TETRACYCLIC COMPOUNDS FROM CYCLOPENT[*b*]INDOLES. SYNTHESIS OF ISOXAZOLO[3',4':5,4]CYCLOPENT[*b*]INDOLES.

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Abstract

Cyclopentan-1',2'-dione-1'-arylhydrazones 3 obtained from the Japp-Klingemann reaction of diazotised aniline derivatives 1 and 2-hydroxymethylenecyclopentanone 2 on acid catalysed cyclization afforded cyclopent[*b*]indoles 4. These on mixed aldol condensation with 4-methoxybenzaldehyde followed by reaction with hydroxylamine hydrochloride gave isoxazolo[3',4':5,4]cyclopent[*b*]indoles 6.

Introduction

The chemistry of Indole alkaloids and related compounds have been studied more extensively during the past few decades owing to their potential applications in diverse pharmacological field[1-8]. In particular they were reported to have antitumour, antibacterial and antifungal activities[1-6]. Based on these facts we proposed to undertake a novel attempt towards the synthesis of cyclopentanone ring fused with indoles, cyclopent[*b*]indoles 4 from the diazotised anilines 1 and 2-hydroxymethylenecyclopentanone 2 followed by acid catalysed cyclisation which were used as synthons to derive the titled isoxazolo[3',4':5,4]cyclopent[*b*]indoles 6 through the intermediates, 2-benzylidenecyclopent[*b*]indoles 5 (scheme1).

Experimental

General information

Purification of the crude products was carried out using chromatographic columns. Melting points were determined on a Mettler fp-5 instrument. Infrared spectra of the compounds were recorded in KBr pellets using PERKIN- ELMER model-1600 spectrometer. The ^{1}H-NMR spectra were recorded on AMX-400 spectrometer using tetramethylsilane (TMS) as an internal referance and chemical shifts are reported in parts per million (δ) downfield from the internal standard. The signal multiplicities are represented by s (singlet), d (doublet), b s (broad singlet) and m (multiplet). The microanalytical data are obtained on carlo Erba 1106 Perkin Elmer model 240 CHN analyzer.

General procedures.

Preparation of 2-hdroxymethylenecyclopentanone 2

Cyclopentanone (1.6 ml, 0.02 mol) was added to a well cooled, vigorously stirred mixture of sodium methoxide (from 5.17 g of sodium in 5 ml of abolute methanol), dryether (4 ml) and ethyl formate (1.8ml , 0.02 mol) in a small portions over a period of 10 minutes. The resulting mixture was stirred continuously for one hour in an ice bath and kept at room temperature . After a period of 24 hours, the yellow solid mass obtained was dissolved by adding ice water and neutralized with concentrated HCl. The oily mass that separated out upon acidification was extracted with ether, washed with brine and cold water and dried over anhydrous sodium sulphate. The residual oil after the removal of solvent by distillation to give 2-hydroxymethylenecyclopentanone 2 as viscous liquid in good quantity (65% yield).

Preparation of cyclopentan-1',2'-dione-1'-aryl hydrazones 3.

A mixture consisting of 2-hydroxymethylenecyclopentanone 2 (0.004 mol) and sodium acetate trihydrate (1g) in methanol (6ml) was kept in ice bath. A solution of the respective aniline derivative (0.004 mol) in aqueous hydrochloric

acid (1.8 ml of HCl in 2.12 ml of water) was diazotised with cold saturated solution of sodium nitrate (0.35g in 0.8 ml of water) in the 0°C to -5°C temperature range, and this solution was added in several portions over a period of 0.5 hour to the ice cold 2-hydroxymethylenecyclopentanone 2 with stirring and allowed to stand as such for another 0.5 hour.The solid formed was filtered, washed with water, dried and crystallized from ethanol.The analytical and spectral data of the hydrazones 3 have been presented in Table1.

Cyclisation of the hydrazones 3 to cyclopent[*b*]indoles 4

The cyclisation of hydrazones were effected by refluxing the suitable hydrazone 3 (0.001 mol) in a mixture of acetic acid (20 ml) and concentrated hydrochloric acid (5 ml) for 2 hours in an oilbath pre-heated to 125-130°C followed by cooling the reaction mixture and poured into ice water with stirring. The brown solid obtained, was filtered and purified by passing through a column of silica gel and eluting with petroleum ether-ethyl acetate mixture (95:5) as eluent. The analytical and spectral data of all the cyclised products 4 a-e have been summarized in Table 2.

Mixed aldol condensation of cyclopent[*b*]indole 4 with 4-methoxybenzaldehyde.

A mixture of approprite cyclopent[*b*]indole 4 (0.001 mol) and 4-methoxybenzaldehyde (0.001 mol) was treated with 4% alcoholic potassium hydroxide (10 ml) and stirred for 12 hours at room temperature. The product precipitated as crystalline mass was filtered off and washed with 50% ethanol (20 ml). Another quantum of the same crystallined compound was obtained from the filterate on neutralization with acetic acid followed by dilution with water. The products 5 were crystallised from methanol, and their physical and spectral data were given in Table 3.

Synthesis of 3-(4″- methoxy)-phenylisoxazolo[3′,4′:5,4]cyclopenta[*b*]indole 6

The appropriate 2-(4'-methoxy)-benzylidenecyclopent[*b*]indole 5 (0.001 mol) was treated with hydroxylamine hydrochloride (1.5g) in pyridine (5 ml) at 130°C for 10 hours. The resulting reaction mixture was then poured into crushed ice. The product separated as semisolid mass was extracted with chloroform, washed with dilute hydrochloric acid and water successively and dried over anhydrous sodium sulphate. Solvent removed on evaporation gave the crude product which was then purified by passing through a silica gel column and eluting with petroleum ether-ethyl acetate mixture (85:15) to derive the titled compound 6. The physical and spectrtal data were compiled in Table 4.

Results and discussion

The product 3a with m.p.188°C obtained from the Japp-Klingemann[9] reaction of the diazonium salt solution of p-toluidine 1a and 2-hydroxymethylenecyclopentanone 2, showed the following spectral characteristics. It's IR spectrum showed the strong absorption at 1698 cm^{-1} corresponding to carbonyl strecting and another band due to C=N stretching at 1616 cm^{-1}. The proton NMR spectrum of compound 3a exhibited the signal due to C_7 methyl protons as a singlet at δ 2.34. The signal corresponding to $C_{3'}$,$C_{4'}$ and $C_{5'}$ protons appeared as a multiplet in the region δ 2.13-2.64. The multiplet appeared around δ 7.10-7.66 corresponding to four protons has been assigned to aromatic protons and the sharp singlet observed at δ 12.97 corresponding to one proton was assigned as due to NH group. From the IR, proton NMR, and spectral characteristics, the structure of the compound was confirmed as 3a.

The product 4a was obtained by the acid cyclisation of the appropriate hydrazone 3a using Kent's reagent (acetic acid/HCl, 4:1) which was characterized using it's spectral and analytical data. It's IR spectrum revealed the presence of carbonyl group by exhibiting a strong absorption at 1655 cm^{-1}. The band due to NH stretching was found at 3204 cm^{-1}. The C_5 methyl proton appeared as a singlet at δ 2.46. The ^{1}H-NMR spectrum of 4a showed a multiplet at δ 7.22-7.48(C_4,C_6,andC_7 protons). The two multiplets appeared at δ 2.99-3.01 and δ 3.09-3.12 have been assigned to the C_3 and

C_2 protons respectively. The presence of a broad singlet at δ 9.07 corresponding NH proton indicates clearly that the product 3a is cyclised to 4a. The elemental analysis of 4a was in good agreement with the proposed molecular formula $C_{12}H_{11}NO$, which also supports the structure assigned to 4a. The generality of the reaction to yield a series of similar cyclopent[*b*]indoles 4b-e was successful with 3b-e under identical conditions.

Mixed aldol condensation of cyclopent[*b*]indole 4a with 4-methoxy benzaldehyde under basic condition afforded 2-(4′-methoxy)-benzylidinecyclopent[*b*]indole 5a. The compound 5a was characterized on the basis of spectral and analytical data. The IR spectrum showed a strong absorption due to the α,β-unsaturated carbonyl group at 1671 cm^{-1} and another band at 3185 cm^{-1} assignable to NH group. The formation of 5a from the mixed aldol condensation of 4a with 4-methoxybenzaldehyde was proved by the disappearance of C_2 proton resonance of 4a and appearance of signal due to benzylic proton as a singlet at δ 7.24. The aromatic cluster exhibited for seven protons envelop at δ 6.99-7.65 as a multiplet. The resonance owing to C_3 proton appeared as a multiplet at δ 3.96-3.97 while that of indole NH appeared as a broad singlet at δ 8.81 respectively. Two singlets appeared at δ 2.48 and δ 3.87 for C_5 methyl protons and C_4′-OCH_3 protons.The elemental analysis C : 79.12; H : 5.60 and N : 4.62 is compatible with the molecular formula $C_{20}H_{17}NO$. A series of similar compounds 5a-e were realized with 4a-e.

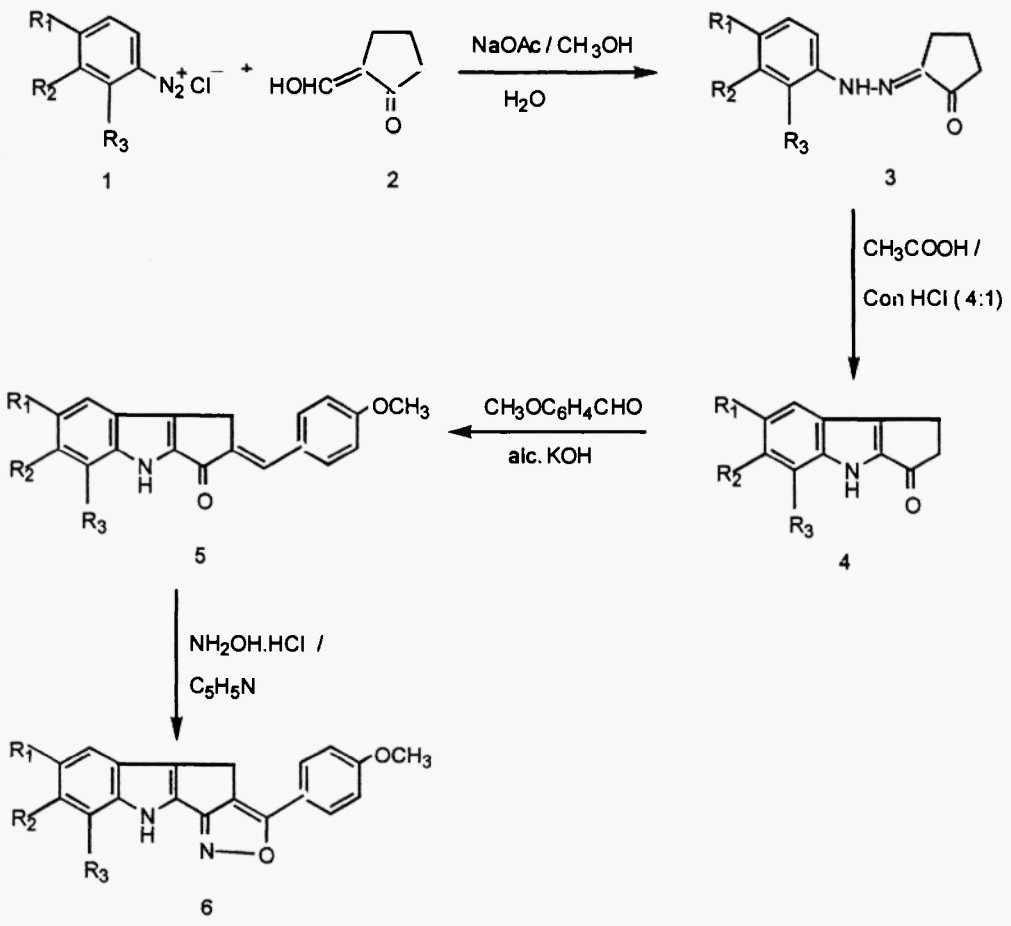
The reaction of 2-(4′-methoxy)-benzylidineindolo[2,3-*b*]cyclopentan-1-ones 5a-e with hydroxylamine hydrochloride in pyridine yielded 3-(4″-methoxy)-phenylisoxazolo[3′,4′:5,4]cyclopenta[*b*]indoles 6a-e in moderate yields. The IR spectrum of 6a exhibited an absorption around 1590 cm^{-1} indicating the transformation of 5a to 6a. The ^{1}H-NMR spectrum of 6a in $CDCl_3$ showed a singlet at δ 3.75 for C_4″-OCH_3 protons. The complex multiplet at δ 6.75-7.45 is assigned to the seven aromatic protons. The signals due to protons attached to C_6 methyl carbon and indole NH were registered at δ 2.17 and δ 8.82 as a singlet and a broad singlet respectively. The CHN analysis of the compound 6a is in good agreement with the proposed molecular formula $C_{20}H_{16}N_2O_2$ which also gave considerable support to the structure of 6a.

Table 1. Physical and spectral data of cyclopentan-1′,2′-aryl hydrazones 3

Compound	M.P.(°C) Solvent	Yield (%)	IR (v)	Molecular Formula		Analysis(%) Calcd	Found
3a	188 PE-EA	45	3271 1698,1616	$C_{12}H_{14}N_2O$ (202.24)	C	71.26	71.22
					H	6.98	6.99
					N	13.85	3.81
3b	182 PE-EA	48	3267 1697,1634	$C_{12}H_{14}N_2O$ (202.24)	C	71.26	71.31
					H	6.98	6.90
					N	13.85	13.89
3c	150 PE-EA	48	3419 1707,1654	$C_{12}H_{14}N_2O$ (202.24)	C	71.26	71.23
					H	6.98	6.92
					N	13.85	13.81
3d	178 PE-EA	46	3257 1699,1604	$C_{11}H_{12}N_2O$ (185.21)	C	71.34	71.31
					H	4.90	4.97
					N	15.13	15.09
3e	176 PE-EA	50	3253 1701,1602	$C_{11}H_{11}N_2OCl$ (223.45)	C	59.12	59.15
					H	5.31	5.39
					N	12.54	12.50

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

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 : $R_1 = R_2 = R_3 = H$

e : $R_1 = Cl. R_2 = R_3 = H$

Table 2. Physical and spectral data of indolo[2,3-*b*]cyclopentan-1-ones 4

Compound	M.P.(°C) Solvent	Yield (%)	IR (v)	Molecular Formula	^{1}H-NMR
4a	221 PE-EA	32	3204 1655	$C_{12}H_{11}NO$ (185.22)	2.46 (s, 3H, C_5-CH_3), 2.99-3.01 (m, 2H, C_3-H_2), 3.09-3.12 (m, 2H, C_2-H_2), 7.22 (d, 1H, C_6 –H, J_{ortho} =8.54 Hz), 7.35 (d,1H, C_7-H, J=8.54 Hz), 7.48 (s, 1H, C_4-H), 9.07 (b s, 1H, NH).
4b	220 PE-EA	35	3180 1691	$C_{12}H_{11}NO$ (185.22)	2.65 (s,3H,C_6-CH_3), 3.00-3.02 (m, 2H,C_3-H_2),3.26-3.28 (m, 2H, C_2-H_2), 7.02 (m, 1H, C_5-H), 7.25-7.59 (m, 2H, C_4 –H and C_7-H), 8.87 (b s, 1H, NH).
4c	208 PE-EA	35	3225 1673	$C_{12}H_{11}NO$ (185.22)	2.51(s,3H,C_7-CH_3), 3.01-3.03 (m,2H,C_3-H_2), 3.10-3.12 (m,2H,C_2-H_2), 7.11 (t,1H,C_5-H), 7.22 (d,1H,C_6-H, J_{ortho}=7.50 Hz), 7.56 (d,1H,C_4-H, J_{ortho}=7.50Hz), 8.77 (b s, 1H, NH).
4d	218 PE-EA	34	3199 1657	$C_{11}H_9NO$ 171.19	3.01-3.04 (m,2H,C_3-H_2), 3.11-3.14 (m,2H,C_2-H_2),7.17-7.21 (m,1H,C_5-H),7.37-7.40(m,1H,C_6-H),7.49(d,1H,C_4-H,J_{ortho} =8.26),7.72 (d,1H,C_7–H, J_{ortho} =8.26 Hz), 8.99 (b s,1H,NH)
4e	249 PE-EA	32	3199 1664	$C_{11}H_8NOCl$ (205.64)	3.01-3.04 (m, 2H, C_3-H_2), 3.08-3.11 (m, 2H, C_2-H_2), 7.34-7.36 (d, d, 1H ,C_6-H, J_{meta}=1.80 Hz, J_{ortho}=8.88 Hz), 7.41 (d,1H, C_7-H, J_{ortho}=8.88 Hz), 7.70 (s, 1H,C_4-H), 8.92 (b s, IsH, NH).

PE : Petroleum ether : 60-80°C, EA : Ethyl acetate
Elemental analyses are in good agreement with proposed structure.

Table.3 Physical and spectral data of 2-benzylideneindolo[2,3-*b*]cyclopentan-1-ones 5

Compound	M.P.(°C) Solvent	Yield (%)	IR (v)	Molecular Formula	Analysis(%)		
						Calcd	Found
5a	288 PE-EA	89	3185 1671,1601	$C_{20}H_{17}NO_2$ (303.36)	C	79.19	79.12
					H	5.65	5.60
					N	4.62	4.69
5b	265 PE-EA	89	3168 1669,1619	$C_{20}H_{17}NO_2$ (303.36)	C	79.19	79.10
					H	5.65	5.26
					N	4.62	4.69
5c	250 PE-EA	92	3202 1676,1623	$C_{20}H_{17}NO_2$ (303.36)	C	79.19	79.20
					H	5.65	5.69
					N	4.62	4.67
5d	262 PE-EA	86	3160 1666,1599	$C_{19}H_{15}NO_2$ (289.33)	C	78.87	78.81
					H	5.23	5.29
					N	4.84	4.85
5e	295 PE-EA	92	3163 1671,1621	$C_{19}H_{14}NO_2Cl$ (323.78)	C	70.48	70.41
					H	4.36	4.39
					N	4.37	4.41

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

Table 4. Physical and spectral data of 3-(4"-methoxy)phenylisoxazolo[3',4'-5,4]cyclopenta[*b*]indoles6

Compound	M.P.(°C) Solvent	Yield (%)	IR (v)	Molecular Formula	^{1}H-NMR
6a	182	43	3440 1590	$C_{20}H_{16}N_2O_2$ (316.36)	2.17 (s, 3H, C_6-CH_3), 3.75 (s, 3H,C_4" -OCH_3), 3.80-3.85 (m, 2_4-H_2), 6.75-7.45 (m, 7H, C_5-H ,C_7-H C_8 –H, C_2"-H,C_3"-H, C_5"-H, C_6"-H), 8.82 (b s, 1H, NH).
6b	178	46	3415 1599	$C_{20}H_{16}N_2O_2$ (316.36)	2.45 (s, 3H, C_7-CH_3), 3.71 (s, 3H, C_4"-OCH_3), 3.77-3.85 (m, 2H, C_4-H_2), 6.92-7.78 (m, 7H, C_5-H, C_6-H, C_8-H, C_2"-H, C_3"-H, C_4"- H, C_5"-H), 8.87 (b s, 1H, NH).
6c	153	46	3371 1663	$C_{20}H_{16}N_2O_2$ (316.36)	2.07 (s, 3H, C_8-CH_3), 3.72 (s, 3H, C_4"-OCH_3), 3.79-3.84 (m, 2H, C_4-H_2), 6.77-7.78 (m, 7H, C_4-H, C_5-H, C_6-H, C_2"-H, C_3"-H, C_5"-H, C_6"-H), 9.03 (b s, 1H, NH).
6d	162	54	3406 1603	$C_{19}H_{14}N_2O_2$ (302.33)	3.80 (s, 3H, C_4"-OCH_3), 3.82-3.83 (m, 2H, C_4-H_2),6.00-7.75 (m, 8H, C_5-H, C_6-H, C_7-H, C_8-H, C_2"-H, C_3"-H, C_5"-H, C_6"-H), 8.79 (b s, 1H, NH).
6e	173	48	3395 1603	$C_{19}H_{13}N_2O_2Cl$ (337.78)	3.67 (s, 3H, C_4"-OCH_3), 3.80-3.84 (m, 2H, C_4-H_2), 6.72-7.44 (m, 7H, C_5-H, C_7-H, C_8-H, C_2"-H, C_3"-H, C_5"-H, C_6"-H), 9.14 (b s, 1H, NH).

PE : Petroleum ether : 60-80°C, EA : Ethyl acetate
Elemental analyses are in good agreement with proposed structures.

Referances

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