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RESEARCHES ON QUINAZOLINES. XXXVII. SOME PRELIMINARY OBSERVATIONS ON THE BEHAVIOR OF PHTHALIC ANHYDRIDE WITH THE REACTIVE METHYL GROUPS OF CERTAIN QUINAZOLINES

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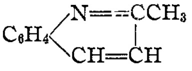
Introductory

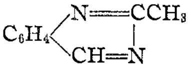
Quinoline Yellow is to-day the only quinoline dye of any commercial importance. Although expensive, it possesses certain fine qualities which more than counterbalance its high price.

Since it is manufactured by condensing quinaldine (I) with phthalic anhydride and sulfonating the product, it seemed likely that the 2-methyl-(II) or 4-methyl-(III)quinazoline would yield similar products, especially when it is recalled that both 2-methyl-4-quinazolone (IV)[2] and α-methylbenzimidazole[3] do so.



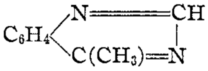
$C_6H_4\left\langle\begin{matrix}N{=}CCH_3\\ |\\ CH{=}CH\end{matrix}\right.$

I



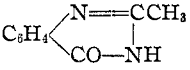
$C_6H_4\left\langle\begin{matrix}N{=}CCH_3\\ |\\ CH{=}N\end{matrix}\right.$

II



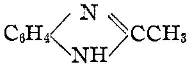
$C_6H_4\left\langle\begin{matrix}N{=}CH\\ |\\ C(CH_3){=}N\end{matrix}\right.$

III



$C_6H_4\left\langle\begin{matrix}N{=}CCH_3\\ |\\ CO{-}NH\end{matrix}\right.$

IV



$C_6H_4\left\langle\begin{matrix}N\\ NH\end{matrix}\right\rangle CCH_3$

V

The quinazolines selected for the experiments were the 2-methyl, 4-methyl, 2,4-dimethyl and 2-phenyl-4-methyl. These were heated with phthalic anhydride at temperatures in the neighborhood of 200°. In all cases the products were amorphous and very difficult to purify. A methyl group in Position 2 appeared to condense more rapidly than one in Position 4, and the course of the reaction was not the same in the two instances, the product from the former being insoluble in dil. alkali and that from the latter freely soluble therein. In the case of the condensation product from the 2,4-dimethylquinazoline, only a very small amount dissolved in dil. caustic alkali, thus indicating that the 2-methyl had reacted rather than the 4-methyl group. With 2-phenyl-4-methylquinazoline, but little condensation was accomplished even by heating for eight hours at 210°.

The phthalones from 2-methyl- and from 2,4-dimethyl-quinazoline were

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[1] Without the financial assistance provided by the generosity of E. I. du Pont de Nemours and Company, Inc., this research could not have been undertaken, for Dr. Nabenhauer was du Pont Fellow at Columbia University during the prosecution of the work.—M. T. B.

[2] Bogert and Heidelberger, THIS JOURNAL, **34,** 183 (1912).

[3] Bamberger and co-workers, *Ber.,* **24,** 2053 (1891); **25,** 274 (1892); *Ann.,* **273,** 315 (1893).

obtained in relatively pure condition, but those from 4-methyl- and from 2-phenyl-4-methyl-quinazoline could not be purified satisfactorily with the quantity of material available.

The sulfo acids of these condensation products gave water-soluble salts which dyed silk yellow or brown. Although some of these dyeings were of fine golden yellow, the dyes themselves cannot compare with Quinoline Yellow in valuable properties.

The results are of interest in conjunction with recent articles dealing with reactive methyl groups in nitrogen heterocycles,[4,5] but discussion would be premature at present, for the work on these phthalones is incomplete. The preliminary results are published because the withdrawal of one of the investigators (Dr. Nabenhauer) makes it uncertain when the research can be resumed.

Experimental Part

2-Methyl-quinazoline was prepared from *o*-aceto-aminobenzaldehyde, methyl alcohol and ammonia, essentially as recommended by Bischler[6] and by Bischler and Lang.[7] Pale yellow, glassy prisms were obtained, m. p. 40–41° (corr.), b. p. 255°, of characteristic powerful mousy odor.

The same compound was secured, albeit much less conveniently, by the action of heat upon 2-methyl-quinazoline-4-carboxylic acid, and melted likewise at about 41°. When the two products were intimately mixed, the melting point of the mixture was also 40–41°. This melting point agrees with that reported by Gabriel.[8] Bischler and Lang found 35.5°.

4-Methyl-quinazoline.—A mixture of 1 g. of 4-methyl-quinazoline-2-carbonamide with 10 cc. of dil. (20%) hydrochloric acid was boiled for two hours. This effected simultaneous hydrolysis of the amide and expulsion of carbon dioxide from the acid so formed. The solution was made alkaline, extracted with ether, and the ether distilled. There remained a small quantity of a viscous oil, b. p. about 260° (corr.), with an odor recalling somewhat that of quinoline but less unpleasant. On standing, it slowly solidified in pale yellow prisms; m. p., 36–37° (corr.).

Anal. Calc. for $C_9H_8N_2$: N, 19.44. Found: 18.92.

The *picrate* crystallized from alcohol in glistening yellowish-green flakes, m. p., 183.5° (corr.).

2,4-Dimethyl-quinazoline was prepared from *o*-aceto-amino-acetophenone (25 g.), methyl alcohol (75 cc.) and ammonia (gas) (5.5 g.), by heating the mixture in a sealed tube for 16 hours at 150°, following the method of Bischler and Burkart.[9] The contents of two such tubes were combined, the alcohol was removed on a steam-bath and the residue distilled at ordinary pressure. A pale yellow oil came over at 257° (uncorr.), of characteristic mousy odor; yield, 41 g., or 91%. It formed a hydrate readily, which crystal-

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[4] Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

[5] Bogert and Clark, This Journal, **46**, 1294 (1924).

[6] Bischler, *Ber.*, **24**, 507 (1891).

[7] Bischler and Lang, *Ber.*, **28**, 280 (1895).

[8] Gabriel, *Ber.*, **36**, 810 (1903).

[9] Bischler and Burkart, *Ber.*, **26**, 1350 (1893).

lized in long, colorless, silky hairs; m. p., 72° (corr.). These results coincide with those of Bischler and Burkart, except that they distilled at a different pressure and reported a boiling point of 249° (713 mm.).

2-Phenyl-quinazoline.—2-Phenyl-quinazoline-4-carboxylic acid (0.5 g.) was heated above its melting point until the evolution of gas (carbon dioxide) had ceased. The residue was heated carefully in a small test-tube, so that it distilled and condensed in the upper cooler portion of the tube as a crystalline sublimate. This was removed and crystallized from alcohol, giving pale yellowish, flattened needles, m. p. 101° (corr.), identical with the 2-phenyl-quinazoline obtained by Bischler and Lang[7] from *o*-benzoylamino-benzaldehyde, and by Gabriel and Jansen[10] from *o*-aminobenzyl-benzamide.

2-Phenyl-4-methyl-quinazoline.—A mixture of *o*-benzoylamino-acetophenone (12 g.) and methyl alcohol (60 g.) containing gaseous ammonia (7 g.) was heated in a sealed tube for five hours at 150°, as recommended by Bischler and Howell.[11] As the tube cooled, the contents crystallized. The product was removed and crystallized from alcohol, when it appeared in colorless, glistening scales, m. p. 90° (corr.), in agreement with the figure given by Bischler and Howell.

2-Methyl-quinazophthalone.—Equal weights of 2-methyl-quinazoline and phthalic anhydride were heated together for an hour or more at 205°. The crude product was purified by dissolving it in glacial acetic acid, filtering and pouring the filtrate into water with stirring. Part of the phthalone precipitated, and the remainder was formed by the addition of ammonium hydroxide solution. This treatment was repeated twice, and the phthalone so purified formed a yellowish-brown powder, soluble with yellow color in alcohol, glacial acetic acid, sulfuric acid, or ethyl benzene, but insoluble in dil. alkali.

Anal. Calc. for $C_{17}H_{10}O_2N_2$: N, 10.22. Found: 10.94, 10.62.

By warming this compound with fuming sulfuric acid, it was sulfonated, and solutions of this sulfo acid dyed silk a dull golden-yellow, not very fast to washing.

4-Methyl-quinazoline and Phthalic Anhydride were heated together and the crude product was purified, in just the same manner as the 2-methyl derivative described above, but the properties of the product were strikingly different, in that it was insoluble in ethyl benzene, but dissolved completely in dil. caustic alkali to a brown solution. It was purified by dissolving it in such an alkaline solution and reprecipitating with acid, and then formed a brownish-yellow powder.

Anal. Calc. for $C_{17}H_{10}O_2N_2$: N, 10.22. Found: 7.66, 8.05.

These figures indicate that either the product was only about 80% pure, or it was not the expected phthalone. If impure, the impurity was probably phthalic acid not wholly removed by the method of purification adopted.

The product is a very strong dye. Silk boiled for one or two minutes in very dil. alkaline solutions (0.1–0.5%) of the dye was colored a deep golden-yellow without exhausting the bath. These dyeings were not very fast to washing with soap, but exhibited much better fastness to light.

2,4-Dimethyl-quinazoline Monophthalone.—When equal weights of 2,4-dimethyl-quinazoline and phthalic anhydride were heated together at 210° for an hour and a half, a brown, tarry condensation product resulted. As the condensation seemed to take place about as well without zinc chloride as with it, although somewhat more slowly, none of this condensing agent was used. The product was soluble in alcohol, glacial acetic acid or sulfuric acid, but dissolved with difficulty in hydrochloric acid. It could not be crystallized from any of these solvents and hence was purified by solution in acetic acid and reprecipitation by dilution and addition of ammonium hydroxide solution, as in the

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[10] Gabriel and Jansen, *Ber.*, **23**, 2810 (1890).

[11] Bischler and Howell, *Ber.*, **26**, 1391 (1893).

case of the 2-methyl-quinazophthalone. The purified substance consisted of a dark brown powder, insoluble in water, and was evidently still impure, judged by the analyses.

Anal. Calc. for $C_{18}H_{12}O_2N_2$: C, 75.00; H, 4.17; N, 9.73. Found: C, 72.55; H, 4.40; N, 9.46.

These figures, however, check closely enough to show that the product is a mono- and not a di-phthalone. It seems probable that the condensation took place mainly with the 2-methyl and only to a slight extent with the 4-methyl group.

When it was warmed gently with fuming sulfuric acid, a soluble sulfonic acid was obtained, whose ammonium salt in dil. aqueous solution dyed silk a brown shade.

Comparison of the Behavior of 2-Methyl, 4-Methyl- and 2,4-Dimethyl-quinazolines with Phthalic Anhydride under Identical Conditions.—Three tubes containing equal weights of the quinazoline and phthalic anhydride were suspended in the vapors of boiling nitrobenzene, so as to maintain a uniform temperature of approximately 205°.

After ten minutes, bubbles appeared in the 2-methyl- and 4-methyl-, but not in the 2,4-dimethyl-quinazoline melt. The 2-methyl melt turned orange, the 4-methyl olive-green, and the 2,4-dimethyl deep orange. After 50 minutes, the first had become a deep orange, the second was brown showing a greenish shade in thin layers, and the third was brown and by that time giving off some bubbles of vapor.

At the end of 75 minutes' heating, each was dissolved in glacial acetic acid, the solution poured into water, and potassium hydroxide solution added until the reaction was nearly neutral. The precipitates formed were, in the above order, orange, brown with a greenish cast and very dark brown. These were collected separately and washed first with water and then with dil. potassium hydroxide solution. The product from the 2-methyl-quinazoline was apparently insoluble in the dil. alkali, that from the 4-methyl- dissolved therein almost completely, with the formation of a brown solution, while of the product from the 2,4-dimethyl- only a small amount dissolved, giving an orange solution.

These results appeared to us to indicate that there is a marked difference in the behavior of the 2- and 4-methyl groups on the quinazoline nucleus when fused with phthalic anhydride under the conditions of our experiments. Judged by the insolubility of the product in dil. alkali, the 2,4-dimethyl-quinazoline reacts with phthalic anhydride through its 2-methyl and not through its 4-methyl group.

2-Phenyl-4-methyl-quinazoline and Phthalic Anhydride.—2-Phenyl-4-methyl-quinazoline (2.7 g.) was heated with an equivalent amount (1.8 g.) of phthalic anhydride at 210°. The interaction was very slow, and even after heating for eight hours the melt consisted largely of unaltered initial materials. By washing the pulverized melt with dil. alkali, a small quantity of condensation product was dissolved, together with phthalic acid. This gave a red solution and was precipitated by acid as a green, amorphous, flocculent solid.

That portion of the original melt undissolved by the treatment with alkali, and still containing unchanged 2-phenyl-4-methyl-quinazoline, was warmed with fuming sulfuric acid. This gave a product which, when treated with dil. ammonium hydroxide solution and filtered, yielded a clear yellow filtrate which dyed silk an orange.

Summary

1. 2-Methyl-, 4-methyl-, 2,4-dimethyl-, 2-phenyl- and 2-phenyl-4-methyl-quinazolines have been prepared, in part by old methods, in part by new ones. Of the quinazolines themselves, the 4-methyl derivative has not been described previously.

2. A preliminary study has been made of the behavior of these quinazolines (except the 2-phenyl derivative) when heated with phthalic an-

hydride, and it has been ascertained that a methyl group in Position 4 condenses less readily with the anhydride than one in Position 2 and that the course of the reaction is not the same in the two cases.

3. The reaction with the 2-methyl-quinazoline led to the phthalone; that with the 2,4-dimethyl- to a monophthalone. The nature of the products obtained from the 4-methyl- and from the 2-phenyl-4-methyl remains to be determined.

4. By warming these condensation products with fuming sulfuric acid, sulfo acids were obtained which dyed silk golden-yellow to brown. Although of considerable tinctorial strength, these dyes appeared to be decidedly inferior to Quinoline Yellow.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

THE INFLUENCE OF SULFUR ON THE COLOR OF AZO DYES FURTHER INVESTIGATIONS

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In a previous paper from this Laboratory[2] a study has been made of the influence of sulfur in the *para* position upon the color of azo dyes. The purpose of the present investigation has been to show the effect of the sulfur atom and the sulfone group, as before, but in the *ortho* instead of the *para* position. We have made no attempt to duplicate the many dyes previously prepared, a large proportion of which were obtained simply by coupling the same bases with different standard intermediates, but have merely selected those bases which seemed to be representative, prepared the *ortho* analogs and coupled them with the intermediate which had, in the *para* series, given the best-defined color differences, namely with R-salt. By this means we have confirmed in some respects the results found with the *para* compounds, and have uncovered some interesting and unexpected facts connected with the relative influence of the sulfur atom in the two positions.

As in the previous investigation, we have prepared intermediates of two classes.

1. A series of mono-amines,—CH_3,—OCH_3,—SCH_3,—SO_2CH_3, containing the methyl group, methoxyl, thio-ether and sulfone groups in the *ortho* position to the amino group. In the same class falls a series of alkyl thioethers from methyl to *iso*-amyl: $NH_2C_6H_4.S.R$, including the phenyl

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[1] From a dissertation by Duncan Graham Foster, 1923.

[2] Waldron and Reid, THIS JOURNAL, **45**, 2399 (1923). Wherever, in this article, we refer "to the previous paper" or to "the methods employed with the *para* series" detailed descriptions of procedures will be found in this reference.