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SYNTHESIS OF NITROGEN-OXYGEN HETEROCYCLES FROM CARBOHYDRATE PRECURSOR

Synthesis and Spectra of 2-(5'-Aryl-1', 3',4'-Oxadiazol-2'-yl)-1, 6, 6-Trimethyl-4-Oxo-4, 5, 6, 7-Tetrahydroindoles

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6, 6-Dimethyl-4-oxo-4, 5, 6, 7-tetrahydroindol-2-carboxaldehyde (2) condensed with benzoylhydrazine to afford the corresponding benzoylhydrazone derivative '3'. Oxidative cyclization of 3 gave the corresponding 1, 3, 4-oxadiazole-mercuric complex '4'. On the other hand, the methylated aldehyde '5' condensed with a number of aryl and acylhydrazines to afford the corresponding hydrazones '6-18'. Oxidative cyclization of the acylhydrazones gave the corresponding 1, 3, 4-oxadiazoles '19-27'. The structures were confirmed by IR, ^{1}H-NMR and mass spectra.

Key words: Tetrahydroindole, Benzoylhydrazone, Oxadiazole.

Introduction

It has been shown that oxadiazoles possess central nervous system (CNS) properties [1-3] and that the 1, 3, 4,-oxadiazoles have a large number of uses in drug synthesis [4-5]. So, we start a project for the synthesis of such derivatives by the use of a cheap precursor such as carbohydrate materials.

Experimental

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on Unicam SP 1025 and Unicam SP 2000 Infrared Spectrophotometer. ^{1}H-NMR spectra were recorded on Varian EM 390, 90 MHz NMR Spectrometer. Mass spectrum was recorded on Hewlett Packard GC/MS 5998A. Microanalyses were performed at the Microanalytical Laboratory, Faculty of Science, Cairo University, Cairo, Egypt. Solutions were evaporated under diminished pressure unless otherwise stated.

2-Formyl-6, 6-dimethyl-4-oxo-4, 5, 6, 7-tetrahydroindol-2-benzoylhydrazone (3). A solution of 2 (10 mmol) in ethanol (20 ml) containing acetic acid (0.1 ml) was treated with benzoylhydrazine (10 mmol). The reaction mixture was refluxed on a water bath for 15 mins, and the hydrazone derivative that separated on cooling was filtered off, washed with ethanol, dried and crystallized from ethanol. The analytical data are given in Table 1.

Oxidative cyclization of 3 (4). A solution of 3 (6.5 mmol) was treated with yellow mercuric oxide (3 g), magnesium oxide (0.4 g) and iodine (1.5 g) at room temperature for 48 hrs under anhydrous condition. The reaction mixture was filtered off, and the organic layer washed with potassium iodide solution (50 ml), sodium thiosulphate (50 ml) and water resectively and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a reddish-brown solid '4' which crystallized from ethanol. The analytical data are given in Table 1.

1, 6, 6-Triethyl-4-oxo-4, 5, 6, 7-tetrahydroindol-2-carboxaldehyde (5). Method A. A mixture of 2 (50 mmol), anhydrous potassium carbonate (4.0 g), methyl iodide (150 mmol) and acetone (120 ml) was heated under reflux for 5 hrs. The solvent was removed by distillation to give 5.

Method B. To an acetone solution (120 ml) of 2 (50 mmol) was added powdered potassium hydroxide (14 g) with cooling. After few minutes, methyl iodide (100 mmol) was added to the solution and stirred for 10 minutes at room temperature. Benzene (90 ml) was added to the reaction mixture and the insoluble materials were removed by filtration. Evaporation of the solvent gave 5 which recrystallized from ethanol. The analytical data are given in Table 1.

2-Formyl-1, 6,6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydroindol-2-hydrazones (6-18). A solution of 5 (9.8 mmol) in ethanol (20 ml) containing acetic acid (0.2 ml) was treated with the required hydrazine (9.8 mmol). Worked up as before (as in compound 3) gave the hydrazone derivative. The analytical data are given in (Table 1).

2-(5'-Aryl-1', 3', 4'-oxadiazol-2'-yl)-1, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydroindoles (19-27). A solution of the required acylhydrazone (10-18) in dry ether (50 ml) was treated with yellow mercuric oxide (3 g), magnesium oxide (0.4 g) and iodine (1.5 g) at room temperature for 48 hrs under anhyrous condition. Worked up as before (as in compound 4) gave the oxadiazole derivative. The analytical data are given in Table 1.

Results and Discussion

Periodate oxidation of 6,6-dimethyl-4-oxo-4, 5, 6, 7-tetrahydro-2-(*D*-arabino-tetrahydroxybutyl) indole [6] (1)

Table 1. Analytical Data of the Prepared Compounds (3-27).

Compound	m.p. (°C)	Yield %	Molecular formula	E.A. calc. / found (%) C	H	N	X
3	190	93	$C_{18}H_{19}N_3O_2$	69.9	6.15	13.59	–
				70.0	6.15	13.62	–
4	190	25	$C_{36}H_{32}N_6O_4.Hg$	53.14	3.94	10.33	–
				53.18	4.0	10.18	–
5	128	95	$C_{12}H_{15}NO_2$	70.24	7.32	6.83	–
				70.25	7.4	6.77	–
6	172	89	$C_{18}H_{21}N_3O$	73.22	7.12	14.24	–
				73.50	7.21	14.20	–
7	265	76	$C_{18}H_{20}N_4O_3$	63.53	5.88	16.47	–
				63.35	5.91	16.51	–
8	227	95	$C_{18}H_{20}N_4O_3$	63.53	5.88	16.47	–
				63.24	6.12	16.50	–
9	255	88	$C_{18}H_{19}N_5O_5$	56.10	4.94	18.18	–
				55.93	5.10	18.19	–
10	203	64	$C_{19}H_{21}N_3O_2$	70.59	6.50	13.00	–
				71.00	6.51	13.00	–
11	257	80	$C_{19}H_{20}N_3O_2Cl$	63.78	5.59	11.75	9.93
				63.81	6.00	11.91	10.01
12	253	76	$C_{20}H_{23}N_3O_2$	71.22	6.82	12.46	–
				71.23	6.85	12.41	–
13	185	74	$C_{20}H_{23}N_3O_3$	67.99	6.52	11.90	–
				68.02	6.55	11.48	–
14	260	76	$C_{19}H_{21}N_3O_3$	67.26	6.19	12.39	–
				67.30	6.18	12.51	–
15	251	76	$C_{19}H_{21}N_3O_3$	67.26	6.19	12.39	–
				67.29	6.16	12.43	–
16	79	67	$C_{19}H_{20}N_3O_2Br$	56.72	4.98	10.45	19.9
				56.72	4.97	10.5	20.01
17	260	86	$C_{19}H_{20}N_4O_4$	61.96	5.43	15.22	–
				62.00	5.42	15.25	–
18	240	81	$C_{18}H_{20}N_4O_2$	66.64	6.17	17.28	–
				66.50	6.20	17.30	–
19	186	60	$C_{19}H_{19}N_3O_2$	71.03	5.92	13.08	–
				71.22	6.11	13.12	–
20	202	50	$C_{19}H_{18}N_3O_2Cl$	64.14	5.06	11.81	9.99
				63.83	5.20	11.86	10.01
21	168	33	$C_{20}H_{21}N_3O_2$	71.64	6.27	12.54	–
				71.50	6.41	12.32	–
22	179	50	$C_{20}H_{21}N_3O_3$	68.38	5.98	11.97	–
				68.56	6.03	12.00	–
23	211	25	$C_{19}H_{19}N_3O_3$	67.66	5.64	12.46	–
				68.00	5.42	12.50	–
24	214	50	$C_{19}H_{19}N_3O_3$	67.66	5.64	12.46	–
				67.70	5.60	12.51	–
25	235	50	$C_{19}H_{18}N_3O_2Br$	57.00	4.50	10.50	20.00
				57.00	4.13	10.29	20.37
26	205	50	$C_{19}H_{18}N_4O_4$	62.30	4.92	15.30	–
				62.16	5.33	15.31	–
27	220	33	$C_{18}H_{18}N_4O_2$	67.05	5.59	17.38	–
				67.11	5.73	17.62	–

Note: In compound 4, Hg calc./found 24.6/24.8

afforded the corresponding formyl derivative [7] '2'. Acid catalyzed condensation of this aldehyde '2' with benzoylhydrazine afforded the corresponding hydrazone derivative '3' (Scheme 1), that characterized by bands at 1610 (C=N), 1645 (C=O), 1665 (CONH) and 3240 cm^{-1} (NH) in its IR spectrum.

In continuation to our work [8-11], when 2-formyl-6,6-dimethyl-4-oxo-4, 5, 6, 7-tetrahydroindol-2-benzoylhydrazone '3' was oxidized with iodine and yellow mercuric oxide, it gave reddish-brown mercuric complex '4' (Scheme 1).

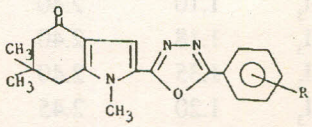
On the other hand, methylation [12,13] of the aldehyde '2' afforded 1,6,6-trimethyl-4-oxo-4,5,6,7-tertrahydroindol-2-carboxaldehyde '5' in crystalline form (Scheme 1). This aldehyde was characterized by the disappearance of the NH absorption band in its IR spectrum. ^{1}H-NMR($CDCl_3$) spectrum appeared as expected, with no NH proton resonance and new (N-CH_3) protons signal at δ 4.05 as singlet in addition to the already present signals.

Furthermore, condensation of this aldehyde with a number of aryl-and acylhydrazines gave the corresponding arylhydrazones '6-9' and acylhydrazones '10-18' respectively (Scheme 1). The infrared spectral data of these hydrazones revealed absorption bands at 1605-1625 (C=N), 1645-1680 (C=O) and 3270-3450 cm^{-1} (NH).

^{1}H-NMR(DMSO-d_6) spectrum of the arylhydrazone '8' showed resonance at δ 1.6 (6H, s, $2CH_3$), 2.8 and 3.1 (4H, 2s, $2CH_2$), 4.18 (3H, s, N-CH_3), 6.25 (1H, s, CH, of pyrrole ring), 7.3-8.4 (4H, 2d, Ar-H), 8.63 (1H, s, CH=N) and 12.9 ppm (1H, s, NH). Mass spectral data of 18 showed *m/z*: 324 (36%), 146 (100%) and 106(38%).

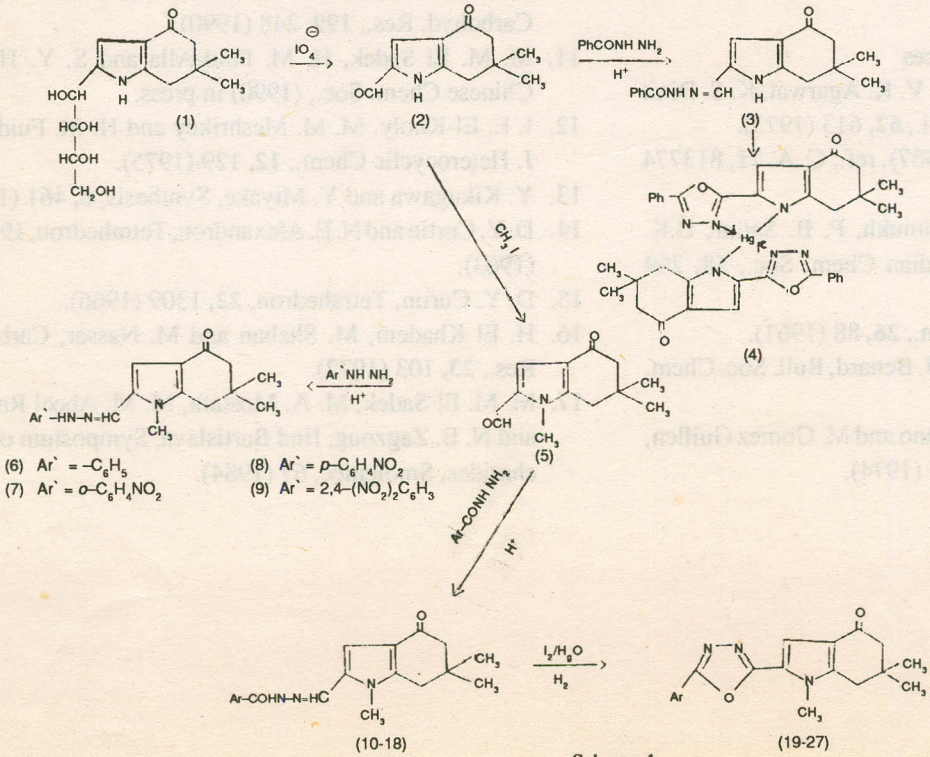
Oxidative cyclization of 2-formyl-1, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydroindol-2-acylhydrazones '10-18' with iodine and yellow mercuric oxide in dry ether afforded [14-17] the corresponding 2-(5'-aryl-1', 3', 4'-oxadiazol-2'-yl)-1, 6, 6-

TABLE 2. INFRARED SPECTRAL DATA OF 2-(5'-ARYL-1', 3', 4'-OXADIAZOL-2'-YL)-1, 6, 6-TRIMETHYL-4-OXO-4, 5, 6, 7-TETRAHYDROINDOLES.



R	IR (KBr) cm^{-1}	
	C=N	C=O
H	1625	1670
p-Cl	1625	1660
p-CH_3	1620	1670
p-OCH_3	1625	1670
o-OH	1625	1665
p-OH	1625	1665
p-Br	1620	1675
p-NO_2	1620	1675

Notes: (1). In case of pyridinyl derivative, the IR spectrum showed bands at 1625 (C=N) and 1675 cm^{-1} (C=O). (2). In case of *o*-and *p*-hydroxyphenyl, the OH band appeared at 3500 cm^{-1}.



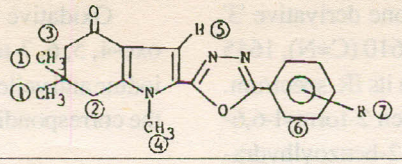
(6) Ar` = $-C_6H_5$
(7) Ar` = *o*-$C_6H_4NO_2$
(8) Ar` = *p*-$C_6H_4NO_2$
(9) Ar` = 2,4-$(NO_2)_2C_6H_3$

(10) Ar = $-C_6H_5$
(11) Ar = *p*-C_6H_4Cl
(12) Ar = *p*-$C_6H_4CH_3$
(13) Ar = *p*-$C_6H_4OCH_3$
(14) Ar = *o*-C_6H_4OH
(15) Ar = *p*-C_6H_4OH
(16) Ar = *p*-C_6H_4Br
(17) Ar = *p*-$C_6H_4NO_2$
(18) Ar = *p*-C_5H_4N

(19) Ar = $-C_6H_5$
(20) Ar = *p*-C_6H_4Cl
(21) Ar = *p*-$C_6H_4CH_3$
(22) Ar = *p*-$C_6H_4OCH_3$
(23) Ar = *o*-C_6H_4OH
(24) Ar = *p*-C_6H_4OH
(25) Ar = *p*-C_6H_4Br
(26) Ar = *p*-$C_6H_4NO_2$
(27) Ar = *p*-C_5H_4N

Scheme 1.

TABLE 3. ^{1}H-NMR SPECTRA OF 2-(5'-ARYL-1', 3', 4'-OXADIAZOL-2'-YL)-1, 6, 6-TRIMETHYL-4-OXO-4, 5, 6, 7-TETRAHYDROINDOLES.



R	Solvent	δppm						
		H-1	H-2	H-3	H-4	H-5	H-6	H-7
H	$CDCl_3$	1.20	2.45	2.75	4.05	7.35	7.55-8.2	—
p-Cl	$CDCl_3$	1.10	2.40	2.51	4.10	6.90	7.45-8.0	—
p-CH_3	$CDCl_3$	1.18	2.40	2.45	4.02	7.30	7.33-7.95	2.72
p-OCH_3	$CDCl_3$	1.35	2.40	2.67	3.85	6.47	6.70-7.35	3.72
o-OH	$CDCl_3$	1.20	2.45	2.75	4.05	7.30	7.35-8.40	12.5
p-OH	$CDCl_3$	1.15	2.30	2.50	4.05	7.30	7.40-8.30	12.5
p-Br	$CDCl_3$	1.20	2.45	2.75	4.05	7.33	7.65-7.95	—
p-NO_2	$CDCl_3$	1.20	2.50	2.75	4.05	7.0	7.80-8.40	—

Note: In case of pyridinyl derivative, the NMR ($CDCl_3$) showed proton resonance at δs1.1 (H-1), 2.22 (H-2), 2.38(H-3), 4.05 (H-4) 6.65 (H-5) and 8.0-8.45 ppm (Py-H).

trimethyl-4-oxo-4, 5, 6, 7 - tetrahydroindoles '19-27' in crystalline forms. IR spectra of these oxadiazoles indicated the disappearance of the amide absorption bands (CO and NH), (Table 2).

^{1}H-NMR ($CDCl_3$) spectra showed in all cases the disappearance of both the imino proton of the hydrazone residue as well as the formyl proton at (C-2) of the tetrahydroindole ring (Table 3).

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