

STUDIES IN THE ISOQUINOLINE SERIES

Part II. Oxidation of 1-Benzyl-3 : 4-Dihydroisoquinolines

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THE remarkable ease of oxidation of 1-benzyl-3 : 4-dihydroisoquinolines was first observed by Buck, Haworth and Perkin¹ who found that exposure to air of alcoholic solutions of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3 : 4-dimethoxybenzyl)- and 3 : 4-dihydro-6 : 7-dimethoxy-1-(3 : 4-methylenedioxybenzyl)-isoquinolines caused their conversion to the corresponding 1-benzoyl-3 : 4-dihydroisoquinolines, the latter also being obtained by oxidation of the 1-benzyl-3 : 4-dihydro bases with iodine. Similar auto-oxidations of 1-benzyl-3 : 4-dihydroisoquinolines have been reported by other authors, the auto-oxidations proceeding with such facility that the 1-benzoyl-3 : 4-dihydroisoquinolines are the only products obtained in the Bischler-Napieralsky reaction.^{2, 3}

Gulland and Haworth⁴ observed however that 3 : 4-dihydro-1-(2-nitrobenzyl)-isoquinolines are remarkably stable to auto-oxidation. We have also found that 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)-isoquinoline was recovered unchanged after prolonged exposure of the alcoholic solution to air or after treatment with iodine. Apparently, substituents in the benzyl portion of the molecule control the ease of oxidation and in this paper we present a systematic study of the oxidation of various 1-benzyl-3 : 4-dihydroisoquinolines, which were synthesised for this purpose and whose properties were recorded in an earlier paper.⁵

Exposure to air of alcoholic solutions of these bases resulted in auto-oxidation to the corresponding 1-benzoyl-3 : 4-dihydroisoquinolines (Table I) with one exception. The products gave a green colour with hot acetic anhydride, a test specific for 1-benzoyl-3 : 4-dihydroisoquinolines.¹ That these were not 1-benzoylisoquinolines was shown by the oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-(4-methoxybenzyl)-isoquinoline with alcoholic potassium hydroxide to 6 : 7-dimethoxy-1-(4-methoxybenzoyl)-isoquinoline which was shown to be different from the product of auto-oxidation. Only 3 : 4-dihydro-6 : 7-dimethoxy-1-(2-nitrobenzyl)-isoquinoline was recovered unchanged after prolonged exposure of its alcoholic solution to air. The

TABLE I
1-Benzoyl-3:4-Dihydro-6:7-Dimethoxyisoquinolines

Substituent in benzoyl residue	Method of prepara- tion*	B A S E						P I C R A T E					
		Mol. formula	M.P., °C.	Found %		Required %		Mol. formula	M.P. °C.	Found %		Required %	
				C	H	C	H			C	H	C	H
4-OMe	<i>a, b</i>	C ₁₉ H ₁₉ O ₄ N	110-12	69.83	6.02	70.15	5.85	C ₂₅ H ₂₂ O ₁₁ N ₄	220 (decomp.)	54.41	4.02	54.16	3.97
2-OMe	<i>a, b</i>	C ₁₉ H ₁₉ O ₃ N	93-95	73.41	6.13	73.77	6.15	C ₂₅ H ₂₂ O ₁₁ N ₄	180	54.03	4.05	54.16	3.97
4-Me	<i>a, b</i>							C ₂₅ H ₂₂ O ₁₀ N ₄	183 (sinters at 172)	55.54	4.26	55.76	4.09
2-Me	<i>a, b</i>							C ₂₆ H ₂₂ O ₁₀ N ₄	172 (decomp.)	55.68	4.07	55.76	4.09
2-Br	<i>b</i>	C ₁₈ H ₁₆ O ₃ NBr (decomp.)	159-60	57.81	4.10	57.76	4.28	C ₂₄ H ₁₉ O ₁₀ N ₄ Br	159-60 (decomp.)	47.89	3.01	47.76	3.15
3-Br	<i>b</i>	C ₁₈ H ₁₆ O ₃ NBr	126-27	57.88	4.69	57.76	4.28	C ₂₄ H ₁₉ O ₁₀ N ₄ Br	173-74 (decomp.)	47.48	3.54	47.76	3.15
4-Br	<i>b</i>	C ₁₈ H ₁₆ O ₃ NBr	132	57.31	4.45	57.76	4.28	C ₂₄ H ₁₉ O ₁₀ N ₄ Br	193-94 (shrinks above 180)	48.09	3.21	47.76	3.15
3-Nitro	<i>b</i>	C ₁₈ H ₁₆ O ₅ N ₂	175-76	63.82	4.87	63.53	4.71	C ₂₄ H ₁₉ O ₁₂ N ₅	165-57 (sinters at 147)	50.24	3.69	50.62	3.34

* *a* iodine oxidation.*b* air oxidation.

corresponding 4-nitrobenzyl compound under the same conditions yielded a resin from which no pure product could be isolated.

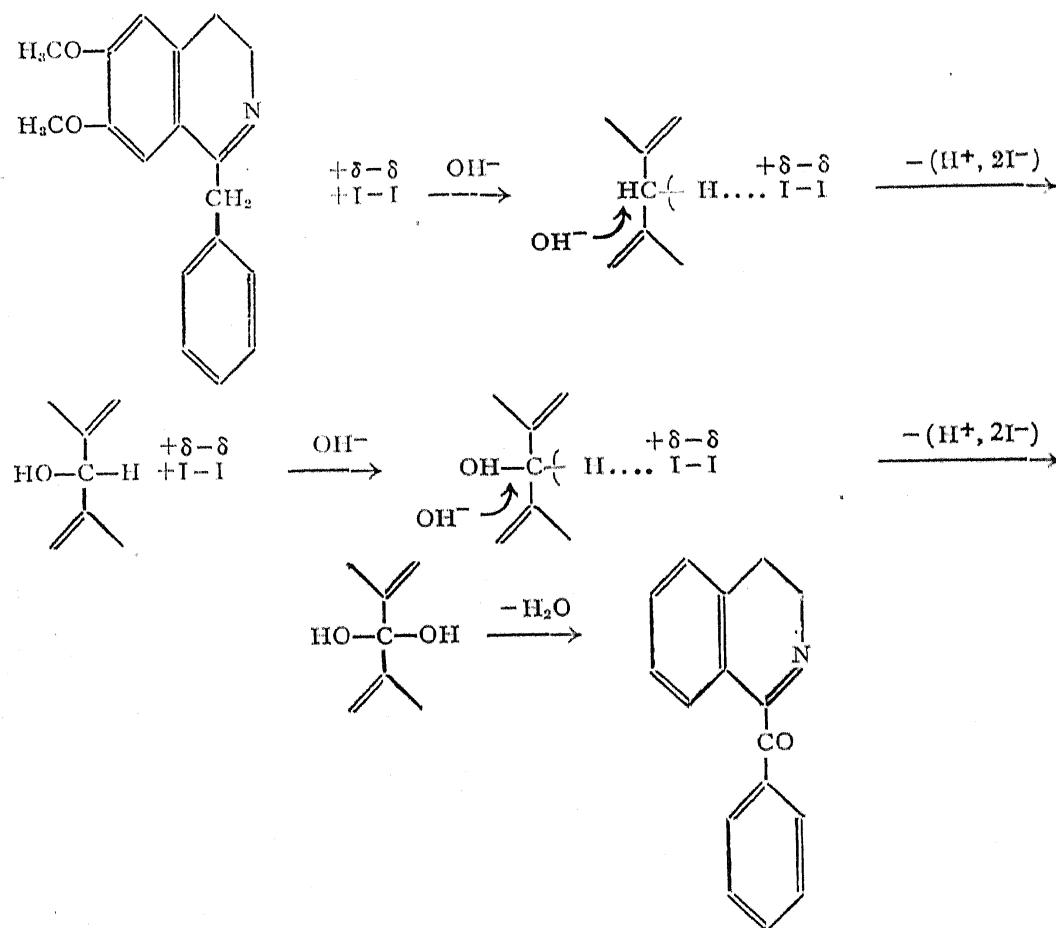
Air oxidations must necessarily proceed by a free radical mechanism. It is not surprising therefore that these auto-oxidations proceed in all cases irrespective of the electrical nature of the substituents in the benzyl portion of the molecule, though it is not clear why 3:4-dihydro-6:7-dimethoxy-1-(2-nitrobenzyl)-isoquinoline alone should resist air oxidation.

It is of interest that oxidation with iodine yields the same product as in the auto-oxidation, although they must proceed by different mechanisms. In order to obtain a semi-quantitative idea of the relative ease of oxidation of the various 1-benzyl-3:4-dihydroisoquinolines, equimolecular quantities were treated with a known excess of a standard solution of iodine for the same period and the excess iodine then determined. The results of the study are presented in Table II. It is seen that 3:4-dihydro-6:7-dimethoxy-isoquinoline is unaffected by iodine, showing that iodine does not bring

TABLE II
Reaction between Alcoholic Iodine and 3:4-Dihydroisoquinolines

6:7-Dimethoxy-3:4-dihydroisoquinoline with substituent at 1-position	Wt. of hydrochloride in gm.	Thiosulphate (0.07658 N) equivalent of iodine uptake c.c.	Iodine uptake %
Nil	0.1572	0	0
Benzyl	0.1989	4.60	14.1
2-Bromobenzyl	0.2479	0	0
3-Bromobenzyl	0.2449	4.75	14.7
4-Bromobenzyl	0.2476	4.70	14.1
2-Methylbenzyl	0.2098	6.60	20.0
3-Methylbenzyl	0.2282	5.80	16.0
4-Methylbenzyl	0.2051	14.35	44.0
2-Methoxybenzyl	0.2158	16.50	50.9
3-Methoxybenzyl	0.2127	6.55	20.5
4-Methoxybenzyl	0.2158	23.50	72.5
2-Nitrobenzyl	0.2395	1.70	4.9
3-Nitrobenzyl	0.2380	4.50	13.7
4-Nitrobenzyl	0.2334	3.85	11.5
4-Cyanobenzyl	0.2146	3.50	10.7

about dehydrogenation. The iodine taken up by various 1-benzyl-3:4-dihydroisoquinolines must be solely utilised for oxidation of the methylene group. In four cases where there was considerable uptake of iodine, the 1-benzoyl-3:4-dihydro bases were isolated in pure condition. In three cases where iodine uptake was negligible, the original compounds were recovered. In two cases where the iodine uptake was about 20%, only impure compounds could be isolated.



A study of the results presented in Table II reveals that the oxidation of 1-benzyl-3:4-dihydroisoquinolines by iodine is influenced both by steric and polar effects. Thus the uptake of iodine by 3:4-dihydro-1-(2-methylbenzyl)-isoquinoline is considerably less than that of 3:4-dihydro-1-(4-methylbenzyl)-isoquinoline. The presence of a nitro group in any position of the benzyl group inhibits oxidation by iodine, the effect being maximum when *ortho*- to the methylene group. A bromine atom *ortho*- to the methylene group completely inhibits oxidation, whereas when present in other positions, the iodine consumption is of the same order as for the unsubstituted compound. A plausible mechanism for the oxidation of

1-benzyl-3:4-dihydroisoquinolines may be postulated as below involving the direct approach of a polarised iodine molecule or a I^+ ion to the methylene group.

It is unlikely that a hypoidite ion is involved since in blank experiments with alcoholic iodine and potassium acetate, very little iodine was consumed.

EXPERIMENTAL PROCEDURE

Determination of the relative ease of oxidation of 3:4-dihydro-6:7-dimethoxyisoquinolines with iodine

The base hydrochloride (*ca.* 0.0006 mole) was weighed accurately and dissolved in alcohol (10 c.c.). An aqueous solution of potassium acetate (3 c.c., 1.82 N) and an alcoholic solution of iodine (20 c.c., 0.22 N) were pipetted into the solution of the hydrochloride and the mixture was kept for 1 hr. with occasional shaking. Unreacted iodine was then estimated against standard sodium thiosulphate solution with starch indicator. The difference between this and a blank gave the thiosulphate equivalent of the iodine consumed by the dihydroisoquinoline. The ratio of iodine uptake to the quantity of iodine required for complete oxidation of the benzyl-dihydroisoquinoline to benzoyldihydroisoquinoline, *i.e.*, 3 moles of iodine per 1 mole of the compound, was computed. The results are presented in Table II.

1-Benzoyl-3:4-dihydro-6:7-dimethoxyisoquinolines

(a) *By oxidation of the benzyl bases with iodine.*—A solution of the base hydrochloride (0.2 g.) in alcohol (5 c.c.) containing sodium acetate (1 g.) was treated with iodine (0.3 g.) in alcohol (10 c.c.). After 1 hr. excess iodine was discharged by addition of the requisite quantity of sodium thiosulphate. Addition of a solution of picric acid (0.5 g.) in water precipitated the picrate, which was collected and recrystallised from alcohol.

1-(4-Methoxybenzoyl)-, 1-(2-methoxybenzoyl)-, 1-(4-methylbenzoyl)-, and 1-(2-methylbenzoyl)-3:4-dihydro-6:7-dimethoxyisoquinolines were obtained by this procedure in yields of 78, 63, 59 and 43% respectively. Almost quantitative recovery of the starting material was obtained in the cases of 3:4-dihydro-6:7-dimethoxyisoquinoline, and 1-(2-bromobenzyl)- and 1-(2-nitrobenzyl)-3:4-dihydro-6:7-dimethoxyisoquinolines. Impure products were obtained in the cases of 1-(3-bromobenzyl)- and 1-(4-bromobenzyl)-3:4-dihydro-6:7-dimethoxyisoquinolines. These are probably mixtures of the original and the oxidised bases.

(b) *By air oxidation*.—A solution of the benzylidihydro base (1 g.) in alcohol was kept exposed to air for several days. The sticky solid so obtained gave the benzoyldihydro derivative on repeated crystallisation from alcohol. 3 : 4-Dihydro-6 : 7-dimethoxy-1-(2-nitrobenzyl)-isoquinoline was recovered completely unchanged by this method, while the corresponding (4-nitrobenzyl)-base gave a resin which could not be crystallised or made to yield suitable derivatives.

The benzoyldihydro bases are listed in Table I.

6 : 7-Dimethoxy-1-(4-methoxybenzoyl)-isoquinoline

A solution of 3 : 4-dihydro-6 : 7-dimethoxy-1-(4-methoxybenzyl)-isoquinoline (0.7 g.) was digested on a water-bath with methanolic potassium hydroxide (10%, 10 c.c.) for 4 hr. with addition of methanol at intervals. The sticky mass was washed with water and crystallised from alcohol to yield the benzoyl base as colourless needles (0.2 g.), m.p. 145–46° (Found: C, 70.2; H, 5.5; $C_{19}H_{17}O_4N$ requires C, 70.6; H, 5.2%).

SUMMARY

The oxidation of several 1-benzyl-3 : 4-dihydroisoquinolines in alcoholic solution by air and by iodine has been studied. A mechanism is proposed for the action of iodine on these bases.

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