# 529. *Quinazolines. Part II.*[1] 1,4- *and* 3,4-*Dihydroquinazoline.*

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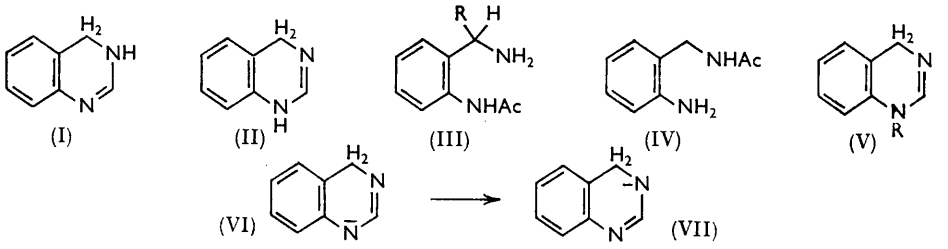
Syntheses of 1,4-dihydro-1-methyl and 1-benzyl-1,4-dihydro-quinazoline are described. Surprisingly, debenzylation of the latter gave 3,4-dihydro-quinazoline. The dihydro-compound obtained by catalytic reduction of 2-methylquinazoline has been shown to be 3,4-dihydro-2-methylquinazoline. It is identical with the supposedly isomeric bases prepared by Bischler and by Gabriel and Jansen.

Dihydroquinazoline, obtained by the catalytic reduction of quinazoline,[2] can be regarded as a cyclic formamidine which may be 3,4- (I) or 1,4-dihydroquinazoline (II). As with the dihydronaphthalenes,[3] the 3,4-dihydroquinazoline seems to be more stable to prototropic change than the 1,4-isomer because the dihydroquinazoline obtained by reducing quinazoline has now been shown by direct methylation to be mainly, or maybe entirely, the 3,4-isomer. In order to make a more direct comparison, the synthesis of 1,4-dihydroquinazoline was attempted.




Although 3,4-dihydroquinazolines have long been known [4] and Carrington reported the synthesis of some 1,2-dihydroquinazolines in 1955,[5] only two 1,4-dihydroquinazolines are claimed in the literature. These are 1,4-dihydro-2-methyl- and 2,4-dimethyl-quinazoline which Bischler [6] prepared by cyclisation of the acetyl derivatives (III; R = H or Me). The constitution of this " 1,4-dihydro-2-methylquinazoline " was assigned (incorrectly as will be shown *) on the grounds that it appeared to differ from the dihydro-2-methyl-quinazoline prepared by Gabriel and Jansen [7] by dehydration of the amide (IV). Gabriel and Jansen [8] proved that their substance was the 3,4-dihydro-derivative since on methylation it gave 3,4-dihydro-2,3-dimethylquinazoline identical with that prepared unambiguously. Ried and Stahlhofen [9] also obtained what they claimed to be 3,4-dihydro-2-methylquinazoline by catalytic reduction of " 2-methyl-6,7-benzo-3,1,4-oxadiazepine " (now known to be 2-methylquinazoline 3-oxide [10]) and, although this dihydro-compound agreed in many respects with that of Gabriel and Jansen, its picrate melted 17° higher.

These compounds were synthesised by us for comparison. For the Bischler synthesis *o*-acetamidobenzaldoxime was prepared more conveniently from *o*-nitrobenzaldehyde

* However, Beilstein's " Handbuch der Organischen Chemie " (1944, **23**, pp. 155, 169) misquotes Bischler's compounds as 3,4-dihydro-derivatives.

[1] Part I, preceding paper.
[2] Bogert and Marr, *J. Amer. Chem. Soc.*, 1935, **57**, 729; Higashino, *J. Pharm. Soc. Japan*, 1960, **80**, 245.
[3] Roth and von Auwers, *Annalen*, 1915, **407**, 145; Williams, *J. Amer. Chem. Soc.*, 1942, **64**, 1395.
[4] Paal and Busch, *Ber.*, 1889, **22**, 2683.
[5] Carrington, *J.*, 1955, 2527.
[6] Bischler, *Ber.*, 1893, **26**, 1891.
[7] Gabriel and Jansen, *Ber.*, 1890, **23**, 2807.
[8] Gabriel and Jansen, *Ber.*, 1891, **24**, 3091; Gabriel, *Ber.*, 1903, **36**, 800.
[9] Ried and Stahlhofen, *Chem. Ber.*, 1954, **87**, 1814.
[10] Sternbach, Kaiser, and Reeder, *J. Amer. Chem. Soc.*, 1960, **82**, 457.

diacetate which was converted into *o*-nitrobenzaldoxime and then reduced catalytically to the amine which was acetylated. The *o*-acetamidobenzaldoxime was reduced and cyclised as before.[6] In the Gabriel–Jansen synthesis [*o*-nitrobenzylamine ⟶ *o*-(acetamidomethyl)nitrobenzene ⟶ *o*-acetamidomethylaniline ⟶ 3,4-dihydro-2-methylquinazoline] the nitro-compound was reduced catalytically instead of with zinc and acid. The two dihydro-bases had the same b. p. and ultraviolet spectra and gave the same hydrochloride (with very similar $pK_a$ values) and the same picrate. Both picrates were dimorphic and the lower-melting (189—190°) was formed directly from the hydrochloride or free base and was converted after several recrystallisations into the more stable, higher-melting form (203—204°). This removes the only anomaly between the work of Gabriel and Jansen and that of Ried and Stahlhofen.

By comparison with quinazoline, 2-methylquinazoline should also be reduced to 3,4-dihydro-2-methylquinazoline. In the catalytic reductions we found that whereas quinazoline is hydrogenated to its dihydro-derivative with Adams platinum at atmospheric pressure, 2-methylquinazoline resisted reduction. This is probably due to poisoning of the platinum since 5% palladium–charcoal smoothly reduced 2-methylquinazoline to a dihydro-derivative, identical with that obtained by syntheses as above. The $R_F$ values of the three bases when run together in two different solvent systems were the same. These bases are thus all 3,4-dihydro-2-methylquinazoline. Further, the ultraviolet spectrum of the last sample resembles more closely that of 3,4-dihydroquinazoline (and 3,4-dihydro-3-methylquinazoline) than that of 1,4-dihydro-1-methylquinazoline (cf. ref. 1).

The second " 1,4-dihydro "-compound prepared by Bischler was undoubtedly 3,4-dihydro-2,4-dimethylquinazoline and thus no 1,4-dihydroquinazoline was known before the 1,4-dihydro-1-methylquinazoline [1] which will now be described. *N*-Methylanthranilic acid was converted, *via* the isatoic anhydride, into *o*-methylaminobenzamide [11] which was reduced with lithium aluminium hydride to *o*-methylaminobenzylamine and this, after formylation, was cyclised to the base (V; R = Me).

On the other hand, the base (V; R = $CH_2Ph$) resisted catalytic hydrogenolysis with 10% palladium charcoal (although debenzylation of tertiary benzylamine is easy [12]), and 25% hydrobromic acid in glacial acetic acid opened the heterocyclic ring to give 2-(*N*-benzylformamido)benzylamine; but debenzylation with sodium in liquid ammonia unexpectedly gave 3,4-dihydroquinazoline (in 70% yield). This reaction could be due to conversion of the anion (VI) into the anion (VII) followed by addition of a proton on $N_{(3)}$, or, addition of a proton on $N_{(1)}$ followed by a prototropic change. The latter mechanism is less likely in the circumstances, but whichever takes place the postulated higher stability of the 3,4-dihydro-isomer is confirmed.

## Experimental

*Paper Chromatography.*—The ascending technique was used with Whatman paper No. 1 and solvent system (A) (3% aqueous amonium chloride) or (B) (5N-acetic acid–butan-1-ol, 1 : 3). The radiation at 254 mμ from a mercury lamp with a " Chance Brothers " OX7/19874 filter was used to detect the fluorescent spots. Non-fluorescent spots were revealed by placing over the irradiated chromatogram a Perspex screen coated with a fine spray of cadmium borate suspended in chloroform. A pink background was obtained and the spots were deep blue. Ionisation constants were determined potentiometrically in water at 20°.[13]

*3,4-Dihydro-2-methylquinazoline.*—(a) *By catalytic reduction.* 2-Methylquinazoline (2·0 g.) in ethanol (50 ml.) and 5% palladium–charcoal (1·0 g.) was shaken with hydrogen at 713 mm. (absorption of 1 mol.). After filtration and evaporation the residue was distilled (b. p. 126—127°/0·9 mm.; 1·2 g., 60%); the distillate crystallised slowly. It had $\lambda_{max.}$ 220·5, 290 mμ (log ε 4·13, 3·82 in aqueous buffer of pH 12·3) and 211, 215, 276 mμ (log ε 4·30, 4·31, and 3·74

[11] Heilbron, Kitchen, Parkes, and Sutton, *J.*, 1925, **127**, 2171
[12] Hartung and Simonoff in " Organic Reactions," Wiley, New York, 1953, Vol. III, p. 277.
[13] Albert and Phillips, *J.*, 1956, 1294.

in aqueous buffer of pH 7·0) (Found: C, 73·4; H, 7·1. Calc. for $C_9H_{10}N_2$: C, 73·9; H, 6·9%), and $R_F$ in (A) 0·75 and in (B) 0·53. It gave a hydrochloride, needles (from ethanol), m. p. 286—290° (decomp.), p$K_a$ 10·17 ± 0·04 (M/200) (Found: C, 59·2; H, 5·9; N, 15·2; Cl, 19·4. Calc. for $C_9H_{10}N_2$,HCl: C, 59·2; H, 6·0; N, 15·3; Cl, 19·5%), and a picrate, m. p. 189—190°, needles from ethanol or water (Found: C, 48·1; H, 3·4; N, 18·8. Calc. for $C_{15}H_{13}N_5O_7$: C, 48·0; H, 3·5; N, 18·7%). The higher-melting picrate had m. p. 203—204° (rosettes from ethanol; lit.,[9] 204—205°) (Found: C, 47·8; H, 3·4; N, 18·6%).

o-*Nitrobenzaldoxime.*—*o*-Nitrobenzaldehyde diacetate [14] (40 g.) in ethanol (200 ml.) was refluxed in aqueous hydroxylamine hydrochloride (100 g. in 400 ml.) and 3N-sodium hydroxide (48 g.) for 1 hr. After cooling, the deposited oxime recrystallised from benzene (21·4 g., 82%); it had m. p. 100—102° (lit.,[15] for *anti*-isomer 102°) (Found: C, 50·7; H, 3·6; N, 16·6. Calc. for $C_7H_6N_2O_3$: C, 50·6; H, 3·6; N, 16·9%).

o-*Aminobenzaldoxime.*—The above oxime (20 g.) and Adams platinum oxide (320 mg.) in ethanol (220 ml.) was shaken with hydrogen at 713 mm. (absorption 3 mol.). Removal of the catalyst and solvent gave the base which, recrystallised from benzene–light petroleum (b. p. 40—60°), had m. p. 134—135° (lit.,[16] 134—135°) (14·8 g., 90%) (Found: C, 61·8; H, 5·95. Calc. for $C_7H_8N_2O$: C, 61·75; H, 5·9%).

o-*Formamidobenzaldehyde* O-*formyloxime.*—*o*-Aminobenzaldehyde oxime (177 mg.) in an excess of acetic formic anhydride [17] (1·0 ml.) was left at room temperature for 24 hr. Light petroleum (b. p. 40—60°) was added and the *diformyl derivative* filtered off and crystallised from benzene–light petroleum (b. p. 40—60°) (174 mg., 70%), having m. p. 140·5—141·5° (Found: C, 56·3; H, 4·3; N, 14·3. $C_9H_8N_2O_3$ requires C, 56·25; H, 4·2; N, 14·6%).

o-*Acetamidobenzaldoxime.*—*o*-Aminobenzaldehyde oxime (5·4 g., 1 mol.), suspended in dry benzene (50 ml.), was treated with acetic anhydride (4·2 ml., 1·1 mol.) and left at room temperature for 24 hr. Excess of anhydride and benzene was removed *in vacuo*. The residue, crystallised from ethanol, had m. p. 194—195° (lit.,[6] 194°) (5·4 g., 75%) (Found: C, 60·4; H, 5·8; N, 15·6. Calc. for $C_9H_{10}N_2O_2$: C, 60·7; H, 5·7; N, 15·7%).

3,4-*Dihydro*-2-*methylquinazoline.*—(b) *By Bischler's synthesis.* The preceding oxime was reduced with sodium amalgam to the benzylamine and cyclised with anhydrous zinc chloride to the dihydroquinazoline according to Bischler's method.[6] The benzylamine (2 g.) gave 1·06 g. (60%) of the dihydro-compound, b. p. 126°/0·8 mm., 113°/0·2 mm. (lit.,[6] 260—270°/1 atm.). The ultraviolet spectrum at pH 12·3 and 7·0 was identical with that given above and the $R_F$ in solvent (A) was 0·75 and in (B) 0·52. The base gave a hydrochloride, m. p. 285—290° (decomp.) (lit.,[6] no m. p.) with p$K_a$ 10·13 ± 0·05 (M/200) (Found: C, 59·3; H, 6·2; N, 15·2; Cl, 19·5%). The picrate had m. p. 189—190° (lit.,[6] 166—167°) (Found: C, 47·8; H, 3·4%), and under conditions described above it also gave a picrate, m. p. 204—205°.

(c) *Gabriel and Jansen's synthesis.* *o*-Acetamidomethylnitrobenzene (5·55 g.) with 10% palladium–charcoal (1·0 g.) in ethanol (100 ml.) was hydrogenated at 715 mm. The amino-compound, crystallised from benzene–light petroleum (b. p. 40—60°), had m. p. 112—113° (lit.,[4] 112·5—113·5°) (4·2 g., 90%). This base (1·75 g.) was dehydrated by heating at 240° under nitrogen for 6 hr., and the dihydro-compound (1·39 g., 90%) was obtained according to Gabriel and Jansen's method.[4] It had b. p. 112—113°/0·2—0·3 mm. (lit.,[4] 300°/1 atm.), $R_F$ in solvent (A) 0·74 and in (B) 0·53. The ultraviolet spectrum was as above. The hydrochloride had m. p. 288—290° (decomp.) (lit.,[4] 250°) and p$K_a$ 10·06 ± 0·05 (M/200) (Found: C, 59·2; H, 6·0; N, 15·3; Cl, 19·5%), and the picrate m. p. 189—190° (lit.,[4] 180—200°, 185—187°) (Found: C, 48·1; H, 3·4%). This picrate also was dimorphic.

1,4-*Dihydro*-1-*methylquinazoline.*—*o*-Methylaminobenzamide (10 g., 1 mol.) in a Soxhlet apparatus was extracted by boiling ether into a stirred suspension of lithium aluminium hydride (6·1 g., 2·4 mol.) in anhydrous ether (450 ml.) during 6 hr., and the solution was then stirred at room temperature for 12 hr. Excess of the reducing agent was decomposed by water followed by 2N-sodium hydroxide (170 ml.). The aqueous layer extracted with ether (2 × 150 ml.). The combined ethereal solutions were dried (KOH) and evaporated. The residue was triturated with ether and filtered from unchanged amide (2·1 g.). The filtrate was evaporated to dryness, and the residue left in acetic formic anhydride (15 ml.) at room temperature for 48 hr. Excess

[14] Tsang, Wood, and Johnson, *Org. Synth.*, 1944, **24**, 75.
[15] Brady and Dunn, *J.*, 1913, **103**, 1614.
[16] Bamberger and Demuth, *Ber.*, 1901, **34**, 1330.
[17] Béhal, *Compt. rend.*, 1889, **128**, 1460.

of anhydride was removed *in vacuo* and the residue distilled. The distillate in ethanol (20 ml.) was treated with an excess of picric acid solution, and the *picrate* (3·4 g., 17%) isolated (needles from ethanol; m. p. 176—177°) (Found: C, 48·0; H, 3·6; N, 18·6. $C_{15}H_{13}N_5O_7$ requires C, 48·0; H, 3·5; N, 18·7%). The picrate (3·2 g.) was decomposed with 2·5N-sodium hydroxide (150 ml.), and the base extracted with chloroform (3 × 25 ml.). The extract was dried ($Na_2SO_4$), the solvent removed *in vacuo*, and the residue distilled (b. p. 90—91°/2·5 mm.). The *methyl derivative* (1·1 g., 91%), a pale yellow, very hygroscopic liquid, was sampled in a dry box (Found: C, 71·7; H, 6·9; N, 18·7. $C_9H_{10}N_2,H_2O$ requires C, 71·7; H, 7·0; N, 18·6%).

N-*Benzylisatoic Anhydride*.—*N*-Benzylanthranilic acid [18] (34·1 g., 1 mol.) was refluxed with ethyl chloroformate (42·6 ml., 3 mol.) for 15 min. Acetyl chloride (11·5 ml., 1·1 mol.) was then added and the mixture boiled for a further 30 min. On cooling, N-*benzylisatoic anhydride* crystallised; it recrystallised from benzene–light petroleum (b. p. 40—60°) as needles (29·5 g., 78%), m. p. 140—141° (Found: C, 70·9; H, 4·4; N, 5·4. $C_{15}H_{11}NO_3$ requires C, 71·1; H, 4·4; N, 5·5%).

o-*Benzylaminobenzamide*.—The above anhydride (12·6 g.) and ammonia (400 ml.; *d* 0·91) were heated on a steam-bath for 3 hr. with occasional shaking. The *amide* was filtered off and recrystallised from methanol as needles (10·9 g., 96%), m. p. 171—172° (Found: C, 74·1; H, 6·2; N, 12·2. $C_{14}H_{14}N_2O$ requires C, 74·3; H, 6·2; N, 12·4%).

o-*Benzylaminobenzylamine*.—The amide (13·6 g., 1 mol.), in a Soxhlet apparatus, was extracted as above into a suspension of lithium aluminium hydride (10·5 g., 5 mol.) in anhydrous ether (600 ml.) during 10 hr. The mixture was then stirred at room temperature for 20 hr. and worked up as above with 2·5N-sodium hydroxide (375 ml.). The unchanged amide (1·1 g.) was filtered off and the product was passed in benzene through alumina (B.D.H.; 6″ × ¾″). Elution with benzene gave o-*benzylaminobenzylamine* (7·8 g., 61%), needles [from benzene–light petroleum (b. p. 40—60°)], m. p. 50—51°, sublimed at 40—50°/0·2 mm. (Found: C, 78·9; H, 7·7; N, 13·2. $C_{14}H_{16}N_2$ requires C, 79·2; H, 7·6; N, 13·2%).

1-*Benzyl*-1,4-*dihydroquinazoline*.—The preceding amine (3·5 g.) was refluxed in 98—100% formic acid (20 ml.) for ¾ hr. The excess of acid was removed *in vacuo* and the residue distilled (b. p. 160—180°/0·6 mm.). The solid distillate of 1-*benzyl*-1,4-*dihydroquinazoline* recrystallised from light petroleum (b. p. 60—80°) as needles (3·2 g., 87%), m. p. 101—102° (Found: C, 80·8; H, 6·3; N, 12·5. $C_{15}H_{14}N_2$ requires C, 81·05; H, 6·35; N, 12·6%). The *picrate*, m. p. 199—200°, crystallised from ethanol (Found: C, 55·65; H, 3·9; N, 15·7. $C_{21}H_{17}N_5O_7$ requires C, 55·9; H, 3·8; N, 15·5%).

This base (222 mg.) in glacial acetic acid (0·6 ml.) was left with a 50% w/v solution of hydrobromic acid in glacial acetic acid (0·6 ml.) at 20—25° for 2 hr. The product, 2-(N-*benzylformamido*)*benzylamine hydrobromide*, recrystallised from methanol as needles (253 mg., 79%), m. p. 224—225° (Found: Br, 25·0; N, 8·7. $C_{15}H_{16}N_2O,HBr$ requires Br, 24·9; N, 8·7%).

*Debenzylation of* 1-*Benzyl*-1,4-*dihydroquinazoline*.—The dihydro-base (1·11 g., 1 mol.), suspended in liquid ammonia (120 ml.), was treated with sodium (0·46 g., 4 atom-equiv.). After 15 min. the excess of sodium was removed by addition of ammonium chloride and the ammonia evaporated. The residue was extracted with dry benzene (100 ml.), and the solvent removed from the extract *in vacuo*. The residue was distilled (b. p. 134—136°/0·3—0·4 mm.; 446 mg., 69%), and had m. p. and mixed m. p. with 3,4-dihydroquinazoline 125—126° (m. p. and mixed m. p. of the picrates 219—220°) (Found: C, 72·7; H, 6·1; N, 20·9. Calc. for $C_8H_8N_2$: C, 72·7; H, 6·1; N, 21·2%), $pK_a$ 9·21 ± 0·03 (M/200), $\lambda_{max.}$ 221·5, 290 mμ (log ε 4·09, 3·76 in aqueous buffer of pH 12) (cf. ref. 1), and $R_F$ values identical with those of 3,4-dihydroquinazoline in solvents (A) or (B).

*Methylation of* 3,4-*Dihydroquinazoline*.—The base (1·32 g.) in methanol (10 ml.) was left with methyl iodide (0·62 ml., 1 equiv.) at room temperature. After 48 hr., paper chromatography showed that the reaction was apparently complete and the solid hydriodide had crystallised. The mixture was diluted with water and extracted with benzene. This extract consisted mainly of the starting material, together with a small amount of 3,4-dihydro-3-methylquinazoline as shown by paper chromatography. The aqueous layer was made alkaline and extracted with benzene. The extract was dried (KOH) and evaporated *in vacuo*. The residue solidified and was shown, chromatographically, to consist mainly of 3,4-dihydro-3-methylquinazoline and a trace of the starting material. No 1,4-dihydro-1-methylquinazoline

[18] van Alphen, *Rec. Trav. chim.*, 1942, **61**, 201.

was detected. The methylation product, purified from benzene–light petroleum (b. p. 40—60°), had m. p. 89—91° (lit.,[19] 90—91°) (0·72 g., 49%). Its picrate had m. p. 197—199° (lit.,[20] 197—199°).

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[19] Gabriel and Colman, *Ber.*, 1904, **37**, 3642.
[20] Osborn and Schofield, *J.*, 1956, 3977.