Reduction of Some Fused (Benzo[*d*]- and Pyrido[3,2-*d*]-) Pyrimidinones

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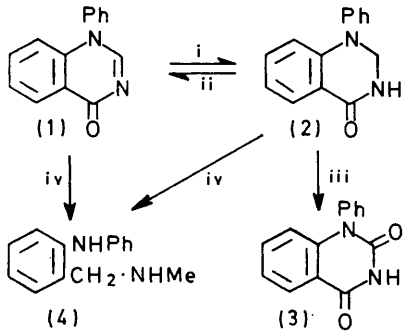
The reduction of some fused pyrimidin-4(1*H*)- and -4(3*H*)-ones with sodium borohydride and with lithium aluminium hydride is described. When *N*-phenyl substituents are present a specific ring-opening reaction occurs.

REDUCTION of pyrimidines,[1] quinazolines,[2] quinazolin-4(3*H*)-ones,[3-6] pteridines,[7] and pyridopyrimidin-4(3*H*)-ones [6,8] has been shown to yield di- and tetra-hydro-derivatives and also products derived from fission of the pyrimidine ring. No ring-opening reactions have been observed with quinazolin-4(1*H*)-ones, although dihydro-derivatives have been isolated from the sodium borohydride reduction of 1-alkylaminoalkyl compounds.[9] Previous work [6,8] suggested that ring opening would be favoured by the presence of 1-aryl substituents, and in an attempt to realise this reaction the preparation of 1-phenylquinazolin-4(1*H*)-one (1) was undertaken.

A synthesis of this compound from *N*-phenlyanthranilic acid and formamide has been described,[10] but a repetition of this preparation did not yield any of the required quinazolinone, although in an analogous preparation *N*-benzylanthranilic acid and formamide give the expected 1-benzylquinazolin-4(1*H*)-one.[11] The product which was isolated showed an i.r. absorption at 3100 cm^{-1} (N–H) in addition to the expected carbonyl peak at 1660 cm^{-1}, and a two-proton doublet ^1H n.m.r. signal at τ 5·0, which collapsed to a singlet on shaking with deuterium oxide. It was thus identified as 1-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (2). The mass spectral

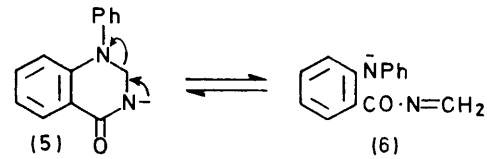


Reagents: i, $NaBH_4$ or $HCO{\cdot}NH_2$; ii, Pd–C; iii, $KMnO_4$; iv, $LiAlH_4$.

fragmentation pattern confirmed this assignment, indicating a molecular ion (*m/e* 224) and a main breakdown initiated by H loss (*m/e* 223) with subsequent loss of CO to yield the base peak (*m/e* 195).

Oxidation of the dihydro-compound (2) with aqueous permanganate yielded 1-phenylquinazoline-2(1*H*),4(3*H*)-dione (3), but dehydrogenation with palladised charcoal in xylene yielded the required 1-phenylquinazolin-4(1*H*)-one (1) in high yield. The disappearance of N–H absorption and the reduction in carbonyl frequency (1655 cm^{-1}) indicated that aromatisation had been effected, and this was confirmed by the appearance of a ^1H n.m.r. singlet (2-H) at τ 1·75 together with the loss of the absorption at τ 5·0. The mass spectrum showed a molecular ion (*m/e* 222) which underwent successive losses of HCN (*m/e* 195, base peak) and CO (*m/e* 167).

The production of 1-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (2) from *N*-phenylanthranilic acid and formamide undoubtedly proceeds *via* the quinazolinone (1), which undergoes reduction *in situ*. A possible reducing agent in this reaction is formate,[12] and although the conversion (1) ⟶ (2) could not be effected with formic acid alone, the dihydro-compound (2) was obtained when 1-phenylquinazolin-4(1*H*)-one (1) was heated with formamide. 1-Phenyl- and 1-benzyl-quinazolin-4(1*H*)-ones were converted into the corresponding 2,3-dihydro-derivatives by treatment with sodium borohydride. More vigorous reduction of the 1-phenyl compounds (1) and (2) with lithium aluminium hydride resulted in the desired ring fission to yield 2-(methylaminomethyl)-*N*-phenylaniline (4), presumably *via* the anions (5) and (6).



2-Methyl-3-phenylquinazolin-4(3*H*)-one (7) has been shown [3] to yield 2-ethylaminobenzanilide (10) on treatment with sodium borohydride at 100° but is unchanged at room temperature. 3-Phenylquinazolin-4(3*H*)-one (8), however, yields the 1,2-dihydro-derivative (12) when treated with borohydride at room temperature. The quinazolinones (8) and (12) yielded 2-(anilinomethyl)-*N*-methylaniline (13) on treatment with lithium aluminium hydride. 2-Methyl-3-phenylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (9) was found to be more susceptible to

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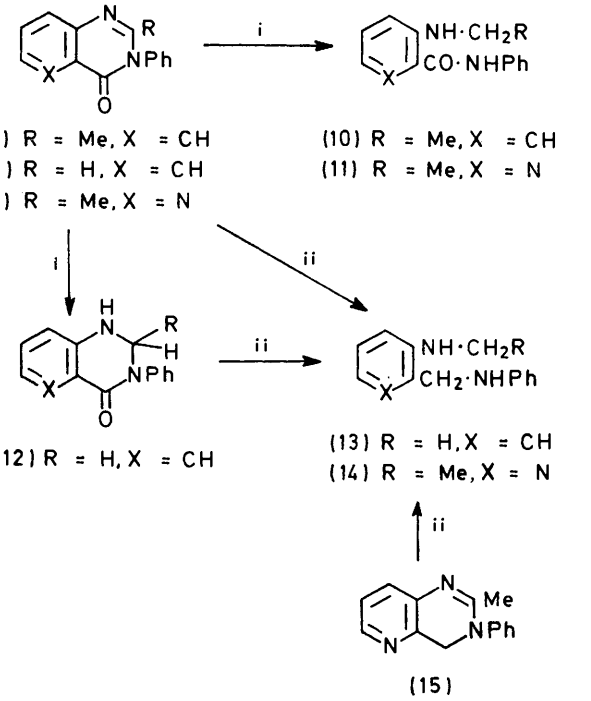
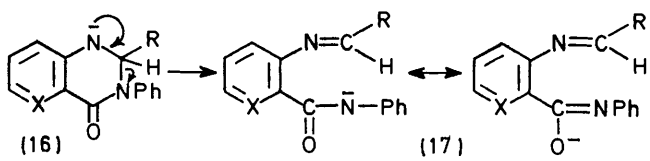
reduction, and yielded 3-ethylamino-*N*-phenylpyridine-2-carboxamide (11) on treatment with borohydride at room temperature. More vigorous reduction of the



Reagents: i, $NaBH_4$; ii, $LiAlH_4$.

pyridopyrimidines (9) and (15) with lithium aluminium hydride yielded 2-anilinomethyl-3-ethylaminopyridine (14).

The fused pyrimidin-4(3*H*)-ones have two sites which are susceptible to hydride attack; the endocyclic C=N and the exocyclic C=O. The specificity of the ring-opening reactions observed suggests that the initial attack takes place at the C=N system, probably producing an intermediate (16) which initiates bond cleavage to yield a stabilised anion (17).



EXPERIMENTAL

^1H N.m.r. spectra were determined for solutions in deuteriochloroform with a Varian A60A spectrometer (tetramethylsilane as internal reference). I.r. spectra were obtained with a Unicam SP 200 spectrophotometer. Mass spectra were measured with an A.E.I. MS9 spectrometer (ionising voltage 70 eV, trap current 100 μA, accelerating voltage 8 kV). Samples were introduced through the heated inlet system at 200°.

2,3-*Dihydro*-1-*phenylquinazolin*-4(1H)-*one* (2).—(i) *N*-Phenylanthranilic acid (5 g) and formamide (10 g) were heated together under reflux for 4 h. The cooled melt was washed with water to yield the *quinazolinone* (4·8 g, 91%), prisms, m.p. 198—199° (from 2-ethoxyethanol).

(ii) 1-Phenylquinazolin-4(1*H*)-one (1 g), sodium borohydride (0·65 g) and propan-2-ol (20 cm³) were stirred together at room temperature for 18 h. Dilution with water (30 cm³) and extraction with chloroform yielded the quinazolinone (0·82 g, 81%).

(iii) 1-Phenylquinazolin-4(1*H*)-one (0·2 g) and formamide (5 cm³) were heated together under reflux for 4 h to yield the quinazolinone, $\nu_{max.}$ (Nujol) 3100 (N–H) and 1660 cm^{-1} (C=O), τ ($CDCl_3$) 5·0 (d, collapsing to s on shaking with D_2O,CH_2), 2,5—3·2 (aromatic protons), and 1·98 (q, 5-H) (Found: C, 75·2; H, 5·4; N, 12·4. $C_{14}H_{12}N_2O$ requires C, 75; H, 5·4; N, 12·5%), *m/e* 225 (6%), 224 (M^+, 40), 223 (27), 222 (7), 196 (19), 195 (100), 168 (5), 167 (29), 166 (13), 140 (6), 139 (8), 78 (4), 77 (27), 76 (4), 64 (7), 63 (7), 58 (4), 50 (8), and 39 (7).

1-*Phenylquinazolin*-4(1H)-*one* (1).—2,3-Dihydro-1-phenylquinazolin-4(1*H*)-one (1 g) and 10% palladised charcoal (0·2 g) were heated together under reflux in xylene for 8 h. Filtration of the hot suspension through Celite and cooling of the clear filtrate yielded the *quinazolinone* (0·7 g, 70%), prisms, m.p. 180—181° (from ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 1655 cm^{-1} (C=O), τ ($CDCl_3$) 2·28—3·18 (aromatic protons), 1·75 (s, 2-H), and 1·63 (m, 5-H) (Found: C, 75·4; H, 4·6; N, 12·3. $C_{14}H_{10}N_2O$ requires C, 75·6; H, 4·5; N, 12·6%), *m/e* 223 (14%), 222 (M^+, 84), 196 (15), 195 (100), 194 (6), 168 (4), 167 (32), 166 (15), 140 (7), 139 (9), 97·5 (6), 92 (12), 83·5 (15), 78 (3), 77 (28), 76 (6), 75 (6), 74 (6), 70·5 (6), 64 (7), 63 (6), 58 (4), 51 (23), 50 (9), 44 (21), and 39 (7), *m** 171·1 (222 ⟶ 195) and 143 (195 ⟶ 167).

1-*Phenylquinazoline*-2(1H),4(3H)-*dione* (3).—2,3-Dihydro-1-phenylquinazolin-4(1*H*)-one (1 g) was stirred with potassium permanganate (0·8 g) in water (10 cm³) for 4 h. Excess of oxidant was destroyed with ethanol and the manganese dioxide was removed. The residue and the neutralised filtrate were extracted with chloroform to yield the quinazolinedione (0·68 g, 64%), plates, m.p. 296—297° (from 2-ethoxyethanol) (Found: C, 70·6; H, 4·3; N, 11·6. Calc. for $C_{14}H_{10}N_2O_2$: C, 70·6; H, 4·2; N, 11·8%), *m/e* 238 (M^+).

2-(*Methylaminomethyl*)-N-*phenylaniline* (4).—(i) 2,3-Dihydro-1-phenylquinazolin-4(1*H*)-one (1·5 g), lithium aluminium hydride (0·75 g), and dry ether (15 cm³) were heated together under reflux for 4 h. The cooled mixture was treated with water (0·8 cm³), sodium hydroxide solution (15%; 0·8 cm³), and water (2·5 cm³), and the ethereal solution was separated and dried ($MgSO_4$). Evaporation and bulb-distillation yielded the diphenylamine (1·2 g, 84%) as a yellow oil which gave an *acetyl derivative*, m.p. 96—97° (from light petroleum), $\nu_{max.}$ ($CHCl_3$) 3300 (N–H) and 1640 cm^{-1} (C=O), τ ($CDCl_3$) 7·92 (s, Ac), 7·05 (s, NMe), 5·42 (s, CH_2), 2·6—3·3 (aromatic protons), and 2·2br (s, exchangeable NH) (Found: C, 75·8; H, 7·1; N, 11·0. $C_{16}H_{18}N_2O$ requires C, 75·6; H, 7·1; N, 11·0%), *m/e* 254 (M^+).

(ii) Reduction of 1-phenylquinazolin-4(1*H*)-one under similar conditions yielded the *diphenylamine* (80%), τ ($CDCl_3$) 7·72 (s, Me), 6·38 (s, CH_2), and 2·7—3·3 (aromatic protons) (Found: M^+, 212·130541. $C_{14}H_{16}N_2$ requires *M*, 212·131342).

1-*Benzyl*-2,3-*dihydroquinazolin*-4(1H)-*one*.— 1-Benzylquinazolin-4(1*H*)-one (1 g), sodium borohydride (0·65 g), and propan-2-ol (20 cm³) were stirred together at room temperature for 18 h. Dilution with water (30 cm³) and extraction with chloroform yielded the *quinazolinone* (0·79 g, 78%), needles, m.p. 162—163° (from 2-ethoxy-

ethanol and ethyl acetate), τ ($CDCl_3$) 5·46 (s, $PhCH_2$), 5·37 (d, 2-H_2), 3·05 (2H, m), 2·72 (s, NH), 2·5 (aromatic protons), and 1·86 (d, 5-H) (Found: C, 75·5; H, 5·9; N, 11·7. $C_{15}H_{14}N_2O$ requires C, 75·7; H, 5·9; N, 11·8%), *m/e* 238 (M^+).

1,2-*Dihydro*-3-*phenylquinazolin*-4(3H)-*one* (12).—3-Phenylquinazolin-4(3*H*)-one (1 g), sodium borohydride (1 g), and propan-2-ol (20 cm³) were stirred together at room temperature for 18 h. Dilution with water (30 cm³) and extraction with chloroform yielded the quinazolinone (0·52 g, 58%), identical with a sample prepared from anthranilanilide and formalin;[13] m.p. 179—180°.

2-*Anilinomethyl*-N-*methylaniline* (13).—1,2-Dihydro-3-phenylquinazolin-4(3*H*)-one (0·6 g), lithium aluminium hydride (0·6 g), and dry ether (12 cm³) were heated under reflux for 24 h. Excess of hydride was destroyed and evaporation of the ethereal extract yielded the diamine (13) (0·45 g, 71%), which gave a *diacetyl derivative*, m.p. 109—110° (from light petroleum), τ ($CDCl_3$) 8·54 (s, Ac), 8·02 (s, Ac), 7·13 (s, NMe), 5·05 (d, CH_2), and 2·2—3·0 (aromatic protons) (Found: C, 73·2; H, 6·9; N, 9·5. $C_{18}H_{20}N_2O_2$ requires C, 73·0; H, 6·8; N, 9·5%), *m/e* 296 (M^+).

(ii) 3-Phenylquinazolin-4(3*H*)-one (0·3 g), lithium aluminium hydride (0·3 g), and dry ether (10 cm³) were heated under reflux for 8 h to yield the diamine (0·17 g, 59%), τ ($CDCl_3$) 7·32 (s, Me), 6·6br (s, exchangeable, NH), 5·98 (s, CH_2), 5·5br (s, exchangeable, NH), and 3·1—3·5 and 2·6—3·0 (aromatic protons) (Found: M^+ 212·131441. $C_{14}H_{16}N_2$ requires *M*, 212·131342).

3-*Ethylamino*-N-*phenylpyridine*-2-*carboxamide* (11).—2-Methyl-3-phenylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (1 g), sodium borohydride (0·65 g), and propan-2-ol (20 cm³) were stirred together at room temperature to yield the *anilide* (0·71 g, 72%), yellow prisms, m.p. 65—66° (from light petroleum), $\nu_{max.}$ ($CHCl_3$) 3340 (N–H), 1660 (C=O), and 1530—1500 cm^{-1} (amide II), τ ($CDCl_3$) 8·68 (t, *J* 7 Hz, Me), 6·82 (m, collapsing to q, *J* 7 Hz, when shaken with D_2O,CH_2), 2·2—3·1 (aromatic protons), and 1·6br (s, exchangeable, NH) (Found: C, 69·8; H, 6·2; N, 17·4. $C_{14}H_{15}N_3O$ requires C, 69·7; H, 6·2; N, 17·4%), *m/e* 241 (M^+).

2-*Anilinomethyl*-3-*ethylaminopyridine* (14).—(i) 2-Methyl-3-phenylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0·5 g), lithium aluminium hydride (0·4 g), and dry ether (10 cm³) were heated together under reflux for 8 h to yield the *pyridine* (0·32 g, 61%), yellow prisms, m.p. 55—56° [from light petroleum (b.p. 40—60°)].

(ii) 3,4-Dihydro-2-methyl-3-phenylpyrido[3,2-*d*]pyrimidine (0·22 g), lithium aluminium hydride (0·2 g), and dry ether (10 cm³) were heated together under reflux for 8 h to yield the pyridine (0·11 g, 49%), $\nu_{max.}$ ($CHCl_3$) 3400 cm^{-1} (N–H), τ ($CDCl_3$) 8·89 (t, *J* 7 Hz, Me), 7·02 (m, collapsing to q, *J* 7 Hz, when shaken with D_2O,$MeCH_2$), 5·8 (s, which sharpened when shaken with D_2O,CH_2·NH), 5·3br (s, exchangeable, NH), 2·65—3·5 (aromatic protons), and 2·13 (q, $J_{5,6}$ 4·5, $J_{4,5}$ 1·5 Hz, 6-H) (Found: C, 73·7; H, 7·3; N, 18·2. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%), *m/e* 227 (M^+).

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