Synthesis of Some Phenolic and Amino derivatives of Cinchoninic Acid

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الملخص

تتضمن الدراسة معاملة حامض السنكونينيك (1a,b) مع بروميد الاليل لتكوين المركبات (2a,b) ، اما تحلل المركب (2a) فانه ينتج 2–(4`–اليلوكسي فينيل) حامض السنكونينيك (4) ، في حين عملية كلايسدلة المركب (1a) يعطي المركب (3a) بينما كلايسدلة المركب (1b) يعطي المركبين (3bb,3b) . وعند اسيلة المركبين (1a,b) ينتج مشتقات الاسيتيل (5a,b) . اما تفاعل مركب الامينو (1b) مع ميتا–فلورو كلوريد البنزيل فانه يتكون المركب (6) . وعند تفاعل المركبين (1a,b) مع ايزوثايوسيانات الاليل او المركب الاميني مع ثنائي كبريتيد الكاربون ينتج الثايوكاربامات (7a)،الثايويوريا (7b) وثنائي ثايوحامض الكاربامك (8) والذي يستخدم كمادة اولية لتحضير استر الليل ثنائي ثايوكارباميت (9) على التوالي . واخيرا حول المركب (1b) الى احد مشتقات الكلايسين لحامض السنكونينيك (10) . تم تشخيص المركبات المحضره باستخدام الطرائق الفيزياوية والطيفية فضلاً عن التشخيص النظامي للمجاميع الفعاله .

ABSTRACT

Treatment of cinchoninic acids (1a,b) with allyl bromide afforded compounds (2a,b), and the hydrolysis of (2a) gave the 2-(4`-allyloxyphenyl) cinchoninic acid (4) . Glycedylation of compound (1a) afforded compound (3a), while glycedylation of compound (1b) gave compounds (3b) and (3bb). The acetylation of the acids (1a,b) gave the acetyl derivatives (5a,b) . Benzylation of the amino compound (1b) with m-fluorobenzyl chloride afforded compound (6) . The reaction of compounds (1a,b) with allyl isothiocyanate or amino compound with carbon disulfide afforded thiocarbamate (7a), thiourea (7b) and dithiocarbamic acid (8) which is used as a synthone to prepare allylic ester of dithiocarbamate (9) respectively . Finally Compound (1b) can be transformed to a glycene derivative of cinchoninic acid (10). The synthesized compounds were confirmed by the physical and spectral means in addition to the functional groups systematic identification .

INTRODUCTION

As a part of our continuing study of the derivative of cinchoninic acid, we have turned our attention to use atophan (2-phenyl cinchoninic acid) containing OH or NH_2 groups attached to phenyl ring at para

position as precursor to synthesis a new derivative of cinchoninic acid. The precursor cinchoninic acids (1a,b) were synthesized using a reported Pfitzinger reaction [(1)] between an isatin and 4-hydroxy or 4-amino acetophenone respectively. The substituted cinchoninic acid, present in the core of many physiologically active agent, display interesting therapeutic properties. Such compounds have been shown to inhibit several enzymes as well as to modulate the activity of many receptors [(2)]. Thus, the physiological and the wide range of potential pharmaceutical application of such compounds [(3-9)] prompted us to synthesis a new derivatives of cinchoninic acid as promising sources of bioactive molecules.

EXPERIMENTAL

General procedures:

Melting points were measured on an Electrothermal 9300 series digital melting point apparatus and are uncorrected. Infrared spectra were recorded from KBr discs on Thermo Nicolet FTIR spectrophotometer, and only characteristic absorptions are reported . UV spectra were measured for solutions in ethanol on Shimadzu (UV-160) spectrophotometer. The compounds (1a,b) were synthesized using the published methods [(1)] , and the physical and spectral data were listed in Table 1 .

Table (1): The physical and spectral data for compounds (1a,b)

Compd. No.	M.p. ^{o}C	Yield (%)	Colour	IR ν cm^{-1} (KBr disk)				U.V λ (nm) EtOH
				C = N	C = C	O - H	N -H	
1a	335-337	98	Faint yellow	1612 (s)	1630 (s)	3250 (b)	…..	303 , 365
1b	290-291	88	Red	1583 (s&b)	1643 (s)	3392 (b)	3300 (b)	301 , 361

Preparation of allyl 2-(4`-allyloxyphenyl) cinchoninate (2a) and allyl 2-(4`-allylaminophenyl) cinchoninate (2b) : [(10)]

A solution of substituted cinchoninic acid (1) (0.02 mole) , anhydrous potassium carbonate (5.5 g , 0.04 mole) and allyl bromide (5.2 ml , 0.06 mole) in dry acetone (100 ml) was refluxed with stirring overnight . The solution was concentrated , then the yellow residue was treated with dry diethyl ether (100 ml) and the insoluble salt was removed by filtration . Evaporation of the solvent gave the product (2a,b) . The physical and spectral data were listed in Table 2 .

Table (2): The physical and spectral data for compounds (2a,b,4)

Compd. No.	M.p. °C	Yield (%)	Colour	IR ν cm^{-1} (KBr disk)					U.V λ (nm) EtOH
				C = N	C = C	C = O	C - O	N – H O – H	
2a	90-91	72	Faint yellow	1588 (sh)	1649 (m)	1722 (s)	1293(m) 1257(s)	…...	301 , 366
2b	178-179	73	Deep orange	1597 (s&b)	1645 (sh)	1728 (s)	1294 (s)	3394 (b) …...	316 , 372
4	217-218	82	Yellow	1600 (s)	1649 (m)	…..	1245 (s)	…… 3482 (b)	286 , 399

Preparation of glycidyl 2-(4`- glycidyloxyphenyl) cinchoninate (3a) : [11]

To a mixture of compound (1a) (2.65 g , 0.01 mole) and anhydrous potassium carbonate (2.75 g , 0.02 mole) in dry acetone (50 ml) , epichlorohydrin (2.3 ml , 0.03 mole) was added dropwise with stirring . Then the mixture was refluxed overnight . The salts was filtered off and the filtrate was treated with dry diethyl ether (50 ml) , upon constration , a bright faint yellow precipitate was formed . The physical and spectral data were listed in Table 3 .

Preparation of glycidyl 2-(4`- glycidylaminophenyl) cinchoninate(3b):[11]

To a solution of compound (1b) (2.15 g , 0.0082 mole) in dry pyridine (20 ml), epichlorohydrin (1.3 ml , 0.0164 mole) was added dropwise with stirring . The reaction mixture was refluxed for 1.5 hrs. and the solvent was removed under reduced pressure . A mixture of water (5 ml) and ethanol (5 ml) was added to the residue and allowed to stand overnight . The resulted precipitate was filtered off to give compound (3b) (0.4 g) , which was recrystallized from ethanol . The filtrated was concentrated and acidified with hydrochloric acid and the precipitate collected , washed with hot water until the washing water become colorless , then dried to give 2-(4`-glycidylaminophenyl) cinchoninic acid (3bb) (1.9 g) [Scheme 1] . The physical and spectral data were listed in Table 3 .

Table (3): The physical and spectral data for compounds (3a,b,bb,6)

Compd. No.	M.p. °C	Yield (%)	Colour	IR ν cm^{-1} (KBr disk)						U.V λ (nm) EtOH
				C = N	C = C	C = O ester	C – O ester	C – O epoxide	N –H O - H	
3a	130-132	67	Bright yellow	1549 (m)	1592 (s)	1730 (s)	1295 (s)	1254 (s)	……	345,359
3b	132-134	13	Orange	1589 (s)	1636 (m)	1745 (s)	1284 (m)	1257 (m)	3365 (s)	286,377
3bb	186-188	75	Red	1588 (s)	1642 (m)	1705 (s) acid	1380 (s) acid	1246 (s)	3363 (s) 3368 (s)	305,377
6	180-182	65	Red	1558 (m)	1647 (s)	1733 (m)	1290 (s)	……	3365 (b)	291,365

Preparation of 2-(4`-allyoxy phenyl) cinchoninic acid (4) [12]

A solution of allyl cinchoninate (2a) (0.69 g , 0.002 mole) in ethanol (20 ml) and (5 ml , 6N) sodium hydroxide was refluxed for 15 min. , then allowed to stand at room temperature overnight . The mixture was acidified with acetic acid, then concentrated under reduced pressure and upon cooling a yellow precipitate was formed . The precipitate was filtered off , washed with cold water, then dried to give (78%) of compound (4) . Compound (4) (0.3 g , 0.001mole) was treated with hydrogen peroxide (1 ml , 30%) and sodium hydroxide (0.4 ml , 6N) with stirring at room temperature for 12 hrs .The mixture was acidified with acetic acid , a yellow precipitate was formed , filtered off , washed with cold water, then dried to give (Compound 4) . The physical and spectral data were listed in Table 2 .

Preparation of 2-(4`-acetoxyphenyl) cinchoninic acid (5a) and 2-(4`-acetamidophenyl) cinchoninic acid (5b) : [13]

To a solution of substituted cinchoninic acid (1a,b) (0.0074 mole) in dry pyridine (10 ml) , acetyl chloride (1.04 ml , 0.0148 mole) was added . Hydrogen chloride gas was evolved and a precipitate was formed. The reaction was completed by refluxing the mixture for 4 hrs. (until hydrogen chloride gas is cessed). The mixture was poured into an ice-water (50 ml) containing hydrochloric acid (25 ml , 10%) to form a precipitate . The precipitate was filtered off, washed with cold water, then dried. The physical and spectral data were listed in Table 4 .

Table (4): The physical and spectral data for compounds (5a,b,10)

Compd. No.	M.p. °C	Yield (%)	Colour	IR ν cm^{-1} (KBr disk)					U.V λ (nm) EtOH
				C = N	C = C	C = O	C – O	O –H N- H	
5a	324-326	58	Brown	1577 (s)	1684 (sh)	1717 (sh) ester	1293 (s) ester	3446(b) ……	342 , 366
5b	194-196	75	Redish brown	1590 (s)	1643 (sh)	1602 (s) amide	……	3351(s) 3330(s)	289 , 361
10	288-290	78	Purple	1586 (s)	1643 (s&sh)	1705 (sh) acid	1385 (m) acid	3350(m) 3200(s)	286 , 359

Preparation of m-fluorobenzyl-2-[4`-(m-fluorobenzylamino)phenyl] cinchoninate (6) : [10]

A mixture of substituted cinchoninic acid (1b) (1.32 g , 0.005 mole) , dry pyridine (0.8 ml , 0.01 mole) , m-fluorobenzyl chloride (1.8 ml , 0.015 mole) in dry acetone (20 ml) was refluxed for 12 hrs. After the precipitate of pyridinium chloride was filtered off , the solvent was removed under reduced pressure and the residue was recrystallized from ethanol . The physical and spectral data were listed in Table 3 .

Preparation of O-[4-(2`-cinchoninyl)phenyl] allylthiocarbamate (7a) and N`-allyl-N-[4-(2`-cinchoninyl)phenyl] thiourea (7b) : [14]

A mixture of substituted cinchoninic acid (1a,b) (0.0056 mole) , allyl isothiocyanate (0.54 ml , 0.0056 mole) in absolute ethanol (50 ml) was refluxed for 12 hrs .The solvent was removed under reduced pressure and the residue was cooled to give a solid product , washed with hot water and recrystallized from ethanol . The physical and spectral data were listed in Table 5 .

Preparation of N-[4-dithiocarbamylphenyl] cinchoninic acid (8) :[15]

2-(p-aminophenyl)cinchoninic acid (1b) (2.16 g , 0.0082 mole) was dissolved in alcoholic solution of potassium hydroxide (0.91 g , 0.0164 mole of KOH in 50 ml absolute ethanol) .To this mixture carbon disulfide (2.5 ml , 0.041 mole) was added gradually . The mixture was refluxed for 12 hrs. The hot solution was treated with charcoal, then filtered, cooled and acidified with dilute hydrochloric acid to produce a precipitate. The precipitate was filtered off, washed thoroughly with water (to pH ~7) and dried. The physical and spectral data were listed in Table 5.

Preparation of allyl-N-[4-S-allyldithiocarbamylphenyl]cinchoninate (9) : [10]

Dithiocarbamic acid (8) (1 g , 0.00294 mole) was dissolved in an alcoholic solution of potassium hydroxide (0.33 g , 0.00588 mole in 50 ml absolute ethanol) , then allyl bromide (1.4 ml , 0.01764 mole) was added .The mixture was refluxed for 12 hrs. with stirring .The resulted precipitate of potassium bromide and the product was filtered off , washed thoroughly with water to remove the potassium salt , dried to give deep orange powder . The physical and spectral data were listed in Table 5.

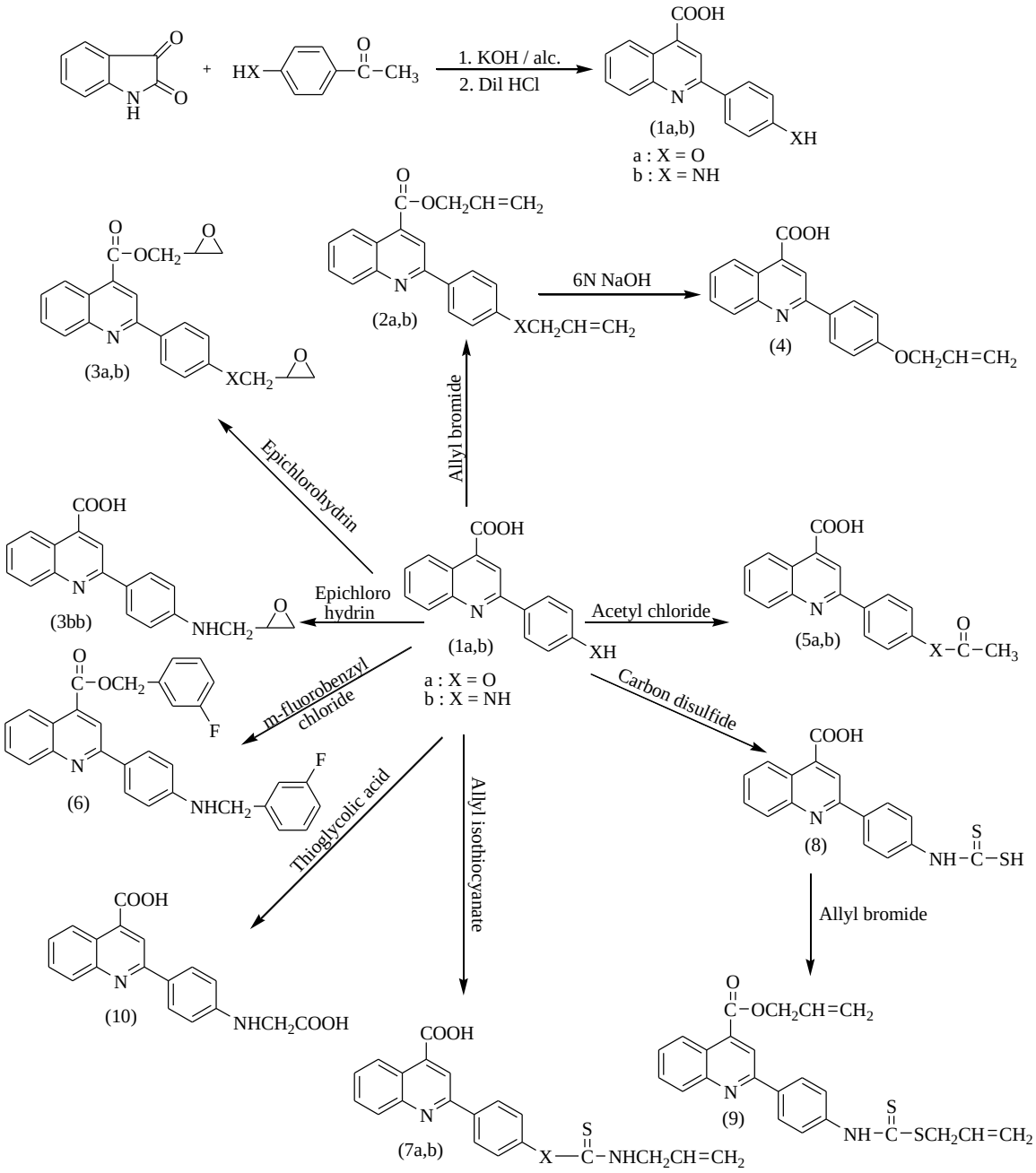
Table (5): The physical and spectral data for compounds (7a,b,8,9)

Compd. No.	M.p. ^{o}C	Yield (%)	Colour	IR ν cm^{-1} (KBr disk)					U.V λ (nm) EtOH
				C = N	C = C	C = S	O – H N - H	{C = O COO} ester	
7a	323-325	66	Deep yellow	1631 (s)	1699 (s&sh)	1337 (s)	3396(b) 3170(b)	……	337 , 341
7b	216-218	75	Orange	1591 (s)	1644 (m)	1332 (s)	3321(s) 3250(b&w)	…..	301 , 345
8	268-270	70	Orange	1594 (s)	1643 (s)	1328 (s)	3222 (b) (NH&OH)	…..	302 , 345
9	294-295	65	Deep orange	1540 (s)	1592 (s)	1317 (s)	…… 3284 (b)	1717(s) 1245(s)	308 , 356

Preparation of 2-(4`carboxymethylaminophenyl)cinchoninic acid (10)

A mixture of 2-(p-aminophenyl)cinchoninic acid (1b) (1.47 g , 0.0056 mole) in alcoholic solution of potassium hydroxide (0.95 g , 0.017 mole in 50 ml absolute ethanol) and thioglycolic acid (0.8 ml , 0.0.1136 mole) was refluxed for ~ 12 hrs. until the evolution of hydrogen sulfide was cessed . The reaction mixture was cooled and poured into an ice-

water (25 ml), then acidified with dilute hydrochloric acid .The resulted precipitate was filtered off, washed with water then dried. The physical and spectral data were listed in Table 4.



Scheme 1

RESULTS and DISCUSSION

The synthetic route of cinchoninic acid derivatives (1-10) was depicted in Scheme 1 . The preparation of the precursors (1a,b) employed isatin and 4-hydroxy and amino acetophenone respectively through pfitizinger method [1] under alcoholic alkaline condition . Allylation of (1a,b) using allyl bromide under basic condition gave (2a,b) respectively

in a good yield . The allylation took place at two positions , at the carboxylate oxygen and at the phenolic oxygen or the aminic nitrogen through nucleophilic substitution reaction . The structures can be confirmed by physical and spectral data [16]. The IR spectra of the compounds (2a,b) showed a specific absorptions at 1722 and 1728 cm^{-1} respectively for the ester carbonyl bond stretching . The disappearance of the absorption peaks of the O – H bond stretching at 3250 cm^{-1} (broad peak) and the negative iodide-iodate and ferric chloride [17] for compound 2a , indicates the complete conversion of the acidic group to the ester group and phenolic OH group to the allylic ether , and instead , the IR spectra showed absorption peak at 1293 cm^{-1} for the ester C – O bond stretching and at 1257 cm^{-1} for the ether C – O bond stretching . Also, the disappearance of the absorption peaks at 3392 cm^{-1} for the acidic O – H bond stretching and the negative diazotization test and iodide-iodate test indicating the complete conversion of compound 1b to 2b . Moreover, the two compounds gave positive hydroxamate and Bayer tests for the ester and allyl groups respectively [17] . The UV spectra of compounds (2a,b) showed a new absorption bands at 301 and 316 nm respectively due to $\pi \rightarrow \pi^*$ transition which occurred in these compound, while the λ max for these compound appeared at 366 and 372 nm respectively due to the $n \rightarrow \pi^*$ transition . The glycedylation of compounds (1a,b) was performed with epichlorhydrin under mild anhydrous condition , in presence of anhydrous potassium carbonate in dry acetone or pyridine , respectively , as a solvent , to prevent the ring cleavage and polymerization of epichlorohydrin .

The reaction of 1a gave one product (3a) While the compound (1b) gave two products (3b and 3bb) . The formation of two products may be attributed to the stronger higher nucleophilicity of nitrogen atom than oxygen atom . The structure of these product was confirmed by the positive ferric hydroxamate test for compounds (3a and b) and positive iodide-iodate test for compound (3bb) [17] . Furthermore , the IR spectra of compounds (3a,b) showed a strong absorption peaks at 1730 and 1745 cm^{-1} , respectively , for the ester C = O bond stretching , while compound 3bb showed absorption peaks at 1705 and 1380 cm^{-1} for the acid C = O and C – O bonds stretching respectively , in addition to two absorption peaks at 3368 and 3363 cm^{-1} for the O – H and N – H bond stretching . Moreover, the three compounds showed absorption peaks at 1246 – 1257 cm^{-1} related to the C – O bond stretching for the epoxide moiety . Furthermore , the appearance of absorption bands at 345,286,305 nm in the UV spectra of compound (3a,b,bb) respectively due to $\pi \rightarrow \pi^*$ transition, while the λ max for these compound appeared at 359 , 377 , 377 nm respectively due to the $n \rightarrow \pi^*$ transition (red shift), would suggest the formation of epoxide compounds .The benzylation of

compound (1b) can be conducted in the same manner by the reaction of this compound with 3-fluoro benzyl chloride to afford the corresponding ester (6) . The IR spectra of this compound showed the presence of carbonyl group at 1733 cm^{-1} and N – H bond at 3365 cm^{-1} in addition to C – O ester bond at 1290 cm^{-1} Table 3 . The UV spectra showed a bathochromic shift for the absorption bands at 291 , 365 nm due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition respectively. Moreover the hydrolysis of compound 2a with aqueous sodium hydroxide (6N) gave compound (4) as identified by systematic identification and the spectral data. Since the product gave positive iodide-iodate, Bayer and bromine/CCl_4 tests [17] . Moreover , the IR spectra of the product showed a characteristic peak at 3482 cm^{-1} which was attributed to the acidic O – H bond stretching and a medium absorption peak at 1245 cm^{-1} related to ether C – O bond stretching Table 2 . It seemed that these results would indicate the loss of alleloxy group through a saponification process of the ester according to the tetrahedral addition-elimination mechanism. The UV spectra showed a red shift for the absorption bands at 286 , 399 nm belong to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition respectively .

Acetylation of compound (1a,b) with acetyl chloride in dry pyridine would afford the corresponding acetyl derivative (5a,b) . The IR spectra of these compounds showed abroad absorption peak at 3446 cm^{-1} and a strong one at 3351 cm^{-1} attributed to O – H bond stretching of compounds (5a,b) respectively and strong absorption peak at 3330 cm^{-1} related to the N – H bond stretching for compound 5b . The UV spectra showed a bathochromic shift for the absorption bands at 342 , 289 nm due to $\pi \rightarrow \pi^*$ transition, while the λ max for these compound appeared at 366 , 361 nm respectively due to the $n \rightarrow \pi^*$ transition, Table 4 .

Treatment of compounds (1a,b) with allyl isothiocyanate gave the thiocarbamate (7a) and the thiourea (7b) respectively through nucleophilic addition reaction . The IR spectra of compounds (7a,b) showed thio carbonyl C = S bond stretching at 1337 and 1332 cm^{-1} respectively . The other general absorption peaks were listed in Table 5. The UV spectra showed a red shift for the absorption bands at 337 , 301 nm respectively due to $\pi \rightarrow \pi^*$ transition and at 341 , 345 nm respectively due to $n \rightarrow \pi^*$ transition . Compound (1b) , also underwent nucleophilic addition with carbon disulfide under basic condition in presence of alcoholic potassium hydroxide to give the dithiocrbamic acid (8) . The structure of this compound was confirmed by positive sulfur element test [17.], moreover it give an IR spectral peak at 1327 cm^{-1} for C = S bond stretching and additional UV absorption band at 302 and 345 nm due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition respectively. The thiocarbamic acid (8) was used to synthesis the allylic dithiocarbamate (9) by refluxing of compound (8) with excess of allyl bromide in alcoholic solution

potassium hydroxide. This process involve formation of allyl ester of the carboxylic group in addition to formation of allyl ester of dithiocarbamic acid . This compound was confirmed by using IR spectroscopy . The IR spectra showed a characteristic peaks at 1316 , 1717 and 3283 cm^{-1} for C = S , C = O and N – H bonds stretching respectively . The UV spectra showed a bathochromic shift and showed λ max at 308 and 356 nm respectively due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition .

The reaction of compound (1b) with thioglycolic acid gave the α–acetic acid derivative (10) this compound showed the IR characteristic peak at 3200 , 3350 and 1705 , 1385 cm^{-1} for N – H , O – H and acid C = O , C – O bonds stretching respectively , Table 4 . The UV spectra showed a red shift for the absorption bands at 286 , 359 nm due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition respectively .

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