[A CONTRIBUTION FROM THE EATON LABORATORIES, DIVISION OF NORWICH PHARMACAL CO.]

Chemotherapeutic Nitrofurans. II.[1] The Formation and Some Reactions of Derivatives of 3-Amino-2-iminoöxazolidine

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The action of thionyl chloride on 5-nitro-2-furaldehyde 2-(2-hydroxyalkyl)-semicarbazones has been shown to produce the corresponding N-(5-nitro-2-furfurylidene)-3-amino-2-iminoöxazolidine hydrochlorides in excellent yield. These cyclic iminoethers are quite reactive and may be readily hydrolyzed to the corresponding 3-amino-2-oxazolidone derivatives.

As part of an investigation of variations of 5-nitro-2-furylalkylidene semicarbazides for chemotherapeutic action,[2] the action of thionyl chloride on the corresponding 2-(2-hydroxyethyl)-semicarbazone[2b] (I) was studied. The solid product of the reaction (II) was very soluble in water and absorbed in the ultraviolet at shorter wave lengths than is characteristic of 2-alkylated semicarbazones of 5-nitro-2-furaldehyde.[2c] This soluble product was shown to be the hydrochloride of a base IIa which differed from the starting material, I, by the loss of one molecule of water.

It was postulated that II was a cyclic iminoether hydrochloride of the structure, N-(5-nitro-2-furfurylidene)-3-amino-2-iminoöxazolidine hydrochloride. This hypothesis was deduced from the related work of Gabriel,[3] who observed the formation of 2-iminoöxazolidine on cyanation of β-bromoethylamine or by the melting, heating or long standing of β-bromoethylurea.

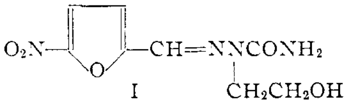
Fromm[4] had demonstrated that nitrous acid acted on 2-iminoöxazolidine to yield 2-oxazolidone. This suggested a possible proof of structure since the N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidone (IIb) structure had been postulated previously and proved for another interesting chemotherapeutic agent derived from I.[1] The 2-iminooxazolidine hydrochloride structure of II was confirmed by its ready conversion to IIb by treatment with nitrous acid. Indeed this was the first practical preparative method developed for the oxazolidone IIb. It was observed later that refluxing II or IIa with dilute sulfuric acid or heating II alone in water gave a good yield of the oxazolidone derivative IIb with some of the hydroxyethylsemicarbazone I being regenerated.

This ready formation of the 3-amino-2-iminooxazolidine derivative from the 2-β-hydroxyalkylated semicarbazone probably is facilitated by the formation of the stable, five-membered ring system. The mechanism of the formation of the cyclic iminoether has not been established. It may proceed by a dehydration of the carboxamide group to a nitrile with subsequent iminoether hydrochloride formation by action of the hydrogen chloride on the propitiously situated nitrile and alcoholic hydroxyl. It is of interest to note that 2-(2-hydroxyethyl)-semicarbazide hydrochloride cannot be dehydrated with thionyl chloride under the conditions that are effective with the 5-nitro-2-furaldehyde derivative.

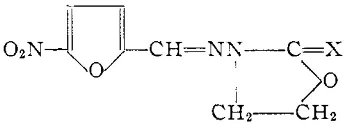
Salts other than the hydrochloride, such as the acid sulfate and β-naphthalene sulfonate, have been prepared by treating a methanolic solution of the free-base IIa with an excess of the appropriate acid.

Other variously substituted 2-β-hydroxyalkylated semicarbazones of 5-nitro-2-formylfurans yield the corresponding substituted 3-amino-2-iminooxazolidine hydrochlorides when treated with thionyl chloride alone or in an inert solvent such as benzene. These are presented in Table I.

The 2-iminoöxazolidine derivatives were converted to the analogous 2-oxazolidones in each case.[1]



I



II, X = NH·HCl
IIa, X = NH
IIb, X = O

Experimental[5]

Starting Materials.—The 2-(2-hydroxyalkyl)-semicarbazones of 5-nitro-2-furaldehyde were prepared in general by the method of Stillman, *et al.*,[2b] from hydrazinoalkanols as described in detail by Gever.[6] Similarly the vinylog of I was formed by the condensation of 2-(2-hydroxyethyl)-semicarbazide and β-(5-nitro-2-furyl)-acrolein. The latter was prepared by the method of Takahashi, *et al.*[7] The β-(5-nitro-2-furyl)-acrolein 2-(2-hydroxyethyl)-semicarbazone had a m.p. 209–210°.

Anal. Calcd. for $C_{10}H_{12}N_4O_5$: C, 44.75; H, 4.51; N, 20.85. Found: C, 44.81; H, 4.68; N, 21.14.

N-(5-Nitro-2-furfurylidene)-3-amino-2-iminoöxazolidine Hydrochloride (II).—A suspension of 2.32 kg. of 5-nitro-2-furaldehyde 2-(2-hydroxyethyl)-semicarbazone in seven liters of dry benzene was heated to 40° and treated with a solution of 4.9 kg. of thionyl chloride in five liters of benzene at such a rate as to keep the heavy foaming under control. When the vigorous escape of sulfur dioxide and hydrogen chloride had abated, the suspension was heated at 55–65° for one hour. After cooling, the light yellow solid was filtered with suction and dried in a well ventilated oven at 110°. The yield of N-(5-nitro-2-furfurylidene)-3-amino-2-iminoöxazolidine hydrochloride was 2.40 kg. (96%), m.p. 190° dec.

The hydrochloride II was conveniently converted to the free base IIa by solution in a minimum of water, clarifying by filtration, followed by precipitation with a cold solution

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[1] For the first paper in this series, see G. Gever, *et al.*, THIS JOURNAL, **77**, 2277 (1955).

[2] (a) A. B. Scott, W. B. Stillman and J. Clapit, U. S. Patent 2,319,481 (1943); (b) W. B. Stillman and A. B. Scott, U. S. Patents 2,416,233–2,416,239 (1947); (c) G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949); (d) K. Hayes, U. S. Patent 2,610,181 (1952).

[3] S. Gabriel, *Ber.*, **22**, 1139 (1889); S. Gabriel, *ibid.*, **50**, 826 (1917).

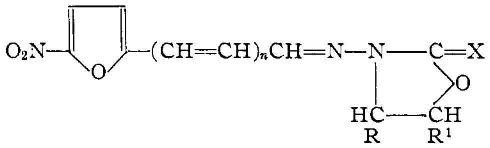
[4] E. Fromm, *et al.*, *Ann.*, **442**, 130 (1925).

[5] All melting points are taken on the Fisher–Johns apparatus and are corrected.

[6] G. Gever, THIS JOURNAL, **76**, 1283 (1954).

[7] T. Takahashi, *et al.*, *J. Pharm. Soc. Japan*, **69**, 284 (1949); (*C. A.*, **44**, 5372e (1950)).

TABLE I



X	R	R¹	n	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. Other	Found[a] C	Found[a] H	Found[a] Other	Molar absorption in water E_{max}	mμ
NH	H	H	0	170–171	$C_8H_8N_4O_4$	42.86	3.59	N, 25.00	42.55	3.29	N, 25.39	16200	356
$NH \cdot H_2SO_4$	H	H	0	203 d.	$C_8H_{10}N_4O_8S$			S, 9.93			S, 9.63	16000	355
$NH \cdot C_{10}H_7SO_3H$	H	H	0	222–224	$C_{18}H_{16}N_4O_7S$			S, 7.40			S, 7.39	16000	355
NH.HCl	H	H	0	190	$C_8H_9ClN_4O_4$	36.86	3.44	Cl, 13.60	37.00	3.05	Cl, 13.89	17000	355
NH	H	CH_3	0	170–173	$C_9H_{10}N_4O_4$	45.38	4.23	N, 23.52	45.78	4.51	N, 23.34	15600	356
NH.HCl	H	n-C_4H_9	0	139–140	$C_{12}H_{17}ClN_4O_4$	45.50	5.41	N, 17.69	45.28	5.22	N, 17.77	17000	355
NH	H	H	1	182	$C_{10}H_{10}N_4O_4$	48.00	4.03	N, 22.39	48.03	3.81	N, 22.26	22100	392.5
NH.HCl	CH_3	H	0	202–203	$C_9H_{11}ClN_4O_4$	39.35	4.04	Cl, 12.91	39.06	4.03	Cl, 12.69	16700	355

[a] We are indebted to Mr. Joseph Corrado for the determination of all the analytical data reported.

of 10% sodium carbonate. The yellow solid was purified further by recrystallization from ethanol; m.p. 170–171°.

N-(5-Nitro-2-furfurylidene)-3-amino-2-oxazolidone (IIb). A.—N-(5-Nitro-2-furfurylidene)-3-amino-2-iminoöxazolidine hydrochloride (900 g.) was dissolved in 10 liters of water at 35–40° and filtered to remove a small amount of insoluble material. The solution was cooled to 5–7° in an ice-bath and by addition of 5 kg. of chopped ice. After the addition of 1.5 l. of glacial acetic acid, 3.40 kg. of sodium nitrite was introduced during 30 minutes. A yellow solid separated rapidly and after four hours it was removed by filtration. After drying at 60° the crude product was recrystallized from hot, glacial acetic acid. The yield of IIb was 442 g. (60%), m.p. 253–256°.

This material was identical with IIb produced by other methods[1] as shown by mixed melting point and ultraviolet light absorption characteristics.

B.—N-(5-Nitro-2-furfurylidene)-3-amino-2-iminoöxazolidine hydrochloride (1800 g.) was dissolved in 38 l. of water. After clarifying, the solution was heated at 90° to 100° for 90 minutes. A yellow solid formed and was separated while hot (filtrate must be above 70°) by centrifugation. The solid was washed with hot water and dried at 110°; yield 752 g. (49%) of IIb, m.p. 253–256°.

Cooling the hot aqueous mother liquor to 10° yielded crude 5-nitro-2-furaldehyde 2-(2-hydroxyethyl)-semicarbazone (32%) which may be reconverted to II and recycled.

N-β-(5-Nitro-2-furyl)-acrylal-3-amino-2-iminoöxazolidine.—Forty-one and six-tenths grams of β-(5-nitro-2-furyl)-acrolein 2-(2-hydroxyethyl)-semicarbazone was treated rapidly with 250 cc. of thionyl chloride in a large beaker. Gas was evolved and the red solid rapidly became yellow. After standing at room temperature for 12 hours the yellow solid was filtered and washed repeatedly with dry ether; yield 44.7 g. (100%) of N-β-(5-nitro-2-furyl)-acrylal-3-amino-2-iminoöxazolidine hydrochloride of m.p. 229° dec. This hydrochloride was converted to the free base by dissolving it in cold water, clarifying, followed by treatment with sodium carbonate solution to *p*H of about 9. The orange, voluminous precipitate of the free base was filtered, washed with water, well dried and recrystallized from absolute ethanol; m.p. 182° with resolidification on further heating, yield 32.3 g. (82.5%).

N-β-(5-Nitro-2-furyl)-acrylal-3-amino-2-oxazolidone.—The crude N-β-(5-nitro-2-furyl)-acrylal-3-amino-2-iminoxazolidine can be converted to the corresponding oxazolidone by heating with dilute acid.

Twenty-eight grams of N-β-(5-nitro-2-furyl)-acrylal-3-amino-2-iminoöxazolidine was dissolved in 1250 cc. of water containing 13 cc. of concentrated hydrochloric acid. The clarified solution was boiled for 30 minutes and the precipitated solid filtered from the hot solution. The filtrates were reboiled and refiltered after 30 minutes and the process repeated until no further solid formed. The crude product thus collected (23.2 g.) was a mixture of β-(5-nitro-2-furyl)-acrolein derivatives of 3-amino-2-oxazolidone and of 2-(2-hydroxyethyl)-semicarbazide. These were separated by treatment with thionyl chloride in benzene which converted the hydroxyethylsemicarbazide derivative to the water-soluble 3-amino-2-iminoöxazolidine hydrochloride compound which can be extracted and recycled. Four cycles of this process yielded 20.2 g. (72%) of N-β-(5-nitro-2-furyl)-acrylal-3-amino-2-oxazolidone. This can be purified by recrystallization from nitromethane to give a yellow material of m.p. 270° dec.

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