356. 4-*Phenylquinazoline.*

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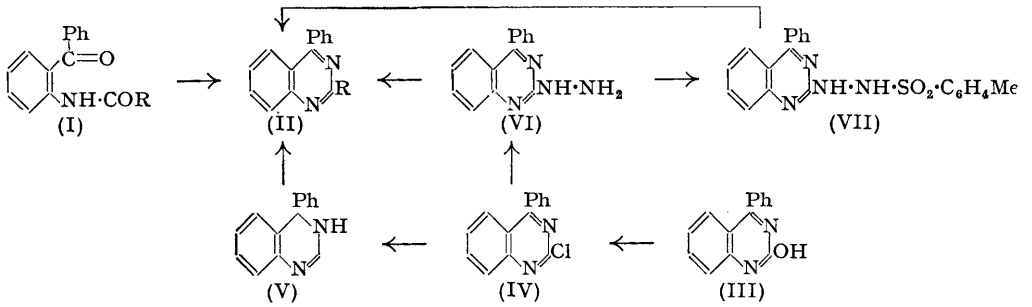
Four methods of preparing 4-phenylquinazoline are described. The most practicable one consists in the catalytic reduction of 2-chloro-4-phenylquinazoline to 3 : 4-dihydro-4-phenylquinazoline, followed by oxidation of the latter with alkaline potassium ferricyanide.

THE behaviour of phenyl-substituted heterocyclic compounds on nitration is of some theoretical interest (Schofield, *Quart. Reviews*, 1950, **4**, 382). 4-Phenylquinazoline has therefore been synthesised so that its nitration (to be reported later) can be studied.

By the cyclisation of *o*-acetamidobenzophenone (I; R = Me) with ammonia under pressure, Bischler and Barad (*Ber.*, 1892, **25**, 3080) obtained 2-methyl-4-phenylquinazoline (II; R = Me). Subsequent oxidation, and decarboxylation of the resulting acid, made possible the isolation of 4-phenylquinazolinium picrate, but the free base was not described. Clearly, it would be advantageous if the use of pressure equipment could be obviated, and encouraging experience with *o*-acylaminoacetophenones (Schofield, Swain, and Theobald, preceding paper) suggested that *o*-formamidobenzophenone (I; R = H) might be converted directly into 4-phenylquinazoline (II; R = H) by passage of ammonia through its solution in molten ammonium acetate. The result was disappointing, for although 4-phenylquinazoline was formed (< 20%) in this reaction, it was contaminated with *o*-aminobenzophenone, and purification was difficult. The difficulty of cyclisation as compared with derivatives of *o*-aminoacetophenone must be attributed to the lower carbonyl-group reactivity of the benzophenone, but the method might still be useful with acyl derivatives other than the formamido-compound.



Attention was next centred on 2-hydroxy-4-phenylquinazoline (III), originally prepared by Gabriel and Stelzner (*Ber.*, 1896, **29**, 1300) by heating *o*-aminobenzophenone and urea. Improvements in the preparation of this compound and of the derived 2-chloro-4-phenylquinazoline (IV) are described below. By reducing the chloro-compound with red phosphorus and hydriodic acid, Gabriel and Stelzner (*loc. cit.*) obtained 3 : 4-dihydro-4-phenylquinazoline (V). We have found this method to be less satisfactory on the large than on the small scale, and prefer the catalytic procedure detailed in the Experimental section (*cf.* Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405). Gabriel (*Ber.*, 1903, **36**, 800) oxidised 3 : 4-dihydroquinazoline to quinazoline by means of potassium ferricyanide in alkaline solution, and Elderfield *et al.* (*loc. cit.*) applied the method to *Bz*-substituted 3 : 4-dihydroquinazolines. The same reagent oxidised (V) to 4-phenylquinazoline in high yield. The sequence of reactions [III ⟶ IV ⟶ V ⟶ II (R = H)] is the preferred method of preparing 4-phenylquinazoline.

The catalytic reduction of 2-chloro-4-phenylquinazoline to 3 : 4-dihydro-4-phenylquinazoline under the conditions so far examined, whilst satisfactory, did not give such high yields as were obtained by Elderfield and his co-workers (*loc. cit.*) in certain cases, and two alternative routes were considered.

The 2-chloro-compound (IV) was readily converted in high yield into 4-phenyl-2-

quinazolylhydrazine (VI), and oxidation of this compound with copper sulphate (*cf.* Schofield and Swain, *J.*, 1950, 392) gave 4-phenylquinazoline, but in poor yield. 2-Chloro-4-phenylquinazoline did not react satisfactorily with toluene-*p*-sulphonhydrazide, but (VII) was easily prepared from (VI). Decomposition of (VII) in alkaline solution (*cf.* Dewar, *J.*, 1944, 619; Albert, Brown, and Duewell, *ibid.*, 1948, 1284; Clinton, *J. Amer. Chem. Soc.*, 1949, **71**, 755; Albert and Royer, *J.*, 1949, 1148) produced 4-phenylquinazoline, but the four-stage process [IV ⟶ VI ⟶ VII ⟶ II (R = H)] was not as efficient as that through 3 : 4-dihydro-4-phenylquinazoline.

4-Phenylquinazoline was characterised as its picrate (Bischler and Barad, *loc. cit.*), and 2-chloro-4-phenylquinazoline by conversion into 2-ethoxy-4-phenylquinazoline. The salts of 4-phenylquinazoline give characteristic yellow solutions with acids.

A single attempt to condense formamide with *o*-aminobenzophenone failed, not unexpectedly in view of Gabriel's experience (*loc. cit.*) with *o*-aminobenzaldehyde.

Experimental

M.p.s are uncorrected.

o-*Formamidobenzophenone.*—*o*-Aminobenzophenone (10 g.) and formic acid (80 c.c.; 95—100%) were refluxed for 1 hour and the excess of acid was then removed at reduced pressure. The residual oil (11·2 g.) slowly crystallised. o-*Formamidobenzophenone* formed white prisms, m. p. 54—55° (Found : C, 74·6; H, 5·1. $C_{14}H_{11}O_2N$ requires C, 74·6; H, 4·9%), when crystallised from ether–light petroleum (b. p. 40—60°).

2-*Hydroxy*-4-*phenylquinazoline.*—*o*-Aminobenzophenone (50 g.) and urea (25 g.) were heated at 190—200° with vigorous stirring in a vessel large enough to accommodate the considerable initial frothing. A crust slowly formed on the reaction mixture, and by the end of the experiment (*ca.* 1 hour) the whole had solidified. The product was thoroughly digested with alcohol (150 c.c.) and collected [50·8 g.; m. p. 250—252° (Gabriel and Stelzner, *loc. cit.*, give m. p. 250—251°)].

2-*Chloro*-4-*phenylquinazoline.*—The hydroxy-compound (20 g.) was refluxed with phosphorus oxychloride (80 c.c.) for ½ hour, and rather more than half of the latter was then removed by distillation. The remaining solution was poured on ice, and the mixture was carefully basified with sodium hydroxide (the yellow acid solution became colourless at neutrality) and extracted with ether. Removal of the solvent from the dry extract (Na_2SO_4) gave 2-chloro-4-phenylquinazoline (*ca.* 20 g.), m. p. 114—115° (Gabriel and Stelzner, *loc. cit.*, give m. p. 113°).

2-*Ethoxy*-4-*phenylquinazoline.*—The chloro-compound (0·5 g.) was refluxed with a solution of sodium (0·2 g.) in ethanol (10 c.c.) for 2 hours. The mixture was then poured into water, and the product (0·48 g.; m. p. 105—107°) was collected. 2-*Ethoxy*-4-*phenylquinazoline* formed crisp, pale yellow tablets, m. p. 106—107° (Found : C, 77·0; H, 6·0. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%), from light petroleum (b. p. 40—60°).

4-*Phenyl*-2-*quinazolylhydrazine.*—2-Chloro-4-phenylquinazoline (3 g.), hydrazine (3 g.; 90%), and ethanol (100 c.c.) were refluxed for 7 hours. After the mixture had cooled the precipitate was collected and washed with a little water, giving 2·8 g. of product, m. p. 154—156°. 4-*Phenyl*-2-*quinazolylhydrazine* formed yellow needles (evidently slightly impure), m. p. 155—156° (Found : C, 72·2; H, 5·2. $C_{14}H_{12}N_4$ requires C, 71·1; H, 5·1%), when crystallised from alcohol.

The hydrazine (2·5 g.), dissolved in warm pyridine (75 c.c.), was treated with toluene-*p*-sulphonyl chloride (2·25 g.), and the solution was set aside at room temperature for 12 hours and then heated at 95° for ½ hour. The product, obtained by dilution with water, gave a fawn solid (2·5 g.), m. p. 202—203° (decomp.), when digested with hot alcohol. The *toluene*-p-*sulphonyl* derivative formed glistening fawn crystals, m. p. 203—205° (decomp.) (Found : C, 64·6; H, 4·9. $C_{21}H_{18}O_2N_4S$ requires C, 64·6; H, 4·6%), on crystallisation from alcohol.

3 : 4-*Dihydro*-4-*phenylquinazoline.*—(i) 2-Chloro-4-phenylquinazoline (1 g.), red phosphorus (1 g.), and hydriodic acid (8 c.c.; *d* 1·7) were refluxed for 2½ hours. When cool, the mixture was basified with ammonia and extracted with ether. Removal of the solvent from the dried extract (Na_2CO_3) gave an oil which soon crystallised to a white solid (0·27 g., 62%), m. p. 165—167°, after one crystallisation from ethyl acetate (Gabriel and Stelzner, *loc. cit.*, give m. p. 165—166°). The stated yield was regularly obtained in small-scale experiments, but could not be reproduced on the large scale (*e.g.* a similar experiment with 20 g. of the chloro-compound gave only 6·7 g. of product).

(ii) The chloro-compound (8 g.) was dissolved in warm methanol (400 c.c.) and the solution

was shaken with palladium–calcium carbonate (24 g.; Busch and Stöve, *Ber.*, 1916, **49**, 1063) and hydrogen. Reduction was complete in 1·5—1·75 hours. (During the reaction the solution became yellow, but towards the end it became grey—colour changes presumably attending the formation and reduction of 4-phenylquinazoline.) After removal of the catalyst and evaporation of the methanol the oily residue was shaken with sodium hydroxide solution and ethyl acetate. On concentration, the dried (Na_2SO_4) ethyl acetate extract deposited 3 : 4-dihydro-4-phenylquinazoline (4·8 g.), m. p. 161—164°.

4-Phenylquinazoline.—(i) Preliminary experiments showed that acetamide and *o*-aminobenzophenone were contaminants of the 4-phenylquinazoline obtained by cyclisation of *o*-formamidobenzophenone. The latter (5·1 g.) and previously fused ammonium acetate (50 g.) were maintained at 175—180° for 8 hours during the passage of a vigorous stream of ammonia. During this time the initial suspension became clear. The product was cooled, diluted with water, and extracted with ether. The ethereal solution was washed with sodium hydroxide solution, then with water, and finally itself extracted with hydrochloric acid. The yellow acid solution was basified with sodium hydroxide and re-extracted with ether. The dried (Na_2SO_4) ethereal solution was concentrated to a small volume and treated whilst hot with light petroleum (b. p. 40—60°) until a permanent turbidity resulted. When the solution cooled, a yellow solid formed (3·2 g.; m. p. 70—80°) which gave a positive diazotisation test. This material (0·5 g.) was dissolved in hydrochloric acid (4 c.c. of concentrated acid and 6 c.c. of water), and the mixture was washed with ether and then diazotised at 0° with aqueous sodium nitrite (0·35 g. in 3 c.c. of water). After being heated for 1 hour at 95° and then washed with ether, the solution was basified and extracted with the latter solvent. Removal of the ether after drying (Na_2CO_3) gave a white solid (0·23 g.; m. p. 92—93°). Recrystallisation (charcoal) from light petroleum (b. p. 40—60°) gave a white crystalline product, m. p. 97—99°, identical with that described in (ii).

(ii) 3 : 4-Dihydro-4-phenylquinazoline (5 g.) was dissolved by warming it in a mixture of water and dioxan (100 c.c. of each). Potassium hydroxide solution (11 g. in 32·5 c.c. of water) was added and the mixture was heated on the steam-bath during the quick addition of a solution of potassium ferricyanide (16·5 g.) in water (132 c.c.). Heating, with occasional shaking, was continued for 5 minutes, and the turbid mixture was then diluted with water, basified with sodium hydroxide solution, and extracted with ether. Removal of the solvents, finally at reduced pressure, from the dried (Na_2SO_4) extract gave a fairly pure product (4·8 g.), m. p. 97—99°. *4-Phenylquinazoline* formed pearly, glistening leaflets, m. p. 99—100° (Found : C, 77·0; H, 6·0. $C_{14}H_{10}N_2$ requires C, 76·8; H, 5·6%), when crystallised from light petroleum (b. p. 40—60°) containing a trace of ether.

The picrate was formed in alcohol solution. From this solvent it gave soft felted yellow needles, m. p. 176—178° (with some preliminary sublimation) (Found : C, 55·2; H, 3·3. Calc. for $C_{14}H_{10}N_2,C_6H_3O_7N_3$: C, 55·2; H, 3·0%). Bischler and Barad (*loc. cit.*) give m. p. 178°.

(iii) 4-Phenyl-2-quinazolylhydrazine (0·2 g.) was heated at 95° with water (2 c.c.), and the mixture treated during 5 minutes with copper sulphate (0·27 g. in 2·7 c.c. of water). After being heated for 15 minutes more the mixture was basified with sodium hydroxide solution and extracted with ether. Removal of the solvent after drying (Na_2SO_4) gave 4-phenylquinazoline (35 mg.), m. p. 97—98°, identical with a specimen from (ii).

(iv) The toluene-*p*-sulphonyl derivative (0·4 g.) described above was added to a warm solution containing dioxan (10 c.c.), water (40 c.c.), and anhydrous sodium carbonate (4 g.). On boiling, the solution became deep red, effervescence occurred, and finally the whole became brown. Boiling was continued for 20 minutes and the mixture was then diluted with water and extracted with ether. Removal of the solvent from the dry (Na_2SO_4) extract, finally under reduced pressure, gave a sticky solid (0·16 g.), which on recrystallisation (charcoal) from ether–light petroleum (b. p. 40—60°) provided 4-phenylquinazoline (0·14 g.), m. p. 95—97° alone and when mixed with an authentic specimen.

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