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1,2-DIHYDROISOQUINOLINES—XIV[1]

ALKYLATION

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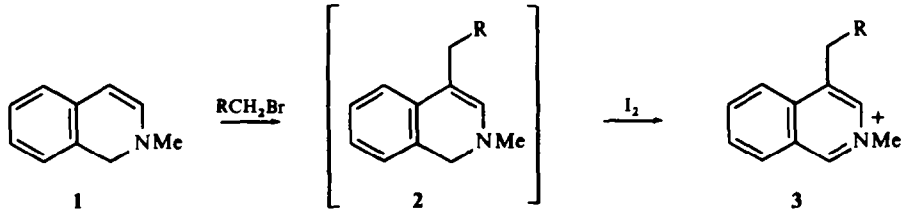
Abstract—The reactions between 2-methyl-1,2-dihydroisoquinoline and various alkyl halides have been studied, and the preparation of 4-substituted isoquinolines from 4-lithioisoquinoline has been explored.

IN PART VI[2] we reviewed and developed some methods for C_4-benzylation of isoquinoline derivatives and mentioned that we had succeeded in preparing 2-methyl-4-benzylisoquinolinium iodide (**3**, R = C_6H_5) from 2-methyl-1,2-dihydroisoquinoline (**1**) and benzyl bromide, followed by oxidation of the intermediate (**2**) with iodine. We have now examined this fundamental[3] alkylation reaction of enamines in more detail.



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The results, collected into Table 1, were obtained under essentially standard conditions in which equimolar amounts of the enamine (**1**) and the alkyl halide in ethanol solution containing one mole of triethylamine were heated under reflux for 4 hr. To this mixture was added iodine and potassium acetate to effect dehydrogenation. The product quaternary salts were isolated as crystalline solids; attempts to identify other products present in the residual dark oils usually failed, although small additional amounts of the main products were sometimes obtained. The structures of the products listed in Table 1 were allocated on the basis of analytical and spectral data; the NMR spectra were especially informative (Table 2). Although yields are seemingly low, they compare favourably with those expected if the more traditional synthetic routes were adopted.

Of all the types of alkyl halide studied, benzyl bromides were the most successful, although rather surprisingly *o*-methoxybenzyl bromide failed to yield a C-benzylated

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TABLE 1. 2-METHYL-4-ALKYLISOQUINOLINIUM SALTS

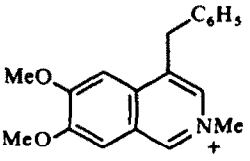
No.	-C_4-substituent	M.p.	Mol. Formula	% Yield§	Analysis							
					Calculated				Found			
					C	H	N	I	C	H	N	I
1	$C_6H_5CH_2$—	185–186°	$C_{17}H_{16}NI$	27	56·5	4·5	3·9	35·1	56·7	4·7	3·7	35·25
2	*o*-$O_2NC_6H_4CH_2$—	188–189°	$C_{17}H_{15}N_2O_2I$	14*	50·2	3·7	6·9	31·3	50·6	4·1	6·9	30·45
3	*m*-$O_2NC_6H_4CH_2$—	245–246°	$C_{17}H_{15}N_2O_2I$	21	50·2	3·7	6·9	31·3	50·4	4·0	6·7	30·8
4	*p*-$O_2NC_6H_4CH_2$—	236–237°	$C_{17}H_{15}N_2O_2I$	23	50·2	3·7	6·9	31·3	50·1	4·3	7·1	30·6
5	*m*-$MeOC_6H_4CH_2$—	199–200°	$C_{18}H_{18}NOBr$‡	5*	62·8	5·7	4·1	—	62·4	5·7	3·8	—
6	*p*-$MeOC_6H_4CH_2$—	235–236°	$C_{18}H_{18}NOI$	25	55·0	4·6	3·6	32·5	55·2	4·3	3·8	32·3
7	$C_6H_5CH\ CH_3$	99–100°	$C_{18}H_{18}NI_3$†	11	34·4	2·9	2·2	60·5	33·9	2·6	2·5	61·3
8	*o*-$ClC_6H_4CH_2$—	189–190°	$C_{17}H_{15}NICl$	9*	51·7	3·8	3·55	32·2	51·6	4·1	3·7	32·5
9	*p*-$ClC_6H_4CH_2$—	202–203°	$C_{17}H_{15}NICl$	19	51·7	3·8	3·55	32·3	51·5	4·1	3·6	32·15
10	*p*-$MeC_6H_4CH_2$—	195–196°	$C_{18}H_{18}NI$	10*	57·65	4·8	3·7	33·8	57·5	5·1	3·8	33·95
11	$C_6H_5COCH_2$—	241–242°	$C_{18}H_{16}NOBr$‡	13	63·1	4·7	4·1	23·4	62·9	4·8	4·2	23·8
12	3,4-$(MeO)_2C_6H_3COCH_2$—	229–230°	$C_{20}H_{20}NO_3I$	17	59·8	5·0	3·5	19·95	59·3	4·9	3·6	20·3
13	3,4-CH_2O_2-6-$NO_2C_6H_2CH_2$—	219–221°	$C_{18}H_{15}N_2OI$	15	48·0	3·3	6·2	28·2	48·0	3·5	6·8	28·6

* Without triethylamine. ‡ Isolated as bromide. † Isolated as periodide. § Based on isoquinoline methiodide.

TABLE 2. SPECTRAL DATA FOR 2-METHYL-4-ALKYLISOQUINOLINIUM SALTS

No.	NMR (in CF_3CO_2H)				IR cm^{-1}	UV λ_{max} nm (ε_{max})
	C_1	C_3	C_4—CH_2—	NCH_3		
1	8·68	8·5	5·2	3·89	1645, 1610	233(49,000), 283(4,250), 340(5,100)
2	9·41		4·96	4·41	1650, 1610, 1525, 1350	234(48,700), 270(2,020), 340(6,740)
3	9·75		4·66	4·46	1650, 1610, 1530, 1350	234(42,100), 270(3,350), 340(3,500)
4	9·63	7·66	4·83	4·66	1650, 1610, 1510, 1350	233(38,200), 270(6,680), 340(5,250)
5	9·48		4·63	4·5	1650, 1610, 1260	234(56,200), 283(7,000), 340(6,950)
6	9·50		4·60	4·5	1650, 1610, 2840	233(58,400), 284(6,950), 340(5,050)
7	9·91	8·7		4·5	1650, 1610	232(51,400), 293(9,720), 342(4,450)
8	9·47		4·74	4·5	1650, 1610	234(49,000), 284(2,580), 341(5,260)
9	9·47		4·58	4·53	1650, 1610	229(56,300), 293(6,540), 342(5,720)
10	9·41		4·58	4·53	1650, 1610	222(52,300), 230(49,700), 281(6,340), 340(6,260)
11	9·56		5·02	4·66	1685, 1650, 1610	—
12	9·50		5·16	4·58	1645, 1630, 1510, 1030	233(40,100), 278(12,500), 348(3,000)
13	9·40		4·95	4·5		—

product. With 6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline and benzyl bromide, the yield of **4** was 48%. Of particular interest to us was the success with ω-bromoacetophenones, which yielded compounds of the type **5**, previously prepared[4] by the interaction of 1,2-dihydroisoquinolines and phenylglyoxals.



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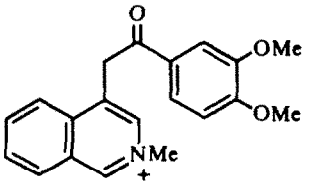

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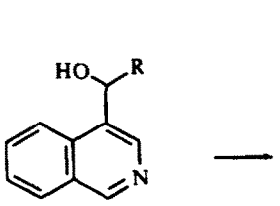
We were unable to isolate any C_4-alkylated products when **1** was reacted with ethyl chloroformate, allyl bromide, propargyl bromide or simple aliphatic halides. With allyl and crotyl halides, the N-allylated-1,2,3,4-tetrahydroisoquinolines were the only identifiable products.

From the above studies we conclude that the reaction between 1,2-dihydroisoquinolines and aryl aldehydes[5] is a superior method for the preparation of 4-benzylisoquinoline derivatives. A modified procedure, leading to 4-benzyl-1,2,3,4-tetrahydroisoquinolines has recently[6] been described, based upon a reaction first described by Grewe *et al.*[7] Some of this latter work has been corrected.[8]

Some time ago the preparation of isoquinoline-4-carboxylic acid was described[9] involving the carbonation of 4-lithioisoquinoline, obtained from 4-bromoisoquinoline.[10] Our interest in 4-substituted isoquinolines prompted a study of the scope of 4-lithioisoquinoline as a synthetic intermediate. It has now been successfully reacted with the carbonyl compounds listed in Table 3. The expected alcohols were obtained in each case and their structures follow from elemental and spectral analysis; NMR spectra are diagnostic in some cases, for example for **6**(R = *p*-methoxyphenyl) (Table 4). The compounds obtained from acetone[12] and from acetophenone[12,13]



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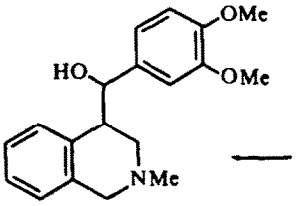

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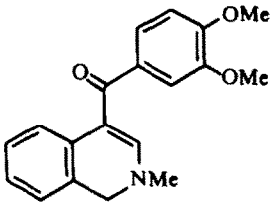

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are known compounds. The products resulting from 4-lithioisoquinoline and acetaldehyde and benzaldehyde (**6**, R = CH_3 and C_6H_5) respectively, were oxidized to the known 4-acetyl[12] and 4-benzoylisoquinolines.[12,13] The compound **6** (R = 3,4-$(MeO)_2C_6H_3$) obtained from veratraldehyde was N-methylated and reduced with

TABLE 3. THE REACTION OF 4-LITHIOISOQUINOLINE WITH CARBONYL COMPOUNDS

No.	Carbonyl compound	% Yield†	Product Mol. Formula	M.p.	Analysis Calculated C	H	N	I	Found C	H	N	I
1	CH_3CHO	72	$C_{11}H_{11}NO$	177°*	45·7	4·4	4·4	40·5	46·0	4·3	4·5	40·5
2	$(CH_3)_2CHCHO$	58	$C_{13}H_{15}NO$	125–126°	77·6	7·5	7·0	—	77·5	7·55	6·7	—
3	CH_3COCH_3	65	$C_{12}H_{13}NO$	108–109°	77·0	7·0	7·5	—	76·3	7·3	7·9	—
4	$CH_3COCH_2CH_3$	51	$C_{13}H_{15}NO$	215–216°*	49·1	5·25	4·1	37·0	49·4	5·5	3·9	36·9
5	Cyclohexanone	58	$C_{15}H_{17}NO$	179–180° 274–275°*	79·3	7·5	6·2	—	79·1	7·7	6·4	—
6	C_6H_5CHO	61·5	$C_{16}H_{13}NO$	213–215°*	54·1	4·3	3·7	33·65	54·4	4·5	3·8	34·0
7	*m*-$MeOC_6H_4CHO$	52	$C_{17}H_{15}NO_2$	184–185°*	53·0	4·4	3·4	31·2	52·75	4·7	3·6	31·2
8	*p*-$MeOC_6H_4CHO$	58	$C_{17}H_{15}NO_2$	128–129°	77·0	5·6	5·3	—	76·85	5·6	5·5	—
9	3,4-$(MeO)_2C_6H_3CHO$	58	$C_{18}H_{17}NO_3$	219–220°	52·6	4·6	2·9	—	52·3	4·8	3·5	—
10	*p*-Cl—C_6H_4CHO	54	$C_{16}H_{12}NOCl$	120–121°	71·4	4·5	5·2	Cl, 13·2	71·6	4·6	5·3	13·5
11	$C_6H_5COCH_3$	38	$C_{17}H_{15}NO$	167–168°	81·9	6·1	5·6	—	82·1	6·2	5·75	—
12	Acetoveratrone	53·3	$C_{19}H_{19}NO_3$	201–202°	73·7	6·15	4·6	—	73·4	6·0	4·8	—
13	Furfuraldehyde	48	$C_{14}H_{11}NO_2$	187–188°*	48·1	3·7	3·7	33·9	47·95	3·7	3·9	33·9
14	Pyridine-2-aldehyde	45	$C_{15}H_{12}N_2O$	148–150°	76·25	5·1	11·9	—	76·3	5·1	11·8	—
15	$(CH_3)_2NCHO$	68	$C_{10}H_7NO$	103°	76·4	4·5	8·9	—	76·2	4·7	8·7	—

* O-acetate methiodide

† Based on 4-bromoisoquinoline.

TABLE 4 SPECTRAL DATA OF 4-HYDROXY-ALKYLISOQUINOLINES

No.	NMR C_1H	NMR C_3H	NMR —OH	Others	IR cm^{-1}	UV λ_{max} nm(ε_{max})
1	8·9	8·5	4·7	5·45q[1] (—CH—CH_3, J = 7 Hz) 1·6d[3] (—CH—CH_3, J = 7 Hz)	3,120, 1,630 1,590	—
2	8·85	8·45	4·55	4·88d[1] (—CH—, J = 7 Hz) 2·17m[1] (—CH(CH_3)(CH_3), J = 7 Hz) 1·0d[3], 0·75d[3] (2 × CH_3, J = 7 Hz)	3,260, 1,620, 1,580	219(33,000) 274(1,500) 311(1,440) 324(2,400)
3	9·0	8·3	4·45	0·755[3] (2 × CH_3)	3,270 1,620 1,590	219(33,800) 272(1,170) 309(1,040) 322(2,080)
4*	10·1	—	3·3	0·9t[3] (—CH_2CH_3) 1·8s[3] (—CH_3) 2·1q[2] (—CH_2CH_3) 4·78s[3] (—N—CH_3)	3,400 1,040 1,610	231(50,000) 280(3,350) 340(6,650)
5	8·9	8·3	2·92	1·9m[10] (5 × —CH_2—)	3,240 1,620 1,585	220(33,600) 273(1590) 310(1,275) 322(2,400)
6	9·1	8·62	5·0 Broad	6·25[1] (—CH—)	3,150, 1,625 1,590	220(37,500) 273(1,360) 310(1,190) 323(2,380)
7	8·95	8·45	4·45	6·3s[1] (—CH—), 3·68[3] (—OCH_3)	3,200 1,625 1,600	220 274 310 323

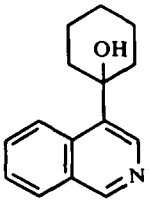
TABLE 4—*continued*

No.	NMR $C_1\underline{H}$	NMR $C_3\underline{H}$	NMR —O$\underline{H}$	NMR Others	UV IR cm^{-1}	UV λ_{max} nm(ε_{max})
8	9·7	8·8	—	3·95[3] (O—C$\underline{H}_3$)	3,300 1,630 1,590	220(51,400) 275(5,620) 310(3,610) 323 (4,820)
9	9·4*	8·6	—	2·3s[3] (OCOC$\underline{H}_3$) 4·5[1] (C$\underline{H}$] 3·9s[6] (2 × OC$\underline{H}_3$) 4·7s[3] (⟩N$^+$—C$\underline{H}_3$)	1,750 1,640 1,610	206(27,500) 232(29,700) 282(2,850)
10	8·98	8·4	5·0	6·3s[1] (Ar—C$\underline{H}$—Ar)	3,100 1,625 1,590	220(39,500) 274(1,660) 310(1,250) 323(2,500)
11	9·4*	8·8	6·15	3·4[3] (⟩N$^+$—C$\underline{H}_3$) 2·1[3] (⟩C—C$\underline{H}_3$)	3,340 1,645 1,610	220(52,000) 279(3,850) 325(5,300)
12	9·5	8·8	6·1	2·0s[3] (C—C$\underline{H}_3$) 3·7s[6] (2 × OC$\underline{H}_3$)	3,150 1,620 1,585	219(74,000) 274 (8,040) 308 (4,480) 322(5,710)
13	10·2*	8·9	4·3 broad	6·4s[1] (Ar—C$\underline{H}$—Ar) 4·7s[3] (⟩N$^+$—CH$_3$)	3,300 1,640 1,600	228 (55,000) 277(3,490) 338(6,240)
14	9·15	8·5	5·95	6·3s[1] (Ar—C$\underline{H}$—Ar)	3,200 1,630 1,590	—

* Methiodide

$NaBH_4$ to **7**, which was shown to be identical with the material obtained by reduction of the vinylogous amide[14] (**8**). The structure of **9**, from cyclohexanone was proven by dehydration and dehydrogenation of it to the known[15] 4-phenylisoquinoline.

The interaction of aliphatic aldehydes and ketones with 4-lithioisoquinoline is the most straightforward method so far for the synthesis of 4-alkylisoquinoline derivatives. When 4-lithioisoquinoline was reacted with dimethylformamide or with N-formylmethylaniline, the yield of isoquinoline-4-aldehyde reached 70%. This method is now the best method of preparation of this aldehyde; previous preparations[11] were rather laborious.



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EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured in EtOH solution and IR spectra refer to nujol mulls. NMR spectra were recorded using a Varian A60 spectrometer; chemical shifts are expressed in ppm downfield from TMS as internal standard.

General procedure for benzylation of 2-methyl-1,2-dihydroisoquinolines. 2-Methyl-1,2-dihydroisoquinoline, from isoquinoline methiodide (10 g), in ether (250 ml) was treated with equimolar quantities of the benzyl bromide and Et_3N dissolved in EtOH (100 ml). The soln was heated under reflux for 4 hr under N_2, the ether being slowly replaced by EtOH. AcOK (4 g) was introduced and a soln of I_2 in warm EtOH added dropwise until the I_2 colour persisted. Refluxing was continued for 30 min. After cooling, excess I_2 was destroyed with SO_2 and the volume of the soln reduced to ca. 30 ml. Water, (100 ml), was then added and the mixture quickly extracted with $CHCl_3$ (3 × 50 ml). Evaporation of the combined, dried $CHCl_3$ extracts gave a red gum which crystallized on trituration with EtOH or acetone. Recrystallization was usually carried out with EtOH. The relevant data are collected in Tables 1 and 2.

2-Methyl-4-benzyl-6,7-dimethoxyisoquinolinium iodide. 6,7-Dimethoxyisoquinoline methodide was reduced with LAH in THF. The benzylation of the resulting 2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline was performed as described above. The yield of 2-methyl-4-benzyl-6,7-dimethoxyisoquinolinium iodide, m.p. 214–215° (from EtOH) was 48·0%. (Found: C, 53·9; H, 4·8; N, 3·1; I, 30·8. $C_{19}H_{20}NO_2I$ requires: C, 54·2; H, 4·75; N, 3·3; I, 30·2%).

Preparation of 4-bromoisoquinoline. A mixture of isoquinoline (200 gm) and HBr (48%, 180 ml) was evaporated to dryness. Br_2 (80 ml) was added to the resulting white solid, and the mixture was heated under reflux so that HBr was allowed to escape. On cooling, the brick-red solid was basified (30% NaOH) and steam distilled. After a forerun of 1·23 g isoquinoline + 4-bromoisoquinoline, pure 4-bromoisoquinoline was collected as a white solid m.pt. 40°, total yield = 90 gms = 28%.

General procedure for alkylation of 4-lithioisoquinoline. A soln of n-BuLi in ether (50 ml) was prepared under N_2 from finely cut Li (0·45 gm) and n-BuBr (4·0 ml) as previously described, and cooled in an acetone-dry ice bath to an internal temp of −60° to −70°. 4-Bromoisoquinoline (5 g) was added portionwise; the soln slowly changed to a bright yellow colour. After stirring for 15 min 0·025 mole of the carbonyl compound in ether (50 ml) was added. The whole was then allowed to warm up to room temp, after which the complex was destroyed by the addition of water. At this point, many of the tertiary alcohol products

precipitated. In other cases, the ether layer was extracted with acid (2NHCl 3 × 50 ml), the acid layer was then basified (2N NH_4OH) and extracted with ether (3 × 50 ml). The ether extract was washed, dried ($MgSO_4$) and evaporated to give a dark red oil which solidified when triturated with petrol. The resulting bases were then purified by recrystallization, usually from a petrol fraction. In cases where the free base was difficult to isolate, the red oil from above was treated with either iodomethane or acetic anhydride to give the base methiodide or alcohol acetate respectively. Results are collected in Tables 3 and 4.

Preparation of isoquinoline-4-aldehyde. 4-Lithioisoquinoline was prepared from 4-bromoisoquinoline (5 g) and BuLi as detailed above, when N,N-dimethylformamide (2·0 ml) in ether (30 ml) at −60° was added. The mixture was allowed to warm to room temp, after which the complex was decomposed with water. The organic layer was separated and shaken vigorously with an equal volume of sat $NaHSO_3$ aq. The ppt was filtered off and washed with ether to remove organic matter and then added to an excess of 10% Na_2CO_3 aq. The resulting fluffy white solid was collected and recrystallized from water to give 2·55 g (68%) of isoquinoline-4-aldehyde m.p. 103°. (Lit. 103–104°C) λ_{max} (ε)nm 219(37,300) 285(3350), 322(4780) ν_{max} cm^{-1} 2750, 1690 (—CHO) 1620 (C=N—); NMR ($CDCl_3$), 10·4[1] (—CHO), 9·3[1] ($—C_1—\underline{H}$), 8·9[1] ($—C_3—\underline{H}$), 8·3–7·5 m[4] (remaining aromatic protons). (Found: C, 76·1; H, 4·7; N, 8·7. Cal'd. for $C_{10}H_7NO$: C, 76·4; H, 4·5; N, 8·9%).

4-Benzoylisoquinoline. A soln of the product obtained from 4-lithioisoquinoline and benzaldehyde (1·0 g) in $CHCl_3$ (50 ml) was stirred at room temp with MnO_2 (2·0 g) for 24 hr. The MnO_2 was removed, and the filtrate was evaporated to leave a pale red oil which crystallized from petrol (40–60°) as silky needles (0·83 g; 84%), m.p. 74–75°. 4-Benzoylisoquinoline has[12,13] m.p. 76–78°.

4-Phenylisoquinoline. A soln of the product obtained from 4-lithioisoquinoline and cyclohexanone (0·5 g) in decalin (25 ml) was heated under reflux for 5 hr with 10% Pd–C (100 mg). After cooling and filtering, the soln was extracted with 2N HCl (2 × 20 ml), and the acid extract was washed with ether, basified (NH_3) and extracted with ether (2 × 50 ml). The combined ethereal extracts were washed with water (2 × 20 ml), dried ($MgSO_4$) and evaporated to leave a pale red oil which slowly solidified to an off-white solid m.p. 63°, yield: 52%. The picrate was crystallized from EtOH, m.p. 209–210°, (Lit.[15] m.p. 209°). (Found: C, 57·9; H, 4·0; N, 12·9. Cal'd. for $C_{21}H_{14}N_4O_7$: C, 58·1; H, 3·25; N, 12·9%).

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