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Synthesis and Characterization of 1,3- Oxazepine and Benz [1,2-e][1,3] Oxazepine-4,7-Diones

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Abstract

N- Benzylidene m-nitrobenzeneamines (Schiff bases) were prepared by condensation of m-nitroaniline with aromatic aldehydes . These Schiff bases were found to react with maleic anhydride to give 2-Aryl-3-(m-nitrophenyl)-2,3- dihydro [1,3] oxazepine –4,7 – diones and with phthalic anhydride to give 2-Aryl-3 – (m- nitrophenyl) –2,3 – dihydrobenz [1,2-e] [1,3] oxazepine –4,7- diones which were reacted with pyrrolidine to give the anilide – pyrrolidides of maleic acid and phthalic acid.

Introduction

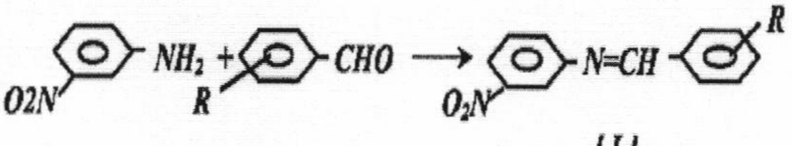
The 7-membered heterocyclic ring system: 1,3-oxazepine has already been reported in the literature(1-6).

Irradiation of 4-phenyl-2-oxa-3-azabicyclo[3.4.0]-hepta-3,6-diene in n-hexane gave 2-phenyl-1,3-oxazepine in 80% yield. Pyrylium tetraflurorborate underwent ring expansion on treatment with excess sodium azide in anhydrous 1,4-dioxane to give 58-96% substituted 1,3-oxazepine. Furthermore, thermal rearangment of ketovinylazirines gave substituted 1,3-oxazepine(7-10).

The discovery of the central nervous system (CNS) activity of 1,4-benzodiazepine(11-12) encouraged further searching for new ways to build up this 7-membered heterocyclic ring system. The first of these ways was the one involving addition of maleic anhydride and phthalic anhydride to Schiff bases(13-15).

Discussion

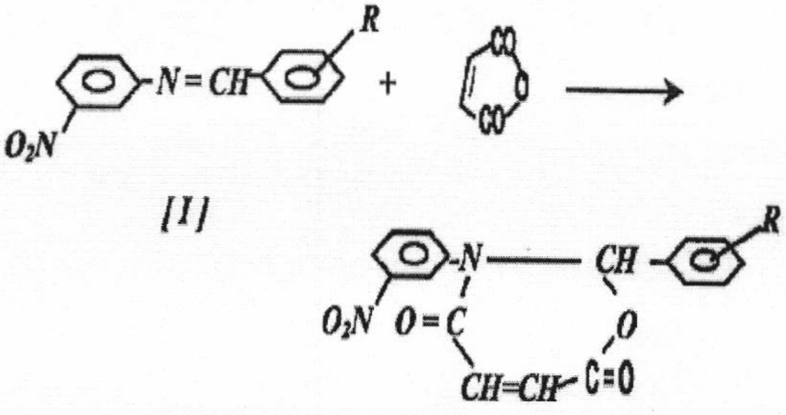
Schiff bases are prepared by condensation of m-nitroaniline with aromatic aldehydes to give N-Benzylidene m-nitrobenzeneamines according to well-known procedure(13) and identified by their m.ps, elemental analysis, IR, and UV spectra.



[I]

It is known that Schiff bases react smoothly with acid chlorides and anhydrides to give the corresponding addition products(13-15).

In this paper, the reaction of maleis and phthalic anhydrides with N-benzylidene m-nitrobenzeneamine is presented:

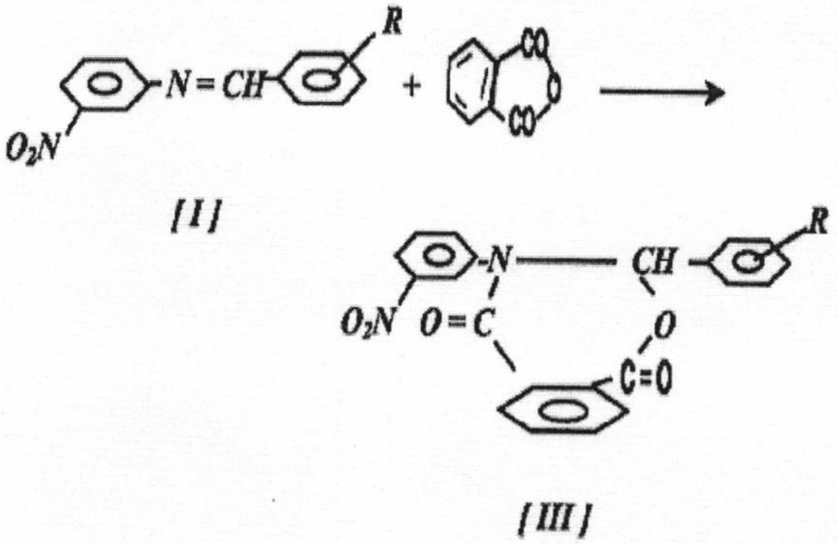


[I]

[II]

where:

a) R=H b)R=3-NO_2 c)R=4-Cl d) R=4-Br e) R=2-Br
f) R=2-OMe g) R=NMe_2



[I]

[III]

where:
a) R=H b) R=4-Cl c) R=3-NO_2 d)R=4-Me e) R=2-OMe

The reaction is followed by the disappearance of (N=C) absorption band (1600-1610)cm, and the appearance of the absorption bands of the expected groups in IR spectra of 2-aryl-3-(-m-nitrophenyl) –2,3-dihydro [1,3] –oxazepine –4,7- diones [II] and 2- aryl –3-(-m-nitrophenyl)-2,3-dihydrobenz[1,2-e] [1,3] – oxazepine-4,7- diones [III] .

Structure [II OR III] is a combination of both lactone and lactam in a 7-membered heterocyclic ring. This is indicated by the appearance of the characteristic (C=0) (Lactone / Lactam) absorption band at (1680-1700)cm in their IR spectra .

The UV spectra of 2-aryl-3(m-nitrophenyl)-2,3-dihydro [1,3]-oxazepine-4,7-diones [II] and 2-aryl –3-(m-nitrophnyl)-2,3-dihydrobenz [1,2-e] [1,3] – oxazepine –4,7 – diones and 2-aryl-3-(m-nitrophenyl) –2,3-dihydrobenz [1,2-e] [1,3] – oxazepine-4,7-diones are identified by their m.ps, elemental tables (1,7), IR spectra tables (2,8) and UV spectra tables (3,9) .

It is noticeable that the values of C-Hstr (benzylic) absorption bands are rather high. This is, in fact, explained by the shift towards longer wavelengths, that takes plase when the benzylic carbon is linked to three electron –withdrawing groups, phenyl, CL and N as in the title compounds .

It is impressive to note that the two absorption bands at (1740 – 1780) cm and at (1800-1850) cm in the IR spectrum of pure maleic or phthalic anhydride have disappeared when the anhydride became part of the 7-membered heterocyclic ring of [1,3] – oxazepine –4,7-dione or benz [1,2-e] [1,3] –oxazepine –4, 7 dione. This may be attributed to the fact that [1,2-e] [1,3] –oxazepine –4,7-dione. This may be attributed to the fact that the combined (C=O) of the loctone and the (C=O) of the lactom . Absorb in the same region of the IR spectra of these cyclic products Moreover, the (C=O) group in the IR spectra of the title [1,3]-oxazepine-4,7-diones or benz[1,2-e][1,3]-oxazepine-4,7-diones and 2-aryl-3-methyl-5,6-dihydro07H-pyrrolo[1,2-d][1.4]benzodiazepine-6-ones(8), absorbs in the same region (1680-1700)cm^{-1}, thus confirming the assigned 7-membered ring structure.

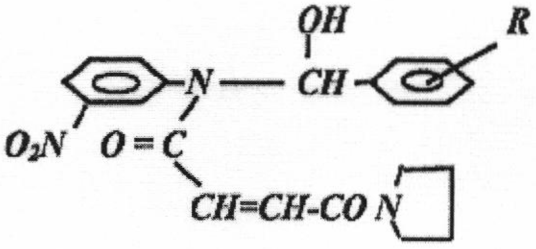
The reaction of maleic anhydride or phthalic anhydride with various Schiff bases is a sort of cycloaddition reaction. Cycloaddition is a ring formation that results from the addition of π bonds to either σ or π bonds with formation of new σ bonds. This class of reactions and its reverse encompasses a large number of individual types. Huisgen (16) has formulated a useful classification of diverse cycloadditions in terms of the number of the new σ bonds, 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 $5+2\rightarrow7$, and it is one of the first cycloadditions of this type, although in principle, one would predict that the pentadienyl cation might add to an olefin through a (4n+2) transition state to yield the cycloheptenyl cation (17).

The mechanism of the reaction of maleic anhydride and phthalic anhydride with Schiff bases and evidence supporting the 7-membered heterocyclic ring system for the products have already been reported (13-15).

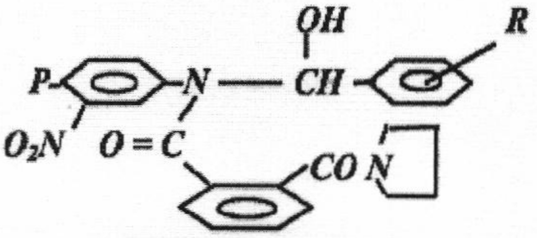
Previously, it was demonstrated that the basic hydrolysis of 2,3-diaryl-2,3-dihydro-1,3-oxazepine-4,7-diones is unsuccessful due to the immediate reclosure on acidification. The reclosure is easily achieved due to the closeness of the involved COOH and OH groups within the cis configuration of maleic acid or phthalic acid moiety. The evidence supprting this stems from the fact that both the original 1,3-oxazepine-

4,7-diones or benz [1,2-e][1,3] oxazepine-4,7-dione and the assumed hydrolysis product have identical m.p., mixed m.p., and IR spectra.

In order to avoid reclosure, the original title compounds (II or III) are treated with pyrolidine to give the open-chain anilide-pyrrolidide derivatives of maleic acid or phthalic acid [IV, V].



(IV)



(V)

Since none of the two nitrogen atoms in structure [IV or V] carries hydrogen, reclosure through elimination of water molecule to the cyclic structure is not expected.

Male- or phthal-N-(α-hydroxybenzyl) anilide-pyrrolidides are identified by their m.ps., elemental analysis table (4,10), IR spectra table (5,11) and UV spectra table (6, 12).

Experimental

Melting points were recorded with Gallenkamp Melting point apparatus and were uncorrected. Elemental analyses were carried out in Mousil University on Carlo Erba Type 1106 CHN Elemental Analyzer. IR spectra were recorded with PYE UNICAM SP-300 Infrared Spectrophotometer in (KBr) ND UV-Visible spectra were recorded (in methanol) on Schimadsu Recc-160 spectrophotometer .

N-Benzylidene arenamines :

N-Benzylidene arenamines were prepared by condensation of subtitled aniline and aromatic benzaldehydes in hot ethanol and recrystallized from the same solvent according to a previously published procedure(9). They are characterized by their m.ps, elemental analyses, IR spectra and UV-Visible spectra.

2-Phenyl –3-(m-nitrophenyl)-2,3-dihydro[1,3] –oxazepine –4,7-diones or 2-phenyl –3-(m-nitrophenyl)-2,3-dihydrobenz[1,2-e][1,3]- oxazepine –4,7- diones

In a(100ml) round bottom flask, equipped with double surface condenser fitted with Calcium chloride guard tube, was placed with a mixture of (0.01) mole of N-benzylidene m-nitrobenzenamine and (0.01) mole of maleic anhydride or phthalic anhydride suspended in (50ml) of dry benzene. The reaction mixture was refluxed in a water bath at 90 C° for 2hrs. The solvent was removed and the resulting yellow crystalline solid was recrystallized from dry 1,4-dioxane .

This experiment was repeated using different N-benzylidene nitrobenzenamines in order to obtain other 1,3-oxazepine –4,7-dones .

Reaction of pyrrolidine with 2-aryl-3-(m-nitrophenyl)-2,3-dihydro[1,3] –oxazepine –4, 7- diones or 2-aryl –3-(m-nitrophenyl) - 2,3- dihydrobenz[1,2-e][1,3] –oxazepine –4,7-diones

To a mixture of 0.005 mole of 2-aryl-3-(m-nitrophenyl)-2,3-dihydrobenz[1,2-e] [1,3] –oxazepine –4,7-dione suspended in dry 1,4-dioxane was added an excess (0.02 mole) of dry pyrrolidine. After (10min) of stirring the mixture was heated to (80 C°) in water bath for (30 min) then left to cool to room temperature and the separated crystalline solid was filtered and recrystallized from 1,4- dioxane .

Several other derivatives of male – or phthal – N- (a-hydroxybenzyl) anilide – pyrrolidides were obtained following the same procedure and using the same amounts of pyrrolidine and the chosen 2-aryl-3-(m-nitrophenyl)-2,3-dihydro-1,3-oxazepine –4,7-diones.

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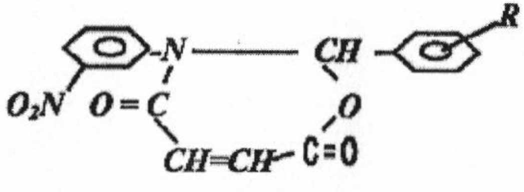
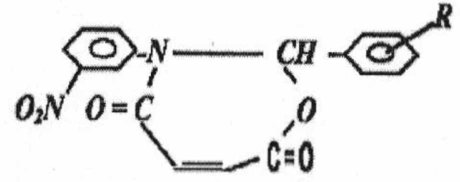
Table (1) Melting points, percentage yield, molecular formula and elemental analysis of 2-Aryl-3- (m-nitrophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione(II)



[II]

Comp.	R	M.P C°	Yield %	M.F	Calc.			Found		
					C%	H%	N%	C%	H%	N%
IIa	II	193	78	$C_{19}H_{12}N_2O_5$	65.52	3.45	8.05	65.60	3.65	8.11
IIb	3-NO_2	200	72	$C_{19}H_{11}N_3O_7$	58.02	2.80	10.69	58.65	2.85	10.80
IIc	4-Cl	198	71	$C_{19}H_{11}N_2O_5Cl$	59.69	2.88	7.33	60.05	2.91	7.48
IId	4-Br	194	70	$C_{19}H_{11}N_2O_5Br$	53.27	2.57	6.54	53.51	2.62	6.63
IIe	2-Br	196	71	$C_{19}H_{11}N_2O_5Br$	53.27	2.57	6.54	53.54	2.63	6.65
IIf	2-OMe	184	69	$C_{20}H_{11}N_2O_6$	63.49	3.70	7.41	60.42	3.81	7.35
IIg	4-NMe_2	198	65	$C_{21}H_{17}N_3O_5$	64.45	4.35	10.74	65.02	4.43	10.83

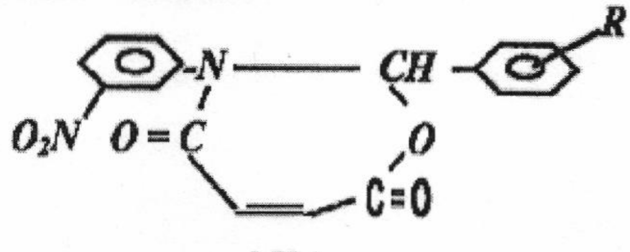
Table (2) Major IR Absorption (cm^{-1}) of 2-aryl-3-(p-nitrophenyl)-2,3,dihydro-1,3-oxazepine-4,7-diones(II)



[II]

Comp.	C-H str. Benzylic	=CH str. Olefinic	C-H str. Aromatic	C=O str. Lactone/ Lactam	C=C str. Olefinic	C=C str. Aromatic	C-NO: Aromatic	C-H bend Benzylic	C-O str. Lactone	Cis=CH bend	Others
IIa	3230	3180	3035	1690	1605	1560.1535	1510.1340	1425	1250	840	---
IIb	3240	3178	3040	1695	1605	1570.1540	1510.1340	1425	1250	840	---
IIc	3240	3170	3045	1690	1605	1580.1540	1520.1340	1425	1250	840	C-Cl:720
IId	3240	3180	3045	1690	1605	1580.1540	1515.1340	1415	1250	840	C-Br:445
IIe	3235	3180	3040	1690	1610	1580.1540	1520.1340	1420	1250	845	C-Br: 445
IIf	3230	3180	3040	1690	1610	1580.1540	1510.1340	1420	1250	845	C-H str. Aldih. :2900.2820
IIg	3235	3180	3040	1690	1605	1580.1540	1510.1340	1425	1250	845	C-N: 1350 C-H str. Aldih. 299.2820

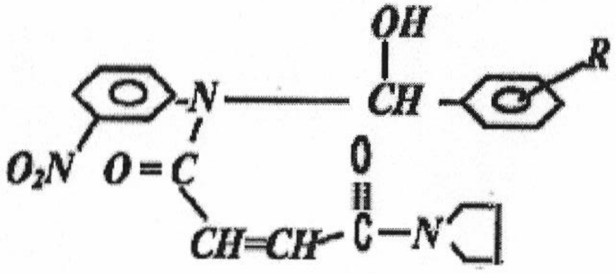
Table (3) The UV-Visible absorption maxima of 2-aryl-3-(m-nitrophenyl)-2,3-dihydro-1,3-oxazepine-4,7-diones (II)



[II]

Compound	UV-Visible absorption maxima λ/nm
IIa	312, 253, 231
IIb	350, 340, 257, 232
IIc	325, 267, 232
IId	350, 318, 253, 231
IIe	349, 315, 250, 230
IIf	318, 260, 230
IIg	360, 325, 260, 232

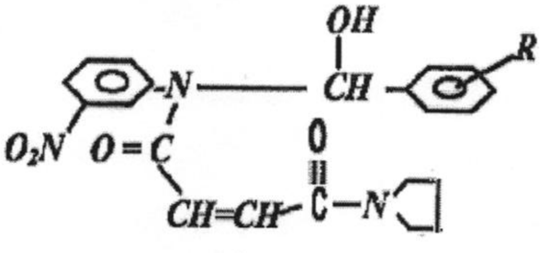
Table (4) Melting points, percentage yield, molecular formula and elemental analysis of N-(α-hydroxybenzyl)-nitro-anilide-pyrrolides.(III)



[III]

Comp.	R	M.P C°	Yield %	M.F	Calc.			Found		
					C%	H%	N%	C%	H%	N%
IIIa	II	210	76	$C_{21}H_{21}N_3O_5$	63.80	5.32	10.63	64.06	5.45	10.95
IIIb	3-NO_2	232	70	$C_{21}H_{20}N_4O_7$	57.27	4.55	12.73	57.11	4.58	13.03
IIIc	4-Cl	230	70	$C_{21}H_{20}N_3O_5Cl$	58.74	4.66	9.79	58.90	4.70	10.00
IIId	4-Br	223	70	$C_{21}H_{20}N_3O_5Br$	53.05	4.21	8.84	53.11	4.12	9.01
IIIe	2-Br	224	72	$C_{21}H_{20}N_3O_5Br$	53.05	4.21	8.84	53.30	4.37	9.12
IIIf	2-OMe	218	71	$C_{22}H_{23}N_3O_6$	62.12	5.41	9.88	62.50	5.40	10.03
IIIg	4-NMe_2	243	67	$C_{23}H_{26}N_4O_5$	60.01	5.94	12.79	61.00	6.01	13.03

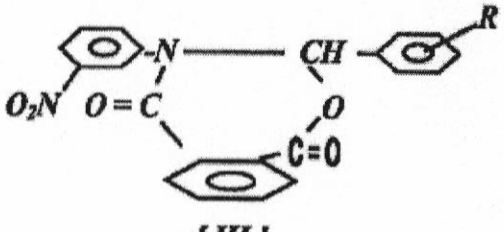
Table (6) The UV-Visible absorption maxima of male N-(α-hydroxybenzyl)-m-nitroanilide-pyrolidides (IV).



[IV]

Compound	UV-Visible absorption maxima λ/nm
IIIa	280, 235, 220
IIIb	305, 255, 235
IIIc	286, 232, 219
IIId	285, 231, 220
IIIe	295, 235, 220
IIIf	300, 245, 231
IIIg	305, 254, 230

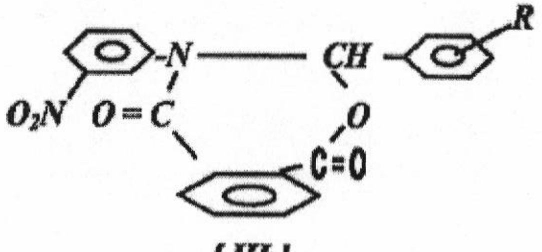
Table (7) Melting points, percentage yield, molecular formula and elemental analysis of 2-aryl-3-m-nitrophenyl-2,3-dihydrobenz[1,2-e][1,3]-oxazepine-4,7-diones(III)



[III]

Comp.	R	M.P Co	Yield %	M.F	Calc.			Found		
					C%	H%	N%	C%	H%	N%
IIa	II	170	57	$C_{21}H_{14}N_2O_5$	67.38	3.74	7.99	67.48	3.81	7.58
IIb	4-Cl	191	50	$C_{21}H_{13}N_2O_5Cl$	61.76	3.19	6.86	61.93	3.13	7.03
IIc	3-NO_2	210	50	$C_{21}H_{13}N_3O_7$	60.14	3.10	10.02	60.22	3.20	10.14
IId	4-NMe^2	216	57	$C_{23}H_{19}N_3O_5$	66.19	4.56	10.07	66.35	4.69	11.03
IIe	2-OMe	203	59	$C_{22}H_{16}N_2O_6$	65.35	3.96	6.93	65.40	4.13	7.10

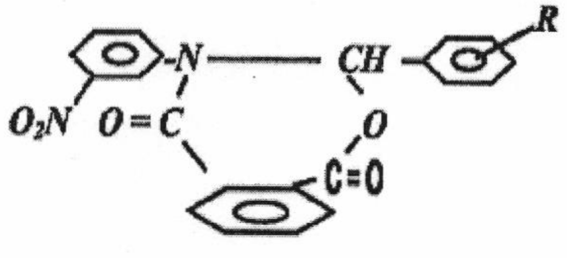
Table (8) Major IR Absorption (cm^{-1}) of 2-aryl-3-m-nitrophenyl-2,3-dihydrobenz[1,3-e][1,3]-oxazepine-4,7- diones(III).



[III]

Comp.	C-H str. Benzylic	C-H str. Aromatic	C=O str. Lactone/ Lactam	C=C str. Aromatic	C=C bend benzylic	C-O str. Lactone	C-H bend aromatic	C-NO$_2$ str. aromatic	Others
IIa	3190	3030	1630	1600,1480	1400	1300	815, 735	1520 1340	---
IIb	3200	3030	1685	1600,1485	1400	1310	830, 740	1520 1340	---
IIc	3210	3030	1690	1600, 1490	1405	1300	820, 790	1520 1340	C-Cl:720
IId	3210	3030	1700	1600, 1490	1410	1280	835, 740	1520 1340	C-Br:445
IIe	3215	3030	1700	1600, 1490	1410	1285	840, 780	1520 1340	C-Br: 445

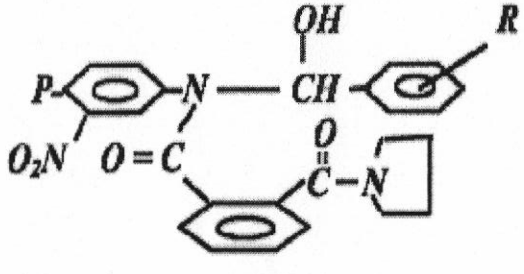
Table (9) The UV-Visible absorption maxima of 2-aryl-3-(m-nitrophenyl) -2,3- dihydro-1,3-oxazepine-4,7-diones (II)



[III]

Compound	UV-Visible absorption maxima λ/nm
IIa	312, 253, 231
IIb	350, 340, 257, 232
IIc	325, 267, 232
IId	350, 318, 253, 231
IIe	349, 315, 250, 230
IIf	318, 260, 230
IIg	360, 325, 260, 232

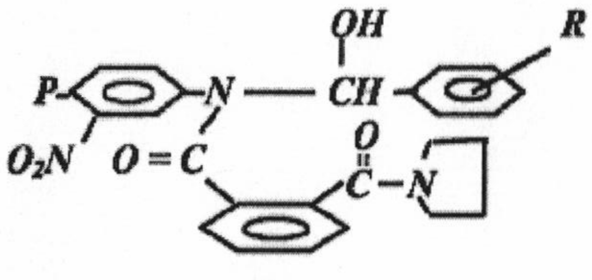
Table (10) Melting points, percentage yield, molecular formula and elemental analysis of N-(α-hydroxybenzyl)-nitro-anilide-pyrrolides.(III)



(V)

Comp.	R	M.P Co	Yield %	M.F	Calc.			Found		
					C%	H%	N%	C%	H%	N%
IIIa	II	213	61	$C_{25}H_{23}N_3O_5$	67.42	5.17	9.44	67.61	5.25	9.61
IIIb	4-Cl	143	53	$C_{25}H_{22}N_3O_5Cl$	62.63	4.59	8.77	62.75	4.69	8.90
IIIc	3-NO_2	230	52	$C_{25}H_{23}N_4O_7$	61.22	4.49	11.43	61.36	4.61	11.56
IIId	4-NMe_2	245	60	$C_{27}H_{28}N_4O_5$	66.22	5.71	11.48	66.50	5.85	11.63
IIIe	2-OMe	234	60	$C_{26}H_{25}N_3O_6$	65.68	5.20	8.84	65.64	5.35	9.03

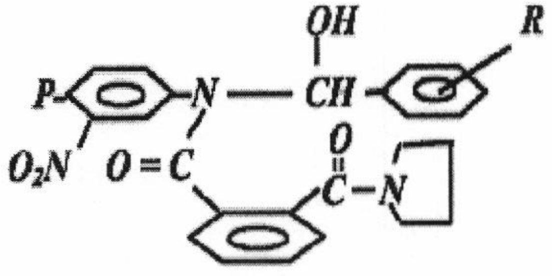
Table (11) The Major IR Absorption (cm^{-1}) of N-(α-hydroxybenzyl)-m-nitroanilide-pyrolidides (V).



(V)

Comp.	O-H str.	C-H str. Benzylic	$-CH_2$ str.	C=O str. 39amide	C=C str. Aromatic	$C-NO_2$: Aromatic	C-H bend Benzylic	O-H bend	Others
IIIa	3400	3200	2920	1680	1580,1470	1520, 1340	1390	1280	---
IIIb	3380	3230	2900	1690	1580, 1490	1520, 1340	1390	1270	---
IIIc	3400	3200	2910	1680	1580, 1500	1520, 1340	1380	1260	C-Cl:735
IIId	3380	3200	2940	1690	1590, 1490	1520, 1340	1390	1280	C-Br:440
IIIe	3370	3200	2935	1690	1590, 1480	1520, 1340	1390	1270	C-Br: 440

Table (12) The UV-Visible absorption maxima (in methanol) of the Derivatives of phthal N-(α-hydroxybenzyl)-anilide-pyrolidides (V)



(V)

Compound	UV-Visible absorption maxima λ/nm
IIIa	254, 361
IIIb	252, 370
IIIc	260, 362
IIId	263, 380
IIIe	258, 370

مجلة ابن الهيثم للعلوم الصرفة والتطبيقية المجلد 19 (3) 2006

تحضير وتشخيص 3,1- أوكسازبين و بينز [1,2-e] [1,3]- اوكسازبين 4,7- دايون

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الخلاصة

تم تحضير عدد من n- بنزليدين-بنزين أمين (قواعد شيف) بتكاثف ميتا-نيتروأنلين مع الالديهايدات الاروماتية. فوعلت قواعد شيف هذه مع انهيدريد المالييك فاعطت 2-اريل-3-(ميتا-نيتروفنيل)-2,3 ثنائي هيدروبنز [1,2-e 3,1] اوكسازيبين – 7,4 – دايون . فوعلت الاخيرة مع البيروليدين الجاف فاعطت مشتقات الاننيليد – البيروليديد لحامض المالييك وحامض الفثاليك .