

Synthesis of Some Five and Six-membered Fused Heterocycles and Study Their Expected Biological Activity

A.J. Al-Hamdany, T. Waleed Jihad

Dept. of Chem., College of Science, Univ. of Mosul, Mosul, Iraq

Abstract

A series of chalcones (1,3-diaryl-2-propen-1-one) (1-8) has been prepared via Claisen-Schmidt reaction and condensed with hydrazines, urea and thiourea through Michael-Claisen condensation to afford the corresponding fused heterocycles (9-16), their structures were supported in the light of spectral methods (UV, IR, $^1\text{H-NMR}$). The suggested mechanisms for these reactions were investigated on the basis of theoretical calculations of the heat of formation (H.F.) and the steric energy (S.E.).

Furthermore some of the reactants and the products had been tested for their expected biological activity.

Key words: Fused pyrazolines, pyrimidinones, pyrimidinethiones, chalcones.

Introduction

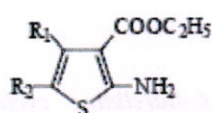
Pyrimidinones and pyrimidine thiones are well-known heterocycles

and wide uses caused the importance of their synthesis. A type of dihydropyrimidinone had been used as a combat malaria, and as a drug for the heart arrhythmia^[1] also used for prostate inflammation^[2]. The derivatives 3,4-dihydropyrimidine-2(1H)-ones had been carefully studied

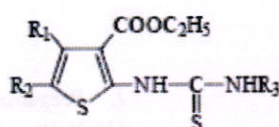
last few years owing to its pharmacological properties, it was found that it acts as an antihypertension and as neuropeptide antagonists^[3]. The alkaloid betzelladine^[4]

(which includes the dihydropyrimidine in its structural formula) seems to be an active inhibitor for HIVgp-120-CD4^[5].

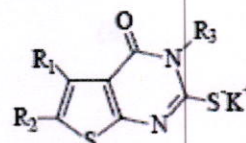
Many methods used to afford the fused pyrimidinone such as the condensation^[6] of 2-amino-3-ethoxy carbonyl-4,5-disubstituted thiophene (1) with alkyl or aryl isothiocyanate to give thienyl thiourea (2) which upon ring closure in the presence of KOH, EtOH and refluxing the mixture for (2-6) hours affords the fused heterocycle (3)



(1)



(2)



(3)

R_1R_2

$(\text{CH}_2)_4$

$(\text{CH}_2)_5$

$(\text{CH}_2)_4$

$(\text{CH}_2)_5$

R_3

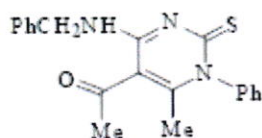
C_6H_5

C_6H_5

$p\text{-ClC}_6\text{H}_4$

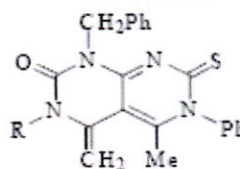
$p\text{-ClC}_6\text{H}_4$

While the addition^[7] of substituted 4-amino-5-acetyl-2(1H)-pyrimidine thione (4) to the substituted isocyanates leads to the formation of 1-benzyl-5-methyl-



(4)

R: Ph, Me



(5)

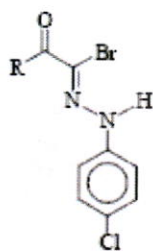
3,6-diphenyl-7-thioxo-3,4,6,7-tetrahydro-2(1H) pyrimido [4,5-d] pyrimidinone (5).

Pyrazolines found to possess many effective and known medical applications. They are used as an active antibiotic, antioxidants^[8]. The pharmaceutical importance of pyrazolines lay in the truth that they may be used effectively as an antibacterial, antifungal, antiviral and as an antiparasitic, as well as the use of them as an

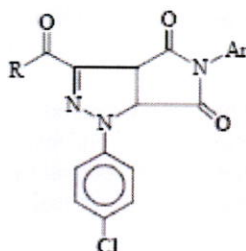
insecticidal, and antitubercular^[9]. It was also known that pyrazolines used as an anti-inflammatory agent, antidiabetic, and as an anaesthetic^[10]. Furthermore, several pyrazolines possess an important biological activity and found to be antimicrobial and possess an effective immunosuppressive property^[11].

The synthesis of fused pyrazolines arises from the treatment of hydrazonoyl bromide (6) with a suitable N-

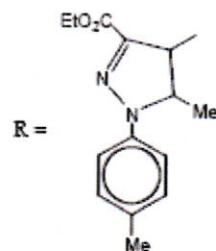
arylmaleimide in benzene contains Et_3N to afford pyrrolidino [3,4-d] pyrazoline^[12] (7).



(6)



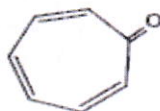
(7)



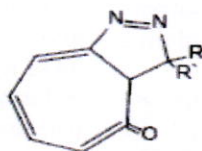
R =

the treatment of α,α -unsaturated ketone (8) with dimethyl azomethane through 1,3-dipolar cyclic

addition^[13] will afford the corresponding fused pyrazoline (9).



(8)



(9)

R = R' = H
R = R' = Me
R = Me, R' = H

Experimental

a. Materials

Melting points were determined by Electrothermal 1A 9000 Digital – series 1998 apparatus (uncorrected).

Ultra-Violet spectra were obtained using Shimadzu UV-Visible spectrophotometer UV-160.

Fourier-Transform Infrared spectra were recorded on Brucker Tensor spectrophotometer 2003 (Germany).

Nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were registered at 400 MHz Brucker spectrometer with using tetramethylsilane (TMS) as an internal standard, and CDCl_3 , DMSO-d_6 as solvents.

The theoretical calculations based on the data obtained from the minimized geometry were computed using semi-empirical AM1 module in the CS ChemOffice 2003 version 6.0 molecular modeling package.

The preliminary biological study was carried out in the Dept. of Biology, College of Education, Univ. of Mosul. The standard Kirby and Bauer method was used.

b. Starting materials

1. Preparation of 2,6-diarylidine cyclic hexanones (1t,2t,3t), 2-arylidine-6-methoxy-1-tetralone (4), 2,6-diarylidine cycloheptanone (5t), 2,7-diarylidine cyclooctanone (6t), 2-arylidine indanone (7t) and 2,5-diarylidine cyclopentanone (8t)

These compounds were prepared by stirring 0.0075 mole of the cyclic alkanone, indanon or tetralone with 0.0075 mole of the desired benzaldehyde, and 5 ml of 5% ethanolic sodium hydroxide in 25 ml ethanol in a 100 ml round-bottomed flask. After (3) hours the reaction mixture was filtered to get the crude precipitate which then washed several times by ethanol. The precipitate then dried and recrystallized from ethanol (Table-1, Table-2)

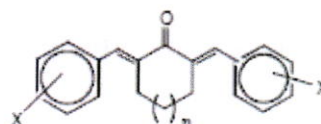
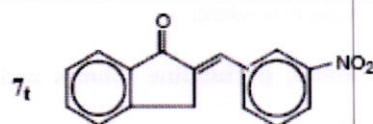
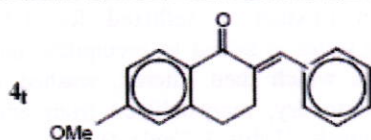


Table-1 Names and some physical properties of (1_t-6_t)

Cpd No.	Name	n	X	Recryst . From	m.p. (°C)	Yield (%)	colour
1 _t	2,6-Di(2,4-dichlorobenzylidene) cyclohexanone	1	2,4-DiCl	ethanol	182-184	26	Pale yellow
2 _t	2,6-Di(pchlorobenzylidene) cyclohexanone	1	4-Cl	ethanol	146-147	28	Distinct yellow
3 _t	2,6-Dibenzylidene cyclo hexanone	1	H	ethanol	119-120	19	Distinct yellow
4 _t	2-Benzylidene-6-methoxy-1-tetralone	-	H	ethanol	97-98	28	Pale yellow
5 _t	2,7-Di(4-Methoxy benzylidene) cycloheptanne	2	4-OCH ₃	ethanol	124-126	15	Pale yellow
6 _t	2,8-Dibenzylidene cyclooctanone	3	H	ethanol	113-116	38	White
7 _t	2-(3-Nitrobenzylidene)-1-indanone	-	3-NO ₂	Chlorof orm	208-210	50	Distinct violet
8 _t	2,5-(4-methoxy benzylidene) cyclopentanone	0	4-OCH ₃	carbon tetra chloride	214-217	13	Pale yellow

Table-2 Spectral data of (1_t-8_t)

Cpd No.	Structure	UV (CHCl ₃) λ _{max} , nm	IR (KBr), v cm ⁻¹						¹ H-NMR (CDCl ₃ , d6-DMSO) δ ppm				
			C=O	C=C	C≡C	C-O-C	C-Cl	C-NO ₂	δ ppm				
1 _t		280	1676	1623	1554	-	778	-	1.7 H ₂ 2H p	2.2 H ₁ , H ₃ 4 H t	7.3 ArH 6H m	7.7 Olefinic 2H s	-
2 _t		308	1666	1605	1575	-	732	-	1.71 H ₂ 2H p	2.22 H ₁ , H ₃ 4 H t	7.2-7.4 ArH 8H dd	7.8 Olefinic 2H s	-
3 _t		322	1661	1607	1573	-	-	-	1.72 H ₂ 2H p	2.2 H ₁ , H ₃ 4 H t	7.3 ArH 10H m	7.78 Olefinic 2H s	-
4 _t		326	1659	1605	1490	2840	-	-	2.3 H ₁ 2H t	2.5 H ₂ 2H t	3.8 OCH ₃ 3H s	7.1-7.8 Ar-H + olefinic 9H m	-

S: singlet , d: doublet , t: triplet , p: pentet , m: multiplet , dd: doublet of doublet

5 _t		314	1660	1599	1508	2834	-	-	1.95 H ₂ , H ₃ 4H p	2.3 H ₁ , H ₄ 4H t	-	7.1-7.3 ArH 10H m	7.5 Olefinic 2H s
6 _t		278	1676	1615	1462	-	-	-	1.7 H ₅ 2H p	1.9 H ₂ , H ₄ 4H p	2.2 H ₁ , H ₃ 4H t	7.1-7.2 ArH 10H m	7.5 Olefinic 2H s
7 _t		258	1703	1614	1529	-	-	1350	3.4 H ₁ 2H s	-	7.3-8.2 Ar-H 8H m	7.7 Olefinic 1H s	-
8 _t		360	1697	1597	1508	2831	-	-	2.3 H ₂ , H ₃ 4H s	3.83 2OCH ₃ 6H s	-	6.9-7.4 Ar-H 8H dd	7.7 Olefinic 2H s

Note: In order to get heterocycles by the treatment of the prepared diarylidene cyclanones, arylidene tetralone and indanone with active hydrogen compounds such as urea, thiourea and phenyl hydrazine, an eighteen trials had been attempted with no acceptable results, finally it was decided to use the following procedure:

c. Final products

Synthesis of pyrimidinones, pyrimidine thiones and pyrazolines (9_t-16_t)

General procedure:^[16, 17]

A 0.001 mole of the desired diarylidene cyclanone, the arylidene tetralone or indanone was brought to react with

0.003 mole of urea, thiourea or phenyl hydrazine in a 50 ml round-bottomed flask with 5 ml DMSO, then a drop-wise addition of 50% ethanolic NaOH cause the colour to be changed. Stirring is continued for (5) hours till the colour being dark brown (in case of no colour change the reaction mixture is refluxed for 1-5 hours). After cooling, water is added to precipitate the corresponding products which then filtered, washed with water and allowed to dry, recrystallized from ethanol or carbon tetrachloride. (Table-3, Table-4).

Table-3 Names and some physical properties of 9_t-16_t.

Cpd No.	Name	X	m.p. (°C)	Yield (%)	colour
9 _t	8-(2,4-Dichlorobenzylidene) cyclohexano[1,2-d]-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidin-2(1H)-one	2,4-DiCl	113-115	25	Distinct brown
10 _t	7-(4-Chlorobenzylidene) cyclohexano[1,2-c]-3-(4-chlorophenyl)-2-phenyl-Δ ² -pyrazoline	4-Cl	126-128	86	Distinct yellow
11 _t	8-Benzylidene cyclohexano[1,2-d]-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione	H	133-135	22	Yellow
12 _t	8-Methoxy tetralino[1,2-d]-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione	H	81-83	26	Black
13 _t	9-(4-Methoxy benzylidene) cycloheptano[1,2-d]-4-(4-methoxy phenyl)-3,4-dihydropyrimidin-2(1H)-one	4-OCH ₃	111-113	24	Distinct yellow
14 _t	10-Benzylidene cyclooctano[1,2-d]-4-phenyl-3,4-dihydropyrimidin-2(1H)-one	H	103-105	17	Milky
15 _t	Indano[1,2-d]-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one	3-NO ₂	196-199	24	Pale brown
16 _t	6-(4-Methoxy benzylidene) cyclopentano[1,2-c]-3-(4-methoxy phenyl)-2-phenyl-Δ ² -pyrazoline	4-OCH ₃	129-132	51	Brown

□²: the site of double bond in pyrazoline ring

Table 4- Spectral data (UV, IR, $^1\text{H-NMR}$) for compounds (9_t-16_t)

Cpd No.	Structure	UV (CHCl ₃) λ_{max} , nm	IR (KBr), ν cm ⁻¹							¹ H-NMR (CDCl ₃ , d ₆ -DMSO) δ ppm							
			N	C-Cl	C-O-C	C=O	C=C	N-H	C=C								
9 _t		248	-	776	-	1679	1597	3443	1556	1.75 H ₄ 2H p	2.45 H ₅ , H ₆ 4H t	2.65 H ₆ 1H s	4.33 OCH ₃ 1H s	-	7.4 Ar-H 6H m	7.65 NH 2H s	
10 _t		266	-	778	-	C=N 1699	1591	3441	1516	1.65 H ₅ 2H q	1.9 H ₄ 2H p	2.2 H ₃ 1H q	2.6 H ₆ 2H t	3.0 H ₆ 1H d	4.6 OCH ₃ 1H s	7.3 Ar-H 13H m	
11 _t		242	-	-	-	C=S 1175	1601	3385	1547	1.5 H ₄ 2H q	1.85 H ₅ , H ₆ 4H t	-	4.51 H ₆ 1H s	5.2 OCH ₃ 1H s	7.4 Ar-H 10H m	2.3 NH 2H s	
12 _t		320	-	-	-	C=S 1138	1603	3444	1585	2.9 H ₄ 2H t	3.1 H ₅ 2H t	3.9 OCH ₃ 3H s	4.5 H ₆ 1H s	-	7.4 Ar-H 8H m	2.15 NH 2H s	

13 _t		304	-	-	2933	1660	1599	3445	1506	2.0 H ₄ , H ₅ 4H p	2.75 H ₅ , H ₆ 4H t	-	3.8 OCH ₃ 1H s	5.1 H ₆ 1H s	7.2 Ar-H 8H dd	7.37 NH 1H s
14 _t		248	-	-	-	1669	1596	3243	1493	1.5 H ₅ 2H p	1.98 H ₄ , H ₅ 4H m	2.6 H ₆ , H ₇ 4H m	3.0 H ₆ 1H s	4.9 OCH ₃ 1H s	7.3 Ar-H 10H m	7.5 NH 2H s
15 _t		250	1349	-	-	C=S 1200	1603	3356	1528	2.6 H ₅ 2H s	2.7 H ₄ 1H s	-	-	-	7.3 Ar-H 8H m	2.8 NH 2H s
16 _t		242	-	-	2835	C=N 1698	1597	3444	1511	1.8 H ₅ 2H q	1.9 H ₄ 2H t	2.65 H ₆ , H ₇ 2H m	3.8 OCH ₃ 6H s	3.95 OCH ₃ 1H s	7.0 Ar-H 13H m	-

Preliminary biological study:

Preface

The dibenzylidene cyclic pentanones and dibenzylidene cyclic hexanones were found to possess an inhibitory effect to Glutathione-Transferase and had been used to examine the sub-acute and sub-chronic toxicity and ulcerogenicity^[18]. On the other hand pyrimidinones and pyrimidine thiones found to possess an antipyretic, anti-inflammatory properties and used as herbicides as well^[19], while pyrazolines was found to possess an effective biocidal against arthropods, especially insects^[20].

In the present work, it is decided to investigate 4_t, 12_t and 13_t and study their inhibitory effect on the growth of two kinds of bacteria Grampositive staphylococcus aureus and Gram-negative E.Coli by using disc diffusion method, (the standard Kirby and Bauer method)^[21].

The isolates were isolated and identified in the Dept. of Biology, College of Education, Univ. of Mosul.

Procedure

Of each bacterial species a loopful were cultured in a nutrient broth and incubated at 37°C for 14-16 hr, then eventually distributed on the nutrient agar by using a sterile swab. The plates were incubated at 37°C for 30 min.

A Whatmann No. 1 type filter paper discs were distributed on the agar and a certain equal (1 mg/ 1 ml) or (1 ml / 1 ml) of the compound per solvent (DMSO) was added. The controls here were Stryptomycin, Vancomycin and Gentamycin for comparison. The plates were then incubated at 37°C for 18-24 hr. Prescott^[22] method was used to illustrate the sensitivity of the studied compounds. The results were interpreted according to the report of (W.H.O.), the resistive (R) represented the diameter of inhibition <11 mm, while the sensitive (S) was over 16 mm, but moderately sensitive (MS) was regarded when zone inhibition is (12-16) mm.

Table-5 Inhibition effect of compounds (4_t, 12_t, 13_t) on growth of staphylococcus aureus and Escherichia coli.

Compound number		Test organism	
		E.coli	St. aureus
4 _t		R	S
12 _t		R	R
13 _t		R	R
Stryptomycin	Control	MS	-
Vancomycin		-	S
Gentamycin		R	R

R= resistive

S= sensitive

MS= moderately sensitive

Results and Discussion

The structures of the starting materials (1_t-8_t) and the final products (9_t-16_t) were known and supported by the spectral data (UV, IR, ¹HNMR) as well as some physical properties (see Tables 1-4). Figure (1)

The biological activities of sample compounds 4_t (□□-unsaturated carbonyl compound), 12_t (pyrimidine thione) and 13_t (pyrimidinone) had been investigated compared with some common antibiotics (Stryptomycin, vancomycin and gentamycin).

The compound number (4_t) showed a sensitivity towards staphylococcus aureus while E.coli resisted it, but both St. aureus and E. coli displayed a resistivity against 12_t and 13_t (Table-5).

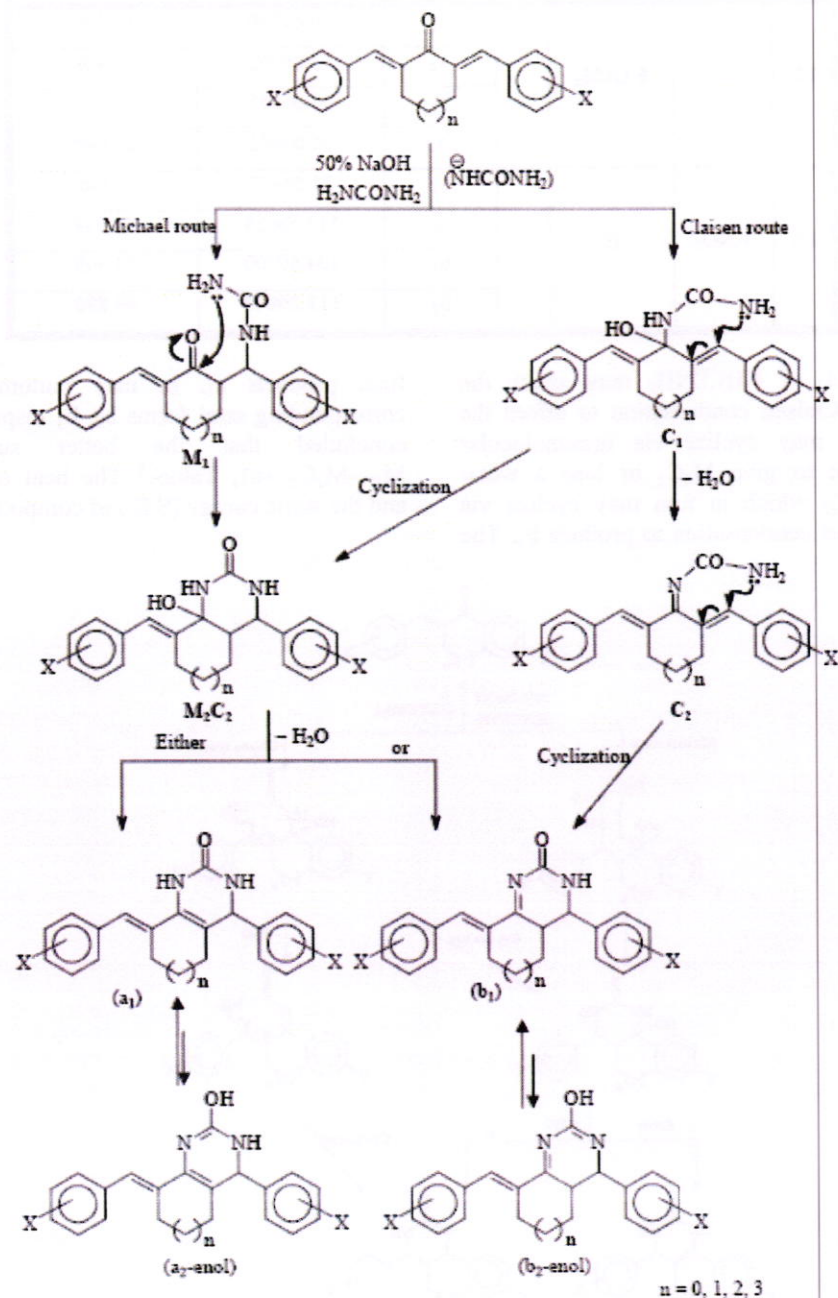
According to the spectral data showed on Tables 1-4, the suggested mechanism for the reaction of diarylidine cyclanones with urea (Scheme 14 1) and the reaction of 2-arylidine substituted tetralones with thiourea (Scheme-2) may proceed via Michael or Claisen routes.

i- Michael route

The anion NHCONH₂^[23] or NHCSNH₂(24) may attack the □carbon of the cyclanone or tetralone

Table-6 The heat of formation (H.F.) and steric energy (S.E.) for the compounds (9_t, 11_t, 13_t, 14_t)

Cpd No.	X	n (C=O C=S)	Form	Heat of formation H.F. (Kcal/mole)	Steric energy S.E. (Kcal/mole)
9 _t	2,4-DiCl	1 (C=O)	a ₁	16.87415	17.169
			a ₂	27.67488	24.803
			b ₁	25.98332	23.973
			b ₂	38.31419	35.076
11 _t	H	1 (C=S)	a ₁	94.51598	8.669
			a ₂	101.21819	15.560
			b ₁	103.78250	27.943
			b ₂	103.75983	22.550
13 _t	4-OCH ₃	2 (C=O)	a ₁	-39.11283	45.601
			a ₂	-24.68983	51.687
			b ₁	-27.12673	50.204
			b ₂	-16.04993	68.913
14 _t	H	3 (C=O)	a ₁	39.82879	28.954
			a ₂	53.60824	32.085
			b ₁	93.22442	75.534
			b ₂	59.30983	49.877



Scheme (1): The Mechanistic route of the condensation of diarylidene cyclanones with urea and thiourea

To afford the intermediate (M_1) via Michael condensation. M_1 in turn may cyclize via intramolecular Claisen condensation to afford M_2C_2 which upon the elimination of water molecule may give either a_1 or b_1 . Both a_1 and b_1 may tautomerize to produce the

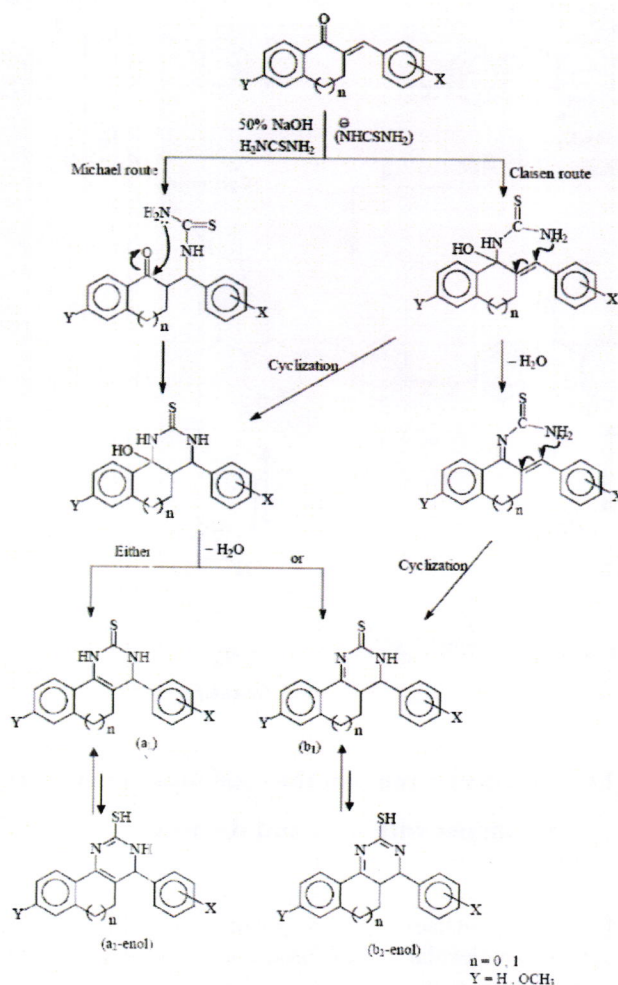
corresponding enol forms. From the values of the heats of formation (Table-6 and Table-7) it was found that a_1 , b_1 are both more stable than a_2 -enol, b_2 -enol respectively, and hence will predominate.

ii-Claisen route

Cpd No.	X	Y	n	Form	Heat of formation H.F. (Kcal/mole)	Steric energy S.E. (Kcal/mole)
12 _t	H	6-OCH ₃	1	a ₁	46.81520	18.299
				a ₂	53.86702	25.469
				b ₁	55.68165	27.712
				b ₂	56.04481	25.646
15 _t	3-NO ₂	H	0	a ₁	52.24477	9.256
				a ₂	113.55058	41.534
				b ₁	104.69700	53.509
				b ₂	111.29649	49.898

The anion NHCONH_2 or NHCSNH_2 may attack the carbonyl carbon via Claisen condensation to afford the intermediate C_1 . C_1 may cyclize via intramolecular Michael condensation to give M_2C_2 or lose a water molecule to afford C_2 which in turn may cyclize via intramolecular Michael condensation to produce b_1 . The

final products a_1 , b_1 may tautomerize to the two corresponding enol forms a_2 , b_2 respectively. It may be concluded that the better suitable route is $\text{M}_1 \rightarrow \text{M}_2\text{C}_2 \rightarrow \text{a}_1$, Table-7 The heat of formation (H.F.) and the steric energy (S.E.) of compounds (12_t, 15_t)



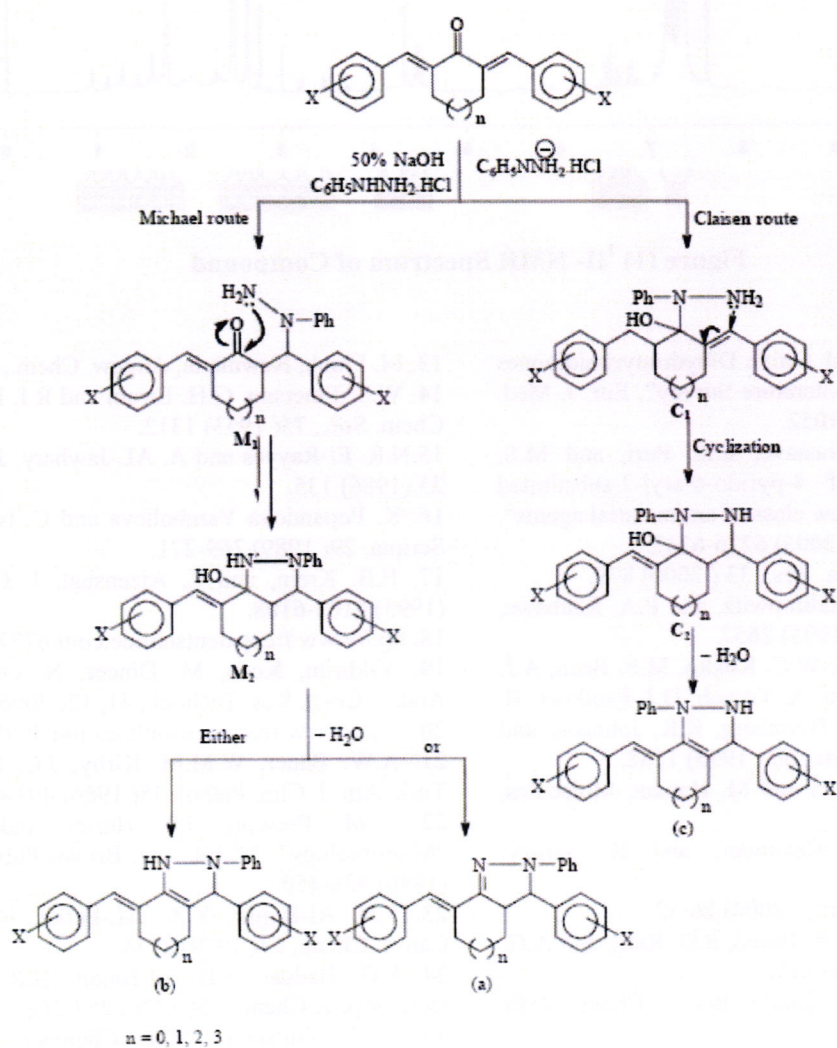
Scheme (2) The mechanistic route of the condensation of tetralone and indanone with thiourea

rather than $\text{C}_1 \rightarrow \text{C}_2 \rightarrow \text{b}_1$ (Tables 6, 7). The reaction of diarylidene cyclanones with phenyl hydrazine may pass through two possible routes (Scheme 3) Michael or Claisen.

The most probable route is $\text{M}_1 \rightarrow \text{M}_2 \rightarrow \text{a}$ rather than $\text{M}_1 \rightarrow \text{M}_2 \rightarrow \text{b}$ nor $\text{C}_1 \rightarrow \text{C}_2 \rightarrow \text{C}$. (Table-8).

Table-8 The heat of formation (H.F.) and steric energy (S.E.) for the compounds (10_t, 16_t)

Cpd No.	X	n	Form	Heat of formation H.F. (Kcal/mole)	Steric energy S.E. (Kcal/mole)
10 _t	4-Cl	1	a	128.06594	34.508
			b	138.05215	36.060
			c	166.58262	28.514
16 _t	4-OCH ₃	0	a	80.61823	61.079
			b	99.30460	71.186
			c	94.75544	49.870

**Scheme (3)** The mechanistic route of the condensation of diarylidene cyclonone with phenyl hydrazine

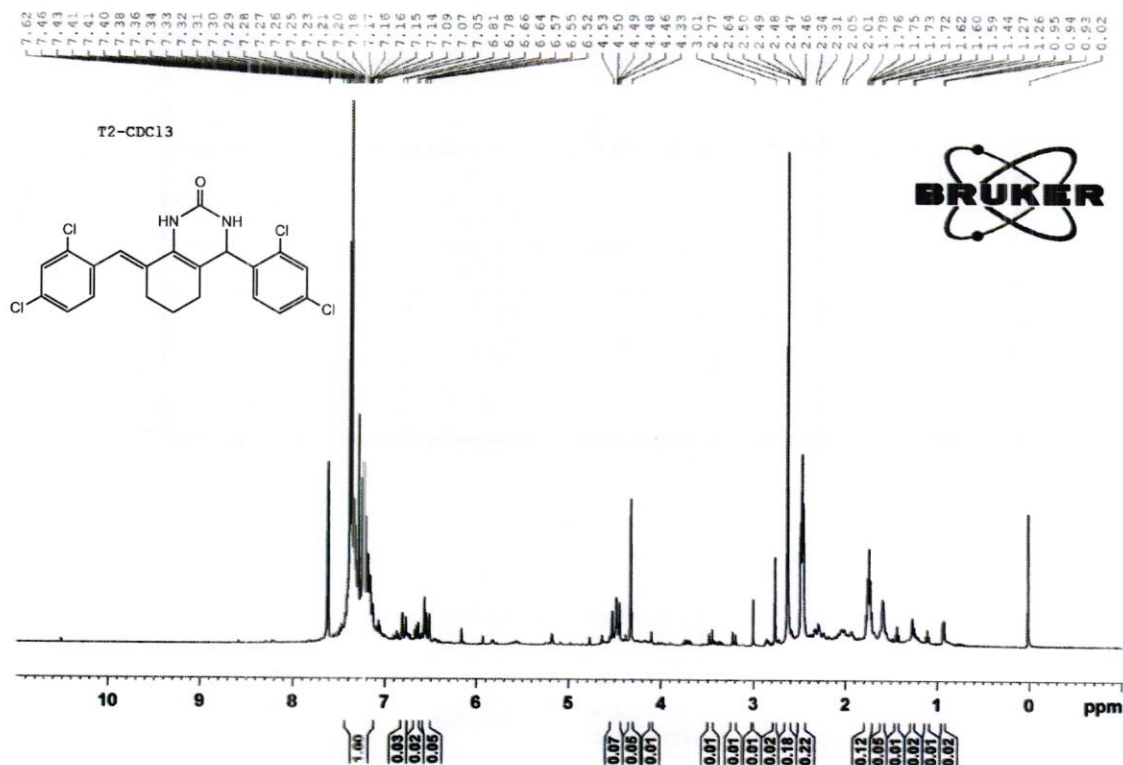


Figure (1) ^1H - NMR Spectrum of Compound

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تشبيد بعض الحلقات غير المتجانسة الخماسية والسداسية ودراسة الفعالية البايولوجية المتوقعة لها

عبد الوهاب جعفر الحمداني ، تهاني وليد جهاد

قسم الكيمياء كلية العلوم جامعة الموصل ، موصل ، العراق

الملخص

تم تحضير سلسلة من الجالكونات (1₁-8₁) (1,3-ثنائي اريل -2-جروبين-1-ون) من خلال تفاعل كلينزن-شميدت حيث تم تكثيفها مع الهيدرازينات اليوريا والثايويوريا من خلال تفاعل مايكل-كلينزن لاعطاء الحلقات غير المتجانسة المندمجة المقابلة (9₁-16₁) ، وتم دعم تراكيبها في ضوء الطرق الطيفية (H-NMR¹ , I.R ,U.V). وتم التحقق من الميكانيكيات المقترحة لهذه التفاعلات استنادا الى الحسابات النظرية لحرارة التكوين (H.F.) وطاقة الاعاقة (S.E). اضافة لذلك بعض المتفاعلات والنواتج قد تم فحصها لبيان فعاليتها البايولوجية.