82. *Reactions of Substituted 3 : 4-Dihydro-4-oxoquinazolines with Grignard Reagents.*

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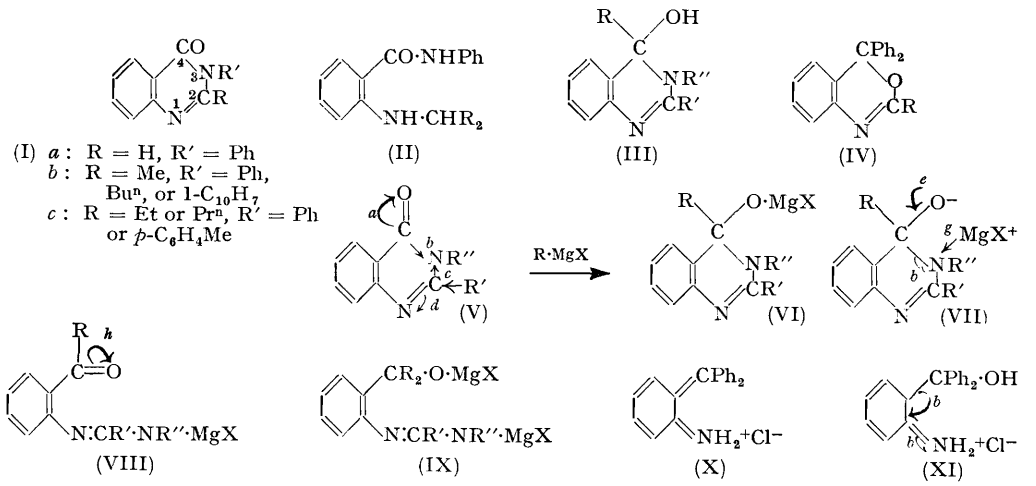
Condensation of 3-aryl-3 : 4-dihydro-4-oxoquinazolines with Grignard reagents yields *N*-substituted anthranilamides, but the 2-ethyl or 2-*n*-propyl derivatives give benzoxazine derivatives and the arylamine.

Koelsch [1] reported that 3 : 4-dihydro-4-oxo-3-phenylquinazoline (I*a*) and benzylmagnesium chloride yield *N*-α-benzylphenethylanthranilanilide (II; R = CH_2Ph) and explained its formation by postulating that an electrophilic centre is possible only at position 2 in (I*a*). Sen *et al.*[2] reported the formation of 2 : 3 : 4-trisubstituted 3 : 4-dihydro-4-hydroxyquinazolines (III) by the reaction of the quinazoline derivatives (I*b*) with alkyl- or aryl-magnesium halides and postulated a normal Grignard reaction at the carbonyl group with exclusion of an electrophilic centre at position 2 when it bore a methyl substituent. In our experiments, phenylmagnesium bromide and the compound (I*a*) yielded *N*-(diphenylmethyl)anthranilanilide (II; R = Ph). With its 2-methyl derivative most of the starting material was recovered, but there was obtained a small quantity of a product which was not an anthranilamide or a benzoxazine. Re-examination of the product described by Sen *et al.* as 4-hydroxy-2-methyl-3 : 4-diphenylquinazoline (III; R = R″ = Ph) showed it to be only the hydrochloride of the starting quinazoline. Phenylmagnesium bromide reacted with the 3-aryl-2-ethyl or 3-aryl-2-*n*-propyl derivatives (I*c*) to yield the 4 : 4-diphenyl-



3 : 1 : 4-benzoxazines (IV; R = Et or Pr^n) and aniline or *p*-toluidine. After reaction of these quinazolines and alkylmagnesium halides, most of the starting material was recovered, with a little aniline or *p*-toluidine.

Hydrolysis of the anthranilamide (II; R = Ph) with sodium hydroxide in ethylene glycol yielded aniline and *N*-(diphenylmethyl)anthranilic acid. The latter was synthesised by treating anthranilic acid with diphenylmethyl chloride in pyridine and conversion of the product into its anilide.

Alcoholic alkali converted the benzoxazines (IV; R = Et or Pr^n) into *o*-aminophenyldiphenylmethanol (prepared also by Baeyer and Villiger's method [3]); hot hydrochloric acid yielded, in addition, benzophenone and aniline. Treating the first of these products with propionic and butyric anhydride gave the benzoxazines (IV; R = Et or Pr^n),

[1] Koelsch, *J. Amer. Chem. Soc.*, 1945, **67**, 1718.
[2] Sen *et al.*, *J. Indian Chem. Soc.*, 1948, **25**, 437; 1950, **27**, 40.
[3] Baeyer and Villiger, *Ber.*, 1904, **37**, 3192.

whether or not fused sodium acetate was also added. However, we confirmed Baeyer and Villiger's finding [3] that acetylation in absence of fused sodium acetate leads to *o*-acetamidophenyldiphenylmethanol, while presence of fused sodium acetate leads to the 3 : 1 : 4-benzoxazine derivative (IV; R = Me). Treatment of this with hydrochloric or acetic acid opens the ring (cf. Baeyer and Villiger [3]). When R is ethyl or *n*-propyl, the 2-acylaminophenyldiphenylmethanol produced rapidly cyclises again to the benzoxazine.

Thus the reaction of these substituted quinazolines with Grignard reagents depends on the nature of the 2-substituent. When there is no 2-substituent an electrophilic centre develops there and not at position 4, and the reaction proceeds as described by Koelsch.[1] With a 2-ethyl or 2-*n*-propyl substituent the predominant electrophilic centre is at position 4, and leads to formation of a 3 : 1 : 4-benzoxazine derivative and an aromatic amine. This may be explained as follows.

Polarisations *a* and *b* (cf. V) create a strong electrophilic centre at position 4, but polarisation *d*, helped by process *c*, tends to produce electron-deficiency at position 2, which is counteracted by the electron-feeding property of the entrant group R′ (Et or Pr^n). Hence the normal 1 : 2-addition of R^-MgX^+ takes place at the carbonyl group, giving rise to the compound (VI). MgX^+ is then split off from this, yielding structure (VII), wherein processes *e*, *f*, and *g* assist to form (VIII) which is a more stable form. Addition of a second molecule of R·MgX across the carbonyl group (assisted by process *h*) gives the material (IX), which in turn yields the benzoxazine (IV) with the elimination of $R''{\cdot}N(MgX)_2$.

The benzophenone and aniline obtained in small amount on acid hydrolysis of the benzoxazines (IV) are also obtained on prolonged treatment of the primary products, *o*-aminophenyldiphenylmethanols, with acid (cf. Baeyer and Villiger [3]). They doubtless arise by way of the compounds (X) and (XI).

[Added, 9.9.55.] Since this paper was submitted, the formation of a benzoxazine from 3 : 4-dihydro-4-oxo-2 : 3-diphenylquinazoline and phenylmagnesium bromide has been reported.[4]

Experimental

2 : 3-Dihydro-4-oxo-3-phenylquinazoline was prepared according to Koelsch's method.[1] The other quinazolines were prepared by the method of Grimmel, Guenther, and Morgan.[5]

Reaction of Phenylmagnesium Bromide with 3 : 4-Dihydro-4-oxo-3-phenylquinazoline.—Phenylmagnesium bromide (from 9·42 g. of bromobenzene and 1·44 g. of magnesium) and the quinazoline (4·4 g.) in dry toluene (100 ml.), caused to react as described by Koelsch,[1] yielded *N*-(diphenylmethyl)anthranilanilide (7 g.), which after recrystallisation from alcohol–benzene, had m. p. and mixed m. p. 174—176° (Found: C, 82·4; H, 5·9; N, 7·4. Calc. for $C_{26}H_{22}ON_2$: C, 82·5; H, 5·9; N, 7·4%).

Heating this anilide (1 g.) with 10% aqueous sodium hydroxide (10 ml.) for 12 hr. on a water-bath did not result in hydrolysis. However, heating it (2 g.) with sodium hydroxide (2 g.) in ethylene glycol (20 ml.) for 1 hr. and then steam-distillation yielded aniline (acetyl derivative, m. p. 114—115°), The residue was acidified and extracted with ether; and the extract yielded *N*-(diphenylmethyl)anthranilic acid, m. p. and mixed m. p. 192—194° (from alcohol) (purple fluorescence).

N-(*Diphenylmethyl*)*anthranilic Acid.*—Anthranilic acid (6·8 g.), diphenylmethyl chloride (10·1 g.), and pyridine (1 ml.) were heated on a steam-bath for 15 min., then triturated with dilute hydrochloric acid, and the separated solid was collected, dissolved in dilute sodium hydroxide solution, and reprecipitated with hydrochloric acid. Recrystallisation from alcohol (purple fluorescence) yielded the pale yellow substituted *acid* (10 g., 66%), m. p. 192—194° (Found: C, 79·0; H, 5·6; N, 4·5. $C_{20}H_{17}O_2N$ requires C, 79·2; H, 5·7; N, 4·6%).

With thionyl chloride, followed by aniline, this gives the pale yellow *anilide* (from alcohol–benzene), m. p. 174—176° (Found: C, 82·1; H, 6·1; N, 7·1%).

Reaction of Phenylmagnesium Bromide with 2-Ethyl-3 : 4-dihydro-4-oxo-3-phenylquinazoline.—To a well-stirred solution of phenylmagnesium bromide (from bromobenzene, 31·4 g., and magnesium, 4·8 g.) in ether (150 ml.), cooled in ice–salt, was added dropwise a solution of the quinazoline (25 g.) in benzene (100 ml.). The mixture was then refluxed for 6 hr. and poured on

[4] Mustafa, Asker, Kamel, Shalaby, and Hassan, *J. Amer. Chem. Soc.*, 1955, **77**, 1612.
[5] Grimmel, Guenther, and Morgan, *ibid.*, 1946, **68**, 542; cf. Zaheer and Kacker, *J. Indian Chem. Soc.*, 1951, **28**, 344.

crushed ice; ammonium chloride was added. The solvent layer was dried (Na_2SO_4) and the solvents were removed. From the dark red viscous residue, by the addition of a little alcohol and prolonged cooling, a solid (13·5 g.) was obtained, which on recrystallisation from alcohol–benzene, gave colourless crystals (B), m. p. 154—155°. The mother-liquors slowly gave a further 2·6 g. By extracting the combined mother-liquors with dilute hydrochloric acid, aniline (5·6 g.) was isolated. The solvent layers, after acid-extraction, yielded small quantities of the starting quinazoline and of diphenyl.

In an alternative method of working up, the solvent layer, after decomposition of the complex, was steam-distilled, and from the viscous residue, by working up with a little alcohol, the compound B (25 g.) was isolated. Recrystallised as before, this melted at 154—155°. From the steam-distillate, aniline (6·5 g.) was obtained. The benzoxazine (B) yielded a picrate, m. p. 186—187°, a picrolonate, m. p. 177—178° (decomp.), and did not depress the m. p. of 2-ethyl-4 : 4-diphenyl-3 : 1 : 4-benzoxazine (Found : C, 84·4; H, 6·2; N, 4·7%; *M*, 315. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%; *M*, 313·4).

Reaction of Phenylmagnesium Bromide with 2-*Ethyl*-3 : 4-*dihydro*-4-*oxo*-3-p-*tolylquinazoline.*—This reaction, carried out as in the previous experiment (quinazoline, 26·4 g., in dry benzene, 150 ml.), yielded the crystalline oxazine (26 g.) obtained in the previous experiment. *p*-Toluidine (6·8 g.) (acetyl derivative, m. p. 146°) was also obtained.

Reaction of Phenylmagnesium Bromide with 3 : 4-*Dihydro*-4-*oxo*-3-*phenyl*-2-n-*propylquinazoline.*—Bromobenzene (6·28 g.), magnesium (0·96 g.), and this quinazoline (5·28 g.), in benzene (80 ml.) gave aniline and 4 : 4-diphenyl-2-*n*-propyl-3 : 1 : 4-benzoxazine (3 g.), m. p. and mixed m. p. 156—157° (from alcohol) (Found : C, 84·3; H, 6·5; N, 4·2%; *M*, 327. $C_{23}H_{21}ON$ requires C, 84·4; H, 6·5; N, 4·3%; *M*, 327·4).

3 : 4-Dihydro-4-oxo-2-*n*-propyl-3-*p*-tolylquinazoline (5·5 g.) gave *p*-toluidine and the same benzoxazine (2·5 g.).

Hydrolysis of the Benzoxazines.—(*a*) A suspension of either of the preceding benzoxazines (2 g.) in 10% alcoholic potassium hydroxide (100 ml.) was refluxed on a steam-bath for 16 hr. The mixture was then treated with water (200 ml.), acidified, and cooled. Unchanged starting material (1·2 g.) separated. The filtrate, made alkaline with sodium carbonate, yielded *o*-aminophenyldiphenylmethanol (0·2 g.), m. p. and mixed m. p. 120—121° (from alcohol).

(*b*) Either benzoxazine (10 g.) was heated with 15% hydrochloric acid (150 ml.) for 4—5 hr. in an oil-bath (120—130°); almost all the solid dissolved. Water (250 ml.) was added, and the mixture cooled and extracted with ether. The ether extract, washed successively with water, dilute sodium carbonate solution, and water, was dried (Na_2SO_4), and evaporated. The residue on distillation yielded benzophenone (4·1 g.), b. p. 185—190°/15 mm. (2 : 4-dinitrophenylhydrazone, m. p. 235—236°; oxime, m. p. 142—143°). The acid layer was made alkaline and steam-distilled, yielding a small quantity of aniline. The residue was extracted with ether, most of the ether removed from the extract, and hydrogen chloride passed through the residue, yielding a solid (2 g.) which on trituration with cold dilute aqueous ammonia and recrystallisation from alcohol had m. p. and mixed m. p. with *o*-aminophenyldiphenylmethanol, 121—122° (Found : C, 82·8; H, 6·4; N, 5·1. Calc. for $C_{19}H_{17}ON$: C, 82·9; H, 6·2; N, 5·1%). Its acetyl derivative had m. p. and mixed m. p. 196—197°.

Hydrolysis of o-*Aminophenyldiphenylmethanol.*—(*a*) The alcohol (1 g.) was heated with 10% alcoholic potassium hydroxide (15 ml.) for 6 hr., then diluted, acidified with hydrochloric acid, and extracted with ether. From the extract, on removal of the ether, a few drops of a brown liquid were obtained, which did not give the usual test for a keto-group. The residue from the ether-extraction was made alkaline with ammonia; the unchanged alcohol (0·8 g.) was recovered.

(*b*) After hydrolysis of 1 g. with 15% hydrochloric acid (12 ml.) as described for the benzoxazines most of the starting material was recovered, but small quantities of aniline and benzophenone were identified.

2-*Ethyl*-4 : 4-*diphenyl*-3 : 1 : 4-*benzoxazine.*—*o*-Aminophenyldiphenylmethanol (0·5 g.), propionic anhydride (3 ml.), and fused sodium acetate (0·5 g.) were heated together for 30 min. on a steam-bath. Working up as usual gave the *benzoxazine* (0·3 g.), m. p. 144—145° (from alcohol–benzene) (also obtained if the sodium acetate was omitted) (Found : C, 84·2; H, 6·0; N, 4·5. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%).

4 : 4-*Diphenyl*-2-n-*propyl*-3 : 1 : 4-*benzoxazine.*—*o*-Aminophenyldiphenylmethanol (0·5 g.) and *n*-butyric anhydride (3 ml.), with or without fused sodium acetate, treated as above, yielded 0·2 g. of this *benzoxazine*, m. p. 156—157° (from alcohol) (Found : C, 84·4; H, 6·2; N, 4·3. $C_{23}H_{21}ON$ requires C, 84·4; H, 6·5; N, 4·5%).

*Attempted Preparation of Diphenyl-*o*-propionamidophenylmethanol.*—(*a*) Hydrogenchloride was passed through a cooled solution of 2-ethyl-4 : 4-diphenylbenzoxazine (2 g.) in ether–benzene (20 ml.), a solid separating. This, on filtration and washing with ether, had m. p. 185—189° (decomp.). On recrystallising from alcohol, the m. p. was lowered and after three recrystallisations the benzoxazine was regenerated (m. p. 154—155°).

(*b*) A solution of the benzoxazine (1 g.) in glacial acetic acid (8 ml.) was heated on a steam-bath for 1 hr. It was then poured on crushed ice, and the separated solid filtered off. This melted at 190—195° (decomp.) but behaved similarly to the product obtained as in (*a*).

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