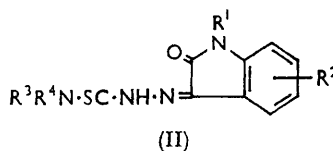
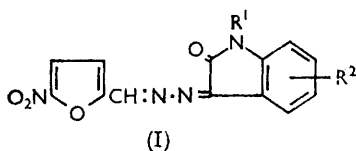


**913. Antimicrobials. Part II.<sup>1</sup> Nitrofuran Analogues Containing a 2-Hydranomethyl Side-chain.**

By R. G. JOHNSTON and DAVID KIDD.

A series of isatin azines prepared from 5-nitrofurfuraldehyde and the new aldehydes described in Part I, and water-soluble 5-nitrofurfurylidene sugar azines, have been prepared and their activities examined against gram-positive and gram-negative bacteria, and fungi.

In this section the second criterion<sup>1</sup> required for a furan antimicrobial has been examined. The requisite  $-\text{CH}=\text{N}-\text{N}<$  side-chain was introduced into the 5-nitro-furan molecule by the synthesis of azines (I) of substituted isatins. The parent azine of the series provided an amido-side-chain, and the series as a whole has some structural similarity to the isatin thiosemicarbazones<sup>2</sup> (II) useful as antiviral agents. Whilst this work was in progress, a



report of an investigation of a series of 5-nitrofurfurylidene azines with aldehydes and ketones (*e.g.*, benzaldehyde and acetophenone) was published,<sup>3</sup> and antibacterial activity was claimed<sup>4</sup> for a series of azines of 3-methyl-2-benzothiazolone with furfuraldehyde and sugars.

Condensation of 5-nitrofurfuraldehyde with the appropriate isatin hydrazone in alcohol or glacial acetic acid was the preferred method of synthesis. The alternative condensation of 5-nitrofurfuraldehyde hydrazone<sup>5</sup> with an isatin did not give encouraging results. With *N*-hydroxymethylisatin, and Mannich condensation products from piperidine and morpholine,<sup>6</sup> the attempted preparation of hydrazones led to scission of the *N*-substituent and formation of isatin 3-hydrazone. The azine (I;  $\text{R}^1 = \text{CH}_2\text{OH}$ ,  $\text{R}^2 = \text{H}$ ) was obtained from the parent azine (I;  $\text{R}^1 = \text{R}^2 = \text{H}$ ) and formaldehyde in dimethylformamide, but this method was unsuccessful when formaldehyde and a base were employed together. Isatin azines were also obtained from the aldehydes previously prepared.<sup>1</sup>

5-Nitrofurfurylidene azines with good water-solubility were similarly prepared from sugar hydrazones.<sup>7</sup> Using 100% hydrazine hydrate in place of anhydrous material, the sugar hydrazones were obtained, in most cases quite readily, as crystalline solids. D(-)-Ribose, however, gave a mixture of products. The only reducing sugar found to be active

<sup>1</sup> Part I, preceding Paper.

<sup>2</sup> Bauer and Sadler, *Brit. J. Pharmacol.*, 1960, **15**, 101.

<sup>3</sup> Haber, Guri, and Menachemoff, *Bull. Res. Council Israel*, 1961, **10**, A, 1323.

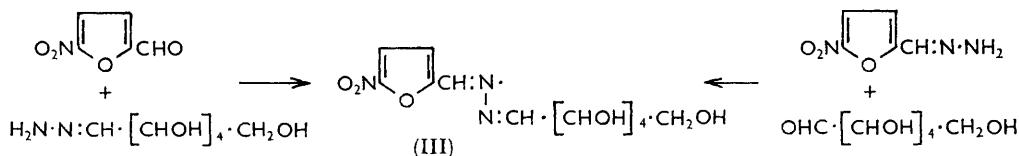
<sup>4</sup> Riemschneider, Georgi, and Nowack, *Monatsh.*, 1960, **91**, 639.

<sup>5</sup> Hull, B.P. 816,886.

<sup>6</sup> Hellmann, *Chem. Ber.*, 1954, **87**, 1689.

<sup>7</sup> Tipson, *J. Org. Chem.*, 1962, **27**, 2272.

enough to give an azine with 5-nitrofurfuraldehyde hydrazone was D(+)-mannose, and the two methods of synthesis gave the same product (III). The azine syntheses gave predominantly one isomer and there was little evidence to suggest production of isomeric mixtures.<sup>8</sup>



*N*-Ethylisatin 5-nitrofurfurylidenehydrazone gave the most promising *in vitro* results with regard to both activity and a wide spectrum of effectiveness. This parallels the findings of Bauer and Sadler,<sup>2</sup> whose most active compound was also derived from *N*-ethylisatin. Our compounds, however, were so extremely insoluble in water that the tests had to be carried out with acetone present. The sugar azines had only a low level of activity.

### EXPERIMENTAL

Infrared spectra were measured with a Perkin-Elmer Infracord spectrophotometer for potassium bromide discs.

*Isatin 3-(5-Nitrofurfurylidenehydrazone)* (I; R<sup>1</sup> = R<sup>2</sup> = H).—Solutions of 5-nitrofurfuraldehyde (1.0 g.) and isatin 3-hydrazone (1.3 g.) in glacial acetic acid (10 ml.) were mixed and boiled (2 min.). On cooling, the *azine* separated as needles (1.3 g., 65%). Recrystallisation from nitromethane gave material of m. p. 245—246° (decomp.) (Found: C, 54.7; H, 2.8; N, 20.0. C<sub>13</sub>H<sub>8</sub>N<sub>4</sub>O<sub>4</sub> requires C, 54.9; H, 2.8; N, 19.7%,  $\nu_{\text{max}}$ . 3400 (NH), 1710 (C=O), 1610 (C=N), 1510 and 1375 cm.<sup>-1</sup> (NO<sub>2</sub>).

The *azines* from substituted isatins (Table 1) were prepared by the same method, and had similar infrared absorption curves.

TABLE I.  
Substituted isatin azines.

Subst.	Ref.	Yield (%)	M. p.	Found (%)				Formula	Required (%)			
				C	H	Cl	N		C	H	Cl	N
1-Me	<i>a</i>	80	216	56.8	3.3	—	18.5	C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub>	56.4	3.4	—	18.8
1-Et	<i>b</i>	62	172	57.3	3.9	—	18.2	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub>	57.7	3.9	—	18.0
1-CH <sub>2</sub> -CH:CH <sub>2</sub>	—	51	145	59.1	3.8	—	17.0	C <sub>16</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub>	59.3	3.7	—	17.3
1-CH <sub>2</sub> -Ph	<i>c</i>	87	190	64.0	3.6	—	14.9	C <sub>20</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub>	64.1	3.8	—	15.0
4-Cl	<i>d</i>	75	203	49.4	2.4	11.0	18.0	C <sub>13</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>4</sub>	49.1	2.2	11.2	17.6
5-Me	<i>e</i>	85	247	56.4	3.6	—	18.5	C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub>	56.4	3.4	—	18.8
6-Cl	<i>d</i>	60	225	48.9	2.4	10.8	17.7	C <sub>13</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>4</sub>	49.1	2.2	11.2	17.6

<sup>a</sup> Hantzsch, *Ber.*, 1921, **54**, 1244. <sup>b</sup> Michaelis, *Ber.*, 1897, **30**, 2815. <sup>c</sup> Antrick, *Annalen*, 1885, **227**, 364. <sup>d</sup> Sadler, *J. Org. Chem.*, 1956, **21**, 169. <sup>e</sup> *Org. Synth.*, Coll. Vol. I, p. 331.

*N-Allylisatin*.—Sodioisatin (84.5 g.) and allyl bromide (60.5 g.) were boiled in dry benzene (500 ml.) for 48 hr. The inorganic salt was removed by hot filtration and the filtrate concentrated. The residue gave *N-allylisatin*, blades (66.6 g., 71%), m. p. 87—88° (from ethanol) (Found: C, 70.6; H, 4.9; N, 7.7. C<sub>11</sub>H<sub>9</sub>NO<sub>2</sub> requires C, 70.6; H, 4.9; N, 7.5%,  $\nu_{\text{max}}$ . 1730 (C=O) and 1615 cm.<sup>-1</sup> (CO·N).

*N-Allylisatin 3-Hydrazone*.—*N*-Allylisatin (10 g.) in ethanol (100 ml.) was boiled with 100% hydrazine hydrate (20 ml.) for  $\frac{1}{2}$  hr., and, on cooling, the *hydrazone* separated as blades (6.5 g., 60.5%), m. p. 108—109° (Found: C, 65.6; H, 5.6; N, 21.2. C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O requires C, 65.6; H, 5.5; N, 20.9%,  $\nu_{\text{max}}$ . 3400, 3200 (NH); 1680 (C=O) and 1600 cm.<sup>-1</sup> (C=N).

*4-Chloroisatin 3-Hydrazone*.—On recrystallisation from ethanol the *hydrazone* formed blades (63%), m. p. 210—212° (Found: C, 49.4; H, 3.2; Cl, 18.5; N, 21.3. C<sub>8</sub>H<sub>6</sub>ClN<sub>3</sub>O requires C, 49.1; H, 3.1; Cl, 18.2; N, 21.5%).

<sup>8</sup> Fleming and Harley-Mason, *J.*, 1961, 5560.

*6-Chloroisatin 3-Hydrazone*.—When recrystallised from ethanol the *hydrazone* formed needles (70%), m. p. 247—248° (Found: C, 48.9; H, 3.0; Cl, 18.2; N, 21.2%).

*N-Hydroxymethylisatin 3-(5-Nitrofurfurylidenehydrazone)*.—Isatin 3-(5-nitrofurfurylidenehydrazone) (12.4 g.) and 33% aqueous formaldehyde (25 ml.) were heated (water-bath) in dimethylformamide (50 ml.) for 1 hr. The solution was concentrated, and the residue triturated with ethanol (100 ml.). The red solid obtained (6.5 g.) was twice crystallised from nitromethane to remove unreacted isatin azine (1.7 g.). The *product* crystallised in needles or blades (3.6 g., 26%), m. p. 191—193° (Found: C, 53.7; H, 3.0; N, 17.9.  $C_{14}H_{10}N_4O_5$  requires C, 53.5; H, 3.2; N, 17.8%),  $\nu_{\max}$ . 3300, 3100 (furan ring, OH) 1740 (C=O), 1610 (C=N), 1510 and 1345  $cm^{-1}$  ( $NO_2$ ).

*Miscellaneous Isatin Hydrazones*.—2-Formylbenzofuran (1.1 g.) and isatin 3-hydrazone (1.5 g.) gave *isatin 3-(2-benzofuran-2-ylmethylenehydrazone)* as needles (1.7 g., 73%), m. p. 222—225° (Found: C, 70.2; H, 4.0; N, 14.6.  $C_{17}H_{11}N_3O_2$  requires C, 70.5; H, 3.9; N, 14.5%).

*Isatin 3-(4,9-Dimethoxy-5-oxo-5H-furo[3,2-g]chromen-7-ylmethylenehydrazone)*.—This *compound* crystallised from dimethylformamide-acetone in flocculent needles (65%), m. p. 261—263° (decomp.) (Found: C, 63.3; H, 3.5; N, 9.9.  $C_{23}H_{15}N_3O_6$  requires C, 63.3; H, 3.6; N, 10.1%).

*Isatin 3-(6-Nitro-4-oxo-4H-chromen-2-ylmethylenehydrazone)*.—This *azine* crystallised from dimethylformamide-acetone in needles (90%), m. p. 251—254° (decomp.) (Found: C, 59.9; H, 2.9; N, 15.4.  $C_{18}H_{10}N_4O_5$  requires C, 59.7; H, 2.8; N, 15.5%).

*Isatin 3-(6-Nitro-2-benzothiazolylmethylenehydrazone)*.—This *azine* crystallised from glacial acetic acid in needles (74%), m. p. 296—298° (decomp.) (Found: C, 54.5; H, 2.7; N, 19.7; S, 8.7.  $C_{16}H_9N_5O_3S$  requires C, 54.7; H, 2.6; N, 19.9; S, 9.1%).

*D(+)-Mannose Hydrazone*.—D(+)-Mannose (8.0 g.) was added in portions to an ice-cold mixture of 100% hydrazine hydrate (20 ml.) and methanol (25 ml.). The clear solution obtained on shaking was set aside at room temperature for 24 hr. Evaporation in a vacuum desiccator over phosphorus pentoxide and soda-lime gave a viscous colourless syrup which yielded white crystals of the *hydrazone* (4.8 g., 55.5%), m. p. 150—154° (decomp.), on trituration with methanol (Found: N, 14.5.  $C_6H_{14}N_2O_5$  requires N, 14.4%),  $\nu_{\max}$ . 1620  $cm^{-1}$  (C=N). The other *sugar hydrazones* (Table 2) were similarly prepared.

TABLE 2.  
Sugar hydrazones.

Sugar	Yield (%)	M. p.	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
D(+)-Xylose .....	82	gum	—	—	—	$C_5H_{12}N_2O_4$	—	—	—
D(-)-Arabinose .....	70	120°	35.8	7.5	17.1	$C_5H_{12}N_2O_4$	36.6	7.4	17.1
L(+)-Arabinose .....	40	119	37.6	7.5	16.9	$C_5H_{12}N_2O_4$	36.6	7.4	17.1
L(+)-Rhamnose .....	68.5	123	39.8	7.7	15.5	$C_6H_{14}N_2O_5$	40.4	7.9	15.7
D(+)-Glucose .....	90	gum	—	—	—	$C_6H_{14}N_2O_5$	—	—	—

*D(+)-Mannose 5-Nitrofurfurylidenehydrazone*.—(a) 5-Nitrofurfuraldehyde (1.6 g.) and D(+)-mannose hydrazone (2.2 g.) were boiled in propan-2-ol (120 ml.) for 12 hr. The solution was filtered hot and deposited the *azine* (1.75 g., 50%) when cold. Two crystallisations from methanol gave blades, m. p. 168—170° (Found: C, 41.5; H, 4.9; N, 13.0.  $C_{11}H_{15}N_3O_8$  requires C, 41.6; H, 4.7; N, 13.2%),  $\nu_{\max}$ . 1605 (C=N), 1510 and 1355  $cm^{-1}$  ( $NO_2$ ).

(b) D(+)-Mannose (3.6 g.) and 5-nitrofurfuraldehyde hydrazone (3.1 g.) were boiled in propan-2-ol (125 ml.) for 4 hr. After 3 hr. the clear yellow solution began to deposit the *azine* (4.1 g., 65%). Recrystallisation from methanol gave blades, m. p. 168—170°, identical (infrared spectrum and mixed m. p.) with the above product.

The *azines* recorded in Table 3 were prepared by method (a), since all other sugars tried were unreactive in method (b).

TABLE 3.  
Sugar 5-nitrofurfurylidenehydrazones.

Sugar	Yield (%)	M. p.	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
D(+)-Xylose .....	25	169°	41.8	4.4	14.4	$C_{10}H_{13}N_3O_7$	41.8	4.5	14.6
D(-)-Arabinose .....	78	139	41.6	4.3	14.6	$C_{10}H_{13}N_3O_7$	41.8	4.5	14.6
L(+)-Arabinose .....	62	133	41.5	4.7	14.4	$C_{10}H_{13}N_3O_7$	41.8	4.5	14.6
L(+)-Rhamnose .....	74	168	43.7	5.2	13.7	$C_{11}H_{15}N_3O_8$	43.9	5.0	14.0
D(+)-Glucose .....	25	168	41.4	4.4	13.2	$C_{11}H_{15}N_3O_8$	41.6	4.7	13.2

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The authors thank Mr. A. Brown, Mr. A. Harrison, and Mr. J. Spanswick for technical assistance, Mr. W. R. Buckett and Mr. D. Watt for the bacteriological results, and Miss M. M. Dickson for spectroscopic determinations.

EDINBURGH PHARMACEUTICAL INDUSTRIES LTD.,  
RESEARCH DEPARTMENT, EDINBURGH 11.

[Received, February 13th, 1964.]

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