Journal of Medicinal and Pharmaceutical Chemistry

VOL. 3, No. 2 (1961)

The Synthesis and *in Vitro* Antibacterial Activity of Some New Nitrofuran Derivatives

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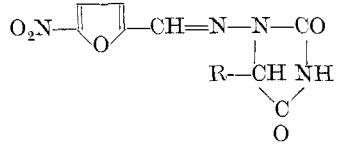
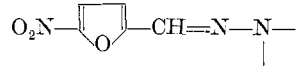
Although nitrofurans have been used extensively for the treatment of localized infections, it was not until recently with the introduction of furaltadone that it has been possible to treat systemic infections with a nitrofuran administered by mouth. Most nitrofurans are rapidly excreted in the urine, which forms the basis of their use as urinary disinfectants, or are metabolized to inactive products with the result that bactericidal tissue concentrations are not reliably achieved. This difficulty may be overcome with nitrofurantoin,[1] for example, by administering the drug as an intravenous drip but the method of administration is a disadvantage.

The objective of this work was to prepare new nitrofurans, essentially modified nitrofurantoins, which might provide better systemic activity following oral administration. In general, these new compounds contain more non-polar groupings than nitrofurantoin since it is known that 5-monoalkyl-nitrofurantoins (I) provide higher blood levels than nitrofurantoin[2] and it was considered that this was likely to be related to their reduced overall polarity.



R = C_1–C_4 alkyl

(I)



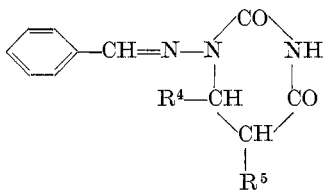
(II)

Most nitrofurans known to have satisfactory *in vivo* activity contain the grouping (II) and are prepared by condensing 5-nitro-2-furaldehyde or its diacetate with substituted hydrazines or with

derivatives thereof which are easily hydrolysed to form the free hydrazines. Therefore, the preparation of hydantoin-modified nitrofurantoins depends on the preparation of suitably substituted 1-aminohydantoins.

1-Isopropylideneamino-5-phenylhydantoin was prepared from acetone semicarbazone and ethyl α-chloro-phenylacetate by a modification of the method recently reported for 1-aminohydantoin.[3] 1-Isopropylideneamino-3-carbethoxymethylhydantoin was obtained by a further modification of the same method and, by acid hydrolysis, gave 1-amino-3-carboxymethylhydantoin. These 1-aminohydantoins were converted to their 5-nitro-2-furfurylidene derivatives by treatment with 5-nitro-2-furaldehyde or its diacetate in acid solution.

The other new nitrofurans reported in this work are 3-(5-nitro-2-furfurylideneamino)-4,5-dihydrouracils. They were prepared by hydrolysing the appropriate 3-benzylideneamino-4,5-dihydrouracils (III) with acid, followed by condensation of the free 3-amino-4,5-dihydrouracils formed with 5-nitro-2-furaldehyde as already



$R^4 = H$ or CH_3
$R^5 = H$ or CH_3 or C_6H_5

(III)

described for aminohydantoins. Derivatives of 3-amino-4,5-dihydrouracil have not been previously reported. 3-Benzylideneamino-4,5-dihydrouracil was first prepared by condensing benzaldehyde semicarbazone with ethyl β-bromopropionate, a reaction analogous to that reported between the semicarbazone and ethyl monochloroacetate.[3] Later it was found more convenient to prepare this compound from 3-isopropylideneamino-4,5-dihydrouracil obtained by the interaction of acetone semicarbazone and methyl acrylate under dry strongly basic conditions. The 3-benzylideneamino-4- or 5-substituted-4,5-dihydrouracils required were obtained by using α- or β-substituted acrylates

under similar conditions. The substituted acrylate may also be formed in the reaction mixture as shown by the formation of 3-benzylideneamino-5-methyl-4,5-dihydrouracil from either methyl methacrylate or ethyl α-bromoisobutyrate and of 3-benzylideneamino-5-phenyl-4,5-dihydrouracil from ethyl α-bromo-α-methyl-phenylacetate. A more detailed analysis of the chemical problems encountered will be published later.

The nitrofurans prepared are listed in Table I together with the results obtained from *in vitro* antibacterial tests. These tests

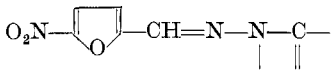
Table I. Antibacterial activity of some nitrofurans

Compound	Organism	Inhibition (−) or growth (+) at concentration (per cent) (± = very slight growth)					
		0·02	0·01	0·005	0·0025	0·00125	0·001
1. 1-(5-Nitro-2-furfuryl-ideneamino)-3-carb-ethoxymethylhydantoin	*Staph. aureus*	−	−	−	±	+	
	S. typhi	−	−	±	+	+	
	Proteus vulgaris	−	±	±	+	+	
	Ps. aeruginosa	+	+	+	+	+	
2. 1-(5-Nitro-2-furfuryl-ideneamino)-3-carb-oxymethylhydantoin	*Staph. aureus*	±	+	+	+	+	
	S. typhi	+	+	+	+	+	
	Proteus vulgaris	+	+	+	+	+	
	Ps. aeruginosa	+	+	+	+	+	
3. 1-(5-Nitro-2-furfuryl-ideneamino)-5-phenyl hydantoin	*Staph. aureus*		−	−			+
	Strep. faecalis		−	−			+
	E. coli		+	+			+
	Ps. aeruginosa		+	+			+
4. 3-(5-Nitro-2-furfuryl-ideneamino)-4,5-di-hydrouracil	*Staph. aureus*		−				+
	S. typhi		−				+
	Strep. faecalis		−				+
	Proteus vulgaris		−				+
	Ps. aeruginosa		+				+
5. 3-(5-Nitro-2-furfuryl-ideneamino)-4-methyl-4,5-dihydrouracil	*Staph. aureus*		−	−			+
	Strep. faecalis		+	+			+
	E. coli		−	−			+
	Ps. aeruginosa		+	+			+
6. 3-(5-Nitro-2-furfuryl-ideneamino)-5-methyl-4,5-dihydrouracil	*Staph. aureus*		−	−			+
	Strep. faecalis		+	+			+
	E. coli		−	−			+
	Ps. aeruginosa		+	+			+
7. 3-(5-Nitro-2-furfuryl-ideneamino)-5-phenyl-4,5-dihydrouracil	*Staph. aureus*		−	−			+
	Strep. faecalis		+	+			+
	E. coli		+	+			+
	Ps. aeruginosa		+	+			+

were carried out by Galloway and Barton-Wright, Consultant Microbiologists. The compounds were provided as one per cent w/v solutions in polyethyleneglycol 300 which were diluted with beef broth for serial dilution tests. Control dilutions containing only the polyethyleneglycol were also made. After inoculation with the organisms the dilutions were incubated at 37° for 48 h when the results were read.

Discussion

Apart from compound 2, all the compounds possess considerable *in vitro* antibacterial activity which, however, is generally of a rather lower order than that of the nitrofurans currently used in medicine. That compound 2 is inactive whereas compound 1, its ethyl ester, is active is not unexpected since a similar result has been reported for 5-nitrofuroic acid and ethyl 5-nitrofuroate.[4] It seems likely, therefore, that nitrofurans containing a free carboxyl group are unlikely to be active. This may be due to poor penetration of the bacterial cell membrane or other reasons. The inactivity of compound 2 also indicates that the proposed optimum molecular skeleton (IV) for nitrofurans[4] does not necessarily confer activity. This has also been shown by the author with 4-(5-nitro-2-furfurylideneamino)-urazole which is poorly active.



(IV)

The variability of the results obtained with the active compounds further supports the view[4] that the degree of activity and the detailed spectrum of activity of 5-nitrofurans depends on the nature of the 2-substituent. An interesting result is the inactivity of compound 3, the 5-phenyl analogue of nitrofurantoin, to *E. coli*, an organism which is usually very highly sensitive to nitrofurantoin. Similarly, introduction of a 4- or 5-methyl group into compound 4, as in compounds 5 and 6 respectively, appears to abolish activity against *Strep. faecalis* and the introduction of a 5-phenyl group as in compound 7 further abolishes activity against

E. coli. These differences are common in the nitrofuran series but are, as yet, unexplained.

Preliminary acute toxicity tests carried out in mice indicated that compounds 4, 5 and 6 were relatively non-toxic, the LD_{50} for each being about 1,500–2,000 mg/kg. Accordingly, examination of these compounds for *in vivo* antibacterial activity might be worthwhile. Compound 3 is highly toxic, the LD_{50} in mice being about 50 mg/kg which is an unusually low value for nitrofurans. This might be due to slow excretion of the compound or of its degradation products. The compound is unlikely to be a useful drug. The remaining compounds were not tested for toxicity; compounds 2 and 7, because of poor *in vitro* activity and compound 1 because it would almost certainly be hydrolysed in the body to give the inactive compound 2.

Experimental*

1-Isopropylideneamino-3-carbethoxymethylhydantoin. Acetone semicarbazone (57·5 g) was dissolved with heating in a solution of sodium (11·5 g) in dry ethanol (250 ml). Ethyl chloroacetate (62 g) was added with stirring at a rate sufficient to maintain reflux. The mixture was refluxed for 10 min. A solution of sodium (11·5 g) in dry ethanol (250 ml) was added and the mixture stirred for a few minutes. Ethyl chloroacetate (62 g) was added as before and the mixture refluxed for 1 h. Some of the ethanol (about 380 ml) was removed by distillation, the residue cooled and diluted with water (250 ml). A colourless crystalline solid separated from the mixture and was filtered off, washed with aqueous alcohol (25 per cent v/v) and dried at 60° *in vacuo* to give almost pure 1-isopropylideneamino-3-carbethoxymethylhydantoin (120·5 g; 62 per cent), m.p. 131–132°. The compound crystallized readily from water as colourless rods, m.p. 131–132°.

Anal. Calcd. for $C_{10}H_{15}N_3O_4$: C, 49·8; H, 6·23; N, 17·4. Found: C, 49·4; H, 6·10; N, 17·5.

1-(5-Nitro-2-furfurylideneamino)-3-carbethoxymethylhydantoin. A mixture of 1-isopropylideneamino-3-carbethoxymethylhydantoin (2·41 g), 5-nitro-2-furaldehyde (1·41 g) and aqueous alcohol (30 ml of 50 per cent, v/v) was refluxed for 1 h and then cooled. A slightly oily yellow solid separated, was filtered off, washed well

* Melting points are uncorrected.

with alcohol and dried at 60° *in vacuo* to give slightly impure 1-(5-nitro-2-furfurylideneamino)-3-carbethoxymethylhydantoin (2·57 g; 79 per cent) m.p. 154–155°. The product (1·88 g) was crystallized from a mixture of dimethylformamide (6 ml) and alcohol (19 ml) to give bright yellow prisms (1·1 g), m.p. 153–155°.

Anal. Calcd. for $C_{12}H_{12}N_4O_7$: C, 44·4; H, 3·70; N, 17·3. Found: C, 44·6; H, 3·90; N, 17·4.

1-(5-Nitro-2-furfurylideneamino)-3-carboxymethylhydantoin. A mixture of 1-isopropylideneamino-3-carbethoxymethylhydantoin (2·41 g) and hydrochloric acid (10 ml of 20 per cent, w/w HCl) was heated at 100° for 1 h and then cooled. 5-Nitro-2-furaldehyde (1·41 g) was added and the mixture heated at 50–60° for 15 min and then cooled. The yellow solid was filtered off, washed with water and dried at 60° *in vacuo* to give slightly impure 1-(5-nitro-2-furfurylideneamino)-3-carboxymethylhydantoin (2·55 g; 86 per cent), m.p. 249–250° (d.). The product (2·1 g) was crystallized from alcohol (100 ml) to give lemon yellow needles (1·5 g) m.p. 251–252° (d.).

Anal. Calcd. for $C_{10}H_8N_4O_7$: C, 40·6; H, 2·70; N, 18·9; equiv. wt. 296. Found: C, 40·7; H, 2·80; N, 18·6; equiv. wt. (aqueous titration to phenolpthalein) 293.

1-Isopropylideneamino-5-phenylhydantoin. Acetone semicarbazone (11·5 g) and sodium methoxide (10·8 g) were dissolved with heating in dry alcohol (100 ml). The mixture was cooled to 40–45° and ethyl α-chlorophenylacetate (19·9 g) was added dropwise with stirring, the temperature being held at 40–45°. After the addition was complete, the mixture was stirred for 50 min at 40–45° and then most of the alcohol was removed by distillation. Sufficient dilute hydrochloric acid was added with cooling to neutralize the mixture (pH 7–8). The colourless crystalline solid which separated was filtered off, washed with water and dried to give slightly impure 1-isopropylideneamino-5-phenylhydantoin, (10·9 g; 47 per cent), m.p. 198–200°. The compound crystallized from benzene as colourless needles, m.p. 200–202°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62·4; H, 5·68; N, 18·2; equiv. wt., 231. Found: C, 62·3; H, 5·78; N, 17·9; equiv. wt., 232 (titration with sodium methoxide in dimethylformamide).

1-(5-Nitro-2-furfurylideneamino)-5-phenylhydantoin. A mixture of 5-nitro-2-furaldehyde diacetate (1·9 g), alcohol (10 ml) and

concentrated hydrochloric acid (10 ml) was heated at reflux for 20 min and then cooled. 1-Isopropylideneamino-5-phenylhydantoin (1·8 g), alcohol (50 ml) water (150 ml) and sodium acetate (15 g) were added and the mixture heated at 60° for 15 min and then cooled. A yellow solid separated, was filtered off, washed with aqueous alcohol (25 per cent v/v alcohol) and dried at 60° *in vacuo* to give slightly impure 1-(5-nitro-2-furfurylideneamino)-5-phenylhydantoin (1·1 g; 45 per cent), m.p. 168–172°. The product (1 g) was crystallized from aqueous alcohol (120 ml of 33 per cent v/v alcohol) to give clusters of pale yellow prisms (0·8 g) m.p. 170–172°.

Anal. Calcd. for $C_{14}H_{10}N_4O_5$: C, 53·5; H, 3·21; N, 17·8. Found: C, 53·2; H, 3·29; N, 17·9.

3-Benzylideneamino-4, 5-dihydrouracil. (*i*) *From ethyl β-bromopropionate.* Benzaldehyde semicarbazone (16·3 g) was dissolved with heating in a solution of sodium (2·3 g) in 'super-dry' alcohol (50 ml). To this mixture was added, with stirring, ethyl β-bromopropionate (9·05 g) at a rate sufficient to maintain refluxing without external heating. When the addition was complete, refluxing was continued for 15 min. Then sodium (2·3 g) dissolved in 'super-dry' alcohol was added and the mixture stirred and refluxed for a few minutes. Ethyl β-bromopropionate (9·05 g) was added as previously, the mixture refluxed for 40 min and then cooled. Dilute sulphuric acid (100 ml of 5 per cent w/v) was added when a white crystalline solid separated rapidly. After 1 h the solid was filtered off, washed with aqueous alcohol and then dried at 100°. Yield 19·3 g; m.p. 205–210°. The crude yield was crystallized from aqueous acetic acid (250 ml of 50 per cent v/v) to give 3-benzylideneamino-4,5-dihydrouracil in colourless needle-like prisms, (12·1 g; 55 per cent.) m.p. 221–223°.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60·8; H, 5·08; N, 19·4. Found: C, 60·7; H, 5·10; N, 19·3.

(*ii*) *From methyl acrylate.* Acetone semicarbazone (23·0 g) sodium methoxide (10·8 g) and methyl acrylate (17·2 g) were dissolved in 'super-dry' alcohol by heating, the mixture refluxed for 3 h and then cooled. Concentrated hydrochloric acid (18 ml) diluted with water (100 ml) was added followed by benzaldehyde (21·2 g). 3-Benzylideneamino-4,5-dihydrouracil separated rapidly, was filtered off after 1 h and dried at 70° *in vacuo*. Yield 30·6 g (71

per cent); m.p. 217–223° rising to 221–223° after crystallization from aqueous acetic acid as described previously. This compound was identical with that obtained from ethyl β-bromopropionate as shown by a mixed melting point and by identical infrared absorption.

3-(5-Nitro-2-furfurylideneamino)-4,5-dihydrouracil. A mixture of 3-benzylideneamino-4,5-dihydrouracil (2·17 g) and dilute hydrochloric acid (25 ml of 20 per cent w/w HCl) was distilled until the distillate was free from benzaldehyde. To the residue was added water (25 ml), alcohol (25 ml) and 5-nitro-2-furaldehyde diacetate; the mixture was refluxed for 30 min and then cooled. The yellow solid was filtered off, washed with water and then dried at 60° *in vacuo* to give slightly impure 3-(5-nitro-2-furfurylideneamino)-4,5-dihydrouracil (2·4 g; 95 per cent) m.p. 280–282° (d.). The product (2·5 g) was crystallized from a mixture of dimethylformamide and alcohol (140 ml of 50 per cent v/v) to give lemon yellow needles (1·75 g) m.p. 281–283° (d.).

Anal. Calcd. for $C_9H_8N_4O_5$: C, 42·3; H, 3·20; N, 22·2. Found: C, 42·5; H, 3·40; N, 21·9.

3-Benzylideneamino-5-methyl-4,5-dihydrouracil. (*i*) *From ethyl α-bromoisobutyrate.* Benzaldehyde semicarbazone (16·3 g) was dissolved with heating in a solution of sodium (2·3 g) in 'super-dry' alcohol (50 ml). Ethyl α-bromo-isobutyrate (9·75 g) was added dropwise without external heating in about 5 min and the mixture refluxed with stirring for 1 h. A solution of sodium (2·3 g) in 'super-dry' alcohol (50 ml) was added and the mixture heated and stirred for 3 min. Ethyl α-bromoisobutyrate (9·75 g) was added as before and the mixture refluxed for 3 h. Most of the alcohol was removed by distillation and to the residue was added water (100 ml) and sufficient hydrochloric acid (20 per cent w/w) to pH 3. The reaction mixture was filtered and the white solid washed with water and dried at 100° *in vacuo* (20·1 g; m.p. 170–190°). This solid was crystallized from a mixture of dioxan (75 ml) and water (50 ml) to give 3-benzylideneamino-5-methyl-4,5-dihydrouracil, (8·9 g; 38·5 per cent) m.p. 224–226°. From the mother liquors was obtained a further quantity of less pure compound. For analysis the compound was crystallized from 50 per cent v/v aqueous acetic acid; colourless large rod-like prisms, m.p. 225–227°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62·3; H, 5·67; N, 18·2. Found: C, 62·3; H, 5·60; N, 18·2.

(*ii*) *From methyl methacrylate.* A mixture of acetone semicarbazone (23 g), sodium methoxide (10·8 g), methyl methacrylate (20 g) and 'super-dry' alcohol (100 ml) was refluxed for 8 h and then poured into a mixture of concentrated hydrochloric acid (18 ml) and water (100 ml). Benzaldehyde (21·2 g) was added, the mixture heated to 60° and then cooled. The white solid was filtered off, washed with aqueous alcohol and dried at 100°; (32·7 g; m.p. 185–215°). The solid was stirred in a solution of sodium hydroxide (6 g) in water (150 ml) and ice (50 g) and the mixture filtered into diluted hydrochloric acid (55 ml of 10 per cent w/v HCl) when a white crystalline solid separated immediately. The filter residue, after washing with water and drying, was shown to be crude benzaldehyde semicarbazone, (9 g) m.p. 208–215°. From the filtrate was obtained by filtration, washing with water and drying, a white solid (22·3 g), m.p. 205–220°. This was crystallized from a mixture of dimethylformamide (150 ml) and alcohol (500 ml) to give colourless stout rods of 3-benzylideneamino-5-methyl-4,5-dihydrouracil (18·2 g; 39·4 per cent), m.p. 225–227°. This product was identical with that obtained from ethyl α-bromoisobutyrate as shown by mixed melting point determination and by infrared absorption.

3-(5-Nitro-2-furfurylideneamino)-5-methyl-4,5-dihydrouracil. A mixture of 3-benzylideneamino-5-methyl-4,5-dihydrouracil, water (60 ml) and concentrated hydrochloric acid (70 ml) was distilled until the distillate was free from benzaldehyde. To the residue was added 5-nitro-2-furaldehyde diacetate (3·16 g) and alcohol (40 ml) and the mixture refluxed for 15 min and then cooled. The yellow prisms were filtered off, washed with aqueous alcohol and then dried to give 3-(5-nitro-2-furfurylideneamino)-5-methyl-4,5-dihydrouracil (2·2 g; 64 per cent) m.p. 258–260° (d.).

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 45·1; H, 3·79; N, 21·0. Found: C, 45·3; H, 3·88; N, 20·8.

3-Benzylideneamino-4-methyl-4,5-dihydrouracil. This compound was prepared in the same way as the corresponding 5-methyl derivative described above substituting ethyl crotonate (22·8 g) for the methyl methacrylate. The time of reflux was 11 h and the weight of crude benzylidene derivative obtained was 22·9 g,

m.p. 170–180°. This solid was stirred with a solution of sodium hydroxide (4 g) in water (100 ml) and crushed ice (100 g) and then filtered into diluted hydrochloric acid (40 ml of 10 per cent w/v HCl). The filter residue washed with water and dried was crude benzaldehyde semicarbazone (6·5 g), m.p. 205–215°. Filtration of the solid from the acidified filtrate gave, after washing with water and drying slightly, impure 3-benzylideneamino-4-methyl-4,5-dihydrouracil (15·7 g; 34 per cent) m.p. 179-181°. Crystallization from absolute alcohol (350 ml) gave clusters of colourless needles (11·0 g) m.p. 180·5–182°.

Anal. Calcd. for $C_{12}H_{23}N_3O_2$: C, 62·3; H, 5·67; N, 18·2. Found: C, 62·5; H, 5·50; N, 18·5.

3-(5-Nitro-2-furfurylideneamino)-4-methyl-4,5-dihydrouracil. This compound was prepared in the same way as the corresponding 5-methyl derivative above starting from 3-benzylideneamino-4-methyl-4,5-dihydrouracil (2·75 g). The crude product (2·8 g; m.p. 228–237°) was crystallized from aqueous acetic acid (100 ml of 50 per cent v/v) to give pale yellow prisms of 3-(5-nitro-2-furfurylideneamino)-4-methyl-4,5-dihydrouracil (2·3 g; 72 per cent), m.p. 235–236°.

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 45·1; H, 3·75; N, 21·0. Found: C, 44·2; H, 3·90; N, 20·7.

3-Benzylideneamino-5-phenyl-4,5-dihydrouracil. Acetone semicarbazone (5·75 g) was dissolved in a solution of sodium (1·15 g) in 'super-dry' alcohol (20 ml). This solution was added with stirring to a mixture of ethyl α-bromo-α-methylphenylacetate (6·5 g) and 'super-dry' alcohol (10 ml) the temperature being maintained at 50° during the addition. The reaction mixture became almost impossible to stir and 'super-dry' alcohol (20 ml) was added to facilitate stirring. After the addition was complete, the mixture was stirred at 40–50° for 20 min. Sodium (1·15 g) dissolved in 'super-dry' alcohol (20 ml) was added, the mixture heated till homogeneous and then cooled. Ethyl α-bromo-α-methylphenylacetate (6·5 g) was added, the mixture stirred at 40–45° for 15 min and then refluxed for 15 min. Dilute hydrochloric acid (25 ml of 5 per cent w/w HCl) was added followed by benzaldehyde (5 ml). A white crystalline solid separated on cooling and was filtered off, washed with aqueous alcohol and dried (7·1 g; m.p. 180–190°). This solid (6·5 g) was crystallized from

alcohol (260 ml) to give 3-benzylideneamino-5-phenyl-4,5-dihydrouracil (5·2 g; 38·8 per cent) m.p. 195–196°.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69·6; H, 5·15; N, 14·3. Found: C, 69·1; H, 5·55; N, 14·5.

3-(5-Nitro-2-furfurylideneamino)-5-phenyl-4,5-dihydrouracil. This compound was prepared in the same way as the corresponding 5-methyl derivative above starting from 3-benzylideneamino-5-phenyl-4,5-dihydrouracil to yield yellow prisms of slightly impure 3-(5-nitro-2-furfurylideneamino)-5-phenyl-4,5-dihydrouracil (1·9 g; 68 per cent) m.p. 260–263·5° (d.). The product (1·8 g) was crystallized from aqueous acetic acid (10 ml of 50 per cent v/v) to give orange-yellow prisms (1·3 g), m.p. 263–263·5° (d.).

Anal. Calcd. for $C_{15}H_{12}N_4O_5$: C, 54·9; H, 3·69; N, 17·1. Found: C, 54·8; H, 3·56; N, 17·3.

Summary. The preparation of new 1-(5-nitro-2-furfurylideneamino)-hydantoins and 3-(5-nitro-2-furfurylideneamino)-4,5-dihydrouracils from semicarbazones is described. Their *in vitro* antibacterial activities and acute oral toxicities in mice are reported.

Acknowledgements. The work reported in this paper forms part of the content of a Ph.D. thesis submitted to the University of London. The author thanks Dr. A. H. Beckett for help and advice and the Analytical Staff of Smith Kline and French Laboratories for carrying out analyses and infrared determinations.

(*Received 9 August, 1960*)

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