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SYNTHESIS OF SOME MALEIMIDE DERIVATIVES VIA REGIO AND STEREOSELECTIVE REDUCTION USING SODIUM BOROHYDRIDE

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ABSTRACT

Synthesis of specific maleimide derivatives was performed through the stereospecific use of sodium borohydride. The reduction took place on only one of the carbonyl which is adjacent to the phenylamino group or the alkyl amino group. Our results were confirmed by the presence of the formed hydroxyl group using chromatographic and spectroscopic techniques.

INTRODUCTION

Numerous maleimide derivatives were synthesized and tested for different biological effects. Some of them possess antibacterial and fungicidal effects[1]. There are several other maleimide derivatives have antiviral[2] and antidiabetic[3]. Some indolomaleimides have anti-inflammatory, analgesic[4], antiarrhythmic[5], anticonvulsant and anesthetic[6] and even anticancer activities[7].

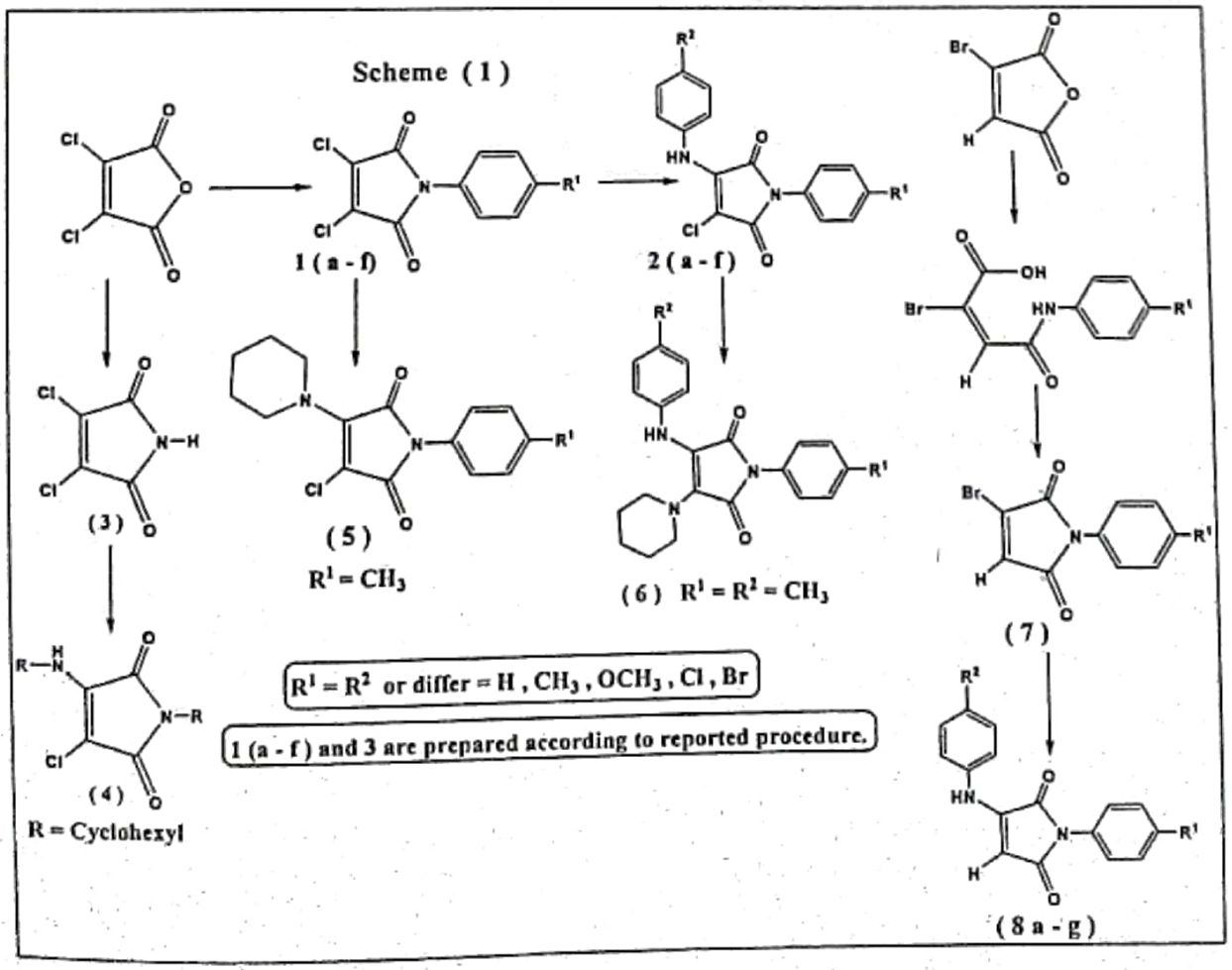
RESULTS AND DISCUSSION

A- Materials:

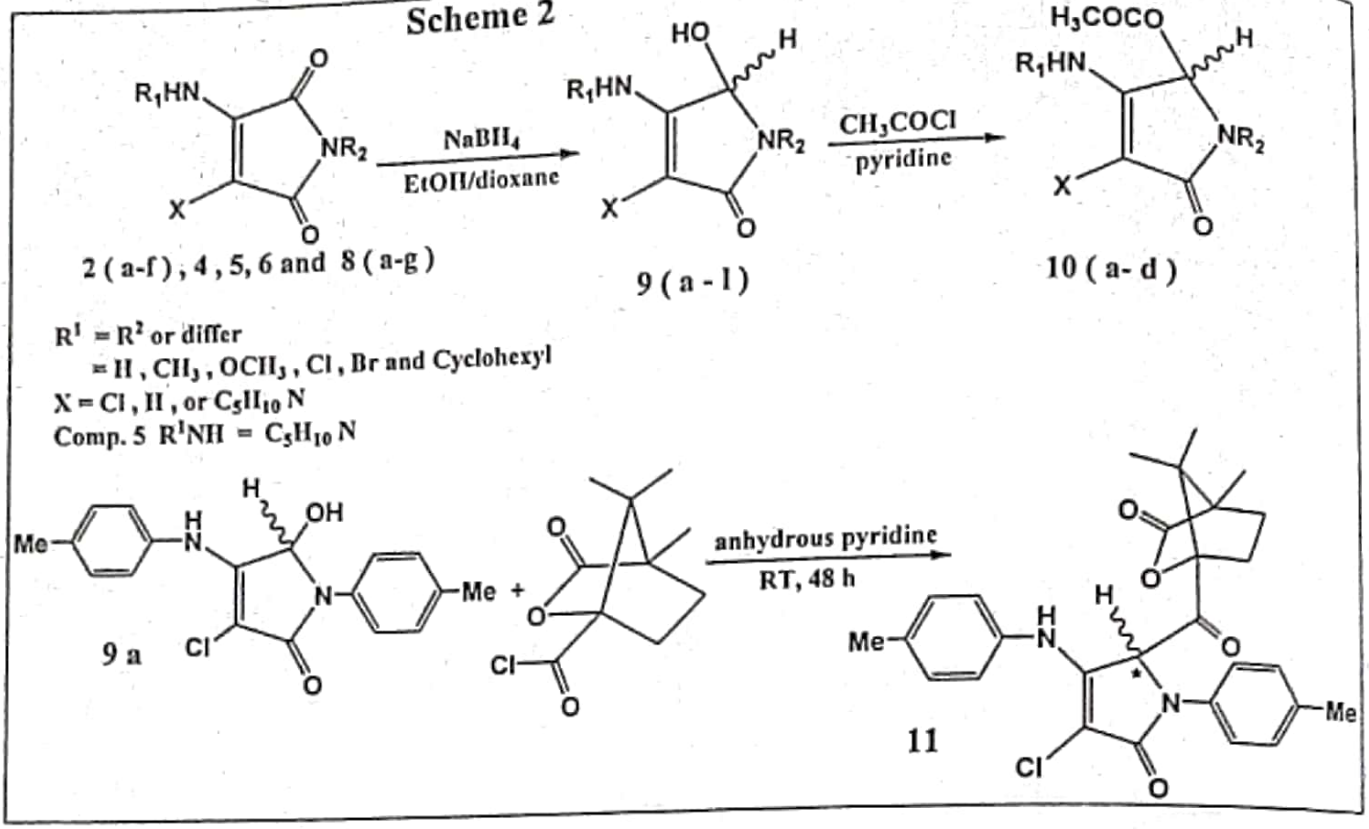
In view of the previously reported biological values of maleimide and their derivatives, this part is concerning further with the exploration of some aspects of special importance both from synthetic and chemistry points of views. Previous studies have supported these views on the light of their recent reports which principally concern with the conversion of certain maleimides to the corresponding succinimides[8].

In continuation to the previous reports, this work aimed first to synthesize and study the effect of substitution pattern in maleimides on their reduction profile using sodium borohydride.

Secondly, the authors would like to give explanations and answers for regiospecific or regioselective reduction that might come out if one carbonyl is got reduced and what is the site of reduction and why if there is any. In our opinion, reduction of one carbonyl would confer asymmetry to molecule and hence, products isolated racemate Thus, one of our big objectives is resolution of the racemates using chiral molecule. The core of this study is shown in scheme 1 and 2.

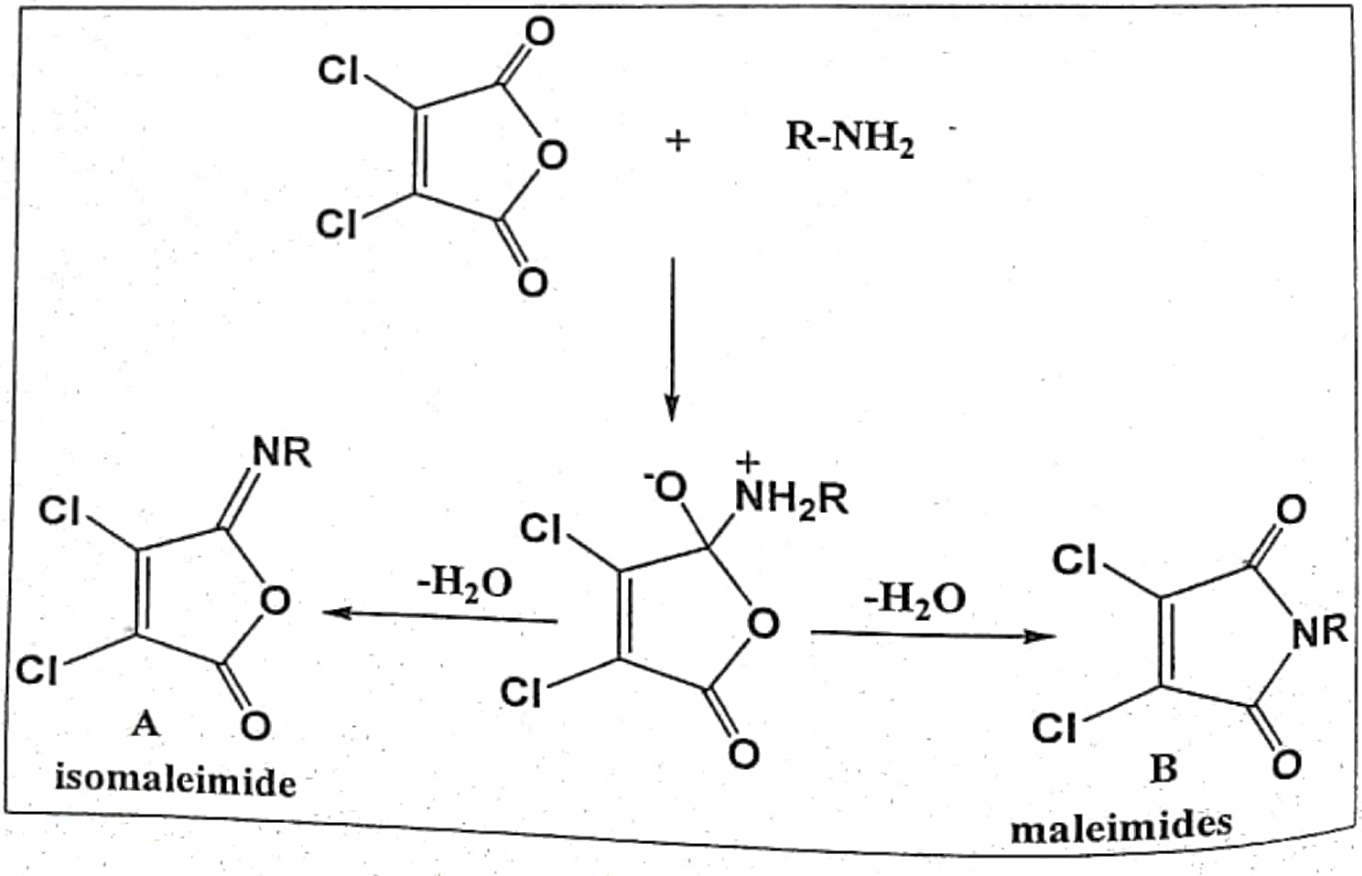


Scheme 2



To realize our main objectives previously described, the synthesis of several maleimides enjoying the general structure of compounds **2 (a-f), 5 and 6** has been adopted. 3,4-Dichloro-N-aryl maleimide was prepared following reported procedures either by halogenation[9] of N-aryl maleimide using pyridine/$SOCl_2$ mixture or by aminolysis[10] of dichloromaleic anhydride in acetic acid (shown below).

Aminolysis using one molecular ratios of the amine can take place at C1 to give two products (A) and (B) as illustrated below. Isomaleimides were prepared[11] by reaction of acetylen-dicarbonyl fluoride and primary amines in non acidic medium Spectral data were used discriminate between products (A) and (B). The latter compounds showed identical carbonyls in their IR spectra. Likewise ^{13}CNMR is also of great value. Compilation of these data proved that products in our hand were of type (B) and trials to get isomaleimides of type (A) were unsuccessful.



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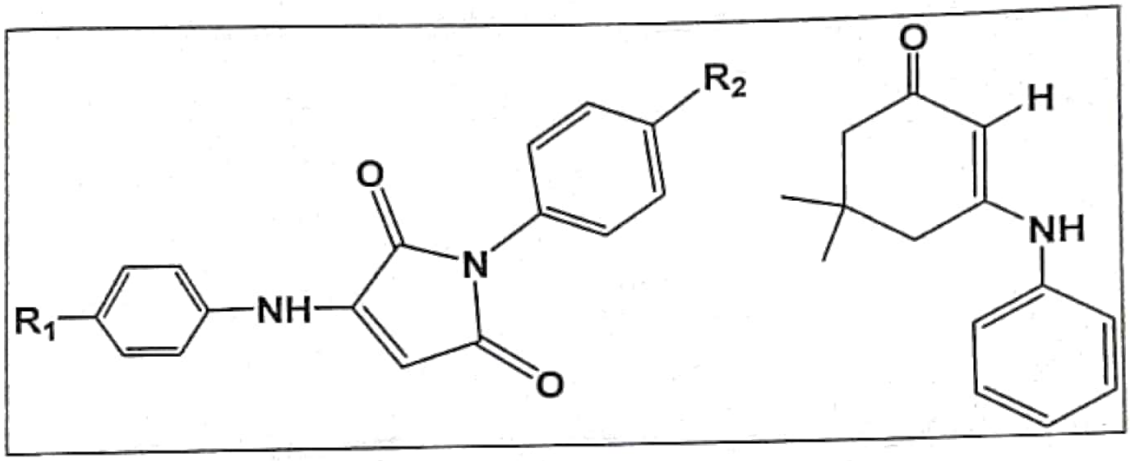
3-Substituted-arylamino-4-chloro-2,5-dihydro-2,5-dioxopyrroles (2 a-f) were prepared by reacting (1 a-f) and large amounts (2 moles) of the appropriate amine in refluxing methanol.

It is worth mentioning, that further attack of C_4 by I^{ry} aromatic nitrogen nucleophiles is not allowable. This is explained on the basis of the outweighing releasing property of enamine nitrogen relative to the activating negative electronic effects of the conjugated carbonyl at C_2. However, aminolysis by I^{ry} aliphatic and 2ry amines can be performed smoothly. Thus maleimides having nitrogen residues at C_3 and C_4 were prepared by first insertion of primary aromatic amines followed by reacting product with aliphatic (piperidine) rather than applying the reverse as shown in scheme (1).

Compound 4 is the new intermediates were prepared by reaction of dichloromaleimide with (3 moles) of primary aliphatic amine in refluxing ethanol for 2 hours[12].

Compounds 8 (a – g) showed enaminone structure motivated the authors to hold a comparative study between these compounds and enaminodimedone that have been intensively studied in our laboratory[13].

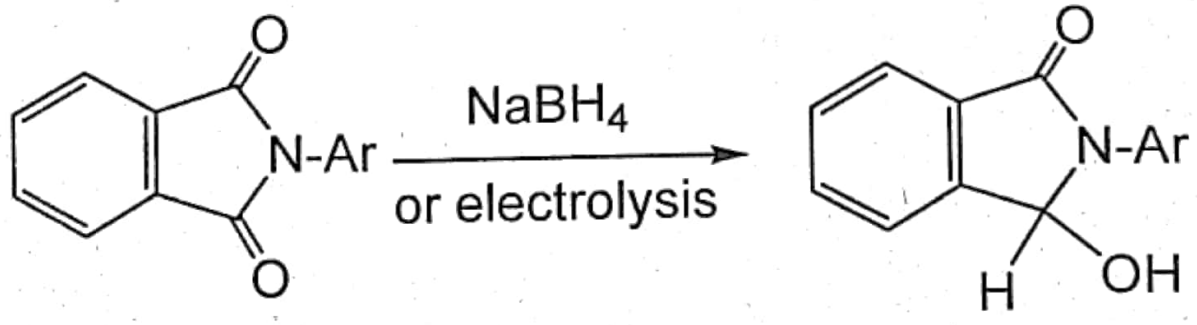
The main differences between these compounds and those previously described are the ring size (5 versus 6) and the presence of an extra-carbonyl group which certainly would affect the behavior as well as the chemical outcomes in each case. Enaminodimedone reacts as nitracarbanion with Michael acceptors in basic solution to give good yield of the corresponding adducts. These were simultaneously cyclized to give a variety of heterocycles.



On the other hand, enaminomaleimides were reacted under similar conditions to give inferior yield (67%) versus (90%) at very low rates (15 h versus 2 h) of pyrrolopyridine in respect to enaminodimedone. This controversy in behavior between enaminomaleimide and enaminodimidones could be attributed to the planarity and the presence of negative electronic effects induced by the conjugated carbonyl group in their molecules. 5-Membered enaminomaleimides are more planner than 6-membered derivatives which permits maximal stability of their nitracarbanion and hence become less reactive nucleophiles. Likewise, the presence of extra-carbonyl group in their molecules detracted their nucleophilic character. This is proved chemically by reduction of these carbonyl groups followed by conversion to their esters as the former are insoluble in the reaction media.

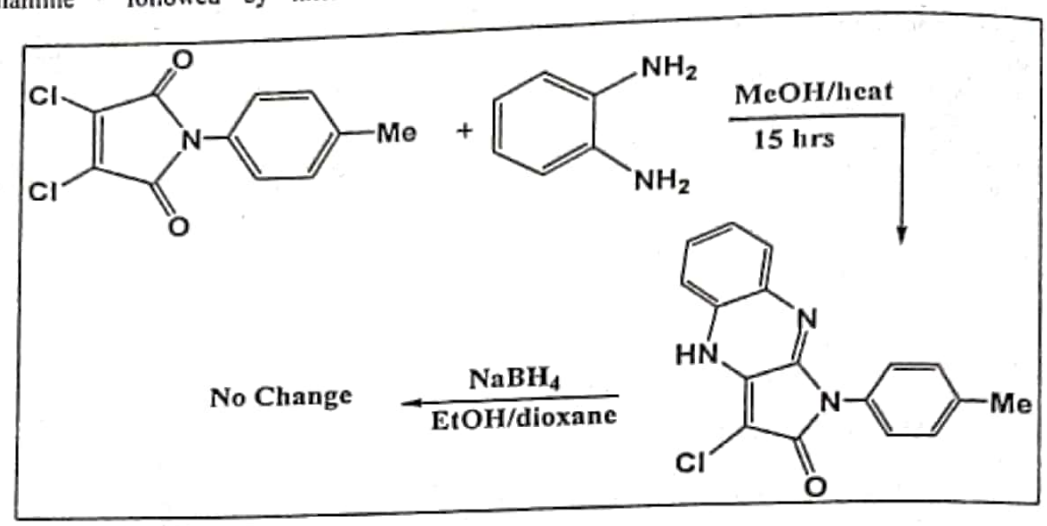
It has been reported that some fused maleimides underwent reduction to their hydroxy derivatives either by electrolytic method (14) or sodium borohydride[15].

Contrasting this behavior N-phenylmaleimides can not be reduced with sodium borohydride[11]. This can be ascribed to the relative higher polarity of fused and substituted maleimides compared to the unsubstituted ones.



In this context, we aimed to explore the sodium borohydride reduction profile on a variety of new synthesized maleimides [2 (a-f) , 4 ,5 , 6 and 8 (a-g)]. The results revealed that, substitution at position 1 and 3 by aromatic amines showed greater yield percent and reaction rate compared to aliphatic amines due to the greater interaction between nonbonding electron and the conjugated residue in case of aromatic enaminones. Also, it has been noticed that reduction takes place preferentially at the carbonyl adjacent to the

substituted-amino residue without any sign of reduction at position-5 i.e. regiospecific reduction. This can be proved by masking the carbonyl at position-2 by reaction of dichloromaleimide with o-phenylenediamine[16] followed by interaction with sodium borohydride.Expectively no reaction was observed which confirmed that the reduction is only displayed by the carbonyl at position-2 as illustrated by the following scheme.



Spectral data were complying with our conclusions. The higher frequency carbonyl, the non conjugated enaminocarbonyl, disappeared in IR spectra, while new bands for OH were observed, likewise, ^{1}HNMR data revealed two doublets at range 5.2 - 6.5 and 6.5 – 6.9 ppm which becomes one singlet after deuteration signifying the formation of hydroxyl group. Failure of **C=O** group at position -5 to react with $NaBH_4$ is probably due to the positive releasing effect of the amine residue at position 3. ^{1}HNMR showed a sharp singlet signal at 5.2 - 5.4 integrating one vinylic proton prior and after reduction which proved that the C=O at position 5 is not susceptible to hydride reduction.

The esters **10 (a-e)** are prepared by esterfication of their alcohols. The resulting alcohols were acylated by two methods either by using acetic anhydride in refluxing dioxane or through interaction with acetyl chloride/pyridine while stirring at room temperature. The structure of the prepared esters **10 (a-e)** were established by IR, ^{1}HNMR, mass spectroscopy and elemental analysis.

2-Camphanoyloxy-1-(4-methylphenyl)-3-(4-methylphenyl)amino-4chloro-5-oxo-2,5 dihydropyrrole diasteromers (11). This part aimed to resolve the racemates resulted from sodium borohydride reduction of 3,4-disubstituted maleimides. Resolution was achieved through reaction of these racemates with chiral camphanic acid chloride in pyridine solution (scheme 2), to afford a diastereomeric mixture of the corresponding esters in 53% yield. Successful formation of diasteromers was revealed by TLC (scheme 2) which showed two prominent and clean spots at different Rf values versus one spot in case of racemates. GC/MS of the diastereomeric mixture signifies the presence of two bands at retention time of 12.03 (31.2%) and 12.268 (68.72%) respectively. Mass spectrum of these bands showed identical fragmentation pattern.

Meanwhile, mass spectrum revealed molecular ion peak at m/z 508.20 complying with the molecular formula of the ester ($C_{28}H_{29}ClN_2O_5$). ^{1}HNMR as well as ^{13}CNMR were parallel with the chemical constitution of the obtained camphanic acid ester α [D] of racemic aminal showed These data proved that sodium borohydride reduction of 3,4-disubstituted maleimides is stereoselective and that the presence of vicinal functionality of a 2ry aminal residue to the amide carbonyl is crucial compared to 3ry amine or halogen residues. The non identical amounts of racemic aminals (31.2% versus 68.7%) is probably stemed from hydride ion reduction of the intermediately formed from enaminomaleimides which inherited unequal steric interactions at one face.

Assignment of the absolute configuration of diastereoisomers will be determined in future as one part of our goal in separation of diastereomers.

EXPERIMENTAL

Melting points were determined using Reichert Termovar melting point apparatus and were uncorrected. IR were mesured on Varian Perkin Elmer 710 B. ^{1}HNMR spectra were conducted on Varian **VXR** 300 at **300 MHz** ^{13}CNMR were determined on Varian VXR 300 at **75 MHz** spectrophotmeter using TMS as an internal standard. Mss Spectrometry was measured on Varian **MAT 311a**. Microanalysis were conducted at the Pharmaceutical Chemistry Institute, Dusseldorf University. All other spectral data reported herin were consistent with the assigned molecular structures.

1-Aryl-3,4-dihydro-2,5-dioxo-2,5-dihydropyrroles 1 (a–f) and 3,4-dichloro-2,5-dioxo-2,5-dihydropyrrole (3) [10 ,17] were prepared according to reported procedures .

1-Alkyl-3-arylamino-2,5-dioxo-2,5-dihydropyrroles [18] **(2 a-f):** To a boiling solution of 1 (a-f) (0.008 mol) in methanol (50 ml) was added the substituted anilines (0.016 mol) in methanol (10 ml). The mixture was heated under reflux for 30 min. It was then cooled and the resulting crystalline product was collected, filtered, washed with methanol and recrystallized from ethanol to give yellowish products (Table 1).

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Table (1): 1-Alkyl-3-arylamino-2,5-dioxo-2,5-dihydropyrroles (2 a-f)

№	R^1	R^2	m.p. °C	Yield %	M.F	Elemental analysis		
						%C	%H	%N
2a	H	H	189-92	85	$C_{16}H_{11}ClN_2O_2$ (298.5)			
2b	p-CH_3	p-CH_3	179-83	82	$C_{18}H_{15}ClN_2O_2$ (326.5)	66.22 65.95	4.63 4.50	8.58 8.40
2c	P-OCH_3	H	156-7	78	$C_{17}H_{13}ClN_2O_3$ (328.5)	62.10 62.16	3.95 3.98	8.52 8.50
2d	p-OCH_3	p-OCH_3	190-3	73	$C_{18}H_{15}ClN_2O_4$ (358.7)	60.27 60.27	4.21 4.18	7.80 7.50
2e	p-Cl	p-Cl	195-6	75	$C_{16}H_9Cl_3N_2O_2$ (367.6)	52.28 52.0	2.46 2.50	7.62 7.90
2f	p-Br	p-Br	205-6	81	$C_{16}H_9ClBr_2N_2O_2$ (455.5)	42.19 42.00	1.99 1.65	6.15 5.90

IR (KBr) Cm^{-1}, Major Frequencies: 3320 (NH) 2950 (CH) aliphatic, 3050 (CH) aromatic, 1680, 1725 (C=O) amide I band, 1600 (C=C). ^{1}HNMR (DMSO-d6) for compound 2a. δ = 7.1-7.6 (m, I0H, aromatic protons), 10 (s,1H,NH). Mass spectrometry for compounds 2a. M/e (298.5, M^+, 100% is M.W). ^{1}HNMR (DMSO-d_6) for compound 2d, 3.75 (s, 6H, OCH_3), 7-7.5 (m, 8H, aromatic protons), 9.8 (s, 1H, NH).

4-Chloro-l-(4-methylphenyl)-3-piperidin-l-yl 2,5-dioxo-2,5-dihydropyrroles (5): To a solution of N-(4-methylphenyl)3,4-dichloro2,5-dioxo-2,5-dihydropyrroles (1 g , 0.0039 mol) in EtOH (30 ml) was added piperidine (0.66 g , 0.0078 mol). The mixture was heated under reflux for 2h, cooled and diluted with water. The resulting solid was collected by filtration, washed with EtOH and recrystallized from EtOH as yellow crystals 0.9 mg, 76%, m.p 126-8 °C. IR (KBr) cm^{-1} 2950 (CH) aliphatic, 3050 (CH) aromatic, 1640, 1725 (C=O) amide I band. ^{1}HNMR (DMSO-d_6) δ 1.9 (m, 6H., piperidine),2.3(s, 3H, CH_3), 3.7 (m, 4H, piperidine, 7.1 (d,2H, aromatic protons), 7.55 (d, 2H, aromatic protons). $C_{16}H_{17}N_2O_2Cl$ (304.7); Elemental analysis, %C, %H, %N; Calcd 63.07, 5.62, 9.19; Found 63.20, 5.60, 9.30

1-(4-Methylphenyl)-3-[4-methylphenylamino]-4-piperidin-1-yl2,5-dioxo-2,5-dihydropyrroles [19] (6): To a solution of 2b (1.00 g, 0.003 mol) in absolute dioxane was added piperidine (0.78 g, 0.009 mol). The mixture was heated in an oil bath for 24h. The reaction was monitored by TLC every two hours until completion. The reaction mixture was concentrated under reduced pressure. The product was separated as a red crystalline substance, washed and recrystallized from chloroform/pet. ether: 0.7 g, 61%, m.p 162 °C. IR (KBr) (16) 3331(NH) 2929 (CH) aliphatic, 3050 (CH) aromatic 1644, 1697 C=O amide I band. ^{1}HNMR ($CDC1_3$) δ 1.5 (m, 6H piperidine, 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.4 (m, 4H, piperidine) 5.6 (s, 1H, NH), 7.1-7.5 (m, 8H, aromatic protons. $C_{23}H_{25}N_3O_2$(375.47); Elemental analysis, %C, %H, %N; Calcd 73.58, 6.71, 11.19, Found 73.50, 6.40, 10.90

1-Alkyl-3-alkyl amino-4-chloro-2,5-dioxo-2,5-dihydropyrroles[12] (4): A solution of dichloromaleimide (1.66 g, 0.01 mol) in ethanol 30 ml) was treated with the cyclohexyl amine (0.03 mol) in ethanol (10 ml). The mixture was heated on water bath at 60°C for 2h. The solution was concentrated under reduced pressure, then cooled. The target product was separated and collected by filtration and recrystallized from ethanol . M.F. $C_{16}H_{23}ClN_2O_2$ (310.81) , m.p. 150-151°C , IR (KBr) cm^{-1} 3350 (NH), 2923 (CH) aliphatic, 1615, 1705, C=O amide I band. ^{1}HNMR (DMSO-d_6) δ = 1 - 1.9 (m, 20H, CH_2 cyclohexyl), 3.7-3.9 (2H, cyclohexyl) 7.6 (s, 1H, NH). Elemental analysis, %C, %H, %N; Calc; 61.83, 7.45, 9.01 Found, 61.70, 7.50, 9.30

1-Aryl-3-arylamino-2,5-dioxo-2,5-dihydropyrroles (8 a-g) AND 2-Bromomaleamic acids (7) are prepared as reported[20].

A mixture of (7) (0.003 mol), aromatic amine (0.003 mol) and TEA (1 ml) in xylene (30 ml) was heated at 160 °C for 4h. The reaction mixture was concentrated under reduced pressure. The formed solid was collected by filtration and recrystallized from the suitable solvent (table 2).

Table (2): 1-Aryl-3-arylamino-2,5-dioxo-2,5-dihydropyrroles (8 a-g)

№	R^1	R^2	m.p °C	Yield %	Solvent of recrystallization	M.F / M.Wt
8a	H	H	235-6°C	56	acetic acid	$C_{16}H_{12}N_2O_2$ (264.28)
8b	H	p-CH_3	213-5°C	58	acetic acid	$C_{17}H_{14}N_2O_2$ (278.32)
8c	p-Cl	p-CH_3	267-8°C	55	acetic acid	$C_{17}H_{13}C1N_2O_2$ (312.76)
8d	p-CH_3	p-CH_3	225-7°C	53	acetic acid	$C_{18}H_{16}N_2O_2$ (292.35)
8e	p-OCH_3	p-OCH_3	221-3°C	52	acetic acid	$C_{18}H_{16}N_2O_4$ (324.31)
8f	p-Cl	p-Cl	244-5°C	49	chloroform/n-hexan	$C_{16}H_{10}C1_2N_2O_2$ (333.16)
8g	p-Br	p-Br	262-4°C	54	chloroform/n-hexan	$C_{16}H_{10}Br_2N_2O_2$ (420)

IR (KBr) cm^{-1} Major frequencies. 3280 (NH), 1650, 1720 (C=O) amide I band, 1600 (C=C), 3050 (CH) aromatic, 2950, (CH) aliphatic. ^{1}HNMR (DMSO-d_6) for compound 8a. δ = 5.8 (s,1H, CH vinylic, 9.9, (s, lH, NH), 7.1-7.6 (m, 10H, aromatic protons). Mass spectrometry for compound 8a. m/e, M^+, 264 (83.86%) is M.W. Elemental analysis, %C, %H, %N; Calcd 72.72, 4.57, 10.60, Found 72.12, 4.10, 10.60 ^{1}HNMR for compound (8b) (DMSO-d_6) δ 2.3 (s, 3H, CH_3), 5.8 (s, 1H, CH vinylic), 9.85 (s, 1H, NH) 7.1-7.6 (m, 9H, aromatic protons. Elemental analysis, %C, %H, %N; Calcd 73.38, 5.03, 10.07, Found 72.9, 4.8, 10.3

^{1}HNMR (DMSO-d_6) for compound (8c), δ = 2.3 (s, 3H, CH_3), 5.9, (s, 1H, CH vinylic), 10 (s, 1H, NH) 7.1-7.5 (m, 8H, aromatic protons). Elemental analysis, %C, %H, %N; Calcd 65.29, 4.18, 8.95, Found 65.55, 4.38, 9.00 ^{1}HNMR (DMSO-d_6) for compound 8d. δ = 2.3 (2 ,6H, $2CH_3$), 5.8 (s, 1H, vinylic CH), 9.9 (s, 1H, NH) 7.1-7.6 (m, 8H, aromatic protons). Elemental analysis, %C, %H, %N; Calcd 73.97, 5.47, 9.58, Found 74.1, 5.5, 9.7

l-Alkyl or aryl or aryl amino 4-chloro-2- hydroxy-5-oxo-2,5-dihydropyrrole (9 a-l): A solution of 2 a-f ,4 , 5, 6 and 8 a-g (0.01 mole) in ethanol (25 ml) dioxane (35 ml) mixture and sodium borohydride (0.03 mol) was allowed to stir at room temperature for the proper time (table 3). The completion of the reaction was noticed by the disappearance of the colored maleimides after complete reduction. Acetic acid (1 ml) was added to get rid of the excess sodium borohydride, the solvent was concentrated under reduced pressure using rotary evaporator. The product was collected by filtration, washed with water and crystallized from ethanol or dioxane (table 3).

Table (3):

No	R^1	R^2	X	m.p. °C	Yield %	Time	Solvent of crystalln.	M.F / M.wt	Calcd/ found		
									%C	%H	%N
9a	C_6H_5	C_6H_4	Cl	230	88	3h	Aq.Dioxane	$C_{16}H_{13}ClN_2O_2$ (300.73)	63.90 63.80	4.35 4.20	9.31 9.40
9b	p-$CH_3C_6H_4$	p$CH_3C_6H_4$	Cl	202-4	76	1h	-	$C_{18}H_{17}ClN_2O_2$ (328.785)	65.76 65.50	5.21 5.30	8.52 8.60
9c	P-$OCH_3C_6H_4$	p-OCH3C6H4	Cl	218	75	1h	-	$C_{18}H_{17}ClN_2O_4$ (360.775)	59.93 59.50	4.74 4.60	7.76 7.80
9d	P-$OCH_3C_6H_4$	C_6H_5	Cl	196-7	80	15h	Aq. Ethanol	$C_{17}H_{15}ClN_2O_3$ (330.757)	61.74 61.40	4.57 4.60	8.48 8.30
9e	P-ClC_6H_4	p-ClC_6H_4	Cl	207-8	80	1/2h	-	$C_{16}H_{11}Cl_3N_2O_2$ (369.623)	51.99 51.60	2.99 2.70	7.57 7.50
9f	C_6H_5	p-$CH_3C_6H_4$	H	222-4	80	2h	Aq. Dioxane	$C_{17}H_{16}N_2O_2$ (280.325)	72.8 72.80	5.75 5.60	9.99 9.80
9g	P-ClC_6H_4	P-$CH_3C_6H_4$	H	280	77	1.45h	-	$C_{17}H_{15}ClN_2O_2$ (314.767)	64.87 64.60	4.80 4.80	8.90 8.70
9h	C_6H_5	C_6H_5	H	248-50	83	3h	-	$C_{16}H_{14}N_2O_2$ (266.297)	72.17 71.90	5.29 5.50	10.52 10.40
9i	P-$CH_3C_6H_4$	p-CH3 C6H4	H	240-2	74	2h	-	$C_{18}H_{18}N_2O_2$ (294.35)	73.45 73.60	6.16 6.40	9.51 9.70
9j	P-$CH_3C_6H_4$	p-$CH_3C_6H_4$	$(CH_2)5N$	216-18	79	3.5	Aq. Ethanol	$C_{23}H_{27}N_3O_2$ (377.492)	73.18 72.90	7.20 7.50	11.13 11.0
9k	$(CH_3)5N$	p--$CH_3C_6H_4$	Cl	169-70	72	1h	-	$C_{16}H_{19}ClN_2O_2$ (306.787)	62.64 62.80	6.24 6.30	9.13 9.50
9l	Cycohexyl	Cycohexyl	Cl	168-70	61	4.5h	-	$C_{16}H_{25}ClN_2O_2$ (312.83)	61.43 61.50	8.05 7.90	8.95 8.50

IR (KBr) cm^{-1} Major frequencies disappearance of high imide carbonyl at 1725 and appearance of (OH) at 3200, 3380 (NH), 1660 (C=O), 3050 (CH) aromatic, 2950 (CH) aliphatic. ^{1}HNMR (DMSO-d_6) for compound (9a) δ = 6.25 (d, 1H, CH), 6.9 (d, 1H, OH), 7.1-7.7 (m, 10H, aromatic protons), 9.3 (s,1H, NH). Mass spectrometry for compound (9a) m/e (%) 300.5, (100%), M^+ is M.W, 282,5 (87%). ^{1}HNMR (DMSO-d_6) for compound (9b) δ = 2.3 (s, 6H, $2CH_3$), 6.15 (d, 1H, CH), 6.8 (d, 1H, OH), 7.1-7.5 (m, 8H, aromatic protons), 9.1 (s, 1H, NH). using D_2O showed disappearance of NH and OH.

^{1}HNMR (DMSO-d_6) for compound (9c) δ = 3.8 (s, 6H, OCH_3), 6.05 (d, 1H, CH), 6.8 (d, 1H, OH), 7.15 - 7.5 (m, 8H, aromatic protons)9.2 (s,.1H, NH) for compound (9d) δ = 3.75 (s, 3H, OCH_3); 6.1 (d, 1 H, CH), 6.9 (d, I H, OH), 7.1-7.5 (m, 9H, aromatic protons), 9.1 (s, 1H, NH). Mass spectrometry for compound (9e) , m/z (%) 370 (38.83%) is M.W), 353 (10.8%), 352 (40.41%). ^{1}HNMR (DMSO-d_6) for compound (9f) δ = 2.3 (s, 3H, CH_3), 5.3 (s, 1H, CH vinylic), 5.9 (d, 1H,CH), 6.75 (d, 1H, OH), 7-7.6 (m, 9H, omatic protons), 9.35 (s, 1H, NH). ^{1}HNMR (DMSO-d_6) for compound (9i) δ = 2.3 (s, 6H, CH_3), 5.3. (s, H, vinylic CH), 5.9 (d, 1H, CH), 6.75 (d, 1H, OH), 7-7.6 (m, 8H omatic protons), 9.35 (s, 1H, NH). ^{1}HNMR ^{1}HNMR (DMSO-d_6) for compound (9j) δ = 1.5 (im, 6H, piperidine), 2.2 (s, 6H, CH_3), 3.5 (4H,

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piperidine), 4.4 (s, 1H, NH), 6.05 (d,1H, CH), 6.6 (d, 1H, OH), 7-7.5 (m, 8H, aromatic protons).). ^{1}HNMR (DMSO-d_6) for compound (9k) δ = 1.5 (S, 6H, piperidine), 3.6 (4H, piperidine), 2.3 (s, 3H, CH_3), 6.1 (d, 1H, CH), 6.8 (d, 1H, OH), 7.1 (d, 2H, aromatic protons), 7.5 (d, 2H, aromatic protons). (DMSO-d_6) for compound (9l) δ = 1-1.9 (m, 20H, cyclohexyl), 3.5-3.6 (2H cyclohexyl adjacent to N), 6.25 (d, 1H, CH), 6.3 (d, 1H, OH), 6.6 (d, 1H, NH) .

1-Aryl-2-acetyloxy-3-arylamino-4-chloro-5-oxo-2,5-dihydropyrrole (10 a-d): To a solution of intermediate (9 a,b,d,i) (1 mol), in dry pyridine (7 ml) was added acetyl chloride (4 mol) in a dropwise fashion. The reaction was allowed to stir at room temperature for 2 days. The reaction was monitored by TLC until completion. The reaction mixture was filtered to remove pyridine HCl salt.

The filtrate was extracted with methylene chloride, washed with distilled water several times and dried over anhydrous magnesium sulphate. The solvent was concentrated under reduced pressure and the separated solid was purified by column chromatography using silica gel as stationary phase and ethyl acetate/chloroform (1:1) as eluting system.

Table (4): 1-Aryl-2-acetyloxy-3-arylamino-4-chloro-5-oxo-2,5-dihydropyrrole (10 a-d)

№	R^1	R^2	X	m.p °C	Yield %	M.F / M.Wt	Calcd/found		
							C%	H%	N%
10a	H	H	Cl	176	63	$C_{18}H_{15}ClN_2O_3$ (342.76)	63.08 62.80	4.41 5.16	8.17 7.90
10b	p-CH_3	p-CH_3	Cl	159-60	61	$C_{20}H_{19}ClN_2O_3$ (370.825)	64.78 65.00	6.15 4.90	7.55 7.20
10c	p-OCH_3	H	Cl	145-46	59	$C_{19}H_{17}ClN_2O_4$ (372.78)	61.22 61.00	4.59 4.50	7.51 7.40
10d	p-CH_3	p-CH_3	H	161-2	58	$C_{20}H_{20}N_2O_3$ (336.38)	71.41 70.90	5.99 5.60	8.32 8.20

IR (KBr) cm^{-1} Major frequencies 3290 (NH), 3050 (CH) aromatic, 2950 (CH) aliphatic, 1645 (C=O) imide, 1750 (C=O) ester, 1600 (C=C), disappearance of (OH). ^{1}HNMR ($CDCl_3$) for compound (10a) δ = 1.9 (s, 3H, CH_3) CH_3-C=O), 6.75 (s, lH, CH), 7.1-7.5 (m, 10H, aromatic protons). ^{1}HNMR ($CDCl_3$) for compound (10b) δ = 1.9 (s, 3H, CH_3) CH_3C=O, 2.3 (s, 3H, CH_3), 2.35 (s, 3H, CH_3) C_6H_4 CH_3, 6.6 (s, 1H, CH), 7-7.5 (m, 8H, aromatic protons , 9.2 (s , 1H , NH) . Mass spectrometry for compound (10c). m/e (%) 372 (1.30% is M.W.), 311.9 (100%), 43 (70.78%), 59 (3.54%). Mass spectrometry for compound (10d) m/z (%) 43 (51.15%), 59 (1.65%), 336 (0.60%) is M. W , 277.8 (16.63%).

2-Camphanoyloxy-4-chloro-l-(4-methylphenyl)3-(4-methylphenyl)amino-5-oxo-2,5-dihydropyrrole (11): A mixture of (9b) (0.25 g, 0.0007 mol), camphanoyl chloride (0.8 g, 0.0036 mol) in pyridine (7.5 ml) was allowed to stir at room temperature. A brown color appeared after 10 min. The reaction was continued for 48h. The mixture was filtered to remove pyridine HCl and the filtrate was diluted with water (20 ml). The reaction mixture was kept in the refrigerator for 2 days. The resulting turbid solution was extracted with methylene chloride (3 x 30 ml). The total extract was dried over anhydrous $MgSO_4$, concentrated to provide (0.28 gm, 0.55 mmol) 70% of the racemates. The solid was purified by column chromatography using silica gel and chloroform: ethyl acetate (1:1) as eluting system to afford crystalline substance (0.21 g, 53%).

^{1}HNMR ($CDCl_3$) for compound (11): δ 1.1 (s, 3H, CH_3), 1.5 (s, 311, CH_3), 1.75 (m, 1H), 1.9 (s, 3H, CH_3), 2.1 (m, 1H), 2.21 (m, 1H), 2.3 (s, 3H, *p*-CH_3), 2.32 (s, 3H, *p*-CH_3), 2.56 (m, 1H), 6.6 (s, 1H, CH), 7.1 (d, 2H, aromatic protons), 7.2 (d, 2H, aromatic protons), 7.26 (d, 2H, aromatic protons), 7.49 (d, 2H, CH aromatic proton) , 9.2 (s , 1H , NH). Ms m/z 508.2 M.W. 6.06, 328 (1.33), 312 (3.01), 198 (6.57), 181 (3.68), 180 (15.66), 179 (1.41), 127 (9.86), 125 (35.99), 111 (13), 93 (25.11), 83 (100), 79 (12.88), 69 (26.30), 67 (25.48), 57 (10.58), 55 (57.38), 45 (10.62), 43 (48.79), 42 (10.02), 41 (71.70), 39 (35.14), 32 (19.83). GC-MS. Two compounds with % area 31.27 and 68.73 at retention times 12.03 and 12.246, respectively.

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تشييد بعض مشتقات الماليميد عن طريق الاختزال الفراغى الموضعى والاختيارى باستخدام بورهيدريد الصوديوم

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تشييد بعض مشتقات الماليميد المختلفة وتم دراسة تأثير الصوديوم بورهيدريد على المشتقات المختلفة، ولقد ثبت أن الاختزال يحدث في مجموعة الكربونيل المجاورة لمجموعة الفنيل أمينو او الكيل امينو وذلك بإستخدام التحاليل الطيفية المختلفة، ولقد تم إثبات ذلك بالطرق الكيميائية وذلك بإلغاء مجموعة الكربونيل التي يحدث بها الإختزال عن طريق تفاعل 3،2- داى كلورومالييمدين- فنيل مع اورثو فينيلين دياميين وبعد ذلك إختزال الناتج بإستخدام الصوديوم بوروهيدريد ، وجد أنه لا يحدث تغيير وكذلك تم إثبات وجود مجموعة الهيدروكسيل الناتجة عن إختزال مجموعة الكربونيل بواسطة الصوديوم بوروهيدريد وذلك بتحويلها إلى إستر إما بالتسخين مع أستيك انهيدريد او تفاعلها مع أستيل كلوريد في بيريدين على البارد، ولقد وجد أن المركبات الناتجة عن الإختزال عبارة عن راسيمات حيث تم التأكد منها عن طريق تفاعلها مع مركب غير متماثل (كمفنك أسيدكلوريد) الذي أعطى مركبين وذلك من خلال ظهور بقعتين في TLc وكذلك بعض التحاليل الطيفية المختلفة.