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Synthesis and Biological Study of Some New Pyrrolidines

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الخلاصة

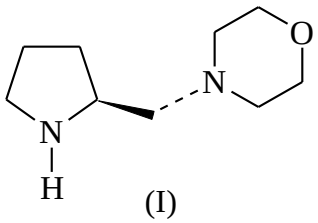
تم تحضير سلسلة من قواعد شيف N–ارايليدين بنزايل امين (1–6) من خلال الاضافة الحلقية الانيونية نوع 1،3 وتحت ظروف قاعدية قوية تمت اضافتها على البنزوكوينون لتنتج البايروليدينات الجديدة الملتحمة (7–12). تم استعمال الطرق الطيفية لاثبات تراكيب النواتج الجديدة. ان الميكانيكيات المقترحة لاكثر التفاعلات تم التحقق منها نظريا اعتمادا على قيم حرارة التكوين وطاقة الاعاقة للنواتج . ان الفعالية البايولوجية الاولية لهذه النواتج على نوعين من البكتريا هما صبغة كرام الموجبة و صبغة كرام السالبة قد تم اختبارها كذلك.

ABSTRACT

A series of Schiff bases N-Arylidene benzylamie (1-6) have been prepared, and through 1,3-anionic cycloaddition under strong basic conditions were added to benzoquinone to afford the fused new pyrrolidines (7-12). The spectroscopic methods were used to confirm the structures of the new products, as well as melting points. The suggested mechanisms of most of the reactions were investigated theoretically on the basis of the values of heat of formation and steric energy of the products. A preliminary biological activity on *E. coli* and *Staph. aureus* of the products had also been tested.

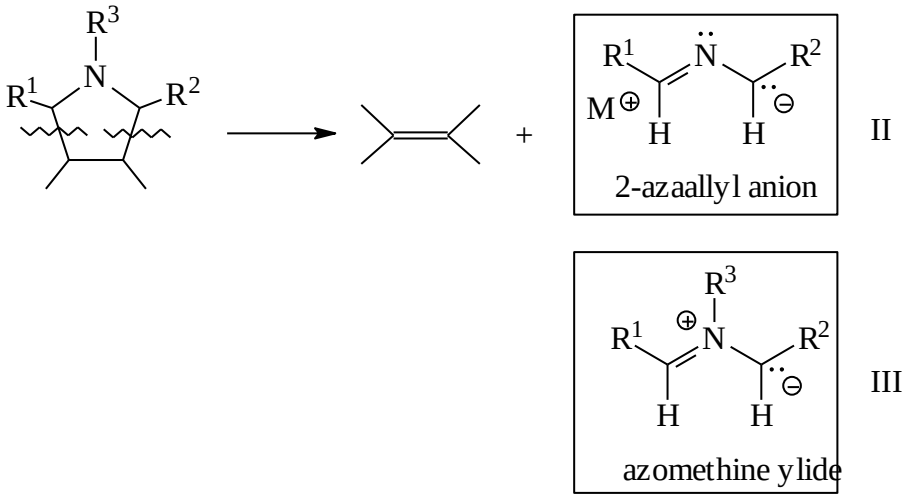
INTRODUCTION

Pyrrolidines are a series of important compounds which reflect an intriguing structures and potent biological activity, which concentrates about among their ability to inhibit a variety of glycosidases[(1)]. Many experiments were performed using (s)-1-(2-pyrrolidinyl methyl) pyrrolidine as catalyst in catalytic direct asymmetric Michael reactions[(2)]. It was found that (s)-2-(morpholinomethyl) pyrrolidine (I) was the most effective catalyst in terms of stereochemical control. Providing a high level of diastereoselection and good enantioselection[(3)].



(I)

Cycloadditions are of a clear significance, when considering methods to ring-containing structures, since they have the advantages of synthetic efficiency and potentially high stereoselectivity. Among the possible cycloadditions strategies that might be used to make a pyrrolidine ring. So it was chosen to display disconnection of the C2/C3 and C4/C5 bonds, thus need to use either azaallyl anion (II) or an azomethine yield (III) in a (□4s + □2s) cycloaddition with an alkene[(4)].



Scheme (1): (3+2) Approaches to the pyrrolidine

It is worth mentioning that there are many compounds known as a natural and others are synthetic and both are biologically active[5], in addition to chiral auxiliaries and ligands[6] containing a pyrrolidine moiety, and consequently new methods providing access to enantiopure derivatives of this heterocycle are of current interest, that is to say that the synthesis of pyrrolidine ring is of a great importance, due to its biological interest.

EXPERIMENTAL

I. Instrumentation:

1. Melting points were determined by Electrothermal 9000 Digital-Series 1998 Apparatus (uncorrected).
2. Boiling points were determent by inverted capillary in a Thiele tube using paraffin colourless[7] oil.
3. Ultraviolet spectra were obtained using SPECORD 200 UV-Visible double beam Analytikjena Spectraphotometer.
4. Fourier-Transform Infrared (FT-IR) spectra were recorded using Thermo-Nicolte Fourier-Transform Infrared (FT-IR) Spectrophotometer.
5. The data obtained from the minimized geometry were used for the theoretical calculations. The theoretical calculations were computed using semi-empirical AM_1 module in the CS ChemOffice molecular modeling package.

II. Synthesis:

Preparation of Schiff bases (1-6):

General procedure[8]:

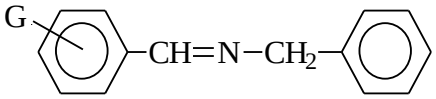
Benzylamine (1.1 ml ,0.01 mole) was heated with (0.01) mole of substituted benzaldehyde in(10)ml n-butanol for (10) min. in a 100 ml beaker at (100) °C. The reaction mixture then cooled and the product being purified (the solid products were recrestallized from ethanol whereas the liquid products were distilled for purification). The structure, names, some physical properties and spectral data were illustrated in Table (1). The spectra data were in a good agreement with the reported values[9,10].

Preparation of fused heterocycles (7-12):

General procedure[11]:

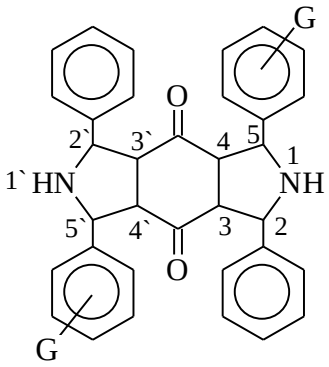
A mixture of (10) mmole Schiff base and (0.55 gm, 5 mmole) mmole of benzoquinone was stirred in the presence of (3) ml of 50% alcoholic sodium hydroxide solution. and dimethyl sulfoxide (10) ml stirring continued for (2) hrs at room temperature, then the mixture allowed to stand overnight. A (100) ml of water was added, the separated precipitates were filtered, washed with water till the filtrate being clear and neutral. The solid products were dried and recrystallised from methanol-ethyl acetate. Table (2) illustrates physical properties and spectral data of products.

Table (1): Structures, names, physical and spectral data of Schiff bases (1-6)



Comp. No.	G	Name	m.p. (°C)	Yield (%)	UV ($CHCl_3$) λ_{max} (nm)	IR (KBr) ν (cm^{-1})	
						C=N	Others
1	H	N-Benzylidene benzylamine	275-276 Liquid	70	292	1660	-
2	o-Cl	N-(o-Chlorobenzylidene) benzylamine	139-140	40	290	1665	750 C-Cl
3	p-Br	N-(p-Bromobenzylidene) benzylamine	39-41	85	336	1668	700 C-Br
4	p-NO_2	N-(p-Nitrobenzylidene) benzylamine	50-52	60	338	1675	1500 asym. 1340 sym. N⋯O
5	p-OCH_3	N-(p-Methoxybenzylidene) benzylamine	202-204	75	290	1650	1145 C-O-C
6	2,4-di-OCH_3	N-(2,4-Dimethoxybenzylidene) benzylamine	125-126 Liquid	60	339	1645	1140 C-O-C

Table (2): Physical and spectral data of products (7-12)



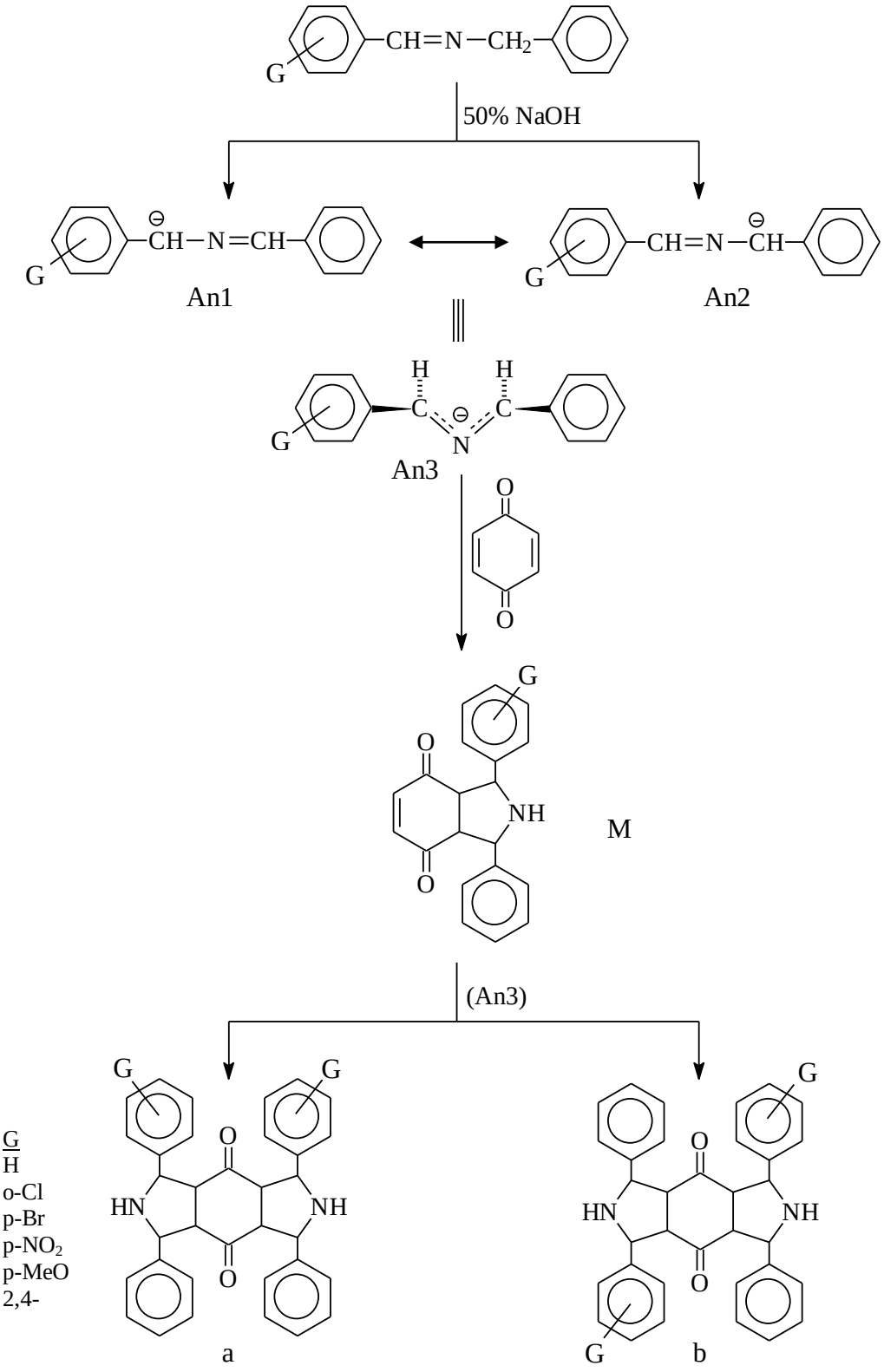
Comp. No.	G	Name	m.p. (°C)	Yield (%)	UV ($CHCl_3$) λ_{max} (nm)	IR (KBr) ν (cm^{-1})		
						C=O	N-H	NH_2^+
7	H	Bis-[2,5-diphenyl pyrrolidino]-[4,3-b:4`,3`-e]-1,4-cyclohexadione	144-146	58	346	1637	3062	2360
8	o-Cl	Bis-[2-phenyl-5-(o-chlorophenyl) pyrrolidino]-[4,3-b:4`,3`-e]-1,4-cyclohexadione		30	340	1628	3385	2361
9	p-Br	Bis-[2-phenyl-5-(p-bromophenyl) pyrrolidino]-[4,3-b:4`,3`-e]-1,4-cyclohexadione	82-84	50	294	1698	3060	2360
10	p-NO_2	Bis-[2-phenyl-5-(p-nitrophenyl) pyrrolidino]-[4,3-b:4`,3`-e]-1,4-cyclohexadione	190-192	45	303	1633 N⋯O 1527	3383	2360
11	p-OCH_3	Bis-[2-phenyl-5-(p-methoxyphenyl) pyrrolidino]-[4,3-b:4`,3`-e]-1,4-cyclohexadione	142-144	35	291	1633	3235	2360
12	2,4-di-OCH_3	Bis-[2-phenyl-5-(2`,4`-dimethoxyphenyl) pyrrolidino]-[4,3-b:4`,3`-e]-1,4-cyclohexadione	158-160	45	297	1670	3421	2360

RESULTS AND DISCUSSION

The condensation of substituted benzaldehydes with benzylamine in n-butanol leads to the corresponding imines[9,10] (Schiff base 1-6 which had been confirmed depending on spectral data).

The UV spectra showed a range of (290-339) nm which agree with the literature values[12] for such compounds. On the other hand the IR spectra manifested a range of stretching vibrations of (1675-1645) cm^{-1} related[13] to the carbon-nitrogen double bond (νC=N). Table (1) illustrates the spectral data of the prepared Schiff bases in addition to structures, names and melting points.

The suggested mechanism[14] of this cycloaddition may pass through the following route (Scheme 1): The strong alkaline medium abstracts the acidic hydrogen from -CH_2- in the Schiff base to produce the anion An1 which may resonate to give the anion An2. The equivalent hybrid of An1 and An2 is An3 (Scheme 2).



Comp. No	G
7	H
8	o-Cl
9	p-Br
10	p-NO_2
11	p-MeO
12	2,4-

Scheme (2): 1,3-Anionic cycloaddition of Schiff bases to benzoquinone

Table (3): Heat of formation (H.F) and steric energy (S.E) of final products (7-12)

Comp. No.	G	H.F (Kcal/mole)	S.E (Kcal/mole)
7	H	75.67686	32.041
8a	o-Cl	67.84922	36.677
8b	o-Cl	69.36917	37.992
9a	p-Br	85.13160	32.364
9b	p-Br	85.36518	32.868
10a	p-NO_2	82.25546	60.478
10b	p-NO_2	83.03306	62.642
11a	p-MeO	- 0.22045	56.436
11b	p-MeO	- 0.21508	56.537
12a	2,4-DiMeO	- 70.90630	79.403
12b	2,4-DiMeO	- 69.79603	80.163

One mole of An3 is added to one mole of benzoquinone may lead to the production of the intermediate M through 1,3-anionic cycloaddition. The carbon-carbon double bond of M is still ready for another 1,3-anionic cycloaddition of another mole of An3 to afford either a or b. The heat of formation of 8a is (67.84922) Kcal/mole and the steric energy is (36.677) Kcal/mole while 8b has a heat of formation of (69.36917) Kcal/mole and steric energy of (37.992) Kcal/mole. It may be concluded that according to the values of heat of formation (a) may be predominate among (b) (Table 3). On the light of spectroscopic evidences, the structures of final products (7-12) may established (Table 2).

The UV spectra showed a range of (294-346) nm for the wavelengths at maximum absorption which lies in the range of similar compounds[15].

The FT-IR spectra showed a range of strong absorption bands for carbonyl group (1670-1600) cm^{-1} which fits the values for quinones[16] or saturated diones[17], while broad bands in the range of (3421-3062) cm^{-1} related to the stretching vibration[18] of N-H. The pyrrolidine exhibits a weak basic properties which may lead to the protonation of N-H group to afford the cation NH_2^+ that reflects an absorption[19] band range of (2361-2360) cm^{-1}. For compound number (10) a strong band seemed at (1527) cm^{-1} which is related to the symmetric stretching of nitrogen-oxygen bond of nitro group (□N⋯O).

It is concluded from the values of the heat of formation of the final products (Table 3) that the type of the substituent on the aromatic ring of the Schiff base may play an important role in controlling the rate of the reaction. The electron withdrawing groups (deactivators) in the electrophilic aromatic substitution such as (o-Cl, p-Br, p-NO_2) needs

values of heat of formation in the range of (±10) Kcal/mole compared with the unsubstituted rings whereas electron-donating groups (activators) such as (p-OMe, 2,4-DiMeO) exhibits a negative values of (H.F), i.e: occurred spontaneously.

Biological activity of pyrrolidines:

I. Preface:

Some pyrrolidines possess biological activities such as anticancer[20], antiaids[21] and anti-inflammatory properties, while others, however, have analgesic[22] and anti pyretic values[23].

In the present work, it is decided to choose some synthesized fused pyrrolidines to test their inhibition activity on the growth of two kinds of bacteria (Gram positive and Gram negative using the sensitivity test by disk diffusion method)[24].

II. Disk diffusion method:

In nutrient broth a loopful of each type of bacteria species was cultured and incubated at (37) °C for (18-24) hours. The colloid is then diluted by normal saline and compared with the standard test tube Macferland No. 1, which prepared by the addition of (0.6) ml of barium chloride, the volume is completed to (10) ml by the addition of 0.1% sulfuric acid in a manner permit the solution to contain about 1×10^8 cell/ml of the colloid, then evenly distributed on the nutrient agar by using a sterile swab.

The plates were incubated at (37) °C for (30) minutes for the diffusion to be occurred. To study the biological activity of the pyrrolidines on the growth of bacteria, different concentrations of pyrrolidines were prepared (100, 50, 25, 12.5) mg/ml. The filter paper (Whatmann No. 1) disc were distributed on the agar and a certain equal amounts (1 mg/1 ml) or (1 ml/1 ml) of the compound per solvent (DMSO) were added[25].

The control here were standard antibiotics like Cephalothine and Chloramphenicol, the comparison depends on the diameter of the inhibition zone. The tested compound will be considered as sensitive (S) if the diameter of its inhibition zone is equal or larger than that of the standard antibiotic, and it is resistant (R) if its diameter of the inhibition zone is less than the antibiotic's zone. It was found that *S. Aureus* seemed sensitive to Cephalothine with inhibition zone of (17) mm, while *E. coli* was sensitive to Chloramphenicol and has a diameter of (22) mm. The tested compounds, however, reflect a different effects. So it seemed that compounds (1-5) with different concentrations have no considerable effect on *E. coli* and it was resistant to these and the diameters of inhibition zones were (7, 8, 8) mm for (5-7) respectively. While *S. aureus* was resistant to compounds (1-3) in different concentration, but for (4-7) at 100 mg/ml, the inhibition zones were (7, 9, 9, 9) respectively.

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