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1,2-DIHYDROISOQUINOLINES—IX[1]

ACYLATION II

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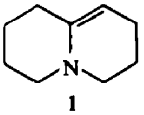
Abstract—The reaction between 1,2-dihydroisoquinolines and a variety of acid chlorides is described, and some properties of the resulting 4-acyl-1,2-dihydroisoquinolines are reported.

THE formation of β-diketones by the interaction of an enamine with an acid chloride, in the presence of triethylamine, followed by acid hydrolysis, is now well-known,[2,3] although applications to purely heterocyclic enamines seem to be few. However, the acetylation of **1**[4] and **2**[5] proceed normally to yield the acylated enamines and 5-cyanoindole has[6] been acylated at C_3 by acid chlorides in the presence of stannic chloride. In part IV of this series[7] we described acylation reactions of 2-methyl-1,2-dihydroisoquinoline (**3**) with four acid chlorides, in the presence of triethylamine.



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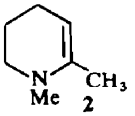

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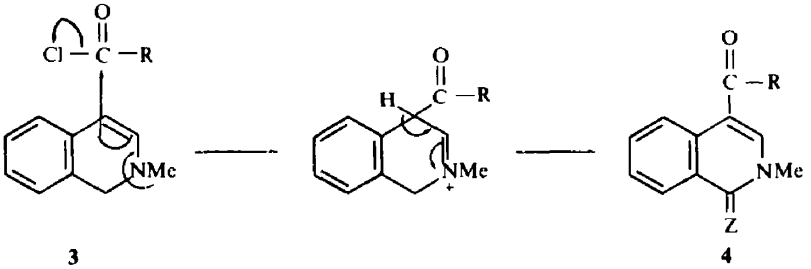
The products were the expected acylated enamines, (**4**, Z = H_2) or the related isocarbostyrils (**4**, Z = O) formed from them by aerial oxidation; yields, however, were rather low.



3 **4**

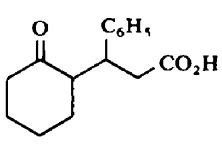
We have now examined the reaction in more detail; we have been able to improve yields considerably, and more closely define the type of acyl compound that can be used. With phenylacetyl chloride in refluxing ether in the presence of one mole of triethylamine we originally[7] obtained **4** (R = $CH_2C_6H_5$, Z = H_2) in only 12% yield, but this is increased to 30% simply by lowering the reaction temperature to 0–5°.

A base other than the enamine itself is necessary to neutralize the HCl formed in the acylation reaction, and we have found that triethylamine functions efficiently in this role. We have not studied the effect of other bases and we have used only ether or benzene as solvents. The interaction of **3** and phenylacetyl perchlorate gave only black tars, whereas no reaction at all was observed when N-benzoylpyridinium chloride was used as the acylating agent. Friedel–Crafts' reactions with $AlCl_3$ or $SnCl_4$ as catalysts also failed. We eventually standardized on the use of an ether solution of **3** and the acid chloride, in the presence of Et_3N, with the temperature held to 0–5° for all of the acid chlorides listed in Table 1. We also examined the use of 2-benzyl-1,2-dihydroisoquinoline as the enamine in some cases, but it offers no real advantage over **3**.

The acylation proceeds most satisfactorily with aromatic acid chlorides, and as may be anticipated, the nitrobenzoyl chlorides gave the highest yields of acylated product, although the reaction failed completely with 6-nitro-3,4-methylenedioxybenzoyl chloride. Unaccountably the reaction failed also with *p*-methoxy, *p*-chloro- and *p*-methylbenzoyl chlorides, whereas acylated enamines were obtained with the 3,4-dimethoxy-, 3,4-dichloro- and 3,4-dimethyl-benzoyl chlorides. The acid chlorides from cinnamic and phenylpropiolic acids also failed to react. It has been reported[8] that cinnamoyl chloride reacts with cyclohexanone enamine in a Michael reaction to yield **5**, but the only acidic compounds isolated with 2-methyl-1,2-dihydroisoquinoline as the enamine were cinnamic and phenylpropiolic acids.

Of the heterocyclic acid chlorides so far examined (indole-3-acetic, thiophene-2-carboxylic and 2-furoic) only 2-furoic acid chloride yielded an acylated enamine.

Acetyl and n-butyryl chlorides failed to yield an acylated enamine with **3**; keten formation is possible as a side reaction with the triethylamine, and presumably **3** is insufficiently reactive to add to these ketens. Pivaloyl chloride, where keten formation is not possible also failed to react with **3**, but chloracetyl chloride worked satisfactorily as did the phenylacetyl chlorides mentioned in Table 1. Acryloyl, crotyl, fumaroyl, methylmalonoyl, methylsuccinoyl chlorides, ethyl chloroformate, pyruvic acid chloride, phenylcarbamoyl, N-methylphenylcarbamoyl chlorides and benzyl-chloroformate all failed to react with 2-methyl-1,2-dihydroisoquinoline. Finally, whereas benzene sulphonyl and *p*-toluenesulphonyl chlorides did not react with **3**, *m*-nitrobenzenesulphonyl chloride gave the vinylogous amide in reasonable yield. β-Ketosulphones have been[9] obtained from cyclohexanone enamines and aromatic



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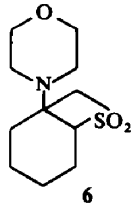

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sulphonyl chlorides, but with methanesulphonyl chloride aminosulphones of type **6** have been reported.[9–11] Methanesulphonyl chloride did not react with 2-methyl-1,2-dihydroisoquinoline.

Structures for these neutral, acylation products were assigned on the basis of analytical data, spectral properties and chemical reactions. The relevant UV, IR

TABLE 1. ACYLATION OF 2-METHYL-1,2-DIHYDROISOQUINOLINE

Acyl Chloride	% Yield*	m.p.°	Molecular formula	Analysis					
				Found			Required		
				C	H	N	C	H	N
C_6H_5COCl	33†	137–138	$C_{17}H_{13}NO_2$	77·8	5·2	5·2	77·55	5·0	5·3
$2\text{-}NO_2C_6H_4COCl$	65	219–222	$C_{17}H_{14}N_2O_3$	68·8	4·8	9·7	69·4	4·8	9·5
$3\text{-}NO_2C_6H_4COCl$	85	168–170	$C_{17}H_{14}N_2O_3$	68·7	4·7	9·8	69·4	4·8	9·5
$4\text{-}NO_2C_6H_4COCl$	73	193–196	$C_{17}H_{14}N_2O_3$	68·7	4·7	9·8	69·4	4·8	9·5
$2\text{-}NO_2\text{-}3\text{-}OMeC_6H_3COCl$	5	186–187	$C_{18}H_{16}N_2O_4$	66·7	4·8	8·8	66·6	4·9	8·6
$3,4\text{-}(MeO)_2C_6H_3COCl$	33	148–150	$C_{19}H_{19}NO_3$	73·7	6·1	4·35	73·8	6·2	4·5
$3,4\text{-}Cl_2C_6H_3COCl$	11	170–171	$C_{17}H_{13}NOCl_2$	64·1	4·0	3·8	64·2	4·1	4·4
$3,4\text{-}Me_2C_6H_3COCl$	14	143–144	$C_{19}H_{19}NO$	81·6	6·9	4·5	82·3	6·9	5·1
$C_6H_5CH_2COCl$	30	112–113	$C_{18}H_{17}NO$	82·1	6·5	5·2	82·1	6·5	5·3
$2\text{-}NO_2C_6H_4CH_2COCl$	20	217–219	$C_{18}H_{16}N_2O_3$	70·1	5·2	9·1	70·2	5·3	9·2
$3,4\text{-}(MeO)_2C_6H_3CH_2COCl$	14	112–114	$C_{20}H_{21}NO_3$	73·9	6·6	4·5	74·3	6·55	4·3
2-Furoyl chloride	33	71–72	$C_{15}H_{13}NO_2$	74·0	5·2	5·9	73·3	5·5	5·9
$ClCH_2COCl$	20	94–95	$C_{12}H_{12}NOCl$	64·8	5·4	5·7	65·0	5·4	6·3
$EtO_2C\cdot COCl$	21	131–132	$C_{14}H_{15}NO_3$	68·5	6·0	5·5	68·6	6·2	5·7
$3\text{-}NO_2C_6H_4SO_2Cl$	28	117–119	$C_{16}H_{14}N_2O_4S$	59·1	4·5	9·1	58·2	4·2	8·5

* From isoquinoline methiodide. † The isocarbostyril.

and NMR spectral data are summarized in Table 2, and Fig. 1 illustrates a typical NMR spectrum in this series.

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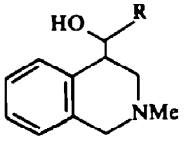

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All the IR carbonyl frequencies are low, in agreement with other experience[13,14] with vinylogous amides. Some of the 4-acyl-1,2-dihydroisoquinolines (**4**, Z = H_2) reacted with perchloric acid to give the O-perchlorate, in agreement with previous work,[7,15] and in several cases the acylated enamines were oxidized with perchloric acid, or better with iodine, to the fully aromatic isoquinolinium salts (**7**). UV spectra for these quaternary salts were characteristic of the isoquinolinium cation, and the NMR spectra were found to be diagnostic for 4-substituted-2-methylisoquinolinium salts[12] (see Table 3 and Fig. 2). The reduction of some of the acylated enamines mentioned in Table 1 was examined, using both LAH and $NaBH_4$. For those compounds containing a nitro group the reduction reaction was a complicated one and will be described in a later paper, but in the other cases examined reduction of the carbonyl group and the Δ^3 double bond occurred with both reagents to yield the 1,2,3,4-tetrahydroisoquinoline alcohols (**8**). This is contrary to other experience[16,17] on the reduction of enamino ketones with LAH.

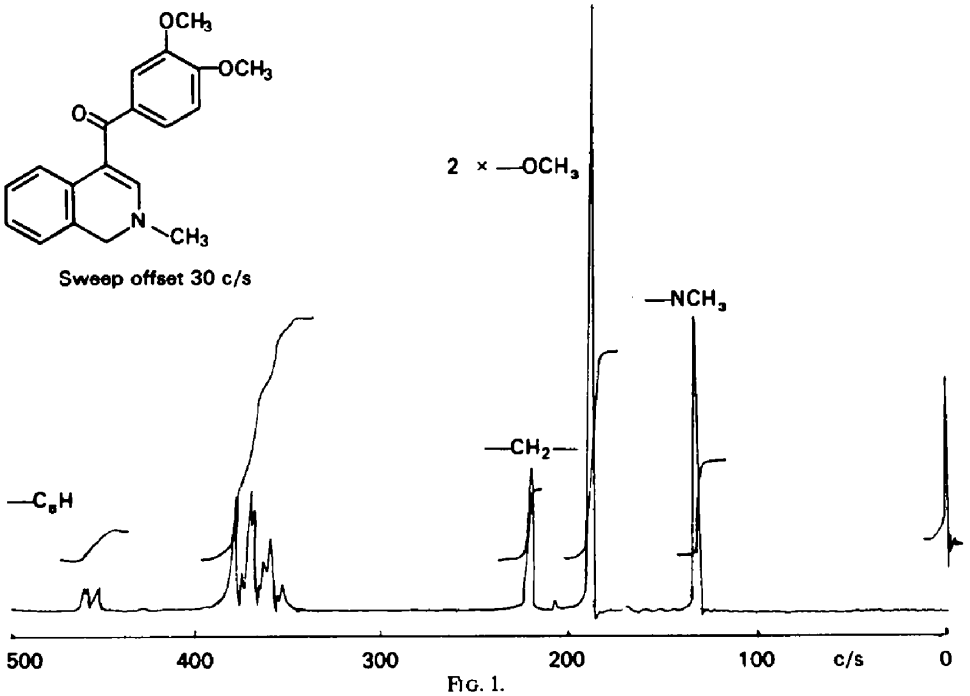


FIG. 1.

TABLE 2. SPECTRA DATA FOR THE ACYLATED ENAMINES (4, Z = H_2)

Acyl group	UV		IR	NMR				
	λ_{max} mμ	ε_{max}	ν cm^{-1}	Solvent	Ar—CH_2—N	NMe	C_5H (multiplet)	Others
2-$NO_2C_6H_4CO$	208 284 343	15,350 4305 4500	1630 1600	CD_3SOCD_3	4·65	3·00		
3-$NO_2C_6H_4CO$	220 345	10,880 1090	1630 1570	$CDCl_3$	4·55	3·00		
4-$NO_2C_6H_4CO$	205 283 340	16,070 9330 4670	1620 1590	CF_3CO_2H	5·1	3·7		
2-NO_2-3-OMe-C_6H_3CO	208	32,400	1620 1600 1580	CD_3SOCD_3	4·64	3·06		3·95 OMe
3,4-$(OMe)_2C_6H_3CO$	208 225 305 340	19,340 13,880 10,180 8120	1620 1600 1560	$CDCl_3$	4·20	2·7	8·1	3·65 2 × OMe
3,4-$Cl_2C_6H_3CO$	206 340	21,130 8450	1620 1580	$CDCl_3$	4·50	2·92	8·5	
3,4-$Me_2C_6H_3CO$	204 320	13,380 6150	1620 1600 1580	$CDCl_3$	4·40	2·80	8·5	2·25 2 × Ar—CH_3

Table 2—continued

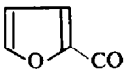
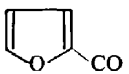
$C_6H_5CH_2CO$	208 225 290 340	21,400 14,500 14,640 12,390	1630 1600 1570	$CDCl_3$	4·00	2·50	8·33	3·75—CH_2CO
2-NO_2 $C_6H_4CH_2CO$	212 285 345	5900 2900 2000	1640 1590	CF_3CO_2H	4·84	3·67		4·5 CH_2 COAr
3,4-$(OMe)_2$ $C_6H_3CH_2CO$	230 287 345	25,120 23,990 18,200	1625 1605 1580	$CDCl_3$	4·40	3·00	7·5	3·95 CH_2CO + 2 × OCH_3
	230 275 315 365	25,190 17,855 24,495 24,495	1620 1595	$CDCl_3$	4·10	2·80	8·1	
$ClCH_2CO$	215 230 300 352	5475 5900 6120 6350	1640 1600 1580	$CDCl_3$	4·20	3·00	8·7	4·43 $COCH_2Cl$
EtO_2C CO	210 228 300 350	7915 8130 6478 7205	1715 1630 1570	$CDCl_3$	5·30	3·00	8·6	5·2q $\underline{CH_2}CH_3$ 1·5t CH_2 $\underline{CH_3}$
3-NO_2 -$C_6H_4SO_2$	207 240 255 327	20,840 17,440 14,880 7030	1610 1600 1560	CD_3SOCD_3	4·55	2·94		

TABLE 3. UV AND NMR SPECTRA DATA FOR THE ISOQUINOLINIUM SALTS

C_4-Acyl group	UV		NMR				
	λ_{max} mμ	ε_{max}	Solvent	C_1H	C_3H	NMe	Others
$2\text{-}NO_2C_6H_4CO$	216	30,800	CD_3SOCD_3	10·22	8·90	4·55	
$3\text{-}NO_2C_6H_4CO$	219 340	40,000 6200	CD_3SOCD_3	10·30	9·00	4·33	
$4\text{-}NO_2C_6H_4CO$	205 279	25,000 1300	CD_3SOCD_3	10·20	9·00	4·55	
$3,4\text{-}(OMe)_2C_6H_3CO$	205 235 290 335	29,300 43,750 12,250 13,130	CF_3CO_2H	9·25	8·10	4·50	4·05 2 × OCH_3
$C_6H_5CH_2CO$	220 265 335	37,200 4180 7500	CF_3CO_2H	9·67	9·00	4·60	4·65 —CH_2CO
	235 295 340	39,700 18,240 16,000	CF_3CO_2H	9·50	8·40	4·50	

A chemical proof of structure of these 4-acyl-1,2-dihydroisoquinolines was forthcoming by utilising the observation of Gilman and Soddy[18] that 4-bromoisoquinoline reacts with n-butyllithium at low temperatures to form 4-lithioisoquinoline. Thus, reaction of this organometallic compound with 3,4-dimethoxybenzaldehyde yielded the alcohol **9**, isolated as its O-acetylmethiodide. Reduction of this derivative with LAH gave **8** (R = 3,4-dimethoxyphenyl), identical with the product formed by the reduction of **4** (R = 3,4-dimethoxyphenyl, Z = H_2) with the same reagent.

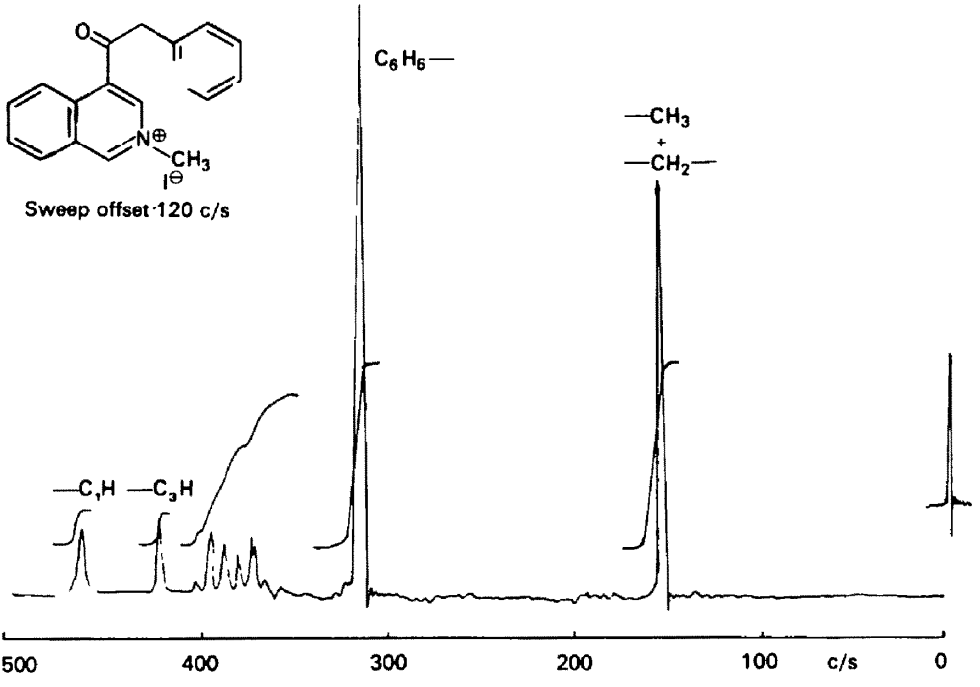
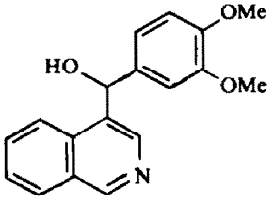


FIG. 2.

Our interest in benzo[c]phenanthridine chemistry[19,20] stimulated a study of some acylation reactions of the 2-methyl-3-aryl-1,2-dihydroisoquinoline (**12**), which was prepared as indicated from the known[21] 1,2,3,4-tetrahydroisoquinoline (**10**). The interaction of **12** with ethoxalyl chloride gave a low yield of the acylated enamine **13**, which was easily oxidized to, and further characterized as, the isoquinolinium salt **14**. Various attempts were made to cyclize **14** to **15**, but the only product isolated was assigned structure **16** on the basis of its analysis and spectral characteristics.



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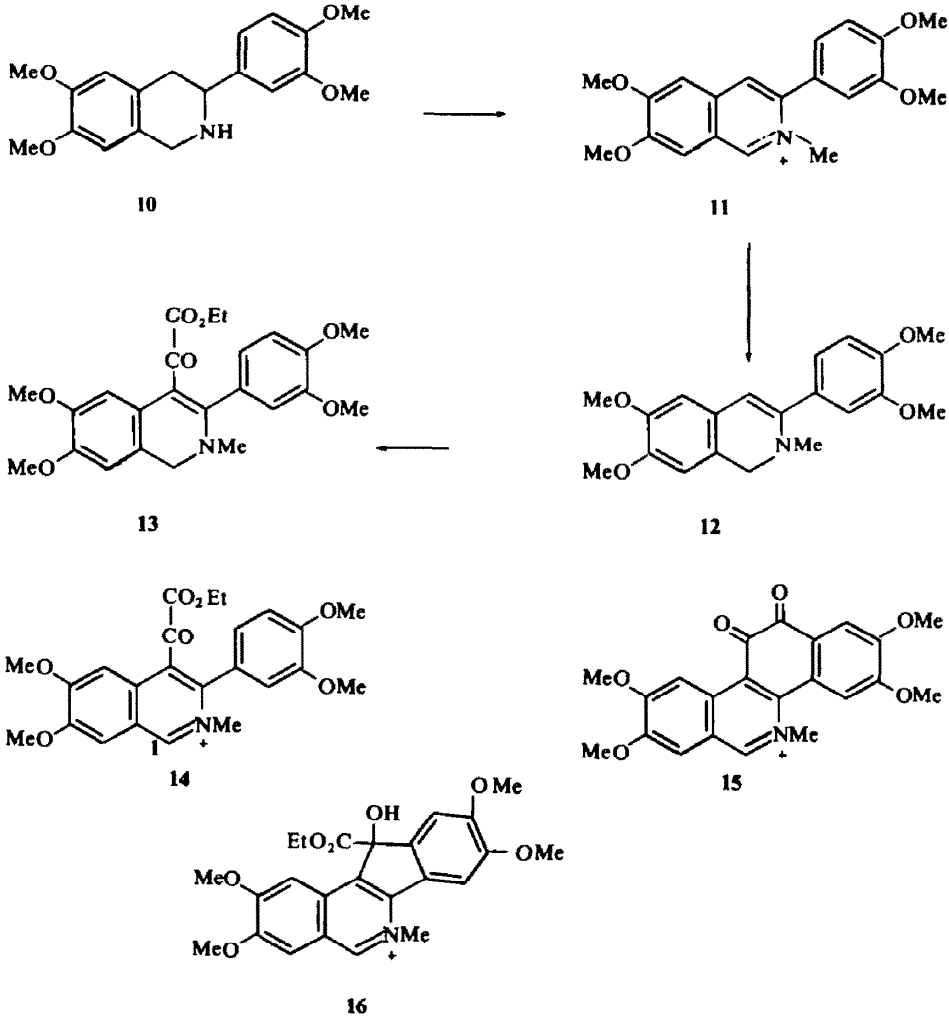
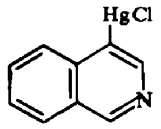


Other methods of acylation of 2-methyl-1,2-dihydroisoquinoline have been briefly examined. When isoquinoline is treated with mercuric acetate, then with sodium chloride, the product is reported[22] to be **17**, on the grounds that bromination yields 4-bromo-isoquinoline, and we hoped to be able to acylate this compound. However, we found that the NMR spectrum of the intermediate mercuriacetate derivative is completely consistent with its formulation as **18** and not as a 4-substituted isoquinoline. Thus, the spectrum (in $CDCl_3$ soln) exhibited a one proton singlet at 9·4 ppm (C_1—H), a one proton *doublet* at 8·7 ppm (J = 6·5 c/s) (C_3—H) and a three proton singlet at 2·1 ppm (CH_3CO—). Since the C_3—H absorption appears as a doublet, there must be a hydrogen atom at C_4 of the isoquinoline ring. A molecular weight determination in cyclohexanol is also consistent with structure **18**.

The Vilsmeier formylation reaction is well known,[23,24] and our application of it to 1,2-dihydroisoquinolines will be described in detail in a later paper. The acylation



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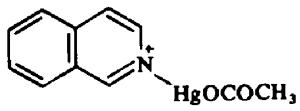


18

reaction using a tertiary acid amide in place of dimethylformamide is not so common, although some 3-acylindoles have been prepared by this method.[25] We have now found that 2-methyl-1,2-dihydroisoquinoline (3) reacts with N,N-dimethylacetamide, in the presence of $POCl_3$, to form the corresponding acylated enamine (4, R = CH_3, Z = H_2) in 36% yield.

EXPERIMENTAL

UV spectra were measured on a Perkin–Elmer Model 137UV spectrophotometer and refer to EtOH solns unless otherwise stated. IR spectra were measured, in Nujol, on a Perkin–Elmer Model 237 spectrophotometer. NMR spectra were recorded with a Varian A-60 spectrometer and chemical shifts are measured in ppm downfield from internal TMS as standard. M.ps are uncorrected.

2-Methyl-1,2-dihydroisoquinoline (3) was prepared as previously described[7] and *2-benzyl-1,2-dihydroisoquinoline* was prepared similarly.

Acylations

General procedure. The acid chloride (0·04 mole), in ether or benzene soln, was added dropwise to a stirred soln of 2-methyl-1,2-dihydroisoquinoline (0·04 moles) in ether containing Et_3N (4·0 g). An atmosphere of N_2 was maintained in the reaction flask throughout. After 3 more hr of stirring, during which time a considerable amount of ether evaporated, thus keeping the temp to 0–5°, the reaction mixture was left overnight, then filtered. The solid was stirred well with water (75 ml) and the undissolved residue of 4-acyl-1,2-dihydroisoquinoline was crystallized, usually from EtOH. The relevant data are collected into Table 1.

The O-perchlorates were prepared simply by adding 60% aqueous perchloric acid soln to a soln of the acylated enamine (4, Z = H_2) in EtOH soln. The precipitated perchlorate was collected and crystallized.

(a) From 2-methyl-4-(2-nitrobenzoyl)-1,2-dihydroisoquinoline m.p. 131–132°; λ_{max} (ε) mμ, 208 (12,350), 283 (3642), 345 (4265). ν_{max} cm^{-1}, 3500, 1660, 1590. NMR (CD_3SOCD_3) 3H singlet 3·0 (=NC$\underline{H}_3$); 2H singlet 4·6 (Ar—C$\underline{H}_2$—N=). (Found: C, 51·1; H, 3·7; N, 7·1. $C_{17}H_{15}N_2ClO_7$ requires: C, 51·7; H, 3·8; N, 7·1%).

(b) From 2-methyl-4-(3-nitrobenzoyl)-1,2-dihydroisoquinoline m.p. 170–171°; λ_{max} mμ (ε_{max}) 222 (12,160), 345 (3200); ν_{max} cm^{-1} 3220, 1662, 1595. NMR (CD_3SOCD_3); 3H singlet 3·0 (=NC$\underline{H}_3$); 2H singlet 4·65 (Ar—C$\underline{H}_2$—N<); 1H singlet 5·9 removed by D_2O (—O$\underline{H}$); 9H multiplet ca. 8·0 (aromatic hydrogens). (Found: C, 51·9; H, 3·7; N, 8·1%).

(c) From 2-methyl-4-(4-nitrobenzoyl)-1,2-dihydroisoquinoline m.p. 151–152°; λ_{max} mμ (ε_{max}): 205 (8217); 285 (6575); 340 (2300); ν_{max} cm^{-1}: 3430, 1670, 1590; NMR (CD_3SOCD_3), 3H singlet 3·0 (=NC$\underline{H}_3$); 2H singlet 4·6 (Ar—C$\underline{H}_2$N=). (Found: C, 49·9; H, 4·0; N, 6·8%).

The isoquinolinium salts

(a) In some cases, treatment of the acylated enamine with perchloric acid yielded, not the O-perchlorate, but the fully aromatic isoquinolinium perchlorate.

(a)′ 2-methyl-4-(3,4-dimethoxybenzoyl) isoquinolinium perchlorate m.p. 236–238° λ_{max} (ε) mμ, 205 (29,300); 235 (43,750); 290 (12,250); 335 (13,130); ν_{max} cm^{-1}, 1655, 1595, 1580, 1510, 1100; NMR (CF_3CO_2H) 1H singlet 9·25 (C_1—H); 1H singlet 8·1 (C_3—H) 3H singlet 4·5 (=NC$\underline{H}_3$); 6H singlet 4·05 (2 × —OC$\underline{H}_3$). (Found: C, 51·4; H, 4·3; N, 3·5; Cl, 8·7. $C_{19}H_{18}NO_7Cl$ requires: C, 51·0; H, 4·3; N, 3·4; Cl, 8·7%).

(b)′ 2-Methyl-4-(α-furoyl)isoquinolinium perchlorate m.p. 162–163°; λ_{max} (ε) mμ, 235 (21,000); 290 (4080); 340 (3460); ν_{max} cm^{-1}, 1650, 1610, 1100; NMR (in CF_3CO_2H) 1H singlet 9·7 (C_1—H); 1H singlet 8·78

($C_3\underline{H}$); 3H singlet 4·8 (=N—$C\underline{H}_3$). (Found: C, 53·6; H, 3·5; N, 4·1; Cl, 11·0. $C_{15}H_{12}NO_6Cl$ requires: C, 53·35; H, 3·55; N, 4·15; Cl, 10·5%).

(b) A more satisfactory method of oxidation of the acylated enamine to the isoquinolinium salt involved heating under reflux a mixture of the acylated enamine (1·0 g), EtOH (50 ml), and I_2 (1·0 g) for 3 hr. Water (20 ml) was then added and SO_2 passed through the mixture until only a straw colour remained. Concentration of the soln caused crystallization of the isoquinolinium iodide, which was then recrystallized from EtOH. The data are summarized in Table 4.

2-Methyl-4-[1-hydroxy-2-(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline

Compound **4** (Z = H_2, R = 3,4-dimethoxyphenyl) in EtOH (25 ml) was treated with $NaBH_4$ (1·0 g) in small portions. The mixture was heated under reflux for 2 hr, cooled and water (50 ml) was added. The soln was extracted with $CHCl_3$ (3 × 25 ml) and the combined extracts were evaporated to leave a yellow gum which crystallized from EtOH to give 2-methyl-4-[1-hydroxy-2-(3,4-dimethoxy)phenylethyl]-1,2,3,4-tetrahydroisoquinoline (0·81 g) m.p. 158–160°; λ_{max} (ε) mμ, 206 (35,100); ν_{max} cm^{-1}, 1610; 1590. (Found: C, 72·6; H, 7·4; N, 4·4. $C_{19}H_{23}NO_3$ requires: C, 72·8; H, 7·35; N, 4·5%).

4-[-1-Hydroxy-1-(α-furyl)]methyl-2-methyl-1,2,3,4-tetrahydroisoquinoline

This was prepared by reduction of **4** (R = 2-furyl, Z = H_2) with $NaBH_4$ at room temp during 18 hr and was obtained crystalline from MeOH m.p. 103–104°; λ_{max} (ε) mμ, 217 (14,850). (Found: C, 73·9; H, 7·1; N, 5·9. $C_{15}H_{17}NO_2$ requires: C, 74·05; H, 7·0; N, 5·8%). The O-acetate was obtained from EtOH, m.p. 60–61° and this was analysed as the methoperchlorate m.p. 180–181°. (Found: C, 53·5; H, 5·4; N, N, 3·4; Cl, 8·4. $C_{18}H_{24}NO_7Cl$ requires: C, 54·1; H, 5·5; N, 3·5; Cl, 8·9%).

Acylation of 2-benzyl-1,2-dihydroisoquinoline

This was carried out essentially as described for 2-methyl-1,2-dihydroisoquinoline, and the relevant data are collected into Table 5. In *all* cases studied, the product was the acylated enamine.

The product with furoyl chloride was further characterized by oxidation with I_2 in the usual way to yield 2-benzyl-4-furoylisoquinolinium iodide m.p. 122–124°; λ_{max} (ε) mμ, 240 (44,330); 293 (31,680); 350 (15,200). ν_{max} cm^{-1}, 1640; NMR in CD_3SOCD_3, 1H singlet 10·03 (C_1—$\underline{H}$); 1H singlet 8·9 (C_3—$\underline{H}$); 1H multiplet 8·22 (C_5—$\underline{H}$); 2H singlet 5·9 (Ar—$C\underline{H}_2$—$\overset{+}{N}$≡). (Found: C, 57·35; H, 3·6; N, 3·0; I, 28·9. $C_{21}H_{16}NO_2I$ requires: C, 57·2; H, 3·6; N, 3·2; I, 28·8%).

The 1,2,3,4-tetrahydroisoquinoline was prepared by reducing the vinylogous amide with $NaBH_4$ and was obtained as white crystals from EtOH m.p. 111–113°. (Found: C, 78·8; H, 6·9; N, 4·6. $C_{21}H_{21}NO_2$ requires: C, 79·0; H, 6·6; N, 3·4%). This compound was further characterized as the O-acetate, m.p. 123–124°. (Found: C, 75·8; H, 6·4; N, 4·1. $C_{23}H_{23}NO_3$ requires: C, 76·4; H, 6·4; N, 3·9%).

4-[1-Hydroxy-1-(3,4-dimethoxyphenyl)methyl]isoquinoline (**9**, R = *3,4-dimethoxyphenyl*)

A soln of veratraldehyde (4·1 g) in dry ether (100 ml) was added dropwise with stirring during 20 min to a soln of 4-isoquinolyllithium (prepared[18] from 5·2 g 4-bromoisoquinoline) in dry ether (50 ml) maintained at −50°. After 2 hr stirring the mixture was treated with NH_4Cl aq, the ether layer was separated, washed and dried ($MgSO_4$). Evaporation left a red oil which could not be crystallized. Ac_2O (15 ml) was added and the mixture was warmed on the water-bath for 20 min. After working up in the usual way, the red, oily product was heated under reflux with an excess of MeI for 15 min. After evaporation of the soln and crystallization of the residue from EtOH, 2-methyl-4-[1-acetoxy-1-(3,4-dimethoxyphenyl)methyl]-isoquinolinium iodide was obtained (7 g; 45%) as yellow needles m.p. 220–221°; λ_{max} (ε) mμ, 204 (41,870); 232 (36,630) ν_{max} cm^{-1}, 1750, 1650, 1600, 1025; NMR (CD_3SOCD_3), 1H singlet 10·25 ppm (C_1—$\underline{H}$), 1H singlet 9·0 ppm (C_3—$\underline{H}$); 3H singlet 4·66 ppm (≡$\overset{+}{N}$—$C\underline{H}_3$); 3H singlets at 3·83 and 3·76 ppm (2 × $OC\underline{H}_3$); 3H singlet 2·3 ppm ($C\underline{H}_3$ CO—). (Found: C, 52·3; H, 4·8; N, 3·5. $C_{23}H_{25}NO_6I$ requires: C, 52·6; H, 4·6; N, 2·9%).

2-Methyl-4-[1-hydroxy-1-(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline (**8**, R = *3,4-dimethoxyphenyl*)

The above methiodide (1·0 g) was dissolved in boiling dry benzene (150 ml) and LAH (1 g) was added portionwise. The mixture was heated under reflux for 2 hr, and then worked up in the usual way to yield **8**, (R = 3, 4-dimethoxyphenyl) as white needles from EtOH. (0·65 g) m.p. 159–160°; mixed m.p. with material obtained by reducing **4** (R = 3,4-dimethoxyphenyl) with LAH = 159°.

Table 4. The isoquinolinium iodides

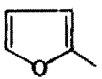
4-Acyl Group	m.p.°	Molecular Formula	Analysis							
			Found				Required			
			C	H	N	I	C	H	N	I
$C_6H_5CH_2$—	191–193	$C_{18}H_{16}NOI$	53·6	3·8	3·5	32·1	53·3	3·95	3·5	31·4
2-$NO_2C_6H_4$—	167–168	$C_{17}H_{13}N_2O_3I$	48·15	3·4	6·8	—	48·7	3·1	6·65	—
3-$NO_2C_6H_4$ -	233–234	$C_{17}H_{13}N_2O_3I$	48·5	3·35	6·65	—	48·7	3·1	6·65	
4-$NO_2C_6H_4$—	207–208	$C_{17}H_{13}N_2O_3I$	48·2	3·0	6·8		48·7	3·1	6·65	
	215–216	$C_{15}H_{12}NO_2I$	49·5	3·2	3·8	34·9	49·3	3·3	3·8	34·8

TABLE 5. ACYLATION OF 2-BENZYL-1,2-DIHYDROISOQUINOLINE

Acyl Chloride	Yield %	m.p.°	λ_{max} mμ	ε_{max}	ν_{max} cm^{-1}	Molecular formula	Found			Required		
							C	H	N	C	H	N
C_6H_5COCl	36	128–129	207 227 307 350	25,400 18,700 11,900 13,050	1625 1600 1585	$C_{23}H_{19}NO$	85·7	6·1	4·5	84·9	5·9	4·3
$3\text{-}NO_2—C_6H_4COCl$	69	136–138	207 222 350	19,260 17,000 8610	1610 1580 1530	$C_{23}H_{18}N_2O_3$	74·8	4·7	7·7	74·6	4·9	7·6
$4\text{-}NO_2—C_6H_4COCl$	75	163–164	207 274 340	31,500 20,000 12,900	1610 1575	$C_{23}H_{18}N_2O_3$	75·1	4·8	8·1	74·6	4·9	7·6
2-Furoyl	34		237 280 316 370	14,400 10,860 14,400 15,470	1620 1570 1540	$C_{21}H_{17}NO_2$	79·6	5·0	4·6	80·0	5·4	4·4

3-(3,4-Dimethoxyphenyl)6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline (**12**)

The methiodide **11**, yellow needles m.p. 248–250 (from EtOH), was reduced with LAH in the normal way to give the corresponding **12** in 80% yield. Recrystallization of this material from THF afforded colourless prisms, m.p. 118–120°; λ_{max} (ε) mμ, 254 (10, 720), 342 (17,580); ν_{max} cm^{-1}, 1645; NMR, ($CDCl_3$) 2H singlet 7·1 (C_5—H, C_8 —H); 3H complex ~6·6 (three protons of 3-aryl group); 1H singlet 5·9 (C_4—H); 2H singlet 4·2 (—CH_2—N=) 12H three singlets ~3·9. (4 × —OCH_3); 3H singlet 2·5 (=N—CH_3). (Found: C, 70·1; H, 6·8; N, 4·4. $C_{20}H_{23}NO_4$ requires: C, 70·4; H, 6·8; N, 4·1%).

3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-4-ethoxalyl-2-methyl-1,2-dihydroisoquinoline (**13**)

The foregoing 1,2-dihydroisoquinoline (1·87 g) in benzene, containing Et_3N (0·55 g), was treated with ethoxalylchloride (0·75 g) during 1 hr. the reaction mixture being protected by an atmosphere of N_2. After heating at reflux for 2 hr, the contents of the flask were cooled and EtOAc (100 ml) added. The solvent layer was washed with water, dried and the solvent removed to yield a gum, which crystallized on trituration with 1:1 benzene, light petrol and recrystallized from EtOH as colourless prisms, m.p. 146–148° (29%); λ_{max} (ε) mμ, 232 (10,470), 301 (8510); ν_{max} cm^{-1}, 1700, 1640, NMR ($CDCl_3$), 1H singlet 8·3 (C_3—H); 3H singlet 6·9 (three protons on 3-aryl group); 1H singlet 6·5 (C_8—H); 2H singlet 4·5 (CH_2—N=), 12H singlet 3·9 (4 × —OCH_3); 2H quartet 3·4 J = 8 c/s (—CH_2—CH_3); 3H singlet 2·9 (=N—CH_3); 3H triplet 1·1 J = 8 c/s (—CH_2—CH_3). (Found: C, 64·9; H, 6·0; N, 3·4. $C_{24}H_{27}NO_7$ requires: C, 65·3; H, 6·2; N, 3·2%).

Oxidation of this compound with I_2 in EtOH soln gave **14** in almost quantitative yield, as yellow needles m.p. 199·5–201·5° (EtOH); λ_{max} (ε) mμ, 221 (10,900); 257 (57,540); ν_{max} cm^{-1}, 1745, 1720, 1620, 1610. (Found: C, 50·0; H, 4·8; N, 2·6; I, 22·3. $C_{24}H_{26}NO_7I$ requires: C, 50·8; H, 4·6; N, 2·5; I, 22·4%).

The corresponding isocarbostyril was also isolated as an almost colourless solid m.p. 199–200° (from EtOH) when solns of **13** were allowed to stand in contact with the air. (Found: C, 63·1; H, 5·8; N, 3·0. $C_{24}H_{25}NO_8$ requires: C, 63·3; H, 5·5; N, 3·1%).

Catalytic hydrogenation of **14** in EtOH soln using Adams' catalyst at atm press gave the corresponding 1,2,3,4-tetrahydroisoquinoline, colourless solid m.p. 146–148° (EtOH); λ_{max} (ε) mμ, 232 (10,960), 301 (850); ν_{max} cm^{-1}, 1700. (Found: C, 64·9; H, 6·2; N, 3·35. $C_{24}H_{29}NO_{07}$ requires: C, 65·0; H, 6·6; N, 3·2%).

Reaction of (**14**) *with polyphosphoric acid*

Compound **14** was heated with five times its weight of polyphosphoric acid at 60° for 20 min, after cooling for 20 min, the reaction mixture was poured onto ice and the solid product collected. After crystallization from MeOH this material m.p. 250–251° was dissolved in MeOH and perchloric acid added. 2 Hr later, the yellow crystals which had deposited, were collected and recrystallized from water to give 11-carboethoxy-11-hydroxy-6-methyl-2,3,8,9-tetramethoxy-11-H indeno [1,2—C]isoquinolinium iodide. m.p. 299–299·5° (20%); λ_{max} (ε) mμ, 261 (14,790), 308 (1690); ν_{max} cm^{-1} 3400, 1740, 1625, 1620, 1100; NMR (CF_3CO_2H), 1H singlet 9·0 (C_5—H); 2H singlet 7·7 (C_1—H, C_4—H); 2H singlet 7·5 (C_{10}—H, C_7—H); 3H singlet 4·8 (=N—CH_3); 14H complex 4·2–3·8 (—CH_2—CH_3. 4 × OCH_3); 3H triplet 1·0, J = 7 c/s (CH_3CH_2—). (Found: C, 52·9; H, 4·6; N, 2·9; Cl, 6·8. $C_{24}H_{26}NO_{11}Cl$ requires: C, 53·4, H, 4·9; N, 2·6; Cl, 6·6%).

Reaction of isoquinoline with mercuric acetate

A mixture of isoquinoline (13 g) in MeOH (100 ml) and mercuric acetate (32 g) was heated under reflux for 4 hr as previously described.[19] On concentration and cooling of the soln, the mercuric acetate complex **18** crystallized (38 g), m.p. 131–133° (Lit.[22] m.p. 131–133); λ_{max} mμ (ε_{max}): 217 (62,100) ν_{max} cm^{-1}: 1630, 1580; NMR (in $CDCl_3$): 1H singlet 9·4 (C_1—H); 1H *doublet* 8·7 (J = 6·5 c/s) (C_3—H); 5H multiplet 7·2–8·0 (C_5H, C_6H, C_7H, C_8H, C_4H); 3H singlet 2·1 ($COCH_3$). [Found: C, 35·0; H, 3·6; N, 3·6. $C_{11}H_{10}NO_2$ Hg requires: C, 34·4; H, 2·6; N, 3·0%; Mol. wt. (in cyclohexanol). Found: 397. Calc. 389].

2-Methyl-4-acetyl-1,2-dihydroisoquinoline (**4**, R = Me, Z = 2H)

$POCl_3$ (5 ml) and N,N-dimethylacetamide (28 ml) were mixed together so that the temp did not rise above 20°. To this mixture was added a soln of 2-methyl-1,2-dihydroisoquinoline (5·5 g) in ether (50 ml) under a protective atmosphere of N_2. After heating for 2 hr at the reflux, the reaction mixture was cooled, added to water (50 ml) and made alkaline with NaOH (40·0 g) in water (150 ml). The following morning the two phase system was treated with $CHCl_3$ and the solvent layer removed and evaporated to give a red gum (2·7 g) which did not crystallize; λ_{max} (ε) mμ, 225 (8150), 285 (6440), 345 (6440); ν_{max} cm^{-1}, 1630 (>C=O), 1600 (>C=C<), 1350 (CH_3CO); NMR (in $CDCl_3$) 1H multiplet 8·6 (C_5—H); 4H multiplet,

6·9—7·3 (C_3—H, C_6—H, C_7—H, C_8—H); 2H singlet, 4·4 ($\rangle$N—$\underline{CH}_2$—Ar); 3H singlet, 3·0 ($\rangle$N—$\underline{CH}_3$); 3H singlet, 2·3 ($\underline{CH}_3$—CO—). The perchlorate was prepared as colourless prisms, m.p. 166–168° (from EtOH); ν_{max} cm^{-1}, 3500 (OH), 1660 ($\rangle$C=C$\langle$), 1350, 1100. (Found: C, 50·5; H, 4·9; N, 4·9. $C_{12}H_{14}NO_5Cl$ requires: C, 50·1; H, 4·9; N, 4·9%).

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