HETEROCYCLES 2[1] : SYNTHESIS OF 1-HYDROXYCARBAZOLES AND MUKONINE ISOMERS

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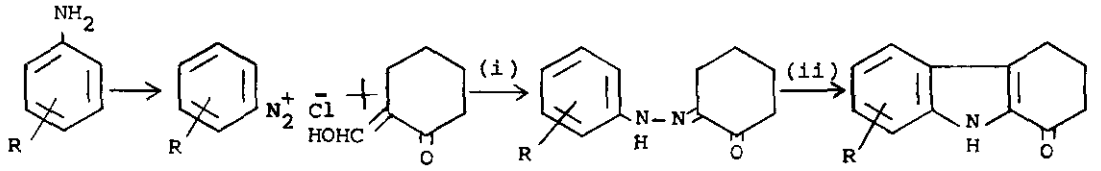
Abstract - Cyclohexan-1',2'-dione-1'-diazabenzoic acids obtained from diazotised aminobenzoic acids and 2-hydroxymethylenecyclohexanone on cyclization afford 1-oxo-1,2,3,4-tetrahydrocarbazole derivatives. These on esterification followed by aromaisation and methylation gave the Mukonine isomers, 19, 20 and 22.

Carbazole derivatives[2], tetrahydrocarbazoles[3], oxotetrahydrocarbazoles[4] and Glycozoline isomers[5,6] have been reported to possess antitumour, anti-convlsant, psychotropic, anti-inflammatory, antihistamine and antibiotic properties. Mukonine, a simple carbazole, has been isolated by Chakraborty et al. from Murraya Koenigii spreng and has been reported to be active against most of the organisms[7]. With a view to exploring structure activity correlation, we first report here the synthesis of isomers of mukonine.

In the present study, Japp-klingemann reaction[8,9] of diazonium salt solutions of ortho-, meta- and paraamino benzoic acids, 1, 2 and 3, with 2-hydroxymethylene cyclohexanone gave 2-, 3- and 4-(cyclohexane-1',2'-dione-1'diaza)benzoic acids, 4, 5 and 6 respectively. The cyclization of hydrazones, 4 and 6 with PPA gave the 1-oxo-1,2,3,4-tetrahydrocarbazole carboxylic acids, 7 and 10 respectively; where the same cyclization of 5 gave two positional isomeric products, 8 and 9. The products obtained during cylization were pure and difficult to crystallise in common organic solvents. Thats why all these cyclized products were identified as their methyl esters. These esters are the stable intermediates for the synthesis of 2,2-dimethyl-2H-pyrano [2,3-a] carbazoles[10], Indolo [3,2-h] coumarins 3H-pyrazino[3,2,1-J,K] carbazoles and carbazolyl-1-oxypropanalamines[11]. After esterification, the esters were hydrolysed with 10% sodium hydroxide to give pure corresponding carboxylic acids.

Esters, 11, 13 and 14, obtained from their corresponding acids on treatment with diazomethane, were aromatised by using Pd/C (10%) in diphenyl ether to methyl esters of 1-hydroxycarbazoles, 15, 17 and 18 respectively along with a small amount of a simple carbazole, 16.[12]

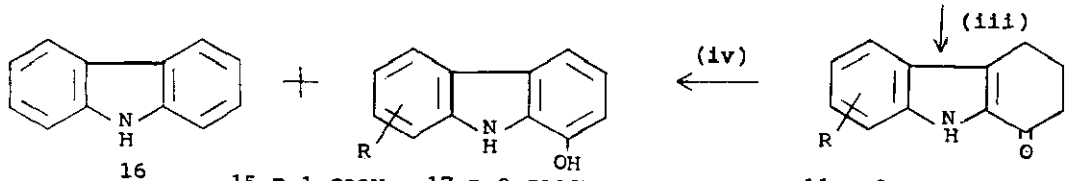
Methylation of 15 with dimethyl sulphate-K_2CO_3 - acetone gave exclusively one product, 19 and it was identified as an isomer of mukonine. However, the same reaction of 17 and 18 afforded the normal O-methylated products, 20 and 22 (isomers of mukonine) besides the O- and N-dimethylated products, 21 and 23, respectively. These were separated by passing through silica gel column and eluting with a suitable solvent system.



1 R=o-COOH
2 R=m-COOH
3 R=p-COOH

4 R=o-COOH
5 R=m-COOH
6 R=p-COOH

7 R=8-COOH
8 R=5-COOH
9 R=7-COOH
10 R=6-COOH



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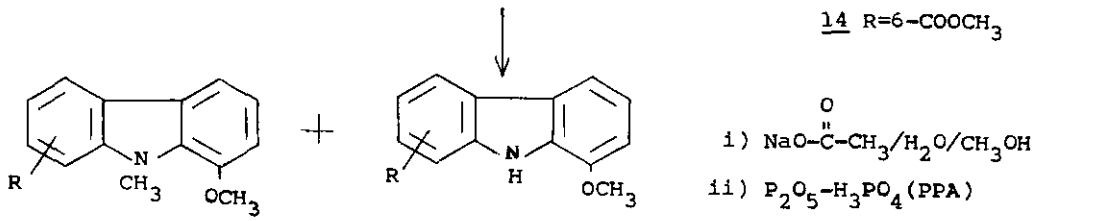
15 R=1-$COOH_3$ 17 R=2-$COOCH_3$
18 R=3-$COOCH_3$

11 R=8-$COOCH_3$
12 R=5-$COOCH_3$
13 R=7-$COOCH_3$
14 R=6-$COOCH_3$

v) $(CH_3)_2SO_4/K_2CO_3$/Acetone



21 R=2-$COOCH_3$
22 R=3-$COOCH_3$

19 R=1-$COOCH_3$
20 R=2-$COOCH_3$
22 R=3-$COOCH_3$

i) $NaO-\overset{O}{\overset{\|}{C}}-CH_3/H_2O/CH_3OH$
ii) $P_2O_5-H_3PO_4$(PPA)
iii) CH_2N_2
iv) Pd/C(10%) in ϕ_2O

TABLE I

+Compound No	mp °C	Yield %	Molecular formula	'N' Analysis Calcd	Found
4	177 - 179	73	$C_{13}H_{14}N_2O_3$	11.38	11.20
5	181 - 182	65	$C_{13}H_{14}N_2O_3$	11.38	11.30
6	210 - 211	81	$C_{13}H_{14}N_2O_3$	11.38	11.30
7	268 - 270	87	$C_{13}H_{11}NO_3$	6.11	5.98
8	210 - 212	66	$C_{13}H_{11}NO_3$	6.11	6.10
9	313 - 315	66	$C_{13}H_{11}NO_3$	6.11	6.21
10	285 - 286	83	$C_{13}H_{11}NO_3$	6.11	6.09

+ Compounds 4 to 10 were crystallised from methanol

TABLE II

++Compound No	mp °C	Yield %	ν_{max} cm^{-1}	Molecular formula	Analysis Calcd	Found
11	130 - 131	90	3450	$C_{14}H_{13}NO_3$	C 69.15	69.00
			1690		H 5.34	5.20
			1650		N 5.76	5.70
12	161 - 162	8	3250	$C_{14}H_{13}NO_3$	C 69.15	69.00
			1710		H 5.34	5.18
			1645		N 5.76	5.60
13	175 - 176	42	3250	$C_{14}H_{13}NO_3$	C 69.15	69.00
			1700		H 5.34	5.10
			1650		N 5.76	5.50
14	246 - 248	86	3240	$C_{14}H_{13}NO_3$	C 69.15	69.20
			1700		H 5.34	5.20
			1650		N 5.76	5.60
15	179 - 180	56	3460	$C_{14}H_{11}NO_3$	C 69.72	69.71
			3310		H 4.49	4.50
			1675		N 5.81	5.76

17	242 - 244°	50	3450	$C_{14}H_{11}NO_3$	C 69.72	69.71
			3320		H 4.49	4.50
			1675		N 5.81	5.65
18	213 - 215	52	3300	$C_{14}H_{11}NO_3$	C 69.72	69.69
			1700		H 4.49	4.65
			1625		N 5.81	5.84
19	180 - 181	71	3450	$C_{15}H_{13}NO_3$	C 70.58	70.40
			1700		H 5.09	5.30
			1610		N 5.49	5.28
20	202 - 204	62	3320	$C_{15}H_{13}NO_3$	C 70.58	70.36
			1700		H 5.09	5.20
			1650		N 5.49	5.25
21	219 - 220	14	1690	$C_{16}H_{15}NO_3$	C 71.37	71.40
			1625		H 5.57	5.40
					N 5.20	5.18
22	128 - 129	86	3320	$C_{15}H_{13}NO_3$	C 70.58	70.33
			1700		H 5.09	5.10
			1625		N 5.49	5.30
23	188 - 189	9	1700	$C_{16}H_{15}NO_3$	C 71.37	71.20
			1610		H 5.57	5.60
					N 5.20	5.16

++ Compounds 11 to 14 were crystallised from benzene while the rest were crystallised from Petroleum ether -ethyl acetate.

TABLE III

Compound No	NMR ($CDCl_3$/TMS_{int}) of the Product (100 MHz)
12	2.28(q,2H,J=6Hz,C_3-methylene); 2.72(t,2H,J=6Hz,C_2-methylene); 3.28 (t,2H,J=6Hz,C_4-methylene); 4.03(s,3H,C_5-$COOCH_3$), 7.4(m,1H,C_7-H),7.7 (d,1H,J=7Hz,C_8-H), 7.8(d,1H,J=7Hz,C_6-H) and 11.3(broad s,1H,N-H,D_2O exhangeable).
13	2.3(q,2H,J=6Hz,C_3-methylene);2.62(t,2H,J=6Hz,C_2-methylene); 3.08 (t,2HJ=6Hz, C_4-methylene); 3.96(s,3H,C_7-$COOCH_3$), 7.78(d,2H,C_5-H and C_6-H,J=2Hz), 8.26(s,1H,C_8-H) and 12.2(broad s,1H,N-H,D_2O exchangeable).

19 4.08(s,6H,C_1-$COOCH_3$ and C_8-OCH_3), 6.96(d,1H,J=7Hz,C_7-H); 7.24(m,2H, C_5H and C_6-H), 7.75(d,1H,J≈7Hz,C_5-H), 8.10(d,1H,J=7Hz,C_2-H), 8.28 (d,1H,J=7Hz,C_4-H) and 10.0(s,1H,NH, D_2O exchangeable).

20 4.04(s,3H,C_2-$COOCH_3$), 4.09(s,3H,C_8-OCH_3), 6.98(d,1H,J=8Hz,C_7-H); 7.19(m,1H,C_6-H); 7.74(d,1H,J=8Hz,C_5-H); 7.94(d,1H,J=8Hz,C_3-H); 8.12(d,1H,J=8Hz,C_4-H), 8.03(s,1H,C_1-H) and 8.44(broad s,1H,NH,D_2O exchangeable).

21 4.04(s,3H,C_2-$COOCH_3$),4.1(s,3H,C_8-OCH_3), 4.24(s,3H,N-CH_3), 6.8(d,1H, J=8Hz,C_7-H), 7.18(m,1H,C_6-H), 7.70(d,1H,J=8Hz,C_5-H), 7.96(d,1H,J= 6Hz,C_3-H), 8.08(s,1H,C_1-H) and 8.2(d,1H,J=6Hz,C_4-H).

22 4.02(s,6H,C_3-$COOCH_3$ and C_8-OCH_3), 6.94(d,1H,J=8Hz,C_7-H), 7.24(m,1H, C_6-H), 7.46(d,1H,J=8Hz,C_1-H), 7.76(d,1H,J=8Hz,C_5-H), 8.15(d,1H, J=8Hz, C_2-H), 8.55(s,1H,N-H, D_2O exchangeable) and 8.81(s,1H,C_4-H).

23 4.04(s,3H,C_3-$COOCH_3$),4.06(s,3H,N-CH_3), 4.23(s,3H,C_8-OCH_3), 6.95 (d,1H,J=8Hz,C_7-H), 7.25(m,2H,C_1-H and C_6-H); 7.78(d,1H,J=8Hz,C_5-H), 8.20(d,1H,J=8Hz,C_2-H) and 8.8(s,1H,C_4-H).

EXPERIMENTAL

General Procedures

Prepration of O-, m- and p-(Cyclohexan-1',2'-dione-1'-diaza)benzoic Acids

A mixture of 2-hydroxymethylenecyclohexanone (12.6 g, 0.1 M), sodium acetate (20 g) methanol (100 ml) and water (500 ml) was cooled in ice. A pasty mass of the amino benzoic acid (13.7 g, 0.1 M) in concentrated hydrochloric acid (28 ml) was cooled and diazotised with cold saturated aqueous solution of sodium nitrite (13.8 g in 55 ml of water) between 0°C and -5°C. The diazotised solution was added in small portions to the ice cooled mixture containing 2-hydroxymethylene-cyclohexanone over a period of 0.5 h with constant stirring. After standing for 0.5 h more, the resulting solid was filtered, washed with water, dried and crystallised.

Cyclization of the Hydrazones to 1-Oxo-1,2,3,4-tetrahydrocarbazole Derivatives using PPA

A 1:4 (W/W) mixture of phosphorous pentoxide (5 g) and phosphoric acid (20 ml) was prepared freshly in a flask fitted with a calcium chloride guard tube. Hydrazone (2.5 g, 0.01 M)was added to this with stirring. The mixture was then kept for 40 min in an oil bath pre-heated to 125°C. It was then cooled and poured in cold water (100 ml). The solid separated was allowed to stand for about 0.5 h and filtered. It was washed with water dried and weighed.

Esterification of 1-Oxo-tetrahydrocarbazolecarboxylic Acids

1-Oxo-1,2,3,4-tetrahydrocarbazolecarboxylic acid (5 g; 0.02 M) was suspended in methanol (20 ml) and chilled to 0°C. Ethereal solution of dry diazomethane (1.3 g diazomethane in 50 ml of ether) was added in drops. After the complete addition of diazomethane, it was kept at 15°C for 1 h. Solvent was distilled off, and generally the solid was adsorbed over silica gel and chromatographed using benzene as eluant. The removal of solvent gave the methyl 1-oxo-1,2,3,4-tetrahydrocarbazolecarboxylates.

Aromatisation of Methylcarboxylates of 1-Oxo-1,2,3,4-tetrahydrocarbazoles

A mixture of methyl carboxylates of 1-oxo-1,2,3,4-tetrahydrocarbazole (4.86 g, 0.02 M) and palladium on charcoal (10%, 0.5 g) was refluxed in diphenyl ether (20 ml) under oxygen free nitrogen atmosphere for about 2 h using an air condenser. The reaction mixture was cooled, filtered and diphenyl ether was removed under reduced pressure. The residue was chromatographed over silica gel. Fraction (a) (petroleum ether : ethyl acetate, 20:1) on removal of solvent gave fluffy crystals of a simple carbazole. Yield 0.1 g (4%), mp 240 - 242°C (Lit.[12] 242°C)

Fraction (b) (petroleum ether : ethyl acetate, 10 : 1) on removal of solvent gave methyl 8-hydroxycarbazolecarboxylates.

Synthesis of Methyl-8-Methoxycarbazolecarboxylates (Mukonine Isomers)

A mixture of methyl 8-hydroxycarbazolecarboxylates (0.24 g, 0.001 M) dimethyl sulfate (0.12 g), anhydrous potassium carbonate (1.5 g) in dry acetone was refluxed for 2 h. The excess acetone was distilled off. To the remaining portion, water (25 ml) was added. The whole mixture was extracted with ether and washed succesively with water. The solution was dried over anhydrous sodium sulfate. The dried solution on removal of ether gave a solid.

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