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THE SYNTHESIS AND STUDY OF CERTAIN NEW DERIVATIVES OF PHENACETIN

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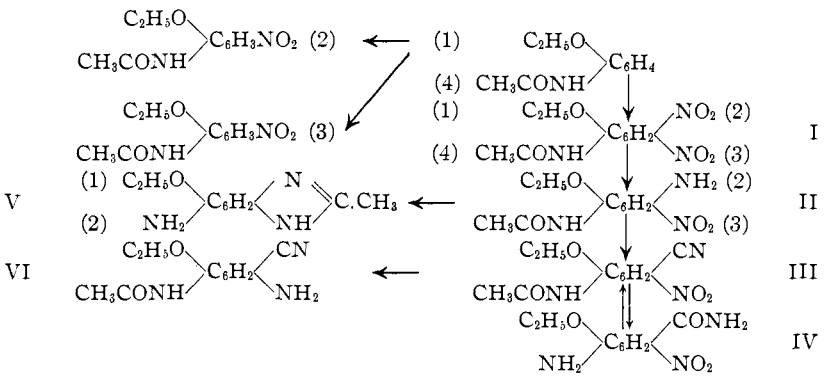
Introduction

In view of the well recognized therapeutic value of phenacetin,[2] it has seemed to us desirable to prepare and study some new derivatives thereof, in the hope of obtaining other products of service in the treatment of disease.

The syntheses carried out are outlined below.



One structure we had in mind was that of a molecule which would be simultaneously both a phenacetin and an aspirin, $C_6H_2(OC_2H_5)(1)(CO\text{-}OH)(OCOCH_3)(NHCOCH_3)(4)$.

Although this goal has not been attained, due to the expiration of the leave of absence of the junior author, it seems desirable to record the results obtained to date.

Salicyl *p*-phenetidide, $C_2H_5OC_6H_4NHCOC_6H_4OH$, was prepared by Bolezzi[3] in 1898 and by Cohn[4] in 1900, the former describing also its acetyl (m. p., 132°) and various other derivatives. However, it was hydrolyzed with difficulty and but little absorbed by the system, for the most part passing through unaltered and hence having no important physiological effect.[5] In this respect it resembled the behavior of salicylates of certain other antipyretic bases.

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[2] The phenacetin used in these experiments was supplied by Lehn and Fink, Inc., and by Merck and Co., for whose assistance we are most grateful.

[3] Bolezzi, *Gazz. chim. ital.*, **28** [II], 198 (1898).

[4] Cohn, *J. prakt. Chem.*, [2] **61**, 547 (1900).

[5] Schubenko, *Inaug. Diss.*, St. Petersburg, 1892.

In our experiments, phenacetin was dinitrated by the method of Blanksma,[6] and the resulting 2,3-dinitro derivative (I) was converted into the 2-amino-3-nitro-4-acetylaminophenetole (II) by heating it with alcoholic ammonia under pressure, following the experience of Laubenheimer[7] in the preparation of *o*-nitro-aniline from *o*-dinitrobenzene. That it was the nitro group in Position 2, not 3, which was displaced by the amino group was proved by elimination of the latter, when the product obtained was the *m*-nitrophenacetin (3-nitro-4-acetylaminophenetole).

This is contrary to the conclusion arrived at by Reverdin and Roethlisberger[8] that these nitro-amines are formed by replacement of the nitro group in Position 3, for they saponified the compound $C_6H_2(OC_2H_5)(1)(NO_2)(2)(NHCH_3)(3)NHCOCH_3(4)$, reduced the nitro-amine with stannous chloride and obtained "a compound showing all the characteristics of a *m*-diamine," but the tests used are not described nor how they proved that the *m*-diamine reactions observed were not really due to the monomethylated *m*-diamine which would result from the entrance of the $NHCH_3$ group in Position 2. In a later article, Reverdin[9] also assigns Position 3, without citing any additional proof, to the product obtained by the action of aniline upon the 2,3-dinitro derivative of *o*-nitrotoluene-*p*-sulfonyl-*p*-phenetidine.

The preparation of the nitronitrile (III) from the nitro-acetylamino derivative (II) was carried out by the usual diazo reaction. This nitrile proved very resistant to hydrolyzing agents, acid or alkaline, possibly because of the steric hindrance of the two adjoining groups, especially the nitro group. Claus and Beysen,[10] in their experiments with 2,6-dinitro-*p*-tolunitrile, found that it was resinified by the action of alkali, that sulfuric acid of moderate concentration yielded the amide, and it was only by heating for eight hours with concd. hydrochloric acid at 220° in sealed tubes that the free acid was obtained. When our nitrile was subjected to the action of concd. sulfuric acid, at 100° for ten minutes, the product was the de-acetylated amide (IV) and not the corresponding acid.

The action of an excess of acetic anhydride upon this amide dehydrated the amide to the nitrile again, but failed to acetylate the free amino group.

Reduction of the nitronitrile (III) yielded the corresponding amino-nitrile (VI), and of the nitro-acetylamino derivative (II) what appeared to be the acetylamidine (V).

Experimental Part

2-Nitro-4-acetylaminophenetole.—This nitro derivative (m. p. 125°,

[6] Blanksma, *Rec. trav. chim.*, **27**, 49 (1908).

[7] Laubenheimer, *Ber.*, **11**, 1155 (1878).

[8] Reverdin and Roethlisberger, *Helv. Chim. Acta*, **5**, 310 (1922).

[9] Reverdin, *ibid.*, **8**, 608 (1925).

[10] Claus and Beysen, *Ann.*, **266**, 225 (1891).

uncorr.) was obtained by the direct nitration of phenacetin, following the process described in Example I, of German patent 101,778.[11]

Its reduction to the amino derivative has not been accomplished satisfactorily as yet. Experiments have been conducted with tin and hydrochloric acid, and also by electrolytic reduction, using a mercury cathode, a platinum anode and a porous cup, and 5% sulfuric acid as the electrolyte.

3-Nitro-4-acetylaminophenetole resulted when phenacetin was nitrated in glacial acetic acid instead of in sulfuric acid. The yield was excellent, and the product melted at 103°, in agreement with the figure reported by Hinsberg[12] and by Elbs,[13] while Butler[14] gave it as 101°.

This gave a deep red solution when treated with zinc and acetic acid, or reduced electrolytically, but no crystalline product was isolated from these solutions.

2,3-Dinitrophenacetin (I) was prepared by nitrating phenacetin with fuming nitric acid, at low temperature, following the procedure of Blanksma.[6] The yield was considerably lower if the acid employed was not colorless and free from the lower oxides of nitrogen or if the temperature was not maintained at about 0°. The crude product was crystallized from alcohol and then formed pale yellow needles, m. p. 206° (corr.), in agreement with the figure reported by Blanksma;[6] yield, 86%.

2-Amino-3-nitro-4-acetylaminophenetole (2-Nitro-3-acetylamino-6-ethoxy-aniline) (II).—Attempts to reduce the dinitro derivative by the action of ammonium sulfide solution resulted unsatisfactorily. Therefore, recourse was had to the action of alcoholic ammonia under pressure,[7] whereby one nitro group was replaced by an amino group.

In the conversion of resorcinol into *m*-aminophenol by the action of ammonia under pressure, the presence of some ammonium chloride has been found to enable the reaction to be accomplished at lower temperatures and pressures and with better yields,[15] but in the case of the dinitrophenacetin the presence of that salt was of no obvious advantage.

Occasionally fusion with ammonium acetate in the presence of ammonia has been found preferable to the use of alcoholic ammonia under pressure, for the replacement of mobile atoms or groups,[16] but applied to the dinitrophenacetin it proved less satisfactory.

Laubenheimer[7] states that *o*-dinitrobenzene can be converted into *o*-nitro-aniline by the action of alcoholic ammonia for two hours at 110° or for ten weeks at laboratory temperature; but the 2,3-dinitrophenacetin remained unchanged at laboratory temperature.

A mixture of 50 g. of the dinitro derivative with 500 cc. of 95% alcohol previously saturated with ammonia gas was heated in an iron autoclave for 10 to 12 hours at 110–120°. At higher temperatures, resinification reduced the yield. Better results were

[11] Farbw. vorm. Meister, Lucius and Bruening, *Friedländer*, **5**, 68 (1901).

[12] Hinsberg, *Ann.*, **305**, 279 (1899).

[13] Elbs, *J. prakt. Chem.*, [2] **83**, 8 (1911).

[14] Butler, *Ber.*, **39**, 3807 (1906).

[15] Leonhardt and Co., German pat. 49,060 (1888); *Winther*, **1**, 320 (1908).

[16] *Soc. chim. Grande Paroisse*, Brit. pat. 169,688 (1921); *C. A.*, **16**, 721 (1922).

secured with 95% than with absolute alcohol. The cooled tube contents was filtered and the crude product purified by decolorization and crystallization from alcohol until the melting point remained constant at 160° (corr.). The pure substance formed golden-orange needles; yield, 20 g., or 45%.

Anal. Calcd. for $C_{10}H_{13}O_4N_3$: N, 17.54. Found: 17.84, 17.56.

With concd. hydrochloric acid, it formed a cream-colored salt which was dissociated immediately by dilution with water, with separation of the insoluble, orange-free base.

The facts that the product was not the amidine and that it did not pass into an amidine by loss of water when heated, indicated that it was the 2- and not the 3-nitro group which had been replaced by the ammonia residue, and this conclusion was corroborated by replacing the amino group by hydrogen by diazotizing in the presence of alcohol, following the method developed by Remsen and his co-workers.[17,18] Attempts to eliminate the amino group by the method which Blanksma[6] used to convert dinitrophenetidine into dinitrophenetole proved unsuccessful, the product isolated in yellow needles being the 2,3-dinitrophenacetin, as shown by its melting point and analysis for nitrogen, and the fact that on saponification it yielded the 2,3-dinitrophenetidine; m. p., 145°. This result was wholly unexpected, in view of the fact that no excess of nitrous acid was used to accomplish the diazotization. That an amino group may be diazotized without affecting acetylamino groups has been demonstrated frequently.[19]

The product resulting from the elimination of the amino group from the nitro-aminophenacetin crystallized from water in yellow needles, m. p. 103° (corr.), which is the melting point recorded in the literature[12] for *m*-nitrophenacetin (3-nitro-4-acetyl-aminophenetole).

Anal. Calcd. for $C_{10}H_{12}O_4N_2$: N, 12.50. Found: 12.65, 12.48.

Diacetyl Derivative (3-Nitro-2,4-diacetylaminophenetole).—By the action of acetyl chloride upon the nitro-aminophenacetin, the free amino group was also acetylated, thus yielding a compound which was simultaneously both a *p*- and an *o*-phenacetin. Acetic anhydride was not so satisfactory as the chloride. It was recrystallized repeatedly by dissolving it in hot, glacial acetic acid, diluting and chilling, and was finally obtained in pale yellow, microscopic crystals; m. p., 258° (corr.).

Anal. Calcd. for $C_{12}H_{15}O_5N_3$: N, 14.95. Found: 15.06, 15.08.

By hydrolysis with concd. sulfuric acid, the acetyl groups were removed and the nitro-ethoxydiamine (m. p., 95°, corr.) obtained.

3-Nitro-2,4-diaminophenetole (2-Nitro-6-ethoxy-1,3-diaminobenzene).—Hydrolysis of the nitro-aminophenacetin into this *m*-phenylenediamine derivative proved unexpectedly troublesome.

A solution of 8 g. of the nitro-aminophenacetin in 25 cc. of concd. sulfuric acid was heated at 100° for 15 minutes, the solution was cooled and then poured into 500 cc. of water. The resulting deep red liquid was added slowly to a solution of 60 g. of anhydrous sodium carbonate in 250 cc. of water. The dark purple precipitate was cooled, dissolved in boiling water, the solution decolorized and allowed to cool. Dark purple, nearly black, long, silky needles separated, m. p. 95° (corr.), freely soluble in alcohol.

[17] (a) Beeson, *Am. Chem. J.*, **16**, 235 (1894). (b) Chamberlain, *ibid.*, **19**, 531 (1897). (c) Griffin, *ibid.*, **19**, 163 (1897). (d) Moale, *ibid.*, **20**, 298 (1898). (e) Winston, *ibid.*, **31**, 119 (1904).

[18] Cain, "Chemistry and Technology of the Diazo Compounds," Arnold, London, **1920**, pp. 45–49.

[19] (a) Farbw., Friedrichsfeld, German pat. 86,791; *Friedländer*, **4**, 961 (1899); (b) German pat. 96,667, 96,769; *Winther*, **2**, 1528 (1908).

Anal. Calcd. for $C_8H_{11}O_3N_3$: N, 21.31. Found: 21.42.

With concd. hydrochloric acid, it formed a yellow salt which dissolved when water was added. When sodium nitrite was introduced into the acid solution, the color of the latter changed immediately to an intense brown, due presumably to the formation of an analog of Bismarck Brown, while addition of ferric chloride caused a momentary red coloration, followed by the separation of a finely divided, reddish-brown, amorphous precipitate.

3-Amino-4-ethoxy-*o*-phenylene-acetylamidine (2-Methyl-4-amino-5-ethoxybenzimidazole) (V).—Reduction of the 2-amino-3-nitro-4-acetylaminophenetole, either by tin and glacial acetic acid or by stannous chloride and hydrochloric acid, gave a small yield (3%) of what appeared to be a slightly impure acetylamidine. It crystallized from 30% alcohol in dull, colorless, matted, minute needles, m. p. 147° (corr.), which were soluble in hydrochloric acid, acetic acid, alcohol or ether.

Anal. Calcd. for $C_{10}H_{13}ON_3$: C, 62.85; H, 6.84. Found: C, 62.12, 61.48; H, 7.27, 6.75.

2-Nitro-3-acetylamino-6-ethoxybenzonitrile (III) was prepared from the 2-amino-3-nitro-4-acetylaminophenetole by the process developed by Bogert and Hand[20] for the conversion of *o*-nitro-aniline into *o*-nitrobenzonitrile. After decolorizing the crude product, it was crystallized from alcohol until the melting point remained constant at 219° (corr.); yield, 13 g., or 52%. The fine, pale yellow, lustrous needles or scales so obtained were moderately soluble in boiling alcohol, but only slightly soluble in the cold. They dissolved also in concd. sulfuric acid and in concd. aqueous potassium hydroxide solution, and this latter solution, when heated, evolved ammonia with formation of tarry decomposition products.

Anal. Calcd. for $C_{11}H_{11}O_4N_3$: N, 16.87. Found: 16.85, 16.81.

2-Nitro-3-amino-6-ethoxybenzamide (IV).—The nitrile just described proved very resistant to saponifying agents. Hydrochloric acid, potassium hydroxide and sodium carbonate of various concentrations, and moderately concentrated sulfuric acid failed to hydrolyze it. A partial hydrolysis was accomplished as follows.

Five g. of the nitrile was dissolved in 15 cc. of concd. sulfuric acid, and the solution heated for ten minutes at 100°. It was then cooled, poured into ice water, the brown mass filtered and the insoluble portion crystallized from alcohol. Yellow, lustrous needles resulted; m. p., 199° (corr.); yield, 1.5 g., or 30%.

Anal. Calcd. for $C_9H_{11}O_4N_3$: N, 18.66. Found: 18.65, 18.82.

This analysis corresponds to a conversion of the nitrile to amide and removal of the acetyl group of the phenacetin.

2-Nitro-3-amino-6-ethoxybenzonitrile.—In an endeavor to acetylate the nitro-amino-ethoxybenzamide by the action of acetic anhydride, before attempting to saponify the amide with nitrous acid by the method of Bouveault,[21] the amide was dehydrated to the aminonitrile, but no acetylation whatever occurred despite the use of a considerable excess of acetic anhydride. This unacetylated aminonitrile crystallized from alcohol in colorless needles; m. p., 201° (corr.); yield, 65%.

Anal. Calcd. for $C_9H_9O_3N_3$: N, 20.30. Found: 20.52, 20.28.

2-Amino-3-acetylamino-6-ethoxybenzonitrile (VI).—To a solution of 12 g. of the

[20] Bogert and Hand, THIS JOURNAL, **24**, 1035 (1902).

[21] (a) Bouveault, *Bull. soc. chim.*, [3] **9**, 368 (1893). (b) Heyl and Meyer, *Ber.*, **28**, 2783 (1895). (c) Sudborough, *J. Chem. Soc.*, **67**, 601 (1895).

corresponding nitronitrile in 50 cc. of hot glacial acetic acid, there was added 9 g. of mossy tin, and the mixture was refluxed with a further addition of 9 g. of tin and 30 cc. of glacial acetic acid, until no unchanged nitronitrile separated when the mixture was cooled. The solution was then diluted, the tin removed by precipitation as sulfide and the filtrate made slightly alkaline with strong sodium hydroxide solution. The crude product so precipitated, when crystallized from alcohol to the constant melting point of 250° (corr.), formed brilliant, colorless needles; yield, 1.5 g., or 14%.

Anal. Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.3; H, 5.98. Found: C, 60.67, 60.42; H, 6.12, 5.73.

The product was soluble in dil. hydrochloric acid, in acetic acid, alcohol or ether. When heated, there was no evidence of the loss of water from this product, either below or above its melting point, which is rather surprising, since one would expect it to pass readily into the acetylamidine with loss of water.

Summary

1. 2,3-Dinitrophenacetin has been converted into the 2-amino-3-nitro-4-acetylaminophenetole by the action of alcoholic ammonia under pressure, and the position of the nitro group has been proved by elimination of the amino group. This is at variance with the conclusions of Reverdin and Roethlisberger[8] that in the action of amines upon this dinitro derivative it is the 3- and not the 2-nitro group which is replaced.

2. From the 2-nitro-3-acetylamino-6-ethoxy-aniline the 2-nitro-3-acetylamino-6-ethoxybenzonitrile was prepared by the usual diazo reaction, and the nitro then reduced to the amino group.

3. Saponification of the nitrocyanide with concd. sulfuric acid gave the amide, which reverted to the cyanide when heated with an excess of acetic anhydride.

4. 2-Amino-3-nitro-4-acetylaminophenetole, upon hydrolysis, gave the nitrodiaminophenetole, a derivative of *m*-phenylenediamine; on further acetylation it gave the diacetylamino compound, which is both an *o*- and a *p*-phenacetin; on reduction it gave what appears to be the corresponding acetylamidine.

5. The following new compounds have been prepared and studied: 2-nitro-3-acetylamino-6-ethoxy-aniline, 2-nitro-3-amino-6-ethoxybenzamide, 2-nitro-3-amino-6-ethoxybenzonitrile and its acetyl derivative, and 2-amino-3-acetylamino-6-ethoxybenzonitrile.

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