with small amounts of ketyl radicals, $2R_2C—ONa \rightleftarrows R_2C(ONa)(NaO)$-$CR_2$. The ketyl radicals are intermediates in the reduction of the ketone to the pinacolate.

Other metals such as lithium, potassium, rubidium, cesium, beryllium, magnesium and calcium react in the manner of sodium. In all cases the products are metal pinacolates which differ from the sodium pinacolate and from each other only in degree.

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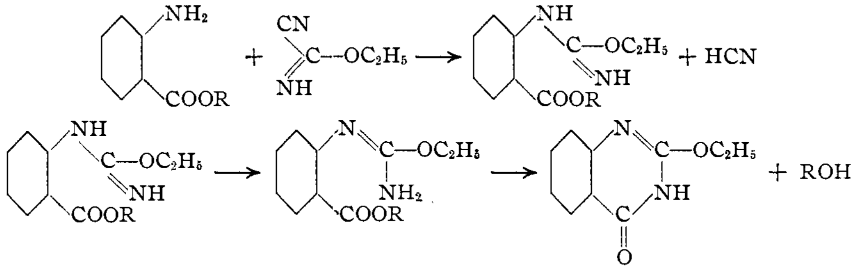
Quinazolines. V. The Partial Hydrolysis of 2,4-Dialkoxyquinazolines with the Formation of 2-Alkoxy-4-ketodihydroquinazolines

BY N. A. LANGE AND F. E. SHEIBLEY

The earliest derivatives of quinazoline on record were prepared by Peter Griess in 1869. By the action of cyanogen on anthranilic acid in alcoholic solution he obtained 2-ethoxy-4-ketodihydroquinazoline, and from this, through hydrolysis with hydrochloric acid, benzoylene urea.[1] In 1910 Finger and Zeh[2] condensed cyanimidocarbonic acid ethyl ester with methyl and ethyl anthranilates, and found that the products were the same in both cases. Their compound was subsequently shown to be identical with the 2-ethoxy-4-ketodihydroquinazoline of Griess, and the reactions leading to its formation were explained as follows[3]



Griess' reaction probably follows a similar course, the addition product, $(CN)_2NH_2C_6H_4COOH$, first formed losing HCN to form a N-cyanoanthranilic acid, which then adds alcohol and rearranges as indicated, the 3,4-dihydro structure[4] being preferred since the substance, on methylation followed by hydrolysis, is transformed into 3-methylbenzoylene urea.[5]

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(1) Griess, *Ber.*, **2**, 415 (1869).

(2) Finger and Zeh, *J. prakt. Chem.*, [2] **81**, 468 (1910).

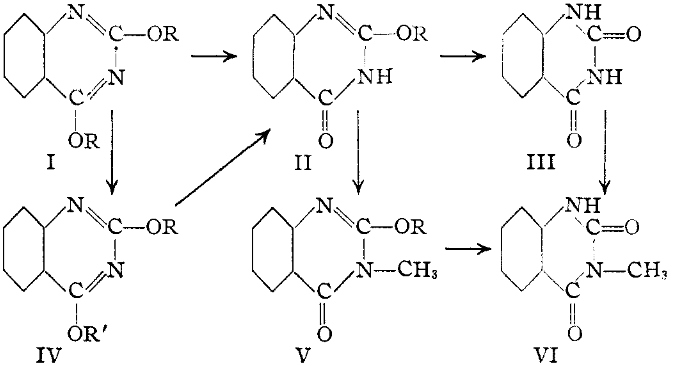
(3) Finger and Günzler, Berichtigung, *ibid.*, [2] **83**, 198 (1911).

(4) See also Bogert and Gortner, THIS JOURNAL, **32**, 123 (1910).

(5) Finger, *J. prakt. Chem.*, [2] **81**, 470 (1910).

With a view of confirming the alcohol splitting and subsequent ring closure at the anthranilic ester portion of the molecule, as written above, rather than the explanation originally proposed by Finger and Zeh,[6] McKee[7] in 1911, treated ethyl anthranilate with cyanimidocarbonic acid methyl ester and obtained the expected 2-methoxy-4-ketodihydroquinazoline. This compound possessed properties similar to those of the ethoxy derivative of Griess and of Finger and Zeh, and like the ethoxy derivative was readily hydrolyzed to benzoylene urea.

The synthesis to be described may be considered as a reversal of the original synthesis of Griess, as well as that of Finger and Zeh, since by the alkaline hydrolysis of 2,4-diethoxyquinazoline, prepared from benzoylene urea through the intermediate 2,4-dichloroquinazoline, 2-ethoxy-4-ketodihydroquinazoline is obtained. The ester-like character of the 4-alkoxy group as compared with a similar ether substituent in the 2-position of quinazoline is also demonstrated. When 2,4-diethoxyquinazoline (I) is warmed with a methyl alcoholic solution of sodium methylate, a mixed quinazoline diether, 2-ethoxy-4-methoxyquinazoline (IV) results.[8]



Where R = C_2H_5 then R' = CH_3, or when R = CH_3 then R' = C_2H_5

On prolonging this treatment, however, the yield of the mixed diether gradually decreases and an alkali-soluble product, 2-ethoxy-4-ketodihydroquinazoline (II), is formed. By substituting alcoholic sodium ethylate for the sodium methylate the same product is obtained directly from diethoxyquinazoline (I), without any intermediate mixed diether formation taking place.[9] The 2-ethoxy-4-ketodihydroquinazoline (II) thus prepared, possesses all of the properties previously recorded for this substance and, in the presence of hydrochloric acid, is easily hydrolyzed to benzoylene urea (III). It reacts readily with dimethyl sulfate to give 2-ethoxy-3-methyl-4-ketodihydroquinazoline (V), the properties of which agree with those previously

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(6) Ref. 2, p. 466.

(7) McKee, *ibid.*, [2] **84**, 821 (1911).

(8) Lange and Sheibley, THIS JOURNAL, **54**, 4306 (1932).

(9) The hydrolyzing action is due, of course, to the small amount of water present. When the better grades of absolute alcohols were used only a very slight hydrolysis occurred.

described by Finger[5] for the same substance. Hydrolysis with hydrochloric acid now gives 3-methylbenzoylene urea (VI), identical with the same compound prepared directly from benzoylene urea (III) by methylation with methyl iodide and alkali.[10]

2-Ethoxy-4-ketodihydroquinazoline (II) being a known substance, therefore, the position of the partial hydrolysis of diethoxyquinazoline (I) under alkaline conditions is indicated, and the constitution of 2-ethoxy-4-methoxyquinazoline (IV) follows. The isomeric mixed diether, 2-methoxy-4-ethoxyquinazoline,[8] must, by elimination, be as represented, since it is the second of two possibilities in a discussion limited to 2,4-diethers only. This view is confirmed by an analogous system of reactions, starting with 2,4-dimethoxyquinazoline. When this substance (I) is subjected to prolonged boiling with alcoholic sodium ethylate or methyl alcoholic sodium methylate it is converted into 2-methoxy-4-ketodihydroquinazoline (II), 2-methoxy-4-ethoxyquinazoline (IV) being an intermediate product when the former reagent is employed. The 2-methoxy-4-ketodihydroquinazoline (II) thus obtained had a constant melting point of 218° for different preparations and was hydrolyzed smoothly to benzoylene urea (III) by dilute hydrochloric acid. The methoxy keto compound described by McKee, on the other hand, melted at 231–232°; his experiment was, therefore, repeated when a product melting at 226° after crystallization from alcohol was obtained. The accidental isolation, in an earlier experiment, of an apparently higher melting 2-ethoxy-4-ketodihydroquinazoline suggested that the hydrolysis product and the substance obtained by repeating McKee's experiment were nevertheless the same, and the problem resolved itself into showing that the two compounds with different melting points were yet identical. This was accomplished through methylation, both products (II) being converted into a new substance, 2-methoxy-3-methyl-4-ketodihydroquinazoline (V), on treatment with dimethyl sulfate. The new compound (V) was then subjected to acid hydrolysis and 3-methylbenzoylene urea (VI) obtained in both cases. That the variation in melting points is due to small amounts of benzoylene urea being present and affecting the temperature of the decomposition into benzoylene urea which ensues upon melting, remains a matter of conjecture. By condensing cyanimidocarbonic acid methyl ester with methyl anthranilate instead of the ethyl anthranilate employed by McKee, 2-methoxy-4-ketodihydroquinazoline identical, even to the melting point, with the same substance produced by the alkaline hydrolysis method, was obtained.

Two other isolated instances of the same partial hydrolysis in the presence of alkali were also observed. Attempts to remove the chlorine of 2-chloro-4-ethoxyquinazoline by treatment with dilute acids resulted only

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(10) Bogert and Scatchard, THIS JOURNAL, 41, 2062 (1919).

in the formation of benzoylene urea, and showed that the compound is totally unstable under these conditions. When it is boiled with alcoholic potash, however, only the ethoxy group is removed, and 2-chloro-4-ketodihydroquinazoline is formed. Similarly, 2,4-diphenoxyquinazoline, on warming with alcoholic potash, is transformed into 2-phenoxy-4-ethoxyquinazoline,[8] a slow hydrolysis to 2-phenoxy-4-ketodihydroquinazoline then taking place. By substituting sodium ethylate in alcohol for the alcoholic potash a more rapid hydrolysis is realized, both the phenoxyethoxy derivative and its methoxy analog being converted into 2-phenoxy-4-ketodihydroquinazoline.

All melting points given in this paper are corrected.

Experimental Part

The 2,4-dialkoxyquinazolines (I) used in these experiments were prepared by dissolving just two molecular proportions of sodium in a convenient volume of the absolute alcohol, adding a slight excess over one molecular proportion of 2,4-dichloroquinazoline, and refluxing on a steam-bath for two hours. The cooled solution was poured into a large excess of water and the precipitated dialkoxyquinazoline filtered off and crystallized from alcohol. In the following experiments 95% alcohols were employed unless otherwise stated.

Preparation of **2-Ethoxy-4-ketodihydroquinazoline** (II).—Four grams of 2,4-diethoxyquinazoline in 20 cc. of alcohol was added to 0.5 g. of sodium dissolved in 20 cc. of alcohol and the mixture gently boiled on a steam-bath for six hours. On cooling, it was poured into 200 cc. of water and the clear solution made just acid with acetic acid. The 3.3 g. of precipitate that separated was crystallized from alcohol, forming long colorless glistening needles, m. p. 179°. When methyl alcohol was used in place of the ethyl alcohol, the same product was obtained. With shorter periods of heating or when absolute alcohols were employed the hydrolysis was incomplete, and on pouring into water some unchanged diethoxyquinazoline, or 2-ethoxy-4-methoxyquinazoline when methyl alcohol was used, precipitated.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.12; H, 5.30. Found: C, 63.46: H, 5.25.

The substance, on warming with a little hydrochloric acid in alcohol, was completely hydrolyzed to benzoylene urea, m. p. 351°. On methylation with dimethyl sulfate the product described by Finger, 2-ethoxy-3-methyl-4-ketodihydroquinazoline (V), was obtained. Seven-tenths gram of 2-ethoxy-4-ketodihydroquinazoline dissolved in 10 cc. of normal sodium hydroxide was treated with 1 cc. of dimethyl sulfate and allowed to stand for twenty-four hours. The 0.6 g. of precipitate that separated crystallized from dilute alcohol in small prisms, m. p. 75–76°, and on warming with dilute hydrochloric acid was readily hydrolyzed to 3-methylbenzoylene urea, m. p. 242°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.67: H, 5.93. Found: C, 65.20; H, 6.05.

In one preliminary experiment in which diethoxyquinazoline was boiled with absolute methyl alcoholic sodium methylate for eight hours, a substance crystallizing from alcohol in small needles, m. p. 202–205°, was obtained. This material is apparently a higher melting variety of 2-ethoxy-4-ketodihydroquinazoline, but attempts to produce it again were unsuccessful, the normal form of the compound (m. p. 179°) always resulting. When it was mixed with the latter the melting point was 185°, and hydrolysis with dilute hydrochloric acid gave benzoylene urea as before. On methylation with dimethyl sulfate a partial hydrolysis occurred and a pasty product (m. p. 190–220° and 217–230° after an attempted purification), which, however, gave pure 3-methylbenzoylene urea on hydrolysis, was formed. Specimens of the normal compound melting at 179°, when contaminated with a small amount of benzoylene urea, underwent a slight lowering of the melting point.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.12; H, 5.30. Found: C, 62.74; H, 4.98; C, 62.65; H, 5.24.

Preparation of 2-Methoxy-4-ketodihydroquinazoline (II).—Four grams of 2,4-dimethoxyquinazoline and 0.5 g. of sodium, each dissolved in 20 cc. of methyl alcohol, were mixed and the solution boiled gently on a steam-bath for five hours. At the end of this time the cold solution was poured into 200 cc. of water and the 1.2 g. of unchanged dimethoxyquinazoline that precipitated was removed by filtration. The filtrate, acidified with acetic acid, yielded 2.1 g. of crude 2-methoxy-4-ketodihydroquinazoline, a further quantity of more impure material being obtained by salting out the final acid filtrate. Crystallization from alcohol gave short colorless needles, m. p. 218°. On warming an alcoholic solution of the substance with a little hydrochloric acid, benzoylene urea, m. p. 352°, precipitated. When 1.2 g. of dimethoxyquinazoline and 0.2 g. of sodium in 40 cc. of alcohol was boiled for five hours the hydrolysis was complete, the yield of precipitated 2-methoxy-4-ketodihydroquinazoline amounting to 1.0 g. As in the case of the ethoxy derivative, only a slight hydrolysis occurred when absolute alcohols were used as solvents.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.34; H, 4.58. Found: C, 61.90; H, 4.61; C, 61.71; H, 4.78.

Preparation of 2-Methoxy-3-methyl-4-ketodihydroquinazoline (V).—To 1.15 g. of 2-methoxy-4-ketodihydroquinazoline dissolved in 20 cc. of normal sodium hydroxide solution was added 2 cc. of dimethyl sulfate, and the mixture allowed to stand with occasional shaking, an alkaline reaction being maintained by adding small amounts of sodium hydroxide solution whenever necessary. A precipitate began to form immediately and within a few hours had filled the whole solution. After six hours the mixture was warmed on a water-bath to decompose any traces of dimethyl sulfate, the precipitate melting to a more compact mass. This was resolidified by cooling in running water for a few minutes, removed by filtration and dried, and weighed 1.0 g. Crystallization from dilute alcohol yielded 0.85 g. of small white needles, m. p. 93°, with a faint but pleasant odor similar to that of 2,4-dimethoxyquinazoline. The substance dissolved readily in warm dilute hydrochloric acid from which solution, after a few minutes, fine needles of 3-methylbenzoylene urea, m. p. 242°, separated. This hydrolysis product is evidently quite pure, for specimens of 3-methylbenzoylene urea obtained from the hydrolyses of 2-ethoxy-3-methyl-4-ketodihydroquinazoline described above also had m. p. 242°, the melting point of 3-methylbenzoylene urea recorded by previous investigators[10] being 237-238°. A mixed melting point using a sample of 3-methylbenzoylene urea prepared from benzoylene urea and methyl iodide following their procedure, confirmed the identity of the hydrolyzed products.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.12; H, 5.30. Found: C, 63.50; H, 5.44.

Preparation of 2-Methoxy-4-ketodihydroquinazoline by the Direct Method.[7]—Cyanimidocarbonic acid methyl ester, $HN{=}C(CN)OCH_3$, was prepared by McKee's modification of the method employed by Nef[11] in preparing the corresponding ethyl ester. The product was a colorless refractive oil with an odor similar to that of 2,4-dichloroquinazoline or of acetamide, and boiled around 50° at 40 mm. pressure. Six grams of the ester was mixed with 17 g. of ethyl anthranilate and 2.5 g. of cuprous chloride and the mixture immersed in water at 80°, since on gradually heating it to this temperature the reaction followed a different course and unknown products were formed. The 2-methoxy-4-ketodihydroquinazoline was isolated by following McKee's

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(11) Nef, *Ann.*, **287**, 296 (1895).

procedure. Short colorless needles, m. p. 225°, and identical in appearance with the 2-methoxy-4-ketodihydroquinazoline prepared by the alkaline hydrolysis of dimethoxyquinazoline, were obtained.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.34; H, 4.58. Found: C, 61.10; H, 4.74.

The substance was further purified by dissolving it in sodium hydroxide solution, reprecipitating with acetic acid, and recrystallizing from alcohol, m. p. 226°. When it was mixed with a specimen of the above-mentioned hydrolysis product, m. p. 218°, the melting point was 224°. These melting points are not strictly constant, however, and appear to be decomposition temperatures as well as melting points. The compound does not melt to a clear liquid but rather to a mush which only clears at much higher temperatures, and on cooling and reheating melts far above the original melting point. McKee gives the melting point as 231–232° followed by decomposition into benzoylene urea. The 2-methoxy-4-ketodihydroquinazoline prepared by hydrolysis behaved similarly except that the melting point of different preparations was constant (218°). The higher melting variety (226°) by the direct method was, therefore, treated with dimethyl sulfate and a product identical (mixed melting point) with the 2-methoxy-3-methyl-4-ketodihydroquinazoline already prepared by the corresponding methylation of the hydrolysis product, was obtained. This sample, on hydrolysis with dilute hydrochloric acid, also gave 3-methylbenzoylene urea as before, the latter being again identified by mixed melting points with known specimens of 3-methylbenzoylene urea.

A final confirmation of the identity of 2-methoxy-4-ketodihydroquinazoline when prepared by either the direct or the hydrolysis method was afforded by substituting methyl anthranilate for the ethyl anthranilate and repeating the condensation with cyanimidocarbonic acid methyl ester as described above. The product in this case formed colorless needles, m. p. 218°, and was identical in appearance with the alkaline hydrolysis product, m. p. 218°. When it was mixed with the latter there was no depression of the melting point.

Preparation of 2-Chloro-4-ketodihydroquinazoline, $NH—CO—C_6H_4N{=}CCl$, from 2-Chloro-4-ethoxyquinazoline.—One gram of 2-chloro-4-ethoxyquinazoline was dissolved in a lukewarm solution of 0.3 g. of potassium hydroxide in 25 cc. of alcohol and the solution allowed to stand overnight. It was then warmed for an hour and finally diluted with 100 cc. of water which precipitated 0.15 g. of unchanged chloroethoxyquinazoline. The filtrate from this precipitate had a turbid appearance and a neutral reaction; on acidifying it with acetic acid 0.6 g. of 2-chloro-4-ketodihydroquinazoline separated and was collected and dried. The substance is sparingly soluble in alcohol and crystallizes in feathery needles, m. p. 212°; when it was warmed with alcoholic aniline, 2-anilino-4-ketodihydroquinazoline[12] was formed. A second specimen of chloroketodihydroquinazoline, prepared by rubbing 2,4-dichloroquinazoline with normal sodium hydroxide solution,[13] diluting with water, filtering and acidifying the filtrate with acetic acid as before, also had m. p. 212°, and did not depress the melting point of the first product. Small amounts of the chloroketo compound were likewise obtained as a by-product in the preparation of diethoxyquinazoline from dichloroquinazoline by acidifying the aqueous filtrates remaining after the water precipitation already described for isolating the dialkoxy compound. For a general method of preparation, however, the procedure employing dichloroquinazoline and sodium hydroxide in aqueous solution is both simple and direct and gives the best yields of an easily purified product. The chloroketodihydroquinazoline obtained by boiling dichloroquinazoline in alcoholic solution with sodium acetate is at best a by-product, and is difficult to purify.[14]

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(12) Lange and Sheibley, THIS JOURNAL, **54**, 1997 (1932).

(13) British Patent 287,179.

(14) Lange and Sheibley, THIS JOURNAL, **53**, 3871 (1931).

For analysis the substance was simply warmed with dilute nitric acid for a few minutes or until the decomposition appeared to be complete, and the benzoylene urea removed by filtration and weighed, chlorine being determined gravimetrically on the filtrate; recovered: 93.6% of the theoretical amount of benzoylene urea.

Anal. Calcd. for $C_8H_5ON_2Cl$: Cl, 19.64. Found: Cl, 19.45.

Preparation of 2-Phenoxy-4-ketodihydroquinazoline, $\overline{NH-CO-C_6H_4N=C}OC_6H_5$.—One gram of 2,4-diphenoxyquinazoline was added to 0.2 g. of potassium hydroxide dissolved in 25 cc. of alcohol and the mixture warmed on the steam-bath for four hours, the diphenoxy compound dissolving completely in about half this time. The solution was allowed to cool and diluted with 100 cc. of water, the white opaque suspension which resulted coagulating within a day or so to 0.7 g. of 2-phenoxy-4-ethoxyquinazoline. The filtrate, after removal of the ethoxy derivative, was acidified with acetic acid and 0.1 g. of 2-phenoxy-4-ketodihydroquinazoline thus precipitated.

The 0.7 g. of phenoxyethoxyquinazoline in 25 cc. of alcohol containing 0.2 g. of sodium was warmed for four and one-half hours, allowed to cool, and diluted with 80 cc. of water. After adding 3 cc. of normal sodium hydroxide, the solution was boiled to remove most of the alcohol and filtered hot from a trace of precipitate. Acidification of the cold solution as above precipitated 0.65 g. of the product. The 0.75 g. of 2-phenoxy-4-ketodihydroquinazoline thus obtained was crystallized from about 70 cc. of hot alcohol, in which it is somewhat more soluble than the corresponding 2-anilino-4-ketodihydroquinazoline, and separated in glistening silky hair-like needles, m. p. 272°; yield 0.65 g. The compound is soluble with decomposition in warm dilute (1:1) hydrochloric acid, from which solution needles of benzoylene urea separate on cooling.

Anal. Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.56; H, 4.23. Found: C, 70.99; H, 4.58.

Summary

Alkaline conditions have been found to effect a partial hydrolysis of 2,4-dialkoxyquinazolines with the formation of 2-alkoxy-4-ketodihydroquinazolines. These products are shown to be identical with the same substances produced previously by methods involving a ring closure, and demonstrate conclusively the constitutions of 2-ethoxy-4-methoxyquinazoline and 2-methoxy-4-ethoxyquinazoline. Similarly, 2-chloro-4-ethoxyquinazoline and 2-phenoxy-4-alkoxyquinazolines are hydrolyzed to 2-chloro-4-ketodihydroquinazoline and 2-phenoxy-4-ketodihydroquinazoline, respectively. Two new compounds, 2-methoxy-3-methyl-4-ketodihydroquinazoline and 2-phenoxy-4-ketodihydroquinazoline, have been prepared.

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