[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY No. 446]

RESEARCHES ON QUINAZOLINES. XXXVI. A QUINAZOLINE ANALOG OF CINCHOPHEN (ATOPHAN). THE SYNTHESIS OF NEW QUINAZOLINE CARBOXYLIC ACIDS FROM ISATIN AND FROM ORTHO-AMINO-ACETOPHENONE

BY MARSTON TAYLOR BOGERT AND FRED PAUL NABENHAUER[1]

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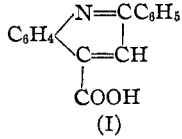
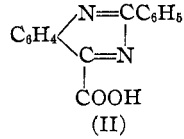
Introductory

Among the most useful synthetic drugs of the quinoline group are the uric acid eliminants of the Cinchophen (I), or Atophan, class. The major purpose of the investigation recorded herein was to prepare a quinazoline analog (II) of this well-known remedy, in order that the therapeutic value of the two might be compared and additional light thrown upon the connection between physiological action and chemical configuration.



(I)



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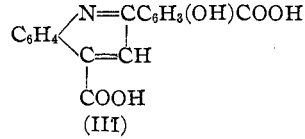

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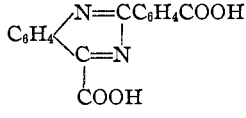
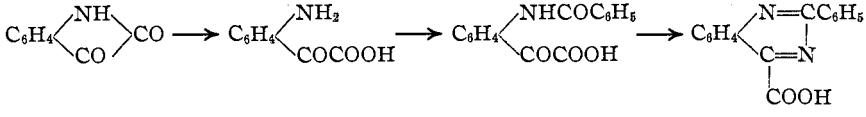
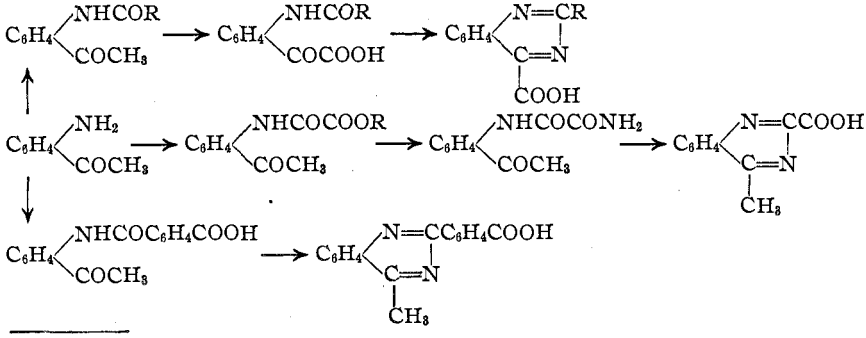


(IV)

The synthesis comprised the following steps, and was entirely successful.

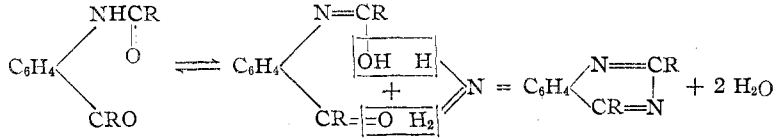


From *o*-amino-acetophenone, other quinazoline carboxylic acids were obtained by one or more of the following series of reactions.



[1] This investigation was made possible through the generous assistance of E. I. du Pont de Nemours and Company, Inc., for Dr. Nabenhauer was du Pont Fellow at Columbia University during the prosecution of the work.—M. T. B.

The final step in all of these syntheses is similar to that employed by Bischler and his co-workers in the synthesis of quinazolines, and may be generalized thus,



Of the new compounds thus produced, the one represented by Formula IV may also prove of pharmacological interest, on account of its resemblance to the Hexophan type (III) of cinchophens,[2] for it has been shown by various workers[3,4,5,6] that the valuable therapeutic effects of the cinchophens are intimately associated with the presence of a phenyl group in Position 2 and a carboxyl at 4.

Through the courtesy of Dr. Max Kahn, of New York, N. Y., some preliminary physiological tests were carried out with the diammonium salt of this new compound (IV), and 5-grain (0.324 g.) doses were administered to rabbits by the mouth. Except for perhaps some slight depression, no deleterious effect was observed. When given in doses of 0.5 grain (0.0324 g.) per kilogram of body weight, the rabbits did not manifest any toxic symptoms.

Experimental Part

o-**Dimethylamino-acetophenone**, $(CH_3)_2NC_6H_4COCH_3$.—A mixture of 30 g. of *o*-amino-acetophenone [b. p., 110°, (1.5 mm.)], 30 g. of methyl iodide and 30 g. of methyl alcohol was heated in a sealed tube for an hour at 100°. When cold, the tube contents formed a mass of red crystals. The mixture was made alkaline and distilled with steam, which carried over 20 g. of a pale yellow oil; b. p., 91–94° (1.5 mm.). From this oil a golden-yellow picrate was obtained, melting with decomposition at 183–184° (corr.), and but very slightly soluble in alcohol. This crystalline picrate was analyzed.

Analysis. Calc. for $C_{16}H_{16}O_8N_4$: C, 48.70; H, 4.04. Found: C, 48.98; H, 4.08.

The odor of this dimethylamino-acetophenone was much less agreeable than that of the unmethylated compound, being more basic and more like dimethylaniline, with a faint menthol-like quality.

o-**Benzoylamino-acetophenone**, $C_6H_5CONHC_6H_4COCH_3$, was prepared from the ketone, benzoyl chloride and dilute alkali, and melted at 98°. Bischler and Howell[7] prepared it from the ketone and benzoic anhydride, and found the same melting point.

o-**Methoxalylamino-acetophenone**, $CH_3OCOCONHC_6H_4COCH_3$.—Equal weights of *o*-amino-acetophenone and methyl oxalate were heated together for 30 minutes at 150°. Methyl alcohol distilled during the reaction and the yield was poor (20%). Recrystallized from alcohol, it formed minute, colorless needles; m. p., 128° (corr.).

[2] Ger. pats. 293,467; 293,905; 303,681; 305,885; etc.

[3] Nicolaier and Dohrn, *Arch. klin. Med.*, **93**, 531 (1908).

[4] Impens, *Arch. intern. pharmacodynamie*, **22**, 379 (1913).

[5] Ciusa and Luzzatto, *Gazz. chim. ital.*, **44**, I, 64 (1914).

[6] Rotter, *Z. exp. Path. Therap.*, **19**, 176 (1918).

[7] Bischler and Howell, *Ber.*, **26**, 1384 (1893).

Inasmuch as Camps[8] had prepared the corresponding ethoxalyl derivative similarly and the quinazolines obtained from our product were analyzed, no separate analysis of this compound was made.

o-**Oxamamino-acetophenone,** $H_2NCOCONHC_6H_4COCH_3$, prepared from the preceding compound and alcoholic ammonia, formed shining, flat needles or scales; m. p., 238° (corr.); yield, approximately that calculated.

o-**Phthaloylamino-acetophenone,** $HOOCC_6H_4CONHC_6H_4COCH_3$.—When equimolar amounts of *o*-amino-acetophenone (13.5 g.) and phthalic anhydride (14.8 g.) were mixed, heat was evolved and the mixture solidified. This cake was pulverized and dissolved in dil. alkali. The addition of hydrochloric acid to the alkaline solution precipitated the phthaloyl derivative as a sticky mass, indicating that the initial reaction had been incomplete.

A much better method was found by dissolving the phthalic anhydride in hot benzene and adding to this a benzene solution of the amino-acetophenone. The phthaloyl derivative soon began to separate in plates, the amount increasing as the solution cooled. The yield was nearly that calculated and the product was practically pure. Recrystallized from alcohol, it formed colorless, glistening prisms; m. p., 151.5° (corr.).

Analysis. Calc. for $C_{16}H_{13}O_4N$: C, 67.82; H, 4.62. Found: C, 67.70; H, 4.68.

Acetyl-isatinic Acid, $CH_3CONHC_6H_4COCOOH$, was secured conveniently and in excellent yield (86%) by the oxidation of *o*-aceto-amino-acetophenone with potassium permanganate at low temperature, a method analogous to that employed by Glücksmann[9] in preparing benzoylformic acid from acetophenone.

A solution of 35 g. of potassium permanganate and 19 g. of potassium hydroxide in 100 cc. of water was cooled to 0° and added with stirring to a suspension of 19 g. of *o*-aceto-amino-acetophenone in 200 cc. of ice water. By external cooling and the occasional addition of small amounts of cracked ice to the solution, the temperature of the latter was maintained below 0° during the oxidation. At the end of four hours the color of the permanganate had disappeared and the oxidation was adjudged complete. The mixture was filtered, and the colorless filtrate evaporated on the steam-bath to a volume of about 150 cc. When cold, this solution was filtered and the filtrate acidified with hydrochloric acid. Acetyl-isatinic acid separated as a colorless, crystalline solid; m. p., 152–154°; yield, 19 g. Suida,[10] who prepared it by the action of alkali upon acetyl-isatin, gave its melting point as 160°. Recrystallization of this compound, generally results, as is true also of other acyl isatinic acids, in considerable hydrolysis and consequent loss. They were, therefore, used in the crude condition, since the quinazolines obtained therefrom were more easily purified and the yield of final pure product was better.

Benzoyl-isatinic Acid, $C_6H_5CONHC_6H_4COCOOH$.—To a solution of 14 g. of isatin in excess of potassium hydroxide solution, there was added 100 g. of benzoyl chloride with constant shaking, while the temperature was kept down by external cooling and the alkalinity of the solution maintained by the occasional addition of more potassium hydroxide. When all of the benzoyl chloride had dissolved, the temperature of the solution was further reduced and hydrochloric acid was added. This precipitated a mixture of benzoic, benzoyl-isatinic and isatinic acids, the last rapidly changing to isatin and thereby imparting an orange color to the precipitate. The dried precipitate was extracted repeatedly with benzene, to remove the benzoic acid; after which, most of the isatin was eliminated by crystallizing the residue from dil. alcohol. There was thus obtained 10 g. (38% yield) of benzoyl-isatinic acid, still yellowish and impure, m. p.,

[8] Camps, *Ber.*, **34,** 2711 (1901).

[9] Glücksmann, *Monatsh.*, **11,** 246 (1890).

[10] Suida, *Ber.*, **11,** 586 (1878).

167–168°, but sufficiently good for our purpose. Schotten[11] obtained the pure compound (m. p., 188°) by oxidation of benzoyl-hexahydroquinoline.

Phthaloyl-isatinic Acid, $HOOCC_6H_4CONHC_6H_4COCOOH$.—An aqueous solution of 25 g. of phthaloylamino-acetophenone, containing also 10 g. of sodium hydroxide, was oxidized with an equivalent amount of potassium permanganate, first at 0°, and later at the laboratory temperature. The oxidation was complete after three hours, when the mixture was filtered, the filtrate concentrated to a small volume, filtered and acidified with hydrochloric acid. The precipitate, weighing 19 g. (64% yield), crystallized from alcohol in minute, colorless scales; m. p., 151.5° (corr.). On account of the hydrolysis occurring in crystallization and the losses involved, no attempt was made to crystallize to constant melting point or to analyze the product, since on hydrolysis it gave phthalic acid and isatin, and with ammonia a quinazoline derivative which was analyzed.

2-Methylquinazoline-4-carboxylic Acid.—A mixture of 10 g. of acetyl-isatinic acid with excess of alcoholic ammonia was heated in a sealed tube for three hours at 100–110°. Alcohol and ammonia were removed from the crude product by evaporation and the residue was dissolved in water. Hydrochloric acid was added very carefully to this solution, since the quinazoline carboxylic acid was soluble in dilute mineral acids. Only a very small quantity of transparent pale yellow, short, thick prisms was obtained. These probably represented the dihydrate of the acid, for when heated they melted at 175.5–176.5° (corr.) with loss of water. On further heating, carbon dioxide was evolved, leaving 2-methylquinazoline (m. p., 41°).

In carrying out this preparation, the temperature should not be permitted to rise above 110° in heating the sealed tube. Experiments conducted at 150° yielded only anthranilic and aceto-anthranilic acids; and this coincided with the experience of Bischler and Muntendam[12] in their efforts to obtain the corresponding 6-methyl derivative, too high a temperature or too long a heating giving only tarry products. These same investigators reported that the 2,6-dimethylquinazoline-4-carboxylic acid crystallized with two molecules of water.

4-Methylquinazoline-2-carbonamide, $C_6H_4\begin{cases} N=\!=\!=CCONH_2 \\ C(CH_3)=N \end{cases}$.—A mixture of 4.5 g. of *o*-methoxalylamino-acetophenone with 70 cc. of alcoholic ammonia was heated for five hours at 150°. When cold, the tubes contained yellow crystals. Recrystallized from alcohol, these crystals appeared in pale yellow, transparent prisms; m. p., 235.5° (corr.); yield, about 3 g.

Analysis. Calc. for $C_{10}H_9ON_3$: C, 64.13; H, 4.85. Found: C, 63.91; H, 4.80.

Instead of the methyl ester used as initial material, the corresponding amide may be employed with equal success, inasmuch as the first step in the reaction is the formation of this amide from the ester.

When this quinazoline amide was boiled with dil. (20%) hydrochloric acid, it gave first the free acid, which then lost carbon dioxide with production of the 4-methylquinazoline (m. p., 36–37°; corr.).

2-Phenylquinazoline-4-carboxylic Acid.—A mixture of 10 g. of the crude benzoyl-isatinic acid with 75 cc. of alcoholic ammonia was heated for five hours at 150° in a sealed tube. The alcohol and ammonia were distilled from the crude product, the residue dissolved in water, the solution filtered and the filtrate precipitated by the addition of hydrochloric acid. The precipitate was crystallized from alcohol; yield, 9.1 g. Recrystallized from 50% alcohol, it formed minute, pale yellow needles, m. p., 150–151° (corr.) with evolution of carbon dioxide.

[11] Schotten, *Ber.*, **24**, 774 (1891).

[12] Bischler and Muntendam, *Ber.*, **28**, 729 (1895).

Analyses. Calc. for $C_{15}H_{10}O_2N_2$: C, 71.95; H, 4.05. Found: C, 71.75; H, 3.90.

A comparison of this quinazoline analog with Cinchophen itself shows some interesting points of resemblance in certain properties. Cinchophen is colorless, while this analog has a pale yellowish shade. Both are but slightly soluble in cold water and moderately soluble in hot. Both can be crystallized from water, but better results are obtained with dil. alcohol. Heated above their melting point, both lose carbon dioxide, one yielding 2-phenylquinoline and the other 2-phenylquinazoline. Both have a slightly bitter first taste, leaving an unpleasant harsh after-taste in the back of the mouth.

2-Phenyl-4-methylquinazoline-2′-carboxylic Acid, $C_6H_4\langle\begin{array}{l}N{=}CC_6H_4COOH\\ C(CH_3){=}N\end{array}$.—A mixture of 10 g. of *o*-phthaloylamino-acetophenone with an excess of alcoholic ammonia was heated for five hours at 140° in a sealed tube. After removal of the alcohol and ammonia, the residue was dissolved in water and the solution acidified with mineral acid. The crude product separated as a sticky mass which was troublesome to purify. By repeated crystallization from methyl alcohol, the acid was finally obtained in minute, colorless needles, of very bitter taste, m. p. 185–186° (corr.) with decomposition; yield, very poor.

Analysis. Calc. for $C_{16}H_{12}O_2N_2$: C, 72.70; H, 4.58. Found: C, 72.90; H, 4.61.

2-Phenylquinazoline-4,2′-dicarboxylic Acid, $C_6H_4\langle\begin{array}{l}N{=}CC_6H_4COOH\\ C(COOH){=}N\end{array}$.—A mixture of 6 g. of phthaloyl-isatinic acid with 50 g. of methyl alcohol containing 5 g. of ammonia was heated for five hours at 140° in a sealed tube. When cold, the tube was filled with colorless platelets of the diammonium salt. This salt was collected, dissolved in water and the free acid precipitated by the addition of mineral acid. It crystallized from alcohol in platelets; m. p., 188–189° (corr.).

The pure diammonium salt was prepared by dissolving this acid in methyl alcohol and precipitating with excess of alcoholic ammonia. It crystallized from absolute methyl alcohol in colorless, glistening plates, very easily soluble in water, and had a mild saline taste becoming somewhat sweetish. This salt was analyzed.

Analyses. Calc. for $C_{16}H_{16}O_4N_4$: C, 58.51; H, 4.91; N, 17.07. Found: C, 58.58; H, 4.87; N, 16.87.

Summary

1. A quinazoline analog of Cinchophen has been prepared, as well as other quinazoline derivatives of cinchophen type.

2. New quinazoline carboxylic acids have been synthesized from isatin and from *o*-amino-acetophenone.

3. A method for producing acyl derivatives of isatinic acid has been utilized, which consists in the oxidation of the corresponding derivatives of *o*-amino-acetophenone with potassium permanganate at low temperature.

4. The following new compounds were obtained pure and were analyzed: *o*-dimethylamino-acetophenone, its picrate, *o*-phthaloylamino-acetophenone, 4-methylquinazoline-2-carbonamide, 2-phenylquinazoline-4-carboxylic acid, 2-phenyl-4-methylquinazoline-2′-carboxylic acid, 2-phenylquinazoline-4,2′-dicarboxylic acid diammonium salt.

5. The following new compounds were either obtained impure, or

were not analyzed: *o*-methoxalylamino-acetophenone, *o*-oxamamino-acetophenone, benzoyl-isatinic acid, phthaloyl-isatinic acid, 2-methyl-quinazoline-4-carboxylic acid, 4-methylquinazoline-2-carboxylic acid and 2-phenylquinazoline-4,2′-dicarboxylic acid.

6. The following compounds, already known, were prepared by new methods: *o*-benzoylamino-acetophenone and acetyl-isatinic acid.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY, NO. 25]

ETHYL-NORMAL-HEXYLBARBITURIC ACID AND OTHER DERIVATIVES OF NORMAL-HEXYLMALONIC ACID

BY ARTHUR W. DOX

RECEIVED APRIL 17, 1924 PUBLISHED JULY 7, 1924

5,5-Dialkylbarbituric acids, in which one alkyl is ethyl and the other methyl, ethyl, propyl, butyl, *iso*butyl, *iso*-amyl and heptyl, have been compared with respect to their hypnotic activity by Carnot and Tiffeneau.[1] The maximum activity was manifested by the butyl, *iso*-butyl and *iso*-amyl derivatives, where the hypnotic effect was thrice that of veronal (diethylbarbituric acid). With the heptyl derivative there was a slight falling off in activity to 2.5 times that of veronal. The *iso*-butyl and *iso*-amyl derivatives, with their branched carbon chains, do not, strictly speaking, fit into the series. Unfortunately, the *n*-amyl and *n*-hexyl derivatives were not included in the tests. Until these are prepared and tested we are still uncertain as to the place in the series where the maximum hypnotic activity is attained.

The present work was undertaken primarily for the purpose of preparing one of the missing homologs, ethyl-*n*-hexylbarbituric acid. With *n*-hexyl alcohol now available as a by-product in the commercial manufacture of *n*-butyl alcohol, hexyl halides may be easily prepared and employed in the various malonic ester syntheses. The successive alkylation of ethyl malonate with hexyl bromide and ethyl bromide, or with these alkyl halides in the reverse order, gives ethyl ethylhexylmalonate which condenses with urea under the conditions of the Fischer and Dilthey synthesis to form ethylhexylbarbituric acid. The initial product, ethyl hexylmalonate, being easily obtained, a portion of this was used in the preparation of certain other derivatives of incidental interest which are included in this paper.

Experimental Part

Hexyl Bromide.—This substance has been previously prepared by Lieben and Janecek[2] from hexyl alcohol and hydrogen bromide in a sealed tube at 100°. The writer

[1] Carnot and Tiffeneau, *Compt. rend.*, **175**, 241 (1922).

[2] Lieben and Janecek, *Ann.*, **187**, 137 (1877).