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Note

Synthesis of 6,7-dihydroxy-3-aryl-5-undecyl-4,1,2-benzoxadiazines

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Condensation of Embelin **1** with different aromatic acid hydrazides **2** in glacial acetic acid to give N^1-5-hydroxy-6-undecyl-*p*-benzoaquinone-2-yl)-benzohydrides **3**. Reductive cyclization of the product **3** with simultaneous acetylation *in situ* resulted in the formation of the compound **4** 1-N-acetyl-6,7-diacetyl-3-aryl-5-undecyl-4,1,2-benzoxadiazine. In the final step the compound **4** is deacetylated to give the title products **5**. The structures of the newly prepared compounds have been confirmed from analytical and spectral data. Some of the compounds exhibited antibacterial and antifungal activity.

Keywords: Embelin, acid hydrazides, acetylation, cyclization reaction, antibacterial, antifungal

Many substituted and fused 1,3,4-oxadiazines as monoamine oxidase inhibitors[1-5], 5,6-dihydro-4*H*-1,3,4-oxadiazines prepared from 2-(β-chloro-alkyl) carboxylic acid hydrazides have anticonvulsant activity[3], DL-*trans* **4a**, 5,6,7,8,8a-hexahydro 3-phenyl-1*H*-4,1,2-benzoxadiazine and their N-benzoyl derivatives are monoamino oxidase, inhibitors and antivirus drugs[6], tetrahydrooxadiazinones derived from ephedrine as monoamine oxidase inhibitors, antidepressants and anticonvulsants[7], some 2-amino-5,6-dihydro-4*H*-1,3,4-oxadiazines as sedative, transquilizers and analgesics[8], 4-substituted 5,6-dihydro-2-*o*-hydroxy phenyl-4*H*-1,3,4-oxadiazin-5-ones as potential psychopharmacological drugs[9] and derivatives of 1,3,4-oxadiazines for antiviral activity[10].

Thus, the chemistry of 1,3,4-oxadiazines is an evolving sphere and the compounds are of much value from the pharmacological activity point of view.

The title compounds 5-undecyl-4,1,2-benzoxadiazines are prepared in a three step reaction process starting from Embelin **1**.

Preparation of N^1-5-hydroxy-6-undecyl-*p*-benzoquinon-2-yl)benzhydrazides, 3 (Scheme I)

The intention is to build up oxadiazines fused to benzene ring of quinone skeleton. Hence, the product **3** has been chosen as the starting material. This undergoes reductive cyclization with simultaneous acetylation *in situ* which resulted in the formation of compound 1-N-acetyl-6,7-di-O-acetyl-3-aryl-5-undecyl-4,1,2-benzoxazine **4** in the presence of Ac_2O, zinc powder and triethyl amine (Et_3N) in catalytic amounts. The above compounds are deacetylated to get the desired product 6,7-dihydroxy-3-aryl-5-undecyl-4,1,2-benzoxadizine **5 (Scheme II)**.

In the first stage, the more nucleophilic amino group of the acid hydrazide **2** attacks the carbonyl carbon of embelin **1** at C_2. Later, dehydration and ketoenol tautomerism would bring about the formation of the product **3**. This is in accordance with the mechanism proposed by Kenneth H. Dudley[11] and Libermann[12,13] in the reaction between hydroxy quinone with amino derivatives.

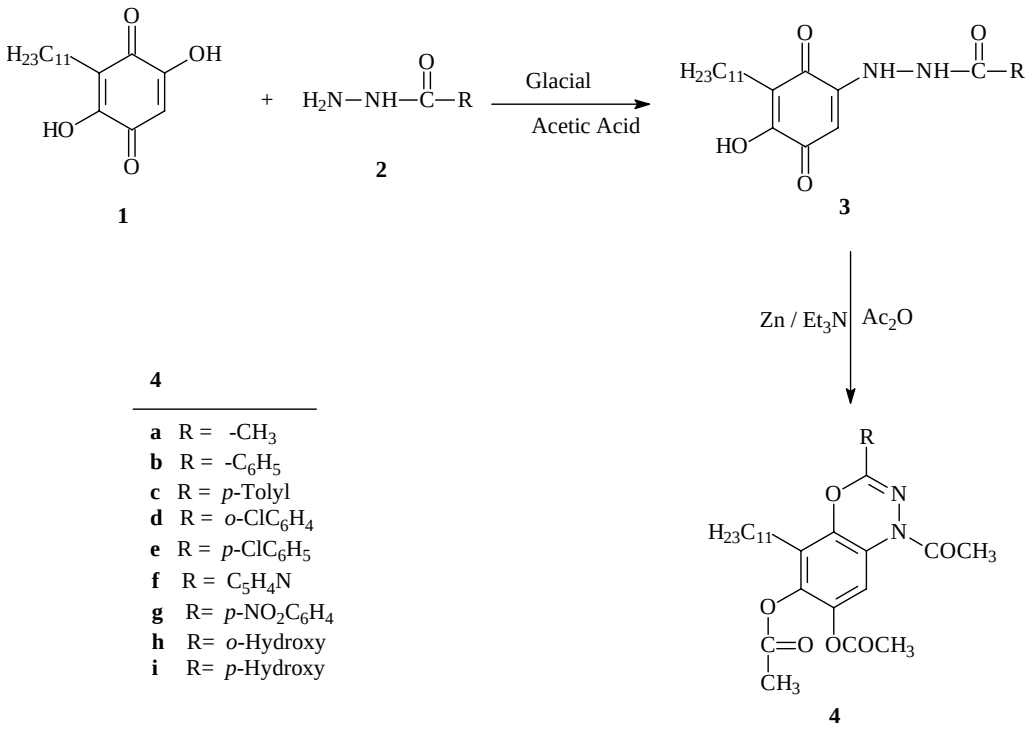
In the second stage during the cyclization the non-bonding electron pair of the hydroxyl oxygen (C_1) attacks the amide carbonyl carbon of the hydrazide leading to cyclization with aromatization followed by subsequent acetylation. The product **4** on deacetylation gives the product **5**.

The products **3**, **4**, **5** were crystallized from suitable solvents, and homogeneity was checked and confirmed by TLC. The proposed structures of newly synthesized compounds **3**, **4**, **5** are in agreement with their spectral (IR, ^{1}H NMR, mass) data and elementary analysis (**Table I, Table II** and **Table III**).

Experimental Section

All melting points were recorded on Cintex melting point apparatus and are uncorrected. IR spectra were recorded in Nujol on IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a Jeol-JMS-D mass spectrometer at 70 eV.

The various substituted 6,7-dihydroxy-3-aryl-5-undecyl-4,1,2-benzoxadiazines have been prepared. Representative methods of preparation of compounds

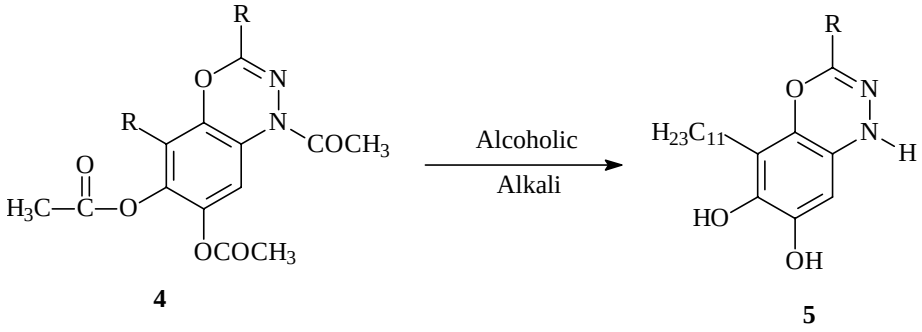


1 **2** **3** **4**

4

a R = -CH_3
b R = -C_6H_5
c R = *p*-Tolyl
d R = *o*-ClC_6H_4
e R = *p*-ClC_6H_5
f R = C_5H_4N
g R= *p*-$NO_2C_6H_4$
h R= *o*-Hydroxy
i R= *p*-Hydroxy

Scheme I



4 **5**

5

a R= -CH_3
b R= -C_6H_5
c R= *p*-Tolyl
d R= *o*-ClC_6H_4
e R= *p*-ClC_6H_4
f R = C_5H_4N
g R = *p*-$NO_2C_6H_4$
h R = *o*-OHC_6H_4
i R = *p*-OHC_6H_4

Scheme II

Table I — Physical characterization data of compounds **3a-i**

Compd	R	Yield (%)	Mol. Formula (Mol. wt.)	m.p. °C	Found % (Calcd) C	H	N
3a	CH_3	60	$C_{19}H_{30}N_2O_4$ (350)	152	65.14 (65.12	8.57 8.52	8.06 8.00)
3b	C_6H_5	72	$C_{24}H_{32}N_2O_4$ (412)	189	69.90 (69.89	7.76 7.70	6.79 6.72)
3c	*p*-Tolyl	60	$C_{25}H_{34}N_2O_4$ (426)	133	70.42 (70.38	7.98 7.97	6.57 6.54)
3d	*o*-ClC_6H_4	68	$C_{24}H_{31}N_2O_4Cl$ (446.5)	165	64.50 (64,49	6.94 6.92	6.27 6.25)
3e	*p*-ClC_6H_4	72	$C_{24}H_{31}N_2O_4Cl$ (446.5)	119	64.50 (64.49	6.94 6.90	6.27 6.21)
3f	C_5H_4N	62	$C_{23}H_{31}N_3O_4$ (413)	155	66.82 (66.79	7.50 7.48	10.16 10.12)
3g	*p*-$NO_2C_6H_4$	60	$C_{24}H_{31}N_3O_6$ (457)	180	63.01 (63.00	6.78 6.72	9.19 9.18)
3h	*o*-OHC_6H_4	81	$C_{24}H_{32}N_2O_5$ (428)	135	67.28 (67.20	7.47 7.41	6.54 6.51)
3i	*p*-OHC_6H_4	75	$C_{24}H_{32}N_2O_5$ (428)	133	67.28 (67.24	7.47 7.43	6.54 6.53)

Table II — Physical characterization data of compounds **4a-i**

Compd	R	Yield (%)	Mol. Formula (Mol. wt.)	m.p. °C	Found % (Calcd) C	H	N
4a	CH_3	86	$C_{25}H_{36}N_2O_6$ (460)	110	64.28 (64.24	8.03 8.00	6.25 6.21)
4b	C_6H_5	65	$C_{30}H_{38}N_2O_6$ (522)	103	68.96 (68.94	7.27 7.26	5.36 5.32)
4c	*p*-Tolyl	68	$C_{31}H_{40}N_2O_6$ (536)	103	69.40 (69.40	7.42 7.40	5.22 5.21)
4d	*o*-ClC_6H_4	87	$C_{30}H_{37}N_2O_6Cl$ (466.5)	101	69.09 (69.04	19.26 19.24	5.37 5.35)
4e	*p*-ClC_6H_4	74	$C_{30}H_{37}N_2O_6Cl$ (466.5)	106	69.09 (69.02	19.26 19.22	5.37 5.35)
4f	C_5H_4N	80	$C_{29}H_{32}N_3O_6$ (511)	133	66.53 (66.49	7.07 7.01	8.03 8.00)
4g	*p*-$NO_2C_6H_4$	75	$C_{30}H_{37}N_3O_8$ (567)	111	63.49 (63.42	6.52 6.49	7.40 7.32)
4h	*o*-OHC_6H_4	75	$C_{30}H_{38}N_2O_7$ (433)	106	66.91 (66.89	7.06 7.00	5.20 5.19)
4i	*p*-OHC_6H_4	72	$C_{30}H_{38}N_2O_7$ (433)	102	66.91 (66.89	7.06 7.00	5.20 5.18)

3, 4 and **5** along with their spectral data are described below.

Preparation of N^1-(5-hydroxy-6-undecyl-*p*-benzoquinone-2-yl)-benzohydrazide, 3

A mixture of Embelin (0.01 mole) and acid hydrazide (0.01 mole) were dissolved in absolute alcohol (20 mL) and refluxed on a water-bath for 3 hr. The solid separated was filtered. The mother liquor was poured over crushed ice. The separated reddish brown solid was filtered, dried and purified by recrystallization from ethanol.

Spectral data of N^1-5-hydroxy-6-undecyl-*p*-benzoquinone-2-yl)-benzohydrazide: IR (Nujol): 3320

Table III — Physical characterization data of compounds **5a-i**

Compd	R	Yield (%)	Mol. Formula (Mol. wt.)	m.p. °C	Found % (Calcd) C	H	N
5a	CH_3	72	$C_{19}H_{30}N_2O_3$ (334)	175	68.26 (68.16	8.92 8.91	8.38 8.29)
5b	C_6H_5	85	$C_{24}H_{32}N_2O_3$ (396)	169	72.72 (72.68	8.08 8.04	7.07 7.00)
5c	*p*-Tolyl	82	$C_{24}H_{34}N_2O_3$ (398)	139	72.36 (72.30	8.54 8.52	7.03 7.00)
5d	*o*-ClC_6H_4	68	$C_{24}H_{31}N_2O_3Cl$ (430.5)	95	66.89 (66.82	7.20 7.10	6.50 6.48)
5e	*p*-ClC_6H_4	70	$C_{24}H_{37}N_2O_3Cl$ (430.5)	140	66.89 (66.84	7.20 7.18	6.50 6.47)
5f	C_5H_4N	69	$C_{23}H_{31}N_3O_3$ (383)	183	72.06 (72.00	8.09 8.06	7.30 7.29)
5g	*p*-$NO_2C_6H_4$	66	$C_{24}H_{31}N_3O_5$ (441)	203	65.31 (65.21	7.02 7.01	6.34 6.28)
5h	*o*-OHC_6H_4	80	$C_{24}H_{32}N_2O_4$ (412)	159	69.90 (69.87	7.76 7.71	6.79 6.77)
5i	*p*-OHC_6H_4	77	$C_{24}H_{32}N_2O_4$ (412)	129	69.90 (69.41	7.76 7.72	6.79 6.72)

(-N-H), 3200 (-OH), 1670 (-C=O), 1480-1580 (aromatic, C-H), 1370-1390 (benzylic protons of the undecyl side chain), 1320-1330 (-CH_3- side chain), 1040-1120 (aromatic C-H), 900 (vinylic H), 760 cm^{-1} (*p*-C_6H_5); ^{1}H NMR ($CDCl_3$): δ 0.90 (3H of CH_3 of C_{11}), 1.25 (18H), 2.6 (Benzylic-2H), 6.1 (vinylic-H), 7.55 (aromatic, 5H), 7.9 (-NH), 8.00 (-NHCO).

1N-Acetyl-6,7-diacetyl-3-aryl-5-undecyl-4,1,2-benzoxadiazines, 4

N^1-(5-Hydroxy-6-undecyl-*p*-benzoquinone-2-yl)-benzhydrazide (0.01 mole) was dissolved in acetic anhydride (15 mL) and to it zinc powder and triethylamine in catalytical amounts were added and refluxed for 6 hr on a water-bath. The reaction-mixture was cooled to RT and poured over crushed ice and left overnight. The separated solid was filtered, dried and purified by recrystallization from suitable solvents.

Spectral data of 4

IR (Nujol): 1680 (-CO-NH_2), 1760 cm^{-1} (-CO-CH_3); ^{1}H NMR ($CDCl_3$): δ 0.8 (t, 3H, end methyl), 1.20 (m, 18H, middle chain), 1.8 (t, 2H, allylic -CH_2), 2.2 (s, 3H, -N-$COCH_3$), 2.3 (s, 6H, 2OAc) and 7.00 - 7.25 (m, 6H, aromatic).

6,7-Dihydroxy-3-aryl-5-undecyl-4,1,2-benzoxadiazines, 5

Compounds **3** (0.01 mole) was treated with 0.05% alcoholic solution (10 mL) and was refluxed on a steam-bath for 30 min. The reaction mixture was cooled to 0°C and neutralized with chilled 1% hydrochloric acid adjusting the *p*H to 7.0. The solid which separated out was filtered and purified by recrystallization from ethanol.

Spectral data of 5

IR (Nujol): 3200 (-NH), 3400 - 3600 cm^{-1} (-OH); ^{1}H NMR ($CDCl_3$): δ 0.8 (t, 3H, end methyl), 1.20 (m, 18H, middle chain), 1.8 (t, 2H, allylic CH_2), 5.4 (br, s, -NH-) and 7.1-7.4 (m, 6H, 5Ar-H and 1H of fused oxadiazine system).

Biological evaluation

Antifungal activity

The results of antifungal tests show that all the substituted N-acetyl-2-aryl-6,7-diacetoxy-8-undecyl benzoxadiazines, have maximum germination inhibition even at low concentration (120 μg/mL) for both the fungi *i.e.*, *Curvularia lunata* and *Fusarium oxysporum* when compared to other compounds, the aryl, methyl substituted benzoxadiazines have maximum inhibition.

Antibacterial activity

The 4-substituted oxadiazines are tested against four bacterial organisms. They are *Bacillus subtilis*, *Bacillus polymyxa*, *Escheria coli* and *Proteus vulgaris*. The aryl substituted benzoxadiazines have activity against all the bacteria.

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