

An explanation of the mechanism of the oxidation of rotenone derivatives by hydrogen peroxide is given.

The behavior of tubaic acid on hydrogenation is analogous to that of desoxycodeine-C. Both contain the same groupings and both give tetrahydrophenols under the same conditions.

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QUINAZOLINES. III. THE INTERACTION OF ANILINE WITH 2-CHLORO-4-ALKOXYQUINAZOLINES AND 2-CHLORO-4-KETODIHYDROQUINAZOLINE

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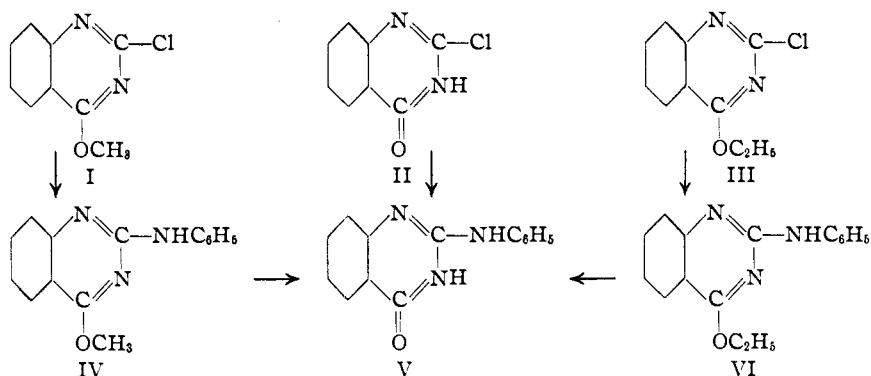
When 2,4-dichloroquinazoline in alcohol is boiled with sodium acetate, a compound with properties and a composition corresponding to a chloro-ketodihydroquinazoline is always found among the reaction products. In an earlier communication it was stated that by analogy with the similarly formed 2-chloro-4-alkoxyquinazolines this substance was most likely 2-chloro-4-ketodihydroquinazoline but that attempts to confirm this view by converting it into the known 4-ketodihydroquinazoline and 2-ethoxy-4-ketodihydroquinazoline were unsuccessful.¹

The ease with which aniline replaces both of the chlorine atoms of 2,4-dichloroquinazoline with phenylamino groups suggested the possibility of transforming 2-chloro-4-alkoxyquinazolines into 2-anilino derivatives. By treating 2-chloro-4-methoxyquinazoline (I) and 2-chloro-4-ethoxyquinazoline (III) with aniline in alcohol, hydrochlorides of 2-anilino-4-methoxyquinazoline (IV) and 2-anilino-4-ethoxyquinazoline (VI), respectively, are obtained. These last, on hydrolysis with dilute hydrochloric acid in the presence of aniline, or simply on heating, when the elements of an alkyl chloride are evolved, revert to the known 2-anilino-4-ketodihydroquinazoline (V), a compound which results directly when the previously mentioned chloroketo compound is treated with an alcoholic solution of aniline, and thus identifies the latter as 2-chloro-4-ketodihydroquinazoline (II).

A confirmation of the orientation of the halogen and alkoxy groups in the chloro-alkoxy derivatives arrived at in a previous paper² is afforded

¹ Lange and Sheibley, *THIS JOURNAL*, **53**, 3871 (1931).

² Lange, Roush and Asbeck, *ibid.*, **52**, 3696 (1930).



by the identity of (V) with a specimen of 2-anilino-4-ketodihydroquinazoline prepared according to the method of previous investigators.³ When phenylpseudomethylthiourea in ethereal solution was treated with anthranilic acid, what appeared to be an anthranilate of the base was precipitated. This product on fusion evolved methyl mercaptan, and the residue, treated with sodium hydroxide, yielded a product identical with (V) in every respect.

The free bases, 2-anilino-4-methoxyquinazoline (IV) and 2-anilino-4-ethoxyquinazoline (VI), are readily obtained from their hydrochlorides by treatment with sodium alcoholates. They are colorless, easily soluble substances, crystallizing in plates rather than the usual needles common to this class of compounds, and form characteristic salts.

All melting points given in this paper are corrected.

Experimental Part

Preparation of $N=COCH_3C_6H_4N=CNHC_6H_5 \cdot HCl$, 2-Anilino-4-methoxyquinazoline Hydrochloride.—A mixture of 2.2 g. of 2-chloro-4-methoxyquinazoline and 1.2 g. of aniline was dissolved in 30 cc. of alcohol and the solution boiled under a reflux condenser on a steam-bath for one hour. The condenser was then removed and the alcohol allowed to evaporate until the total volume of the reaction mixture was about 10 cc. This was cooled slightly, or till crystallization just began, and diluted with 40 cc. of ether; the precipitated mass was disintegrated with a glass rod, filtered and washed with ether, and weighed 3.1 g. A crystallization from alcohol yielded 1.8 g. of slightly yellow needles (m. p. 152°); further purification was effected by recrystallizing from methyl alcohol containing a few drops of concentrated hydrochloric acid, when colorless needles of 2-anilino-4-methoxyquinazoline hydrochloride, melting around 160° (decomp.), were obtained.

Similarly when 1.5 g. of chloromethoxyquinazoline and 0.9 g. of aniline in 25 cc. of methyl alcohol were heated, 0.75 g. of a precipitate (m. p. 295° , and probably impure benzoylene urea) separated after the first half hour of heating and was removed by filtration. Concentration of the filtrate and precipitation with ether as outlined above yielded 1.6 g. of crude 2-anilino-4-methoxyquinazoline hydrochloride.

³ Wheeler, Johnson and McFarland, *THIS JOURNAL*, **25**, 797 (1903).

This compound is soluble in alcohol, methyl alcohol or acetone, and insoluble in water, concentrated hydrochloric acid or ether. Its melting point was found to vary slightly but in general pure specimens melted within the range 158–161° (decomp. and foaming with loss of methyl chloride), the melts then solidifying and remelting within a range of 255–260°, the latter melting points being identical with those of impure specimens of 2-anilino-4-ketodihydroquinazoline (V). Recrystallization from ethyl alcohol gave blunt needles or prisms somewhat shorter than the crystals from methyl alcoholic solutions but of identical melting point.

A platinichloride was immediately precipitated on mixing hot methyl alcoholic solutions of the hydrochloride and platinum chloride. Washed with hot methyl alcohol and dried, it formed a granular, light orange, micro-crystalline mass, softening with decomposition at 225–230°, and soluble only in chlorohydrin. It ignites without melting.

Anal. Calcd. for $C_{15}H_{14}ON_3Cl$: C, 62.59; H, 4.91; N, 14.61; Cl, 12.33. Found: C, 62.94; H, 5.00; N, 14.51; Cl, 12.21. Calcd. for $(C_{15}H_{14}ON_3Cl)_2PtCl_4 \cdot H_2O$: Pt, 20.99. Found: Pt, 20.89, 20.98.

Preparation of $N=COC_2H_5C_6H_4N=CNHC_6H_5 \cdot HCl$, 2-Anilino-4-ethoxyquinazoline Hydrochloride.—This compound was obtained in the same manner as the anilino-methoxy derivative just described: 1.5 g. of 2-chloro-4-ethoxyquinazoline and 0.75 g. of aniline in 25 cc. of alcohol yielded 2.0 g. of crude precipitated product. A crystallization from alcohol gave 1.2 g. of fine needles (m. p. 161°): further recrystallizations from alcohol containing a few drops of hydrochloric acid resulted in colorless needles melting around 170°. The solubilities of this substance are the same as those of the analogous anilinomethoxy salt. Its melting point was also variable, pure specimens fusing within the range 168–171° with evolution of ethyl chloride and consequent solidifying and remelting around 259° due to the formation of 2-anilino-4-ketodihydroquinazoline (V). When kept at 40° for a day or so, these hydrochlorides often acquire a yellow color without any apparent change in composition.

Anal. Calcd. for $C_{16}H_{16}ON_3Cl$: C, 63.66; H, 5.35; Cl, 11.76. Found: C, 64.32; H, 5.27; Cl, 12.00.

Hydrolysis of the Hydrochlorides of 2-Anilino-4-methoxyquinazoline (IV) and 2-Anilino-4-ethoxyquinazoline (VI) to 2-Anilino-4-ketodihydroquinazoline (V).—Originally, instead of precipitating it with ether as described above, 2-anilino-4-ethoxyquinazoline hydrochloride was isolated by pouring the alcoholic reaction mixture into water, adding sufficient hydrochloric acid to dissolve the droplets of excess aniline, and removing the precipitated product by filtration. This method was later found to promote an appreciable hydrolysis; moreover, when it was attempted to prepare the anilino-methoxyquinazoline hydrochloride in the same way, the precipitation of the product was incomplete and on warming hydrolysis ensued. However, when pure specimens of these hydrochlorides were boiled with alcoholic hydrochloric acid and even with concentrated aqueous hydrochloric acid, aniline being absent, no appreciable hydrolysis was observed; this stability toward hydrolysis is in contrast to the non-basic and easily hydrolyzed 2-chloro-4-alkoxyquinazolines which even on standing soon decompose into benzoylene urea. Because of this property, the following procedure was finally adopted. One-half gram of 2-anilino-4-methoxyquinazoline hydrochloride with 5 cc. of alcohol, 10 drops of hydrochloric acid, 2 drops of aniline and 10 cc. of water was slowly taken to dryness on a steam-bath over a period of three hours or longer. The residue was washed with hot water and dissolved in normal sodium hydroxide, the solution diluted, filtered and precipitated from the hot solution by the addition of acetic acid. The white precipitate of 2-anilino-4-ketodihydroquinazoline thus obtained was washed with hot water

and dried, m. p. 261°. A similar treatment of 2-anilino-4-ethoxyquinazoline hydrochloride gave the same product, also in a practically theoretical yield, m. p. 261°.

Preparation of 2-Anilino-4-ketodihydroquinazoline (V) from 2-Chloro-4-ketodihydroquinazoline (II).—One and seventy-five hundredths grams of chloroketodihydroquinazoline and 1.0 g. of aniline were dissolved in 50 cc. of alcohol and the solution warmed on a steam-bath. A precipitate began to separate after the first few minutes of heating; at the end of two and one-half hours the mixture was cooled, diluted with 60 cc. of ether, and the precipitate filtered, washed with ether and dried. The 1.9 g. of material thus obtained was dissolved in hot normal sodium hydroxide and precipitated from the hot solution with acetic acid in the usual manner; this precipitate was filtered, washed with hot water and dried. It crystallized from an alcoholic solution to which water had been added in the form of tiny snow white rosetts of minute needles, m. p. 261°. The compound is sparingly soluble in alcohol, acetone or methyl alcohol, and crystallizes in the same minute needles from all three solvents. It is insoluble in ether or ammonia but soluble in sodium hydroxide or concentrated sulfuric acid. For analysis, drying at temperatures above 100° was necessary in order to remove 2-3% of moisture which adhered to the material crystallized from dilute alcohol.

Anal. Calcd. for $C_{14}H_{11}ON_3$: C, 70.85; H, 4.68. Found: C, 70.80; H, 4.84.

Preparation of 2-Anilino-4-ketodihydroquinazoline (V) from Phenylpseudo-methylthiourea.³—Ten grams of the hydroiodide of phenylpseudomethylthiourea⁴ was dissolved in ether and converted into the free base by shaking with an aqueous solution of sodium carbonate. The ethereal layer, washed three times with water, was treated with 5 g. of anthranilic acid, when a slight evolution of heat occurred and 8.5 g. of a precipitate, m. p. 118°, and evidently an anthranilate of the base, soon separated. This product after filtering from the ether and drying was heated in an oil-bath at 120-130° for three hours; methyl mercaptan was evolved and a red glassy melt remained. Several extractions of this with boiling alcohol removed the viscous red material; the residue was dissolved in twice normal sodium hydroxide, filtered and precipitated with acetic acid as before. The dried precipitate was dissolved by prolonged boiling in alcohol and crystallization effected by diluting with water; m. p. 261°.

Melting points of mixtures of this product with the same compound obtained by the other three methods of preparation (*i. e.*, hydrolysis of the two anilino-alkoxy derivatives and the product of condensation of chloroketodihydroquinazoline with aniline) showed no depression. A mixture composed of samples from each of the products from the four methods of preparation melted at 261°.

Anal. Calcd. for $C_{14}H_{11}ON_3$: C, 70.85; H, 4.68. Found: C, 70.70; H, 4.78.

Preparation of 2-Anilino-4-methoxyquinazoline (IV).—To 0.4 g. of sodium dissolved in 40 cc. of methyl alcohol was added 1.9 g. of 2-anilino-4-methoxyquinazoline hydrochloride and the solution warmed slightly until a considerable quantity of sodium chloride began to separate. After standing overnight the mixture was poured into 100 cc. of water, when a white opaque suspension resulted. This began to crystallize immediately and within three hours the separation was complete. The crystalline product was filtered, dried and amounted to 1.53 g. of the crude base. Recrystallization was effected from either methyl alcohol or a hot methyl alcoholic solution to which a little water was added, the separation being more nearly complete when the latter method was employed.

The compound forms small colorless glistening plates, m. p. 113°. It is soluble in alcohol, methyl alcohol, petroleum ether, acetone or ether and insoluble in water. Treatment with hydrochloric acid in methyl alcohol regenerated the hydrochloride salt

⁴ Bertram, *Ber.*, 25, 49 (1892).

described above. When hot alcoholic solutions of the base and picric acid were mixed, a flocculent yellow precipitate consisting of fine needles of the picrate separated. This was washed with water and recrystallized from alcohol, from which it slowly separates as fine, light yellow, feathery needles, m. p. 210°.

Anal. Calcd. for $C_{15}H_{13}ON_3$: C, 71.68; H, 5.22. Found: C, 72.08; H, 5.15.

Preparation of 2-Anilino-4-ethoxyquinazoline (VI).—This compound was prepared in essentially the same way as the methoxy derivative just described. Ethyl alcohol was employed and the coagulation of the precipitate obtained on pouring the mixture into water was a matter of days rather than hours. One gram of 2-anilino-4-ethoxyquinazoline hydrochloride and 0.3 g. of sodium in 25 cc. of alcohol gave 0.85 g. of the crude precipitated base, which was recrystallized from 50% alcohol.

This compound separates as colorless glistening plates, m. p. 110–111°, somewhat larger than the crystals of 2-anilino-4-methoxyquinazoline. Its solubilities are the same as those given for the last-named substance. Addition of hydrochloric acid regenerated the hydrochloride but attempts to form an addition product with methyl iodide were unsuccessful. The picrate, prepared in the manner outlined above, crystallized from alcohol in rosetts of coarse yellow needles, m. p. 183°; glossy needles were obtained on slow evaporation of the solvent.

Anal. Calcd. for $C_{16}H_{16}ON_3$: C, 72.41; H, 5.70. Found: C, 72.67; H, 5.81.

Summary

Aniline has been found to react with 2-chloro-4-ketodihydroquinazoline and with 2-chloro-4-alkoxyquinazolines to yield 2-anilino-4-ketodihydroquinazoline and hydrochlorides of 2-anilino-4-alkoxyquinazolines, respectively. The constitutions of 2-chloro-4-alkoxyquinazolines and of 2-chloro-4-ketodihydroquinazoline are demonstrated by their conversion into the known 2-anilino-4-ketodihydroquinazoline. The following new compounds have been prepared: 2-anilino-4-methoxyquinazoline, 2-anilino-4-ethoxyquinazoline and their picrates and hydrochlorides.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE BUREAU OF DAIRY
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BETA-SULFHYDRYL-BETA-PHENYLPROPIOPHENONE

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The writer has recently¹ had occasion to examine certain β -mercapto ketones of the type $C_6H_5CH(SR)CH_2COR'$, particularly from the point of view of their instability toward alkaline reagents. These ketones were readily obtained by the addition of mercaptans to α,β -unsaturated ketones in the presence of alkalis. To use β -*p*-tolylmercapto- β -phenylpropio-phenone as an example, two characteristic reactions are as follows: (a) with alkali, easy loss of tolyl mercaptan to form benzalacetophenone; (b) with phenylhydrazine, easy loss of the mercaptan to form 1,3,5-triphenylpyrazoline.

¹ Nicolet, THIS JOURNAL, 53, 3066 (1931).