912. *Antimicrobials. Part I. 5-Nitrofuran Analogues.*

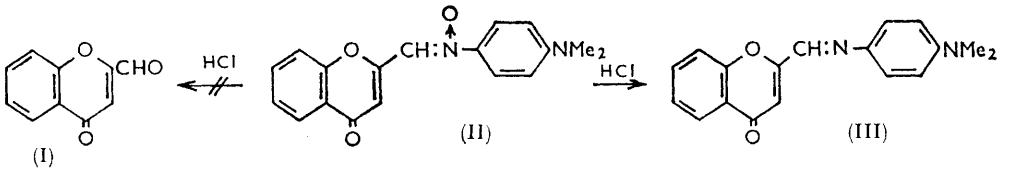
By R. G. Johnston and David Kidd.

2-Formyl-6-nitro-chromone and -benzothiazole have been synthesised. Their derivatives, and new derivatives of 2-formyl-benzofuran and -chromone and 7-formyl-3,5-dihydro-4,9-dimethoxy-2*H*-furo[3,2-*g*]chromen-5-one, have been screened against gram-positive and gram-negative organisms and fungi. β-Vinylogues of 3-(5-nitrofurfurylideneamino)-2-oxazolidone (Furazolidone) have also been examined.

Recognition of the nitrofurans as a distinct class of clinically useful antimicrobial agents began with the investigations of Dodd and Stillman.[1] Recently, nitrofurans have been shown to possess antiviral activity [2] and they have also been investigated as antitumour agents.[3] Most furans with satisfactory *in vitro* activity contain (1) a nitro-group in the 5-position and (2) a $-CH{:}N{\cdot}N<$ side-chain in the 2-position. This indicated that the activity might be associated with the powerful electron-withdrawing capacity of the nitro-group, exerted through a conjugated system of double bonds. However, the derivatives of 2-formylbenzofuran,[4] and indeed the aldehyde itself, exhibit high antibacterial activity. In this section, therefore, criterion (1) has been examined and analogues of 5-nitrofurfuraldehyde semicarbazone (Nitrofurazone), 1-(5-nitrofurfurylideneamino)-hydantoin (Nitrofurantoin), and 3-(5-nitrofurfurylideneamino)-2-oxazolidone (Furazolidone) have been prepared from both unsaturated nitro-aldehydes (2-formyl-6-nitro-chromone and -benzothiazole [5]) and unsaturated aldehydes (2-formyl-benzofuran and -chromone [6] and 7-formyl-3,5-dihydro-4,9-dimethoxy-2*H*-furo[3,2-*g*]chromen-5-one [7]) which do not have a suitably located nitro-group.

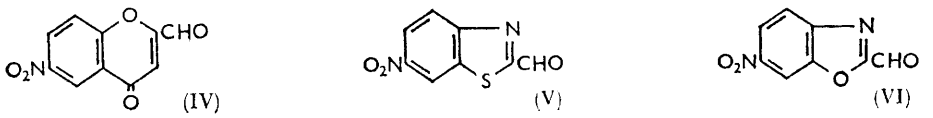
The aldehydes were prepared from the corresponding methyl compounds. The method described by Schmutz, Hirt, and Lauener [6] was used in an endeavour to prepare 2-formyl-chromone (I). Hydrolysis of the nitrone (II) with aqueous hydrochloric acid, followed by basification with ammonia, did not yield the aldehyde (I), but gave instead the azomethine

[1] Dodd and Stillman, *J. Pharmacol.*, 1944, **82**, 11.
[2] Hull and Hurst, *Nature*, 1961, **192**, 807; Gualtieri, Riccieri, and Stein, *Farmaco* (*Pavia*), *Ed. Sci.*, 1962, **17**, 430.
[3] Saldabols and Hillers, *Puti Sintéza i Izyskaniya Protivoopukholevykh Preparatov, Tr. Simpoziuma po. Khim. Protivoopukholevykh Veshchestvm*, Moscow, 1960, 186.
[4] Pan and Wiese, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1960, **49**, 259.
[5] Zubarovskii, *Zhur. obshchei Khim.*, 1954, **24**, 1664.
[6] Schmutz, Hirt, and Lauener, *Helv. Chim. Acta*, 1952, **35**, 1173.
[7] Mustafa, Starkovsky, and Salama, *J. Org. Chem.*, 1961, **26**, 886.



(I) (II) (III)

(III) as the only characterisable product. However, this gave the required derivative directly.[8]

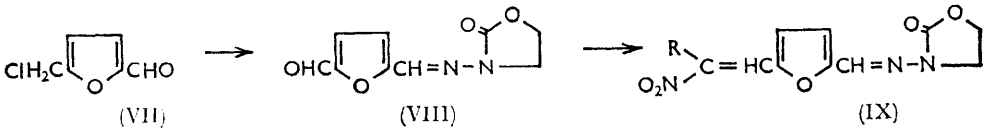


(IV) (V) (VI)

As the hydrolyses proceeded normally, this general method was used successfully in the synthesis of 2-formyl-6-nitro-chromone (IV) and -benzothiazole (V) from the known 2-methyl compounds.[9,10] Because a quaternary pyridinium iodide could not be isolated at the initial stage,[11] a synthesis of 2-formyl-6-nitrobenzoxazole (VI) failed.

Although Mustafa *et al.*[7] formulated the intermediate obtained from the quaternary iodide and *NN*-dimethyl-*p*-nitrosoaniline as an azomethine, in the above instances, analytical results and infrared spectra are in agreement with the nitrone structure.[12]

Using the readily accessible 5-chloromethylfurfuraldehyde[13] (VII) we synthesised 3-(5-formylfurfurylideneamino)-2-oxazolidone (VIII) and from it, by condensation with nitro-alkanes, analogues (IX; R = H, Me) of Furazolidone. 2,5-Diformylfuran was also obtained from the chloromethyl-aldehyde, and with 3-amino-2-oxazolidone gave the aldehyde (VIII).



(VII) (VIII) (IX)

An antimicrobial agent will to some extent affect the metabolic processes of the host, as well as the parasite, and it was hoped that by shielding the nitro-group with an alkyl group, we might obtain a therapeutic agent with relatively less toxicity to the host. The compounds, however, had little activity. This suggests that the particular structural conjunction of a 5-nitro-group and the oxygen of the furan ring are necessary for high activity. If antibacterial potency was largely due to reduction of the nitro-group by bacterial enzymes, this might be expected to be of comparable ease in a nitrofuran derivative and in its vinylogue. The antibacterial action may therefore be partly due to co-ordination of the nitrofuran with trace metals required for activation of enzyme systems, since the vinylogue is probably less capable of forming stable chelates. The vinylogue is also probably less capable of strong attachment to a receptor surface.

From bacteriological screening tests, the derivatives of 2-formyl-6-nitrobenzothiazole appeared to best advantage, but the activities generally were much lower than that of Furazolidone.

[8] Hamana, Umezawa, and Goto, *J. Pharm. Soc. Japan*, 1960, **80**, 1519.
[9] Da Re, *Farmaco* (*Pavia*), *Ed. Sci.*, 1956, **11**, 662.
[10] Brooker, Keyes, and Williams, *J. Amer. Chem. Soc.*, 1942, **64**, 207; Bogust and Cocker, *J.*, 1949, 355.
[11] Teilacker, *J. prakt. Chem.*, 1939, **153**, 54.
[12] De Waal and Brink, *Chem. Ber.*, 1956, **89**, 636; Ried and Bender, *ibid.*, 1956, **89**, 1893; Krohnke, Leister, and Vogte, *ibid.*, 1957, **90**, 2792; Giner-Sorolla, Zimmerman, and Bendich, *J. Amer. Chem. Soc.*, 1959, **81**, 2516.
[13] Haworth and Jones, *J.*, 1944, 667.

Experimental

Infrared spectra were measured with a Perkin-Elmer Infracord spectrophotometer for potassium bromide discs. Light petroleum refers to the fraction boiling between 60 and 80°.

2-(p-*Dimethylaminophenyliminomethyl*)*chromone* (III).—(*a*) The nitrone [6] (II) (7·9 g.), concentrated hydrochloric acid (30 ml.), and water (50 ml.) were heated (water-bath) for 10 min., cooled, diluted with water (200 ml.), and basified with concentrated ammonia to give a dark oil. Chloroform (500 ml.) was added and the organic layer separated, washed with water (2 × 100 ml.), dried (Na_2SO_4), and concentrated. The residue was extracted with boiling toluene (200 ml.) and, after hot filtration, the addition of light petroleum gave a red solid (1·45 g.). Crystallisation from acetone gave the *azomethine* as plates (0·67 g.), m. p. 187—190° (Found: C, 74·1; H, 5·7; N, 9·5. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6%), $\nu_{max.}$ 1640, 1630 (C:O), 1590, and 1575 cm.$^{-1}$ (C:N).

(*b*) Hydrolysis of the nitrone (20·0 g.) by the above method, but using 10N-sulphuric acid (300 ml.) at room temperature for 3 hr., gave the azomethine (3·9 g.), m. p. 192—194° [from acetone (charcoal)].

From this azomethine, *derivatives* of 2-formylchromone were obtained directly and are included in the Table, together with the *derivatives* of the other aldehydes prepared below.

N-(6-*Nitro*-2-*chromenylmethyl*)*pyridinium Iodide*.—2-Methyl-6-nitrochromone [9] (16·8 g., 0·081 mole), powdered iodine (20·6 g., 0·081 mole), and pyridine (30 ml.) were heated together (water-bath) for 1 hr. Acetone (100 ml.) was added, the mixture cooled to 0°, and the *product* (17·5 g., 52%) filtered and washed successively with acetone, cold water, and acetone, m. p. 214—216° (decomp.). An analytical sample was crystallised from dimethylformamide–acetone (Found: C, 43·7; H, 2·7; I, 29·7; N, 6·6. $C_{15}H_{11}IN_2O_4$ requires C, 43·9; H, 2·7; I, 31·0; N, 6·8%).

2-*Formyl*-6-*nitrochromone* N-(p-*Dimethylaminophenyl*)*oxime*.—To the preceding compound (7·9 g.) in water (40 ml.) and ethanol (30 ml.) was added a solution of *NN*-dimethyl-*p*-nitrosoaniline in ethanol (250 ml.). The stirred mixture was cooled to −5° and N-sodium hydroxide solution (22 ml.) slowly added. After 1 hr. the temperature was allowed to rise to 12° over a period of 1 hr. The *nitrone* was collected, washed, and dried at 100°. Washing with hot dimethylformamide–acetone (1 : 2; 50 ml.) greatly improved the quality of the product and gave material (4·5 g., 68·5%) of m. p. 256—258° (decomp.) (Found: C, 61·1; H, 4·2; N, 12·2. $C_{18}H_{15}N_3O_5$ requires C, 61·2; H, 4·2; N, 11·9%), $\nu_{max.}$ 1640 (C:O), 1610 (C:N), 1530 and 1375 cm.$^{-1}$ (NO_2).

2-*Formyl*-6-*nitrochromone* (IV).—The nitrone (1·0 g.) was shaken at room temperature with 10N-sulphuric acid (15 ml.) for 15 min. During this period the solution gradually deposited crystals of the *nitro-aldehyde*. Water (50 ml.) was added and the product collected, washed with water, and dried at 100°. Crystallisation from toluene–light petroleum gave blades, (0·4 g., 61·5%), m. p. 212—214° (Found: C, 55·3; H, 2·2; N, 6·2. $C_{10}H_5NO_5$ requires C, 54·8; H, 2·3; N, 6·4%), $\nu_{max.}$ 1710, 1675 (C:O), 1530 and 1350 cm.$^{-1}$ (NO_2).

Aldehyde derivatives.

			Found (%)					Required (%)			
Aldehyde	Derivative	M. p.	C	H	N	S	Formula	C	H	N	S
2-Formyl-chromone	Thiosemicarbazone	242°	53·6	3·8	16·8	12·6	$C_{11}H_9N_3O_2S$	53·4	3·7	17·0	12·9
	Oxime	243	63·9	3·8	7·8	—	$C_{10}H_7NO_3$	63·5	3·7	7·6	—
	1-Aminohydantoin	308	57·3	3·4	15·6	—	$C_{13}H_9N_3O_4$	57·5	3·4	15·5	—
2-Formyl-6-nitro-chromone	Semicarbazone	280	47·8	3·1	19·8	—	$C_{11}H_8N_4O_5$	47·8	2·9	20·3	—
	Thiosemicarbazone	255	44·9	2·7	19·5	11·2	$C_{11}H_8N_4O_4S$	45·2	2·8	19·2	11·0
	1-Aminohydantoin	341	49·5	2·7	17·9	—	$C_{13}H_8N_4O_6$	49·4	2·6	17·7	—
2-Formyl-6-nitro-benzothiazole	Semicarbazone	270	41·4	2·6	26·6	12·3	$C_9H_7N_5O_3S$	40·8	2·7	26·4	12·1
	1-Aminohydantoin	296	43·6	2·1	23·2	10·4	$C_{11}H_7N_5O_4S$	43·3	2·3	23·0	10·5
2-Formylbenzo-furan	1-Aminohydantoin	272	59·7	4·0	17·3	—	$C_{12}H_9N_3O_3$	59·3	3·8	17·3	—
7-Formyl-3,5-dihydro-4,9-dimethoxy-2*H*-furo[3,2-*g*]-chromen-4-one	Thiosemicarbazone	254	52·1	3·7	11·8	9·0	$C_{15}H_{13}N_3O_5S$	51·9	3·8	12·1	9 ·2
	1-Aminohydantoin	321	55·4	3·7	11·4	—	$C_{17}H_{13}N_3O_7$	55·0	3·5	11·3	—

N-(6-*Nitro*-2-*benzothiazolylmethyl*)*pyridinium Iodide*.—2-Methyl-6-nitrobenzothiazole [10] gave the *pyridinium iodide* (71%), m. p. 215—217° (decomp.) (Found: C, 39·2; H, 2·7; I, 31·6; N, 10·3; S, 8·2. $C_{13}H_{10}IN_3O_2S$ requires C, 39·1; H, 2·5; I, 31·8; N, 10·5; S, 8·0%).

2-*Formyl*-6-*nitrobenzothiazole* N-(p-*Dimethylaminophenyl*)*oxime*.—Reaction of the iodide by the usual method gave the *nitrone*, (60·5%) as blades, m. p. 268—270° (decomp.) (Found: C, 56·4; H, 4·3; N, 16·2; S, 9·4. $C_{16}H_{14}N_4O_3S$ requires C, 56·1; H, 4·1; N, 16·4; S, 9·4%), $\nu_{max.}$ 1610 (C:N), 1520 and 1335 cm.$^{-1}$ (NO_2).

2-*Formyl*-6-*nitrobenzothiazole* (V).—Hydrolysis of the above nitrone with 10N-sulphuric acid gave the nitro-aldehyde (56%), m. p. 174—176° (lit.,[5] 174°) (Found: C, 46·6; H, 2·0; N, 13·0; S, 14·9. Calc. for $C_8H_4N_2O_3S$: C, 46·2; H, 1·9; N, 13·4; S, 15·4%), $\nu_{max.}$ 1695 (C:O), 1570 (C:N), 1520 and 1350 cm.$^{-1}$ (NO_2).

3-(5-*Chloromethylfurfurylideneamino*)-2-*oxazolidone*.—5-Chloromethylfurfuraldehyde [13] (30·0 g.) and 3-amino-2-oxazolidone (21·3 g.) were boiled together in dry acetone (100 ml.) for 1 hr. The *chloromethyl compound* separated as plates (44 g., 90%), m. p. 159—162°, which were washed (light petroleum) and dried at 50° (Found: C, 47·4; H, 3·9; Cl, 15·4; N, 11·9. $C_9H_9ClN_2O_3$ requires C, 47·3; H, 4·0; Cl, 15·5; N, 12·3%). The same product was isolated in good yield when the reaction was carried out in ethanol at room temperature. However, attempted crystallisation of the product from ethanol gave needles of 3-(5-*ethoxymethylfurfuryl-ideneamino*)-2-*oxazolidone*, m. p. 121° (Found: C, 55·7; H, 6·1; N, 12·2. $C_{11}H_{14}N_2O_4$ requires C, 55·5; H, 5·9; N, 11·8%).

N-[5-(2-*Oxo*-3-*oxazolidinyliminomethyl*)*furfuryl*]*pyridinium Chloride*.—The chloromethyl compound gave the *pyridinium chloride*, m. p. 202—204° (70%) (Found: Cl, 11·8. $C_{14}H_{14}ClN_3O_3$ requires Cl, 11·8%).

5-(2-*Oxo*-3-*oxazolidinyliminomethyl*)*furfuraldehyde* N-(p-*Dimethylaminophenyl*)*oxime*.—Reaction of the quaternary chloride with *NN*-dimethyl-*p*-nitrosoaniline by the usual method gave the *nitrone* (68·5%), m. p. 249—250° (Found: C, 59·6; H, 5·4; N, 16·2. $C_{17}H_{18}N_4O_4$ requires C, 59·6; H, 5·3; N, 16·4%), $\nu_{max.}$ 1775 (C:O) and 1610 cm.$^{-1}$ (C:N).

3-(5-*Formylfurfurylideneamino*)-2-*oxazolidone* (VIII).—(*a*) Hydrolysis of the nitrone with 2N-sulphuric acid at 0° gave the aldehyde as blades (61%), m. p. 198—200° (from nitromethane) (Found: C, 51·2; H, 3·9; N, 13·7. $C_9H_8N_2O_4$ requires C, 51·9; H, 3·9; N, 13·5%), $\nu_{max.}$ 1770 (C:O) and 1665 cm.$^{-1}$ (C:N).

(*b*) 2,5-Diformylfuran (0·5 g.) (see below) and 3-amino-2-oxazolidone (0·4 g.) were boiled together in ethanol (15 ml.) for 1½ hr. The brown solid that separated (0·5 g.) was extracted into ethanol and some high-melting solid removed by filtration. Addition of light petroleum gave the aldehyde (0·2 g.) as needles, m. p. 198—200°, identical mixed m. p. and infrared spectrum with material obtained in (*a*).

N-(5-*Formylfurfuryl*)*pyridinium Chloride*.—5-Chloromethylfurfuraldehyde (9·8 g.) was boiled under reflux with AnalaR pyridine (6·5 ml.) in dry acetone (100 ml.) for 4 hr. The acetone was distilled off and the slight excess of pyridine removed *in vacuo*, giving the quaternary salt as a syrup.

2,5-*Diformylfuran* N-(p-*Dimethylaminophenyl*)*oxime*.—Reaction of the quaternary chloride with *NN*-dimethyl-*p*-nitrosoaniline gave the *nitrone* as prisms (33%), m. p. 160—161° (Found: C, 65·4; H, 5·6; N, 11·1. $C_{14}H_{14}N_2O_3$ requires C, 65·1; H, 5·5; N, 10·9%), $\nu_{max.}$ 1675 (C:O) and 1610 cm.$^{-1}$ (C:N).

2,5-*Diformylfuran*.—The nitrone (2·9 g.) was hydrolysed with 2N-sulphuric acid (30 ml.) at 0° for ½ hr. The dialdehyde (1·0 g., 72%), m. p. 108—110° (lit.,[14] 109—110°) was obtained by extraction with ether.

3-(5-β-*Nitrovinylfurfurylideneamino*)-2-*oxazolidone* (IX; R = H).—To a solution of the oxazolidone (VIII) (0·5 g.) in methanol (20 ml.) and nitromethane (0·75 ml.) at −5° was added dropwise with stirring, 50% aqueous sodium hydroxide (4 ml.). After 1 hr. at 0°, ice-cold water (12 ml.) was added and the solution poured into hydrochloric acid (16 ml. conc. acid, 80 ml. water) at 0°. The *nitro-compound* (0·36 g., 57·5%) was collected, washed (water), and dried at 60°. Two crystallisations from nitromethane gave blades, m. p. 227—229° (Found: C, 47·4; H, 3·5; N, 16·5. $C_{10}H_9N_3O_5$ requires C, 47·8; H, 3·6; N, 16·7%), $\nu_{max.}$ 1770 (C:O), 1645 (C:N), 1505, 1495, and 1325 cm.$^{-1}$ (NO_2).

3-[5-(2-*Nitroprop*-1-*enyl*)*furfurylideneamino*]-2-*oxazolidone* (IX; R = Me).—By the same

[14] Raffauf, *J. Amer. Chem. Soc.*, 1950, **72**, 753.

method as above, this *nitro-compound* was obtained as needles (20%), m. p. 212—214° (Found: C, 49·6; H, 4·4; N, 15·7. $C_{11}H_{11}N_3O_5$ requires C, 49·8; H, 4·2; N, 15·8%), $\nu_{max.}$ 1760 (C:O), 1645 (C:N), 1505, 1495, and 1310 cm.$^{-1}$ (NO_2).

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