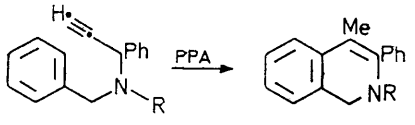
Cyclisation of *N*-(Prop-2-ynyl)benzylamines. Part II.[1] Synthesis of 1,2-Dihydro-3-phenylisoquinolines and an Isopavine Derivative

By **J. Robin Brooks, David N. Harcourt,** and **Roger D. Waigh,***† School of Pharmacy, Bath University, Claverton Down, Bath BA2 7AY

N-(1-Phenylprop-2-ynyl)- and *N*-methyl-*N*-(1-phenylprop-2-ynyl)-benzylamine cyclised in polyphosphoric acid to give good yields of 1,2-dihydro-4-methyl-3-phenylisoquinolines (2). The initial products of cyclisation were unstable and underwent atmospheric oxidation. The tertiary base (2; R = Me) gave an isoquinolin-1(2*H*)-one (7) and the secondary base (2; R = H) an unusual 1,4-dihydroisoquinolin-4-ol (8), which was readily dehydrated to the isoquinoline. Polyphosphoric acid treatment of *N*-(prop-2-ynyl)-1,2-diphenylethylamine (3) caused double cyclisation to give 10,11-dihydro-10,5-(iminomethano)-5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (4) (an isopavine derivative).

We have reported the cyclisation of simple *N*-(prop-2-ynyl)benzylamines with polyphosphoric acid,[1] in which difficulties were encountered owing to the tendency of the primary reaction products to oxidise and disproportionate. We envisaged two ways in which the reaction could be investigated while avoiding these difficulties. In the first instance, we could take advantage of the ease of synthesis of 1-substituted propynols [2] to produce substituted bromo- and hence amino-propynes. Commencing with an aromatic aldehyde the resultant aminopropynes would cyclise to 3-aryl-1,2-dihydroisoquinolines (Scheme 1) which are reputedly stable [3] and are potentially adaptable intermediates in alkaloid synthesis.[4] Here the substituent chosen was phenyl, both for simplicity and because 1-phenylprop-2-yn-1-ol was commercially available.

In the second, a benzyl substituent attached to the



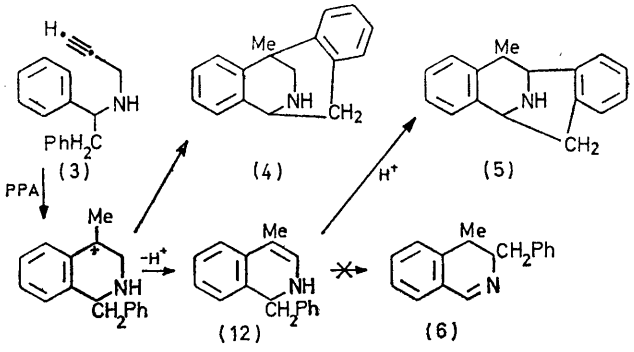
(1) (2)

Scheme 1

first-formed isoquinoline might trap the reactive intermediate in any of three ways [5-7] (Scheme 2).

Reaction of 1-phenylprop-2-yn-1-ol with phosphorus tribromide gave a good yield of the required 1-bromo-1-phenylprop-2-yne.[8] The bromo-compound was highly lachrymatory, like the nitrile analogue.[9] It was possible to distil it, despite a report [10] that the compound polymerised explosively on attempted isolation.

Alkylation of benzylamine and *N*-methylbenzylamine gave moderate yields of the required aminopropynes (1; R = H and R = Me). Cyclisation of the aminopropyne (1; R = Me) with polyphosphoric acid gave the expected 1,2-dihydro-4-methyl-3-phenylisoquinoline (2; R = Me)



Scheme 2

as an oil, identified by its n.m.r. spectrum. On exposure to the air for several days the oil solidified, and chromatography of the solid on alumina gave the isoquinolin-1(2*H*)-one (7). Similar reactions of 1,2-dihydroisoquinolines have been recorded,[11] and presumably a normal autoxidation occurs,[12] followed by dehydration of the peroxide (Scheme 3).

Cyclisation of the aminopropyne (1; R = H) also gave an oil, but in this case the n.m.r. spectrum could not be interpreted, the oil obviously consisting of a mixture of compounds. On trituration with an ether–petroleum mixture the oil solidified, and chromatography on alumina gave two crystalline materials. The first product showed i.r. absorption indicative of the presence of –OH and –C=N– groups. Elemental analysis and the presence in the n.m.r. spectrum of a two-proton AB quartet with geminal coupling (*J* 20 Hz) at δ 4·4 ($ArCH_2$–N=), together with other consistent absorption, suggested the 1,4-dihydroisoquinolin-4-ol structure (8).

† *Present address:* Department of Pharmaceutical Chemistry, University of Strathclyde, Glasgow G1 1XW.

[1] J. R. Brooks and D. N. Harcourt, *J. Chem. Soc.* (*C*), 1969, 625, is regarded as Part I.

[2] *E.g.*, E. R. H. Jones and J. T. McCombie, *J. Chem. Soc.*, 1942, 733.

[3] S. F. Dyke and M. Sainsbury, *Tetrahedron*, 1965, **21**, 1907.

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[11] M. Sainsbury, S. F. Dyke, and A. R. Marshall, *Tetrahedron*, 1966, **22**, 2447; *cf.* E. Hoeft, A. Rieche and H. Schultzr, *Annalen*, 1966, **697**, 181.

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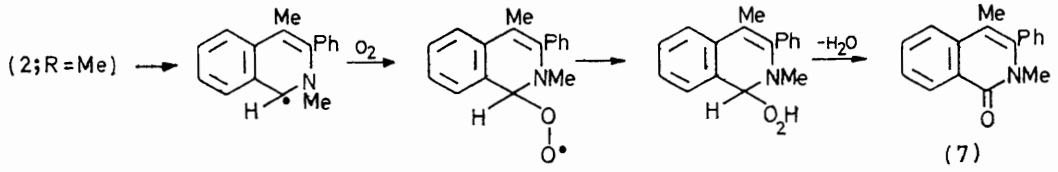
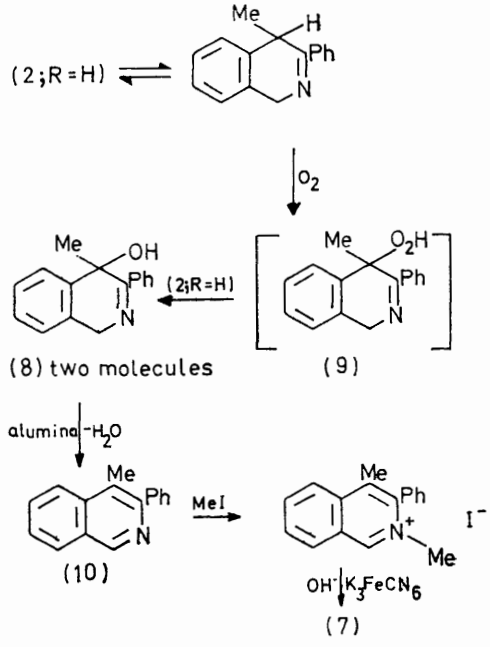
At first the formation of such a product was difficult to rationalise, but by analogy with recent work with other cyclic enamines,[13] it would appear that oxidation to the peroxide (9) may occur, which then ' proportionates ' with a molecule of the 1,2-dihydroisoquinoline (2; R = H) or its tautomer, to give two molecules of the dihydroisoquinolinol [(8), Scheme 4]. It seems that the imino-form of the dihydroisoquinoline (2; R = H) is



SCHEME 3

subject to rapid oxidation, which would explain the difference in oxidation products of the secondary and tertiary bases, since in the absence of acid the latter is



SCHEME 4

unable to tautomerise. The existence of both tautomeric forms of the isoquinoline (2; R = H) may explain the complexity of the n.m.r. spectrum of the crude cyclisation product, compared with that of the tertiary base (2; R = Me).

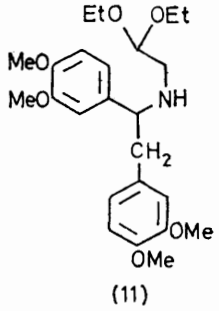
The second crystalline fraction from chromatography of the oxidised cyclisation product [from (1; R = H)] was identified as 3-methyl-3-phenylisoquinoline (10) (i.r., n.m.r., elemental analysis). The suspicion that this was an artefact from chromatography was confirmed on repassing a pure sample of the 1,4-dihydroisoquinolin-4-ol (8) through a similar alumina column, when quantitative conversion into isoquinoline (10) occurred (Scheme 4).

The isoquinoline (10) could be quaternised with methyl iodide, and the quaternary salt thus obtained oxidised with potassium ferricyanide in alkaline solution,[14] to give an isoquinolin-1(2*H*)-one (7), identical with that obtained from cyclisation of aminopropyne (1; R = Me).

No tendency to disproportionate [1] was found with any of the 3-phenylisoquinolines.

Cyclisation of *N*-(prop-2-ynyl)-1,2-diphenylethylamine (3) gave a crude yield (68%) of a viscous oil. The major component of the crude product was the ' isopavine ' derivative (4), for which the n.m.r. spectrum was diagnostic, although complicated by overlapping. Both AB and ABX spin coupling systems could be discerned owing to the non-equivalence of the protons of each $-CH_2-$ group, with large geminal coupling constants. Significantly, the methyl group signal was a sharp singlet, eliminating possible alternative structures (5) and (6). A mass spectrum and accurate mass measurement of the parent ion confirmed the structure of the major product.

Some impurities were indicated in the n.m.r. spectrum of the crude material, notably a sharp singlet at δ 2·1 of unknown origin, and a doublet at δ 1·46 which in theory could have originated from a variety of products, including (5) and (6). Further work by another group [15] interested in the pharmacological activity of the isopavine derivative (4) has indicated that the latter impurity was probably the pavine derivative (5).



It thus appears that the aminopropyne (3) cyclises in a very similar manner to the acetal (11) used by

[13] G. Berti, A. Da Settimo, G. Di Colo, and E. Nannipieri, *J. Chem. Soc.* (*C*), 1969, 2703.

[14] R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 1925, 1434.

[15] D. C. Bishop, personal communication.

Battersby [5] to obtain ' isopavine,' and that the dihydroisoquinoline [(12), Scheme 2] is not formed to any great extent.

EXPERIMENTAL

Unless stated, m.p.s were taken with a Kofler hot-stage apparatus, and are corrected. I.r. spectra were obtained with a Unicam SP 200 instrument for potassium bromide discs or liquid films. N.m.r. spectra were recorded with a Varian A60 instrument (tetramethylsilane as internal reference).

1-*Bromo*-1-*phenylprop*-2-*yne*.—1-Phenylprop-2-ynol (100 g) and dry pyridine (5 g) were dissolved in dry ether (100 ml). Phosphorus tribromide (80 g) was added dropwise with stirring, and the mixture left overnight. The solution was refluxed for 2 h, cooled, poured into water (400 ml), and the ether layer decanted. The water layer was decanted from the heavy oil which had separated, and the oil added to the ether layer. The water layer was extracted with ether, and the ether layers were combined, washed with sodium hydrogen carbonate solution, dried, and evaporated. The residual oil was distilled under high vacuum, the distillation being stopped when the rate slowed appreciably (in one experiment the temperature was allowed to rise and the boiler residue decomposed vigorously, resulting in loss of the product; see text). The *bromide* (90·5 g, 61%) was a mobile, pale yellow liquid with strong lachrymatory properties, sufficiently pure for further reactions. The analytical sample was twice fractionally distilled, b.p. 76—80° at 2·5 mmHg, $\nu_{max.}$ 2120 and 3300 cm^{-1} (Found: C, 55·3; H, 3·6; Br, 40·7. C_9H_7Br requires C, 55·4; H, 3·6; Br, 41·0%).

N-(1-*Phenylprop*-2-*ynyl*)*benzylamine* (1; R = H).—Benzylamine (53·5 g, 0·5 mol), was dissolved in sodium-dried benzene (300 ml). 1-Bromo-1-phenylprop-2-yne (32·5 g, 0·167 mole), in sodium-dried benzene (150 ml), was added dropwise, with stirring. Stirring was continued 2 h, the solution refluxed 2 h, and allowed to stand 48 h. The benzene solution was shaken with 5N-sodium hydroxide solution (100 ml), and separated. The aqueous layer was extracted with benzene. After drying, evaporation of the combined benzene solutions gave an oil. Fractionation (at 1 mmHg) gave benzylamine (32 g) and then the *benzylamine* (1; R = H) (16 g, 43%). The analytical sample was redistilled, b.p. 136—137° at 0·7 mmHg, $\nu_{max.}$ 3300 cm^{-1}, δ (CCl_4) 7·85 (10H, m), 4·45 (1H, m), 3·75 (2H, m), and 0·45 (1H, exchangeable) (Found: C, 86·6; H, 6·8; N, 6·55. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%).

N-*Methyl*-N-(1-*phenylprop*-2-*ynyl*)*benzylamine* (1; R = Me).—The procedure was initially as above, but the distillation was stopped after removal of *N*-methylbenzylamine, and the residue was cooled and extracted with ether. The ether solution was extracted with dilute hydrochloric acid, this solution basified, and re-extracted with ether. Drying and removal of solvent gave the *benzylamine* (1; R = Me) (14·9 g, 38%), as a pale brown oil which crystallised on cooling at 0° for 7 days (m.p. 34—41°). Recrystallisation from aqueous ethanol gave prisms, m.p. 43—45°, $\nu_{max.}$ 3300 cm^{-1}, δ (CCl_4) 7·1 (10H, m), 4·5 (1H, m), 3·45 (2H), 2·35 (1H, m), and 2·05 (3H) (Found: C, 86·9; H, 7·15; N, 6·0. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3; N, 5·95%).

1,4-*Dihydro*-4-*methyl*-3-*phenylisoquinolin*-4-*ol* (8) *and* 4-*Methyl*-3-*phenylisoquinoline* (10).—The aminopropyne (1; R = H) (2·18 g) was heated with polyphosphoric acid (20 g) for 6 h at 140° with stirring. The mixture was cooled, diluted with ice–water, made alkaline with strong ammonium hydroxide solution with addition of ice, and extracted with ether. Drying and evaporation gave a viscous, pale brown oil (1·78 g, 82%), which showed no –OH absorption in the i.r. spectrum. Trituration with ether–petroleum (b.p. 40—60°) caused solidification to a brown granular material, m.p. *ca.* 130°, with strong –OH absorption, $\nu_{max.}$ 3180 cm^{-1}. Chromatography with benzene on an alumina column (B.D.H. alumina, untreated), gave the *dihydroisoquinolinol* (8), a pale yellow, crystalline solid (0·92 g), which was recrystallised from benzene–petroleum (b.p. 40—60°) as needles, m.p. 139—141°, $\nu_{max.}$ 3180 and 1625 cm^{-1}, δ 7·1 (9H, m), 3·95—4·85 (2H, ABq, *J* 20 Hz), 3·35 (1H, exchangeable), and 1·35 (3H) (Found: C, 80·85; H, 6·4; N, 5·9. $C_{16}H_{15}NO$ requires C, 81·0; H, 6·3; N, 5·9%).

Continued elution with benzene gave 4-*methyl*-3-*phenylisoquinoline* (10) as a crystalline solid (0·305 g), which was recrystallised from petroleum (b.p. 40—60°), as prisms, m.p. 103—104°, $\nu_{max.}$ 1620 cm^{-1}, δ 9·2 (1H), 7·7 (9H, m), and 2·6 (2H) (Found: C, 87·7; H, 6·0; N, 6·25. $C_{16}H_{13}N$ requires C, 87·7; H, 5·9; N, 6·4%).

When the chromatography was carried out using petroleum (b.p. 40—60°) initially, with increasing proportions of benzene, the material remained in contact with the alumina for a longer time, and only 4-methyl-3-phenylisoquinoline was isolated (65% yield based on aminopropyne). Similarly, pure isoquinolinol (8) gave a quantitative yield of the aromatic isoquinoline (10) on passing through an alumina column eluted first with petroleum (b.p. 40—60°), then 10, 20, 50%, and finally pure benzene.

2,4-*Dimethyl*-3-*phenylisoquinolinium Iodide*.—The *salt* formed very slowly as long yellow needles when excess of methyl iodide was added to a dry ethereal solution of the isoquinoline (10), m.p. 263—265° (decomp., capillary tube) (Found: C, 56·1; H, 4·65; N, 3·9. $C_{17}H_{16}IN$ requires C, 56·5; H, 4·5; N, 3·9%).

2,4-*Dimethyl*-3-*phenylisoquinolin*-1(2H)-*one* (7).—(a) *From* 2,4-*dimethyl*-3-*phenylisoquinolinium iodide*. The isoquinolinium methiodide (see above, 0·47 g) was dissolved in aqueous ethanol (10 ml). A solution of potassium hydroxide (0·5 g) and potassium hexacyanoferrate(III) (1·4 g) in water (10 ml) was added, giving a white precipitate which dissolved on warming. The solution was cooled and extracted with ether, which on evaporation gave a pale yellow solid (0·285 g, 88%), m.p. and mixed m.p. with the isoquinolin-1(2*H*)-one obtained below, 104—105° and having an identical i.r. spectrum.

(b) *From* N-*methyl*-N-(1-*phenylprop*-2-*ynyl*)*benzylamine* (1; R = Me). The aminopropyne (1; R = Me) (2·32 g), treated as described for cyclisation of aminopropyne (1; R = H) above, gave an oil (2·05 g, 88%). By evaporating solvents under nitrogen and working quickly, the primary product, 1,2-dihydro-2,4-dimethyl-3-phenylisoquinoline, could be obtained in a high state of purity, as determined by the n.m.r. spectrum; δ 7·1 (9H, m), 4·2 (2H), 2·35 (3H), and 1·85 (3H). After several days' exposure to air the oil solidified, and chromatography with petroleum (b.p. 40—60°) on an alumina column gave the *isoquinolinone* (7) (61% based on aminopropyne), as white needles, m.p. 107—108° [from petroleum (b.p. 80—100°)], $\nu_{max.}$ 1640 cm^{-1}, δ 8·2 (1H, m), 7·15 (8H. m), 3·1 (3H), and 1·9 (3H) (Found: C, 81·7; H, 6·0; N, 5·6. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·1; N, 5·6%).

N-(*Prop*-2-*ynyl*)-1,2-*diphenylethylamine* (3) *Hydrochloride*.—3-Bromopropyne (3·0 g) in dry ether (50 ml) was added dropwise to a solution of 1,2-diphenylethylamine (15 g) in ether (20 ml). After 48 h the crystals were filtered off and the solution extracted with dilute hydrochloric acid. A solid (4·3 g) crystallised from the acid solution and was filtered off. Recrystallisation from ethanol–acetone gave the *hydrochloride* as needles, m.p. 198—200° (3·8 g, 60%), δ (free base, CCl_4) 6·9 (10H, m), 3·95 (1H, t, *J* 7 Hz), 2·95 (2H, d, *J* 3 Hz), 2·7 (2H, d, *J* 7 Hz), 1·9 (1H, t, *J* 3 Hz), and 1·35 (1H, exchanged with D_2O) (Found: C, 74·8; H, 6·55; N, 4·8. $C_{17}H_{18}ClN$ requires C, 75·1; H, 6·6; N, 5·2%).

10,11-*Dihydro*-5-*methyl*-10,5-(*iminomethano*)-5H-*dibenzo*-[a,d]*cycloheptene* (4).—*N*-(Prop-2-ynyl)-1,2-diphenylethylamine hydrochloride (2·2 g) was dissolved in polyphosphoric acid (20 g) and heated at 145° for 6 h. The solution was diluted with water (100 ml) and made alkaline after being left for 30 min. The n.m.r. spectrum of the oil was obtained by the Physico-Chemical Measurements Unit, Harwell, at 100 MHz in $CDCl_3$ solution, δ 7·1 (8H, m), 4·2 (1H, t, *J* apparent 3·5 Hz), 3·2 (4H, AB or ABX, J_{AX} apparent = J_{BX} apparent = 3·5, J_{AB} 17 and AB, *J* 12 Hz), 2·0 (1H, exchangeable), and 1·8 (3H). The base, regenerated from the hydrochloride, showed a single peak on g.l.c. using 2½% SE 301 silicone gum rubber on Chromosorb G. The *hydrochloride* was used to obtain the mass spectrum (Found: M^+, 235·1360. $C_{17}H_{17}N$ requires *M*, 235·1361).

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