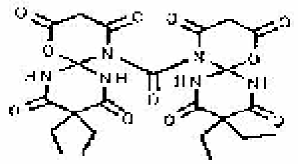




Comp.	υ (NH) Str.	υ (C-H) str. Benzylic	υ(C-H) aliph. (cm⁻¹)	υ (C=O) str. Lacton,lactam	υ (C-N) str.	υ (C-O) str. Lacton
1	3210	3185	2900-3000	1675	1430	1325
2	3190	3210	2890-2990	1675	1440	1335
3	3200	3200	2890-3000	1680	1440	1330
4	3200	3220	2880-2900	1675	1450	1320
5	3185	3220	2870-2980	1680	1430	1325
6	3195	3200	2900-3000	1685	1450	1335
7	3200	3180	2880-2990	1665	1445	1325

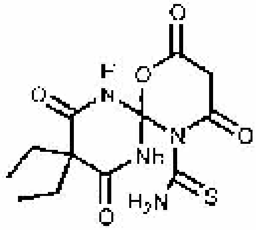
Table (5) : IR Spectral data of compounds (8-14)

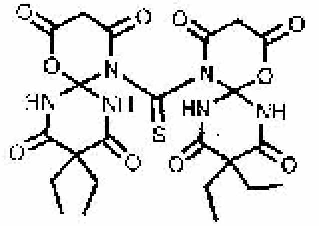




Comp.	υ (C-H) str. Benzylic	υ (NH) Str.	υ(C-H) aliph. (cm^{-1})	υ (C=O) str. Lacton,lactam	υ (C-N) str.	υ (C-O) str. Lacton
8	3200	3290,3200	2870-2980	1660	1435	1330
9	3200	3300,3200	2880-2990	1665	1430	1320
10	3220	3280,3170	2890-3000	1670	1430	1320
11	3180	3270,3180	2900-3000	1670	1430	1320
12	3210	3265,3195	2870-2980	1680	1430	1320
13	3195	-	2880-2900	1675	1445	1335
14	3210	-	2890-2990	1670	1440	1330

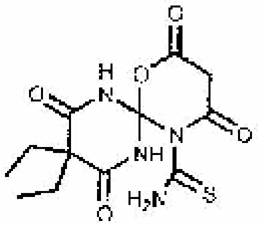
Table (6) : IR Spectral data of compounds (15-21)

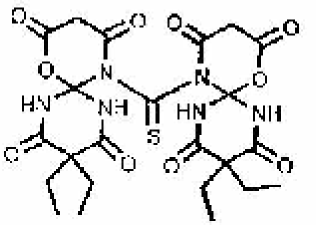




Comp.	Y(NH) Str.	υ (C-H) str. Benzylic	υ (C=O) str. Lacton,lactam	υ (C-N) str.	υ (C-O) str. Lacton	υ (C=S) str.
15	3265,3195	3210	1680	1445	1340	1255
16	3280,3170	3195	1675	1440	1330	1235
17	3270,3180	3220	1660	1435	1330	1230
18	3300,3200	3195	1660	1440	1345	1240
19	3790,3200	3210	1670	1435	1310	1240
20	-	3180	1685	1430	1325	1230
21	-	3200	1670	1445	1340	1235

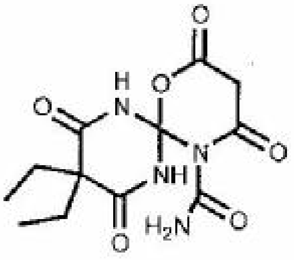
Table (7) : UV-Visible Spectral data of synthesized compounds (1-21)

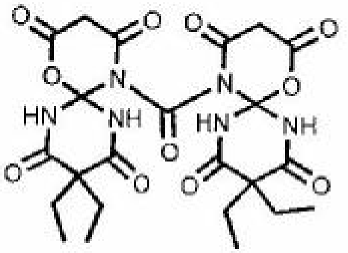




compound	λ_{max} EtOH (99%) (
1	385,345,275,257,225
2	325,270,245,225
3	360,330,276,230.220
4	380,268,259,234,222
5	384,344,266,240.220
6	379,288,250,230,224
7	380,285,250,227
8	370,330,276,240.220
9	365,278.247.227
10	380,288.263.224
11	368,350,240,233,221
12	376,280,240.228
13	381,275.230,227
14	370,258,239,234.220
15	379,269,249,238,225
16	377,250,240,234,221
17	376,280,240,228
18	384,354,256,240.228
19	382,278,253,224
20	379,333,253,240.225
21	360,290,260,230,224

Table (8) : 1 HNMR spectral data of synthesized compound (1,5,12,15,19)

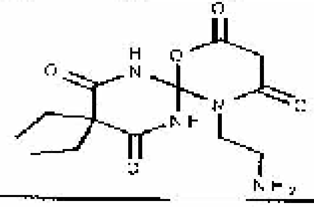
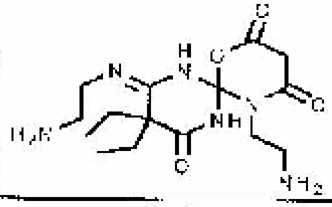
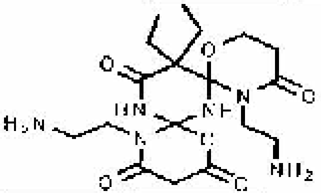
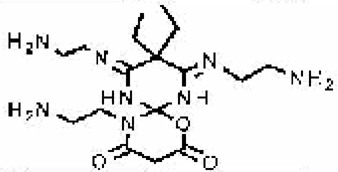
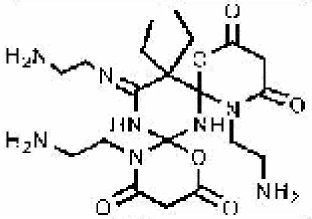
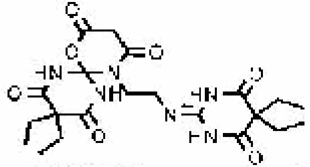
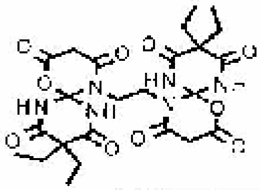
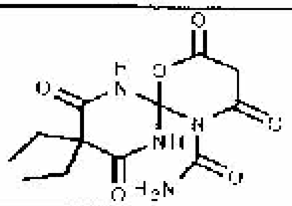


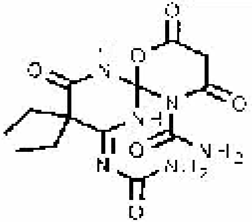
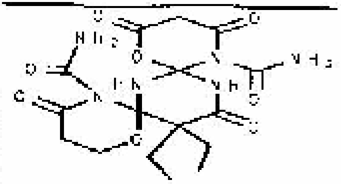
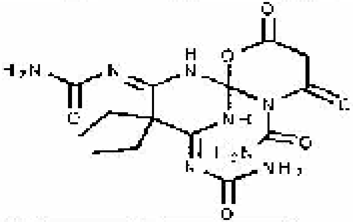
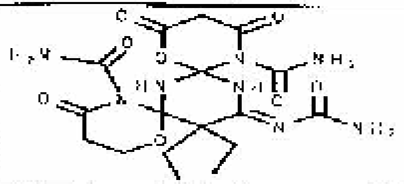
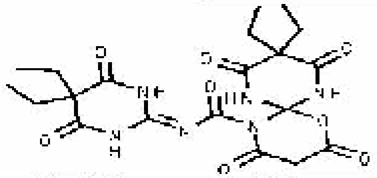
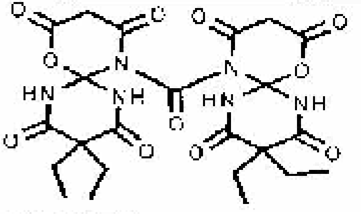
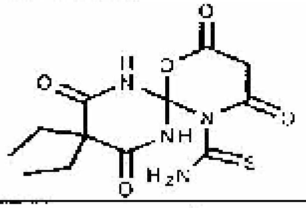
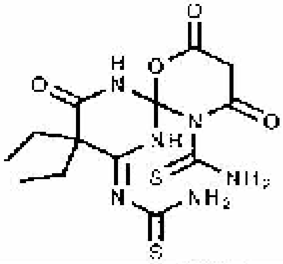


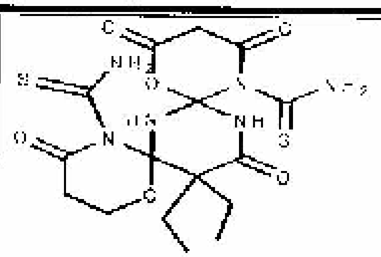
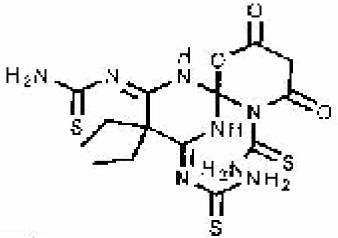
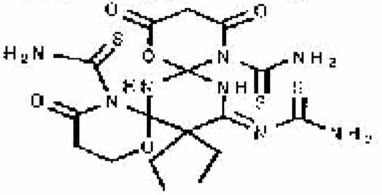
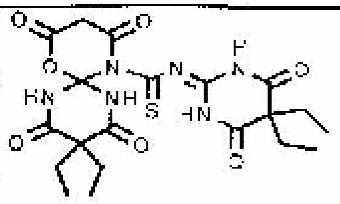
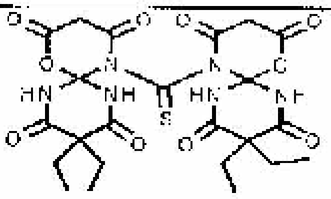
* Chemical shift = δ ** By using DMSO – d_6 as solvent

Compound NO.	CH3	CH_3-CH_2	CO-CH_2-CO	$NH_2CH_2CH_2$-N	N-CX-NH_2
1	0.86	1.75	3.09	1.8, 2.7 ,3.2	-
5	0.85	1.77	3.05	1.9 , 2.7, 3.2	-
12	0.88	1.76	3.1	-	5.6
15	0.89	1.77	3.08	-	2.2
19	0.85	1.79	3.08	-	2.3

The Schiff bases and the oxazinanes prepared in this research

No.	Name of compounds	Structure
1	5-(2-Amino-ethyl)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone	
2	5-(2-Amino-ethyl)-10-(2-amino-ethylimino)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5] undecane-2,4,8- trione	
3	5,13-Bis-(2-amino-ethyl)-16,16-diethyl-1,9-dioxa- 5,7,13,14-tetraaza-dispiro[5.1.5.3] hexadecane-4,10,12,15-tetraone	
4	5-(2-Amino-ethyl)-8,10-bis-(2-amino-ethylimino)-9,9- diethyl-1-oxa-5,7,11-triaza-spiro[5.5] undecane-2,4-dione	
5	5,13-Bis-(2-amino-ethyl)-15-(2-amino-ethylimino)-16,16-diethyl-1,9-dioxa-5,7,13,14-tetraaza-dispiro [5.1.5.3]hexadecane-4,10,12-trione	
6	5-[2-(5,5-Diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylideneamino)-ethyl]-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10- tetraone	
7	5-[2-(9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undec-5-yl)-ethyl]-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone	
8	9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carboxylic acid amide	

9	**8-Carbamoylimino-9,9-diethyl-2,4,10-trioxo-1-oxa-5,7,11-triaza-spiro[5.5] undecane-5-carboxylic acid amide**	
10	**16,16-Diethyl-4,10,12,15-tetraoxo-1,9-dioxa-5,7,13,14-tetraaza-dispiro[5.1.5.3] hexadecane-5,13-dicarboxylic acid diamide**	
11	**8,10-Bis-carbamoylimino-9,9-diethyl-2,4-dioxo-1-oxa-5,7,11-triaza-spiro[5.5] undecane-5-carboxylic acid amide**	
12	**15-Carbamoylimino-16,16-diethyl-4,10,12-trioxo-1,9-dioxa-5,7,13,14-tetraaza-dispiro [5.1.5.3]hexadecane-5,13-dicarboxylic acid diamide**	
13	**9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carboxylicacid(5,5-diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylidene)-amide**	
14	**5-(9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carbonyl)-9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5]undecane-2,4,8,10-tetraone**	
15	**9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5] undecane-5-carbothioic acid amide**	
16	**9,9-Diethyl-2,4,8-trioxo-10-thiocarbamoylimino-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carbothioic acid amide**	

17	**16,16-Diethyl-4,10,12,15-tetraoxo-1,9-dioxa-5,7,13,14-tetraaza-dispiro[5.1.5.3]hexadecane-5,13-dicarbothioic acid diamide**	
18	**9,9-Diethyl-2,4-dioxo-8,10-bis-thiocarbamoylimino-1-oxa-5,7,11-triaza-spiro[5.5] undecane-5-carbothioic acid amide**	
19	**16,16-Diethyl-4,10,12-trioxo-15-thiocarbamoylimino-1,9-dioxa-5,7,13,14-tetraaza-dispiro [5.1.5.3] hexadecane-5,13-dicarbothioic acid diamide**	
20	**9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carbothioicacid(5,5-diethyl-4,6-dioxo-tetrahydro-pyrimidin-2-ylidene)-amide**	
21	**5-(9,9-Diethyl-2,4,8,10-tetraoxo-1-oxa-5,7,11-triaza-spiro[5.5]undecane-5-carbothioyl) -9,9-diethyl-1-oxa-5,7,11-triaza-spiro[5.5] undecane-2,4,8,10-tetraone**	

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الخلاصة

تم تحضير عدد من مشتقات (الاوكسئانات) لحامض البارباجوريك من تفاعل عدد من (قواعد شيف) المحضرة سابقا [من تفاعل ثنائي امينو اثلين ، اليوريا والثايو يوريا مع 5،5- ثنائي اثيل -بيرامادين -2،4،6 -ترايون] مع مول ومولين من انهيدريد المالونيك . تم الحصول على مركبات حلقية غير متجانسة ، (سداسية الحلقة) او حلقتين سداسية غير متجانسة ، شخصت المركبات المحضرة بتعيين درجات انصهارها ،تحليل العناصر ، اطياف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي لبعض المركبات المحضرة واسهمت نتائج التشخيص بالطرق المختلفة في اثبات الصيغ التركيبية للمركبات المحضرة .