Tetrahedron. Vol. 27, pp. 4519 to 4532. Pergamon Press 1971. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—XVII[1]

BENZYLATION, II

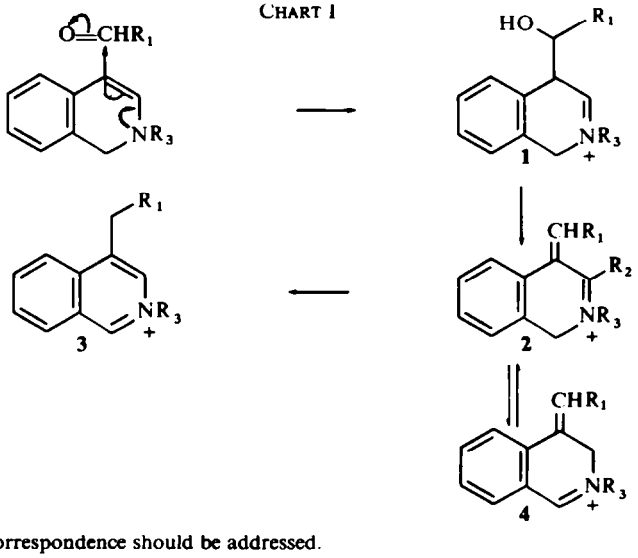
D. W. BROWN, M. SAINSBURY, S. F. DYKE* and W. G. D. LUGTON
School of Chemistry and Chemical Engineering, Bath University of Technology, Bath, Somerset, England

(*Received in the UK* 1 *June* 1971; *Accepted for publication* 24 *June* 1971)

Abstract—The course of the condensation reaction between 1,2-dihydroisoquinolines and aromatic aldehydes in acid solution has been defined by the isolation and characterisation of 4-benzylidene-1, 4-dihydroisoquinoline derivatives. The scope of the base-catalysed condensation between isoquinoline methiodide and aromatic aldehydes has been examined and some earlier literature corrected.

THE acid-catalysed condensation of 1,2-dihydroisoquinolines with aldehydes, originally described by Bobbitt *et al.*,[2] has been developed[3,4] into a very useful method for preparing 4-substituted-isoquinolines (3). The mechanism postulated for this reaction[3a] is summarised in Chart I, and the isolation of intermediates of the type 1 and 2, especially with $R_1 = C_6H_5$, has been claimed.[1,3a,3c,4] When isoquinoline methiodide is condensed with benzaldehyde in the presence of alkali, under certain conditions, the main products are[5] 3, and a compound formulated as either 2 ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = Me$) or 4 ($R_1 = C_6H_5$; $R_3 = Me$). This second compound is formed, presumably, by the disproportionation[6] of the isoquinoline pseudo base, under the influence of the alkali, into 2-methylisocarbostyril and 2-methyl-1,2-dihydroisoquinoline, followed by condensation of the latter with benzaldehyde as indicated in Chart I.

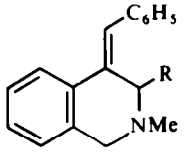
CHART I



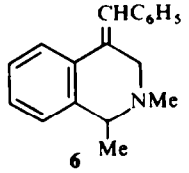
* To whom correspondence should be addressed.

In this paper we *prove* that 1,4-dihydro-4-benzylideneisoquinolines (**2**) are intermediates in the condensation of 1,2-dihydroisoquinolines with aromatic aldehydes, under both acid and alkaline conditions.

When the previously described[5] compound **2** ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = Me$) or **4** ($R_1 = C_6H_5$; $R_3 = Me$) was reacted with methyl magnesium iodide, a tertiary base was obtained, the UV spectrum of the methiodide of which (λ_{max} 285 nm; ε_{max}18,900) is typical of the *trans*-stilbene chromophore. The NMR spectrum, however, is compatible with either structure **5a** (R = Me) or **6** arising respectively from **2** ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = Me$) or **4** ($R_1 = C_6H_5$; $R_3 = Me$). Catalytic hydrogenation of this Grignard reaction product yielded 2,3-dimethyl-4-benzyl-1,2,3,4-tetrahydroisoquinoline (**8**), identical with the compound obtained from 2,3-dimethyl-1,2-dihydroisoquinoline as shown in Chart II. The condensation product in this case has the

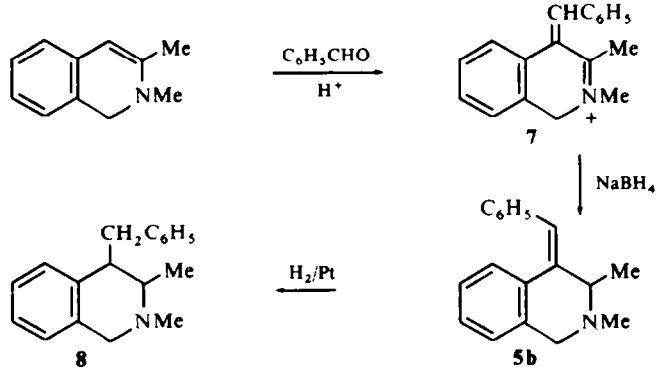


5a



6

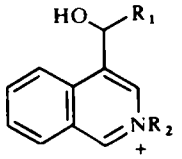
CHART II



1,4-dihydroisoquinoline structure **7** from its UV spectrum, and especially since the NMR resonance associated with the C—Me group at C_3 appears as a *singlet* (at 2·9 δ). The UV spectrum of the methiodide of **5b** (λ_{max} 285 nm; ε_{max}8100) is more in agreement with a *cis*-stilbene rather than a *trans*-stilbene chromophore. The NMR spectrum is also consistent with this interpretation; the shielding effect of the phenyl group of **5b** which is sterically hindered from gaining coplanarity with the isoquinoline system, would explain the observed diamagnetic shifts of the C_5—and olefinic—protons relative to those in **5a** (R = Me).

By modifying the conditions of the condensation of benzaldehyde with 2-benzyl- or with 2-methyl-isoquinolinium iodide in alkaline solution, products of the type **9** ($R_1 = C_6H_5$; $R_2 = CH_2C_6H_5$) or **9** ($R_1 = C_6H_5$; $R_2 = Me$), respectively, were formed.[5] The structure of the former compound was established by showing that the product **10** ($R = CH_2C_6H_5$), obtained by reducing it catalytically, is identical with

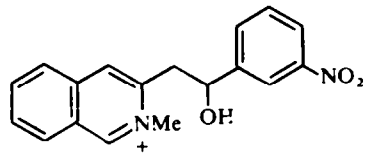
the compound resulting from the reduction of the vinylogous amide **11** (R = $CH_2C_6H_5$) with $NaBH_4$. The structure of **9** ($R_1 = C_6H_5$; R_2 = Me) has now[8] been proven by an alternative synthesis of it involving the interaction of 4-lithioisoquinoline with benzaldehyde, followed by quarternisation with methyl iodide.



9

10

11



12

The simplicity of the procedure involved in the alkali-promoted condensation of isoquinoline methiodide with aldehydes makes this method a potentially useful route to 4-substituted isoquinolines, and the scope of the reaction has therefore been tested. The results are summarized in Tables I and II. The structures of the type **9** were further characterized as the reduction products **10** (Table 3A) and their derived O-acetates (Table 3B). In an effort to extend the scope of these reactions a little more, 2-methyl-6,7-dimethoxyisoquinolinium iodide was examined, but no reaction occurred with benzaldehyde. This is not entirely unexpected because in this case it is known[9] that the equilibrium between the pseudobase and the isoquinolinium hydroxide favours the latter. When 2,3-dimethylisoquinolinium iodide was condensed with *m*-nitrobenzaldehyde, the product was found to be **12**, since upon dehydration the known[10] 2-methyl-3-styrylisoquinolinium iodide was formed.

With the structure of the 1,4-dihydroisoquinolinium salts of the type **2** established, it is now possible, by making comparisons of the relevant characteristic UV and NMR spectral data, to allocate similar structures to a number of compounds prepared in the condensation of 1,2-dihydroisoquinolines with aldehydes in *acid* solution (Table 4). The preparative and analytical data for these compounds appear in Table 5. In all cases, isomerisation of the 1,4-dihydroisoquinolinium salts to the fully aromatic 2-methyl-4-benzylisoquinolinium salts was effected by heating them with acids, or better, with alkali. New compounds prepared in this way appear in Table VI and their spectral data in Table 7.

With the aid of the data now available, the products obtained[3c] by the acid-catalysed reaction between 2-methyl-1,2-dihydroisoquinoline and crotonaldehyde or cinnanaldehyde are the 1,4-dihydroisoquinolinium salts **13** (R = Me) or **13** (R = C_6H_5), respectively.

In an attempt to prepare an example of the postulated intermediate **1** (Chart I), the compound **9** ($R_1 = C_6H_5$; R_2 = Me) was reduced with LAH, but the product was found, by UV and NMR spectral analysis, to be **5a** (R = H), identical with the

TABLE 1. 1,4-DIHYDROISOQUINOLINOLINIUM SALTS (2) BY CONDENSATION OF ISOQUINOLINE METHIODIDE WITH ALDEHYDES

	Aldehyde† (g)	NaOEt (g)	Yield‡ %	m.p.§ °C	Molecular Formula	Analysis Required C	H	N	I	Found C	H	N	I
	C_6H_5CHO (8·2)	3·06	47	151–153	$C_{17}H_{16}IN$	56·5	4·5	3·9	35·1	56·7	4·5	3·95	35·3
p-	MeC_6H_4CHO (8·2)	2·45	34	162–164	$C_{18}H_{18}IN$	57·6	4·8	3·7	33·9	56·8	4·7	3·8	36·0
p-	$MeOC_6H_4CHO$ (8·0)	2·45	20	143–146 (EtOH)	$C_{18}H_{18}INO$	55·2	4·6	3·6	32·5	55·6	4·55	3·4	33·6
m-	$MeOC_6H_4CHO$ (8·0)	2·45	26	147–149	$C_{18}H_{18}INO$	55·2	4·6	3·6	32·5	54·3	4·3	3·2	33·7
p-	ClC_6H_4CHO (7·5)	3·06	6	157–160 (EtOH)	$C_{17}H_{15}ClIN$	51·4	3·8	3·5	32·1	50·9	3·5	3·5	33·2

† 8·1 g isoquinoline methiodide used in each case.
‡ Based upon isoquinoline methiodide.
§ Recrystallized from MeOH unless otherwise stated.

TABLE 2. THE 4-(ARYLHYDROXYMETHYL) ISOQUINOLINIUM SALTS (9)

Aldehyde (g)	Base (ml)	EtOH (ml)	Yield† %	m.p.	Molecular Formula	Analysis Found C	H	N	I	Analysis C	H	N	I
p-$O_2NC_6H_4CHO$‡ (9·0)	10N NaOH (1·7)	45	41	187–189[a]	$C_{17}H_{15}IN_2O_3$	48·4	3·6	6·6	30·1	48·2	3·8	6·8	30·2
m-$O_2NC_6H_4CHO$§ (4·5)	5N NaOH (1·0)	25	70	197–198[a]	$C_{17}H_{15}IN_2O_3$	48·4	3·6	6·6	30·1	48·4	3·5	6·4	30·6
p-$Me_2NC_6H_4CHO$§ (6·0)	5N NaOH (2·0)	30	17	197–198[a]	$C_{19}H_{22}I_2N_2O$	41·6	4·1	5·1		41·3	4·3	4·8	—
m-$MeOC_6H_4CHO$§ (6·2)	5NNaOH (1·0)	30	47	204–205[b]	$C_{18}H_{18}INO_2$	53·1	4·5	3·4	31·2	52·8	4·3	3·7	32·0
p-$MeOC_6H_4CHO$§ (7·8)	5NNaOH (2·0)	40	16	184–186[b]	$C_{18}H_{18}INO_2$	53·1	4·5	3·4	31·2	52·9	4·4	3·6	—
o-ClC_6H_4CHO‡ (8·4)	NaOEt (1·0 g)	40	49	206–208[b]	$C_{17}H_{15}ClINO$	49·6	3·7	3·4	30·8	49·3	3·5	3·7	31·4
p-ClC_6H_4CHO‡ (6·8)	10NNaOH (1·5)	35	5	217–218[b]	$C_{17}H_{15}ClINO$	49·6	3·7	3·4	30·8	49·7	3·5	3·6	31·1

† Based upon isoquinoline.
‡ 8·1 g Isoquinoline methiodide used.
§ 5·4 g Isoquinoline methiodide used.

[a] Recrystallized from MeOH.
[b] Recrystallized from EtOH.

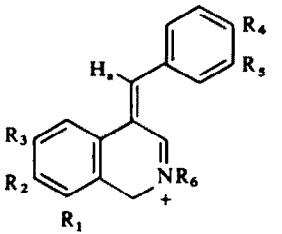
TABLE 3A. THE 4-(ARYLHYDROXYMETHYL) TETRAHYDROISOQUINOLINES (10)

Experiment No.	R_1	R_2	Yield %	m.p. °C	Molecular Formula	Analysis Required % C	H	N	Found % C	H	N
1	3,4—$(MeO)_2C_6H_3$—	CH_3	80	158–160	$C_{19}H_{23}NO_3$	72·8	7·35	4·5	72·6	7·4	4·4
2	2-Furyl	CH_3	65	103–104	$C_{15}H_{17}NO_2$	74·05	7·0	5·8	73·9	7·1	5·9
3	2-Furyl	$C_6H_5CH_2$	75	111–113	$C_{21}H_{21}NO_2$	79·0	6·6	3·4	78·8	6·9	4·6
4	p-$NO_2C_6H_4$—	CH_3	30	197–199	$C_{17}H_{18}N_2O_3$	68·4	6·1	9·4	68·4	5·9	9·2
5	o-$NO_2C_6H_4$—	CH_3	23	187–188	$C_{17}H_{18}N_2O_3$	68·4	6·1	9·4	68·2	6·1	9·2

TABLE 3B. THE O-ACETATES OF 10

Experiment No.	m.p. °C	Molecular Formula	Analysis Required % C	H	N	Found % C	H	N
2	60–61	$C_{17}H_{19}NO_3$	73·7	6·15	4·5	73·6	6·3	4·4
3	123–124	$C_{23}H_{23}NO_3$	76·4	6·4	3·9	75·8	6·4	4·1
4	137–139	$C_{19}H_{20}N_2O_4$	67·1	5·9	8·2	66·9	5·9	8·1
5	89–91	$C_{19}H_{20}N_2O_4$	67·1	5·9	8·2	67·3	6·1	8·1

TABLE 4. SPECTRAL DATA FOR THE 1,4-DIHYDROISOQUINOLINIUM SALTS



Experiment No.	R_1	R_2	R_3	R_4	R_5	R_6	NMR (CF_3CO_2H) C_1-CH_2	C_3H	H_a	C_5H	^+NMe	UV data $\lambda_{max}(\varepsilon)$ nm
1	H	H	H	H	H	Me	5·18	8·67	8·5	7·84	3·88	265(11,700), 370(11,300)
2†	H	H	H	Me	H	Me	5·2	8·8	8·6	—	3·9	289(16,700), 374(16,300)
3	H	H	H	OMe	H	Me	5·2	8·8	8·5		4·0	270(13,600), 405(18,000)
4	H	H	H	H	OMe	Me	5·2	8·8	8·6	—	4·0	278(14,300), 380(10,200)
5	H	H	H	Cl	H	Me	5·1	8·75	8·5	—	3·9	278(9,300), 392(7,600)
6	H	OMe	OMe	H	H	H	5·23	9·0d	8·52	7·5	—	280(10,300), 300(9,700), 412(4,000)
7	OMe	OMe	H	H	H	H	5·23	8·9d	8·51	7·75d	—	298(14,500), 367(6,900)
8	OH	OMe	H	H	H	H	5·2	8·9d	8·5	7·8d	—	298(sh), 298, 365
9	H	OMe	OMe	OMe	OMe	H	5·24	8·9d	8·5	—	—	286, 304, 445
10	OMe	OMe	H	$O-CH_2$	$-O$	H	5·18	8·8d	8·4	—	–	258, 297, 408
11	H	OMe	OMe	$O-CH_2-O$		H	5·2	8·7d	8·3	—	—	279(21,200). 307(21,800), 442(14,500)
12	H	H	H	$O-CH_2-O$		Me	5·2	8·85	8·45	—	4·1	277(8,500)
13	H	OMe	OMe	H	H	Me	5·2	8·9	8·4	7·48	3·87	284(16,400), 312(13,400), 418(9,200)
14	H	OMe	OMe	$O-CH_2-O$		Me	5·17	8·8	8·35	7·43	3·9	279(16,300), 307(16,800), 442(10,300)
15	OMe	OMe	H	$O-CH_2-O$		Me	5·14	8·9	8·4	—	—	298(20.600), 261(9,900)

† In CD_3SOCD_3.

TABLE 5. 1,4-DIHYDROISOQUINOLINIUM SALTS (2) BY ACID-CATALYSED CONDENSATION

Experiment† No.	m.p.	Yield %	Molecular Formula	Analysis Required C	H	N	Cl	Found C	H	N	Cl
6	115–118	69	$C_{18}H_{18}ClNO_2$, EtOH	66·5	6·7	3·8	9·8	67·0	6·4	4·0	9·8
7	104–106	60	$C_{18}H_{18}ClNO_2$, EtOH	66·5	6·7	3·8	9·8	65·8	6·4	3·9	—
8	210–212	30	$C_{17}H_{16}ClNO_2$	67·7	5·35	4·6	10·7	68·0	5·6	4·3	11·1
10	104–106	60	$C_{19}H_{18}ClNO_4$, EtOH	62·1	6·0	3·45	8·8	61·6	5·65	3·2	9·2
11	145–147	53	$C_{19}H_{18}ClNO_4$, EtOH	62·1	6·0	3·45	8·8	62·6	5·9	3·4	-
12	126–128	20	$C_{18}H_{16}NO_2Cl$	68·9	5·1	4·5	11·2	68·5	5·3	4·6	11·3
13	156–158	70	$C_{19}H_{20}ClNO_2$	69·2	6·1	4·25	10·8	68·7	5·8	4·1	11·2
14	146–148	70	$C_{20}H_{20}ClNO_4$	64·3	5·4	3·75	9·5	63·95	5·3	3·5	9·9
15	153–155	65	$C_{20}H_{20}ClNO_4$	64·3	5·4	3·75	9·5	64·1	5·2	3·5	—

† See Table 4.

TABLE 6. 4-BENZYLISOQUINOLINIUM SALTS

Experiment No. †	m.p.	Molecular Formula	Analysis							
			Required				Found			
			C	H	N	Cl	C	H	N	Cl
6	199–200[a]	$C_{18}H_{18}ClNO_2$	68·4	5·75	4·4	11·2	68·5	5·85	4·6	11·6
7	182–183[a]	$C_{18}H_{18}ClNO_2$	68·4	5·75	4·4	11·2	68·35	5·4	4·3	11·4
8‡	220–221[b]	$C_{17}H_{15}NO_2$	77·0	5·7	5·3	—	77·2	5·85	5·1	—
9	234–236[c]	$C_{21}H_{24}INO_4$	52·4	5·0	2·9	26·4(I)	52·6	5·1	3·1	26·9(I)
10‡	123–124[b]	$C_{19}H_{17}NO_4$	70·6	5·3	4·3	—	70·4	5·3	4·4	—
11§	209–211[c]	$C_{20}H_{20}INO_4$	51·6	4·3	3·0	27·3(I)	51·5	4·4	3·2	26·9(I)
13	217—218[a]	$C_{19}H_{20}INO_2$	54·1	4·8	3·3	30·1(I)	53·8	4·7	3·6	30·8(I)
15	178–180[c]	$C_{20}H_{20}INO_4$	51·6	4·3	3·0	27·3(I)	51·9	4·6	3·1	27·3(I)

[a] recrystallized from MeOH.
[b] recrystallized from H_2O/EtOH.
[c] recrystallized from EtOH.

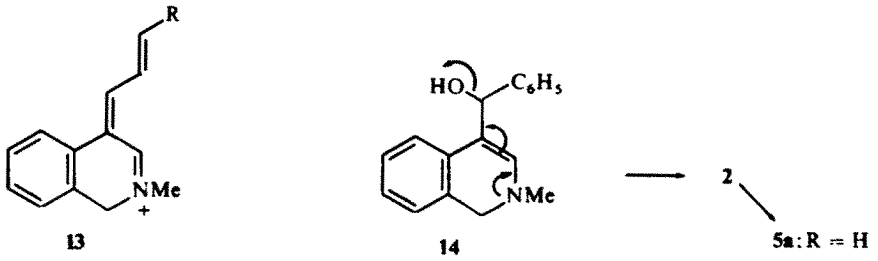
† See Table 4.
‡ Analysed as the free base.
§ Analysed as the methiodide.

Table 7. Spectral data for 4-benzylisoquinolium salts

Experiment†	NMR (CF_3CO_2H)				UV		
No.	C_1H	C_3H	$ArCH_2$	NMe	$\lambda_{max}(\varepsilon)$nm		
1	9·45	8·35	4·6	4·5	235(46,200),	282(8,800),	324(11,500)
2	9·5	8·0–8·6	4·6	4·5	231(53,100),	280(3,400),	341(7,100)
3	9·5	8·1–8·6	4·65	4·55	230(43,500),	280(3,500),	341(4,800)
4	9·5	8·0–8·6	4·6	4·6	231(50,700)	282(5,100),	342(7,100)
5	9·5	7·9–8·5	4·6	4·5	230(48,300),	292(13,200),	343(10,000)
6	9·25(d)	8·1(d)	4·5	—	242(16,700),	313(10,300)	
7‡	9·6	8·45	4·45	4·5	256(55,700),	296 sh(11,200)	318(13,400)
9‡	9·1	7·9	4·3	4·3	256(57,400),	320(11,800)	
10‡	9·55	7·95	4·5	4·5	257(50,000),	321(10,800)	
11‡	9·2	8·0	4·45	4·45	256(47,700),	318(17,900)	
12‡	9·45	8·1–8·6	4·55	4·55			
13	9·3	8·05	4·6	4·5	257(54,700),	319(10,200)	

† See Table 4.

‡ Data concerns the methiodide salt.



13 14

substance obtained by reducing **2** ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = Me$) with either LAH or $NaBH_4$. Presumably, reduction of **9** occurs initially at C_1 to give **14**, which, after elimination of hydroxyl ion to yield **2** ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = Me$) can be further reduced as described. Rather surprisingly it has now been found that **5a** (R = H), is identical with the compound obtained previously[7] by the reduction of **11** (R = Me) with LAH, to which structure **10** (R = Me) was originally allotted, and it is quite different from **10** (R = Me) which results from the catalytic reduction of **9** ($R_1 = C_6H_5$; $R_2 = Me$).

EXPERIMENTAL

M.p's are uncorrected. UV spectra were determined in EtOH soln, and IR spectra were recorded as nujol mulls. Chemical shifts are expressed in ppm downfield from TMS as an internal standard.

The reaction of trans-2-*methyl*-4-*benzylidene*-1,4-*dihydroisoquinolinium* **2** ($R_1 = C_6H_5$; $R_2 = R_3 = CH_3$) *iodide with methylmagnesium iodide.* The finely ground salt (1·25 g), was added portionwise to a stirred suspension of MeMgI prepared in the usual manner in anhyd ether (50 ml) from MeI (1·9 g). The mixture was stirred for 3 hr, warmed to reflux for ½ hr, cooled and then treated with 10% NH_4Cl aq. The ethereal layer was collected and the aqueous phase extracted with ether. The combined, dried ethereal solns, on evaporation, yielded *trans*-2-methyl-4-benzylidene-1,2,3,4-tetrahydroisoquinoline **5a** (R = Me) as a pale oil (0·6 g) λ_{max} nm, 285 ν_{max} (liquid film) cm^{-1}: 3080, 3040, 2790, 1625, 1593; NMR ($CDCl_3$) ppm; 1·27, 3H (d, J = 7Hz), ($\underline{CH_3}$—CH—); 2·35, 3H(s), (—N—$\underline{CH_3}$); 3·64, 1H (d, J = 16Hz), (one —C_1H); 4·06, 1H (q, J = 7Hz), (—$\underline{CH}$—CH_3); 4·14, 1H (d, J = 16Hz), (other —C_1H); 7·05–7·23, 4H (m), (—C=C—H and —C_{6-8}H's); 7·34, 5H (s) ($C_6\underline{H_5}$—); 7·67, 1H (m), (—C_3H). The methiodide was prepared as pale yellow plates m.p. 196–197° from EtOH; λ_{max} (ε) nm, 285 (18,900). (Found: C, 56·3; H, 5·65; N, 3·5; I, 34·4. $C_{19}H_{22}IN$ requires: C, 56·1; H, 5·9; N, 3·8; I, 34·2%).

The reduction of cis-2,3-*dimethyl*-4-*benzylidene*-1,4-*dihydroisoquinolinium* **2** ($R_1 = C_6H_5$; $R_2 = R_3 = CH_3$) iodide. A stirred soln of the salt (0·2 g) in EtOH (20 ml) was treated with $NaBH_4$ (0·05 g) dissolved in 20% aq EtOH (5 ml). After 1 hr the soln was diluted with water (20 ml), EtOH removed by evaporation, and the aqueous residue extracted with ether (3 × 15 ml). Evaporation of the dried extracts yielded a pale oil (0·12 g); λ_{max} 284 NMR ($CDCl_3$) ppm, 1·06, 3H (d, J = 7·0 Hz), (—CH—$\underline{CH_3}$); 2·45, 3H (s), (—NCH_3); 3·39, 1H (q, J = 7·0 Hz), (—$\underline{CH}$—CH_3); 3·82, 2H (broad s), ($ArCH_2N$—); 6·46, 1H (s), (=CH); 6·81, 1H (m), (—C_5H); 6·9–7·35, 3H (m), (—C_{6-8}H's); 7·23, 5H (s), ($C_6\underline{H_5}$—). The methiodide was obtained as colourless plates from EtOH m.p. 219–220°, λ_{max} (ε) nm, 284 (8,100), ν_{max} cm^{-1}, 1610, 1600. (Found: C, 56·3: H, 5·6; N, 3·65; I, 34·5. $C_{19}H_{22}IN$ requires: C, 56·1; H, 5·9; N, 3·8; I, 34·2%).

Preparation (base catalysed) of the 4-*benzylidene*-1,4-*dihydroisoquinolinium salts and their isomerization to* 4-*benzylisoquinolinium salts* (*Tables* 1 *and* 6). Isoquinoline methiodide (8·1 g, 0·0335 mole), the aromatic aldehyde and a soln of NaOEt in EtOH (45 ml) were allowed to stand at RT for 3 days. The soln was then acidified with a few drops of conc HI and cooled to 0°. The product was collected after two days. (Table 1).

The isomerization reaction was effected by heating a soln of the benzylidene salt in MeOH for 20 hr. The soln was evaporated to low bulk and on cooling the isoquinoline salt crystallized in high yield. (Table 6).

2-*Methyl*-4-*phenylhydroxymethylisoquinolinium iodides.* A suspension of isoquinoline methiodide in a soln of aromatic aldehyde and aqueous ethanolic base was allowed to stand at RT. The crystalline product was collected after 4 days. The yields quoted in Table 2 correspond to this material, the mps correspond to the recrystallized material.

Spectral data.

2-*Methyl*-4(4-*nitrophenyl*) *hydroxymethylisoquinolinium iodide* λ_{max} (ε) nm, 231 (51,200), 267 (10,400), 338 (5,000), ν_{max} cm^{-1}, 3315, 1648, 1612, 1530. NMR (DMSO.D_6) ppm: 4·6, 3H (s), ($\overset{+}{N}-CH_3$); 6·6, 1H (s), (=CHOH); 6·85*, 1H(s), (=CHOH); 7·6–8·1, 4H (AA^1 XX^1), ($-C_6H_4NO_2$); 7·9–8·4, 4H(m), (C_{5-8}H's), 8·77, 1H(s), (C_3H), 9·9, 1H(s), (C_1H).

2-*Methyl*-4(3-*nitrophenyl*) *hydroxymethylisoquinolinium iodide*, λ_{max}(ε) nm, 231 (47,500), 264 (9,300), 341 (6,300). ν_{max} cm^{-1}, 3300 1645, 1610, 1535, NMR (DMSO.D_6) ppm, 4·66, 3H(s), ($\overset{+}{N}CH_3$); 6·8, 1H(d, J = 4·5 Hz), (=CHOH); 7·1*, 1H(d, J = 4·5 Hz), (=CHOH); 7·7–8·3, 4H(m), ($-C_6H_4NO_2$); 8·3–8·7, 4H(m), (C_{5-8}H's); 9·0 1H(s), (C_3H); 10·2 1H(s), ($-C_1$H).

2-*Methyl*-4(4-*dimethylaminophenyl*) *hydroxymethylisoquinolinium iodide*, λ_{max} (ε) nm, 280 (2,700), 341 (4,500). ν_{max} cm^{-1}, 3360, 2580, 1645, 1611. NMR (DMSO.D_6), 3·3 and 3·6, 2 × 3H(s), (2 × = $\overset{+}{N}HCH_3$); 4·5 3H(s), ($\overset{+}{N}CH_3$); 6·3, 2H(m), ($-CHOH$); 6·9–7·6, 5H(complex), ($-C_6H_4\overset{+}{N}HMe_2$); 7·8–8·8, 4H(complex), (C_{5-8} H's); 9·93; 1H(s), (C_1H).

2-*Methyl*-4(3-*methoxyphenyl*) *hydroxymethylisoquinolinium iodide*, λ_{max}(ε) nm, 230 (61,700), 278 (3,300), 338 (5,100), ν_{max} cm^{-1}, 3360, 1642, 1608, NMR (DMSO.d_6), 3·84, 3H(s), ($-OCH_3$); 4·55, 3H(s), ($\equiv\overset{+}{N}CH_3$); 6·59, 1H(s), (CHOH); 6·7*, 1H(s), (CH—OH); 6·9–7·3, 4H(complex), ($-C_6H_4OMe$), 8·0–8·95, 5H(complex), ($C_{3\cdot5-8}$H's); 10·1, 1H(s), ($-C_1$H).

2-*Methyl*-4(4-*methoxyphenyl*) *hydroxymethylisoquinolinium iodide*, λ_{max}(ε) nm, 231 (47,300); 279 (3,700), 342 (4,500), ν_{max} cm^{-1}, 3360, 1647, 1598. NMR (DMSO.d_6) ppm; 4·0, 3H(s), ($-OCH_3$); 4·56, 3H(s), ($\equiv\overset{+}{N}CH_3$); 6·65, 2H(s), —CH(OH); 7·0–7·5, 4H(AA^1XX^1), ($-C_6H_4OCH_3$); 8·0–8·6, 4H(m), ($-C_{5-8}$H(s), 8·7, 1H(s) ($-C_3$H), 9·96, 1 H(s), ($-C_1$H).

2-*Methyl*-4(2-*chlorophenyl*) *hydroxymethylisoquinolinium iodide*, λ_{max} (ε) nm, 247 (26,700), 254 (25,900), 314 (4,800), ν_{max} cm^{-1}, 3350, 1648, 1608, NMR (DMSO.d_6); 4·52, 3H(s), ($\equiv\overset{+}{N}CH_3$); 6·63, 2H(s), ($-CHOH$); 7·0–7·3, 4H(m), ($-C_6H_4Cl$); 7·96–8·8, 4H(m), (C_{5-8}H's); 8·95, 1H(s), ($-C_3$H); 10·1, 1H(s), ($-C_1$H).

2-*Methyl*-4(4-*chlorophenyl*) *hydroxymethylisoquinolinium iodine*, λ_{max} (ε) nm, 232 (56,700), 287 (11,500), 341 (8,400) ν_{max} cm^{-1}, 3340, 1645, 1610. NMR (DMSO.d_6) ppm, 4·6, 3H(s), ($\equiv\overset{+}{N}CH_3$); 6·8, 2H(s), ($-CHOH$); 7·2–7·7, 4H(AA^1XX^1), ($-C_6H_4Cl$); 7·9–8·6, 4H(m), (C_{5-8}H's); 8·7, 1H(s), ($-C_3$H); 10·1, 1H(s), ($-C_1$H).

1-(m-*Nitrophenyl*)-2-*hydroxy*-2-[3^1-(2^1-*methyl isoquinolinium*)] *ethane iodide* (**12**). To a stirred suspension of 3-methylisoquinoline methiodide (4·3 g) and 3-nitrobenzaldehyde (3·4 g) in EtOH was added aqueous 5N NaOH (0·75 ml). After standing 4 days at RT the solid product was collected and triturated with EtOH giving a pale yellow product (4·8 g) which gave short yellow needles m.p. 177–178° from MeOH. λ_{max}(ε) nm, 234 (63,600), 265 (10,200), 347 (5,800), ν_{max} cm^{-1}, 3320, 1656, 1615, 1534, NMR (DMSO, d_6) ppm; 3·5, 2H(m), ($-CH_2CH-$) 4·6, 3H(s), ($\equiv\overset{+}{N}CH_3$); 5·4, 1H(m), (CH—OH); 6·1*, 1H(d, J = 5 Hz), ($-CHOH$); 7·7–8·6, 8H(m), (aromatic H's); 8·65, 1H(s), ($-C_4$H); 10·25, 1H(s), ($-C_1$H).

1-(m-*Nitrophenyl*)-2-[3^1-(2^1-*methylisoquinolinium*)] *ethylene iodide*. The salt **12**, (0·5 g) was heated on an oil bath to 130° and maintained at that temp for ½ hr on cooling the solid mass was triturated with acetone, filtered and the solid product (0·2 g) recrystallized from MeOH as dull yellow needles m.p. 260–263°. (Found: C, 51·7; H, 3·6; N, 6·9; I, 30·7. Calc. for $C_{18}H_{15}IN_2O_2$; C, 51·7; H, 3·6; N, 6·7; I, 30·4%).

This 3-styrylisoquinolinium salt was also prepared directly by heating 3-methylisoquinoline (3·0 g) and benzaldehyde (5·0 g) in pyridine (1·5 ml) for 1 hr at 110°. The styryl compound resulted in 45% yield.

Reductions of 4-*phenylhydroxymethylisoquinoline methiodide* (**9**, R_1 = C_6H_5, R_2 = CH_3)

(a) *trans*-4-*Benzylidene*-2-*methyl*-1,2,3,4,-*tetrahydroisoquinoline* (**5a**, R = H). The iodide **10** (1·3 g) was added as a fine powder to a stirred suspension of LAH (0·6 g) in ether (60 ml) and the mixture stirred for 1 hr. By the usual work up a pale yellow oil (0·8 g) was obtained, λ_{max} nm, 220, 285; ν_{max} cm^{-1}, (liquid film), 1630, 1596, NMR ($CDCl_3$) ppm; 2·39, 3H(s), ($-NCH_3$); 3·62, 2H(s), ($-N-CH_2-$); 3·66, 2H(s), ($-N-CH_2-$), 7·1–7·3, 4H(m), ($-C_{6-8}$ H's and = CH); 7·34, 5H(s), (C_6H_5-); 7·82, 1H(m), ($-C_5$H). The methiodide was obtained as yellow plates m.p. 121–122°, λ_{max}(ε) nm, 292 (12,000), ν_{max} cm^{-1}, 1610, 1586, NMR (DMSO.d_6) ppm; 3·18, 3H(s), ($\equiv{}^+NCH_3$); 3·3, 3H(s), ($\equiv{}^+NCH_3$); 4·74, 2H(s), ($-NCH_2-$); 4·87, 2H(s), ($-NCH_2-$); 7·35–7·6, 3H(m), ($-C_{6-8}$H's); 7·49, 5H(s), (C_6H_5-); 7·87, 1H(broad s), (Ph—CH=); 8·17, 1H(m), ($-C_5$H). (Found: C, 55·0; H, 5·7; N, 3·4; I, 32·3; $C_{18}H_{20}IN.H_2O$ requires: C, 54·7; H, 5·6; N, 3·5; I, 32·15%).

* Signal at 6·1 disappeared on deuteration when signal at 5·4 became a triplet (J = 6 Hz). (Found; C, 48·9; H, 4·3; N, 6·2; I, 29·5. $C_{18}H_{17}IN_2O_3$ requires; C, 49·4; H, 4·2; N, 6·4, I, 29·1%).

The same free base (0·71 g) was obtained by reduction, under normal conditions, of **9** (R_1 = C_6H_5, R_2 = CH_3), (1·12 g) using $NaBH_4$. When the methiodide formation was effected under anhydrous conditions and the products recrystallized from dry EtOH the methiodide was obtained as pale yellow plates m.p. 232–234°, λ_{max} (ε) nm, 292 (14,100), ν_{max} cm^{-1}, 1610, 1586. (Found: C, 57·3; H, 5·3; N, 3·6; I, 33·9. $C_{18}H_{20}IN$ requires: C, 57·3; H, 5·35; N, 3·7; I, 33·65%).

(*b*) *2-Methyl-4-(phenylhydroxymethyl)-1,2,3,4-tetrahydroisoquinoline methiodide* (**10**, R = CH_3). 4-Phenylhydroxymethylisoquinoline methiodide (0·9 g) was dissolved in MeOH/EtOH, (100 ml, 1/1) and shaken under H_2 at 30 psi with Adams catalyst (40 mg) for 16 hr. The mixture was filtered, the solvent evaporated, the residue dissolved in water and the base liberated by the addition of aqueous ammonia. This was extracted into ether (3 × 15 ml) and the combined dried ethereal extracts treated with MeI. After 16 hr the solid material was collected and recrystallized from MeOH as cream plates (0·5 g) m.p. 184–185°, ν_{max} cm^{-1} 3250, 1605. (Found: C, 54·55; H, 5·6; N, 3·6; I, 32·6; $C_{18}H_{22}INO$ requires: C, 54·7; H, 5·6; N, 3·5; I, 32·1).

The O-acetates of (**10**). The alcohols **10**, (1·0 g) were dissolved in Ac_2O (5 ml) and heated on a steam bath ½ hr. The mixture was treated with water (50 ml) and the solid material extracted into $CHCl_3$. Evaporation of the dried solvent yielded gums which crystallized on trituration with EtOH. Recrystallization from EtOH afforded the pure products. (Table 3B).

Spectral properties

2-Methyl-4-[1-hydroxy-1-(3,4-dimethoxyphenyl) methyl]-1,2,3,4-tetrahydroisoquinoline, λ_{max} (ε) nm, 285 (3,000), ν_{max} cm^{-1},3500, 1590. NMR ($CDCl_3$) ppm; 2·45, 3H(s), ($-NCH_3$); 2·5–3·5, 3H(m), ($-NCH_2CH-$); 7·15 and 7·4 1H(d, J = 13Hz), ($PhCH_2N-$): 7·7 and 7·85. 3H(s). (2 × $-OCH_3$): 5·25. 1H(d, J = 2·5 Hz), ($-CH-OH$); 6·2, 1H(broad), (−OH, signal removed on deuteration); 6·0, 1H(d, J = 8·0 Hz), ($-C_6H$ of $-C_6H_3(OMe)_2$); 6·4–7·3, 6H(m), ($-C_6H_4-$ and $-C_6H_2(OMe)_2$).

2-Methyl-4-[1-hydroxy-1-(α-furyl) methyl]-1,2,3,4-tetrahydroisoquinoline, ν_{max} cm^{-1}, 3400, 1610. NMR ($CDCl_3$) ppm; 2·3, 3H(s), (−NMe); 2·6, 1H(q, J = 11·5 and 3·0 Hz), (one $-C_3H$); 2·9–3·3, 2H(m), (other $-C_3H$, $-C_4H$); 3·2 and 3·7 1H(d, J = 14·5 Hz), ($PhCH_2N-$); 5·05, 1H(d, J = 2·5 Hz), ($-CHOH$); 5·7–6·2, 3H(m), ($-C_3H$,C_4H furyl and $-C_5H$); 6·5–7·2, 4H(m), ($-C_5H$ furyl and $C_{6-8}H$'s) OH absorption not observed but HDO peak obtained on deuteration.

2-Methyl-4-[1-hydroxy-1-(4-nitrophenyl)methyl]-1,2,3,4-tetrahydroisoquinoline, λ_{max} (ε) nm, 280 (9,200). ν_{max} cm^{-1},3200, 1600, 1510. NMR ($CDCl_3$) ppm; 2·55, 3H(s), ($-NCH_3$); 2·8, 1H(q, J = 11·5 and 3·0 Hz), (one $-C_3H$); 3·0–3·35, 2H(m), (other $-C_3H$ and $-C_4H$); 3·4 and 4·0, 1H(d, J = 15·0 Hz), ($PhCH_2N-$); 5·4, 1H(d, J = 2·5 Hz), ($-CHOH$); 5·95, 1H(d, J = 8·0 Hz), ($-C_5H$), 6·7–7·2, 4H(m), ($-C_{6-8}H$'s and −OH; 7·35 and 8·2, 4H(AA^1XX^1), ($-C_6H_4NO_2$).

2-Methyl-4-[1-hydroxy-1-(2-nitrophenyl)methyl]-1,2,3,4-tetrahydroisoquinoline, λ_{max} (ε) nm, 265 (6,000). ν_{max} cm^{-1},3500, 1610, 1520, NMR($CDCl_3$) ppm; 2·5, 3H(s), ($-NCH_3$); 2·65, 1H(q, J = 12·0 and 2·5 Hz), (one $-C_3H$); 3·0–3·4, 2H(m), (other $-C_3H$ and $-C_4H$); 3·35 and 3·39, 1H(d, J = 14·5 Hz), ($PhCH_2N-$); 5·3, 1H(d, J = 2·5 Hz), ($-CHOH$); 6·05, 1H(d, J = 8·0 Hz), ($-C_5H$); 6·7–7·2, 4H(m), ($-C_{6-8}H$'s and OH); 7·3–8·2, 4H(m), ($-C_6H_4NO_2$).

Preparation (acid catalysed) of the 4-benzylidene-1,4-dihydroisoquinolinium salts (Table 5) and their isomerization to 4-benzylisoquinolines or 4-benzylisoquinolium salts (Table 6).

(a) *The exocyclic hydrochlorides.* A soln of the appropriate benzylaminoacetaldehyde dimethylacetal (0·04 mole) in EtOH/conc HCl, (150 ml, 1:1), was allowed to stand at RT for 16 hr and then the aromatic aldehyde (0·05 mole) was added and the soln heated on a steam bath ½ hr. After cooling the mixture was diluted with water (150 ml) and allowed to stand overnight at 0° when crystalline product separated.

(b) *The exocyclic metho-salts.* A soln of the appropriate N-methylbenzylacetaldehyde dimethylacetal (0·04 mole) and the appropriate aromatic aldehyde (0·05 mole) in EtOH (40 ml) was stirred rapidly while cHCl (40 ml) was added during 1 min. The mixture was then heated on a steam bath ½ hr. cooled diluted with water (80 ml) and stored at 0° for 16 hr. Crystalline products were then collected in the yields quoted in Table 5.

The isomerization reaction

(i) *For exocyclic hydrochlorides.* A soln of the benzylidene salt in EtOH was heated under reflux until the UV spectrum indicated that the reaction has proceeded to completion (½–12 hr). Concentration and cooling of the mother liquors caused the product to separate in very good yields.

(ii) *For exocyclic metho-salts.* The exocyclic salt (2·0 g) was heated under reflux in EtOH (20 ml) containing 30% KOH aq (5 ml). On cooling white needles of the aromatic base separated in very good yield.

REFERENCES

[1] Part XVI: S. F. Dyke, M. Sainsbury, D. W. Brown, M. N. Palfreyman and D. W. Wiggins, *Tetrahedron* **27**, 281 (1971)

[2] J. M. Bobbitt, D. P. Winter and J. M. Kiely, *J. Org. Chem.* **30**, 2459 (1965)

[3] [a] S. F. Dyke and M. Sainsbury, *Tetrahedron* **23**, 3161 (1967);
[b] S. F. Dyke, M. Sainsbury and B. J. Moon, *Ibid.* **24**, 1467 (1968);
[c] D. W. Brown, S. F. Dyke and M. Sainsbury, *Ibid.* **25**, 101 (1969)

[4] W. J. Gensler, K. T. Shamasundar and S. Marbury, *J. Org. Chem.* **33**, 2861 (1968)

[5] M. Sainsbury, S. F. Dyke, D. W. Brown and W. G. D. Lugton, *Tetrahedron* **24**, 427 (1968)

[6] D. W. Brown and S. F. Dyke, *Ibid.* **22**, 2429 (1966)

[7] M. Sainsbury, S. F. Dyke and A. R. Marshall, *Ibid.* **22**, 2445 (1966); S. F. Dyke, M. Sainsbury, D. W. Brown, M. N. Palfreyman and E. P. Tiley, *Ibid.* **24**, 6703 (1968)

[8] M. Sainsbury, D. W. Brown, S. F. Dyke, R. D. J. Clipperton and W. R. Tonkyn, *Ibid.* **26**, 2239 (1970)

[9] D. Beke, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky and A. J. Boulton) Vol. I, p 167 Academic Press, New York (1963)

[10] J. C. Martin, K. R. Barton, P. G. Gott and R. H. Meen, *J. Org. Chem.* **31**, 943 (1966)