Reissert Compound Chemistry. Part II.[1] Synthesis of 1-Benzylisoquinolines *via* the Reissert Carbanion Generated with Sodium Hydride [2]

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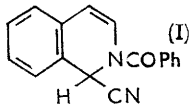
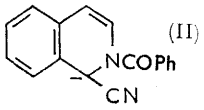
An improved procedure for the preparation of 1-benzylisoquinolines in high overall yields *via* Reissert compound intermediates has been developed. It involves generation of the C-1 carbanion of the Reissert compound with sodium hydride in dimethylformamide.

1-Substituted isoquinolines have been prepared by use of isoquinoline Reissert compounds [3] (*N*-benzoyl-1,2-dihydroisoquinoline-1-carbonitriles) (I) as intermediates. Action of strong base removes the 1-hydrogen in (I) to give the carbanion (II) which, in turn, can effect nucleophilic substitution in alkyl halides,[4] and can add to aromatic aldehydes.[5]



(I)



(II)

Carbanions have previously been generated by use of phenyl-lithium in ether at low temperatures (−10 to −20°);[4] this procedure is inconvenient for a number of reasons. The reagent has to be specially prepared and its strength is not reliably known without titration. Addition of phenyl-lithium to the Reissert compound gives the characteristic deep red colour of the carbanion, and because of the intensity of this colour it is not possible to observe when anion formation is complete. Further, use of ether often introduces solubility difficulties which are not necessarily eliminated easily by use of co-solvents, in view of the instability of the phenyl-lithium. Lastly, the phenyl anion is sterically demanding; this factor can seriously affect the yield of carbanion in 8-substituted isoquinoline Reissert compounds, as shown later. We have overcome these problems by use of sodium hydride in dimethylformamide to generate the carbanion.

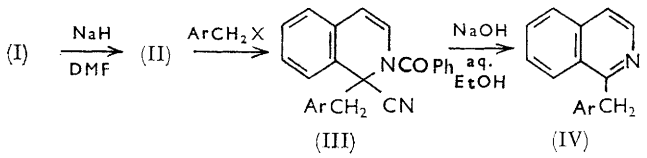
The value of dipolar aprotic solvents in organic chemistry has only recently been realised.[6] Zaugg *et al.*[7] used sodium hydride in dimethylformamide (DMF) to generate the carbanion of active methylene compounds, which could then be alkylated with the appropriate alkyl halide. We have found that treatment of isoquinoline Reissert compound (I) with sodium hydride in dimethylformamide results in immediate generation of the carbanion (II), with the liberation of hydrogen gas. Cessation of gas evolution indicates when carbanion formation is complete. The reaction is carried out at 0° under nitrogen.† Addition of benzyl halide causes the deep red colour to fade and work-up gives the 1-substituted Reissert compound (III). This was not normally isolated, but was converted directly into the 1-benzylisoquinoline (IV) by hydrolysis with sodium hydroxide in aqueous ethanol. A small amount of (IV) was initially isolated along with (III); this presumably arose from some hydrolysis of (III) by the sodium ethoxide produced by destruction of excess of sodium hydride with ethanol.

The results for a number of substituted benzyl halides and isoquinolines are summarised in Table 1; overall

† As indicated in our preliminary communication [2] the procedure for carbanion generation was independently reported by F. D. Popp and J. M. Wefer.[8]

[1] Part I, S. R. Chhabra, J. R. Kershaw, and B. C. Uff, *Tetrahedron Letters*, 1967, 3199.
[2] Preliminary communication, J. R. Kershaw and B. C. Uff, *Chem. Comm.*, 1966, 331.
[3] W. E. McEwan and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511.
[4] V. Boekelheide and J. Weinstock, *J. Amer. Chem. Soc.*, 1952, **74**, 660.
[5] F. D. Popp and W. E. McEwan, *J. Amer. Chem. Soc.*, 1957, **79**, 3773.
[6] A. J. Parker, *Adv. Org. Chem.*, 1965, **5**, 1.
[7] H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Summers, and R. W. DeWet, *J. Org. Chem.*, 1961, **26**, 644.
[8] F. D. Popp and J. M. Wefer, *Chem. Comm.*, 1966, 207; *J. Heterocyclic Chem.*, 1967, **4**, 183.

yields of (IV) from (I) are quoted. Use of the sodium hydride procedure gave high yields of 1-benzylisoquinoline, better than those obtained by the phenyllithium procedure. Particularly notable is the case of 7,8-dimethoxyisoquinoline Reissert compound, which



gave no substitution under phenyl-lithium conditions, but which gave a 65% yield of 7,8-dimethoxy-1-(4-methoxybenzyl)isoquinoline when sodium hydride was used. The small hydride ion is presumably more selective in removing the hindered C-1 methine proton than is benzenide ion. The working temperature (0°) is more convenient and the method avoids any initial preparation of the reagent. Furthermore the production of the Reissert anion can readily be followed by observation of the hydrogen gas evolution.

TABLE 1

Synthesis of 1-benzylisoquinolines

Alkyl halide	Substituted isoquinoline (IV)	Generation of anion	Yield of (IV) (%)
(i) By use of isoquinoline Reissert compound			
$PhCH_2Cl$	1-$PhCH_3$-	NaH–DMF	84
$PhCH_2Br$	1-$PhCH_2$	PhLi	78 [a]
4-MeO·C_6H_4·CH_2Cl	1-(4-MeO·C_6H_4·CH_2)-	NaH–DMF	72
4-MeO·C_6H_4·CH_2Cl	1-(4-MeO·C_6H_4·CH_2)-	PhLi	66
4-MeC_6H_4·CH_2Cl	1-(4-MeC_6H_4·CH_2)-	NaH–DMF	78
4-NO_2·C_6H_4·CH_2Br	1-(4-NO_2·C_6H_4·CH_2)-	NaH–DMF	65
3,4-$(MeO)_2C_6H_3$·CH_2Cl	1-[3,4-$(MeO)_2C_6H_3$·CH_2]-	NaH–DMF	82
3,4-$(MeO)_2C_6H_3$·CH_2Cl	1-[3,4-$(MeO)_2C_6H_3$·CH_2]-	PhLi	53 [b]
3,4-$Me_2C_6H_3CH_2Cl$	1-(3,4-$Me_2C_6H_3$·CH_2)-	NaH–DMF	86
3,4-(CH_2O_2):C_6H_3·CH_2Cl	1-[3,4-(CH_2O_2):C_6H_3·CH_2]-	NaH–DMF	75
(ii) By use of 7,8-dimethoxyisoquinoline Reissert compound			
4-MeO·C_6H_4·CH_2Cl	7,8-$(MeO)_2$-1-(4-MeO·C_6H_4·CH_2)-	Na–DMF	65
4-MeO·C_6H_4·CH_2Cl	7,8-$(MeO)_2$-1-(4-MeO·C_6H_4·CH_2)-	PhLi	0

[a] Ref. 4; [b] ref. 5.

EXPERIMENTAL

Benzyl Chlorides.—The chlorides were prepared by the action of thionyl chloride and pyridine in dry benzene on the appropriate alcohol, according to the procedure of Grice and Owen.[9] 4-Methoxybenzyl chloride had b.p. 56°/1·2 × 10^{-2} mm. (lit.,[9] 59—60°/10^{-2} mm.); 3,4-dimethoxybenzyl chloride had b.p. 90—93°/0·1 mm. (lit.,[10] 118—120°/0·5 mm.); and 3,4-methylenedioxybenzyl chloride had b.p. 71—76°/0·5 mm. (lit.,[11] 126°/15 mm.).

N-Benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (I).—This was prepared from isoquinoline with benzoyl chloride and potassium cyanide in methylene chloride–water according to the method of Popp and Blount,[12] and gave colourless rhombs, m.p. 123—125° (from ethyl acetate) (lit.,[12] 124—125°).

1-(4-Methoxybenzyl)isoquinoline.—*Phenyl-lithium procedure.* To a solution of *N*-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (4·75 g., 0·018 mole) in dry tetrahydrofuran (50 ml.) maintained and stirred at −10° under dry, oxygen-free nitrogen, was added a solution of phenyl-lithium, prepared[13] from bromobenzene (10 ml.) and lithium (1 g.), in dry tetrahydrofuran (50 ml.). A dark red colour appeared. 4-Methoxybenzyl chloride (4 g., 0·025 mole) in dry tetrahydrofuran (10 ml.) was slowly added, and the mixture was stirred for 1 hr. at −10° and then overnight at room temperature; after this time the colour had changed to yellow-brown. The solvent was evaporated off to leave *N*-benzoyl-1-(4-methoxybenzyl)-1,2-dihydroisoquinoline-1-carbonitrile as an oil. This was dissolved in ethanol (250 ml.) and heated under reflux for 2 hr. with potassium hydroxide (100 g.) in water (200 ml.). After removal of alcohol the residue was partitioned between benzene and water. The benzene extract was washed with water, extracted with acid, basified, extracted with chloroform, and dried (K_2CO_3). Evaporation gave 1-(4-*methoxybenzyl*)-*isoquinoline* as an oil (4·54 g., 66%). Column chromatography and recrystallisation from light petroleum (b.p. 60—80°) gave cream needles, m.p. 68·5—69·5° (Found: C, 81·8; H, 6·1; N, 5·8. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·1; N, 5·6%); for n.m.r. spectrum of this and subsequently described 1-benzylisoquinolines see Table 2. The *picrate* was prepared by precipitation from the hydrochloride in water and gave bright yellow needles, m.p. 167—168° (from ethanol) (Found: C, 57·4; H, 3·6. $C_{23}H_{18}N_4O_8$ requires C, 57·7; H, 3·8%).

Attempted Synthesis of 7,8-Dimethoxy-1-(4-methoxybenzyl)-isoquinoline.—*Phenyl-lithium procedure.* By use of the methylene chloride–water method[12] 7,8-dimethoxyisoquinoline[14] (2·4 g.) gave *N-benzoyl-7,8-dimethoxy-1,2-dihydroisoquinoline-1-carbonitrile* (3·2 g., 72%) as cream rhombs, m.p. 158—159·5° (from ethyl acetate) (Found: N, 8·8. $C_{19}H_{16}N_2O_3$ requires N, 8·8%).

(*a*) *N*-Benzoyl-7,8-dimethoxy-1,2-dihydroisoquinoline-1-carbonitrile (2·5 g.) was treated with phenyl-lithium followed by 4-methoxybenzyl chloride and worked up as described for the preparation of 1-(4-methoxybenzyl)isoquinoline. The final product was 7,8-dimethoxyisoquinoline

[9] R. Grice and L. N. Owen, *J. Chem. Soc.*, 1963, 1947.
[10] F. Kröhnke, H. Schmeiss, and W. Gottstein, *Chem. Ber.*, 1951, **84**, 131.
[11] C. Mannich and O. Walther, *Arch. Pharm.*, 1927, **265**, 1.
[12] F. D. Popp and W. Blount, *Chem. and Ind.*, 1961, 550.
[13] H. Gilman and J. W. Morton, *Org. Reactions*, 1954, **8**, 258.
[14] C. Djerassi, F. X. Markley, and R. Ehrlich, *J. Org. Chem.*, 1956, **21**, 975.

(1·1 g., 81%), obtained as an oil which was characterised as its methiodide, yellow needles, m.p. 174—176° (Found: N, 4·1. $C_{12}H_{14}NO_2I$ requires N, 4·2%).

(*b*) The reaction was repeated as in (*a*) but at −15°. The product was again 7,8-dimethoxyisoquinoline.

Synthesis of 1-*Benzylisoquinolines. Sodium Hydride Method.—General procedure.* A suspension of sodium hydride (0·0125 mole) [50% in oil; washed with dry light petroleum (b.p. 60—80°)] in dry dimethylformamide (25 ml.) was stirred at 0° under nitrogen. The *N*-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (0·0115 mole) in dimethylformamide (15 ml.) was added and a deep red colour developed with evolution of hydrogen gas. After about 10 min., the benzyl halide (0·012 mole) (see Table 1) was added during 0·5 hr. The mixture was then stirred for a further 0·5 hr. at 0° and for 2 hr. at room temperature, after which the colour was pale pink.

Ethanol was added to destroy excess of sodium hydride, and most of the solvent was distilled off under reduced pressure. Benzene and water were added and the layers were separated. The benzene layer was washed with water and extracted with acid; the extract was basified, extracted with chloroform, and dried (K_2CO_3). Evaporation left the 1-benzylisoquinoline.

The benzene solution was evaporated to give the substituted Reissert compound as an oil, to which ethanol (150 ml.) and a solution of sodium hydroxide (50 g.) in water (50 ml.) were added. The mixture was heated under reflux for 2½ hr., the ethanol was distilled off, and the product was extracted with benzene. The extract was worked up as described above to give more of the 1-benzylisoquinoline. Column chromatography on neutral alumina was used to purify the 1-benzylisoquinolines. Yields are recorded in Table 1 and n.m.r. data in Table 2.

TABLE 2

Benzylisoquinolines: n.m.r. spectral data (τ values)

Substituents	Aromatic protons	CH_2	Other protons
1-Benzyl	1·43—2·45 (11H)	5·35(s)	
1-(4-Methoxybenzyl)	1·44—3·50 (10H)	5·39(s)	6·42 (3H, s, OMe)
1-(4-Methylbenzyl)	1·51—3·05 (10H)	5·40(s)	7·79 (3H, s, Me)
1-(4-Nitrobenzyl)	1·46—2·65 (10H)	5·23(s)	
1-(3,4-Dimethoxybenzyl)	1·52—3·27 (9H)	5·41(s)	6·25 (6H, s, 2 OMe)
1-(3,4-Dimethylbenzyl)	1·54—3·10 (9H)	5·47(s)	8·00 (6H, s, 2 Me)
1-(3,4-Methylenedioxybenzyl)	1·53—3·25 (9H)	5·47(s)	4·24 (2H, s, O·CH_2·O)
7,8-Dimethoxy-1-(4-methoxybenzyl)	1·68—3·34 (8H)	5·17(s)	6·12 (3H, s, OMe) 6·25 (3H, s, OMe) 6·33 (3H, s, benzyl OMe)

1-*Benzylisoquinoline* was obtained as a pale yellow oil, b.p. 156°/0·9 mm., which solidified (m.p. 56°) (lit.,[15] b.p. 222°/18 mm., m.p. 55—56°); hydrochloride, m.p. 172—173° (lit.,[15] 175°); picrate m.p. 180—182° (lit.,[15] 182°).

1-(4-*Methoxybenzyl*)*isoquinoline* crystallised from light petroleum (b.p. 60—80°) as cream needles, m.p. 68·5—69·5°, identical (mixed m.p.) with the sample prepared previously.

1-(4-*Methylbenzyl*)*isoquinoline* was obtained as a colourless oil and characterised as its *picrate*, yellow needles, m.p. 178—179° (from ethanol) (Found: C, 59·8; H, 3·9; N, 12·1. $C_{23}H_{18}N_4O_7$ requires C, 59·7; H, 3·9; N, 12·1%). The *methiodide* gave yellow plates, m.p. 249—251° (from ethanol) (Found: C, 57·8; H, 4·8; N, 3·8. $C_{18}H_{18}IN$ requires C, 57·7; H, 4·8; N, 3·7%.

1-(p-*Nitrobenzyl*)*isoquinoline* gave cream needles, m.p. 108—109° (from ether) (Found: C, 72·6; H, 4·7; N, 10·5. $C_{16}H_{12}N_2O_2$ requires C, 72·7; H, 4·6; N, 10·6%). The *picrate* gave fine yellow needles, m.p. 212—215° (from ethanol) (Found: N, 14·1. $C_{22}H_{15}N_5O_9$ requires N, 14·2%).

1-(3,4-*Dimethoxybenzyl*)*isoquinoline* gave colourless plates, m.p. 92—93° (from ether) (Found: C, 77·5; H, 6·2; N, 5·0. Calc. for $C_{18}H_{17}NO_2$: C, 77·4; H, 6·1; N, 5·0%). The picrate gave yellow needles, m.p. 165—166° (from ethanol) (lit.,[5] 165—165·5°).

1-(3,4-*Dimethylbenzyl*)*isoquinoline* was obtained as a pale yellow oil and characterised as its *hydrochloride*, which gave colourless needles, m.p. 215° (decomp.) (from ethanol) (Found: N, 4·4. $C_{18}H_{18}ClN$ requires N, 4·4%). The *picrate* gave yellow needles, m.p. 169—170° (from ethanol) (Found: C, 60·5; H, 4·1. $C_{24}H_{20}N_4O_7$ requires C, 60·5; H, 4·2). The *methiodide* gave golden yellow needles, m.p. 188—190° (from ethanol) (Found: C, 56·4; H, 4·8; N, 3·7. $C_{19}H_{20}IN$ requires C, 56·3; H, 5·1; N, 3·6%).

1-(3,4-*Methylenedioxybenzyl*)*isoquinoline* gave colourless needles, m.p. 80—81° (from ether) (Found: C, 77·7; H, 5·2; N, 5·3. $C_{17}H_{13}NO_2$ requires C, 77·5; H, 5·0; N, 5·3%). The *picrate* gave yellow needles, m.p. 179° (decomp.) (from ethanol) (Found: 56·2; H, 3·4; N, 11·2. $C_{23}H_{16}N_4O_9$ requires C, 56·1; H, 3·3; N, 11·4%).

7,8-*Dimethoxy*-1-(4-*methoxybenzyl*)*isoquinoline* was prepared according to the general procedure described above and the intermediate substituted Reissert compound was isolated; crystallisation from benzene gave 2-*benzoyl*-7,8-*dimethoxy*-1-(4-*methoxybenzyl*)-1,2-*dihydroisoquinoline*-1-*carbonitrile* (0·74 g., 27%) as cream rosettes, m.p. 196—198° (Found: C, 73·5; H, 5·5; N, 6·5. $C_{27}H_{24}N_2O_4$ requires C, 73·6; H, 5·5; N, 6·4%), τ 5·82 (3H, s, 8-OMe), 6·17 (3H, s, 7-OMe), 6·33 (3H, s, anisyl OMe); $\nu_{max.}$ 1668 (CO) and 2250w (CN) $cm.^{-1}$.

Work-up of the acid extract and hydrolysis of the substituted Reissert compound gave 7,8-*dimethoxy*-1-(4-*methoxybenzyl*)*isoquinoline* as a pale yellow oil characterised as its *picrate* which gave small yellow needles, m.p. 194° (from ethanol) (Found: C, 55·7; H, 4·0; N, 10·3. $C_{25}H_{22}N_4O_{10}$ requires C, 55·8; H, 4·1; N, 10·4%).

[8/1381 *Received, September 23rd*, 1968]

[15] R. Forsyth, I. Kelly, and F. L. Pyman, *J. Chem. Soc.*, 1925, 1662.