PREPARATION AND IDENTIFICATION OF SOME NEW DERIVATIVES FOR SALBUTAMOL DRUG [+]

تحضير وتشخيص بعض المشتقات الجديدة لدواء السالبيتيمول

Saadiyah A. Dhahir [*] Hind F. Thamer [*] Sanaa A.Al-Sahib [**]

Abstract:

In this research new derivatives of salbutamol were prepared that known high medicinal effectiveness, through the interaction coupling with daizonium salts of the following substituted aniline compounds (4-amino aniline , 4-chloro -2-nitro aniline, 2,3-di methyl aniline ,9-amino naphthol, Benzedine , 2-amino 1,3,4- thiodiazol-5- thiol).
The prepared compounds were identified using spectroscopic methods (UV-Visible, FTIR).

المستخلص:

تم في هذا البحث تحضير مركبات جديدة للمركب الدوائي ا لسالبيتمول المعروف بفعاليته الدوائية العالية من خلال تفاعل ازدواج ملح الديازونيوم لها مع بعض معوضات الانيلين(٤- امينو انيلين ،٤- كلورو-٢- نايترو انيلين ٢،٣، - داي مثيل انيلين ،٩- امينو نفثول ،بنزيدين ،٢- امينو ١،٣،٤- ثايادايازول-٥-ثايول).

تم تشخيص المركبات المحضرة باستخدام بعض الطرق الطيفية UV-Visible, FTIR .

Introduction:

Salbutamol (Ventolin) is a 2-sympathicomimetic drug, which was granted a marketing authorization in 1973. It is indicated for the treatment of reversible airway obstruction in bronchial asthma, chronic bronchitis and emphysema [1] .

In the current study some of new derivatives of salbutamol which were prepared have known high medicinal effectiveness, through the interaction of salbutamol in alkali medium and coupling with daizonium salt.

Peter Griess [2] found in 1858 that primary aromatic amines interacted quickly with nitrous acid at low temperatures to give easy soluble salts in water which called daizonium ion. Daizonium ion always formed from interaction between primary aromatic

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[*]**Lecturer / College Science for women /Baghdad University**
[**] **Asst. Lecturer / College Science for women /Baghdad University**

amine and nitrous acidic (HONO) in acid medium in the temperatures range (0-5)C^0.This reaction called (diazotization) [3].
Daizonium salt produced from primary aromatic amine is stable at low temperatures between (0-5)C^0,but it dissociate rapidly at the high temperatures [4].
Diazonium salt is very active and it is an important and common compound for preparation of azo compounds [5].

Phenols are common compounds that associated in coupling reaction, this reaction happened in alkali medium [6,7] .

Experimental methods

Preparation of azo compounds [6] (1-azo-[substitute benzene]5-salbtumol)

1- Diazonium salt was prepared by addition of (0.021 mole)of various amines in a beaker (100ml) which contain (12.8 ml) hydrochloric acid(50%) over a water bath at temperatures (0-5)C^0, then(8ml) of (20%) sodium nitrate solution were added drop by drop with continuous stirring and cooling .

2- (0.022 mole) salbtomol was dissolved in 18 ml (10%) sodium hydroxide and cooled to zero temperature centigrade in an ice bath.

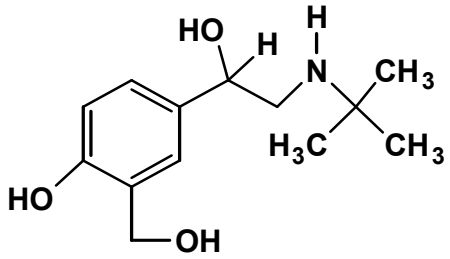
3- Diazonium salt which was obtained in step (1) above added to the solution which was obtained in step(2) slowly with continuous stirring and cooling.

4- The mixture left for two hours at same temperature ,then (30%) hydrochloric acid was added .Precipitation crystals were apparent ,then the crystals were left to get stable for one hour then filtered and washed with appeared cold water.

5-The crystals were dried and recrystallized with ethanol .

Compounds Prepared

The following six compounds were prepared



4-(2-*tert*-Butylamino-1-hydroxy-ethyl)-2-hydroxymethyl-phenol

(Salbutamol)

Derivatives were given in table (1).

Table (1)New derivatives of salbutamol.

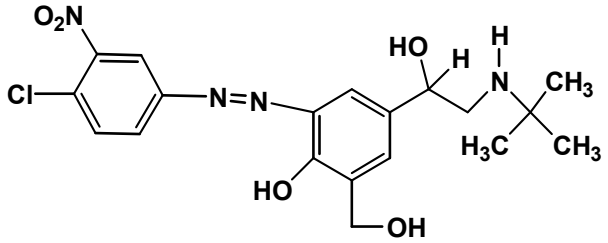
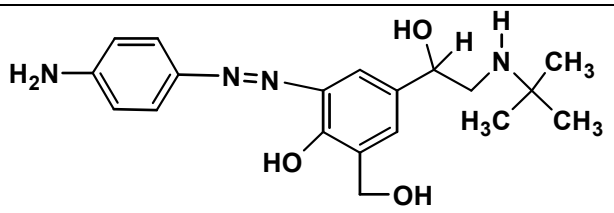
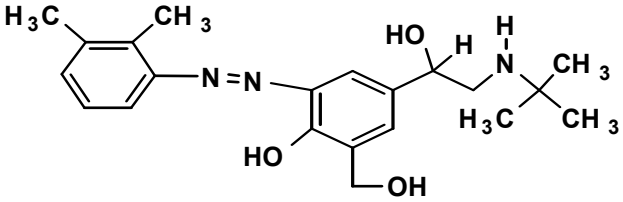
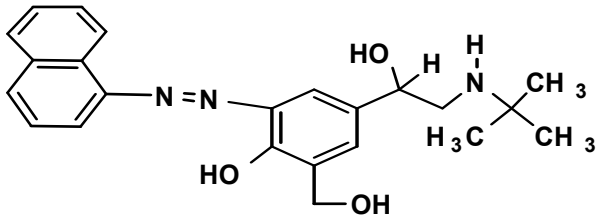
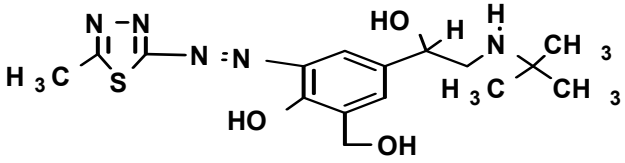
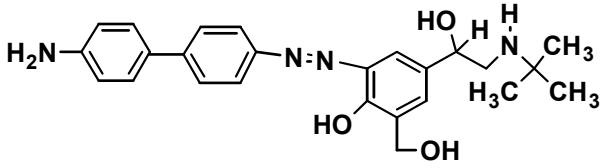
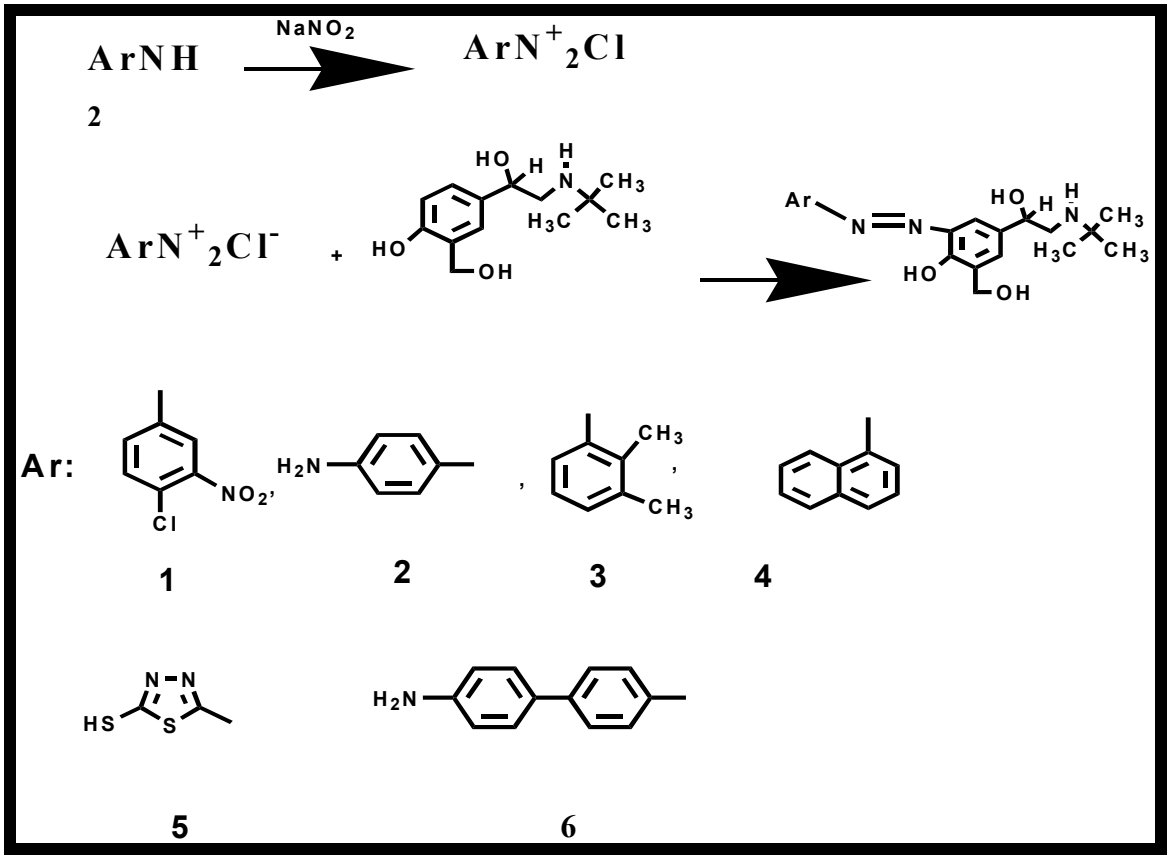
No.	New derivatives	Name
١		4-(2-Tert-Butylamino-1-hydroxy ethyl)-2-(4-chloro-3-nitro-phenylazo)-6-hydroxymethyl-phenol
٢		٢-(4-Amino-phenylazo)-4-(2-tert-butylamino-1-hydroxy-ethyl)-6-hydroxymethyl-phenol
٣		٤-(2-tert-Butylamino-1-hydroxy-ethyl)-2-(2,3-dimethyl-phenylazo)-6-hydroxymethyl-phenol
٤		٤-(2-tert-Butylamino-1-hydroxy-ethyl)-2-hydroxymethyl-6-(naphthalenyl-1-azo)-phenol
٥		٤-(2-tert-Butylamino-1-hydroxy-ethyl)-2-hydroxymethyl-6-(5-methyl-[1,3,4]thiadiazolyl-2-azo)-phenol
٦		٤-(2-tert-Butylamino-1-hydroxy-ethyl)-2-hydroxymethyl-6-azo-(Biphenylyl-4-amine)

Table (2):physical properties of azo compouns

Compounds	Color	Molecular weight	Molecular structure	Melting point C^0
١	Dark Orang	422.86	$C_{19}H_{23}ClN_4O_5$	92-94
٢	Dark Browen	٣٥٨,٤٣	$C_{19}H_{26}N_4O_3$	114-116
٣	magenta (bright pink)	٣٧١,٤٧	$C_21H_{29}N_3O_3$	84-86
٤	Dark violet	٣٩٣,٤٨	$C_{23}H_{27}N_3O_3$	244-246
٥	light Orange	٣٦٥,٤٥	$C_{16}H_{23}N_5O_3S$	94-96
٦	light Browen	٤٥٠,٢٦	$C_{26}H_{34}N_4O_3$	216-218

Discussion:

The new derivatives for salbutamol were prepared by reaction of salbutamol with different amine compounds. The following mechanism has explain the reaction.



The formula structure of salbutamol derivatives were identificated by determination of melting points as it can be seen in table(2) .The IR spectral studies are summarized in table(3)

Table (3):The value of IR spectroscopy for some functional group in salbutamol derivatives.

No.	N=N cm^{-1} str.	N=N cm^{-1} bend.	OH phenolic cm^{-1} str.	CH Aliphatic cm^{-1}	Other cm^{-1}
١	1504	١٤٠٨	٣٤٧٥	٢٩٩٧	Aromatic CH str.3114
٢	1510	١٤٠٠	٣٤٢٠	٢٩٣٨	NH str.3329,3388
٣	١٥٣١	١٤٠٠	٣٣٩٨	٢٨٢٣	Aromatic CH str.3047
٤	١٥٢٨	١٤٠٥	٣٣٧٧	٢٩٥٣	Aromatic CH str. 3020 Out of plan CH bend.742
٥	١٥٣٠	١٤٠٢	٣٣٩٢	٢٩٢٧	Aromatic CH str.3030 Out of plan C=C bend.502
٦	١٤٩٦	١٤٠٨	٣٤١٤	٢٨٦٦	NH str.3329 In plan CH bend.813

The stretching of O-H phenolic and alcoholic groups demonstrate a wide absorption band in the region (3400-3100)cm^{-1} .While disappearance of absorption band of secondary NH_2 group stretching in the region (3000-3400) cm^{-1} [8] .

The appearance of medium intensity band in the region (1595-1490)cm^{-1} attributed to the stretching vibration of N=N group.

The appearance of medium band at (1400-1410)cm^{-1} represent the bending vibration of N=N group. Other absorption bands appeared in the spectrum were explain in table (2).

The UV-Visible spectroscopy demonstrated the absorption bands at (288,360)nm belong to (n-Π^*) transitions of the (N=N) azo group .While other absorption bands at 230 nm belong to the(Π-Π^*) transitions of benzene ring .

Since the diazonium ion is considered a weak or neutral electrophiyl ,this will make it to attack benzene ring of phenoxide group . generally this attack is take place on the para position.. While the attack will be on the ortho position if the para postion is occupied [9] .

Azo dye compounds come in a broad range of colors, including yellows, oranges ,reds , browns, and blues. Each compound has a slightly different color because it has different substituents and a different extent of conjugation in its system [10,11] .

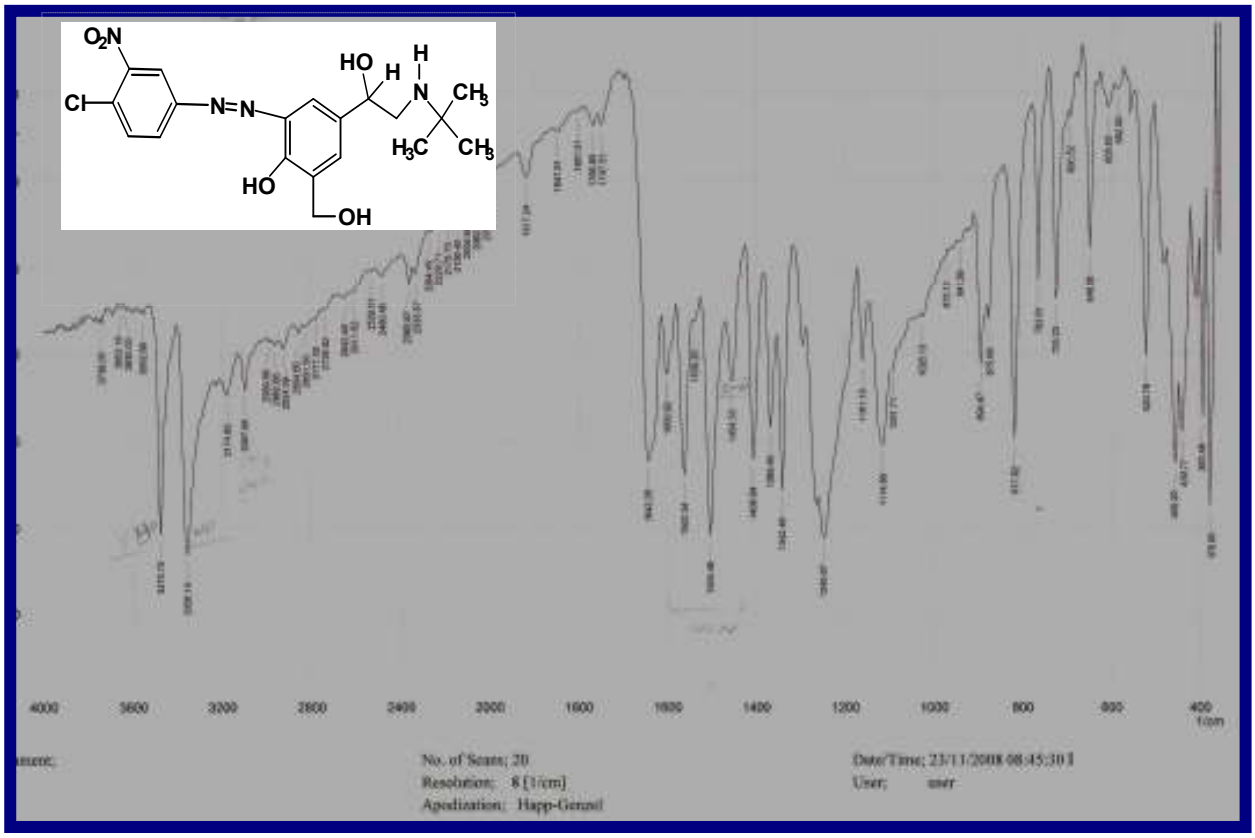


Figure (1) IR spectrum of 4-(2-tert-Butylamino-1-hydroxy-ethyl)-2-(4-chloro-3-nitro-phenylazo)-6-hydroxymethyl-phenol

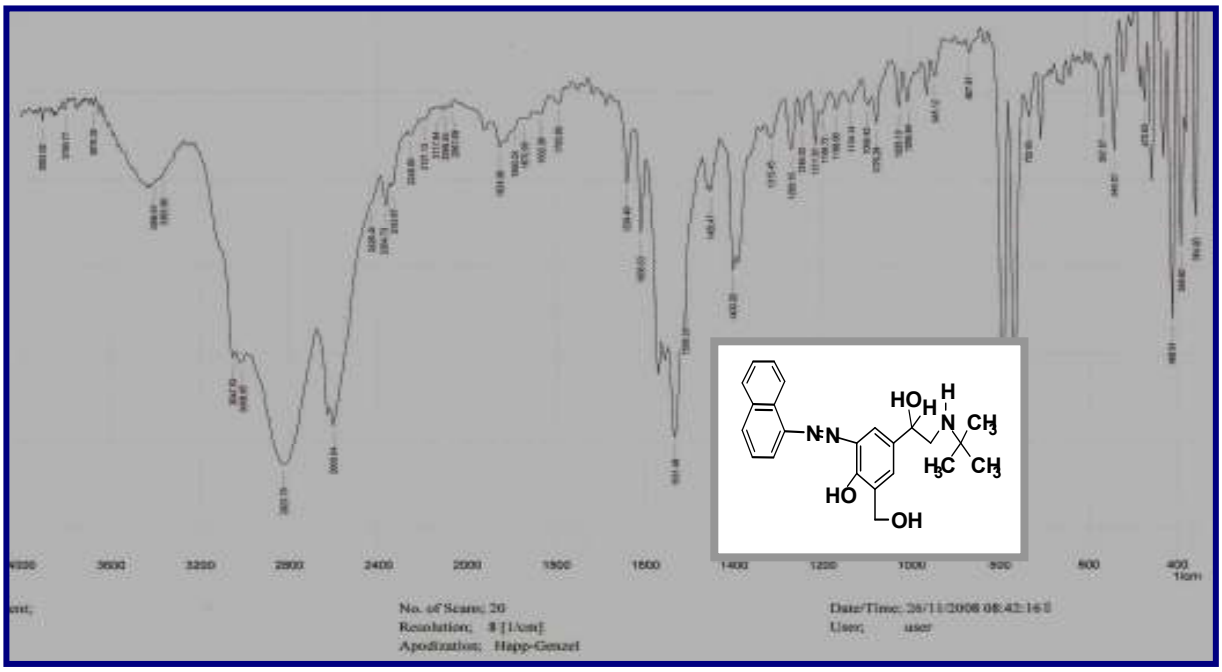


Figure (2) IR spectrum of 4-(2-tert-Butylamino-1-hydroxy-ethyl)-2-hydroxymethyl-6-(naphthalene -1-azo)-phenol

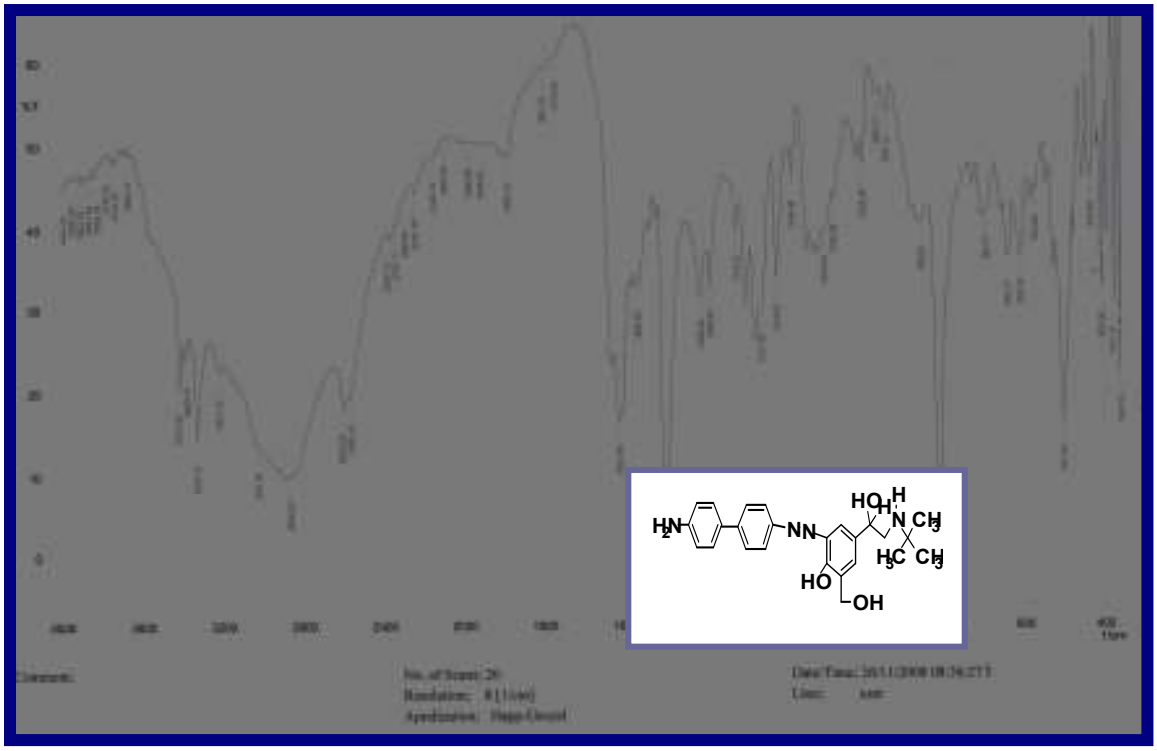


Figure (3) IR spectrum of 4-(2-tert-Butylamino-1-hydroxy-ethyl)-2-hydroxymethyl-6-p-tolylazo-phenol; compound with phenyl amine.

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