pentanol-1, hexanol-1, heptanol-1, methyl-2-butanol-1, methyl-2-pentanol-1, methyl-3-butanol-1, methyl-3-pentanol-1, methyl-3-hexanol-1, methyl-4-pentanol-1, pentanol-2, hexanol-2, pentanol-3, heptanol-4, methyl-2-butanol-2, methyl-3-pentanol-3, α-phenylethyl, α-phenylpropyl and α-phenylbutyl alcohols.

2. The results obtained, together with those from an earlier investigation of the lower fatty alcohols, make possible definite conclusions as to the effect of structure on the reactivity of the hydroxyl-hydrogen atoms of alcohols.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY No. 554]

RESEARCHES ON QUINAZOLINES. XXXVIII. THE SYNTHESIS OF SOME NEW ANALOGS OF CINCHOPHEN AND INTERMEDIATE PRODUCTS

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RECEIVED AUGUST 3, 1927 PUBLISHED OCTOBER 5, 1927

Our knowledge of the pharmacodynamics of the quinazoline group is scattering, fragmentary and meager. It, therefore, seems to us worth while to endeavor to contribute something to this field, not only with the object of throwing additional light upon the connection between chemical constitution and physiological effects, but also in the hope of discovering new compounds of therapeutic value. In this undertaking we have been so fortunate as to enlist the valuable coöperation of two distinguished pharmacologists, Professors Arthur D. Hirschfelder, of the University of Minnesota, and Elbert W. Rockwood, of the State University of Iowa, whose investigations will be published in appropriate journals.

The syntheses recorded in this paper were for the purpose of obtaining quinazoline derivatives of cinchophen (atophan) type, carrying a carboxyl group in Position 4 and hydroxylated phenyls in Position 2, since the preliminary pharmacological examination of the di-ammonium salt of 2-phenylquinazoline-4,2′-dicarboxylic acid, synthesized by Bogert and Nabenhauer,[2] had given results which looked both interesting and promising.

From these carboxylic acids, ethyl esters also were prepared, giving compounds analogous to acitrin; while the 2-hydroxyphenyl-4-carboxylic acids are intermediate between our 4,2′-dicarboxylic acid and the well-known hexophan of the cinchophen series.

These 2-hydroxyphenylquinazolines were synthesized because Kalle and

[1] This research was made possible by a generous grant from the Sigma Xi Foundation, for whose assistance we are most grateful.—M. T. B. and E. M. McC.

[2] Bogert and Nabenhauer, THIS JOURNAL, **46**, 1702 (1924).

Company took out a patent[3] in 1915 for the manufacture of 2-hydroxyphenylquinoline-4-carboxylic acids, in which they claimed that their action was similar to that of cinchophen, but without its bitter taste or irritating action upon the stomach, that the hydroxyl groups endowed them with pronounced antiseptic and antipyretic properties, that they exhibited a definite beneficial action against the plasmodia of malaria similar to that of quinine and that they were also of value in the treatment of pertussis.

The plan of synthesis followed that developed by Bogert and Nabenhauer,[2] and consisted in the preparation of the substituted *o*-amino-acetophenone, oxidation of this to the corresponding isatinic acid and the conversion of the latter into the quinazoline derivative by heating it with alcoholic ammonia under pressure.

$$H_2NC_6H_4COCH_3 \longrightarrow RCONHC_6H_4COCH_3 \longrightarrow RCONHC_6H_4COCOOH \longrightarrow$$

$$\overbrace{RC{:}NC_6H_4C(COOH){:}N}$$

Experimental Part

Quinazoline itself, required for an investigation which will be reported later, was prepared from *o*-nitrobenzaldiformamide by a modification of the excellent method of Riedel.[4] The yield of pure *o*-nitrobenzaldiformamide (m. p. 178°, corr.) was 70%. It was converted into quinazoline as follows.

To a mixture of 20 g. of finely pulverized diformamide with 60 g. of zinc dust, there were slowly added 240 g. of cracked ice and then 80 g. of glacial acetic acid, while the mixture was being well shaken. When a 25% solution of acetic acid was employed, with external cooling instead of using cracked ice in the mixture, local superheating occurred and the yield of quinazoline was much less. After the reduction had been completed by shaking the mixture for about an hour, with frequent additions of small amounts of zinc dust, the acid solution was filtered from the excess of zinc dust. Sufficient caustic alkali (400 cc. of 50% sodium hydroxide solution) was added to this filtrate to redissolve the zinc hydroxide precipitated, the alkaline solution was extracted repeatedly with ether, the ethereal extracts dried over sodium sulfate, the solvent evaporated and the residual quinazoline purified by crystallization from petroleum ether or by distillation; yield of pure product, m. p. 48°, 10 g. or 93%.

Attempts were made to use a crude *o*-nitrobenzaldehyde, containing some of the *m*-nitro isomer, in place of the pure *o*-compound, but it was found that this necessitated a laborious separation of the formamide condensation products and it was, therefore, abandoned.

Salicyl Chloride was prepared from sodium salicylate and thionyl chloride by the process of Kopetschni and Karczag,[5] which was found preferable to that of Wolffenstein.[6]

o-(*o*-**Nitrobenzoylamino**)-**acetophenone**, $O_2NC_6H_4CONHC_6H_4COCH_3$.—To a vigor-

[3] Kalle and Co., Ger. pat. 284,233 (1915).

[4] Riedel, Ger. pat. 174,941 (1905).

[5] Kopetschni and Karczag, *Ber.*, **47**, 235 (1914).

[6] Wolffenstein, Ger. pat. 284,161 (1915).

ously agitated dispersion of 8 g. of *o*-amino-acetophenone in 100 cc. of a 10% aqueous sodium hydroxide solution, there was added 20 g. of *o*-nitrobenzoyl chloride. The mixture was thoroughly shaken while the flask was well cooled externally. When the odor of the acid chloride was no longer perceptible, the precipitate was collected and crystallized from alcohol. Colorless needles were obtained, m. p. 156° (corr.); yield, 13 g. or 78%.

Anal. Calcd. for $C_{15}H_{12}O_4N_2$: C, 63.37; H, 4.26. Found: C, 63.75; H, 4.45.

o-(*m*-**Nitrobenzoylamino**)-**acetophenone,** prepared in a similar manner and in approximately the same yield, formed colorless needles, m. p. 170° (corr.).

Anal. Calcd. for $C_{15}H_{12}O_4N_2$: C, 63.37; H, 4.26. Found: C, 63.32; H, 4.30.

o-**Salicylamino-acetophenone,** $HOC_6H_4CONHC_6H_4COCH_3$.—A benzene solution of 20 g. of salicyl chloride and 15 g. of *o*-amino-acetophenone was refluxed until the evolution of HCl ceased. The solution gradually darkened during this heating and, when finally permitted to cool, a mass of brown needles separated which when decolorized and crystallized from alcohol appeared in colorless needles, m. p. 135° (corr.); yield, 17 g. or 59%.

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 70.58; H, 5.14. Found: C, 70.62; H, 4.90.

Attempts to condense salicyl chloride with the amino-acetophenone in the presence of either alkali or pyridine were unsuccessful.

o-(*p*-**Acetoxybenzoylamino**)-**acetophenone,** $CH_3COOC_6H_4CONHC_6H_4COCH_3$.—To a vigorously shaken dispersion of 8 g. of *o*-amino-acetophenone in 200 cc. of 5% aqueous sodium hydroxide solution, there was added 20 g. of *p*-acetoxybenzoyl chloride, while the flask was cooled under tap water and the shaking was continued until the odor of the acid chloride had disappeared (long continued contact of the acetate so formed with excess of dilute caustic alkali solution gradually causes hydrolysis of this ester). The precipitate, when collected and dried, melted at 95°; yield, 15.2 g. or 89%. Recrystallized from alcohol to the constant melting-point of 97.5° (corr.), it formed colorless plates; yield, about 75%.

Anal. Calcd. for $C_{17}H_{15}O_4N$: C, 68.66; H, 5.09. Found: C, 68.60; H, 5.12.

Dilute aqueous solutions of caustic soda, hydrochloric or acetic acid, when warm, hydrolyzed both the ester and amide unions, giving *p*-hydroxybenzoic acid.

o-(*p*-**Hydroxybenzoylamino**)-**acetophenone** was obtained from the foregoing aceto derivative. The problem was to hydrolyze the ester grouping without simultaneous hydrolysis of the amide union, and two methods of accomplishing this were found. One was based upon the greater sensitiveness of the ester grouping to the continued action of cold dilute caustic alkali, and the other upon the greater stability of ethyl acetate.

In the former case, 15.2 g. of unrecrystallized acetate was shaken with 200 cc. of 5% sodium hydroxide solution until the solid was dissolved completely (three hours). Then the solution was acidified and the precipitate removed, dried and crystallized from 95% alcohol. Colorless needles were obtained, m. p. 219° (corr.); yield, 11.8 g. or 90%.

By the other method, 1 g. of the acetate was dissolved in 20 cc. of ethyl alcohol, 1 cc. of concd. sulfuric acid added, the solution warmed for 30 minutes at 50°, then diluted largely with water, the precipitate collected, dissolved in dilute caustic soda, the solution filtered from a small quantity of unhydrolyzed initial material, acidified, the precipitate removed and crystallized from alcohol; yield, 0.65 g.; m. p. 219° (corr.).

Of these two methods, the former proved the more satisfactory. This product could not be obtained by the method used for the isomeric salicyl derivative.

Anal. Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.14. Found: C, 70.04; H, 5.14.

All efforts to prepare the isomeric *o*-(*m*-hydroxybenzoylamino) derivative proved futile.

o-**Nitrobenzoyl Isatinic Acid,** $O_2NC_6H_4CONHC_6H_4COCOOH$.—To a suspension of 11 g. of *o*-(*o*-nitrobenzoylamino)-acetophenone in 200 cc. of cold water, there was added a solution of 12.2 g. of potassium permanganate and 4 g. of potassium hydroxide in 100 cc. of water, and the mixture was allowed to stand at laboratory temperature for 48 hours with occasional stirring, the color gradually changing from the purple of the permanganate to the dirty green of the manganate. The manganese in solution was precipitated by the addition of 12 g. of ferrous sulfate dissolved in 100 cc. of water. The filtrate from the manganese oxides was acidified and the brownish nitrobenzoyl isatinic acid which separated was collected and dried; yield, 5 g. By repeated extraction of the manganese dioxide sludge with hot alcohol, 3.5 g. of the initial unoxidized acetophenone was recovered. Based upon the 7.5 g. of acetophenone actually oxidized, the yield of isatinic acid was approximately 60%. Because of the instability of these *o*-substituted isatinic acids, as found by Bogert and Nabenhauer,[2] further purification or analysis was not attempted. Hydrolyzed by caustic alkali, the compound formed isatin and *o*-nitrobenzoic acid.

Salicyl Isatinic Acid, $HOC_6H_4CONHC_6H_4COCOOH$.—To a solution of 2.5 g. of *o*-salicylamino-acetophenone in 10 cc. of 10% caustic soda solution, 40 g. of cracked ice was added and then a solution of 2.75 g. of potassium permanganate in 25 cc. of water. The color of the solution changed rapidly to green and, after standing for an hour at laboratory temperature, to a clear yellow. When it had stood for two hours longer at room temperature, the solution was removed from the dioxide sludge, acidified, the light-yellow precipitated isatinic acid collected, dissolved in 25 cc. of hot alcohol, the solution cooled and filtered from a small amount of unoxidized initial ketone, the filtrate heated to boiling and boiling water added carefully until the acid began to separate. As the solution cooled, the acid precipitated in yellowish, fluffy needles; yield, 2.5 g. or 90%. After several crystallizations, it melted with decomposition at about 209–210°, the melting point varying considerably with the rate of heating. Hydrolyzed by dilute sodium hydroxide solution, it yielded isatin and salicylic acid.

Anal. Calcd. for $C_{15}H_{11}O_5N$: C, 63.16; H, 3.86. Found: C, 64.28; H, 4.15.

These analytical figures indicate the difficulty experienced in the purification of the product.

p-**Hydroxybenzoyl Isatinic Acid** was prepared in the same way as the analogous *o*-isomer, in similar yields and of approximately the same melting point. When hydrolyzed, it formed isatin and *p*-hydroxybenzoic acid.

Anal. Calcd. for $C_{15}H_{11}O_5N$: C, 63.16; H, 3.86. Found: C, 63.96; H, 3.93.

2-(*o*-Nitrophenyl)-quinazoline-4-carboxylic Acid, $O_2NC_6H_4C_8H_4N_2COOH$.—A solution of 5 g. of *o*-nitrobenzoyl isatinic acid and 7 g. of dry ammonia in 70 cc. of absolute methanol was heated in a sealed tube for ten hours at 140°, and the reaction product isolated as described beyond for the *o*-hydroxyphenyl derivative. After recrystallizing this crude product seven times from 50% alcohol, it melted at 235° (corr.) but was still impure, as shown by the following analysis.

Anal. Calcd. for $C_{15}H_9O_4N_3$: C, 61.01; H, 3.07. Found: C, 59.37; H, 3.64.

Not enough material was available for further purification, and the experiment was not repeated.

2-(*o*-Hydroxyphenyl)-quinazoline-4-carboxylic Acid, $HOC_6H_4C_8H_4N_2COOH$.—A solution of salicyl isatinic acid in absolute methanol, containing one to three g. of dry ammonia per g. of the isatinic acid, was heated in a sealed tube for 20 hours at 110°, after which the solvent was evaporated, the residue dissolved in hot water, the filtered solution decolorized and acidified carefully, and the yellow flocculent precipitate dried; yield, 99%. After five recrystallizations from dilute alcohol, the fine, yellow needles obtained melted constantly at 171° (corr.).

Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.66; H, 3.79. Found: C, 67.84; H, 3.90.

ETHYL ESTER.—A solution of 1 g. of the acid in a little absolute alcohol was added to 20 cc. of absolute alcohol containing 5 g. of dry hydrogen chloride and after this solution had stood for 13 hours at laboratory temperature, it was heated for an hour and a half at 60°, then concentrated to small volume, about 50 cc. of water added, sodium carbonate added in excess and the cloudy suspension allowed to settle. The ester separated as a yellow solid; yield, 0.76 g. or 70%. After two recrystallizations from dilute alcohol it formed yellow, glistening plates, m. p. 115° (corr.).

Anal. Calcd. for $C_{17}H_{14}O_3N_2$: C, 69.37; H, 4.80. Found: C, 69.72; H, 4.89.

2-(*p*-Hydroxyphenyl)-quinazoline-4-carboxylic Acid, prepared in a similar manner from the corresponding isatinic acid and methanol solution of dry ammonia heated together in a sealed tube for 24 hours at 110°, was purified by crystallization from dilute acid until its melting point remained constant at 251° (corr.). It formed fine, yellow needles of somewhat more orange shade than its *o*-hydroxy isomer; yield, 95%.

ETHYL ESTER.—As only a small amount of the free acid was prepared, it was not analyzed but was all utilized for the production of its ethyl ester, by the method described above for its *o*-hydroxy isomer. After repeated crystallization from dilute acetone, it appeared in yellow plates, m. p. 159° (corr.); yield, 75%.

Anal. Calcd. for $C_{17}H_{14}O_3N_2$: C, 69.37; H, 4.80. Found: C, 69.11; H, 4.85.

2-Phenylquinazoline-4,2'-dicarboxylic Acid, $HOOCC_6H_4C_8H_4N_2COOH$, was synthesized as described by Bogert and Nabenhauer.[3] Inasmuch as the pharmacological tests hitherto carried out had been with the di-ammonium salt, it was thought desirable to examine also the disodium salt, which was obtained as follows.

A saturated solution of 18.5 g. of the acid in hot absolute alcohol (760 cc.) was treated with a sodium ethylate solution prepared from 70 cc. of absolute alcohol and 2.65 g. of metallic sodium. The sodium salt separated rapidly as the solution was stirred. It was collected, washed with absolute alcohol until the washings were neutral to litmus, and it then formed fine colorless needles, easily soluble in water. The solution was neutral to phenolphthalein and to methyl orange and had a saline, slightly bitter taste. In the free flame it melted with decomposition and charring. Its pharmacological properties are now being studied by Professor Rockwood.

Summary

1. Various new acylated *o*-amino-acetophenones have been prepared.

2. These ketones have been oxidized to the corresponding isatinic acids.

3. From the isatinic acids, quinazoline derivatives of cinchophen type have been obtained and are being tested pharmacologically.

NEW YORK, N. Y.