Studies of Benzylisoquinolines. Comparison of the Reactivity of the Methylene Group in 1-Benzyl and 4-Benzylisoquinolines

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While examining the oxidation of 4-benzylisoquinolines to the corresponding 4-benzoylisoquinolines as well as the reactivity of these ketones towards hydroxylamine, reduction reagents and Grignard's reagents, there was found a definite difference in the behavior of the methylene group for these compounds as compared to that of papaverine (1-benzylisoquinolines).

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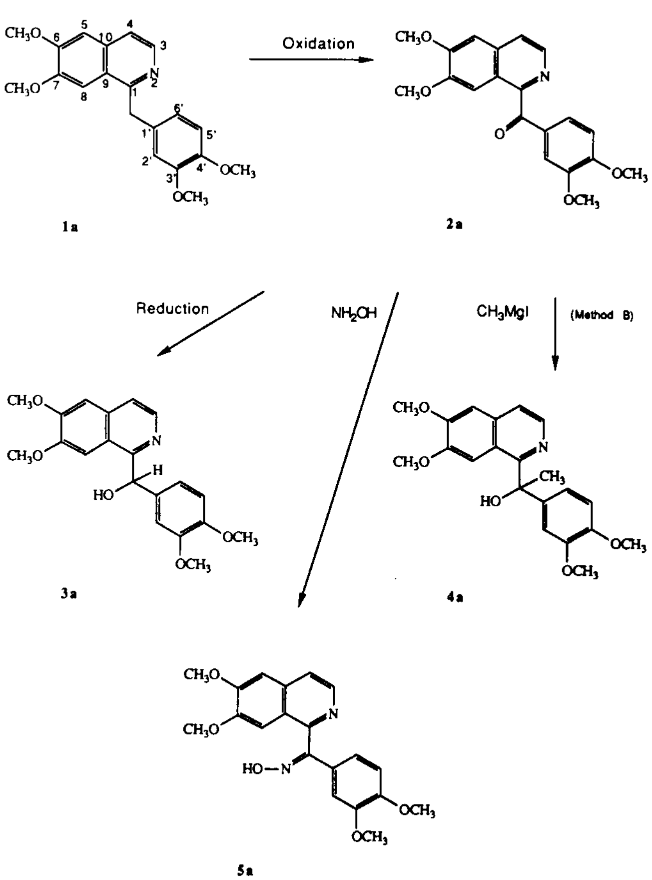
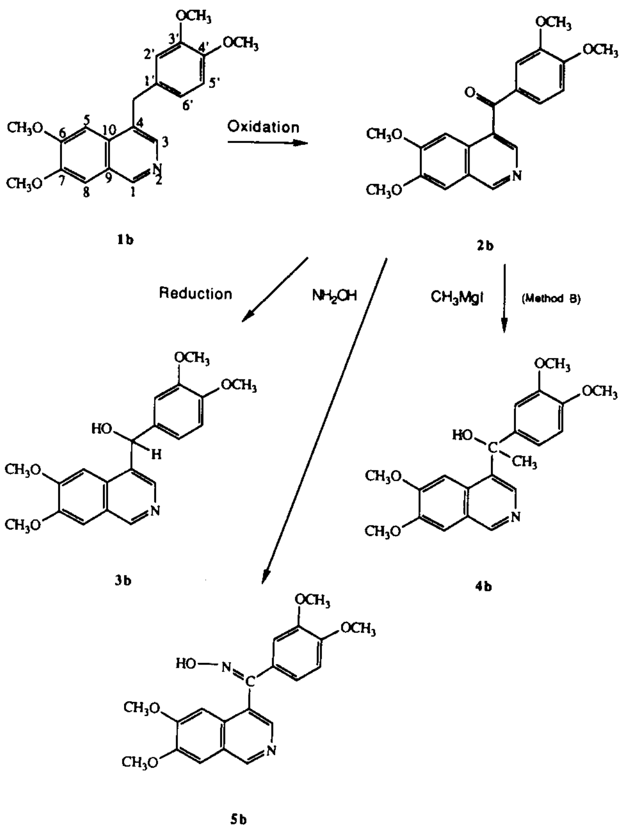
Scheme Ia



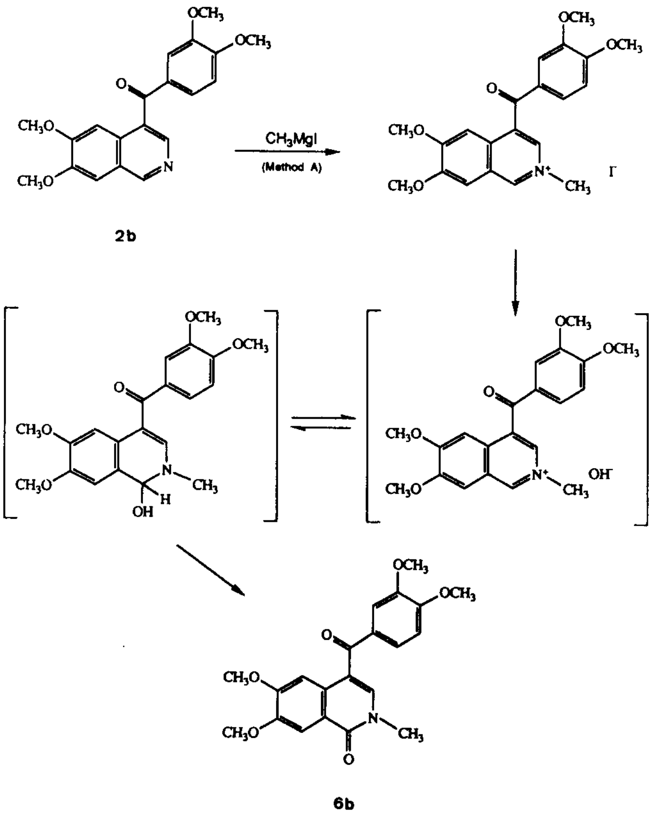
In continuation of our work in the field of papaverine analogues [1] and particularly with 4-benzylisoquinolines derivatives [1e,1f] we found it of interest to synthesize papaveraldine and papaverinol 4-isomers. Papaverine and derivatives are compounds of well-known pharmacological interest [1,6,7]. Thus a comparison between the synthesis and the chemical reactivity of the two series of isomers was possible. Synthetic pathways are summarized in Scheme I and synthetic conditions are listed in Table I. It should have been possible to oxidize the methylene group of **1b** with selenium dioxide [1b]. This reaction, under different conditions of time and temperature, failed in our hands. Oxidation by potassium dichromate, in acidic medium, led to **2b** in satisfactory yield. The reactivity of this ketone **2b** was studied with reducing reagents, hydroxylamine and Grignard's reagents. Preparation of those products can constitute key synthons [1]. Hydroxylamine hydrochloride in alkaline medium led to **5b** in poor yield (30%) as compared to **5a** (85%) [1b]; acid conditions (*p*H 4-5) favoured the reaction (70%). Reduction of **1b** with hydrogen in catalytic conditions (Ni Raney) [1a] was unsuccessful. Reduction by sodium borohydride furnished **3b** in fair yield. All new compounds are characterized by elemental analysis, ^{1}H nmr and mass spectroscopy [12] (Tables II, III, IV).

During the course of exploratory work with methylmagnesium iodide it occurs a side reaction: according to Method A (with a large excess of methyl iodide) we obtained compound **6b**. This can be interpreted as a rearrangement reaction [4] involving an oxidation process (Scheme II). The ir absorption spectrum exhibits a strong double bond at 1620-1640 cm^{-1} which supports the isoquinolone moiety. Structure of **6b** was substantiated by ^{1}H, ^{13}C nmr and mass data. In the lower part of the ^{1}H nmr spectrum [8-11] 1-H deshielded proton has disappeared. A three-protons singlet (3.64 ppm, NCH_3) is appeared. The ^{13}C nmr signals were assigned according to reference data

Scheme Ib



Scheme II



[8,9]. The carbonyl resonance of isoquinolone fall in the range of 160 ppm. The benzoyl carbonyl group is expected to be observed at lower field (193.1 ppm) in reference to the starting compound **2b** (194.7 ppm). Fragmentation of the molecular ion and rearrangement is accounted for the appearance of peaks at m/e 368, 352, 246 with loss of methyl and methoxy group and the isoquinolone ion. The required compound **4b** was obtained through a convenient procedure (Method B) and this technic was extended to **2a** to lead to **4a** previously uncorrectly described [5].

In this paper it can be concluded there is quite different reactivity in these two series of isomers.

Table I

Compound	Method	Yield %	Ref
2a	SeO_2	95	[1b]
2b	SeO_2	0	
	$K_2Cr_2O_7$	65	
3a	H_2/Ni R	85	[1a]
3b	$NaBH_4$	80	
4a	CH_3MgI	30	
4b	CH_3MgI	15	
5a	NH_2OH, HCl; KOH	85	[1b]
5b	NH_2OH, HCl; KOH	30	
	NH_2OH, HCl	70	

Table II

Compound	ir	Mp °C	Formula	Analysis Calcd./Found C	H	N
2b	1645 (C=O)	171-172	$C_{20}H_{19}NO_5$	67.97	5.41	3.96
	1620 (C=N)	ethanol 95°	(353.5)	68.00	5.64	4.04
3b	3200 (OH)	206	$C_{20}H_{21}NO_5$	67.59	5.96	3.94
	1620 (C=N)	ethanol	(355.5)	67.71	5.98	3.97
4a	3200 (OH)	90-92	$C_{21}H_{23}NO_5$, $0.5H_2O$	66.57	6.34	3.70
	1615 (C=N)	cyclohexane	(369.5)	66.73	6.08	4.03
4b	3100 (OH)	163-165	$C_{21}H_{23}NO_5$, $0.5H_2O$	66.57	6.34	3.70
	1615 (C=N)	diisopropyl ether	(369.5)	66.73	6.08	4.03
5b	3300 (OH)	192-193	$C_{20}H_{20}N_2O_5$	65.20	5.47	7.60
		dioxane	(368.4)	65.11	5.55	7.59
6b	1640 (C=O)	225-227	$C_{21}H_{21}NO_6$	65.79	5.52	3.65
	1620	ethanol 95°	(383.4)	65.52	5.43	4.00

Table III

^{1}H NMR Spectral Data

Compound	CH$_3$O	H1 or H4	H3	H5	H8	CH$_2$ or CHOH or C(CH$_3$)OH C=NOH	H2'	R H5'	H6'	Others	Solvent
1a [1a]	3.75 (s, 3H), 3.78 (s, 3H) 3.88 (s, 3H), 3.95 (s, 3H)	7.38 (d, 1H) J = 6	8.38 (d, 1H) J = 6	7.01 (s, 1H)	7.33 (s, 1H)	4.51 (s, 2H)		6.80 (m, 3H)			CDCl$_3$
1b	3.93 (s, 3H), 3.98 (s, 3H) 4.12 (s, 3H), 4.20 (s, 3H)	9.30 (d, 1H) J = 6	8.17 (d, 1H) J = 6	7.65 (s, 1H)	7.69 (s, 1H)	4.56 (s, 2H)		7.02 (m, 3H)			CF$_3$CO$_2$D
	3.75 (s, 3H), 3.83 (s, 3H) 3.89 (s, 3H), 4.00 (s, 3H)	8.96 (d, 1H) J = 6	8.26 (d, 1H) J = 6	7.10 (s, 1H)	7.18 (s, 1H)	4.25 (s, 2H)		6.75 (m, 3H)			CDCl$_3$
2a [1b]	3.97 (s), 4.20 (s)	7.62 (d, 1H) J = 6	8.45 (d, 1H) J = 6	7.12 (d, 1H)	7.54 (d, 1H)		7.70 (d, 1H) $J_{2'6'} = 2$	6.85 (d, 1H) $J_{5'6'} = 8$	7.42 (m, 1H)		CDCl$_3$
2b	3.80 (s, 3H), 3.82 (s, 3H) 3.85 (s, 3H), 3.95 (s, 3H)	9.15 (s, 1H)	8.31 (s, 1H)	7.27 (s, 1H)	7.56 (s, 1H)		7.45 (d, 1H) $J_{2'6'} = 2$	6.95 (d, 1H) $J_{5'6'} = 8$	7.25 (m, 1H)	DMSO-d$_6$	
3a	3.76 (s, 3H), 3.82 (s, 6H) 4.00 (s, 3H)	7.50 (d, 1H) J = 6	8.40 (d, 1H) J = 6	7.05 (s, 1H)	7.10 (s, 1H)	6.16 (s, CH) 5.98 (s, OH)		6.80 (m, 3H)			CDCl$_3$
3b	3.69 (s, 6H), 3.81 (s, 3H) 3.87 (s, 3H)	8.95 (s, 1H)	8.40 (s, 1H)	7.41 (s, 2H)		6.02 (d, OH) 6.20 (d, CH) J = 4	7.10 (s, 1H)		6.85 (s, 2H)		DMSO-d$_6$
4a	3.60 (s, 3H), 3.68 (s, 3H) 3.84 (s, 3H), 4.00 (s, 3H)	8.95 (s, 1H)	8.40 (s, 1H)	7.41 (s, 2H)		2.06 (s, CH$_3$)		6.90 (m, 3H)			CDCl$_3$
4b	3.70 (s, 3H), 3.78 (s, 3H) 3.85 (s, 3H), 3.96 (s, 3H)	8.95 (s, 1H) J = 6	8.60 (s, 1H) J = 6	7.13 (s, 1H)	7.35 (s, 1H)	2.09 (s, CH$_3$) 2.50 (s, OH)	7.05 (s, 1H)		6.85 (m, 2H)		CDCl$_3$
	3.57 (s, 3H), 3.65 (s, 3H) 3.70 (s, 3H), 3.83 (s, 3H)	900 (s, 1H) J = 6	8.57 (s, 1H) J = 6	7.43 (s, 1H)	7.39 (s, 1H)	1.96 (s, CH$_3$) 5.80 (s, OH)	7.07 (d, 1H) $J_{2'6'} = 2$		6.75 (m, 2H)		DMSO-d$_6$
5a	3.74 (s, 9H), 3.95 (s, 3H)	7.71 (d, 1H) J = 6	8.41 (d, 1H) J = 6	6.94 (s, 1H)	7.41 (s, 1H)	11.12 (s, OH)	7.30 (d, 1H) $J_{2'6'} = 2$	6.84 (d, 1H) $J_{5'6'} = 8$	6.52 (dd, 1H)	DMSO-d$_6$	
5b	3.73 (s, 0H), 3.92 (s, 3H)	9.06 (s, 1H)	8.05 (s, 1H)	6.70 (s, 1H)	7.50 (s, 1H)	11.28 (s, OH)	7.32 (d, 1H) $J_{2'6'} = 2$	6.81 (d, 1H) $J_{5'6'} = 8$	6.50 (dd, 1H)	DMSO-d$_6$	
6b	3.96 (s, 6H), 3.98 (s, 3H) 4.05 (s, 3H)		7.50 (s, 1H)	7.84 (s, 1H)	7.82 (s, 1H)		7.45 (d, 1H) $J_{2'6'} = 2$	6.91 (d, 1H) $J_{5'6'} = 8$	7.39 (dd, 1H)	3.64 (s, 3H) NCH$_3$	CDCl$_3$

s singlet, d doublet, d.d double doublet, m multiplet.

Table IV

Mass Spectral Data

Compound	
2b	353 (M^+, 93.1), 338 (M^+ $-CH_3$, 12.7), 322 (M^+ $-OCH_3$, 44.6), 165 (100)
3b	355 (M^+, 94.0), 340 (M^+ $-CH_3$, 4.3), 338 (M^+ $-OH$, 9.6), 324 (M^+ $-OCH_3$, 9.6), 190 (100)
4a	369 (M^+, 30.0), 354 (M^+ $-CH_3$, 41.1), 338 (M^+ $-OCH_3$, 12.0), 43 (100)
4b	369 (M^+, 24.5), 354 (M^+ $-CH_3$, 48.9), 338 (M^+ $-OCH_3$, 10.8), 165 (100)
5a	368 (M^+, 100.0), 351 (M^+ $-OH$, 59.1), 189 (40)
6b	383 (M^+, 93.1), 368 (M^+ $-CH_3$, 5.8), 352 (M^+ $-OCH_3$, 3.8), 246 (12.1)

EXPERIMENTAL

Infrared spectra were recorded with a Beckman-Acculab IV, using a potassium bromide pellet. The ^1H nmr spectra were recorded on a Bruker WP 80 (80.13 MHz) or a Jeol 60 (60 MHz) spectrometers. The ^{13}C nmr (20.15 MHz) spectra were determined with a Bruker WP 80. The ^{13}C nmr spectra were recorded both in the proton-noise decoupled (BB), in the single-frequency-off-resonance decoupled (SFORD). Tetramethylsilane was used as the internal standard of chemical shifts (in ppm); coupling constants (absolute values) are expressed in Hz. Deuterated solvents provided the internal lock signal. Mass spectra were performed on a Ribermag R-10-10 (electronic impact: 70 eV). Melting points were measured with a Büchi SMP-20 capillary melting point apparatus and are uncorrected. Combustion analysis were performed by the C. N. R. S. (Vernaison).

Starting Compounds.

Compound **1b** (6,7-dimethoxy-4-(3′,4′-dimethoxybenzyl)isoquinoline) has been prepared according to described procedure [1a,1e,2,3]. Compounds **2a** (6,7-dimethoxy-1-(3′,4′-dimethoxybenzoyl)isoquinoline) [1b], **3a** (6,7-dimethoxy-1-(3′,4′-dimethoxy-α-hydroxybenzyl)isoquinoline) [1a] and **5a** (6,7-dimethoxy-1-(3′,4′-dimethoxy-α-hydroxyiminobenzyl)isoquinoline) [1b] have been previously described.

For all those compounds ^1H nmr data are remembered or completed in the corresponding Tables for comparison with new products.

6,7-Dimethoxy-4-(3′,4′-dimethoxybenzoyl)isoquinoline **2b**.

To a solution of **1b** (20 g, 0.059 mole) in diluted acetic acid (200 ml ½ *N*) with sulfuric acid (10 ml) was slowly added dichromate potassium (40 g, 0.136 mole) with progressive warming. After complete addition the mixture was refluxed ½ hour and allowed to stand 12 hours at room temperature. The crude precipitate was filtered off and dissolved in water (200 ml). Compound **2b** was obtained by alkalinization with concentrated aqueous sodium hydroxide (10 *N*). The precipitate was washed with water, dried and recrystallized in alcohol 95°; ^{13}C nmr (deuteriochloroform): δ 55.7, 57.3 (CH_3O), 102.8 [a] (C2′), 105.4 [a] (C5′), 109.6 (C5), 111.2 (C8), 124.7 (C9), 126.0 (C6′), 127.9 (C10), 130.4 [b] (C1′), 130.6 [b] (C4), 141.9 (C3), 148.9 (C7), 150.5 (C6), 151.2 (C1), 153.6 [c] (C3′), 154.1 [c] (C4′), 194.7 (CO) ([a], [b], [c]: possible interchange).

6,7-Dimethoxy-4-(3′,4′-dimethoxy-α-hydroxybenzyl)isoquinoline **3b**.

To a stirred suspension of **2b** (3.54 g, 0.01 mole) in methanol, sodium borohydride (0.77 g, 0.02 mole) was slowly added under intensive stirring. After complete addition, stirring was maintained ½ hour. The solvent was removed under vacuum and the residue was hydrolyzed. The precipitate was recrystallized in alcohol 95°.

Grignard's Reagents.

Method A.

6,7-Dimethoxy-4-(3′,4′-dimethoxybenzoyl)-1,2-dihydro-1-isoquinolinone **6b**.

Magnesium (turnings, 0.86 g, 0.036 mole) was added to dried tetrahydrofuran THF (5 ml). A solution of methyl iodide (4.26 g, 0.03 mole) in dried THF (7 ml) was dropwise added to the stirred suspension. A suspension of **2b** (3.53 g, 0.01 mole) in dried THF (25 ml) was added to the methylmagnesium iodide. The solution was stirred 24 hours at room temperature and hydrolyzed with NH_4OH ammonium hydroxide (5 ml)/ammonium chloride (2.15 g, 0.04 mole, 5 ml of water). The precipitate was filtered off, washed with water, boiled in aqueous sodium hydroxide (10%) to eliminate residual iodide and washed with water. The product was recrystallized to furnish **6b** in a yield of 52%; ^{13}C nmr (deuteriochloroform): δ 37.6 (NCH_3), 56.0 (CH_3O), 105.8 [a] (C2′), 107.5 [a] (C5′), 109.8 (C5), 111.8 (C8), 115.2 (C9), 119.7 (C10), 124.6 (C6′), 130.0 [b] (C1′), 131.6 [b] (C4), 139.1 (C3), 149.2 (C7), 149.4 (C6), 153.6 [c] (C3′), 154.0 [c] (C4′), 161.5 (NCO), 193.0 (CO) ([a], [b], [c]: possible interchange).

Method B.

6,7-Dimethoxy-1-(3′,4′-dimethoxy-α-hydroxy-α-methylbenzyl)isoquinoline **4a**. 6,7-Dimethoxy-4-(3′,4′-dimethoxy-α-hydroxy-α-methylbenzyl)isoquinoline **4b**.

Magnesium (turnings, 0.864 g, 0.0356 mole) was added to dried diethyl ether (5 ml). A solution of methyl iodide (50.4 g, 0.356 mole) in dried diethyl ether (7 ml) was dropwise added to the stirred suspension. The reaction was undertaken in dried nitrogen atmosphere. Excess methyl iodide was removed by bubbling nitrogen through the solution. The residue was diluted in dried diethyl ether. A solution of **2** (6.36 g, 0.0179 mole) in dried benzene (10 ml) was added to the methylmagnesium iodide. After complete addition the mixture was refluxed 6 hours and then stirred 16 hours at room temperature. The mixture was hydrolyzed with ammonium hydroxide (9 ml)/ammonium chloride (3.88 g, 0072 mole, 9 ml of water). The organic layer was dried over sodium sulfate, evaporated in vacuum and the residue was triturated with petroleum ether (40-60°) or diisopropyl ether to extract the product. The compound was recrystallized to furnish **4**.

6,7-Dimethoxy-4-(3′,4′-dimethoxy-α-hydroxyiminobenzyl)isoquinoline **5b**.

To a solution of **2b** (7.06, 0.02 mole) in alcohol 95° (700 ml) was added hydroxylamine hydrochloride (5.56 g, 0.08 mole). The solution was refluxed 24 hours under magnetic stirring. The cooled mixture was filtered off and the filtrate was evaporated under vacuum. The residue was hydrolyzed (200 ml of water) and basified (*p*H 10) with sodium carbonate. The precipitate was washed with water, dried and recrystallized.

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