TETRACYCLIC COMPOUNDS FROM INDOLO[2,3-b] CYCLOHEPTAN-1-ONES.
SYNTHESIS OF ISOXAZOLO[4',3':6,7]CYCLOHEPTA[b]INDOLES.

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Abstract

Cycloheptan-1',2'-dione-1'-arylhydrazones 3 obtained from the Japp-Klingemann reaction of diazotised aniline derivatives 1 and 2-hydroxymethylene cycloheptanone 2 on acid catalysed cyclization afforded indolo[2,3-b]cycloheptan-1-ones 4. These on mixed Aldol condensation with benzaldehyde followed by reaction with hydroxylamine hydrochloride gave isoxazolo[4',3':6,7]cyclohepta[b]indoles 6.

Introduction

Indole derivatives were reported to have pharmacological activities such as antitumour[1], antiinflammatory[2], antibacterial[3], antifungal[4], antituberculosis[4] activities. Besides this, the simple cyclooctane ring fused with indole [Iprindole] was found to have antidepressant property[4]. In the above contest our present investigation was aimed at to synthesise the hitherto unknown cycloheptane ring fused with indoles, indolo[2,3-b]cycloheptan-1-ones[5] from the diazotised anilines 1 and 2-hydroxymethylenecycloheptanone 2[6] which were used as synthons to derive isoxazolo[4',3':6,7] cyclohepta[b]indoles 6 (scheme 1).

Experimental

General information

Thin layer chromatography was used to access reactions and purity of products. Preparative separation was performed in columns packed with silica gel. Melting points were determined in a Mettler Fb - 5 apparatus and are uncorrected. The IR spectra were recorded in KBr pellets with a shimadzu FTIR - 8201 (PC)s spectrometer and only noteworthy absorption levels (reciprocal centimeter) are listed. The ^{1}H NMR spectra were recorded on varian AMX 400 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the internal standard, tetramethylsilane (Me_4 Si). Signal multiplicities are represented by s (singlet), d (doublet), b s (broad singlet) and m (multiplet). Satisfactory microanalyses were obtained on Carlo Erba 1106 and Perkin Elmer model 240 CHN analyzers.

Preparation of 2-hydroxymethylene cycloheptanone 2

Cycloheptanone (2.35 mL, 0.02 mol) was added in portions over a period of five minutes to a well cooled, vigorously stirred mixture of sodium methoxide (from 5.17 g of sodium in 5 mL of absolute methanol), dry ether (4 mL) and ethyl formate (1.8 mL, 0.02 mol). The mixture was stirred in the ice bath for another one 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 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-hydroxymethylene cycloheptanone 2 as viscous liquid with 70% yield.

General procedures

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

A mixture of 2-hydroxymethylenecycloheptanone 2 (0.004 mol) and sodium acetate trihydrate (1g) in methanol (6 mL) was cooled in ice. A solution of appropriate aniline derivative (0.004 mol) in aqueous hydrochloric acid (1.8 mL of HCl in 2.12 mL H_2O) was diazotised with cold saturated solution of sodium nitrite (0.35 g 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-hydroxymethylenecycloheptanone 2 over a period of 0.5 hours with constant stirring. After standing for 0.5 hours more, the resulting solid was filtered, washed with water dried and crystallised from ethanol. The physical and spectral data of the hydrazones 3 were presented in Table 1.

Cyclization of the hydrazones to indolo[2,3-b]cycloheptan-1-ones 4

The appropriate hydrazone 3 (0.001 mol) in a mixture of acetic acid (20 mL) and concentrated hydrochloric acid (5 mL) was refluxed on oil bath pre-heated to 125-130°C for 2 hours. The contents were then cooled and poured into ice water with stirring. The separated brown solid was filtered and purified by passing through a column of silica gel and eluting with petroleum ether - ethyl acetate (95:5) mixture. The physical and spectral data of all the compounds 4a-e were given in Table 2.

Mixed Aldol condensation of indolo[2,3-b]cycloheptan-1-ones 4 with benzaldehyde.

A mixture of Indolo[2,3-b]cycloheptan-1-ones 4 (0.001 mol) and benzaldehyde (0.001 mol) was treated with 4% alcoholic potassium hydroxide (10 mL) and stirred for 12 hours at room temperature. The precipitated crystalline product was filtered off and washed with 50% ethanol. A further crop of condensation product was obtained on neutralisation with acetic acid and dilution with water. The products 5 were crystallised from methanol and their physical and spectral data were presented in Table 3.

Synthesis of 3-phenyl isoxazolo[4',3':6,7] cyclohepta[b]indoles 6

A mixture of 2-benzylideneindolo[2,3-b]cycloheptan-1-one 5 (0.001 mol), hydroxylamine hydrochloride (1.5 g) in dry pyridine (5 mL) was heated at 130°C for 10 hours. The reaction mixture was then poured into crushed ice, the resulting semi solid separated was extracted with chloroform and washed successively with dilute hydrochloric acid and water, dried over anhydrous sodium sulphate. Evaporation of the solvent yielded a crude product which was purified by passing through a silica gel column and eluting with petroleum ether-ethyl acetate (98:2) mixture to afford the product 6. The physical and spectral data were given in Table 4.

Results and Discussion

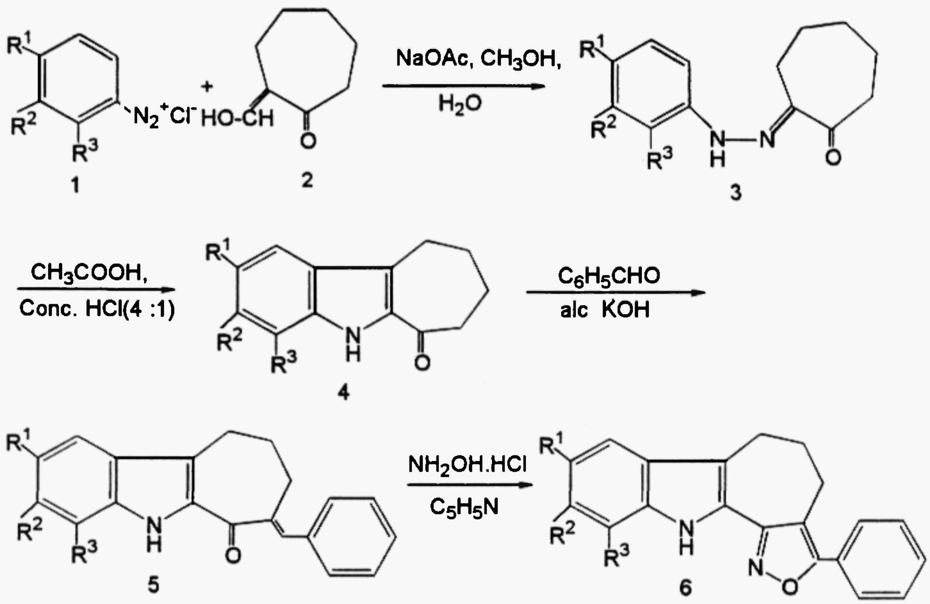
The Japp-Klingemann reaction[9] of diazonium salt solution of p-toluidine derivative 1a with 2-hydroxymethylenecycloheptanone 2 gave the product 3a m.p. 85°C which showed the bands at 1654 cm^{-1} due to carbonyl stretching and 1624 cm^{-1} due to C=N stretching in the IR spectrum. Its proton NMR spectrum registered a singlet at δ 2.30 due to a methyl group at C_4. The $C_{3'}$, $C_{4'}$, $C_{5'}$ $C_{6'}$ and $C_{7'}$ protons resonate as a multiplet at δ 1.77-2.68. The resonance signal corresponding to four aromatic protons appeared as a multiplet at δ 7.05-7.26 and a singlet at δ 13.67 for NH proton. The above spectrum clearly indicates that the structure of the compound is 3a. The elemental analysis of the compound agreed very well with the proposed molecular formula $C_{14}H_{18}N_2O$ augmenting the structure of the compound to be 3a.

The appropriate hydrazone 3a upon acid cyclization using Kent's reagent (acetic acid / HCl, 4:1) gave the product 4a which showed the bands at 1618 cm^{-1} due to carbonyl group and at 3328 cm^{-1} for NH stretching and its ^1H NMR spectrum displayed a singlet at δ 2.45 for C_7 - CH_3, three aromatic protons envelop at δ 7.16-7.42 (C_6, C_8, C_9 protons). C_5 and C_2 protons appeared as two multiplets at δ 3.11-3.14 and δ 2.82 - 2.85, respectively. C_4 and C_3 protons resonate as multiplets at δ 2.05-2.11 and δ 1.95 - 2.02, respectively. The appearance of NH proton as a broad singlet at δ 8.86 clearly indicates that the product 3a cyclised to 4a. The elemental analysis of the compound 4a agreed very well with the proposed molecular formula $C_{14}H_{15}NO$, thereby confirming the structure 4a for the compound formed. A series of similar indolo[2,3-b]cycloheptan-1-ones 4b-e were realised from 1b-e and 2 through the corresponding hydrazones 3b-e.

Mixed Aldol condensation[7] of indolo[2,3-b]cycloheptan-1-one 4a with benzaldehyde under basic condition leads to the formation of 2-benzyhdeneindolo[2,3-b]cycloheptan-1-one 5a. The structure of 5a was established on the basis of elemental and spectral data. The IR spectrum exhibited a strong absorption band at 1641 cm^{-1} characteristic of α, β - unsaturated carbonyl group and a band at 3311 cm^{-1} ascribable to NH group. In its ^1H NMR spectra the disapperance of C_2 protons signal and appearance of benzylic proton signal as a singlet at δ 7.78 proved the mixed Aldol condensation of 4a with benzaldehyde to give 5a. The aromatic cluster accounting for eight protons appeared at δ 7.18-7.43 as a multiplet. The C_3 and C_5 protons appeared as two multiplets at δ 2.89-2.91 and δ 3.18 -3.21, respectively. The C_4 protons resonate as a multiplet at δ 2.17-2.23 while that of methyl group and indole NH as a singlet at δ 2.46 and as a broad singlet at δ 8.99, respectively. The elemental analysis : C 83.70, H 06.39 and N 04.59 is compatible with the molecular formula $C_{21}H_{19}NO$. A series of similar compounds was realised with 4b, 4c, 4d and 4e.

The reaction of 2-benzylideneindolo[2,3-b]cycloptan-1-one 5a-e with hydroxylamine hydrochloride in pyridine gave the desired 3-phenyl isoxazolo[4',3':6,7] cyclohepta[b]indoles[8] 6a-e in moderate yields. The IR spectrum of 6a revealed absorption band around 1600 cm^{-1} indicating the transformation of 5a to 6a. The ^1H NMR spectrum of 6a in $CDCl_3$ showed a multiplet at δ 2.12 - 2.17 for C_5 protons. The eight aromatic protons appeared as a complex multiplet at δ 7.09-7.73. The methyl group protons and indole NH proton exhibited a singlet at δ 2.47 and a broad singlet at δ 8.74, respectively. The elemental analysis agreed well with the molecular formula $C_{21}H_{18}N_2O$.

Scheme 1



1, 2-6 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 1. Physical and spectral data of cycloheptan-1'2'-dione-1'-aryl hydrazones 3

Compound	M.P. (°C) Solvent	Yield (%)	IR (ν)	Molecular Formula	Analysis (%)		
						Calcd	Found
3a	85	79	3271	$C_{14}H_{18}N_2O$	C	73.01	(73.00)
	PE-EA		1654,1624	(230.31)	H	07.88	(07.98)
					N	12.16	(12.10)
3b	73	72	3286	$C_{14}H_{18}N_2O$	C	73.01	(73.07)
	PE-EA		1633, 1604	(230.31)	H	07.88	(07.90)
					N	12.16	(12.20)
3c	90	69	3282	$C_{14}H_{18}N_2O$	C	73.01	(73.13)
	PE-EA		1629, 1602	(230.31)	H	07.88	(07.98)
					N	12.16	(12.18)
3d	87	75	3290	$C_{13}H_{16}N_2O$	C	72.19	(72.28)
	PE-EA		1596, 1601	(216.28)	H	07.46	(07.40)
					N	12.95	(12.91)
3e	105	77	3289	$C_{13}H_{17}N_2OCl$	C	62.28	(62.30)
	PE-EA		1627, 1595	(250.73)	H	06.03	(06.10)
					N	11.17	(11.19)

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

Table 3. Physical and spectral data of 2-benzylidene indolo[2,3-b]cycloheptan-1-ones 5

Compound	M.P. (°C) Solvent	Yield (%)	IR (ν)	Molecular Formula	Analysis (%)		
						Calcd	Found
5a	182.4	80	3311	$C_{21}H_{19}NO$	C	83.69	(83.70)
	PE-EA		1641,1568	(301.39)	H	06.35	(06.39)
					N	04.65	(04.59)
5b	184.9	87	3315	$C_{21}H_9NO$	C	83.69	(83.78)
	PE-EA		1641,1568	(301.39)	H	06.35	(06.28)
					N	04.65	(04.73)
5c	165.3	83	3302	$C_{21}H_{19}NO$	C	83.69	(83.58)
	PE-EA		1637, 1577	(301.39)	H	06.35	(06.25)
					N	04.65	(04.76)
5d	161	79	3311	$C_{20}H_{17}NO$	C	83.59	(83.55)
	PE-EA		1635, 1566	(287.36)	H	05.96	(05.98)
					N	04.88	(04.80)
5e	181	90	3340	$C_{20}H_{16}NOCl$	C	74.65	(74.69)
	PE- EA		1636, 1579	(321.81)	H	05.01	(05.15)
					N	04.35	(04.30)

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

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

Compound	M.P. (°C) Solvent	Yield (%)	IR (ν)	Molecular Formula	Analysis (%)	Calcd	Found	^{1}H - NMR
4a	178 PE-EA	64	3328 1618	$C_{14}H_{15}NO$ (213.28)	C H N	78.84 07.09 06.57	(78.82) (07.15) (06.45)	1.95-2.02 (m, 2H, C_3-H_2), 2.05-2.11 (m, 2H, C_4-H_2), 2.45 (s, 3H, C_7-CH_3), 2.82 - 2.85 (m, 2H, C_2-H_2), 3.11-3.14 (m, 2H, C_5-H_2), 7.16-7.42 (m, 3H, C_6-H, C_8-H, C_9-H) and 8.86 (b s, 1H, NH)
4b	120 PE-EA	67	3329 1610	$C_{14}H_{15}NO$ (213.28)	C H N	78.84 07.09 06.57	(78.91) (07.23) (06.82)	1.91-2.01 (m, 2H, C_3-H_2), 2.06-2.11 (m, 2H, C_4-H_2), 2.46 (s, 3H, C_8-CH_3), 2.77-2.84 (m, 2H, C_2-H_2), 3.11-3.14 (m, 2H, C_5-H_2), 6.81-7.54 (m, 3H C_6-H, C_7-H, C_8-H) and 8.77 (b s, 1H, NH)
4c	139-140 PE-EA	65	3298 1605	$C_{14}H_{15}NO$ (213.28)	C H N	78.84 07.09 06.57	(78.94) (07.21) (06.37)	1.97-2.02 (m, 2H, C_3-H_2), 2.06-2.13 (m, 2H, C_4-H_2), 2.49 (s, 3H, C_5-CH_3), 2.83-2.86 (m, 2H, C_2-H_2), 3.13-3.17 (m, 2H, C_5-H_2), 7.03 - 7.67 (m, 3H, C_6-H, C_7-H, C_8-H) and 8.84 (b s, 1H, NH)
4d	151 PE-EA	61	3292 1635	$C_{13}H_{13}NO$ (199.25)	C H N	78.36 06.58 07.03	(78.43) (06.49) (07.10)	1.99-2.04 (m, 2H, C_3-H_2), 2.06-2.12 (m, 2H, C_4-H_2), 2.83-2.87 (m, 2H, C_2-H_2), 3.14 -3.17 (m, 2H, C_5-H_2), 7.11-7.67 (m, 4H, C_6-H, C_7-H, C_8-H, C_9-H) and 8.96 (b s, 1H, NH)
4e	172 PE-EA	60	3325 1620	$C_{13}H_{12}NOCl$ (233.69)	C H N	66.81 06.00 05.17	(66.78) (06.03) (05.27)	1.96-2.06 (m, 2H, C_3-H_2), 2.08-2.12 (m, 2H, C_4-H_2), 2.83-2.86 (m, 2H, C_2-H_2), 3.08-3.11 (s, 2H, C_5-H_2), 7.26-7.31 (m, 2H, C_8-H, C_9-H), 7.62 (s, 1H, C_6-H), and 8.99 (b s, 1H, NH).

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

Table 4. Physical and spectral data of 3-phenyl isoxazolo[4',3' :6, 7]cyclohepta[b]indoles 6

Compound	M P (°C)	Yield	IR	Molecular	Analysis (%)			^{1}H - NMR
	Solvent	(%)	(ν)	Formula		Calcd	Found	
6a	227 PE-EA	45	3284 1600	$C_{21}H_{18}N_2O$ (314.39)	C H N	80.23 05.77 08.91	(80.32) (05.65) (08.88)	2.12-2.17 (m, 2H, C_5-H_2), 2.47 (s, 3H, C_8-CH_3), 3.06- 3.08 (m,2H, C_4-H_2), 3.16-3.19 (m, 2H, C_6-H_2), 7.09-7.73 (m, 8H, C_7-H, C_9-H, C_{10}-H, C_2'-H, C_3'-H, C_4'-H, C_5'-H, C_6'-H) and 8.74 (b s 1H, NH)
6b	197.2 PE-EA	42	3250 1558	$C_{21}H_{18}N_2O$ (314.39)	C H N	80.23 05.77 08.91	(80.53) (05.98) (08.88)	2.13-2.27 (m, 2H, C_5-H_2), 2.48 (s, 3H, C_9-CH_3), 3.05-3.08 (m,2H, C_4-H_2), 3.16-3.19 (m, 2H, C_6-H_2), 6.83-7.73 (m, 8H, C_7-H, C_8-H, C_{10}-H, C_2'-H, C_3'-H, C_4'-H, C_5'-H, C_6'-H) and 8.69 (b s,1H, NH)
6c	210 PE-EA	55	3200 1558	$C_{21}H_{18}N_2O$ (314.39)	C H N	80.23 05.77 08.91	(80.22) (05.47) (08.82)	2.14-2.17 (m, 2H, C_5-H_2), 2.55 (s, 3H, C_{10}-CH_3), 2.94-2.97 (m,2H, C_4-H_2), 3.18-3.20 (m, 2H, C_6-H_2), 7.07-7.69 (m, 8H, C_7-H, C_8-H, C_9-H, C_2'-H, C_3'-H, C_4'-H, C_5'-H, C_6'-H) and 8.57 (b s,1H, NH)
6d	207.6 PE-EA	49	3274 1598	$C_{20}H_{16}N_2O$ (300.36)	C H N	79.98 05.37 09.33	(79.62) (05.42) (09.21)	2.13-2.18 (m, 2H, C_5-H_2), 3.07-3.10 (m, 2H, C_4-H_2), 3.19-3.22 (m, 2H, C_6-H_2), 7.12-7.73 (m, 9H, C_7-H, C_8-H, C_9-H, C_{10}-H, C_2'-H, C_3'-H, C_4'-H, C_5'-H, C_6'-H) and 8.82 (b s,1H, NH)
6e	235 PE-EA	40	3277 1508	$C_{20}H_{15}N_2OCl$ (334.80)	C H N	71.75 04.51 08.37	(71.65) (04.55) (08.36)	2.11-2.17 (m, 2H, C_5-H_2), 3.06-3.09 (m, 2H, C_4-H_2), 3.13-3.16 (m, 2H, C_6-H_2), 7.20-7.73 (m, 8H, C_7-H, C_9-H, C_{10}-H, C_2'-H, C_3'-H, C_4'-H, C_5'-H, C_6'-H) and 8.92 (b s,1H, NH)

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

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