[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, EATON LABORATORIES DIVISION, THE NORWICH PHARMACAL CO.]

Chemotherapeutic Nitrofurans. IV.[1] Some Derivatives of 1-Amino-2-imidazolidinone, 1-Amino-2-pyrrolidinone and 3-Amino-2-thiazolidinone

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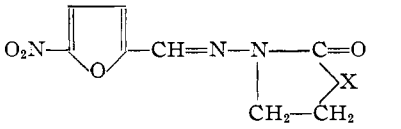
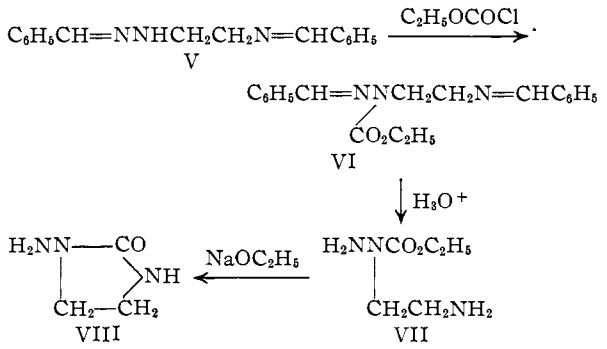
1-Amino-2-imidazolidinone, 3-amino-2-thiazolidinone, 1-amino-2-pyrrolidinone and their 5-nitro-2-furfurylidene derivatives have been prepared.

Since N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidinone (furazolidone) (I) has shown a high order of chemotherapeutic activity,[2] it became of interest to prepare the corresponding compounds in which the heterocyclic oxygen of the oxazolidinone ring was replaced by imino (II), sulfur (III) and methylene (IV) groups. The parent N-aminoheterocycles have not been previously reported.



I, X = O III, X = S
II, X = NH IV, X = CH_2

1-Amino-2-imidazolidinone (VIII) was made by two methods. In the first, the bis-benzylidene derivative of 2-aminoethylhydrazine (V) was allowed to react with ethyl chlorocarbonate to give the carbazic acid derivative VI. The free ethyl 2-(2-aminoethyl)-carbazate (VII) obtained from VI was then cyclized using sodium ethoxide.



The second preparation of 1-amino-2-imidazolidinone started with the known 2-imidazolidinone.[3] Mononitrosation using one equivalent of sodium nitrite, followed by reduction with zinc and acid, gave the desired amino-imidazolidinone, which was isolated as its 5-nitro-2-furfurylidene derivative.

3-Amino-2-thiazolidinone was synthesized from 2-aminoethyl mercaptan hydrochloride. Reaction of the mercaptan with urea by the method of Close[4] gave 2-thiazolidinone. Nitrosation and electrolytic reduction of this compound gave the desired 3-amino-2-thiazolidinone. The intermediate nitrosothiazolidinone was not characterized because of its limited stability.

1-Amino-2-pyrrolidinone was prepared by electrolytic reduction of the known[5] 1-nitroso-2-pyrrolidinone.

The three N-aminoheterocycles were converted to their 5-nitro-2-furfurylidene derivatives by condensation with 5-nitro-2-furfural.

Experimental[6,7]

2-Aminoethylhydrazine Dioxalate. (A) From N-(2-Bromoethyl)-phthalimide.—N-(2-Bromoethyl)-phthalimide was converted to 2-aminoethylhydrazine dioxalate in 45–50% yield essentially by the method of Drewitt and Young.[8]

(B) From Ethylenediamine.—2-Aminoethylhydrazine has been made from ethylenediamine and hydroxylamine-O-sulfonic acid by Sommer, Schultz and Nassau[9,10] and by Gever and Hayes.[11] This method has been modified to give yields of 60–65% as compared to 30–40% reported in the earlier papers.

Ninety-six grams (1.6 moles) of ethylenediamine and 85 cc. of water were heated to 95–100° and the heat removed. A solution of 36.2 g. of 84.6% hydroxylamine-O-sulfonic acid (30.6 g. HOS, 0.27 mole) in 120 cc. of ice-water was added during about 15 minutes with efficient stirring so that the temperature remained between 95° and 100°. Care was taken that the drops of HOS solution were drawn immediately into the reaction mixture and not allowed to react on the surface. The mixture was stirred for 5 minutes at 95–100°, then cooled in ice. Glacial acetic acid was added to bring the *p*H to 7.0–7.5 and the precipitated salts were removed by filtration. The filtrate was warmed to 55° with stirring and treated with 65 g. (0.6 mole) of benzaldehyde. The mixture was kept slightly alkaline by the addition of small amounts of potassium hydroxide solution. After 10 to 15 minutes, when there was no longer any tendency for the *p*H to drop, the reaction mixture was cooled and extracted with ether. To the residue obtained by evaporating the ether was added 75 g. (0.6 mole) of oxalic acid dihydrate and 300 cc. of water. This mixture was then steam distilled to remove all of the benzaldehyde. The resulting solution was boiled with charcoal, filtered and cooled to give 43.5 g. (63%) of 2-aminoethylhydrazine dioxalate melting at 193.5–196° dec.

N-Carbethoxy-N-(2-benzalaminoethyl)-N′-benzalhydrazine (VI).—To a suspension of 47.5 g. (0.186 mole) of 2-aminoethylhydrazine dioxalate in water was added sodium hydroxide solution until a slight permanent basicity was obtained. The precipitate of sodium oxalate was removed by filtration and washed well with water. The alkaline filtrate was warmed to 55° and treated with 40 g. (0.38 mole) of benzaldehyde. The mixture was kept slightly alkaline by the addition of aqueous alkali. When the *p*H no longer showed any tendency to drop, the mixture was cooled and extracted with ether. The ether solution was evaporated in a 400-cc. beaker to leave a residue of 2-ben-

(1) For the previous paper in this series, see K. Hayes, THIS JOURNAL **77**, 2333 (1955).

(2) J. Yurchenco, M. Yurchenco and C. Piepoli, *Antibiotics and Chemotherapy*, **3**, 1035 (1953); A. Cosgrove, *Vet. Med.*, **49**, 393 (1954); R. Gordon, *Vet. Record*, **66**, 828 (1954).

(3) W. E. Bachmann, *et al.*, THIS JOURNAL, **72**, 3132 (1950).

(4) W. J. Close, *ibid.*, **73**, 95 (1951).

(5) S. Gabriel, *Ber.*, **38**, 2405 (1905).

(6) Micro-analyses were carried out by Mr. Joseph Corrado and Mr. Gordon Ginther.

(7) All melting points were taken on the Fisher–Johns apparatus and are corrected.

(8) J. Drewitt and D. Young, U. S. Patent 2,420,702, May 20, 1947.

(9) F. Sommer, O. F. Schultz and M. Nassau, *Z. anorg. u. allgem. Chem.*, **147**, 142 (1925).

(10) F. Sommer and O. F. Schultz, German Patent 338,609 (1921).

(11) G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949).

zalaminoethylbenzalhydrazine (V). This viscous, yellow liquid was dissolved in 100 cc. of SDA #30 (specially denatured ethyl alcohol) and cooled to 20°. The temperature was held at 20 ± 2° while 21.7 g. (0.2 mole) of ethyl chlorocarbonate was dropped in during 33 minutes with stirring. The *p*H was held at 7.0 to 7.5, using a *p*H meter, by the addition of 53 cc. of 15% sodium hydroxide in small portions. Shortly after the addition was completed, a solid formed in the reaction. The temperature and *p*H specified above, were held for one hour after the addition. The solid product was filtered, washed with water and air-dried to give 38 g. (63%) of VI. After two recrystallizations from SDA #30, the melting point was 105–105.5°.

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.6; H, 6.55; N, 13.0. Found: C, 70.6; H, 6.33; N, 13.3.

Ethyl 2-(2-Aminoethyl)-carbazate (VII).—A mixture of 85 g. (0.26 mole) of crude N-carbethoxy-N-(2-benzalaminoethyl)-N'-benzalhydrazine and 200 cc. of 10% sulfuric acid was steam distilled until all of the benzaldehyde was removed. The solution remaining was treated with a slight excess of barium hydroxide solution and filtered. The barium sulfate was washed well with water and the filtrate distilled to remove the water at 60° under reduced pressure. The residue was taken up in methanol, a small amount of solid filtered off and the methanol removed in vacuum. The residue was distilled under vacuum to give 27 g. (70%) of a viscous, colorless oil boiling at 110 to 133° at 1 to 1.5 mm. On redistillation, a center cut boiling at 131–131.5° at 2 mm. was taken for analysis; $n^{23.5}D$ 1.4830.

Anal. Calcd. for $C_5H_{13}N_3O_2$: C, 40.8; H, 8.90; N, 28.55. Found: C, 40.6; H, 9.05; N, 27.8.

1-Amino-2-imidazolidinone (VIII). (A) From Ethyl 2-(2-Aminoethyl)-carbazate.—A solution of 0.5 g. (0.22 mole) of sodium in 25 cc. of absolute ethanol was added to 22.7 g. (0.154 mole) of ethyl 2-(2-aminoethyl)-carbazate. The mixture was heated in an oil-bath at 105 to 120° during 40 minutes so as to distil off the ethanol. A portion of the yellowish residue was distilled under vacuum. The product, which solidified in the receiver, boiled at 134–137° at 2 mm. A second sublimation and four recrystallizations from SDA #30 gave pure VIII melting at 111.5 to 112°.

Anal. Calcd. for $C_3H_7N_3O$: C, 35.6; H, 6.98; N, 41.6. Found: C, 35.8; H, 7.10; N, 41.55.

The undistilled portion of the above 1-amino-2-imidazolidinone was dissolved in water, acidified with hydrochloric acid and treated with an alcoholic solution of 5-nitro-2-furfural to precipitate N-(5-nitro-2-furfurylidene)-1-amino-2-imidazolidinone (II). Three crystallizations from nitromethane, using charcoal, gave a pure product decomposing at 261.5–263°. The freshly crystallized material is lemon-yellow in color. On standing, washing with alcohol or heating to 75–85°, it turns orange; water solubility 109 mg./l.; ϵ_{max} at 3875 and 2730 Å. is 17,550 and 13,200, respectively, in water.

Anal. Calcd. for $C_8H_8N_4O_4$: C, 42.9; H, 3.60; N, 25.0. Found: C, 43.0; H, 3.34; N, 24.95.

(B) From 2-Imidazolidinone *via* 1-Nitroso-2-imidazolidinone.—A solution of 63 g. (0.73 mole) of crude 2-imidazolidinone[3] in two liters of 2 *N* sulfuric acid was cooled at 3–6° in an ice-bath. During 13 minutes, 50.5 g. (0.73 mole) of sodium nitrite was added in small portions. The solution was stirred in the ice-bath for an additional 1.5 hours. Then, 110 g. (1.68 moles) of zinc dust was added in small portions during one hour so that the temperature did not rise above 20°. During most of the addition, the zinc dissolved rapidly and completely, but at the equivalence point, scarcely at all. The mixture was stirred 30 minutes in the ice-bath, then one hour at room temperature, when the excess zinc was filtered off. The product was isolated easily as its 5-nitro-2-furfurylidene derivative by adding to the filtrate a solution of 93 g. (0.66 mole) of 5-nitro-2-furaldehyde in 700 cc. of SDA #30. After chilling thoroughly, the product was filtered and washed well with water and SDA #30. The yield of N-(5-nitro-2-furfurylidene)-1-amino-2-imidazolidinone decomposing at 260–262° was 126 g. (77%). Recrystallization from dimethylformamide gave 80% recovery of a product decomposing at 262–263°.

2-Thiazolidinone.—A mixture of 30 g. (0.26 mole) of 2-aminoethyl mercaptan hydrochloride[12] and 35 g. (0.58 mole) of urea was heated in an oil-bath maintained at 170–180° for 30 minutes. The bath temperature was then raised to 200–210° and heating continued until the evolution of ammonia slackened considerably. The cooled reaction mixture was ground with SDA #32, the insoluble ammonium chloride was filtered off and washed well with SDA #32. The alcohol was removed by distillation under reduced pressure on the steam-bath and the residue stirred with dioxane. The unwanted insoluble material was filtered off and washed well with dioxane. After removal of the dioxane under reduced pressure, the crude 2-thiazolidone was distilled under vacuum. The distilled product (b.p. 138–138.5° at 2.5 mm.) solidified in the receiver and weighed 20 g. (74%). It was further purified to a melting point of 50–52° by first dissolving in benzene, filtering and precipitating with petroleum ether, then recrystallizing several times from carbon disulfide. (Crawhall and Elliott[13] give a melting point of 54° and a boiling point of 160° at 20 mm. for 2-thiazolidinone.)

Anal. Calcd. for C_3H_5NOS: C, 34.9; H, 4.85; N, 13.5; S, 31.1. Found: C, 34.9; H, 4.61; N, 13.7; S, 31.4.

3-Amino-2-thiazolidinone.—A solution of 34.7 g. (0.34 mole) of 2-thiazolidinone in 170 cc. of 10% hydrochloric acid was cooled in an ice-bath at 0 to 5° while a solution of 23.3 g. (0.34 mole) of sodium nitrite in 70 cc. of water was added in small portions during 15 minutes. The mixture was stirred an additional 15 minutes before the solid nitroso compound that had formed was filtered. The product was washed with a small amount of ice-water and then reduced electrolytically using a lead anode, mercury cathode, 10% sulfuric acid electrolyte and current density of 0.159 amp./cm.^{2} for 3 hours at 0 ± 2°. The reduced solution was extracted with ether to remove a small amount of oily material.

For the isolation of the oxalate of 3-amino-2-thiazolidinone, the aqueous solution was treated with excess barium carbonate and warmed until a slightly alkaline reaction was obtained. The barium sulfate–barium carbonate precipitate was filtered off and washed well with water. The filtrate was distilled under reduced pressure to remove all of the water possible and the residue distilled in vacuum. The distillate, which boiled at about 115° at 9 mm. partially solidified and consisted of a mixture of 2-thiazolidinone and 3-amino-2-thiazolidinone. The distillate was dissolved in SDA #32 and treated with a solution of oxalic acid in SDA #32. The precipitated oxalate, after three crystallizations from SDA #30, decomposed at 138–141°.

Anal. Calcd. for $2C_3H_6N_2OS \cdot H_2C_2O_4$: C, 29.4; H, 4.32; N, 17.2; S, 19.65. Found: C, 29.6; H, 4.11; N, 16.9; S, 19.45.

For the isolation of the 5-nitro-2-furfurylidene derivative of 3-amino-2-thiazolidinone, the aqueous solution from the reduction of the nitroso compound, after extraction with ether, was treated with a solution of 25 g. (0.18 mole) of 5-nitro-2-furaldehyde in SDA #30. There was obtained 37.5 g. (46%) of N-(5-nitro-2-furfurylidene)-3-amino-2-thiazolidinone (III) melting at 220–222°. By recrystallizations from a mixture of one part nitromethane to one part SDA #32, a product melting at 226.5–227° was obtained; water solubility 33 mg./l., ϵ_{max} at 3740 and 2775 Å. is 18,900 and 12,800, respectively, in water.

Anal. Calcd. for $C_8H_7N_3O_4S$: C, 39.8; H, 2.93; N, 17.4; S, 13.3. Found: C, 40.1; H, 2.96; N, 17.3; S, 13.1.

1-Amino-2-pyrrolidinone.—1-Nitroso-2-pyrrolidinone, obtained in 75–80% yield by the method of Gabriel,[5] was reduced electrolytically, under the same conditions given above under 3-amino-2-thiazolidinone, for 3.5 minutes per gram of nitroso compound. The colorless reduction solution was extracted with ether to remove a small amount of insoluble oil, then treated with barium carbonate with warming until a neutral reaction was obtained. The inorganic precipitate was filtered off and well water washed. The filtrate was distilled to dryness under reduced pressure. The yellowish liquid residue was dissolved in methanol, filtered from any solids present, the methanol distilled off and the residue distilled under vacuum. The colorless distillate, which boiled at 67–72° at 1 mm., partially crystallized in the receiver. The crystalline material was freed

(12) M. T. Bogert, *et al.*, THIS JOURNAL, **62**, 1173 (1940); **63**, 2361 (1941).

(13) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

of as much oil as possible by pressing between filter paper. After three recrystallizations from benzene, the product melted at 53–54°.

Anal. Calcd. for $C_4H_8N_2O$: C, 48.0; H, 8.05; N, 28.0. Found: C, 48.0; H, 7.89; N, 27.8.

For the preparation of N-(5-nitro-2-furfurylidene)-1-amino-2-pyrrolidinone (IV), the clear aqueous solution from the reduction above was treated with an alcoholic solution containing 0.5 g. of 5-nitro-2-furfural per gram of nitrosopyrrolidinone reduced. The crude yellow product separated in a 30–35% yield and melted at 228–230°. Recrystallization from a mixture of one part of nitromethane to two parts of SDA #30 raised the melting point to 233–233.5°; water solubility 89 mg./l.; ϵ_{max} at 3700 and 2700 Å. is 17,200 and 11,800, respectively, in water.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.4; H, 4.06; N, 18.8. Found: C, 48.1; H, 4.37; N, 18.6.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Benzothiophene-4,5-quinones

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An investigation of the benzothiophene-4,5-quinones was undertaken. The parent compound or its 2-carboxy derivative could not be prepared by the usual procedures employed in the synthesis of *o*-naphthoquinones. It was possible, however, to synthesize various 7-(cyanocarbethoxymethyl)-benzothiophene-4,5-quinones. The compounds previously considered as 3,4-dibromo-5-hydroxybenzothiophene and 3-bromobenzothiophene-4,5-quinone are now assigned the structures 4,6-dibromo-5-hydroxybenzothiophene and 6-bromobenzothiophene-4,5-quinone.

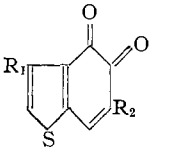
In connection with another problem a 7-(cyanocarbethoxymethyl) - benzothiophene - 4,5 - quinone was required as an intermediate. No such compounds have been reported in the literature. An account of the preparation of several representatives of this class forms the substance of this communication. The method employed was essentially that of condensing ethyl cyanoacetate with a benzothiophene-4,5-quinone under basic conditions, although the intermediate 4,5-quinone was not isolated in all cases.

All the benzothiophene derivatives described were prepared from sodium 5-nitrobenzothiophene-2-carboxylate[2-4] which was converted to 5-hydroxybenzothiophene by a modification of a procedure used previously.[2,3] In this modification which gave slightly better over-all yields the diazotization step was eliminated by making use of the Bucherer reaction.[5] 5-Hydroxybenzothiophene can be converted to its 4-nitroso derivative in excellent yield by sodium nitrite in dilute acetic acid, but all attempts to prepare benzothiophene-4,5-quinone from the nitroso compound failed. Utilization of the modified techniques developed for the preparation of *o*-naphthoquinones in a high state of purity from 1-nitroso-2-naphthols[6] served only to confirm the observations of Fieser and Kennelly[3] on the instability of this quinone. Similarly 5-hydroxy-4-nitrosobenzothiophene-2-carboxylic acid could not be converted into the corresponding 4,5-quinone.

Attempts to prepare benzothiophene-4,5-quinone by the method first extensively investigated by Armstrong and Rossiter[7] and which has been used with success in the preparation of various *o*-naphthoquinones[8-11] also fails, as nitration of 4-bromo-5-hydroxybenzothiophene under the usual experimental conditions yields 4-bromo-5-hydroxy-3-nitrobenzothiophene.[2]

Application to 5-amino-4-bromobenzothiophene-2-carboxylic acid of the diazotization reaction which had been used in two special cases to prepare *o*-naphthoquinones[12,13] also failed to give the 4,5-quinone.

As the parent benzothiophene-4,5-quinone or its 2-carboxy derivative could not be obtained by these procedures, we decided to use a quinone bearing some other substituent capable of subsequent removal. Of the five known benzothiophene-4,5-quinones,[14] only that previously described as the 3-bromo compound Ia,[2] but which the present



Ia, R_1 = Br, R_2 = H
Ib, R_1 = H, R_2 = Br

work would indicate is in reality the 6-bromo compound Ib in accordance with its observed stability by analogy with 3-bromo-1,2-naphthoquinone,[10] would serve as a convenient starting material. It is formed by the action of nitric acid in chloroform on a dibromo compound resulting from the action of two moles of bromine on 5-hydroxybenzothiophene. This dibromo compound was originally assigned the structure of 3,4-dibromo-5-hydroxybenzothiophene,[2] but the recent studies of substitution in the 5-substituted benzothiophene series by Bordwell and Stange[15,16] in which the true 3,4-

(1) Fulbright Exchange Student 1951–1954, Beaunit Mills Fellow 1953–1954.

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(3) L. F. Fieser and R. G. Kennelly, THIS JOURNAL, **57**, 1611 (1935).

(4) F. G. Bordwell and C. J. Albisetti, Jr., *ibid.*, **70**, 1955 (1948).

(5) H. T. Bucherer, *J. prakt. Chem.*, [2] **69**, 49 (1904).

(6) M. Gates, THIS JOURNAL, **72**, 228 (1950).

(7) H. E. Armstrong and E. L. Rossiter, *Proc. Chem. Soc.*, 89 (1891).

(8) R. Flessa, *Ber.*, **17**, 1481 (1884).

(9) Th. Zincke and O. Kegel, *ibid.*, **21**, 3378 (1888).

(10) K. Fries and K. Schimmelschmidt, *Ann.*, **484**, 245 (1930).

(11) L. F. Fieser and J. L. Hartwell, THIS JOURNAL, **57**, 1479 (1935).

(12) Ad. Claus and O. Jack, *J. prakt. Chem.*, **57**, [2] 15 (1898).

(13) Ad. Claus and O. Philipson, *ibid.*, **43**, [2] 54 (1891).

(14) An excellent review of benzothiophene chemistry is to be found in H. D. Hartough and L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954.

(15) F. G. Bordwell and H. Stange, THIS JOURNAL, **77**, 5939 (1955).

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