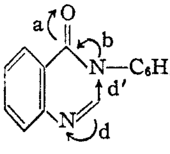
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

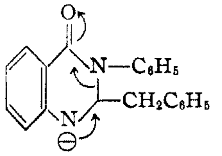
The Reaction of Benzylmagnesium Chloride with 3-Phenylquinazolone-4

BY C. F. KOELSCH

It is shown in the present paper that benzylmagnesium chloride reacts with 3-phenylquinazolone-4 (I) forming IV. This reaction is remarkable if it is compared with the ones that occur when acetanthranil (V)[1] or 1,2-dimethylquinazolone-4 (VI)[2] are treated with Grignard reagents for, in each of the latter cases, addition to a carbonyl group takes place. It is felt, however, that the apparently anomalous behavior of I can be explained in the following way.



I



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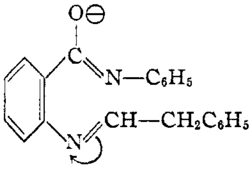

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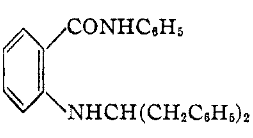
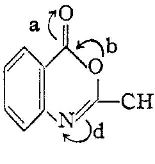
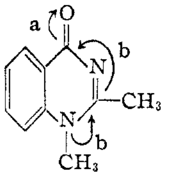


IV



V



VI

In I, polarization a is followed by b. Process d, assisted by induction d', is thus the only way in which an electrophilic center can be developed in the molecule, and attack by R^- takes place at C_2. The resulting primary addition product (II) has a more stable form (III), and the aldimine group of this latter form adds a second molecule of Grignard reagent, yielding the magnesium derivative of IV.

In V, polarization a may be followed by b, as in the case of I, yet because of the comparative difficulty of forming O^+ (*e. g.*, the cations from ketones and ketimines are largely $R_2C^+—OH$ and $R_2C=N^+H_2$, respectively), C_4 retains electrophilic properties greater than those imparted to C_2 by process d.

In VI, polarization a may be followed by b, yet because b confers only cationoid and not electrophilic properties on N_1, no electrophilic center other than the one at C_4 can be developed.

Experimental

3-Phenylquinazolone-4 was obtained[3] in yields averaging 40% by heating 125 g. of anthranilic acid with 110 g. of formanilide for ten hours in an oil-bath at 125–130°. A colorless product, b. p. 229° at 12 mm., m. p. 136° (reported m. p. 139°) was obtained by distilling the once recrystallized material.

3-*p*-Chlorophenylquinazolone-4, b. p. *ca.* 260° at 15 mm., m. p. 183–184° (reported,[4] m. p. 177°) was obtained similarly in a yield of 45%.

N-(β,β'-Diphenylisopropyl)-anthranilanilide (IV).—The use of equimolecular amounts of phenylquinazolone and benzylmagnesium chloride gave a 50% yield of IV, and much phenylquinazolone was recovered. But when 20 g. of phenylquinazolone in warm toluene was added to two to three equivalents of the Grignard reagent in ether, a clear green solution resulted, and decomposition of this with iced hydrochloric acid and removal of the organic solvents with steam gave 34.5 g. (94%) of crude IV. The compound separated from benzene–ligroin or from alcohol in the form of colorless solvated crystals that melted at about 100° with gas evolution, resolidified, and then remelted at about 115°. Dried at 80° under reduced pressure, the compound melted at 119°. Its solutions showed a weak blue-violet fluorescence.

Anal. Calcd. for $C_{28}H_{26}N_2O$: C, 82.8; H, 6.4. Found: C, 82.9; H, 6.0.

N-(β,β'-Diphenylisopropyl)-anthranil-*p*-chloroanilide, obtained similarly from 3-*p*-chlorophenylquinazolone-4 and benzylmagnesium chloride, showed no tendency to separate in a solvated condition. From alcohol it formed colorless strongly electrified needles, m. p. 128–129°.

Anal. Calcd. for $C_{28}H_{25}ClN_2O$: C, 76.2; H, 5.7 Found: C, 76.0; H, 5.5.

Recognition of the course of the Grignard reaction was made difficult by the peculiar properties of IV. It did not form salts with aqueous acids, it was not changed by acetic anhydride in the presence of pyridine or potassium acetate, and it was not affected when it was boiled for four hours with alcoholic potash or with sulfuric acid in acetic acid and water. Also, under the conditions first used it formed an abnormal nitroso derivative.

Ultimately, however, it was found that the Grignard product was much more soluble in acetic acid containing sulfuric acid than it was in acetic acid alone, and that it yielded an acyl derivative with ethyl chloroformate. Under the proper conditions it could be converted into a nitrosamine, recognizable as that of a secondary aromatic amine, and when it was subjected to sufficiently severe treatment, it was susceptible to either acidic or basic hydrolysis. The products isolated from acidic hydrolysis were aniline and N-(β,β'-diphenylisopropyl)-aniline (anthranilic acid loses carbon dioxide when it is heated), identified by degradation and by synthesis. The products isolated from the basic hydrolysis (of the

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(1) Lothrop and Goodwin, THIS JOURNAL, **65**, 363 (1943).

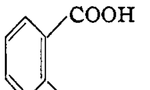
(2) Hamer, Heilbron, Reade and Walls, *J. Chem. Soc.*, 251 (1932).

(3) *Cf.*, Kulisch, *Chem. Zentr.*, **70**, I, 847 (1899); Meyer and Wagner, *J. Org. Chem.*, **8**, 247 (1943).

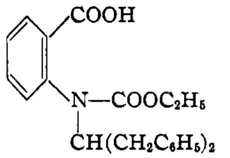
(4) Paal and Krückeberg, *J. prakt. Chem.*, **48**, 547 (1893).

chloro derivative of IV) were *p*-chloroaniline and N-(β,β′-diphenylisopropyl)-anthranilic acid (VII).

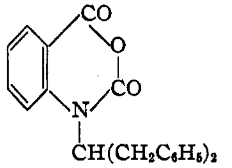
The latter substance was of particular importance in the structure proof of IV. When it was heated, it yielded carbon dioxide and N-(β,β′-diphenylisopropyl)-aniline. It reacted with ethyl chloroformate giving the isatoic ester VIII, this with acetyl chloride gave the isatoic anhydride IX, and finally the latter compound reacted with aniline to form carbon dioxide and IV.



VII



VIII



IX

Acylation of IV.—A solution of 0.5 g. of II in 5 ml. of ethyl chloroformate was boiled for eight hours, and excess reagent was then removed under reduced pressure. The resulting **ethyl N-(β,β′-diphenylisopropyl)-isatanilate** formed flat needles (0.42 g.) from alcohol, that melted at 125–128°, resolidified on keeping at 130° and melted again at 146–147°.

Anal. Calcd. for $C_{31}H_{30}N_2O_3$: C, 77.8; H, 6.3. Found: C, 77.8; H, 6.7.

Abnormal Nitrosation of IV.—A mixture of 0.5 g. of IV, 5 ml. of acetic acid, and 0.3 ml. of sulfuric acid was treated at 10° with 0.2 g. of sodium nitrite in a little water, and then allowed to stand for fifteen minutes at 25°. Ether and water were added, the ether solution was washed with dilute sodium carbonate, and the ether was then removed. Crystallization from alcohol gave 0.25 g. of the **abnormal nitroso derivative**,[5] pale yellow needles that darkened at 141° and melted with gas evolution at 143–144°. The compound gave a positive Liebermann test.

Anal. Calcd. for $C_{28}H_{24}N_4O_3$: C, 72.4; H, 5.2; N, 12.0. Found: C, 71.9; H, 5.2; N, 11.6.

When 2.6 g. of the abnormal nitroso derivative was dissolved in 60 ml. of hot alcohol, treated with 10 ml. of 10 *N* alcoholic hydrogen chloride, and boiled for three minutes, the solution deposited 2.4 g. of yellow crystals. Recrystallized from acetic acid, the substance formed long yellow needles (1.9 g.) that melted at 176–178° without decomposition. A Liebermann test was negative.

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.2; H, 5.8; N, 9.6. Found: C, 76.8; H, 5.8; N, 9.1.

Normal Nitrosation of IV.—A solution of 4 g. of IV in 25 ml. of alcohol containing 1.8 g. of hydrogen chloride was cooled to 0°, treated with 2.5 g. of butyl nitrite, and allowed to stand at 0° for ten hours. The colorless precipitate (3.4 g.) was removed, washed with alcohol and with water, and crystallized from alcohol. The resulting **N-nitroso-N$_1$-(β,β′-diphenylisopropyl)-anthranilanilide** formed colorless prisms that darkened and melted at 135–136°, evolving gas at a slightly higher temperature. A Liebermann test was positive.

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.2; H, 5.8. Found: C, 77.4; H, 5.9.

The N-nitroso compound (2.5 g.) was dissolved in 10 ml. of warm acetic acid and treated with 1 ml. of sulfuric acid in 1 ml. of acetic acid. After thirty minutes, ether and water were added, and the ether solution was washed with dilute sodium carbonate. Removal of the ether and crystallization of the residue from alcohol gave 1.9 g. of **5-nitroso-N-(β,β′-diphenylisopropyl)-anthranilanilide**, brilliant green needles, m. p. 159–160°. The same compound was obtained in a yield of 40% directly from IV with butyl nitrite in acetic acid–sulfuric acid.

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.2; H, 5.8. Found: C, 77.1; H, 5.7.

The 5-nitroso compound (1.25 g.) in 25 ml. of alcohol containing 1 ml. of hydrochloric acid and 0.1 g. of platinum oxide was shaken with hydrogen at 1 atmosphere. Absorption of the gas stopped after forty-five minutes, when slightly more than two equivalents had been taken up. Crystallization of the product from alcohol gave 1.3 g. of **5-amino-N$_2$-(β,β′-diphenylisopropyl)-anthranilanilide monohydrochloride**, colorless needles that slowly became brown in air; m. p. *ca.* 195° with previous blackening.

Anal. Calcd. for $C_{28}H_{27}N_3O + HCl$: C, 73.4; H, 6.1. Found: C, 73.4; H, 5.9.

The free base was decomposed rapidly by air; the **monoacetyl derivative**, from the hydrochloride with acetic anhydride and aqueous sodium acetate, formed colorless needles from acetic acid, m. p. 177–178°.

Anal. Calcd. for $C_{30}H_{29}N_3O_2$: N, 9.0. Found: N, 9.0.

Acidic Hydrolysis of IV.—A mixture of 4.1 g. of IV, 35 ml. of 48% hydrobromic acid, and 15 ml. of acetic acid was boiled for forty hours and then distilled to dryness under reduced pressure. The residue was washed with water, and the soluble part was treated with sodium hydroxide and benzoyl chloride, giving 1.5 g. (calcd. 2.2 g.) of benzanilide. The insoluble part was treated with sodium hydroxide and ether, and the ether-soluble oily base (3.1 g., calcd. 3.0 g.) was converted into its water-insoluble hydrochloride. From dilute alcohol, the **N-(β,β′-diphenylisopropyl)-aniline hydrochloride** separated in the form of fine colorless needles, m. p. 148–150°.

Anal. Calcd. for $C_{21}H_{21}N + HCl$: Cl, 11.0. Found: Cl, 11.2.

The **benzoyl derivative** formed clusters of stout needles from alcohol, m. p. 141–142°.

Anal. Calcd. for $C_{28}H_{25}NO$: C, 86.0; H, 6.4. Found: C, 86.0; H, 6.3.

N-(β,β′-Diphenylisopropyl)-aniline (0.2 g.) was also obtained together with β,β′-diphenylisopropyl alcohol (18.8 g., b. p. 185–190° at 12 mm.) when a mixture of 21 g. of dibenzyl ketone, 9.5 g. of aniline, 0.5 g. of sodium acetate, and 15 ml. of alcohol was shaken for three hours with Raney nickel and hydrogen at 100 atmospheres and 170°. The oily base was identified with the above degradation product by comparing their hydrochlorides and benzoyl derivatives.

A solution of 2.5 g. of N-(β,β′-diphenylisopropyl)-aniline hydrochloride and 0.5 ml. of hydrochloric acid in 10 ml. of alcohol was treated with 0.6 g. of sodium nitrite at 5°. The resulting **N-nitroso-N-(β,β′-diphenylisopropyl)-aniline** (2.0 g.) was crystallized from alcohol (charcoal), giving pale yellow needles, m. p. 90–91°.

Anal. Calcd. for $C_{21}H_{20}N_2O$: C, 79.8; H, 6.3. Found: C, 80.1; H, 6.7.

When 1.3 g. of this N-nitroso compound was allowed to stand for ten hours with 6 ml. of 10 *N* alcoholic hydrogen chloride and then treated with aqueous sodium carbonate, there was obtained 1.3 g. of ***p*-nitroso-N-(β,β′-diphenylisopropyl)-aniline**, bright green plates from dilute alcohol, m. p. 113–114°.

Anal. Calcd. for $C_{21}H_{20}N_2O$: C, 79.8; H, 6.3. Found: C, 80.0; H, 6.4.

A mixture of 0.25 g. of the *p*-nitroso compound with 0.25

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[5] No certain structure can now be proposed for this compound. Its method of formation and its properties suggest a similarity to pernitrosocamphor; *cf.* Forster, Trotter and Weintraube, *J. Chem. Soc.*, **99**, 1982 (1911).

g. of potassium hydroxide in 10 ml. of water and 1 ml. of alcohol was boiled for eight hours. Extraction with ether then yielded β,β'-diphenylisopropylamine, b. p. 177° at 12 mm., m. p. 50° (reported[6] b. p. 330°, m. p. 47°), and acidification yielded *p*-nitrosophenol, m. p. 130° dec. Each of these products was identified by comparison with an authentic sample.

The amine for comparison was obtained by heating 56 g. of dibenzyl ketone with 50 ml. of formamide at 175° for eight hours.[7] The resulting N-formyl-β,β'-diphenylisopropylamine separated from benzene-ligroin in the form of fine white needles (52 g., 82%), m. p. 92–93°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.4; H, 7.1. Found: C, 80.3; H, 7.3.

A mixture of the formyl derivative (50 g.) with 50 ml. of sulfuric acid, 50 ml. of water, and 100 ml. of alcohol was boiled for ninety minutes, then steam distilled to remove ethyl formate and alcohol, and treated with excess alkali, yielding 42.7 g. (96%) of distilled β,β'-diphenylisopropylamine. It formed a hydrochloride, m. p. 200–202° (reported 205°), and both it and the amine obtained by degradation of IV gave a **benzoyl derivative,** needles from alcohol, m. p. 169–170°.

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.8; H, 6.7. Found: C, 83.7; H, 6.6.

Basic Hydrolysis of the Chloro Derivative of IV.—A mixture of 4.4 g. of N-(β,β'-diphenylisopropyl)-anthranil-*p*-chloroanilide, 2 g. of potassium hydroxide, and 20 ml. of glycol was boiled under reflux for ten minutes, then diluted with 75 ml. of water and steam distilled. From the distillate there was obtained 1.15 g. (91%) of *p*-chloroaniline, and from the residual liquid, by acidification, 3.3 g. (100%) of **N-(β,β'-diphenylisopropyl)-anthranilic acid** (VII), m. p. 141–143°. The substance exhibited a strong violet fluorescence in alcohol and separated from this solvent in the form of flat needles, m. p. 149–151°. It was soluble in dilute sodium carbonate but insoluble in dilute hydrochloric acid; it gave an oily salt with concd. aqueous hydrochloric acid or with hydrochloric acid in alcohol and ether.

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.8; H, 6.4. Found: C, 79.9; H, 6.8.

When the acid was heated somewhat above 250°, it evolved carbon dioxide and was converted nearly quantitatively into N-(β,β'-diphenylisopropyl)-aniline.

Synthesis of IV.—A solution of 2.4 g. of the acid VII in 7.5 ml. of ethyl chloroformate was boiled for three hours, then distilled to dryness under reduced pressure and treated with dilute sodium carbonate. The resulting insoluble material (0.4 g.) was the isatoic anhydride (IX, see below), and the soluble part was a mixture of unchanged VII (0.4 g.) and **N-carbethoxy-N-(β,β'-diphenylisopropyl)-anthranilic acid** (VIII, 0.9 g.). These substances were separated by crystallization from ether-ligroin, VIII having a convenient tendency to remain in supersaturated solution. From dilute alcohol, VIII formed small clear prisms, m. p. 168–169°.

Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.4; H, 6.2. Found: C, 74.6; H, 6.2.

When VIII was boiled with excess acetyl chloride for thirty minutes, it was converted quantitatively into **N-(β,β'-diphenylisopropyl)-isatoic anhydride** (IX). This same substance was obtained in a yield of 60% directly from VII (2.3 g.) by boiling it for five hours with 7.5 ml. of ethyl chloroformate, then adding 5 ml. of acetyl chloride and boiling for fifteen minutes longer. From acetic acid IX formed coarse colorless prisms with well-marked hour glass figures, m. p. 184–185°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.4; H, 5.3. Found: C, 77.3; H, 5.3.

The isatoic anhydride dissolved in cold 18% alcoholic ammonia during fifteen minutes, giving **N-(β,β'-diphenylisopropyl)-anthranilamide,** fine white needles from ether-ligroin that were insoluble in aqueous hydrochloric acid; m. p. 97–98°.

Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 80.0; H, 6.7. Found: C, 79.7; H, 7.0.

A mixture of 0.5 g. of the isatoic anhydride with 2 ml. of aniline was heated at 150° until the smooth evolution of carbon dioxide had stopped (ten minutes), then treated with dilute hydrochloric acid. The undissolved oil solidified completely when seeded with IV, and crystallization from alcohol gave 0.55 g. (96%) of IV, m. p. (after thorough drying) 117–119° alone or mixed with the substance obtained from the Grignard reaction.

The author thanks Dr. S. T. Rolfson for several of the analyses reported in this paper.

Summary

Benzylmagnesium chloride attacks a C—N double bond and not the carbonyl group in 3-phenylquinazolone-4, forming N-(β,β'-diphenylisopropyl)-anthranilanilide. The structure of the product has been established by degradation and by synthesis, and an explanation for the apparently anomalous course of the Grignard reaction has been suggested.

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[6] Noyes, *Am. Chem. J.*, **14**, 227 (1892).

[7] *Cf.* Ingersoll, Brown, Kim, Beauchamp and Jennings, THIS JOURNAL, **58**, 1808 (1936); Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).