TETRACYCLIC COMPOUNDS FROM 1-OXO-1,2,3,4,5,6-HEXAHYDROCYCLOOCTA[*b*]INDOLE. SYNTHESIS OF OXAZOLO[4′5′:8,7]CYCLOOCTA[*b*]INDOLES.

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Abstract

Japp-Klingmann method was used to diazotise aniline derivatives and 2-hydroxymethylenecyclooctanone 2 to obtain cyclooctan-1′,2′-dione-1′-arylhydrazone 3 which upon acid cyclisation using kents reagent gave 1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole 4. These on treatment with hydroxylammine hydrochloride in pyridine afforded the respective 1-hydrooxyimino-1,2,3,4,5,6-hexahydrocycloocta[*b*] indole 5. Further 5 was reacted with acetyl chloride at room temperature to give oxazolo[4′5′:8,7]cycloocta[*b*]indoles 6.

Indroduction

Nitrogen heterocyclic compounds play a vital role in the metabolism of living cells, which are widely distributed in nature and are essential to life. Many indole derivatives have been reported which have excellent medicinal properties such as antibacterial[1], antifungal[2], antitumour[3], antiinflammatory[4], antituberculosis[2] activities. Also cyclooctane ring fused with indoles known as iprindoles have antidepressant activities[2]. This fact has aroused the interest in devising a method to synthesise cyclooctane ring fused with indoles. 1-Hydroxyimino-1,2,3,4,5,6-hexahydrocycloocta[*b*] indoles 5 were prepared from 1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indoles 3[5] which served as synthons for the preparation of oxazolo[4′5′:8,7]cycloocta[*b*]indoles 6. (Scheme-1)

Experimental

General Information:

All melting points were determined in open capillary tubes using mettler FB-5 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR – 8201 (PC), spectrometer using KBr pellets and only noteworthy absorption levels (in reciprocal centimeter) are listed. The proton NMR spectra were recorded on varian AMX 400 spectrometer. Chemical shifts were recorded in parts per million (δ) downfield from the internal standard TMS. Signal multiplicities are represented by s (singlet) bs (broad singlet) and m (multiplet). Satisfactory micro analyses were obtained on Carlo Erba 1106 and Perkin Elmer model 240 CHN analyzers.

Preparation of 2-hydroxymethylenecyclooctanone 2

2-Hydroxymethylenecyclooctanone 2 was prepared by formylation of cyclooctanone. For this cyclooctanone (2.52 mL, 0.02 mole) was added in portions over a period of five minutes to a well cooled vigorously stirred mixture of sodium methoxide (from 0.517 g of Sodium in 5 mL of absolute methanol), dry ether (4 mL) and ethyl formate (1.8 mL, 0.02 mole). The mixture was stirred in the ice bath for another 1 hour and then allowed to stand at room temperature for 24 hours. At the end of the period, ice and water were added to the yellow solid mass and acidified with concentrated hydrochloric acid. The oil that separated out was extracted with ether, washed with cold water and brine and dried over anhydrous sodium sulphate. The residual oil after the removal of solvent was distilled under reduced pressure to give 2-hydroxymethylenecyclooctanone 2 as viscous liquid with 70% yield.

Preparation of cyclooctan-1', 2'-dione-1'-arylhydrazones 3

A mixture of 2-hydroxymethylenecyclooctanone 2 (0.004 mole) and sodium acetate trihydrate (1g in 3 mL water) in methanol (6 mL) was cooled in ice. A solution of appropriate aniline derivative 1 (0.004 mole) in aqueous hydrochloric acid (1.08 mL of HCl in 1.04 mL of water) was diazotised with cold saturated solution of sodium nitrite (0.35g in 0.8 mL water) between 0°C and -5°C. The diazotised solution was added in small portions to the ice cooled mixture containing 2-hydroxymethylenecyclooctanone 2 over a period of half an hour with constant stirring. After standing for half an hour more, the resulting solid was filtered, washed with water, dried and crystallised from ethanol.The physical and spectral data of the hydrazones 3 are given in Table 1.

Cyclisation of hydrazones to 1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indoles 4

The appropriate hydrazone 3 (0.01 mole) in a mixture of acetic acid (20 mL) and concentrated hydrochloric acid (5 mL) was refluxed on oil bath pre-heated to 125°C-130°C for 2 hours. The contents were then cooled and poured into ice water with stirring. The separated brown solid was filtered and purified through a column of silica gel and eluting with petroleum ether-ethyl acetate (98:2) mixture. The physical and spectral data of all compounds are given in Table 2.

Preparation of 1-hydroxyimino-1,2,3,4,5,6-hexahydrocycloocta[*b*]indoles 5

A mixture of 1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole derivatives 4 (0.005 mole), hydroxylamine-hydrochloride (3.5g, 0.005 mole), dry pyridine (5 mL) and absolute ethanol (10 mL) was heated on a water bath under nitrogen atmosphere for I hour. The residue obtained on evaporation of excess solvent was diluted with water (10 mL) and extracted using chloroform (3x25 mL). The extract was successively washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulphate. Evaporation of the solvent followed by crystallisation with petroleum ether-benzene mixture yielded 5 as colourless prisms. The physical and spectral data are provided in Table-3.

Preparation of oxazolo[4',5':8,7]cycloocta[*b*]indoles 6

Acetyl chloride (3mL, excess) was added slowly to 1-hydroxyimino-1,2,3,4,5,6-hexahydrocycloocta[*b*]indoles 5 (0.001 mole) under cold condition and stirred at room temperature for 24 hours. The contents were poured into cold water and extracted with chloroform (3x15 mL). The combined organic extracts were washed with water, dried over anhydrous sodium sulphate and concentrated to a brown viscous liquid. This was purified by passing through a silica gel column and eluting with petroleum ether-ethylacetate (75:25) to afford 6 as colourless prism. The physical and spectral data of the compounds are given in Table-4

Result and Discussion

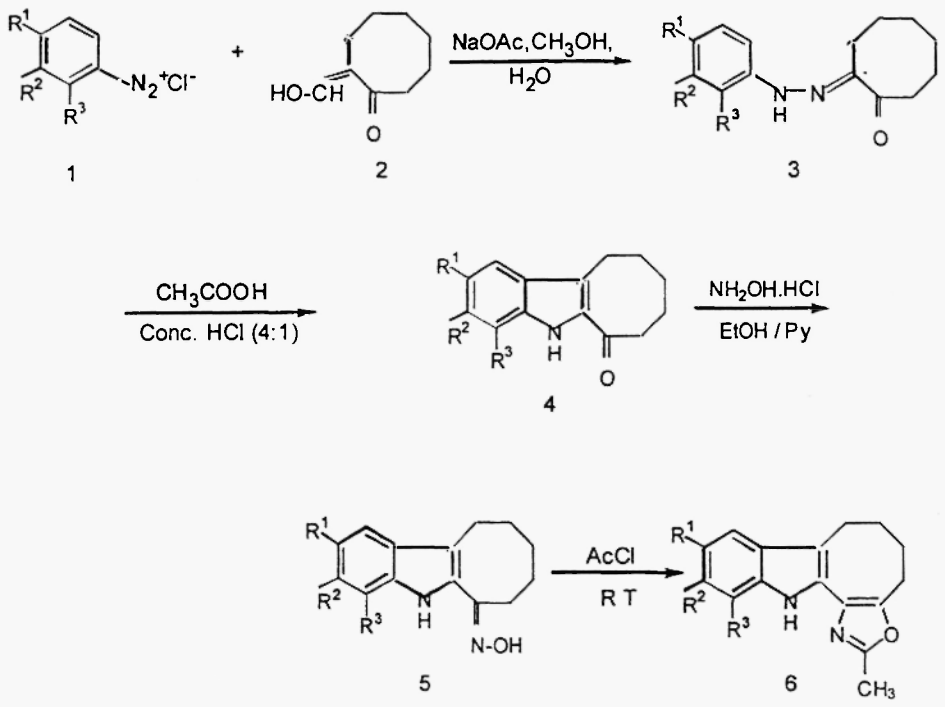
Japp-Klingemann reaction[7] was used to prepare 8-methyl-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole 4a which is needed for synthesising novel type of 2,9-dimethyloxazolo [4',5':8,7]cycloocta[*b*]indole 6a.

Condensation of the diazotised solution of *p*-toluidine derivative 1 with 2-hydroxymethylenecyclooctanone 2 gave an yellow coloured compound. m.p. 90-91°C, its I.R. spectrum showed the absorption bands at 1614 cm^{-1} due to carbonyl stretching and at 1585 cm^{-1} due to C=N stretching. Its proton NMR spectrum registered a singlet at δ 2.30 due to methyl group at C_4. Methylene protons at C_3' and C_8' protons resonate as multiplets at δ 2.73 and at δ 2.66 respectively and C_4' and C_7' methylene protons appeared as multiplets at δ 1.80 and at δ 1.72 respectively, whereas C_5' and C_6' protons resonate as a multiplet at δ 1.50 – 1.60. The resonance signal corresponding to four aromatic protons showed a multiplet at δ 7.09 – 7.26 and a broad singlet at δ 14.00 for NH proton. The above spectrum clearly indicates that the structure of the compound was 3a. The elemental analysis of the compound agreed well with the proposed molecular formula $C_{15}H_{20}N_2O$ augementing the structure of compound to be cyclooctan-1', 2'-dione-1' -*p*-tolylhydrazone 3a.

The cyclooctan-1',2'-dione-1'-*p*-tolylhydrazone 3a upon acid cyclisation using Kent's reagent gave the product, m.p. 176 – 177°C. Its IR spectrum showed absorption bands due to carbonyl stretching at 1626cm^{-1} and NH stretching at 3306 cm^{-1} and its proton NMR spectrum displayed a singlet at δ 2.45 for C_8-CH_3, three aromatic protons envelop at δ 7.16 – 7.46. C_2 and C_6 protons appeared as multiplets centered at δ 3.00 and at δ 3.27 respectively. Methylene protons at C_3, C_4 and C_5 appeared as a multiplet between δ 1.74 – 1.86. The appearance of NH proton as a broad singlet at δ 9.01 clearly indicates that the compound 3a was cyclised to the product 4a. The elemental analysis of the compound 4a C, 79.22%; H, 07.49%; N, 06.09% agreed well with the proposed molecular formula $C_{15}H_{17}NO$. From the above data the structure of 4a was assigned to be 8-methyl-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole. A series of similar 1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indoles 4b-e were realised from 1b-e and 2 through corresponding hydrazones 3b-e. The structures 3b-e and 4b-e were confirmed by spectral and elemental analysis (Scheme 1).

8-Methyl-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole 4a on treatment with hydroxylamine hydrochloride in pyridine afforded brown solid, m.p : 135-136°C. Its IR spectrum showed an absorption band at 3462 cm^{-1} due to OH

Scheme 1



1, 3-6 a : $R^1=CH_3$, $R^2=R^3=H$
b : $R^1=R^3=H$, $R^2=CH_3$
c : $R^1=R^2=H$, $R^3=CH_3$
d : $R^1=Cl$, $R^2=R^3=H$
e : $R^1=R^2=R^3=H$

Table1: Physical and spectral data of compounds 3a-e

Compound	M.P. (°C) Solvent	Yield (%)	IR (ν)	Molecular Formula		Analysis Calcd.	Found
3a	90-91	75	2912,1614,	$C_{15}H_{20}N_2O$	C	73.74	73.69
	PE-EA		1585	(244.34)	H	08.25	08.21
					N	11.47	11.41
3b	45-46	69	2925,1621,	$C_{15}H_{20}N_2O$	C	73.74	73.68
	PE-EA		1589	(244.34)	H	08.25	08.22
					N	11.47	11.42
3c	67-68	68	2924,1628,	$C_{15}H_{20}N_2O$	C	73.74	73.71
	PE-EA		1587	(244.34)	H	08.25	08.20
					N	11.47	11.39
3d	105-106	72	2851,1618,	$C_{14}H_{17}N_2OCl$	C	63.51	63.49
	PE-EA		1508	(264.75)	H	06.47	06.41
					N	10.58	10.53
3e	63-64	73	2920,1624,	$C_{14}H_{18}NO$	C	79.26	79.22
	PE-EA		1599	(230.31)	H	07.54	07.49
					N	12.16	12.09

PE- Petroleum Ether- 60-80°C, EA- Ethyl acetate

stretching and a band at 2923 cm^{-1} ascribable to NH stretching. The proton NMR spectrum showed a three proton singlet at d 2.45 due to C_8-CH_3. Methylene protons at C_2 and C_6 appeared as a multiplet at d 3.08- 3.16 and C_3 and C_5 protons appeared as a multiplet at d 1.75-1.83. The C_4 methylene protons resonate at d 1.48 as a multiplet. The aromatic region indicated a multiplet at d 7.03 – 7.42 for three protons. Two broad singlets at d 8.74 and d 10.55 were due to the presence of indole NH and OH protons respectively. Elemental analysis was compatible with the molecular formula $C_{15}H_{18}N_2O$. From these evidences the structure was assigned to be 1-hydroxyimino-8-methyl-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole 5a. A series of similar compounds 5b-e were realised with 4b-e. The structures of 5b-e were confirmed by spectral and elemental anlaysis.

1-Hydroxyimino-8-methyl-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole 5a was reacted with acetyl chloride at room temperature for 24 hours to afford a single product, m.p: 244 – 245°C. The IR spectrum exhibited absorption bands at 3294 and 1665 cm^{-1} due to a NH stretching and a C=N stretching respectively and its proton NMR spectrum showed the presence of 2 singlets for 2 methyl protons. The methyl proton in the benzene ring, C_9-CH_3, appeared substantially downfield at d 2.46, the other methyl protons in the oxazole ring, C_2-CH_3, appeared at d 2.16. The methylene protons at C_1 and C_7 appeared as two multiplets at d 2.10 and at d 2.77 respectively. The methylene protons at C_5 and C_6 resonate as two multiplets at d 1.65 and d 1.81 respectively. The resonance signal corresponding to three aromatic protons appeared as a multiplet at d 7.06 – 7.34. A broad singlet at d 7.83 was due to the presence of indole NH proton. The molecular ion peak (M+) at m/e 266 in its mass spectrum and elemental analysis C, 76.58%, H, 6.75%, N, 10.48% were in agreement with the molecular formula $C_{17}H_{18}N_2O$. Based on all these above details the compound 6a was assigned the structure 2,9-dimethyloxazolo[4¢5¢8,7]cycloocta[*b*]indole.Similarly oxazolo[4¢5¢8,7]cycloocta[*b*]indole derivatives 6b-e were prepared and their structures were confirmed by spectral and elemental analysis.

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Table 2: Physical and spectral data of compounds 4a - e

Compound	M.P.(°C) solvent	Yield (%)	IR (ν)	Molecular Formula	Analysis Calcd.	Found	^{1}H-NMR
4a	176-177	62	3306,1625	$C_{15}H_{17}NO$ (227.31)	C 79.26 H 07.54 N 06.16	79.22 07.49 06.09	1.74-1.86 (m, 6H, C_3-H_2, C_4-H_2 and C_5-H_2), 2.45 (s, 3H, C_7-CH_3), 3.00 (m, 2H, C_1-H_2), 3.27 (m, 2H, C_2-H_2) 7.16-7.46 (m, 3H, aromatic-H), 9.01 (b s, 1H, Indole NH).
4b	134-135	61	3310, 1622	$C_{15}H_{17}NO$ (227.31)	C 79.26 H 07.54 N 06.16	79.22 07.48 06.11	1.72-1.87 (m, 2H, C_4-H_2), 2.47 (s, 3H, C_7-CH_3), 2.96-3.08 (m,4H, C_1-H_2, C_5-H_2), 3.27 (m, 2H, C_2-H_2) 3.51 (m, 2H, C_5-H_2), 7.17-7.58 (m, 3H, aromatic-H), 9.10 (b s, 1H, Indole NH).
4c	164-165	59	3321, 1636	$C_{15}H_{17}NO$ (227.31)	C 79.26 H 07.54 N 05.16	79.22 07.51 06.51	1.74-1.89 (m, 6H, C_3-H_2, C_4-H_2 and C_5-H_2), 2.50 (s, 3H, C_7-CH_3), 3.02 (m, 2H, C_1-H_2), 3.29 (m, 2H, C_2-H_2), 7.05-7.56 (m, 3H, aromatic-H), 9.02 (b s, 1H, Indole NH).
4d	219-220	58	3312,1630	$C_{14}H_{14}NOCl$ (247.72)	C 67.88 H 05.70 N 05.65	67.81 05.68 05.59	1.73-1.89 (m, 6H, C_3-H_2, C_4-H_2 and C_5-H_2), 3.01 (m, 2H, C_1-H_2), 3.24 (m, 2H, C_6-H_2), 7.25-7.66 (m, 3H, aromatic-H), 9.21 (b s, 1H, Indole NH)
4e	159-160	62	3308,1630	$C_{14}H_{15}NO$ (213.28)	C 78.79 H 07.02 N 06.50	78.84 07.09 05.09	1.76-1.87 (m, 6H, C_3-H_2, C_4-H_2 and C_5-H_2), 3.02 (m, 2H, C_1-H_2), 3.30 (m, 2H, C_6-H_2), 7.12-7.71 (m, 4H, aromatic-H), 9.22 (b s, 1H, Indole NH)

PE - Petroleum Ether- 60-80°C EA - Ethyl acetate

Table 3: Physical and spectral of compounds 5a-e

Compound	M.P.(°C) solvent	Yield (%)	IR (ν)	Molecular Formula		Analysis Calcd.	Found	^{1}H-NMR
5a	135-136 PE-EA	71	3462 2923	$C_{15}H_{18}N_2O$ (242.3)	C H N	74.35 07.49 11.56	74.29 07.41 11.47	1.48 (m, 2H, C_4-H_2), 1.75-1.83 (m, 4H, C_5-H_2, C_3-H_2), 2.45 (s, 3H, C_8-CH_3), 3.08-3.16 (m, 4H, C_1-H_2, C_2-H_2), 7.03-7.42 (m, 3H, aromatic-H), 8.74 (b s, 1H, Indole NH), 10.55 (b s, 1H, OH).
5b	127-128 PE-EA	70	3464 2923	$C_{15}H_{18}N_2O$ (242.3)	C H N	74.35 07.49 11.56	74.30 07.42 11.47	1.43 (m, 2H, C_4-H_2), 1.55-1.80 (m, 4H, C_5-H_2, C_3-H_2), 2.38 (s, 3H, C_9-CH_3), 3.01-3.18 (m, 4H, C_6-H_2, C_2-H_2), 6.92-7.52 (m, 3H, aromatic-H), 8.55 (b s, 1H, Indole NH), 10.45 (b s, 1H, OH).
5c	120-121 PE-EA	74	3444 2923	$C_{15}H_{18}N_2O$ (242.3)	C H N	74.35 07.49 11.56	74.32 07.43 11.50	1.42 (m, 2H, C_4-H_2), 1.67-1.80 (m, 4H, C_5-H_2, C_3-H_2), 2.43 (s, 3H, C_{10}-CH_3), 3.01-3.18 (m, 4H, C_6-H_2, C_2-H_2), 6.92-7.52 (m, 3H, aromatic-H), 8.55 (b s, 1H, Indole NH), 10.45 (b s, 1H, OH).
5d	200-201 PE-EA	68	3429 2927	$C_{14}H_{15}N_2OCl$ (262.7)	C H N	64.00 05.75 10.66	63.95 05.67 10.58	1.40 (m, 2H, C_4-H_2), 1.65-1.79 (m, 4H, C_5-H_2, C_3-H_2), 2.99-3.10 (m, 4H, C_6-H_2, C_2-H_2), 7.06-7.54 (m, 3H, aromatic-H), 8.72 (b s, 1H, Indole NH), 10.54 (b s, 1H, OH).
5e	112-113 PE-EA	69	3389 2922	$C_{14}H_{16}N_2O$ (228.29)	C H N	73.66 07.06 12.27	73.58 07.00 12.23	1.48 (m, 2H, C_4-H_2), 1.73-1.88 (m, 4H, C_5-H_2, C_3-H_2), 3.10-3.30 (m, 4H, C_1-H_2, C_2-H_2), 7.07-7.68 (m, 3H, aromatic-H), 8.80 (b s, 1H, Indole NH), 10.65 (b s, 1H, OH).

PE: Petroleum ether: 60-80°C, EA: Ethyl acetate

Table 4: Physical and spectral of compounds 6a-e

Compound	M.P (°C) solvent	Yield (%)	IR (ν)	Molecular Formula	Analysis	Calcd.	Found	^{1}H-NMR
6a	244-245	64	3294	$C_{17}H_{18}N_2O$	C	76.66	76.58	1.65 (m, 2H, C_5-H_2), 1.81 (m, 2H, C_6-H_2),
	PE:EA		1665	(266.3)	H	06.81	06.75	2.10 (m, 2H, C_4-H_2), 2.16 (s, 3H, C_2-CH_3),
					N	10.52	10.48	2.46 (s, 3H, C_1-CH_3), 2.77 (m, 2H, C_7-H_2),
								7.06-7.34 (m, 3H, aromatic-H), 7.83 (b s, 1H, Indole NH).
6b	264-265	66	3321	$C_{17}H_{18}N_2O$	C	76.66	76.59	1.58 (m, 2H, C_5-H_2), 1.75 (m, 2H, C_7-H_2),
	PE-EA		1652	(266.3)	H	06.81	06.76	2.06 (m, 2H, C_4-H_2), 2.09(s, 3H, C_1-CH_3),
					N	10.52	10.49	2.40 (s, 3H, C_{10}-CH_3), 2.72(m, 2H, C_7-H_2),
								7.02-7.40 (m, 3H, aromatic-H), 7.70 (b s, 1H, Indole NH).
6c	289-290	69	3294	$C_{17}H_{18}N_2O$	C	76.66	76.57	1.64 (m, 2H, C_5-H_2), 1.76 (m, 2H C_6-H_2),
	PE-EA		1650	(266.3)	H	06.81	06.74	2.07 (m, 2H, C_4-H_2), 2.10 (s, 3H, C_2-CH_3),
					N	10.52	10.47	2.41 (s, 3H, C_{11}-CH_3), 2.74(m, 2H, C_7-H_2),
								7.00-7.50 (m, 3H, aromatic-H), 7.72 (b s, 1H, Indole NH).
6d	301-302	65	3304	$C_{16}H_{15}N_2OCl$	C	67.02	66.94	1.64 (m, 2H, C_5-H_2), 1.75 (m, 2H, C_6-H_2),
	PE-EA		1662	(286.76)	H	05.27	05.21	2.06 (m, 2H C_4-H_2), 2.10 (s, 3H, C_2-CH_3),
					N	09.77	09.68	2.69 (m, 2H, C_7-H_2), 7.10-7.45 (m, 3H, aromatic-H), 7.82 (b s, 1H, Indole NH)
6e	268-269	67	3297	$C_{15}H_{16}N_2O$	C	76.16	76.07	1.63 (m, 2H, C_5-H_2), 1.77 (m, 2H, C_6-H_2),
	PE-EA		1669	(252.31)	H	06.39	06.32	2.07 (m, 2H, C_4-H_2), 2.11 (s, 3H, C_2-CH_3)
					N	11.10	11.05	2.74 (m, 2H, C_7-H_2), 7.07-7.50 (m, 4H, aromatic-H), 7.80 (b s, 1H, Indole NH).

PE:Petroleum ether: 60-80°C,EA: Ethyl acetate