

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, No. 433]

RESEARCHES ON QUINAZOLINES. XXXV. STEREOISOMERIC STYRYL DERIVATIVES OF SOME 4-QUINAZOLONE ALKYL IODIDES, AND THEIR BEARING UPON THE PROBLEM OF PHOTSENSITIZING DYES

BY MARSTON TAYLOR BOGERT AND HELEN CLARK

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Introductory

The connection between the chemical structure and the photosensitizing effects of a dye is a problem of both theoretical and practical interest.

As the result of the study of many hundred such dyes, it has been learned that those which are most valuable for this purpose are derivatives of the heterocycles pyridine, quinoline or isoquinoline, although photosensitizing dyes have also been obtained containing the benzothiazole nucleus.^{1,2}

Since quinazoline is structurally both a quinoline and an isoquinoline, it seemed likely that useful sensitizers might be found among its derivatives also. Although the goal sought has not yet been reached, the results reported in this communication throw some additional light upon the problem which was the cause of their initiation, and also bring out some peculiarities in the chemical behavior of quinazoline derivatives.

The methods by which the more important photosensitizing dyes are prepared depend upon either the utilization of the alkyl halide of the heterocyclic base, or the condensation of a reactive methyl group with *p*-dimethylamino-benzaldehyde.

In the case of the particular quinazolines studied, the former of these methods turned out to be unavailable, because of our inability to prepare the necessary alkyl iodide addition products in satisfactory yield and purity. In fact, the few quinazolinium alkyl halides recorded in the literature,^{3,4} appear to have been unstable and secured only with considerable difficulty.

The quinazolines selected were the 2,4-dimethyl, 2-styryl-4-methyl, and 2-phenyl-4-methyl. From no one of these were we successful in preparing quaternary alkyl salts, either with methyl iodide, ethyl iodide or dimethyl sulfate, although experimental conditions were varied widely. Either no addition whatever occurred, or decomposition resulted with formation of amorphous intractable material.

Nor were we more successful in our efforts to condense 2,4-dimethylquinazoline with *p*-dimethylamino-benzaldehyde or with other aromatic

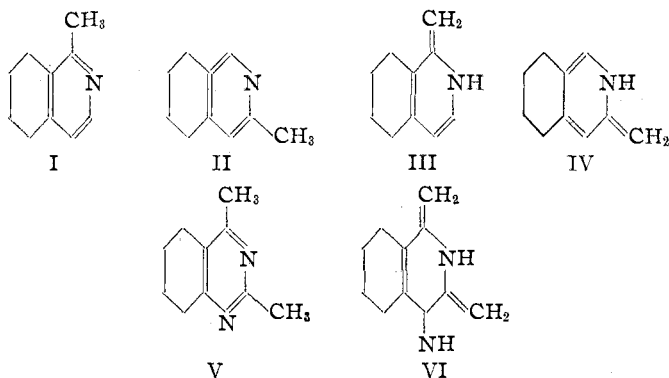
¹ Hofmann, *Ber.*, **20**, 2262 (1887).

² Mills and co-workers, *J. Chem. Soc.*, **121**, 455, 1489, 2004 (1922).

³ Bischler and Barad, *Ber.*, **25**, 3080 (1892).

⁴ Gabriel, *Ber.*, **37**, 3650 (1904).

aldehydes. The failure of these reactions is of interest in connection with recent theories concerning reactive methyl groups on nitrogen heterocycles,⁵ and the support of certain of these hypotheses supplied by the results lately published by Mills and Smith.⁶ These investigators found that 1-methyl-isoquinoline (I) condensed with benzaldehyde, in the presence of zinc chloride, to a styryl derivative, whereas under identical conditions the 3-methyl isomer (II) did not. On the basis of the theories referred to above, this difference in behavior was ascribed to the following causes: (1) the $\text{CH}_3\text{C:N}$ - union has the same loosening effect upon the hydrogens of the methyl group as in the $\text{CH}_3\text{C:O}$ structure of ketones, hence (I) reacts, but not (II); and (2) only these structures can pass into a tautomeric reactive form while still retaining the full benzenoid character of the nucleus, as is true in (III) but not in (IV). 2,4-Dimethyl-quinazoline would appear to conform to both of these requirements (V and VI), yet we were unable to condense it with either benzaldehyde or *p*-dimethyl-amino-benzaldehyde, in the presence of any of the condensing agents used.



Since it had been shown by Bogert and Geiger⁷ that quaternary salts of 4-quinazolones can be obtained without any great difficulty, our attention was directed to them and they became the initial materials for the further experimental work.

In the production of isocyanine dyes from the alkyl iodides of quinoline and quinaldine, Mills and his co-workers² discovered that analogous thiocyanine dyes could be prepared by replacing the quinaldinium salt by a quaternary salt of 2-methyl benzothiazole, but not when an alkyl iodide of benzothiazole was substituted for the quinolinium salt. The same appears to be true in the 4-quinazolone field, for on attempting to

⁵ Henrich, "Theories of Organic Chemistry," transl. by Johnson and Hahn, John Wiley and Sons, Inc., N. Y., 1922, p. 147.

⁶ Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

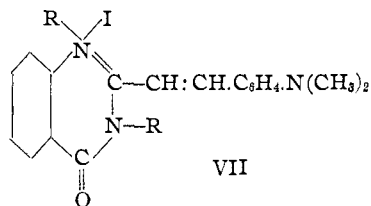
⁷ Bogert and Geiger, *THIS JOURNAL*, **34**, 683 (1912).

condense quinaldine methyl iodide with the methyl iodide of 2,3-dimethyl-4-quinazolone, only 1,1'-dimethyl-carbocyanine iodide was isolated; whereas, when the quinazolone methyl iodide was treated with quinoline methyl iodide and alkali, some condensation between the two occurred, with the formation of a brownish solid with greenish reflex, which was small in amount and impure.

Although Mills and Braunholtz² observed that suitable benzothiazoles could be condensed with themselves, in the presence of pyridine, we have not found the same to be the case with the 4-quinazonium salts investigated.

As 2-(*p*-dimethylaminostyryl)pyridine methyl iodide³ is a very powerful sensitizer for the green region of the spectrum, the styryl derivatives of certain 4-quinazolones were prepared and examined. The 4-quinazolones selected were the 2-methyl, 3-methyl, 2,3-dimethyl and 2-methyl-3-ethyl, whose alkyl iodides were condensed with *p*-dimethylamino-benzaldehyde.

In the first series of experiments, piperidine was employed as the condensing agent, and bright red, acicular crystals resulted. But when acetic anhydride⁹ was substituted for the piperidine in the same condensations, reddish-purple needles were obtained of considerably higher melting point, mixed with the bright red ones, and the interesting fact was disclosed that the two sets of products were *cis* and *trans* isomers of the following structure.



Further investigation made it clear that the higher-melting crystals constituted the stable and the lower-melting ones the labile isomers. The latter could be transformed into the former by prolonged heating with acetic anhydride at 120°, but the reverse change could not be effected. By varying the temperature and duration of the heating with acetic anhydride, it was found possible to obtain either isomer practically free from the other. The yields of labile isomer were much better with this condensing agent than with piperidine. Treated with bromine in chloroform solution, the two isomers gave identical monobromo dibromides, which were orange in color. Theoretically, the derivatives from the *cis* form should have been of the mesotartaric type, and those from the *trans* of racemic type, but evidence of such a result was not obtained. Bogert, Beal

³ Pope and Mills, *J. Chem. Soc.*, **121**, 946 (1922).

⁹ Koenig and Treichel, *J. prakt. Chem.*, [2] **102**, 63 (1921).

and Amend¹⁰ found that when 2-styryl-4-quinazolone itself was brominated in chloroform or glacial acetic acid solution, a monobromo derivative resulted, and no bromine addition was observed.

Neither as dyes, nor as photosensitizers, do these new products appear to be of any value, being fugitive, tinctorially weak, and devoid of any marked photosensitizing effect.¹¹ Undoubtedly, this is due, in part at least, to the presence of the oxygen on the quinazoline nucleus. The non-activity of the dyes was especially disappointing, because we had hoped to find some difference in photosensitizing behavior between the two isomers.

Experimental Part

4-Quinazolone Alkyl Iodides.—The following 4-quinazolone alkyl iodides were prepared according to the directions of Bogert and Geiger.⁷ The uncorrected melting points reported by them are given, together with our own determination of the corrected values and the yields we obtained.

4-Quinazolone	Iodide	Uncorr. m. p. (B. and G.) °C.	Corr. m. p. °C.	Yield %
2-Methyl	Methyl	220	223.7	35
3-Methyl	Methyl	269	271.4	56
2,3-Dimethyl	Methyl	242	246	80
2,3-Dimethyl	Ethyl	237	241	22
2-Methyl-3-ethyl	Methyl	217	220	41

The Interaction of 2-Methyl-4-quinazolone Alkyl Iodides and *p*-Dimethylamino-benzaldehyde

2-*p*-Dimethylaminostyryl-4-quinazolone Methyl Iodide (VII).—Equal molecular equivalents of 2-methyl-4-quinazolone methyl iodide and *p*-dimethylamino-benzaldehyde were dissolved in acetic anhydride and the solution was heated for two hours at 120–130°. The crude, reddish crystals which separated as the solution cooled were washed repeatedly with small amounts of ice-cold methyl alcohol, allowed to dry in the air, and re-crystallized from the same solvent (methyl alcohol). Reddish-purple needles were obtained but, as analysis showed that they were still impure, they were washed again with small amounts of warm methyl alcohol and then dried for 48 hours in a desiccator over solid potassium hydroxide. The purified product consisted of reddish-purple needles, which began to sublime at about 252°, or if rapidly heated darkened at 255–265°, and melted with evolution of gas at 265.7° (corr.); yield, 22%.

Analyses. Calc. for C₁₉H₂₀ON₂I: C, 52.65; H, 4.64. Found: C, 52.81; H, 4.71.

On concentrating the methyl alcohol mother liquors from the above crystals, bright red needles (3 g.) separated. These were recrystallized from methyl alcohol and dried for a few days over solid potassium hydroxide in a desiccator. The compound then melted at 214° (corr.); yield, 27.9%.

Analyses. Calc. for C₁₉H₂₀ON₂I: C, 52.65; H, 4.64. Found: C, 52.34; H, 4.72.

¹⁰ Bogert, Beal and Amend, *THIS JOURNAL*, **32**, 1654 (1910).

¹¹ The authors wish to record their grateful appreciation of the assistance rendered them by Drs. C. E. K. Mees and S. E. Sheppard, of the Eastman Kodak Company, through whose courtesy the photosensitizing properties of these dyes were tested.—M. T. B. and H. C.

It was found possible to regulate this condensation so that either one of the products could be obtained wholly free from, or with but small amounts of, the other. When the acetic anhydride solution was heated for 2 to 2.5 hours at 120° ($\pm 1^{\circ}$), the higher-melting isomer was formed. Longer heating gave small amounts of a brown, amorphous powder, m. p. $250\text{--}260^{\circ}$, which was not accumulated in sufficient quantity to permit its identification. But when the solution was heated for only 15–20 minutes at $145\text{--}150^{\circ}$, the product was the lower-melting form. By heating an acetic anhydride solution of the latter for 2 to 3 hours at 120° , it was changed into the higher-melting isomer.

The reverse change could not be realized. The higher-melting form was exposed in chloroform solution to 96 hours of summer sun, followed by the addition of a crystal of iodine and 96 hours' further exposure, but the original material was recovered unaltered.

When freshly distilled piperidine was used as a condensing agent, in place of acetic anhydride, only the lower-melting isomer was obtained, and the yield was very poor.

Both isomers were freely soluble in water, methyl or ethyl alcohol, chloroform, acetone or acetic anhydride; slightly soluble in benzene or glacial acetic acid; and practically insoluble in ligroin or ether. Of the two, the lower-melting form was generally the more soluble. The higher-melting isomer dissolved in water giving an orange solution. Addition of a few drops of mineral acid to this solution caused the color to fade slightly, but addition of alkali changed the color to lemon-yellow. The aqueous solution of the other isomer was likewise orange. Its color was discharged immediately by a few drops of mineral acid, and alkali changed it to a pale yellow. As recorded beyond, both forms yielded the same tribromo derivative.

3-Methyl-4-quinazolone Methyl Iodide and *p*-Dimethylamino-benzaldehyde failed to condense when heated together in acetic anhydride solution for two hours at $120\text{--}130^{\circ}$, and the initial materials were recovered unchanged. Hence, under the conditions of our experiments, *p*-dimethylamino-benzaldehyde does not condense with a methyl group in Position 3, that is, attached to nitrogen.

2-*p*-Dimethylaminostyryl-3-methyl-4-quinazolone Methyl Iodide.—A solution of 10 g. of 2,3-dimethyl-4-quinazolone methyl iodide, 4.7 g. of *p*-dimethylamino-benzaldehyde and 1.5 g. of freshly distilled piperidine in 300 cc. of methyl alcohol was boiled for four hours under a reflux condenser. It was then allowed to cool. The bright red crystalline precipitate which separated (2.7 g.) was collected after about 15 hours, washed several times with small amounts of ice-cold methyl alcohol and crystallized thrice from the same solvent, in which it dissolved very freely. The pure substance formed bright red needles, which melted with effervescence at 216° (corr.); yield, 12.7%.

Analyses. Calc. for $C_{20}H_{22}ON_3I$: C, 53.68; H, 4.96; I, 28.39. Found: C, 53.76; H, 4.93; I, 28.52.

On allowing the filtrate from these crystals to evaporate spontaneously, 2.9 g. of *p*-dimethylamino-benzaldehyde (m. p., 73°) separated.

The solubilities of the new compound were much the same as those recorded for the 2-methyl-4-quinazolone derivative. The aqueous solution was orange-red. Addition of a little alkali changed it to a pale yellow, but addition of a few drops of mineral acid decolorized the solution very rapidly. Although this behavior of the aqueous solution with mineral acid is a characteristic also of photosensitizing dyes, the compound possessed no appreciable photosensitizing properties. Silk or cotton immersed in a 1% solution was dyed orange, but the dyeing was fast neither to washing nor to light.

In the other series of experiments, acetic anhydride served as the condensing agent, and the following is a representative example. A mixture of 6.4 g. of 2,3-dimethyl-4-quinazolone methyl iodide, 3 g. of *p*-dimethylamino-benzaldehyde and 200 cc. of acetic anhydride was heated for two hours at $125\text{--}130^{\circ}$. When the solution cooled, 4 g. of purplish-red crystals separated. By fractional crystallization from methyl alcohol,

these were separated into two distinct products. One appeared in purplish-red needles, which began to sublime at about 250°, or when rapidly heated darkened at 253–263°, and melted with decomposition at 263.5° (corr.). The other formed bright red needles, melting at 216° (corr.) with effervescence. The two were analyzed with the following results.

Analyses. Calc. for $C_{22}H_{22}ON_2I$: C, 53.68; H, 4.96. Found (m. p., 263.5°): C, 53.50; H, 5.12. Found (m. p., 216°): C, 53.65; 53.62; H, 5.16, 5.19.

The product melting at 216° was identical in appearance, solubilities and other properties with the product of the piperidine condensation, and an intimate mixture of the two melted also at 216°.

The lower-melting isomer was changed into the higher-melting one by heating it with acetic anhydride for two hours at 120°. As explained in the case of the lower homologs, either isomer could be obtained at will, to the practical exclusion of the other, by suitable adjustment of the temperature and duration of the heating with acetic anhydride. Any unchanged quinazolone methyl iodide could be removed very easily by washing the products with a small amount of hot water in which it dissolved freely. Treated with bromine in chloroform solution, the two isomers gave the same tribromo derivative.

2-*p*-Dimethylaminostyryl-3-methyl-4-quinazolone Ethyl Iodide was prepared similarly from 6.6 g. of 2,3-dimethyl-4-quinazolone ethyl iodide, 3 g. of *p*-dimethylaminobenzaldehyde and 50 cc. of acetic anhydride.

When the heating was continued for two hours at 120° and the crude product (5 g.) was purified, purplish-red needles were obtained, which sublimed at 255° or, when heated rapidly, darkened at 257–264° and melted with decomposition at 264.7° (corr.); yield, 2 g.

Analyses. Calc. for $C_{21}H_{24}ON_2I$: C, 54.65; H, 5.21. Found: C, 54.68; H, 5.11.

When the same initial mixture was heated to 145–150°, a vigorous reaction began and continued for five minutes. After heating was continued for five minutes longer at the same temperature, the mass was allowed to cool and from it there were isolated bright red needles, which melted at 205.5° (corr.); yield, 5 g.

Analyses. Calc. for $C_{21}H_{24}ON_2I$: C, 54.65; H, 5.21. Found: C, 54.71; H, 5.19.

The same product was obtained when piperidine was used as the condensing agent in place of acetic anhydride. Heated for two hours at 120° in acetic anhydride solution, it was transformed into the higher-melting isomer. The two isomers yielded the same tribromo derivative.

2-*p*-Dimethylaminostyryl-3-ethyl-4-quinazolone Methyl Iodide.—The higher-melting isomer was obtained most conveniently by heating the lower-melting form for two hours with acetic anhydride at 120°. It crystallized from methyl alcohol in purplish-red needles which sublimed at 245° or, when heated rapidly, darkened at 247–254° and melted with decomposition at 255° (corr.).

Analyses. Calc. for $C_{21}H_{24}ON_2I$: C, 54.65; H, 5.21; I, 27.54. Found: C, 54.26, 54.28; H, 5.29, 5.42; I, 27.52.

The lower-melting isomer was prepared by the process already described for the 2,3-dimethyl-4-quinazolone ethyl iodide, with either acetic anhydride or piperidine as condensing agent. It crystallized from methyl alcohol in bright red needles of bluish luster, which melted at 212° (corr.).

Analyses. Calc. for $C_{21}H_{24}ON_2I$: C, 54.65; H, 5.21. Found: C, 54.91; H, 5.50.

Silk or cotton immersed for 30 minutes in a 1% solution of the higher-melting isomer was dyed a pale orange shade, which turned a pale canary yellow on soaping. In direct sunlight, the color faded rapidly, but returned when the dyed material was left in the

dark for two weeks. The other isomer dyed a paler shade, and the color once bleached by the sun failed to return even on long standing in the dark.

Tribromo Derivatives of 2-*p*-Dimethylaminostyryl-4-quinazolone Alkyl Iodides

Tribromo Derivative of 2-*p*-Dimethylaminostyryl-3-ethyl-4-quinazolone Methyl Iodide.—A chloroform solution of 2.3 g. of the labile form (m. p., 212°) of 2-*p*-dimethylaminostyryl-3-ethyl-4-quinazolone methyl iodide was cooled to 5°, and 0.7 g. of bromine (also in chloroform solution) was added drop by drop. The deep red color of the solution gradually faded, hydrogen bromide was evolved, and by the time all of the bromine had been added it was a cloudy orange. The solvent was evaporated with the assistance of a rapid current of dry air, and the orange residue (2.5 g.) was crystallized fractionally from methyl alcohol. Two products were separated, one the original unchanged dye (m. p., 212°), and the other composed of yellowish-orange needles, m. p. 152° (corr.), in a yield of 0.4 g.

Analyses. Calc. for $C_{21}H_{23}ON_3Br_3I$: C, 36.02; H, 3.32; Br, 34.26. Found: C, 36.55, 36.48; H, 3.71, 3.75; Br, 34.51.

Bromination of the higher-melting form of 2-*p*-dimethylaminostyryl-3-ethyl-4-quinazolone methyl iodide, under similar conditions, yielded the same bromine derivative; m. p., 152° (corr.).

Tribromo Derivative of 2-*p*-Dimethylaminostyryl-3-methyl-4-quinazolone Methyl Iodide.—The same tribromo derivative was obtained from both the lower (m. p., 216°) and the higher-melting (decompn. p., 263.5°) isomers, by the method just described. It formed orange-colored needles, melting at 178° (corr.).

Analyses. Calc. for $C_{20}H_{21}ON_3Br_3I$: C, 35.06; H, 3.09. Found: C, 34.95; H, 3.15.

Summary

1. Great difficulty was experienced in the preparation of alkyl iodides of 2-methyl-quinazolines, although the corresponding derivatives of 2-methyl-4-quinazolones were obtained easily.

2. The non-reactivity of 2,4-dimethyl-quinazoline with aromatic aldehydes is at variance with certain recent hypotheses concerning reactive methyl groups on nitrogen heterocycles.

3. Attempted "cyanine condensations" with 2-methyl-4-quinazolone alkyl iodides resulted negatively.

4. 2-Methyl-4-quinazolone alkyl iodides were condensed with *p*-dimethylamino-benzaldehyde in the presence of acetic anhydride or piperidine, yielding the corresponding styryl derivatives.

5. *Cis* and *trans* forms of these styryl derivatives were separated by fractional crystallization from methyl alcohol. The two forms differed widely in appearance and in melting point.

6. The lower-melting (labile) isomer was convertible into the higher-melting (stable) one, but the reverse change could not be effected.

7. The products were devoid of photosensitizing properties and valueless as dyes.

8. The two stereoisomers gave identical monobromo dibromides when treated with bromine in chloroform solution.

9. In the course of the work, the following new compounds were prepared: *cis* and *trans* forms of the methyl iodides of 2-*p*-dimethylamino-styryl-4-quinazolone, of 3-methyl-4-quinazolone, of 3-ethyl-4-quinazolone, also of the ethyl iodides of 3-methyl-4-quinazolone, and their bromination products.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

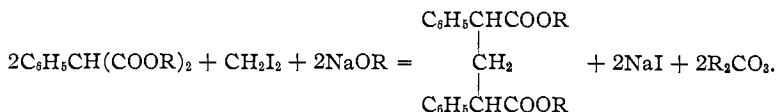
SOME CONDENSATION REACTIONS INVOLVING THE ELIMINATION OF ESTER GROUPS

BY B. L. SOUTHER

RECEIVED FEBRUARY 15, 1924

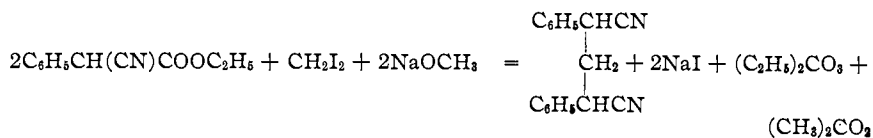
Methylene iodide has been condensed with ethyl malonate giving an excellent yield of ethyl propanetetracarboxylate.¹ A similar reaction applied to substituted malonic esters has not been so successful. Ethyl ethylmalonate² gives an indefinitely boiling mixture, although ethyl benzylmalonate forms the expected product, ethyl α,γ -dibenzylpropanetetracarboxylate.²

The reactions between methylene iodide, ethyl and methyl phenylmalonates and ethyl phenylcyanoacetate have now been studied. The two esters of phenylmalonic acid react similarly, giving good yields of the esters of α,γ -diphenylglutaric acid instead of esters of α,γ -diphenylpropanetetracarboxylic acid as might be expected. The ester of a tetrabasic acid is probably the primary product of the reaction. It then decomposes in the presence of the sodium alcoholate into the compounds isolated.



The carbonic ester was isolated and identified.

When a mixture of sodium methylate, methylene iodide and ethyl phenylcyanoacetate is heated, α,γ -diphenylglutaronitrile is formed. Here, also, the product is apparently a secondary one, arising from a cyano ester by the elimination of two carbethoxyl groups.



¹ Dressel, *Ann.*, **256**, 175 (1890).

² Ref. 1, p. 192.