Dehydrogenation Reactions of 1-Substituted-3-Aryltetrahydroisoquinoline Derivatives

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The 1-substituted-3-aryltetrahydroisoquinolines I have been converted into the corresponding 3,4-dihydro- or isoquinoline derivatives by treatment with several oxidizing agents: iodine in ethanol, palladium on carbon, DDQ and Fremy's salt. The oxidation reactions with iodine always resulted in the formation of the 3,4-dihydroisoquinolines II, whereas the use of palladium on carbon and the DDQ led to the aromatic isoquinolines. Both the 3,4-dihydro- and the isoquinoline derivatives were obtained by means of Fremy's salt.

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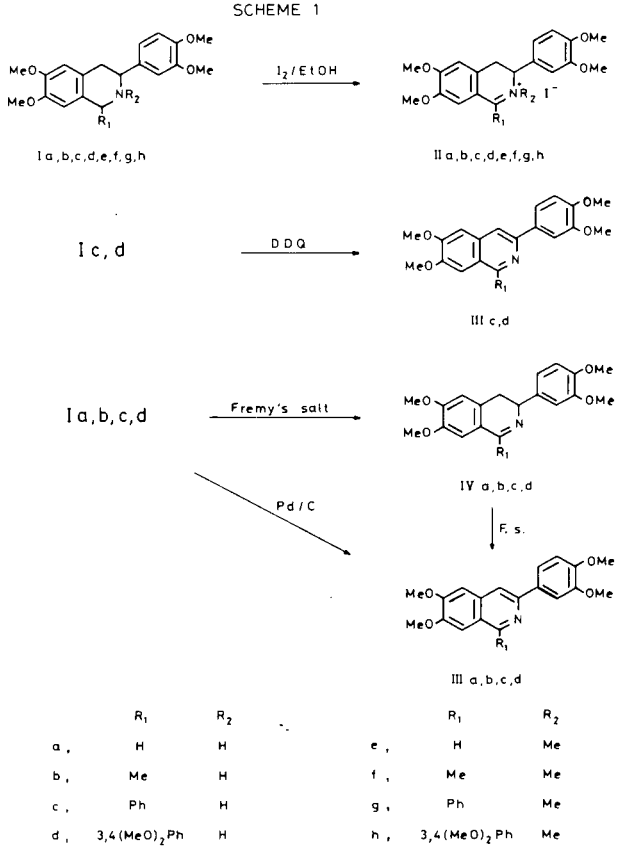
Although the wide selection of catalytic and chemical methods available for the conversion of tetrahydroisoquinolines into 3,4-dihydroisoquinolines or into the fully aromatic derivatives [1], only palladium on carbon [2] and mercuric acetate [3] have been applied to the dehydrogenation of 3-aryltetrahydroisoquinolines. We now wish to describe the dehydrogenation reactions of the 1-substituted 3-aryltetrahydroisoquinolines I [4] with various reagents: iodine in ethanol, palladium on carbon, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and potassium nitrosodisulfonate (Fremy's salt).

Tetrahydroisoquinoline derivatives are known to be oxidized to their 3,4-dihydroisoquinoline analogs by using mercuric acetate and iodine in ethanol, however certain 3,4-dihydroisoquinolines are resistant to further oxidation with these reagents [1]. Since it has already been reported that the oxidation of a 3-aryltetrahydroisoquinoline by means of mercuric acetate stopped at the 3,4-dihydroisoquinoline stage [3], it therefore appeared worthwhile to study the dehydrogenation reactions of the 3-aryltetrahydroisoquinolines I with iodine in ethanol.

Thus, we have observed that the action of an excess of iodine on the 3-aryltetrahydroisoquinolines I in boiling ethanol always gave the corresponding 3,4-dihydro derivatives II and not the desired isoquinolines (Scheme 1). As Table 1 shows, shorter reaction times were required and

SCHEME 1



	R_1	R_2		R_1	R_2
a,	H	H	e,	H	Me
b,	Me	H	f,	Me	Me
c,	Ph	H	g,	Ph	Me
d,	3,4(MeO)$_2$Ph	H	h,	3,4(MeO)$_2$Ph	Me

Table 1

Dehydrogenation of the 3-Aryltetrahydroisoquinolines I with Iodine

Product No.	Reaction time (hours)	Yield (%) [a]	Mp (°C	Formula	Calcd. (%) C	Calcd. (%) H	Calcd. (%) N	Found (%) C	Found (%) H	Found (%) N
IIa	8	52	197-198	$C_{19}N_{22}INO_4$	50.12	4.87	3.08	50.31	4.85	3.07
IIb	8	32	205-207	$C_{20}H_{24}INO_4$	51.18	5.15	2.98	51.36	5.17	2.97
IIc	10	30	215-217	$C_{25}H_{26}INO_4$	56.51	4.93	2.64	56.28	4.90	2.65
IId	10	28	235-237	$C_{27}H_{30}INO_6$	54.83	5.11	2.37	54.65	5.12	2.37
IIe	4	88	204-205	$C_{20}H_{24}INO_4$	51.18	5.15	2.98	51.38	5.18	2.99
IIf	4	86	196-198	$C_{21}H_{26}INO_4$	52.18	5.42	2.90	51.97	5.39	2.92
IIg	4	75	222-223	$C_{26}H_{28}INO_4$	57.26	5.17	2.57	57.48	5.15	2.56
IIh	4	72	195-197	$C_{28}H_{32}INO_6$	55.54	5.33	2.31	55.45	5.30	2.31

[a] Yield of pure isolated product.

Table 2

Spectral Data for the 3-Aryl-3,4-dihydroisoquinoline Methiodides IIe-h [a]

Product No.	R_1	R_3	IR (Potassium bromide) ν C=N (cm^{-1})	UV (Ethanol) λ max nm (log ε)	PMR (DMSO-d_6/TMS) [b] δ (ppm), J (Hz)
IIe	H	Me	1640	253 (3.92) 315 (3.72) 372 (3.68)	3.4 (d, J = 8, 2H, -CH_2CH<), 3.6 (s, 3H, MeN), 3.8 (s, 6H, 2 × MeO), 3.95 (s, 3H, MeO), 4.0 (s, 3H, MeO), 5.4 (m, 1H, -CH$_2$CH<), 7.0-7.6 (m, 5H arom), 9.4 (s, 1H, -CH=N)
IIf	Me	Me	1630	253 (4.25) 309 (4.03) 363 (3.98)	3.0 (s, 3H, MeC=N), 3.4-3.6 (m, 5H, -CH_2CH< and MeN) [c], 3.7 (s, 6H, 2 × MeO), 3.85 (s, 3H, MeO), 3.9 (s, 3H, MeO), 5.4 (m, 1H, -CH$_2$-CH<), 6.6-7.6 (m, 5H arom)
IIg	Ph	Me	1620	259 (4.06) 319 (3.99) 380 (3.94)	3.5 (m, 8H, -CH_2CH<, MeN and MeO) [c], 3.8 (s, 6H, 2 × MeO), 3.95 (s, 3H, MeO), 5.5 (m, 1H, -CH$_2$C*H*<), 6.6-7.2 (m, 5H, arom), 7.7 (broad s, 5H, arom)
IIh	3,4(MeO)$_2$Ph	Me	1620	258 (4.27) 316 (4.03) 372 (4.01)	3.4-3.6 (m, 8H, -CH_2CH<, MeN and MeO) [c], 3.8 (s, 6H, 2 × MeO), 3.85 (s, 3H, MeO), 3.9 (s, 6H, 2 × MeO), 5.5 (m, 1H, -CH$_2$C*H*<), 6.6-7.3 (m, 8H arom)

[a] The ir, uv and pmr spectra data for the 3-aryl-3,4-dihydroisoquinolines IIa-d are very similar to the ones described here. [b] s, singlet, d, doublet, m, multiplet. [c] The signals of the methylene groups are overlapped by those of *N*-methyl and/or methoxylic protons.

Table 3

The 3-Arylisoquinolines III Prepared

Product No	Mp (°C) Solvent	Formula	Calcd.(Found) (%) C	H	N
IIIa	203-205 (Methanol)	$C_{19}H_{19}NO_4$	70.14 (70.35)	5.89 (5.87)	4.30 (4.28)
IIIb	168-170 (Methanol)	$C_{20}H_{21}NO_4$	70.78 (71.00)	6.24 (6.22)	4.13 (4.11)
IIIc	156-158 (Ethanol)	$C_{25}H_{23}NO_4$	74.80 (74.99)	5.76 (5.76)	3.49 (3.48)
IIId	203-204 (Ethanol)	$C_{27}H_{27}NO_6$	70.27 (70.43)	5.90 (5.88)	3.03 (3.01)

much better yields attained when the reaction was applied to the *N*-methyl derivatives. Moreover, it was found that this reaction is sensitive to the nature of the substituent at C-1. Further attempts to aromatize the 3,4-dihydroisoquinolines obtained by this method were unsuccessful. The spectral data of the 3-aryl-3,4-dihydroisoquinoline methiodides IIe-h are listed in Table 2.

Since the oxidation of a 3-aryl-3,4-dihydroisoquinoline to the corresponding isoquinoline derivative can be achieved through palladium on carbon dehydrogenation [2], we have applied the above procedure to the 1-substituted 3-aryltetrahydroisoquinolines Ia-d, thus obtaining the aro-

Table 4

Spectral Data for the 3-Arylisoquinolines III

Product No.	R_1	IR (Potassium) bromide) ν C=N (cm^{-1})	UV (Ethanol) [a] λ max (nm) (log ε)	PMR (Deuteriochloroform/TMS) δ (ppm), J (Hz)
IIIa	H	1630	240 (4.53) 270 (4.57) 310 (4.20) 350 (sh, 3.59)	3.9 (s, 3H, MeO), 4.0 (s, 9H, 3 × MeO), 6.95 (d, J = 8, 1H, H-5'), 7.05 (s, 1H, H-5), 7.15 (s, 1H, H-8), 7.65 (dd, J = 8 and J = 2, 1H, H-6'), 7.5 (d, J = 2, 1H, H-2'), 7.8 (s, 1H, H-4), 9.1 (s, 1H, H-1)
IIIb	Me	1630	239 (4.50) 273 (4.62) 312 (4.15) 350 (sh, 3.49)	2.9 (s, 3H, MeC=N), 3.8 (s, 3H, MeO), 3.9 (s, 9H, 3 × MeO), 6.8 (d, J = 8, 1H, H-5'), 6.9 (s, 1H, H-5), 7.05 (s, 1H, H-8), 7.45 (dd, J = 8 and 2, 1H, H-6'), 7.5 (m, 2H, H-2' and H-4)
IIIc	Ph	1620	245 (4.61) 273 (4.68) 312 (4.28) 360 (sh, 3.67)	3.8 (s, 3H, MeO), 3.9 (s, 3H, MeO), 4.0 (s, 6H, 2 × MeO), 6.6 (d, J = 8, 1H, H-5'), 6.8 (s, 1H, H-5), 7.1 (s, 1H, H-8), 7.2-7.4 (m, 4H arom), 7.45-7.55 (m, 4H arom)
IIId	3,4(MeO)$_2$Ph	1620	238 (4.18) 273 (4.25) 315 (4.14) 360 (sh, 3.41)	3.8 (s, 3H, MeO), 3.85 (s, 6H, 2 × MeO), 3.9 (s, 6H, 2 × MeO), 4.0 (s, 3H, MeO), 6.8-7.05 (m, 2H, H-5' and H-5''),7.1 (s, 1H, H-5), 7.2-7.5 (m, 3H, H-8, H-6' and H-6''), 7.6-7.8 (m, 3H, H-4, H-2' and H-2'')

[a] sh, shoulder. [b] s, singlet, d, doublet, dd, doublet of doublets, m, multiplet.

Table 5

Dehydrogenation of the 3-Aryltetrahydroisoquinolines I with Fremy's Salt

Substrate No.	R_1	R_2	Reaction time	Ratio of IV:III	Yield (%) [a] IV	III
Ia	H	H	2 hours	—	88	—
	H	H	10 days	1:5	12	61
Ib	Me	H	3 hours	—	82	—
	Me	H	10 days	1:3	17	54
Ic	Ph	H	1 day	—	78	—
	Ph	H	12 days	2.5:1	55	21
Id	3,4(MeO)$_2$Ph	H	1 day	—	77	—
	3,4(MeO)$_2$Ph	H	12 days	3:1	54	19

[a] Yield of pure, isolated product.

matic compounds IIIa-d (Tables 3 and 4), with better yields (~60%) than those previously reported in the literature [2] for similar compounds.

On the other hand DDQ has been often used for aromatizations, though in some cases this reagent has led to the formation of oxygen-containing derivatives [5,6]. By oxidation of the 1-aryl substituted 3-aryltetrahydroisoquinolines Ic,d with DDQ in boiling toluene, we have obtained the 3-arylisoquinolines IIIc,d. However, a similar procedure heating the tetrahydroisoquinolines Ia,b with DDQ under reflux afforded a complex mixture of products, probably due to competing oxidation reactions.

Since this procedure was not acceptable for the dehydrogenation of 1-alkyl substituted 3-aryltetrahydroisoquinolines, an alternate method was devised. Thus, the new, mild and stepwise dehydrogenation of tetrahydroisoquinolines involving the use of Fremy's salt [7] at room temperature was chosen, because it has been reported [8] to give good results when no substituents or only small alkyl groups were present at C-1.

The results obtained when this dehydrogenation procedure was applied to the 3-aryltetrahydroisoquinolines Ia-d are summarized in Table 5. In all cases, the yields of the 3,4-dihydroisoquinolines IV were high (80%), while the further oxidation of the 3,4-dihydro- IV [9] to the isoquinolines III was somewhat difficult to perform. In fact, compounds Ia and Ib were still oxidized efficiently to the isoquinolines IIIa and IIIb respectively, whereas the conversion to the aromatized compounds proceeded in only 20% yields for those substrates with aryl substituents at C-1, Ic and Id.

In summary, we may conclude that both iodine in ethanol and Fremy's salt can be used to obtain 3-aryl-3,4-dihydroisoquinolines, starting from the corresponding tetrahydroisoquinoline derivatives, whereas aromatization can be achieved by using palladium on carbon, DDQ and Fremy's salt. However, the latter two reagents are to be considered as complementary methods, since for those substrates with aryl substituents at C-1, good yields were obtained by using DDQ, while for those compounds without substituents or with alkyl groups at C-1 the dehydrogenation by means of Fremy's salt was the method of choice.

EXPERIMENTAL

Melting points were determined on either Electrothermal 1A 6304 or Buchi apparatus and are uncorrected. For thin-layer chromatography Merck Kieselgel GF_{254} plates (0.2 mm thick) were used. Visualization was accomplished by uv light or by spraying with Draguendorff's reagent. Microanalyses were performed by the "Instituto de Química Bio-Orgánica de Cataluña" and the "Colegio Universitario de Alava". The uv and ir spectra were recorded on a Beckman 5260 and a Pye-Unicam SP-1000 spectrophotometers. The nmr spectra were run on a Perkin-Elmer R-12 (60 MHz) and a Brucker WH (90 MHz).

Preparation of the 3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Methiodide (IIe) *via* Dehydrogenation with Iodine in Ethanol (Typical Procedure).

To a solution of the *N*-methyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Ie) (343 mg, 1 mmole) in ethanol (70 ml), iodine (1 g, 4 mmoles) was added and the mixture heated under reflux for 3.5 hours (the reaction can be followed by tlc on silica gel using dichloromethane/methanol, 9.5:0.5). After cooling to room temperature, the excess iodine was decomposed by dropwise addition of 10% thiosulfate solution. The resulting pale yellow solution was extracted with chloroform (3 × 100 ml). The organic layer was washed with water, dried over magnesium sulfate and evaporated to dryness. The residue was recrystallized from ethanol to give the title compound IIe, yield 412 mg (88%), mp 204-205° (Tables 1 and 2).

Preparation of the 1-Phenyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline (IIIc) and the 1,3-Bis(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline (IIId) *via* Dehydrogenation with DDQ.

To a solution of the 1,3-diaryltetrahydroisoquinolines (Ic) (405 mg, 1 mmole) and Id (465 mg, 1 mmole) in dry benzene (100 ml) was added DDQ (280 mg, 2.2 mmoles) and the resulting mixture was stirred and heated under reflux for 1.5 hours. The solvent was removed under reduced pressure and the residue extracted with dichloromethane (3 × 100 ml). The combined extracts were chromatographed through a short column of neutral alumina (grade III) (eluent, dichloromethane), and concentrated. Recrystallization of the resulting oil from ethanol afforded the isoquinolines IIIc (yield, 280 mg, 70%) and IIId (yield, 285 mg, 62%), as colorless crystals (Tables 3 and 4).

Dehydrogenation of the 3-Aryltetrahydroisoquinolines I with Fremy's Salt (Typical Procedures).

A. Preparation of the 3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (IVa).

To a solution of Fremy's salt (0.6 g, 2.2 mmoles) in 4% sodium carbonate solution (45 ml) was added the 3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (Ia) (365 mg, 1 mmole). The resultant suspension was stirred at room temperature for 2 hours. Then, the reaction mixture was extracted with dichloromethane (3 × 40 ml). The organic phase was washed with saturated aqueous sodium chloride solution (50 ml) and dried with anhydrous magnesium sulfate. After evaporation of the solvent, the residue was crystallized from ethanol to afford the title compound (IVa), yield, 288 mg (88%) (Table 5).

B. Synthesis of the 3-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinoline (IIIa).

The tetrahydroisoquinoline hydrochloride Ia (365 mg, 1 mmole) was stirred at room temperature in a solution of Fremy's salt (0.6 mg, 2.2 mmoles) in 4% sodium carbonate solution (45 ml). An excess of Fremy's salt was always maintained as judged by the purple colour of the reaction medium. After 10 days, the reaction mixture was worked up in the same manner as described above. The resulting solid was column chromatographed under pressure on silica gel by eluting with dichloromethane to yield the title compound IIIa (yield, 200 mg, 61%) and the 3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (IVa) (yield, 40 mg, 12%) (Tables 4 and 5).

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