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1,2-DIHYDROISOQUINOLINES—VI[1]

THE BENZYLATION OF ISOQUINOLINE DERIVATIVES[2]

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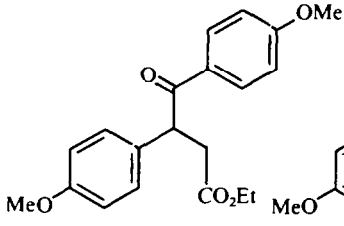
Abstract—Methods of preparation of 4-benzyl-isoquinoline derivatives are briefly reviewed and the condensation of isoquinolinium salts with benzaldehyde under alkaline conditions has been examined; the structure originally proposed by Kröhnke[11] for one of these products has been corrected.

THE methods most usually employed for the synthesis of 4-substituted isoquinoline derivatives have involved the preparation of the appropriately substituted β-arylethylamines, which have then been subjected to the Bischler–Napieralski[3] ring-closure reaction, followed by dehydrogenation. In this way 4-benzylisoquinoline has been prepared[4] in a 6-stage sequence from benzyl cyanide, and Knabe *et al.*[5] have synthesized 1,4-dibenzyl-6,7-dimethoxyisoquinoline in an overall yield of



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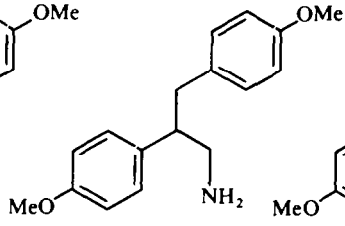

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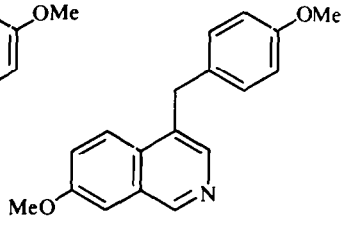

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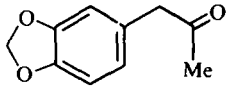

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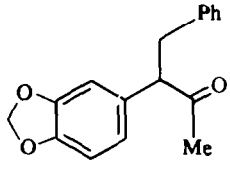
1. $NaNH_2$.
2. $PhCH_2Cl$.



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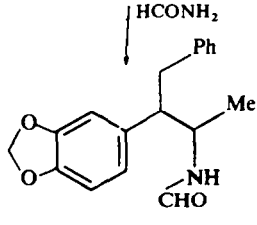
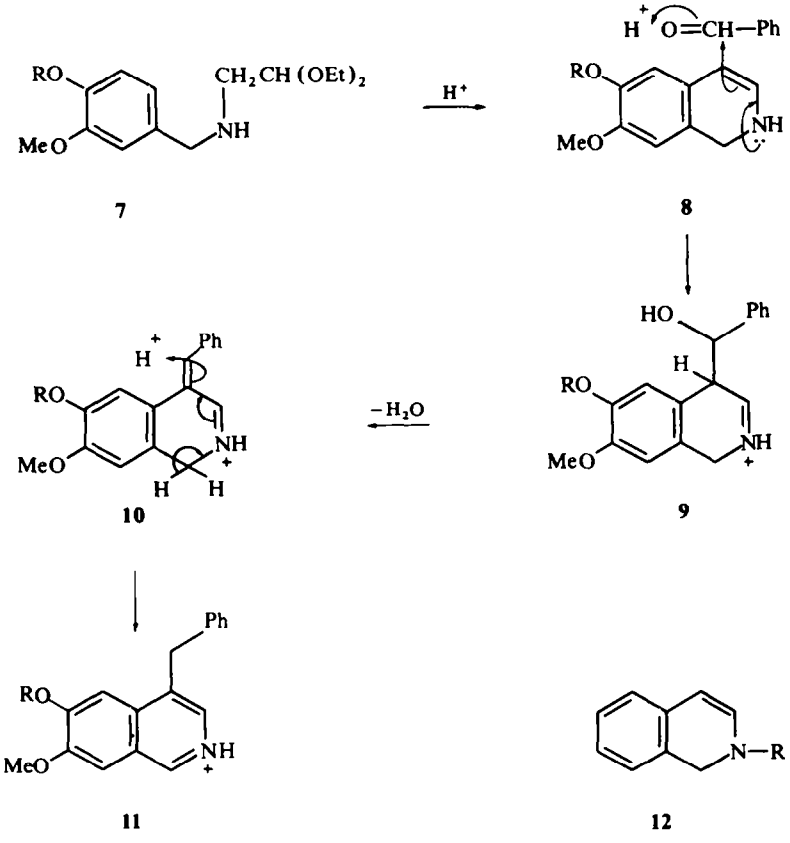


6

etc.

18% by the addition of benzyl magnesium bromide to 3,4-dimethoxy-β-nitrostyrene, followed by reduction and ring-closure. The 4-benzylisoquinoline **3** has been obtained[6] by condensing anisoin with ethyl bromoacetate to yield **1**, followed by reduction, conversion to the amine **2**, ring-closure and dehydrogenation; a further variation is provided[7] by the conversion of **4** through **5** to **6**.

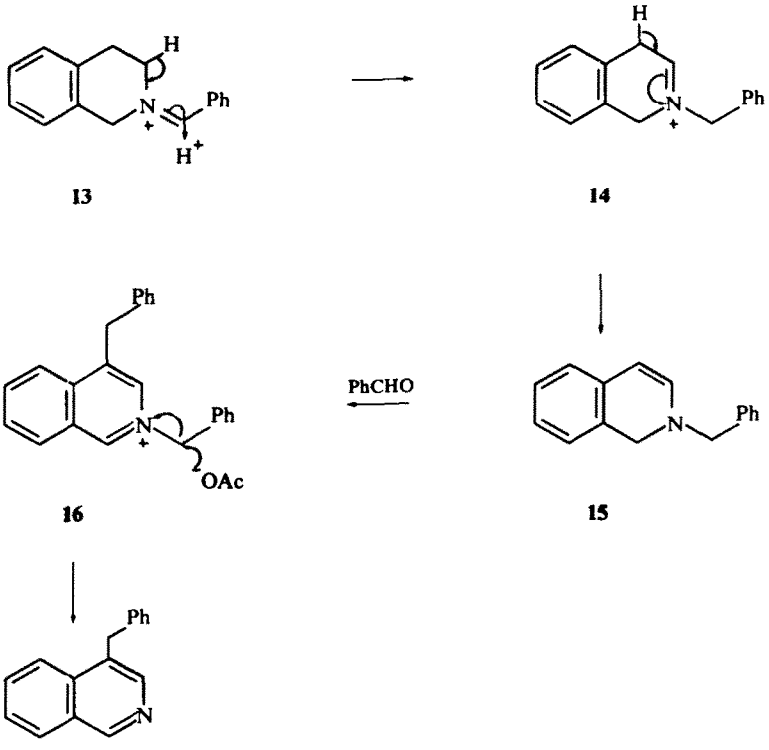
Recently Bobbitt *et al.*[8] have shown that 4-benzylisoquinolines can be obtained simply in good yield by the condensation, in acid solution, of benzaldehyde with phenolic aminoacetals of the type **7** (R = H). The reaction clearly[8] involves the 1,2-dihydroisoquinoline **8** and probably[1,8] proceeds as shown in **8** → **11**. Intermediates of the type **9** have been isolated[1] in some cases.



7 8 9 10 11 12

4-Benzylisoquinoline has been obtained[9] in 34% yield merely by heating a mixture of 1,2,3,4-tetrahydroisoquinoline and benzaldehyde in acetic acid solution. It was suggested[9] that the reaction involves a rearrangement of the originally formed Schiff cation **13** to **14** and then to **15**, which can condense with a second molecule of benzaldehyde in the manner indicated for **8** → **11**, to yield **16**. Finally nucleophilic displacement of the N-benzyl group by acetate anion gives 4-benzylisoquinoline.

We have found that 2-benzyl-1,2-dihydroisoquinoline (**12**, R = CH_2Ph), obtained by reduction of 2-benzylisoquinolinium bromide with LAH, reacts with benzaldehyde in acetic acid solution to give a 40% yield of **16** and, in a separate step, a 12% yield of 4-benzylisoquinoline resulted from heating **16** in acetic acid under the conditions



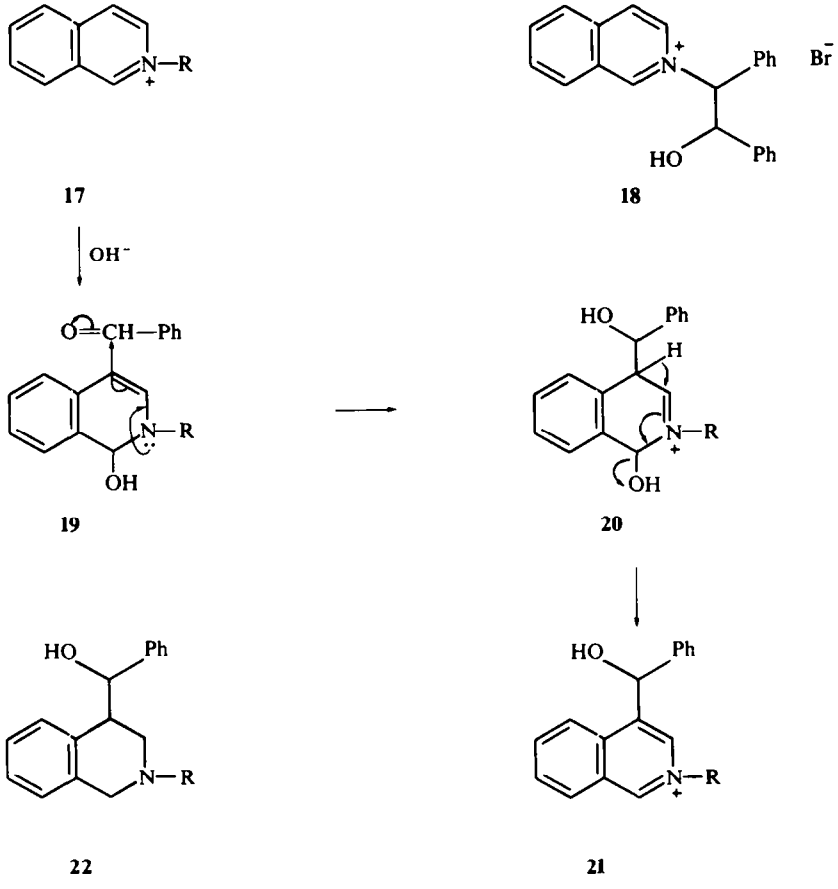
employed by Burrows and Burrows.[9] The yield was increased to 30% by repeating the reaction in the presence of one mole of sodium acetate. Hence, each step in the above mechanism is feasible.

Yet another preparation of 4-benzylisoquinoline, also under acid conditions, has been reported by Grewe *et al.*,[10] who hydrogenated a mixture of isoquinoline and benzaldehyde in acetic acid solution. It was suggested that reduction occurred to give 1,2-dihydroisoquinoline, which then condensed with benzaldehyde to give 4-benzylisoquinoline. The yield was only 13%, and it was difficult to isolate the product in a pure state.

In 1935 Kröhnke[11] reported that benzaldehyde condensed with 2-benzylisoquinolinium bromide (**17**, R = CH_2Ph) in the presence of alkali to yield, after acidification with HBr, an alcohol, m.p. 218° which he formulated as **18** by analogy with previous work[12] in the N-methylpyridine series. Whereas the structure of the pyridine derivative was confirmed by its independent preparation from pyridine and styrene bromohydrin,[12] and later[13] from pyridine and styrene oxide, no structural work was undertaken in the isoquinoline series. It is probable that **17** (R = CH_2Ph) reacts with the alkali to form the pseudobase **19** (R = CH_2Ph) and it occured to us

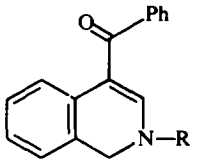
that this may possess some enamine character in alkaline solution. A likely alternative structure for Kröhnke's compound then is **21** (R = CH_2Ph), formed as indicated in **17** → **19** → **20** → **21**.

Accordingly, Kröhnke's directions were repeated and again a quaternary bromide, m.p. 218° was isolated. The UV spectrum was typically that of an isoquinolinium salt, and the presence of a OH group was confirmed by a band at 3250 cm^{-1} in the IR spectrum. The NMR spectrum of the product (taken in CF_3CO_2H with TMS as an



internal standard) was found to be diagnostic for **21** (R = CH_2Ph), with a one proton singlet at 9·7 ppm (C_1–H), and a one proton singlet at 8·9 ppm (C_3–H). Since the latter proton resonates as a singlet, the C_4-position must be substituted. The benzylic methylene group absorbs as a sharp two proton singlet at 6·0 ppm (and at 6·4 ppm in **17** (R = CH_2Ph) itself. Hydrogenation of our compound, m.p. 218° in glacial acetic acid in the presence of Adam's catalyst gave an alcoholic base, m.p. 116°, formulated as **22** (R = CH_2Ph). We have already shown[14] that the interaction of 2-methyl-1,2-dihydroisoquinoline (**12**, R = Me) with aromatic acid chlorides

yields 4-acyl compounds (e.g. **23**, R = Me) and that reduction of these with $NaBH_4$ gives alcohols of the type **22** (R = Me). When 2-benzyl-1,2-dihydroisoquinoline (**12**, R = CH_2Ph) was benzoylated to **23** (R = CH_2Ph), and then reduced, the product (**22**, R = CH_2Ph), m.p. 116° was found to be identical in all respects with the material from the Kröhnke compound.



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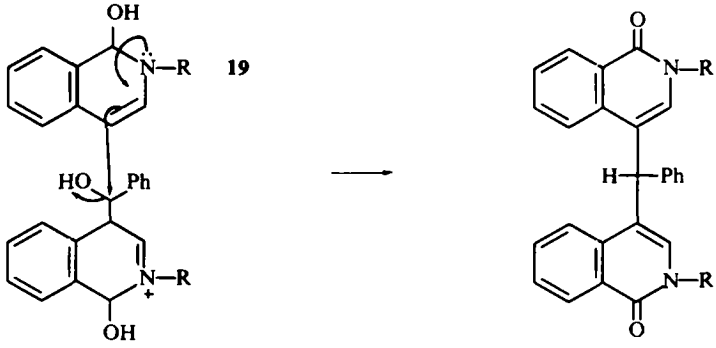
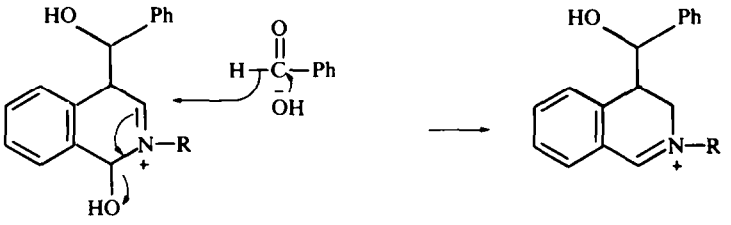
By a slight modification of the experimental conditions (Experimental) the Kröhnke reaction yielded a small amount of a neutral compound, m.p. 220°; an elemental analysis and molecular weight determination indicated a dimeric structure. The UV spectrum was suggestive of an isocarbostyril and the IR spectrum exhibited a band at 1665 cm^{-1} consistent with this. The NMR spectrum (taken in $CDCl_3$ with TMS as an internal standard) showed a two proton multiplet centred at 8·47 ppm typical of the C_8-proton in isocarbostyrils, a 16-proton multiplet 6·9–7·45 ppm (aromatic absorption), a two-proton singlet at 6·37 ppm, and one proton singlet at 5·83 ppm and a quartet, integrating for 4 protons, centred at 4·95 ppm, J = 14 c/s. These features are consistent with the structure **24** (R = CH_2Ph), which may be formed as indicated from **19** and **20**, with oxidation occurring during work-up.



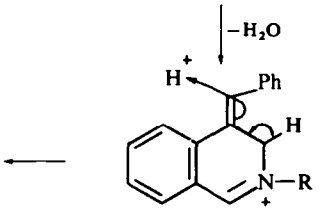
19 **20** **24**

The yield of **21** (R = CH_2Ph) is low (about 10%), and the reaction is a lengthy one, but it does offer a very simple route to 4-substituted isoquinoline derivatives under alkaline conditions, and we decided to investigate the reaction further. Doubling the amount of alkali (to 1·0 mole) resulted in the formation of 2,4-dibenzylisoquinolinium bromide (**16**) in 14% yield, but **21** (R = CH_2Ph) was not isolated. Compound **16** could possibly arise from the initial disproportionation of the pseudobase **19** into 2-benzylisocarbostyril and 2-benzyl-1,2-dihydroisoquinoline—a typical reaction

of isoquinoline pseudobases. The latter **12** (R = CH_2Ph) product could then condense with benzaldehyde and aromatise to **16** in the manner suggested previously. However, since 2-benzylisocarbostyril has not been detected among the products of the condensation, an alternative mechanism for the formation of **16** is summarised in **20** → **25** → **26** → **16** and some support for this process is provided by a study of the condensation of isoquinoline methiodide with benzaldehyde (see below).



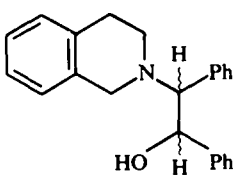
20 **25**



16 **26**

Concentration of the mother liquors from which **16** was obtained gave a quaternary bromide m.p. 240° in low yield. A 70% yield was achieved by condensing 2-benzylisoquinolinium bromide, with benzaldehyde in the presence of one molecular equivalent of sodium ethoxide in ethanol. The UV and IR spectra suggested an isoquinolinium salt containing a OH group, whereas the NMR spectrum (taken in CD_3SOCD_3 with TMS as an internal standard) was consistent with structure **18**, the original proposal by Kröhnke for the first quaternary salt m.p. 218°. In an attempt to confirm this structural assignment, *trans*-stilbene bromohydrin[15] was reacted with isoquinoline in methylethylketone solution. A crystalline quaternary bromide, m.p. 234° was obtained whose UV, IR and NMR spectra were consistent also with structure **18**, although the substance was clearly not identical with that obtained from the Kröhnke reaction. That the two compounds are diastereomorphs was supported by an examination of the NMR spectra of the 1,2,3,4-tetrahydroisoquinolines **27** derived by reducing these quaternary salts with $NaBH_4$. The tetrahydrobase (m.p. 87°) derived from *trans*-stilbene bromohydrin and isoquinoline would be expected to exist preferentially in the conformation **28a** about the asymmetric centres, whereas its diastereoisomer would exist preferentially in the conformation represented by **28b**.

The dihedral angle between the vicinal hydrogen atoms in **28a** is 180° whereas it is only about 60° in **28b**. The hydrogen atoms of the system $>N—C\underline{H}(Ph)C\underline{H}(OH)Ph$ in the two tetrahydrobases resonate as quartets centred at about 4·3 ppm, but whereas a coupling constant of 10 c/s is observed for the base m.p. 87°, this is reduced to 4 c/s



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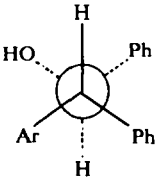
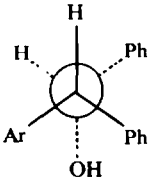
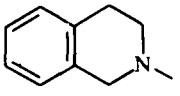


28a

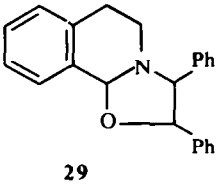


28b

Ar =



in that base m.p. 126° derived from the product of the Kröhnke reaction. In an attempt to destroy the asymmetry in **27**, the two tetrahydrobases were oxidized, but whereas the m.p. 126° base gave the cyclic ether **29**, the "synthetic" base m.p. 87° yielded the expected ketone **30**, identical with the product obtained from tetrahydroisoquinoline and α-bromodeoxybenzoin.[16] Reduction of **30** regenerated **28a**.



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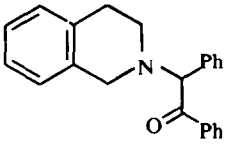

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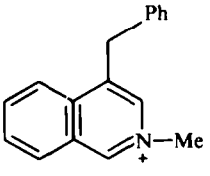

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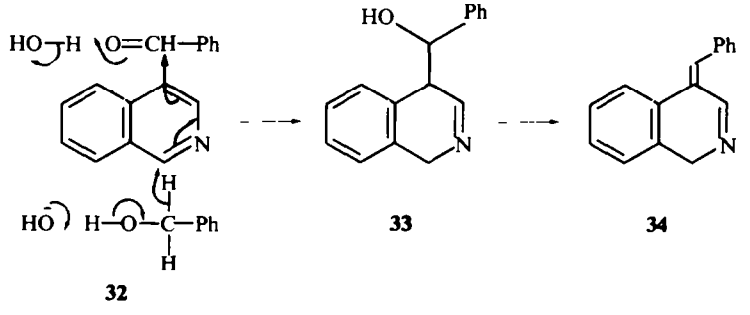
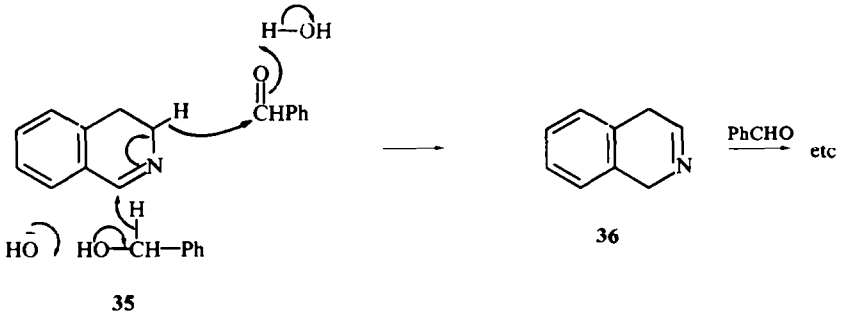
When Kröhnke's original conditions were employed with isoquinoline methiodide, the C_4-substituted compound **21** (R = Me) was obtained in 17% yield and its structure was established by methods similar to those used in the 2-benzyl series. With one mole of sodium hydroxide, a new compound was obtained (30%); the spectral characteristics were interpreted in terms of structure **26** (R = Me), and this was supported by heating the substance in methanol solution when isomerism occurred almost quantitatively to **31**, identical with an authentic specimen. A small amount of the dimer **24** (R = Me) was also isolated from the condensation reaction. When ethanolic sodium ethoxide was used in place of aqueous NaOH, a 40% yield

of **26** (R = Me) was obtained. This constitutes the best yield of a 4-substituted isoquinoline so far obtained by us in these reactions, and in view of the simplicity of the procedure, the yields are acceptable for a synthetic method.

If a mixture of isoquinoline, benzyl alcohol and KOH is heated under anhydrous conditions,[17] a 60% yield of 4-benzylisoquinoline results. The reaction is best regarded as proceeding as shown in **32** → **33** → **34** → etc. A 40% yield of 4-benzylisoquinoline is claimed[17] when an anhydrous mixture of 3,4-dihydroisoquinoline,



benzyl alcohol, KOH and benzaldehyde is heated together. The dihydroisoquinoline **35** presumably undergoes a base-catalysed isomerization to **36**, which can then condense with benzaldehyde in a straightforward manner.



One of the best-known reactions of enamines[18] is C-alkylation, and we have now succeeded in benzylating 2-methyl-1,2-dihydroisoquinoline. Since the product, 2-methyl-4-benzyl-1,2-dihydroisoquinoline is expected to be unstable, it was oxidized with iodine, without isolation, to the fully aromatic isoquinolinium salt. The best result, with a 27% yield of 2-methyl-4-benzylisoquinolinium iodide, was obtained with ethanol as a solvent, but the same product was obtained by using isopropanol, isobutanol, dimethylformamide or acetonitrile as solvents.

EXPERIMENTAL

NMR spectra were recorded upon a Varian A-60 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard. IR spectra were determined as Nujol mulls upon a Perkin–Elmer 237 instrument and UV spectra were recorded as ethanolic solns upon a Perkin–Elmer 137 spectrophotometer. All m.p. are uncorrected.

2-Benzyl-4(phenylhydroxymethyl)isoquinolinium bromide **21** (R = —CH_2Ph)

10N NaOH (0·36 ml) was added slowly to a soln of N-benzylisoquinolinium bromide (2 g) and benzaldehyde (2 ml) in EtOH (10 ml) containing water (0·5 ml) under N_2. After 5 days the soln was acidified with aqueous 48% HBr soln and stored at 0° for 4 weeks. The pale yellow crystalline product was then collected and recrystallized from EtOH to give **21** (R = CH_2Ph) m.p. 218–220°, yield = 10%. λ_{max} (ε) mμ, 284 (21,800), 340 (2750); ν_{max} cm^{-1}, ~3250 (—OH), 1630 (>C=$\overset{+}{N}$<), 1600 (>C=C<). NMR (CF_3CO_2H) ppm, 9·68 singlet [1] (C_1—H), 8·87 singlet [1] (C_3—H), ~8·2 multiplet [4] (four adjacent aromatic protons), 7·35 singlet [5] (Ph group), 7·50 singlet [5] (Ph group), 6·00 singlet [2] (>N—CH_2—Ph). (Found: C, 67·62; H, 5·10; N, 3·30. $C_{23}H_{20}NOBr$ requires: C, 68·00; H, 5·00; N, 3·50%.)

2-Benzyl-4(phenylhydroxymethyl)1,2,3,4-tetrahydroisoquinoline **22** (R = CH_2Ph)

Method 1. Compound **21** (R = CH_2Ph; 0·5 g) in glacial AcOH (15 ml) was hydrogenated at 2 atm press over Adam's catalyst overnight. After removal of the catalyst the soln was basified and the ppt extracted into ether; removal of the solvent gave an oil which crystallized upon trituration with EtOH. Recrystallization of this product from EtOH afforded colourless prisms (0·3 g) m.p. 116°. λ_{max} (ε) mμ, 265 (3700); ν_{max} cm^{-1}, ~3200 (—OH). (Found: C, 84·3; H, 6·9; N, 8·3. $C_{23}H_{22}NO$ requires: C, 84·1; H, 6·8; N, 8·0%.)

Method 2 *via compound* **23** (R = —CH_2Ph). Dry 2-benzylisoquinolinium bromide (11 g) was suspended in dry ether (200 ml) and LAH (3 g) cautiously added: after stirring for 2 hr the excess reagent was destroyed by the addition of 33% sodium potassium tartrate aq. The ethereal soln of the 1,2-dihydroisoquinoline thus obtained was decanted quickly from the ppt and protected under N_2. Et_3N (5 ml) was then introduced and benzoyl chloride (6 ml) added dropwise. A yellow product, contaminated with Et_3NHCl, rapidly formed, this was collected, washed firstly with ether then with water and finally recrystallized from $CHCl_3$ to yield 2-benzyl-4-benzoyl-1,2-dihydroisoquinoline (19%) m.p. 133–134°; λ_{max} (ε) mμ, 227 (18,700), 307 (11,900), 350 (13,050); ν_{max} cm^{-1}, 1620, 1610 (>C=C<), 1585 (>C=O). NMR ($CDCl_3$) ppm 8·68 multiplet [1] (aromatic proton *ortho* to >C=O), 4·08 singlet [2] and 4·33 singlet [2] (benzylic $\underline{CH_2}$ groups). (Found: C, 85·0; H, 6·1; N, 4·5. $C_{23}H_{19}NO$ requires: C, 84·9; H, 5·9; N, 4·3%.)

This material (1 g) was dissolved in 90% EtOH and treated with $NaBH_4$. After heating on a water-bath for 1 hr the solvent was removed and water (10 ml) added. Extraction of the ppt into ether gave, after removal of the ether, a colourless solid which recrystallized from EtOH, yielding small prisms (0·82 g) m.p. 115–116°, identical in every respect with the material obtained in method 1 above.

2,4-Dibenzylisoquinolinium bromide (**16**)

10N NaOH (2 ml) was added slowly to a soln of 2-benzylisoquinolinium bromide (6 g) and benzaldehyde (6 ml) in EtOH (30 ml) containing water (2 ml). After 5 days at R.T. under N_2, 48% HBr aq was added until acid to litmus. EtOH (10 ml) was then introduced and the reaction mixture cooled to 0°, whereupon pale brown crystals of 2,4-dibenzylisoquinolinium bromide (0·98 g) separated. Recrystallization from EtOH yielded almost colourless prisms (m.p. 178–179°). (Found: C, 67·60; H, 5·68; N, 3·32; Br, 20·10. $C_{23}H_{20}NBr$, H_2O requires: C, 67·60; H, 5·39; N, 3·43; Br, 19·57%.)

Debenzylation of 2,4-dibenzylisoquinolinium bromide

2,4-Dibenzylisoquinolinium bromide (5 g), glacial AcOH (30 ml) and AcONa (1.37 g) in dry toluene were heated under reflux for 20 hr. After removal of a small quantity of insoluble material, the cooled filtrate was extracted with 2N HCl (3 × 20 ml). Basification and ether extraction of the combined acid washings gave 4-benzylisoquinoline, m.p. 115–117°, (lit.[19] 118°) identical with an authentic specimen, yield 30%.

The dimeric isocarbostyril **24** (R = CH_2Ph)

10N NaOH (0·36 ml) was added slowly to a soln of N-benzylisoquinolinium bromide (2 g) and benzaldehyde (2 ml) in EtOH (10 ml) containing water (0·5 ml) under N_2. After 5 days the soln was acidified with aqueous 48% HBr soln and set aside for 7 days at 0°. Some crystals of NaBr were removed and the EtOH

evaporated. After a further period of 6 days at 0° some yellow crystals (0·6 g) were obtained* which were recrystallized firstly from EtOH aq and then from EtOH–$CHCl_3$ to give colourless prisms, m.p. 220–221°; λ_{max} (ε) mμ, 297 (4470), 331 (2600); ν_{max} cm^{-1}, 1660 (ArCON$\langle$), 1630 ($\rangle$C=C$\langle$). NMR ($CDCl_3$) ppm, 8·45 multiplet [2] (aromatic protons *ortho* to carbonyl), 6·36 singlet [2] ($\rangle$C<u>H</u>—N$\langle$), 4·76 quartet [4] J = 14 c/s ($\rangle$N—C<u>H</u>$_2$—Ph). (Found: C, 83·67; H, 5·33; N, 5·21; M.W. 525. $C_{33}H_{26}N_2O_3$ requires: C, 83·85; H, 5·41; N, 5·01%; M.W. 558.)

1,2-*Diphenyl*-2(N-*isoquinolinium*)1-*hydroxyethane bromide* (**18**)

Concentration of original mother-liquor, from which **16** had separated, gave an oil which, upon addition of ether, yielded a second quarternary bromide (1·36 g). Recrystallization of this material from EtOH gave pale yellow prisms†, m.p. 240–241°; λ_{max} (ε) mμ, 236 (50,900), 282 (5100), 341 (4200); ν_{max} cm^{-1}, 3230 (—OH), 1647 ($\rangle$C=$\overset{+}{\text{N}}\langle$), 1610 ($\rangle$C=C$\langle$). NMR ($CD_3SOCD_3$) ppm 11·1 singlet [1] ($C_1$—<u>H</u>), 9·4 doublet [1] J = 8 c/s (C_3—<u>H</u>), 6·65 quartet [2] J = 10·5 c/s ($\rangle$N—C<u>H</u>Ph—C<u>H</u>(OH)Ph), 3·7 broad singlet [1] (O<u>H</u>—). (Found: C, 68·00; H, 5·08; N, 3·66; Br, 19·79. Calc. for $C_{23}H_{20}NOBr$: C, 68·29; H, 4·96; N, 3·45; Br, 19·67%.)

1,2-*Diphenyl*-2-(N-1,2,3,4-*tetrahydroisoquinolyl*)1-*hydroxyethane* (**27**)

1,2-Diphenyl-2-(N-isoquinolinium)1-hydroxyethane bromide (4·1 g) prepared in the previous experiment was dissolved in 90% aqueous EtOH and reduced with $NaBH_4$ (2 g). Removal of the solvent and addition of water gave a solid, which was collected and recrystallized from EtOH to give colourless needles (2·6 g) m.p. 121–122°. NMR ($CDCl_3$) ppm 3·5 quartet [2] J = 4 c/s ($\rangle$N—C<u>H</u>(Ph)C<u>H</u>(OH)Ph), ~3·2 broad singlet [1] removed with D_2O (<u>H</u>O—), 2·65 singlet [2] (PhC<u>H</u>$_2$—N$\langle$). (Found: C, 83·85; H, 7·00; N, 4·21. $C_{23}H_{23}NO$ requires: C, 83·85; H, 7·04; N, 4·25%.)

The cyclic ether **29**

1,2-Diphenyl-2-(N-1,2,3,4-tetrahydroisoquinolyl)1-hydroxyethane (1·2 g) in acetone (150 ml) was shaken with MnO_2 (10 g) for 45 hr, then filtered and the solvent removed to yield a yellow oil. Trituration with EtOH and recrystallization from this solvent eventually gave stout colourless needles (0·45 g), m.p. 101–108°. The IR spectrum indicated the absence of OH and CO functions and the NMR in $CDCl_3$ revealed a two proton quartet J = 7·0 c/s centred at 4·25 ppm characteristic of the two adjacent exocyclic protons of the ethane residue. The combined evidence above is best accommodated by the expression **27**; λ_{max} (ε) mμ, 265 (846). (Found: C, 84·07; H, 6·42; N, 4·58. $C_{23}H_{21}NO$ requires: C, 84·37; H, 6·46; N, 4·28%.)

2,4-*Dibenzylisoquinolinium iodide*

Method 1. Compound **15** in ether (200 ml), prepared by the reduction of 2-benzylisoquinolinium bromide (10 g) with LAH, was treated with glacial AcOH (25 ml) and benzaldehyde (3·5 g). The red coloured soln thus formed was heated under reflux, in a protective atmosphere of N_2, for 2 hr and then stood at R.T. for a further 56 hr. Removal of the solvents gave a dark red oil which was diluted with water and extracted with ether. Evaporation of the aqueous phase afforded a dark viscous oil which when treated with sat KI aq yielded crystals of **16**. Recrystallization from a small volume of water gave yellow needles (4·5 g) m.p. 185–189°. Further recrystallization from $CHCl_3$–Et_2O raised the m.p. to 197–199°.

Method 2. EtONa (1·36 g) in EtOH (20 ml) was added slowly to a soln of 2-benzylisoquinolinium bromide (6 g) in EtOH, protected by an atm of N_2. After 10 min a fine ppt of NaBr (1·04 g), which had formed,

* A small quantity of **18** was obtained upon concentration of the mother-liquor from which **24**(R = CH_2Ph) was separated.

† This same compound was also prepared in the following manner, this time however no 2,4-dibenzylisoquinolinium bromide was isolated:

EtONa (2·27 g) in EtOH (50 ml) was added to a suspension of 2-benzylisoquinolinium bromide (10 g) in benzaldehyde (10 ml) under N_2. After 10 days the mixture was acidified with 48% HBr aq and cooled to 0°; during a further 24 hr yellow crystals (8·3 g) separated, these were collected. Concentration of the mother-liquor gave a further crop (2·3 g). The combined yield of **18** was 62%, m.p. 240–241° from EtOH.

was removed and benzyl bromide (7 ml) in EtOH (10 ml) was introduced. After shaking for 48 hr and standing for a further 3 days, 48% HBr aq (7 ml) was added and the reaction mixture cooled to 0°. A further quantity of NaBr (0·52 g) was removed and the filtrate stored at 0° for 2 days. During this time brown crystals formed; these were collected and recrystallized from EtOH to yield 2,4-dibenzylisoquinolinium bromide as colourless prismatic needles (1·4 g) m.p. 178–179°. Treatment of this compound as a conc soln in water with KI gave the corresponding iodide m.p. 197–199° identical in every respect with the material obtained in the previous experiment, Method 1.

Attempted synthesis of structure **18**

A mixture of the bromohydrin (6·7 g), from *trans*-stilbene, and isoquinoline (4·8 g) were dissolved in MeCOEt and heated under reflux for 48 hr. After cooling the crystalline product was collected and recrystallized from EtOH as colourless prisms (3·0 g) m.p. 234–235°. λ_{max} (ε) mμ, 236 (60,500), 283 (5100), 341 (4000); ν_{max} cm^{-1}, 3250 (—OH), 1650 (>C=$\overset{+}{N}$<), 1613 (>C=C<). NMR (CD_3SOCD_3) ppm 10·90 singlet [1] (C_1—H), 9·15 doublet [1] J = 7·5 c/s (C_3—H), 6·53 quartet {2} J = 8·0 c/s (>N—CH(Ph)—CH(OH)Ph), ~3·5 broad singlet [1] (—OH). (Found: C, 68·10; H, 5·02; N, 3·65. $C_{23}H_{20}NOBr$ requires: C, 68·29; H, 4·96; N, 3·45%.) This compound was reduced with $NaBH_4$ in the usual way to give a tetrahydrobase, m.p. 87–91°. NMR ($CDCl_3$) ppm 4·2 quartet [2] J = 10 c/s (>N—CH(Ph)CH(OH)Ph), ~2·25 singlet [1] (—OH removed by deuteration). (Found: C, 83·65; H, 6·95; N, 4·10. $C_{23}H_{23}NO$ requires: C, 83·85; H, 7·04; N, 4·25%.)

1,2-*Diphenyl*-2-(N-*isoquinolinium*)1-*ketoethane bromide*

A mixture of α-bromodeoxybenzoin (4 g) and isoquinoline (3·9 g) in MeCOEt (30 ml) was heated on a steam-bath for 30 min. After cooling a pale brown coloured ppt was collected and recrystallized from EtOH affording a colourless micro-crystalline solid (95%), m.p. 233–234°; λ_{max} (ε) mμ, 286 (40,300), 343 (3800); ν_{max} cm^{-1}, 1690 (>CO), 1645 (>C=$\overset{+}{N}$<), 1605 (>C=C<). NMR (CF_3CO_2H) 9·4 singlet [1] (C_1—H), 8·04 quartet [2] J = 8 c/s (C_3—H, C_4—H). (Found: C, 68·34; H, 4·62; N, 3·79; Br, 20·08. $C_{23}H_{18}NOBr$ requires: C, 68·60; H, 4·49; N, 3·47; Br, 19·76%.) Hydrogenation at 2 atm press in EtOH over Adam's catalyst gave a tetrahydrobase m.p. 87–90° identical in every respect with the compound obtained above.

2-(N-1,2,3,4-*tetrahydroisoquinolyl*)*phenylbenzyl ketone* **30**

Oxidation of the tetrahydrobase m.p. 87° (0·8 g) with MnO_2 in acetone gave, after removal of reagent and solvent, a brown gum which crystallized upon treatment with EtOH. Recrystallization from EtOH afforded colourless prisms (0·11 g) m.p. 128–129°. NMR ($CDCl_3$) ppm ~7·6 multiplet [2] (aromatic protons *ortho* to carbonyl), 4·95 singlet [1] (>N—CH(Ph)R), 3·65 singlet [2] (Ar—CH_2—N<), 2·75 broad singlet [4] (Ar—CH_2—CH_2—N<). (Found: C, 84·27; H, 6·41; N, 4·12. $C_{23}H_{21}NO$ requires: C, 84·37; H, 6·47; N, 4·28%.)

4-*Benzyl*-2-*methylisoquinolinium iodide* **31**

Method 1. 2-Methyl-1-2-dihydroisoquinoline, from isoquinolinium methiodide (10 g), in ether (250 ml) was treated with approximately an equimolar quantity of benzyl bromide and Et_3N dissolved in EtOH* (100 ml). After heating under N_2 at reflux for 4 hr, most of the ether was removed and AcOK (4 g) introduced. I_2 in warm EtOH was then added until the I_2 colour persisted and the period of heating continued for a further 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 reaction mixture extracted with $CHCl_3$ (3 × 30 ml). Evaporation of the combined $CHCl_3$ extracts gave a red gum which crystallized on trituration with EtOH. Recrystallization from EtOH gave pale yellow needles m.p. 185–186° (lit.[20] 188°), yield 27%. (Found: C, 56·66; H, 4·67; N, 3·73. Calc. for $C_{17}H_{16}IN$: C, 56·54; H, 4·46; N, 3·88%.)

* Repetition of this procedure using solvents other than EtOH gave the following results: Acetonitrile 9%, isopropanol 15%, dimethylformamide 8%, isobutanol 13%, dioxan 0%.

Method 2. Isoquinolinium methiodide (8·1 g) in EtOH (30 ml) containing benzaldehyde (8 ml) was treated with 10N NaOH (1·65), water (1·5 ml) and EtOH (10 ml). After shaking for 24 hr under N_2, the reaction mixture was set aside for 4 days; then acidified with HI aq and cooled to 0°. The crystalline product was collected and recrystallized from MeOH to give pale yellow rosettes, (1·90 g) m.p. 205–206°; a mixed m.p. with material from method 1 above caused no depression; λ_{max} (ε) mμ, 280, 340; ν_{max} cm^{-1}, 1645 ($\rangle C{=}\overset{+}{N}\langle$), 1610 ($\rangle C{=}C\langle$), NMR ($CF_3CO_2H$) ppm 8·68 singlet [1] ($C_1$—H), 8·50 singlet [1] ($C_3$—H), 5·20 singlet [2] (—$CH_2Ph$), 3·89 singlet [3] ($\rangle\overset{+}{N}$—$CH_3$).

Method 3. Isoquinolinium iodide (8·1 g) and benzaldehyde (8 ml) in EtOH (30 ml) were heated with EtONa (3·06 g) in EtOH (20 ml) under N_2. After 5 days the dark red soln was acidified with HI aq and cooled to 0°. The crystalline product which formed was collected and recrystallized from MeOH to give deep yellow needles (5·0 g) m.p. 151–153°; λ_{max} (ε) mμ, 265, 370; ν_{max} cm^{-1}, 1660 ($\rangle C{=}\overset{+}{N}\langle$), 1595 ($\rangle C{=}C\langle$). NMR ($CD_3SOCD_3$) ppm, 10·1 singlet [1] (C_1—H), 4·58 singlet [2] (—CH_2—N$\langle$), 4·55 singlet [3] ($\rangle\overset{+}{N}$—CH_3). (Found: C, 56·69; H, 4·46; N, 3·95; I, 35·25. $C_{17}H_{16}NI$ requires: C, 56·54; H, 4·46; N, 3·88; I, 35·14%.)

Repeated recrystallization from MeOH caused an obvious change to occur yielding a much lighter coloured product m.p. 203–205°; this proved to be identical with the product prepared in Method 2.

The mother-liquor from which the deep yellow product m.p. 151–153° originally separated was evaporated almost to dryness and the residue chromatographed upon alumina. After a fore-fraction containing benzaldehyde, benzene eluted a colourless crystalline material (24, R = Me), which recrystallized from EtOH–$CHCl_3$ mixtures, yield 0·6 g, m.p. 279–280°; λ_{max} (ε) mμ, 287, 326; ν_{max} cm^{-1}, 1650 (Ar—CO—N$\langle$) 1625 ($\rangle C{=}C\langle$). NMR ($CDCl_3$) ppm, 8·45 multiplet [2] (aromatic protons adjacent to carbonyl), 6·5 singlet [2] ($\rangle$CH—N$\langle$), 5·96 [1] ($\rangle$CH—Ph). (Found: C, 80·06; H, 5·37; N, 6·75. $C_{27}H_{22}N_2O_2$ requires: C, 79·78; H, 5·46; N, 6·89%.)

2-Methyl-4-(phenylhydroxymethyl)isoquinolinium iodide (21, R = Me)

Isoquinolinium methiodide (8·1 g) in a mixture of benzaldehyde (8 ml) and EtOH (30 ml) was treated under a protective N_2 atm with 10N NaOH (1·65 ml), water (1·5 ml) and EtOH (10 ml). After shaking for 24 hr and standing for 4 days at 0° the yellow crystalline product was collected by filtration and recrystallized from MeOH (1·92 g) m.p. 205–206°; λ_{max} (ε) mμ, 279, 338; ν_{max} cm^{-1}, 3300 (OH), 1645 ($\rangle C{=}\overset{+}{N}\langle$), 1610 ($\rangle C{=}C\langle$). NMR ($CD_3SOCD_3$) ppm, 9·80 singlet [1] (C_1—H), 8·80 singlet [1] (C_3—H), 6·60 singlet [1] (OH removable by deuteration), 6·53 singlet [1] (Ph—CH(OH)—), 4·61 singlet [3] (—NCH_3). (Found: C, 54·21; H, 4·17; N, 3·64; I, 33·60. $C_{17}H_{16}NO_4I$ requires: C, 54·14; H, 4·28; N, 3·71; I, 33·65%.)

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