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Isolation of Piperine compound from Black Pepper Seeds and Synthesis of it some new derivatives

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ABSTRACT

An efficient isolation of Piperine(1) from the black Pepper seed ethanolic extract was reported . the pure isolated piperine was reacted with urea thiourea ,hydrazine , phenyl hydrazine ,and hydroxyl amine hydrochloride to give pyrimidinone , pyrimidinethione pyrazolin, phenylpyrazolin and oxime derivatives (2a-2g). All the reported compounds were confirmed by the available physical and spectral methods.

Key words : piperine , piperine derivatives ,heterocyclic compounds and natural products.

Introduction

Natural or synthetic piperine [1] are known to exhibit various biological activities. They have been reported to possess antioxidant, antimalarial, anti Leishmanial, anti-inflammatory, antitumor and antibacterial activity. The presence of a reactive α , β-unsaturated keto function in piperine is found to be responsible for their antimicrobial activity. Due to interesting activity of various substituted pyrimidinone as biological agent [2]. Pyrazolines [3]derevitives have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis [4], [5], [6].

Pyrazolines and phenyl pyrazoline derevitives [7] are well known and important nitrogen containing five-membered heterocyclic compounds and various methods have been worked out for their synthesis. Several it have been found to possess considerable biological activities, which stimulated research activity in this field.

Piperine occurs in pepper . espicially unripe black pepper (pipernigrum) and in the kernel of the ripe fruit [white pepper].The piperine content of black pepper being (4-6%) percent.It is present in relatively smaller amounts in other piper species

e.g.,piperlongum about (5percent).piper lowong about (1.5 percent).[8], [9]. It was first prepared by oersted in 1819 and crystallies in monoclinic crystals having the flavor and taste of black pepper.[10]. It is an optically inactive crystalline solid (mp=128-129c°) and posses very weakly basic character. The sharp taste of pepper is however not due to piperine but an isomeric compound called chavicine due to its weak basic nature, it forms salts only with strong mineral acids and these salts are readily hydrolysed by water. Piperine is much less toxic than most alkaloids.It acts as a local irritant. [8], [11]. It is paractically insoluble in water but soluble in common organic solvents .It is tasteless and has no physiological importance, It exhibits Cis-trans isomerism.

When piperine was heated with alkali ,it gets hydrolysed to yield pipreric acid and piperidine From the hydrolysis products of piperine Figure(1).

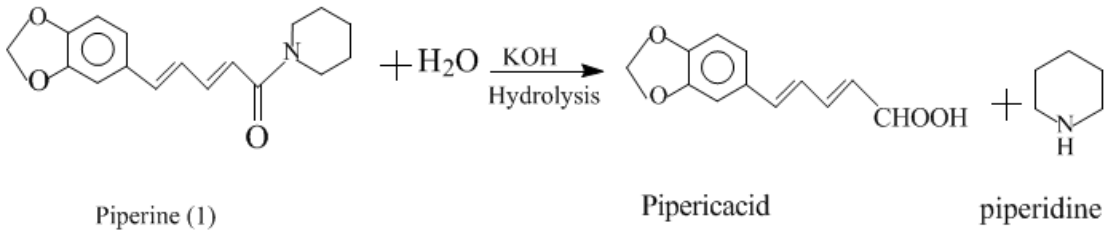


Fig.(1)

It was evident that piperidine and piperic acid moieties were linked by an amide (-CONH-) type linkage.[17].

The acid derived from hydrolysis of the alkaloid have a trans configuration , piperine have been used as a flavouring additive in brandy and as an insecticide for house flies ,it was obtained by warming the well powdered black pepper with milk of lime ,followed by its evaporation to dryness and finally extracted the residue with ether [8].Alternatively ,it caused be isolated from black pepper by extracting the ground black pepper with alcohol and the extract evaporated to dryness. The residue was extracted with ether and the ethereal solution was washed successively first with sodium hydroxide and then with water. The remaining ether solution is evaporated and the residue was crystallized from alcohol to yield piperine . [13] Historically ,pepper have been thought to cure many diseases such as cancer , malaria and cholera ,however; today mostly used as afood additive [15]. Black pepper may be the revolutionary vitiligo treatment one of the promising vitiligo treatment relies on piperine , the main compound in black pepper to stimulate pigment cells (melanocytes) reproduce faster than repigmenting the white patches. At present ,piperine research focus more on mice than on human but never theless the scientists were getting involved in to vitiligocause can only lead to positive result, [16].

EXPERIMENTAL

Melting points (M.P) were measured on Electrothermal ,Gallenkamp melting point apparatus and were uncorrected . Infrared (FT-I.R) spectra were recorded as (KBr) disc using a Bruker , FT. IR ,spectrophotometer tensor ,27 .Ultraviolet (UV) spectra were performed on shimadzu UV- Visible spectrophotometer U.V-1650 PC using ethanol as a solvent .

General method:

Isolation of piperine(1) [8], [17]

A finely ground black pepper seed (30g) was mixed with(350mℓ) of (95%) ethanol . the mixture was kept under reflux for 3hrs. The mixture was cooled ,filtered and evaporated under vacuum .The resulting oil extracts was reacted with 2N alcoholic potassium hydroxide solution with cooling , then filtered and the solid precipitate recrystalized from ethanol to give apale yellow powder m.p.(128-129 cº) Lit. (128-129 cº) [1] ;yield (6%.); IR: (C=O)amid (1660 cm^{-1}) , (C=C)(1630cm^{-1}) and (C-O-C) (1245cm^{-1}1050cm^{-1})sy. and assy. ;UV: at λ_{max} (420 nm).

General method: Synthesis3,4–Dihydro-4-(1'(2"-propylene-1",2" Dioxomethylene benzene)-6-(1-piperidin-1-ylpyrimidine -2-(1H) one . (2a) ; 3,4-Dihydro-4-(1',(2"-propylene -1',2"-Dioxomethylene benzen) 6-(1-pipridin-1-ylpyrimidine -2- (1H) thione.(2b) [17].

A mixture of (5.3g-0.025 mole),(urea or Thiourea)(3.0g) (0.05 mole)(5mL)(50%)aqueous sodium hydroxide solution in (75 mL) ethanol was refluxed for 2hr then cooled to room temperature and pouried on water (125 mℓ), allowed to stand for (15 minutes) then filtered under reduced pressure. the filtrate was cooled in an ice bath and acidified with concentrated hydrochloric acid.The precipitate formed was filtered off ,washed with water then recrystllized from ethanol to give titled compound (2a) 75% yield with m.p(230c°) and (2b) 69% yield with m.p(180-182c°).

General method: Synthesis of oxazoline (2e) [23]

Hydroxyl amine hydrochloride (0.017mole) was dissolved in (5mℓ) water then (0.008 mole) of piperine added to (10 mL) of pyridine . The mixture was refluxed for (4hrs).in an acidic medium , (15 mℓ ,10s% acetic acid).

Then the mixture was kept overnight ,filtered dried in open airspace and recrystalized from benzene to give white powder m.p (238-240c°)(25%yield).

General method:

Synthesis of 3-(2'-propylene-3'-1",2"-dioxo methylenebenzen -5- (1-piperydine)pyrazoline(2f) ;3-(2'-propylene -3'-(1",2" dioxomethylene benzen)-5-(1- piperydine)-1- phenyl pyrazoline (2g).

A mixture of (25mℓ) benzene (6mℓ) of 50% sodium hydroxide solution,(0.0015mole)of(TBAB, Tetrabutylammonium bromide) and (0.005mole) of hydrazine (2f)or phenyl hydrazine (2g)was strirred for (10 minutes) to afford a homogenous mixture ,then (0.005 mole) of the piperine added (25-40c°)for (2hrs) with stirring until no more colourchang . Theoranic layer was separated , washed with water several times until it pH became neutral ,the organic layer was dried with anhydrous magnesium sulfate ,the final filtarate was evapourated under vacume to remove the solvent (benzen). The solid product was recrystallized from methanol to give whit product of (2f) (51%) m.p (160-165c°) and (2g)(55%) m.p (218-220c°)

RESULTS AND DISCUSSION

The α , β–unsaturated carbonyl compounds are considered as principle nucleus to synthesize many important heterocyclic organic compounds , through their reaction with other different compounds urea , thiourea , hydroxyl amine hydrochlorid ,hydrazine and phenyl hydrazine .

The extracts of black pepper seed with alcoholic potassium hydroxide was found mainly to contain piperine as shown by spectroscopic evidences Table(1).

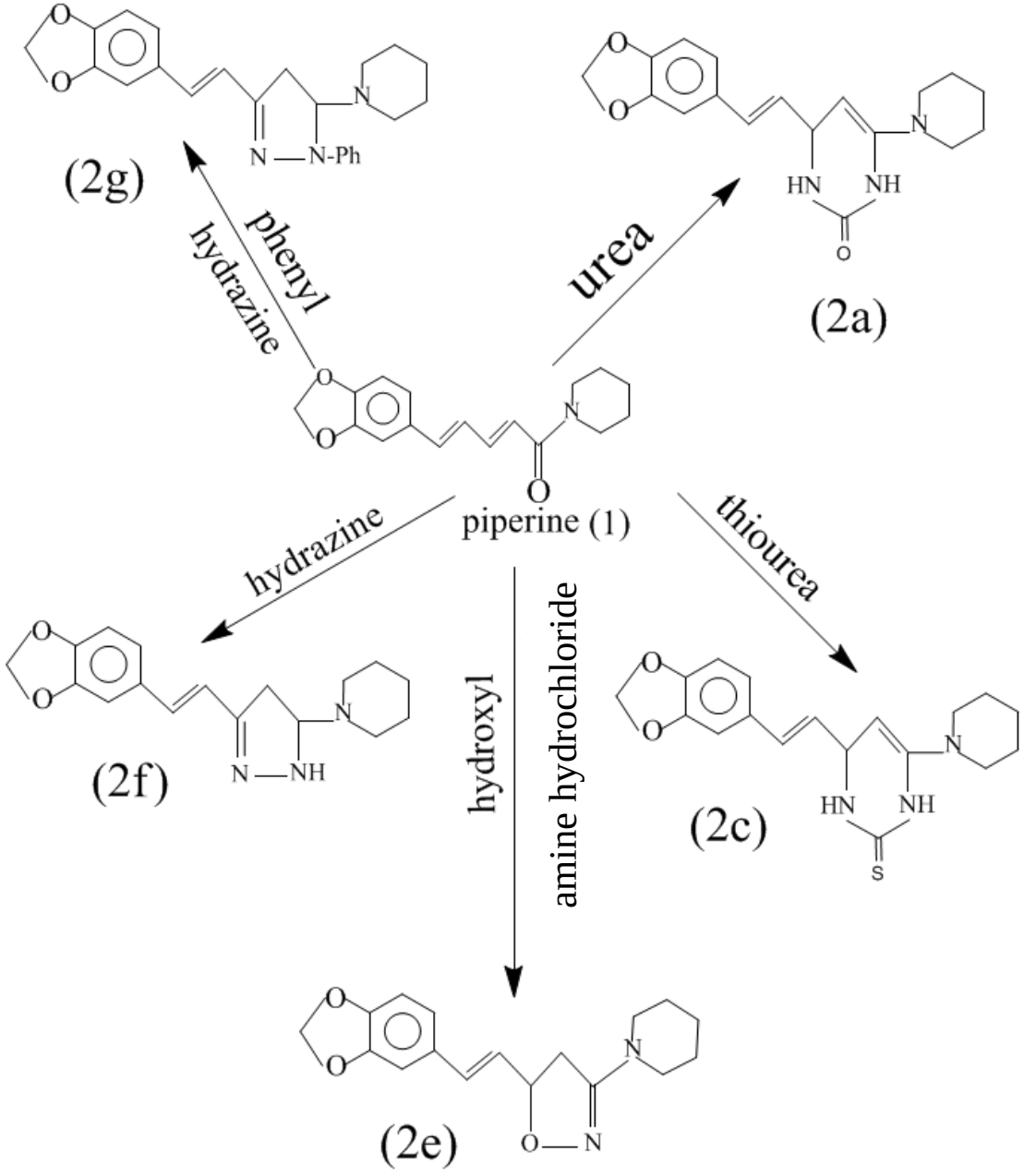
The IR showed strong absorption at (1660 cm^{-1}) which corresponds to (υ C=O).While the band at (1630 cm^{-1}) belong to the υ C=C [19] .the C-O -C stretching band appear at (1245cm^{-1},1050cm^{-1}),sy. and assy.

The U.V spectrum shaw an absorptionan absorption and high at (420nm).which indicate colored compound .

Shceme (1) give Reaction piperine(1) with ammonia derivatives (2a-2g).

Table (1): Spectral data of Piperine derivatives .

Comp. No.	Derivitives	UV $CHCl_3$ λ max(nm)	FT.IR KBr (cm^{-1})			
			C=O	C-O-C	C=C	N-H
2a	Urea	330	1720	1240sym 1050 assym	1630	3400
2c	Thiourea	360	C=S 1250	1240 sym 1140 assym	1620	3300
2e	$NH_2OH.HCl$	450	C=N 1637	1245 sym 1050assym	1620	--------
2f	Hydrazine	361	C=N 1655	1245 sym 1050assym	1620	N-H 3300
2g	Phenyl hydrazine	335	C=N 1670	1245 sym 1050assym	1630	--------



Scheme (1) : Reaction piperine (1) with ammonia derivatives (2a-2g)

General method:

Synthesis pyrimidinones (2a,2b)

Piperine was condensed with different acidic hydrogen compound , Generally speaking the condensation reaction of piperine may proceed by nucleophilic attack at the more electro positive carbon C1 atom (1,2-addition) or at C_3 atom results (Michael, 1,4-addition) according to mechanisms of these reactions were suggested on the basis of the identification of the products and the calculated heat of

formation (H.F.) and steric energy (S.E.) obtained from the minimized geometry for intermediates , transition states and the products of these reactions.

Piperine has been condensed with Urea under 50% aqueous sodium hydroxide solution in solvent ethanol to afford :
3,4-Dihydro -4-1̀(2̀̀-propylene(3̀(1̀̀,2̀̀.dioxo methylene benzene)) 6-piperidin-1-pyrimidine -2(1H) one. (2a,2b)

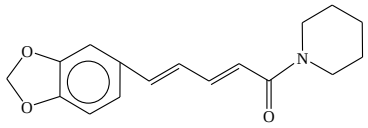
The structure of the product is established by spectroscopic evidences (Table 1) the FT.IR spectrum shows a strong absorpition band at (1720 cm^{-1}) for (υc=o)and a band at (1630 cm^{-1}) for (υc=c), the board band at (3400 cm^{-1}) for (υ N-H) and a band of υ C-O-C at(1240 cm^{-1},1050cm^{-1}),Sy.and assy.

The UV spectrum[19]exhibits ablue shift from the UV (420nm) piperine(1) ,to the λmax of (2b) which it was (330 nm) due to the destruction of conjugation .

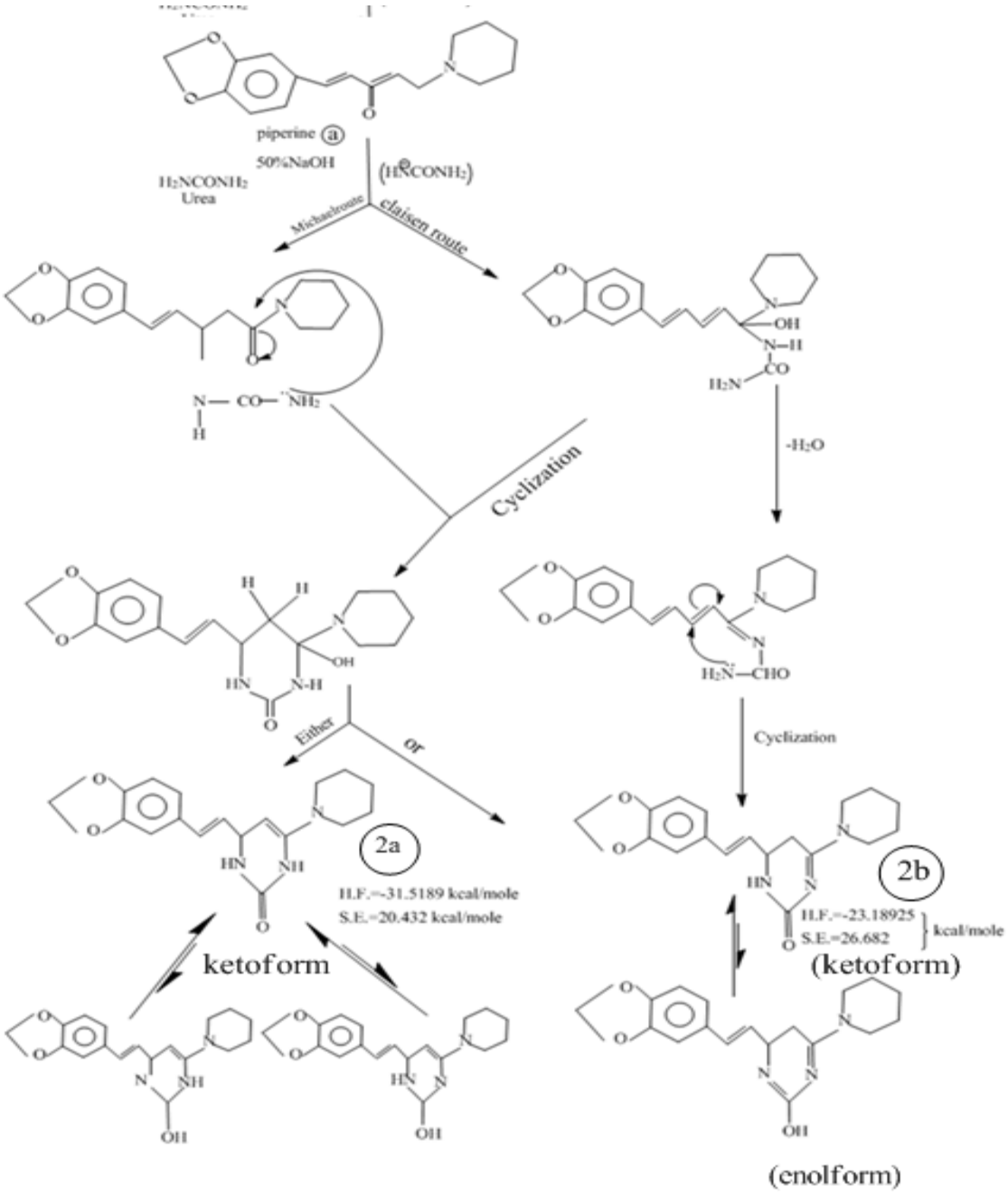
According , it could be suggested that the possible routes for the reaction are illustrated in scheme (2) the Mechanism may proceed via Michael or claisen routes by Michael route (H.F.)=(-31.51898) kcal/mole for compound (2a) and (S.E.)=(20.432)kcal/mole is more stable than compound (2b) proceed by claisen route (H.F)=(-23.18925) kcal/mole and (S.E.)=(26.682)kcal/mole

To synthesize pyrimidinthione (2c,2d) piperine has condensed with thiourea under 50% sodium hydroxide to afford :3,4-Dihydro -4- 1`,(2``-propelyene-3`-(1``,2``-dioxometheylene benzene 6-piperidine ,pyrimidine -2-(1H)-thion (2c,2d).

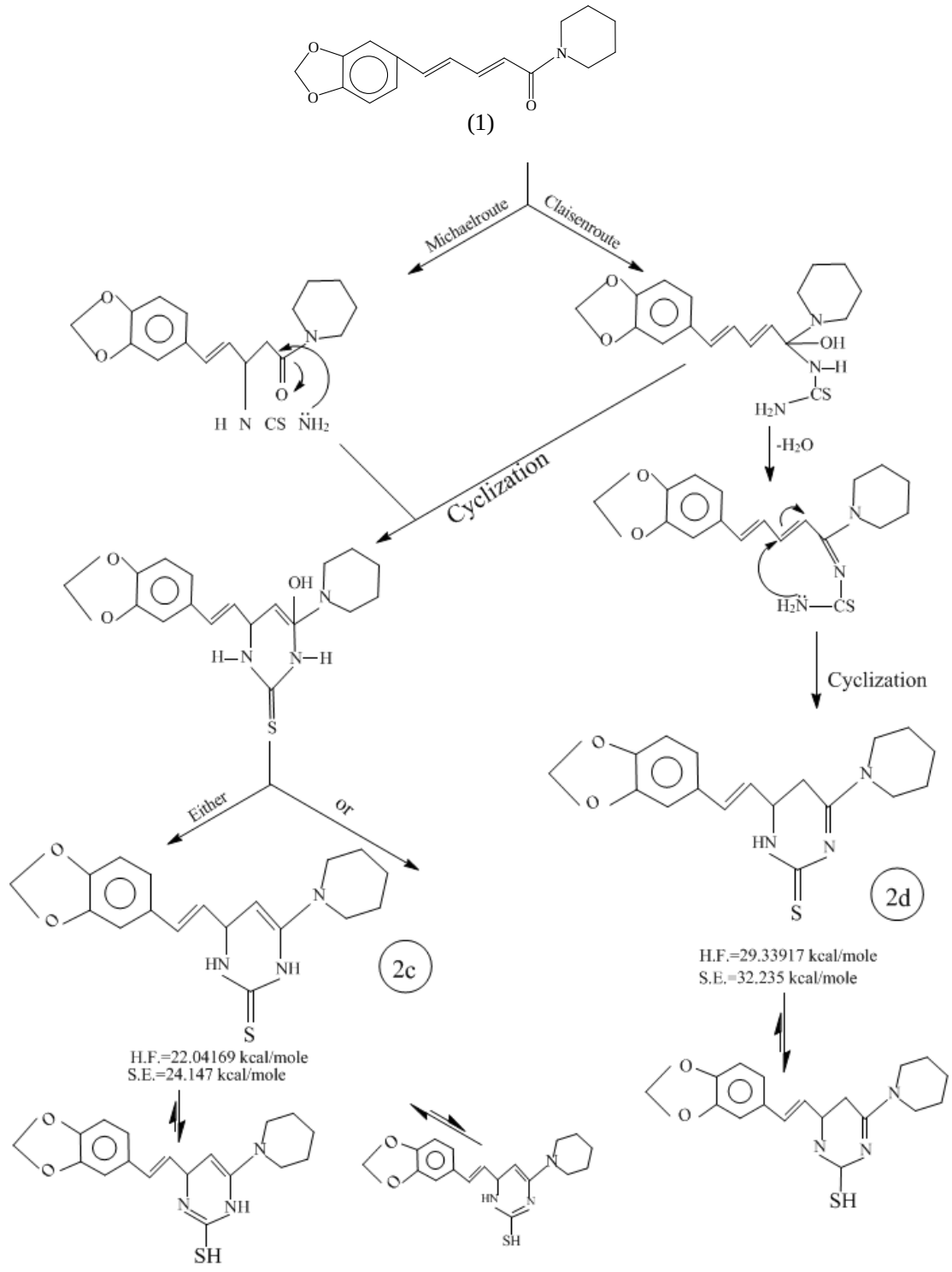
The product identidfied on the bases of spectroscopic evidences (Table(1) , the IR spectrum) [26] exhibits four distinct band appeard at (1250,(1240,1140),1620 and 3300)cm^{-1} attributed to υ C=S, υ C-O-C sy. And assy., υ C=C and υ N-H (broad) respectively.



Piperine (1)



Scheme(2): Mechanism of pyrimidenones (2a,2b)

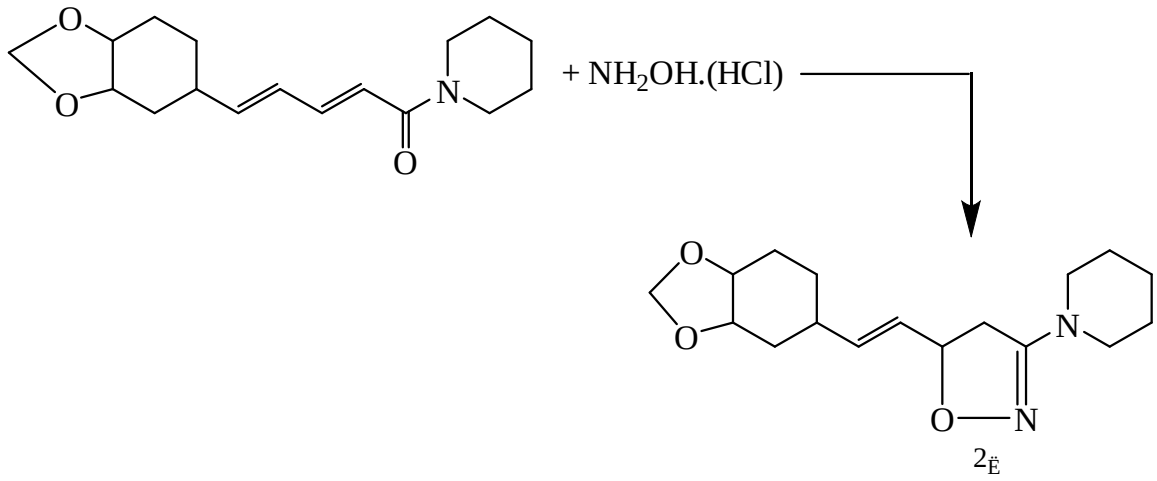


Scheme (3): Mechanism of pyrimidenthiones (2c,2d)

The (U.V) spectrum [22] main fests a red shift at λmax (360nm) due to the conjocation of compound (2c).the suggested mechanisim for the reaction of piperin(1) with thiourea is illustrated in scheme (3).

Synthesis of Oxazoline (2e)

The comp.(1) has been reacted with hydnoxylaminhydrochlorid by pyridine with reflux to obtain oxime which its white precipitate this reaction is given by this equation shceme(4)

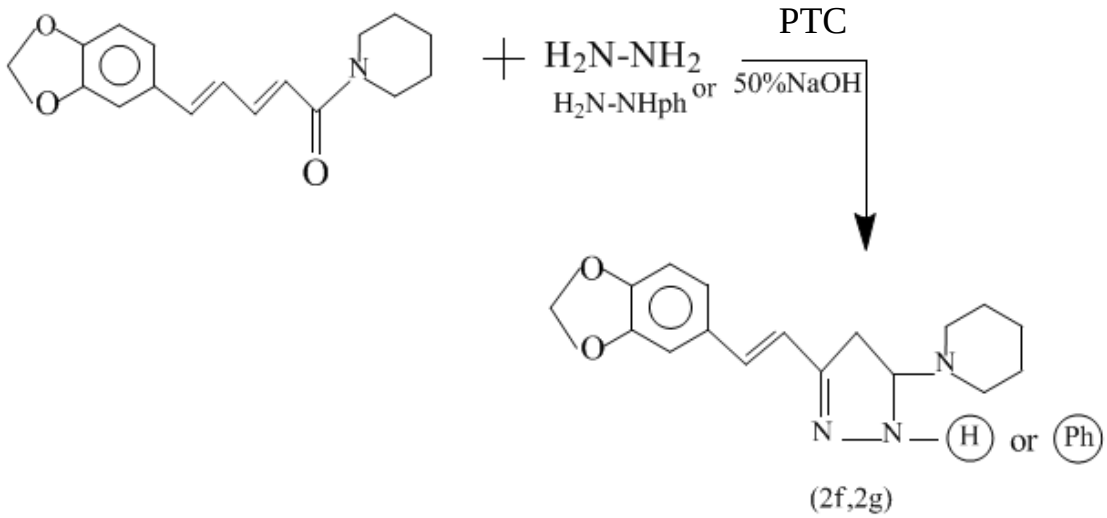


Scheme 4: Reaction comp(1) with hydroxylamine hydrochloride(2e)

The product identified on the basis of spectroscopic evidences (table 1). The IR spectrum [27] exhibits υ C=N band at (1637 cm^{-1}) this value is high compared with piperine due to the conjocated between oximegrop and the double bond , υ C=C at 1620 and υ C-O-C at (1245 cm^{-1} ,1050 cm^{-1})sy. and assy. The UV spectrum main fests red shift λ max (450 nm) due to conjoucate.

Synthesis of pyrazoline (2f) and phenyl pyrazoline (2g)

Comp `.(1) has been reacted with hydrazine and phenyl hydrazine under phase transfer catalysis condition (PTC) with sodium hydroxide 50% to afford : 3-(2`-propylene-3`-(1``,2``-dioxomethylene benzene -5-(1-piperydine) pyrazoline (2f) and 3-(2`-propylene)-3`-(1``,2``-dioxo methylene benzen)-5-(1- piperydine)1-phenyl pyrazoline (2g) show in scheme (5).



(2f,2g)

Scheme (5): reaction comp.(1)with hydrazine(2f)and phenyl hydrazine (2g)

The IR showed strong absorption (2f) at (1655 cm^{-1}) which corresponds to υ C=N. while the band at (1620 cm^{-1}) belongs to the υ C=C , the C-O-C stretching band appear at (1245,1050)cm^{-1} sym. And assym. and υN-H (3300cm^{-1}) (2g) IR showed absorption at (1670 cm^{-1}) which correspond to υ C=N. while the band at (1630 cm^{-1}) belong to the υ C=C, the υ C-O-C appear at (1245,1050)cm^{-1}sy.and assy. The UV spectrum shows (361nm) 2f and (335 nm)2g.

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عزل مركب البايبرين من بذور الفلفل الأسود وتحضير بعض المشتقات الجديدة

هبة أمين إبراهيم
جامعة الموصل \ كلية العلوم

تاريخ الاستلام:11\3\2013 تاريخ القبول:17\6\2013

الخلاصة:

تم عزل مركب البايبرين من مستخلص الايثانولي لبذور الفلفل الاسود ،ثم مفاعلة البايبرين المعزول مع اليوريا والثايويوريا والهيدرازين والفنيل هيدرازين والهيدروكسيل امين هايدرو كلوريد للحصول على مشتقات البريميدون والبريميدينثايون والبايرازولين والفنيل بايرازولين والاوكسازولين (2a-2g). وشخصت جميع المركبات المحضرة باستخدام الطرق الفيزياوية والطيفية المتوفرة.

الكلمات المفتاحية :البايبرين ، مشتقات البايبرين ، المركبات الحلقية غيرالمتجانسةوالمركبات الطبيعية ،البايرازولين والفنيل بايرازولين ،الاوكسازولين ، البريميدينون والبريميدين ثايون .