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Synthesis and Characterization of 1H-2-Ar-3-Ar'-[1,2-e] [1,3]benzodiazepine-4,7- dione compounds

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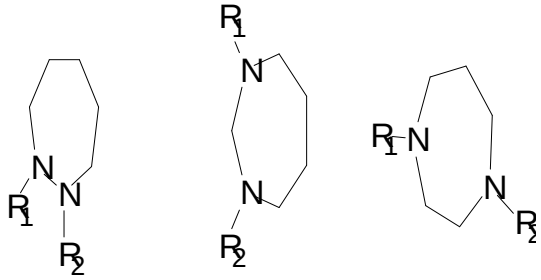
Abstract: The one-step reaction of phthalimide with benzylidene benzeneamine in dry benzene gave 2-Ar-3-Ar'[1,2-e][1,3]benzodiazepine-4,7-diones in good yields.The products were characterized by their melting points and IR and UVspectra.

Keywords: Synthesis , Characterization , 1H-2-Ar-3-Ar'-[1,2-e] [1,3]benzodiazepine-4,7- dione

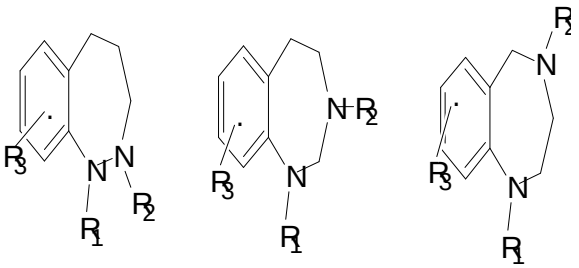
Introduction

Diazepines is a class of seven-membered ring heterocyclic compounds with two nitrogen atom at 1,2- , 1,3- and 1,4- in the heptane ring instead of carbon atom ,and these compounds may be saturated and unsaturated with different substituents.



[1,2] Diazepine [1,3] Diazepine [1,4] Diazepine
R1 , R2 , R3 = H , Alkyl , Aryl

The benzodiazepines are consisting of benzene ring fused with the diazepine ring to give the three analogous(1)



Benzo[1,2]diazepine Benzo[1,3]diazepine
Benzo[1,4]diazepine
R1 , R2 , R3 = H , Alkyl , Aryl

Alarge number of diazepines and benzodiazepines were synthesized by hotochemical isomerization

of reactive compounds and intermediates such as tricyclopentene systems(1) and 1-iminopyridinium ylides(2),earrangement of (z) ketovinylaziridine (3), ring expansion of some chloromethylpyrazolo [1,5-c] quinazolines and 1,2,3-benzothiazolines-1,1- dioxide(4),and from the reaction of cyclic amide(5,6).

The[1,4]benzodiazepine such as chlorodiazepoxide(Librium),diazepam(valium),lorazepam, flunitrazepm flunitrazepam and clonazepam were synthesized from 4-chloro-N-methylaniline and substituted benzoyl chloride in multisteps reaction including intermediate products rearrangement,(7,8)

A one-pot synthesis of novel 1H-pyrimido[4,5-c][1,2]diazepines were achieved by reacting equimolar quantities of 1,3-dimethyl -6-hydrazino uracil and α ,β- unsaturated carbonyl compounds (9).The 1,3-dipolar cycloaddition of mesitonitrile oxide to 1,7-dimethyl-2,3-dihydro-1H-[1,4]diazepine in unexpected one –step formation of new triheterocyclic system was reported (10).And the synthesis of benzofura [3,2-e] [1,4]diazepine 2,5(1H,4H)-dione was recently reported (11).

A short and elegant synthetic pathway was developed for the synthesis of 1,3-dioxo-hexahydropyrido[1,2-c][1,3]diazepine **carboxylate ,a** new 1,3-diazepan-2,4-dione containing bicyclic moiety,starting from pyroglutmate ester (12).

The nucleophilic substitution, reduction ,chlorination debenzylation and amidation gave 5-substituted hexahydro-1H-1,4-diazepine analogues(13), and the reaction of imidazol diester

with guanidine in presence of sodium methoxide [1,3] diazepine -4,8(1H ,5H)-dione(14).

The biochemistry of diazepines and benzodiazepines has been thoroughly and extensively explored owing to their association with wide spectrum of pharmacological activities,such as,sedatives,anxiolytics, hypnotics,anticonvulsants,antipsychotics,and muscle relaxants(15,21).

Experimental:

Melting points were determined for the purified compound in open capillary tubes.IR spectra were recorded .

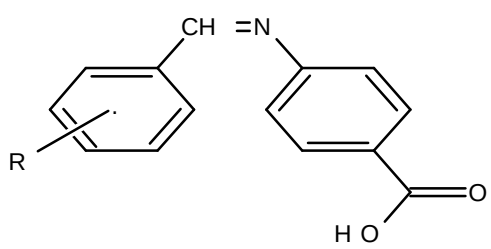
Wave number is expressed in cm-1. UV spectra were recorded in methanol and λmax is expressed in nm.

N-Benzylidene benzene amines (Schiff bases) : A mixture of (0.036) mole of 4-Amino benzoic acid and(0.034) mole of benzaldehyde in 30 ml of ethanol, was placed in a round bottom flask equiped with cordenser and refluxed for 30 min, then left to cool down in an ice-water bath , where by a crystalline solid separated out the solid product was filtered out , washed with 2% HCL solution and then with water and recrystallized twice from ethanol.The analogous compounds were prepared in a similar manner to the described above. The physical prepartiy and the character it bands and UV and IR spectrum as shown in table (1).

1H-2-Ar-3-Ar'-[1,2-e] [1,3] benzodiazepine- 4,7-diones: In a round bottom flask equiped with condenser, mixture of (0.021)mole of anhydrous phthalimide and (0.022)mole of known N-benzylidene benzenamine dissolved in dry benzene was refluxed for two hours,and left to cool down at room temperature .A crystalline solid was separated out after one day,the solid was filtered out and recrystallized from dry benzene. The analogous compounds were prepared in a similar manner to the described above. The physical prepartiy and the character it bands and UV and IR spectrum as shown in table (2).

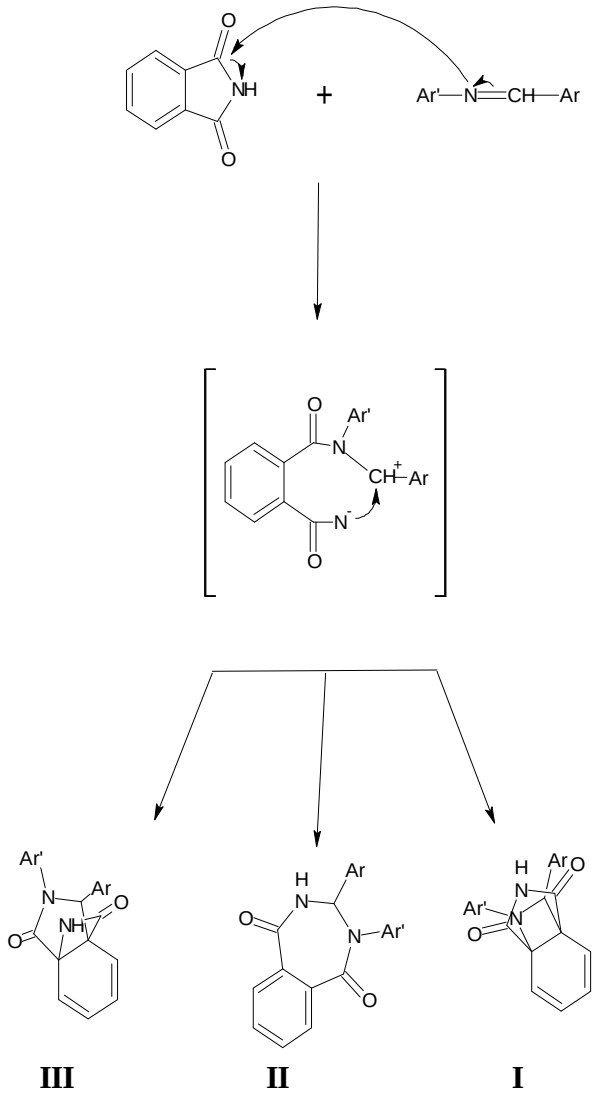
Discussion:

Schiff bases N;(1-6) are prepared by the condensation of aromatic amines and the corresponding aromatic aldehydes in ethanol,and recrystalized from the same solvent and they are identified by their melting points table(1), IRand UV absorption spectra, since the IR spectra showed the disappearance of (C=O) absorption band at 1690-1720 cm-1 and the (-NH2) absorption band at 3650-3400 cm-1 and the appearance of (C=N) absorption band at 1600-1683cm-1, the UV-vissible spectra showed maxima at 280 (π-π*)-365(n-π*) nm due to charge transfer of :



R= H , p-OCH3 ,o -OH ,p-N(CH3) , o-NO2 , p-NO2

The reaction of Schiff bases with phathalimide in dry benzene is suggested to give initially a dipolar intermediate (I) which in turn collapses to the 7-membered heterocyclic system (II)



The structure of the heterocyclic system (II) is a combination and consistent with both β- and ɣ – lactam, this is indicated by the appearance of the characterstic C=O(lactam) absorption band at 1775-1751cm-1,(higher wave nummer).It is impressive to note that the absorption bands at 1850 cm-1 of the pure IR spectrum have disappeared when the phthalimide became part of the 7-membered heterocyclic ring system of the diazepine ,(22)the cycloaddition reaction of the phthalimide and the Schiff bases is ring formation results from the addition ofπ bond to either σ or π bond to from

new σ bond . Two more speculative product structures may proposed III and IV for the final product in addition to structure II of the actual product . Structure (III)is unlikely, because of the higher strain associated with the 4-membered ring system . Moreover, structure III is expected to show the IR absorption bands of C=O (cyclic lactam) above 1840 cm-1, however ,this absorption bands are missing in the IR spectra of the original product . Structure (IV) another one can be proposed , results from the (2+2) cycloaddition of the reactants . This structure is highly strained and would have an IR absorption spectra at higher wave number than that of structure (II) however , there is no evidence for such absorption spectra . In addition, formation of both .(III)and (IV) structures requires loss of aromaticity of the benzene ring of the phthalimide which is most difficult to achieve,and the IR absorption spectra of the product support the retention of the aromaticity.

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تحضير وتشخيص المركب
1H-2-Ar-3-Ar'-[1,2-e] [1,3]benzodiazepine-4,7- dione

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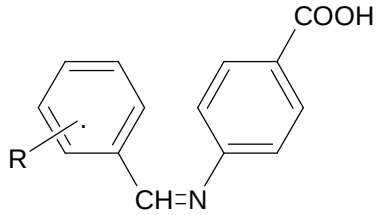
الخلاصة:

أن تفاعل الخطوة الواحدة للفثاليمايد والبنزيليدين بنزين أمين في البنزين الجاف أعطى 2-أريل-3- أريل"(1 ،2 – e) بنزوثنائي أزبين-7،4-ثنائي أون .بنسبة منتوج جيدة.وقد شخصت النواتج من خلال درجات الانصهار وأطياف الأشعة تحت الحمراء والأشعة فوق البنفسجية .

- **يتبع جداول التشخيص**

Table 1. Characterization of N-Benzylidene benzenenamine N-Arylidene Arylamine



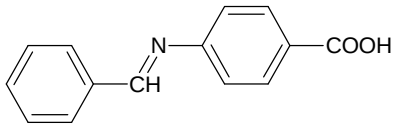
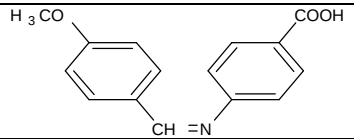
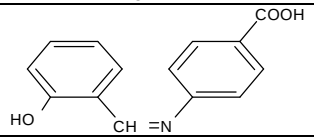
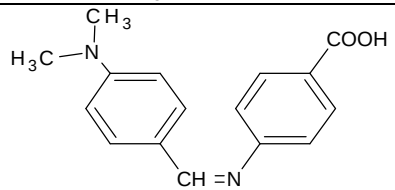
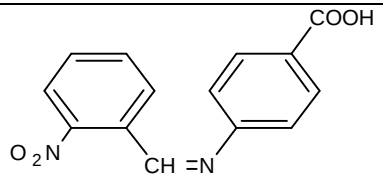
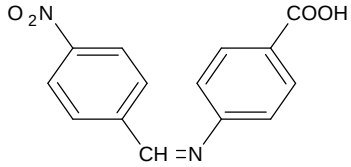
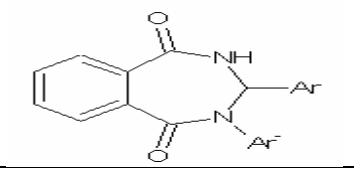
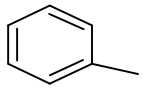
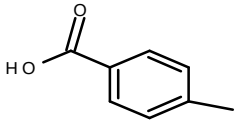
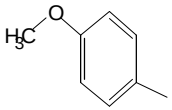
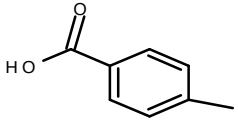
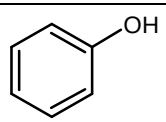
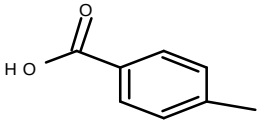
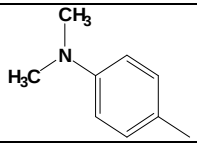
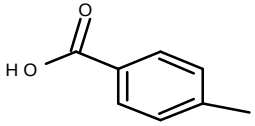
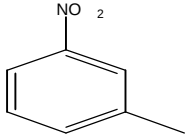
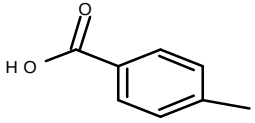
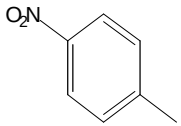
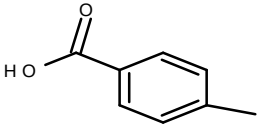
No	structure	formula	M.Wt	m.p C°	IR absorption , Cm^{-1}	UV absorption , nm
1		$C_{14}H_{11}NO_2$	225	258	3004 (C-H Str.aromatic),3018(=C-H Str.),1559(C=C Str.aromatic),1682(C=N Str.),1423(C-H bend.aromatic),1569(C=C bend.aromatic),3202(O-H Str.carboxylic),1779(C=O Str. Carboxylic).	335, 299,270, 224
2		$C_{15}H_{13}NO_3$	255	246	3005(C-H Str.aromatic),3135(=C-H Str.),1571(C=C Str.aromatic),1683(C=N Str.),1423(C-H bend.aromatic),1571(C=C bend.aromatic),3202(O-H Str.carboxylic)	224 , 275 ,316
3		$C_{14}H_{11}NO_3$	241	276	2995(C-H Str.aromatic),3130(=C-H Str.),1598(C=C Str.aromatic),1677(C=N Str.),1450(C-H bend.aromatic),1569(C=C bend.aromatic),3200 (O-HStr.carboxylic)1774(C=O)Str.carboxylic)	324,277,268,219
4		$C_{16}H_{16}N_2O_2$	268	220	3018(C-H Str.aromatic),3024(=C-H Str.),1593(C=C Str.aromatic),1608(C=C bend.aromatic),1647(C=N Str.),1353(C-N aliph),2839(C-H aliph),3208(O-H Str.carboxylic),1774(C=O Str.carboxylic).	338,265,232
5		$C_{13}H_{11}NO_3$	271	240	3030 (C-H str. Aromatic) , 3150 (=C-H str.) 1650 (C=C str . aromatic), 1600 (C=N str.), 1550 (C-NO2) str., 1160 (C-H oen.aromatic) 530 (C=C bend . aromatic,3010(O=H Str.crboxylic),1778(C=O Str.crboxylic).	341,287,235
6		$C_{13}H_{11}NO_3$	271	284	3031 (C-H str. Aromatic) , 3150 (=C-H str.) 1650 (C=C str . aromatic), 1600 (C=N str.), 1550 (C-NO2) str., 1160 (C-H oen.aromatic) 530 (C=C bend . aromatic,3010(O=H Str.crboxylic),1778(C=O Str.crboxylic).	339,265,241

Table .2.Characterization of 1H-2-Ar-3- Ar--[1,2-e][1,3] benzdiazepine – 4,7- dione



No	Ar	Ar-	Formula	m.p	M.Wt	1R absorption, Cm-1	Absorption nm
7			$C_{22}H_{16}N_2O_4$	209	372	3207(O-H str. Carboxylic) , 1774 (C=O str. Carboxylic) , 1751 (C=O str. Amidic) , 1605 (C=C str.) , 1387 (C-H str.) . ,1307 and 1054 (C-O str.) 714 (O-H bend).	200,778,490, 255
8			$C_{23}H_{18}N_2O_5$	224	402	3202 (O-H str. Carboxylic) , 1775 (C=O str. Carboxylic) , 1752 (C=O str. Amidic) ,1605 (C=N str.taut), 1468 (C=C str. aromatic) , 1387 (C-H str.) . ,1307 and 1053 (C-O str.) , 714 (O-H bend).	992,891, 484,264
9			$C_{22}H_{16}N_2O_5$	208	388	3200 (O-H str. . Carboxylic) , 1774 (C=O str. Carboxylic) , 1751 , 1682 (C=O str. Amidic) ,1602 (C=N str.taut),1570, 1468 (C=C str. aromatic) , 1387 (C-H str.) . ,1307 , 1288,and 1053 (C-O str.) , 775 , 749 , and 714 (O-H bend).	994,890,464, 370,331,267, 246
10			$C_{24}H_{21}N_3O_4$	104	415	3208 (O-H Str. Carboxylic),1774(C=O Str.carboxylic),1751(C=O amidic),1611,1568,1486,1457(C=C Str.aromatic),1388(C-H Str.),1273,1184(C-N Str.),1308,1053(C-O Str.)	993,889,457, 340,267,239
11			$C_{22}H_{15}N_3O_4$	178	418	3208(O-H Str.carboxylic),1776(C=O Str. Carboxylic),1755(C=O Str.amidic),1605(C=N Str.)(C=C Str.aromatic),1389(C-H Str.),1305 and 1054(C-O Str.),714 (O-H bend).	990,877,489, 255
12			$C_{22}H_{15}N_3O_5$	197	418	3209 (O-H Str. Carboxylic),1775(C=O Str.Carboxylic),1755(C=O Str. Amidic),1608(C=N Str.)(C=C Str.aromatic),1387(C-H Str.),1305 and1055(C-O Str.),717(O-H bend).	200,877,488, 278