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SYNTHESIS OF NITRO-, AMINO-, AND POLYCYCLIC FURANS

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The synthesis of a number of 5-nitro- and 5-amino-2-furaldehyde derivatives is described in this review. Cyclization of an amino-furan to a furo[2,3-b]pyridine and reductive cyclization of substituted butyrolactones to furo[2,3-b]quinolines and indoles are also discussed.

A. Furo[2,3-b]pyridine

B. Furo[2,3-b]quinoline

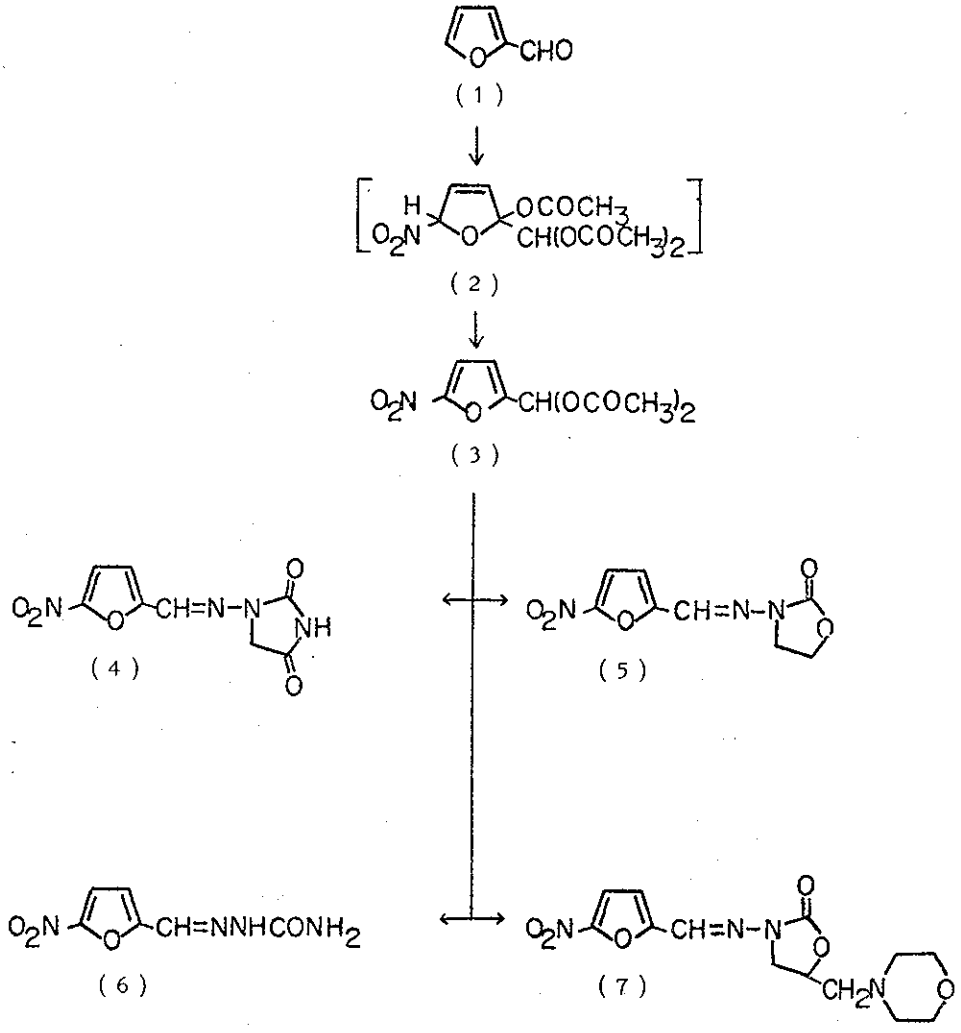
Conclusions

Introduction

One of the most important chemical intermediates for the synthesis of furan derivatives is furfural or 2-furaldehyde (1). Sulfuric acid hydrolysis of pentosans, which are present in waste products such as oat and rice husks and corn cobs, produces pentoses which are dehydrated to furfural. The successful industrial process for the production of furfural from corn cobs and similar materials made this substance readily available.

Nitration of furfural with nitric acid and acetic anhydride, followed by treatment of the intermediate (2) with a base produces 5-nitro-2-furaldehyde diacetate (3), from which 5-nitro-2-furaldehyde[2] can be obtained. These derivatives of furfural have led to the discovery of several important medicinal agents. Examples of four azomethine (-CH=N-) type nitrofurans derived from furfural and available commercially as antimicrobial agents are nitrofurantoin [1-(5-nitrofurfurylideneamino)hydantoin] (4),[3] furazolidone [3-(5-nitrofurfurylideneamino)-2-oxazolidinone] (5),[4] nitrofurazone (5-nitro-2-furaldehyde semicarbazone) (6)[5] and furaltadone [5-morpholinomethyl-3-(5-nitrofurfurylideneamino)-2-oxazolidinone] (7).[6] Each of these drugs is prepared by condensation of the respective N-amino heterocycle, or semicarbazide, with 5-nitro-2-furaldehyde.

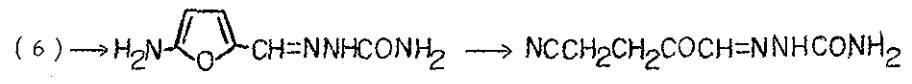
Many other nitrofuran derivatives have been synthesized and evaluated for chemotherapeutic utility, and extensive reviews on the subject are available.[7]


CHO
(1)
H
O2N
OCOCH3
CH(OCOCH3)2
(2)
O2N
CH(OCOCH3)2
(3)
O2N
CH=N-N
O
NH
O
(4)
O2N
CH=N-N
O
O
(5)
O2N
CH=NNHCONH2
(6)
O2N
CH=N-N
O
O
CH2N
O
(7)

A part of this review pertains to research by the author on the synthesis and chemistry of some structural variants of (4), (5), (6), and (7).

Metabolism studies often provide necessary information on the mode of action, toxicity, and elimination of a drug. In some cases, metabolites or structural variations of them have been found to be more efficacious than the parent drug. A number of studies concerning the metabolism and mode of action of nitrofurans have been reported.[7] Although aminofurans had been postulated as metabolites and products of bacterial reduction, their isolation and characterization were not readily accomplished.

Reduction of nitrofurazone (6) with Raney nickel in water gave a solid which was identified as 4-cyano-2-oxobutyraldehyde semicarbazone (9); 5-amino-2-furaldehyde semicarbazone (8) was postulated as an intermediate.[8] The nitrile (9) is isomeric with (8), and, on the basis of changes in the ultraviolet absorption on standing, was thought to be formed from (8). Reduction of (6) in absolute ethanol with hydrogen over palladium on charcoal was reported[9] to give a dark red scaly solid, identified as (8) only by infrared analysis. Spectrophotomeric changes of solutions of chemically and biologically reduced (6) were identical on aging, and similar to those obtained from the Raney nickel reduction.

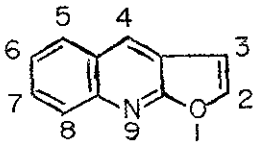


(8) (9)

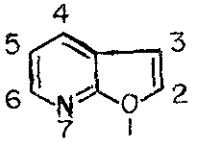
It was later concluded that on the basis of spectral data, certain nitrofurans on reduction with Aerobacter aerogenes yield the corresponding aminofurans which are unstable and undergo furan ring fission to give open-chain nitriles.[10] It was also postulated that certain nitrofurans are unstable because of their inability to form hydrogen bonds with the furan ring oxygen, while compounds such as (8) that are capable of intramolecular bonding are more stable.

These somewhat inconclusive results led to a more extensive study of the reduction of nitrofurans, which is discussed in the review.

The last part of the review covers the author's research on the synthesis of certain polycyclic furans. Since the furo[2,3-b]quinoline (10) alkaloids possess pharmacologic activity,[11] the synthesis of a furo[2,3-b]pyridine (11) from a 5-amino-2-furaldehyde derivative was investigated. Relatively little work had been reported concerning synthesis of this ring system, and none had dealt with the application of furan derivatives as precursors.



(10)



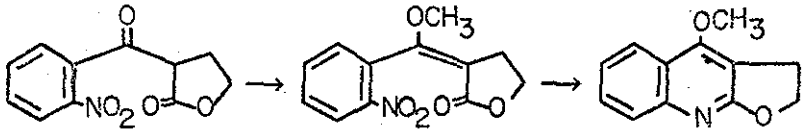
(11)

The importance of the furo[2,3-b]quinoline class of alkaloids led to a consideration of ring closure methods involving furan or γ-lactone derivatives. Some examples of these methods are as follows:

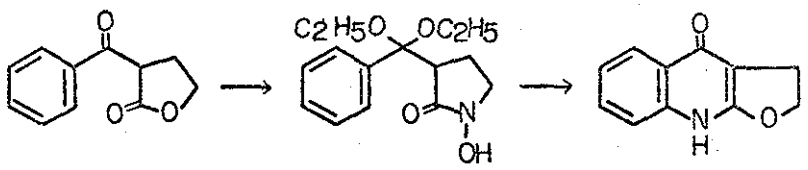
Dihydrodictamnine (14) has been prepared by hydrogenation of α-(α-methoxy-o-nitrobenzylidene)-γ-butyrolactone (13) in acid solution.[12] Lactone (13), which may be considered a dihydrofuranone derivative, was prepared by diazomethane alkylat-

ion of α-(*o-nitrobenzoyl*)-γ-butyrolactone (12).

Although not involving a furan derivative in the cyclization step, Kametani and Nemoto prepared dihydronordictamnine (17) from the benzoyl-lactone (15) via a cyclic hydroxamic acid intermediate (16) and polyphosphoric acid cyclization.[13]



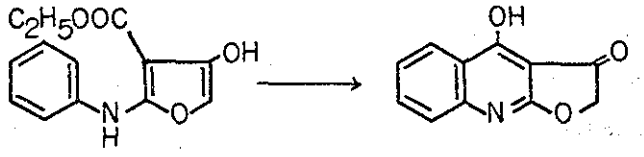
(12) (13) (14)



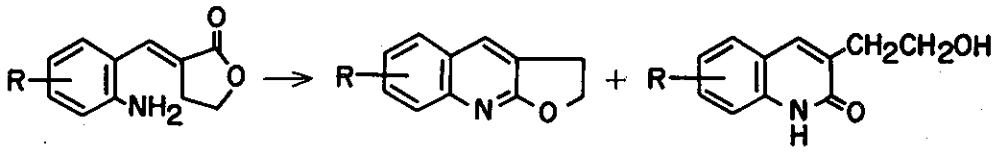
(15) (16) (17)

Ethyl 2-anilino-4-hydroxy-3-furoate (18) has been cyclized in boiling diphenyl ether to the 4-hydroxyfuro [2,3-b]quinolin-3-one (19), which subsequently was converted to dictamnine (10, 4-methoxy).[14]

Zimmer reported the photolytic cyclization of trans-α-(o-aminobenzylidene)-γ-butyrolactones (20) to 2,3-dihydrofuro [2,3-b]quinolines (21).[15] The principal products, however, were the 3-(2-hydroxyethyl)carbostyrils (22).



(18) (19)

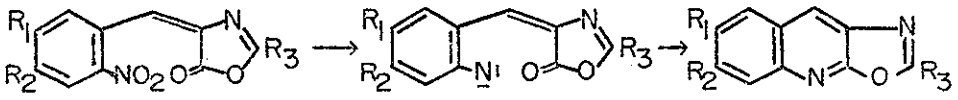


R=H, OCH_2O

(20) (21) (22)

The extensive use of triethyl phosphite in the reductive cyclization of nitro compounds suggested its possible use in the cyclization of lactones (12) and (13) to form furoquinolines (17) and (14), respectively.

Cadogan,[16] Kametani[17] and many others[18] have described the applications of triethyl phosphite. For example, Kametani, Yamanaka and Ogasawara[19] cyclized nitrobenzylideneoxazolinones (23) to tricyclic oxazolo[5,4-b]quinolines (25) with triethyl phosphite. This ring closure, as is the case with many others involving triethyl phosphite, was reported to proceed through nitrene intermediate (24).

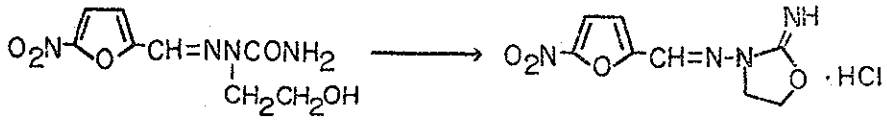


(23) (24) (25)

Although many other nitrobenzylidene and a few nitrobenzoyl compounds have been deoxygenated with triethyl phosphite, the application of this reaction to γ-butyrolactones similar to (12), (13), and the nitro-derivatives of (20) had not been studied. Reduction of substituted γ-butyrolactones of this type is discussed in the review.

SYNTHESIS AND CHEMICAL REACTIONS OF 2-SUBSTITUTED 5-NITROFURANS

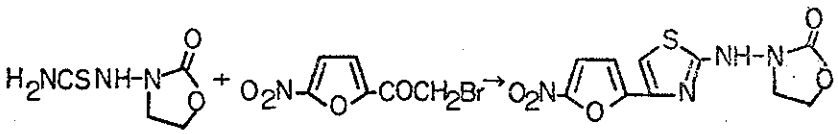
A. 3-Amino-2-iminooxazolidine and 3-Amino-2-oxazolidinone Derivatives: The action of thionyl chloride on 5-nitro-2-furaldehyde 2-(2-hydroxyethyl)semicarbazone (26) produced a water soluble hydrochloride, rather than the anticipated 2-(2-chloroethyl)semicarbazone. Dehydration occurred to give the 2-imino-3-(5-nitrofurfurylideneamino)oxazolidine hydrochloride compound (27).[20]



(26) (27)

The iminooxazolidine (27) was readily converted to furazolidone (5) by treatment with nitrous acid. Heating (27) in dilute sulfuric acid or in water also gave (5), in addition to some of the hydroxyethylsemicarbazone (26).

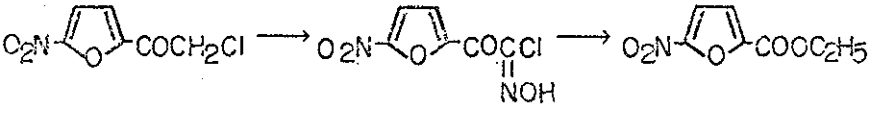
A nitrofuran containing both the thiazole and oxazolidinone moieties was synthesized. Thus, 3-amino-2-oxazolidinone was treated with potassium thiocyanate in hydrochloric acid to give a 64 % yield of 1-(2-oxo-3-oxazolidinyl)-2-thiourea (28). The reaction of (28) with bromomethyl 5-nitro-2-furyl ketone (29) in ethanol produced 3-[4-(5-nitro-2-furyl)-2-thiazolylamino]-2-oxazolidinone (30) in 77 % yield. Thiazole (30) exhibited broad antimicrobial effectiveness.[21]



(28) (29) (30)

The chloromethyl ketone (31), which was also used to prepare (30), was obtained from the bromomethyl ketone (29) and concentrated hydrochloric acid.[22] Purification of (31) by recrystallization from carbon tetrachloride gave an insoluble product which was identified as the nitrosated compound 5-nitro-2-furanglyoxyloyl chloride 1-oxime (32).[23] Oxime (32) was also prepared by nitrosation of the chloromethyl ketone (31) with sodium nitrite in acetic acid.

The nitrous acid was thought to arise from the acidic displacement of the nitro group of either (29) or (31), since it was shown that 5-chloro-2-furaldehyde could be prepared from 5-nitro-2-furaldehyde and hydrochloric acid.[24]



(31) (32) (33)

When (32) was treated with hydroxylamine hydrochloride, in aqueous ethanol, in an attempt to prepare the oxime, the only product isolated was ethyl 5-nitro-2-furoate (33).[23]

B. Rearrangement of 3-Substituted 2-Iminooxazolidines and Formation of 2-Substituted Semicarbazones: As previously described, the action of thionyl chloride on 5-nitro-2-furaldehyde 2-(2-hydroxyethyl)semicarbazone (26) produced a quantitative yield of the iminooxazolidine (27) rather than the chloroethylsemicarbazone (34). However, when (27) was recrystallized repeatedly from 95 % ethanol or from ethanolic hydrogen chloride, a partial transformation to (34) was effected. After 30 minutes in boiling xylene, a 96 % yield of (34) was obtained, while 2 hours in boiling toluene resulted in a 73 % yield of (34). The benzaldehyde analog (35) underwent the same reaction with thionyl chloride and subsequent ring opening of

the iminooxazolidine hydrochloride (36) in boiling xylene to give the chloroethylsemicarbazone (37).[25]

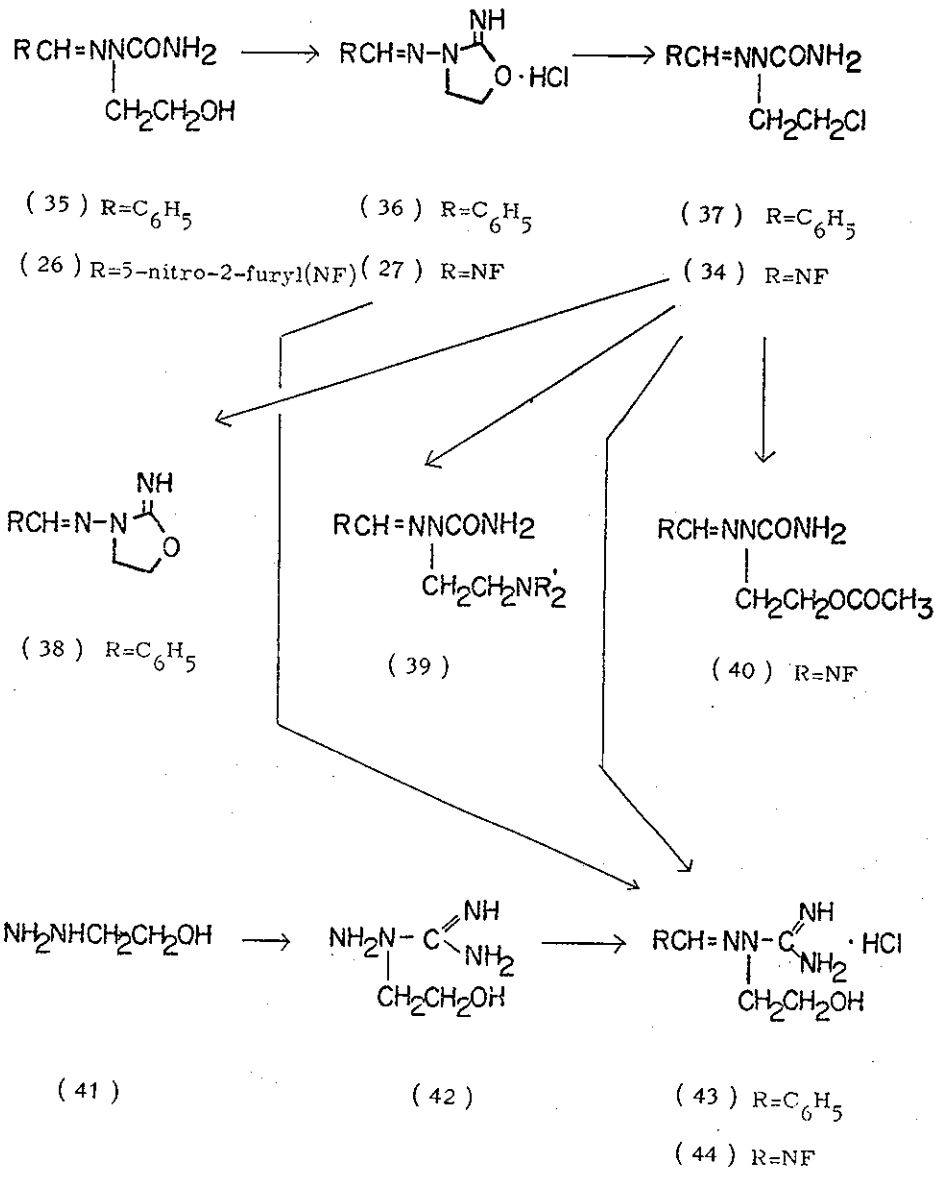
The mechanism of ring cleavage of the iminooxazolidines probably involves chloride ion attack at the C - 5 position. This was supported by the observation that high concentrations of chloride ions in ethanol increased the rate of semicarbazone formation. Since the chloroethylsemicarbazone (34) was recovered unchanged from thionyl chloride, (34) is not an intermediate in the formation of (27) from (26). The cyclization most likely proceeds through a chlorosulfinate intermediate.

The chloroethylsemicarbazones were treated with several secondary amines. Morpholine, 1-piperazineethanol, piperidine and dimethylamine were combined with benzaldehyde 2-(2-chloroethyl)semicarbazone (37) in benzene to give the corresponding aminoethylsemicarbazones (39). These compounds were then converted to nitrofuraldehyde semicarbazones by acid hydrolysis and condensation with 5-nitro-2-furaldehyde. The morpholino derivative was also prepared, but in lower yield, by treating (34) with morpholine in dimethylformamide. If acetic acid was used as the solvent in place of dimethylformamide, the acetoxyethylsemicarbazone (40) was obtained instead of the morpholino derivative.

The dimethylamino derivative was identical to that obtained from the reaction of dimethylaminoethylhydrazine and potassium cyanate followed by condensation of the semicarbazone with 5-nitro-2-furaldehyde.[26] The acetoxy compound was also prepared by a similar alternate route.[27]

Diethylamine failed to give the amino derivative when combined with (37) in dimethylformamide or benzene, but gave a small amount of the iminooxazolidine (38).

Ammonolysis of (37) in absolute ethanol followed by treatment with 5-nitro-2-furaldehyde produced 1-(2-hydroxyethyl)-1-(5-nitrofurfurylideneamino)guanidine hydrochloride (44) rather than the aminoethylsemicarbazone. This compound was

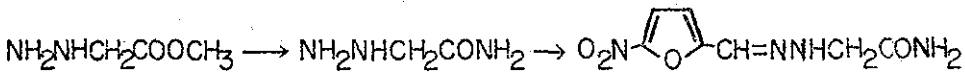

RCH=NNCONH2
CH2CH2OH
RCH=N-N
NH
O·HCl
RCH=NNCONH2
CH2CH2Cl
(35) R=C6H5
(36) R=C6H5
(37) R=C6H5
(26) R=5-nitro-2-furyl(NF)
(27) R=NF
(34) R=NF
RCH=N-N
NH
O
(38) R=C6H5
RCH=NNCONH2
CH2CH2NR'2
(39)
RCH=NNCONH2
CH2CH2OCOCH3
(40) R=NF
NH2NHCH2CH2OH
NH2N-C
NH
NH2
CH2CH2OH
RCH=NN-C
NH
NH2
·HCl
CH2CH2OH
(41)
(42)
(43) R=C6H5
(44) R=NF

also obtained from the reaction of 2-hydrazinoethanol (41) and cyanamide followed by condensation of the aminoguanidine (42) with 5-nitro-2-furaldehyde.[28]

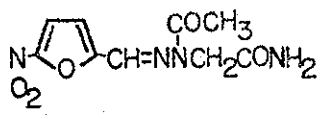
These results indicate that strong nucleophiles, dimethylamine, morpholine, piperidine and 1-piperazineethanol, react by direct displacement of chloride from (34) or (37), whereas weaker nucleophiles, ammonia and diethylamine, cause intramolecular displacement of chloride and cyclization to the iminooxazolidine (38). Ammonia then attacks the C - 2 position of (38) to produce the hydroxyethylguanidine (43). This mechanism was supported by the fact that (43) can be obtained directly from the reaction of (36) with ammonia.

The chloro-(34), morpholino-, piperidino- and 2-hydroxyethylpiperazinoethylsemicarbazones of 5-nitro-2-furaldehyde demonstrated good antimicrobial activity.[29]

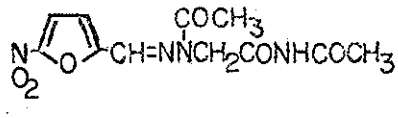
C. Acylhydrazones: Methyl hydrazinoacetate hydrochloride (45), prepared from hydrazine and chloroacetic acid, was converted to the amide (46) with ammonium hydroxide and then condensed with 5-nitro-2-furaldehyde to give 2-(5-nitrofurfurylidenehydrazino)acetamide (47).[30] Treatment of (47) with potassium cyanate in glacial acetic acid did not produce the expected semicarbazone, but gave the acetylated compound (48). The same compound was also obtained by acetylating (47) with acetic anhydride. The diacetylated derivative (49) was prepared from (47) or (48).



(45) (46) (47)



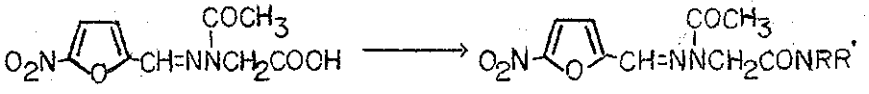
(48)



(49)

The antibacterial screening of (47) and (48) indicated that (48) was highly active *in vivo* against *Staphylococcus aureus* and *Salmonella typhosa*, whereas (47) was inactive. These results led to the synthesis of many other acylhydrazones, which are listed in Table 1.[30]

The general methods for the preparation of these compounds are as follows: (a) Acylation of (47) and other carbonyl derivatives of hydrazinoacetamide (46) with anhydrides or with acid chlorides in dimethylformamide or in pyridine. (b) Reaction of methyl hydrazinoacetate hydrochloride (45) with amines, followed by reaction with a nitrofuran carbonyl reagent and acylation. (c) Condensation of 5-nitro-2-furaldehyde with hydrazinoacetic acid followed by acylation (50), chlorination, and reaction with amines (51). (d) Monoacetylation of (48) or diacetylation of (47) with acetic anhydride and sulfuric acid.

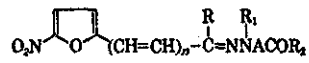


(50) (51)

Compound (48) was isolated in two crystal forms. The α form melts at 254° and was obtained as voluminous pale yellow needles, while the β form melts at 238 - 239° and exists usually as much more dense granular yellow rhomboids. The polymorphs were identical by microanalysis and solution spectra in the infrared and ultraviolet. However, they differed when examined in the solid state in the infrared. The α form, which is the less stable modification, was converted to β by grinding in a mortar, shaking in water, or by recrystallizing from various solvents with rapid cooling. The β form was converted to α by pouring a hot dimethylformamide,

Table I

BIOLOGICAL ACTIVITY



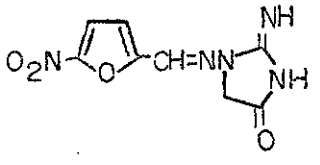
n	A	R	R_1	R_2	ED_{50} (mg./kg.)/MIC (mg./100) *S. aureus*	ED_{50} (mg./kg.)/MIC (mg./100) *S. typhosa*
			I. Variations of R_1			
			a. Hydrogen or alkanoyl			
0	CH_2	H	H	NH_2	>1120/>4	>1120/>4
0 α	CH_2	H	$COCH_3$	NH_2	20/1	22/2
0 β	CH_2	H	$COCH_3$	NH_2	120/1	120/2
1	CH_2	H	H	NH_2	>600/5	>600/3
1	CH_2	H	$COCH_3$	NH_2	93/0.2	>780/0.6
0	$CHCH_3$	H	H	NH_2	>330/>12	>330/>12
0	$CHCH_3$	H	$COCH_3$	NH_2	43/1	>840/5
0	CH_2	CH_3	H	NH_2	>160/>20	>160/>20
0	CH_2	CH_3	$COCH_3$	NH_2	>240/10	>240/10
0	CH_2	H	CHO	NH_2	55/1	28/0.3
0	CH_2	H	COC_2H_5	NH_2	33/1	>360/10
0	CH_2	H	COC_3H_7	NH_2	48/0.6	>132/20
0	CH_2	H	$COCH_2CH(CH_3)_2$	NH_2	195/0.5	>420/>15
0	CH_2	H	$COCH(CH_3)_2$	NH_2	45/0.4	>420/>20
0	CH_2	H	$COCH(CH_3)(CH_2)_2CH_3$	NH_2	>840/1	>840/>8
			b. Chloroalkanoyl			
0	CH_2	H	$COCHCl_2$	NH_2	>1680/—	>1680/—
			c. Arylalkanoyl			
0	CH_2	H	$COCH_2C_6H_5$	NH_2	280/0.2	>1320/>13
			d. Alkenoyl			
0	CH_2	H	$COCH{=}CHCH_3$	NH_2	>840/0.6	>840/5
			e. Aroyl			
0	CH_2	H	COC_6H_5	NH_2	28/0.6	>480/10
0	CH_2	H	$COC_6H_4NO_2$-*p*	NH_2	>840/—	840/—
			f. Sulfonyl			
0	CH_2	H	$SO_2C_6H_5$	NH_2	840/0.4	>840/4
			g. Alkoxycarbonyl			
0	CH_2	H	$COOCH_3$	NH_2	>210/0.8	94/0.4
0	CH_2	H	$COOC_2H_5$	NH_2	75/1	118/1
0	CH_2	H	$COOC_3H_7$	NH_2	780/1	>840/1
0	CH_2	H	$COOC_6H_5$	NH_2	>1680/—	840/—
0	CH_2	H	$COOCH_2CH(CH_3)_2$	NH_2	>420/1	420/10
0	CH_2	H	$COOCH_2CH_2CH_2Cl$	NH_2	590/1	>1680/4
			II. Variations of R_2			
			a. Monoalkylamino			
0	CH_2	H	H	$NHCH_3$	168/>20	168/20
0	CH_2	H	$COCH_3$	$NHCH_3$	92/1	>280/20
0	CH_2	H	H	NHC_2H_5	>280/>20	>280/>20
0	CH_2	H	$COCH_3$	NHC_2H_5	82/3	>1020/10
			b. Dialkylamino			
0	CH_2	H	$COCH_3$	$N(C_2H_5)_2$	136/5	>840/>20
0	CH_2	H	$COCH_3$	$NCH_2CH_2CH_2CH_3$	367/3	>840/>20
0	CH_2	H	$COCH_3$	$NCH_2CH_2OCH_2CH_2$	87/3	>840/>20
0	CH_2	H	$COCH_3$	$NCH_2(CH_2)_3CH_2$	168/3	>600/>10
			c. Arylamino			
0	CH_2	H	$COCH_3$	NHC_6H_5	>840/—	>840/—
			d. Acylamino			
0	CH_2	H	$COCH_3$	$NHCOCH_3$	113/0.6	>1320/5
			e. Hydroxyl			
0	CH_2	H	H	OH	>120/>20	>120/>20
0	CH_2	H	$COCH_3$	OH	>1020/>20	>1020/>20

acetic acid, or dimethyl sulfoxide solution of the compound into cold water. Conversion of β to α also takes place at the melting point of β or on recrystallizing from nitromethane with slow cooling to room temperature and then rapid cooling in an ice bath. The α form is more soluble in water than the β form.

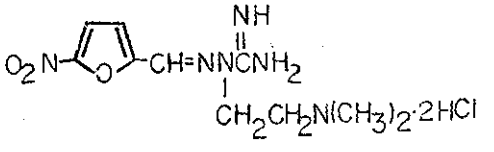
A tabulation of the structural variations of the compounds prepared and their in vitro (minimal inhibitory concentration) and in vivo (mice) antibacterial activities are shown in Table 1.

D. N-Amino Guanidines, Triazoles, Imidazolidinones and Related Compounds: The demonstration that a variety of nitrofurans containing the -CH=N-N-C=O(=N-) group exhibit chemotherapeutic activity led to the synthesis of several other types of compounds containing this group, either in a chain or as part of a heterocyclic ring.

Methyl hydrazinoacetate hydrochloride (45) was treated with cyanamide to produce the cyclic aminoguanidine, 1-amino-2-iminohydantoin, which was isolated as its 5-nitrofurfurylidene derivative (52). Nitrofuran (52) is an imino analogue of nitrofurantoin (4). In the same manner, 2-dimethylaminoethylhydrazine and 2-hydrazinoethanol (41) were converted to the corresponding aminoguanidine derivatives (53) and (44), respectively.[28]



(52)

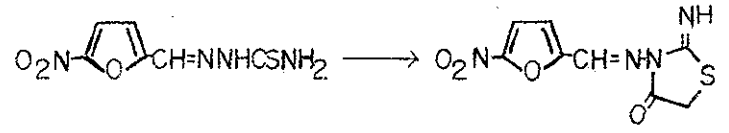


(53)

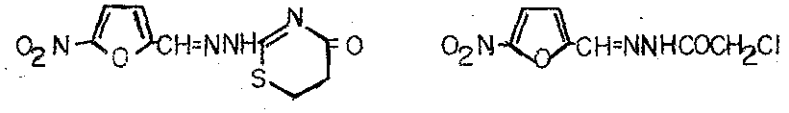
The 5-nitrofurfurylidene derivatives of a number of other N-amino compounds; such as 1,3-diaminoguanidine; 4-amino-1,2,4-triazole; 4-amino-3,5-dimethyl-1,2,4-triazole; 3-amino-2-imino-4-methyl-4-thiazoline; 3,4-diamino-1,2,4-

triazole; 3,4-diamino-5-methyl-1,2,4-triazole and N,N''-diaminooxamidine; were also prepared.[28] All of these nitrofurans contain the -CH=NNC=N- group.

Several other sulfur containing compounds in this general class were prepared.[28] The reaction of 5-nitro-2-furaldehyde thiosemicarbazone (54) with chloroacetic acid in a sodium acetate-acetic acid medium produced 2-imino-3-(5-nitrofurfurylidene-amino)-4-thiazolidinone (55). The structure assigned to (55) was proved by an unequivocal synthesis from 5-nitro-2-furaldehyde chloroacetylhydrazone (56) and potassium thiocyanate. Acylhydrazone (56) was obtained by treatment of 5-nitro-2-furaldehyde hydrazone with chloroacetic anhydride.



(54) (55)

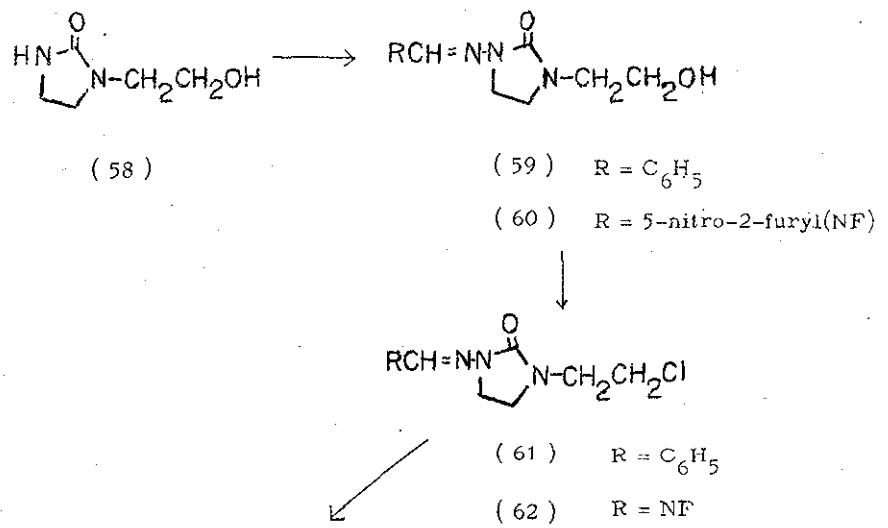


(57) (56)

β-Propiolactone was heated with (54) in acetone or acetic acid to give the cyclic compound 5,6-dihydro-2-(5-nitrofurfurylidenehydrazino)-1,3,4-thiazin-4-one (57).

Several 5-nitrofurfurylidene derivatives of N-aminoimidazolidinones, which can be considered cyclic semicarbazides, were prepared.[31] Nitrosation of 1-(2-hydroxy-ethyl)-2-imidazolidinone (58) with sodium nitrite in 10 % sulfuric acid, followed by reduction with zinc and then condensation with 5-nitro-2-furaldehyde produced

1-(2-hydroxyethyl)-3-(5-nitrofurfurylideneamino)-2-imidazolidinone (60). Condensation with benzaldehyde produced the corresponding benzylidene derivative (59). Chlorination with thionyl chloride readily converted (59) and (60) to the chloroethyl derivatives (61) and (62), respectively. Amination of (61) with morpholine followed by acid hydrolysis in the presence of 5-nitro-2-furaldehyde afforded the 2-morpholinoethyl nitrofuran (63). In addition to their good antimicrobial activity, these nitrofurans were distinguished by their resistance to metabolic destruction when fed to animals.[32]



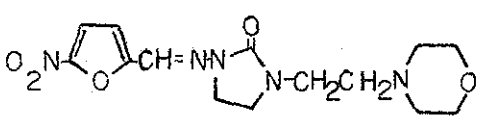
(58)

(59) R = C_6H_5

(60) R = 5-nitro-2-furyl(NF)

(61) R = C_6H_5

(62) R = NF



(63)

REDUCTION OF 5-NITRO-2-SUBSTITUTED FURANS

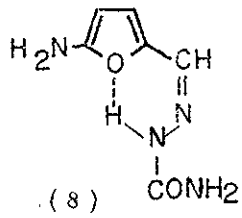
Catalytic hydrogenation of a variety of 5-nitro-2-furaldehyde derivatives produced the corresponding aminofurans. None of the reduction intermediates, hydroxylamino

and nitroso, could be isolated. The aminofurans are stable in the solid state, in most cases can be recrystallized from organic solvents, decompose slowly in aqueous solution and can be acetylated. As expected, the acetylated derivatives are more stable in aqueous solution. Table 2 contains some of the amino- and acetamido-furans prepared.[33]

Most of the hydrogenations were carried out in methanol with 5 % palladium on charcoal catalyst at 2 - 3 atmospheres pressure. With the exception of the thione compounds, the reductions proceed rapidly to completion within one hour. In the case of the thione compounds, it was necessary to use a large excess of catalyst to overcome the poisoning effect of the sulfur and to complete the reduction within 15 hours.

The aminofurans showed infrared absorption bands at approximately 1235 and 1020 cm^{-1} characteristic of the furan ring, bands in the NH region and retention of bands characteristic of the side chain. The ultraviolet data (Table 2) indicate, in most cases, a 20 - 40 nm hypsochromic shift from the maxima of the corresponding nitrofurans.

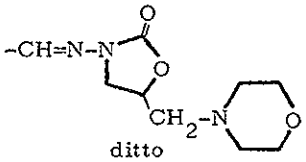
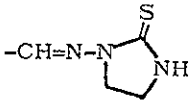
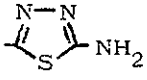
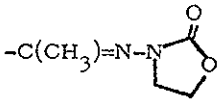
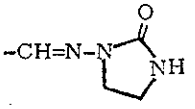
Additional palladium on carbon reductions of nitrofurazone (6) in absolute ethanol or methanol verified the original report[9] on the instability of the corresponding aminofuran (8) in ethanol. The instability of (8) in contrast to the other aminofurans in this series may be explained by the following hydrogen bonded form of (8), which might be more susceptible to furan ring cleavage. In most of the other compounds in Table 2 such hydrogen bonding is impossible.



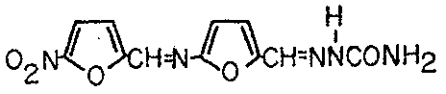
(8)

Table 2

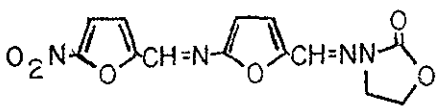
5-Amino-2-substituted Furans

No.	2-Substituent	5-Substituent	Uv max(H_2O),nm
(8)	$-CH=NNHCONH_2$	NH_2	335
(64)	$-CH=NNHCONH_2 \cdot HCl$	NH_2	340
(65)	$-CH=NN(CH_2CH_2OH)CSNH_2$	NH_2	363
(66)	$-CH=NN(CH_3)COCH_3$	NH_2	345
(67)		NH_2	340
(68)	ditto	$NHCOCH_3$	324
(69)		NH_2	360
(70)	$-CHO$	NH_2	350
(71)		NH_2	340
(72)	$-CH=NNHCSNH_2$	NH_2	360
(73)	$-CH=NNHCSNH_2$	$NHCOCH_3$	340
(74)		NH_2	365
(75)	$-CH=NNHCOCH_3$	NH_2	349
(76)		NH_2	335

When a methanolic solution of reduced (6) was treated with 5-nitro-2-furaldehyde in the presence of dilute hydrochloric acid, a dark red Schiff base (77) was obtained. Condensation with 3-(5-aminofurfurylideneamino)-2-oxazolidinone (79) gave the Schiff base (78).[33]



(77)



(78)

Compounds (77) and (78) exhibit maxima in the ultraviolet at 330 - 335 nm in water, which indicates regeneration of the aminofurans.

Since aminofurans are susceptible to ring opening in aqueous or alcoholic solution,[8,9] a non-hydroxylic solvent, such as ethyl acetate, was used for the preparation of (8) and other aminofurans that could not be obtained in methanol or absolute ethanol.

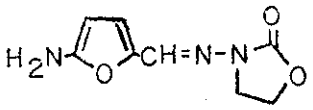
Hydrogenation of a suspension of (6) in ethyl acetate in the presence of 5 % palladium on charcoal and anhydrous magnesium sulfate gave a yellow solution having a single absorption maximum at 340 nm. Evaporation of the solution gave an amorphous solid which showed one maximum at 335 nm in water, with the appearance of a second peak at 275 nm and a concomitant decrease of the 335 nm absorption. Addition of the solid to a minimum of ethanol gave a yellow crystalline material. The infrared spectrum supported structure (8) and ultraviolet absorption properties were identical with those of the amorphous material.

The hydrochloride (64) of (8) was isolated in 67 % yield, by precipitation from a mixture of ethanol and ethyl acetate with 10 % hydrochloric acid. Condensation

of (64) with 5-nitro-2-furaldehyde also gave (77).

Other aminofurans that could not be obtained from alcoholic reductions but were obtainable in ethyl acetate-ethanol are compounds (70), (74) and (75) in Table 2.

The structure of 5-amino-2-furaldehyde (70) was further substantiated by condensation with 3-amino-2-oxazolidinone in the presence of acid to give (79).



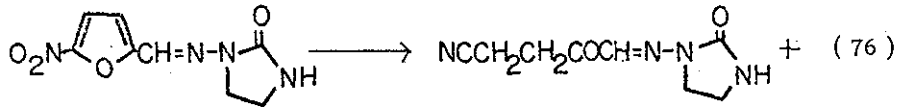
(79)

5-Amino-2-furaldehyde acetylhydrazone (75) on acetylation with acetic anhydride in the presence of pyridine produced a solid that could not be purified by recrystallization. Infrared and ultraviolet spectra and Rf value of the product were identical with those of 5-acetamido-2-furaldehyde acetylhydrazone, a metabolite of the corresponding nitrofuran. The isolation of this metabolite from rabbit urine, and spectral and chromatographic analyses of these compounds were reported by Olivard and co-workers.[34]

For comparative purpose, the 5-nitrothiophene analogs of (6) and 3-(5-nitrofurfurylideneamino)-2-oxazolidinone, furazolidone (5), were reduced catalytically in methanol over 5 % palladium on carbon.[33] Acetic anhydride acetylation of the amines readily produced the acetamidothiophenes. The aminothiophene derivatives are very stable in aqueous solution.

In contrast to the nitrofurans, the aminofurans did not exhibit significant in vitro antibacterial activity.

From the reduction of 1-(5-nitrofurylideneamino)-2-imidazolidinone (80), in addition to the corresponding aminofuran (76), the ring opened compound, 3-(4-cyano-2-oxobutylideneamino)-2-imidazolidinone (81), which is analogous to (9), was isolated in 5.7 % yield.[35]

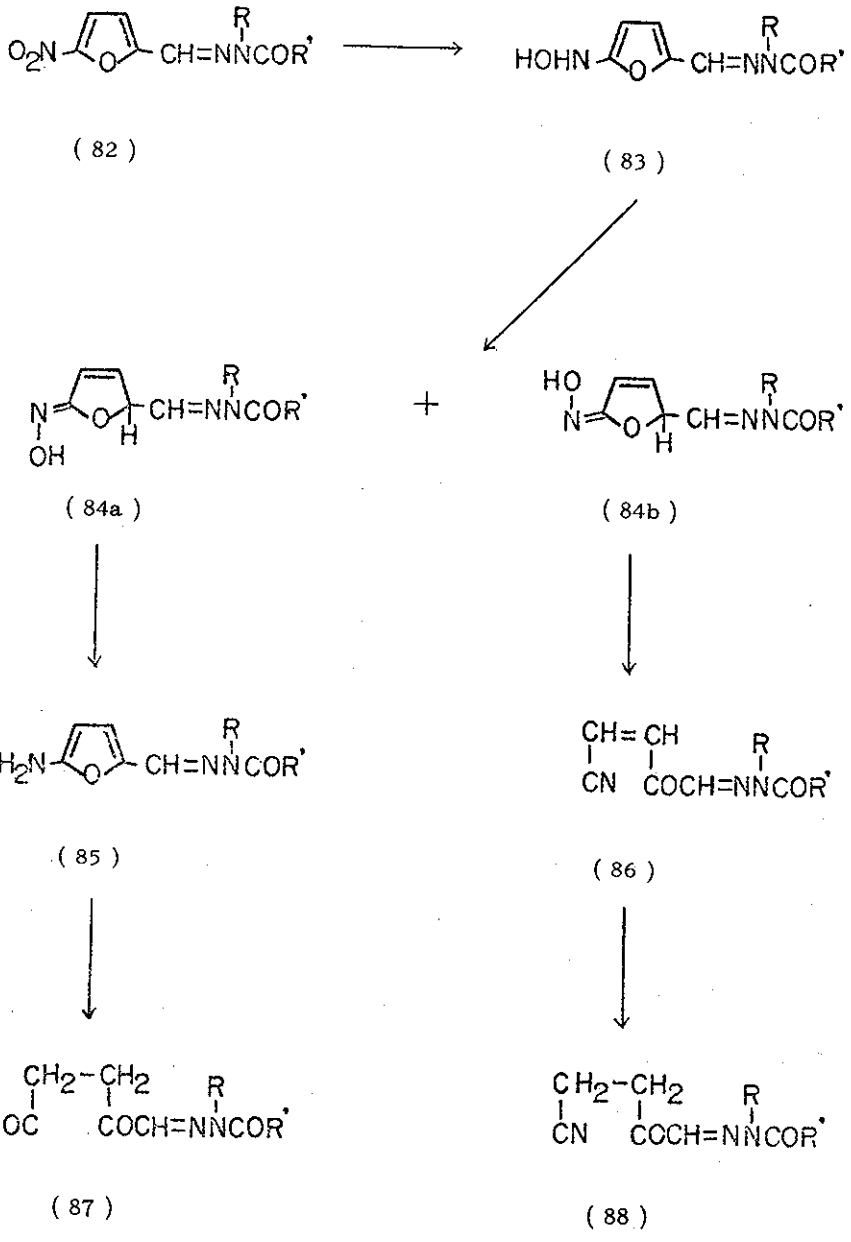


(80) (81) + (76)

The bacterial degradation of (80) by Escherichia coli produced (81) as the major product (60 - 70 % conversion); aminofuran (76) is not an intermediate in this process.[35] Chemical reduction of this type of aminofuran did not produce the corresponding nitrile. Hydrolysis of a similar aminofuran (79) was found to yield a ring-opened levulinic acid derivative; a nitrile is not involved as an intermediate.[36]

Therefore, these results indicate that aminofurans are not intermediates in the formation of open-chain nitriles from type B nitrofurans (82) (R is alkyl or part of a cyclic structure involving R'). Possible pathways for the independent formation of open-chain nitriles and aminofurans from type B nitrofurans are as follows.

The nitrofuran (82) is reduced to the hydroxylamine (83) which tautomerizes to the cis- and trans-oximes (84a) and (84b), respectively. Further reduction of (84a) leads to the formation of an aminofuran (85) which could be hydrolyzed to a ring-opened levulinic acid derivative (87) or be converted to an acetamidofuran. In contrast, the oxime (84b) would be a preferred configuration for trans-elimination of water, ring opening and reduction to nitriles (86) and (88). The similar ultraviolet absorption maxima of (87) and (88) would, therefore, explain the spectral changes observed by Beckett and Robinson.[9,10]

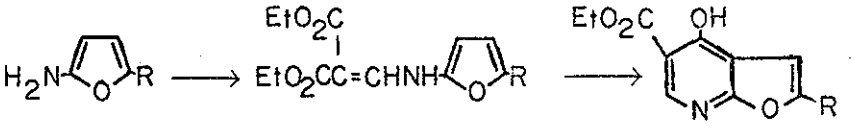


SYNTHESIS OF POLYCYCLIC FURANS

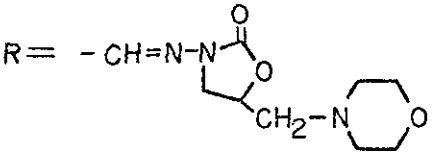
A. Furo[2,3-b]pyridine

Snyder demonstrated that a variety of furo[2,3-b]pyridine-2-carboxylic acid derivatives can be prepared by condensation of ethyl 5-amino-2-furoate with 1,3-dicarbonyl or α-alkoxymethylenecarbonyl compounds followed by thermal cyclization.[37] This general method was also applied to a 5-amino-2-furaldehyde derivative.

Reduced furaltadone (7), 3-(5-aminofurfurylideneamino)-5-morpholinomethyl-2-oxazolidinone (67), was condensed with an excess of diethyl ethoxymethylenemalonate at 130 - 140° to give diethyl [5-(5-morpholinomethyl-2-oxo-3-oxazolidinyl-iminomethyl)-2-furyl]aminomethylenemalonate (89). Thermal cyclization of (89) in boiling Dowtherm A gave a 60 % yield of the furo[2,3-b]pyridine (90).[37]



(67) (89) (90)

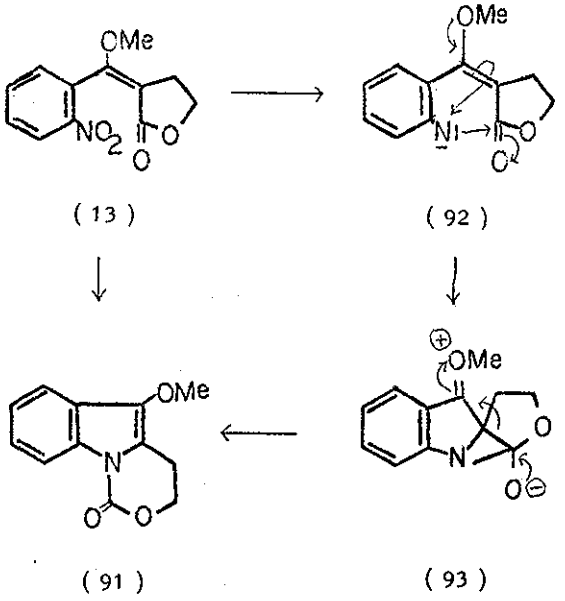


The infrared spectrum of (90) displayed strong absorption bands at 1770 (oxazolidinone carbonyl) and 1680 cm^{-1} (ester carbonyl). There was no absorption band at 1725 cm^{-1}, which is the normal frequency for a 5-ethoxycarbonyl band; neither was there a third carbonyl band, which would arise from a 4-oxo group. These properies supported the assigned 4-hydroxy structure of (90). The shift in absorption of the ester carbonyl from 1725 to 1680 cm^{-1} is attributable to hydrogen bonding with the ortho hydroxy group.

B. Furo[2,3-b]quinoline

Although many cyclization procedures for the preparation of furo[2,3-b]quinolines are known, the triethyl phosphite reductive cyclization of o-nitrobenzoyl- or o-nitrobenzylidene-γ-butyrolactones had not been reported. Recently, the reductions of α-(α-methoxy-o-nitrobenzylidene)- (13), α-(o-nitrobenzoyl)- (12), and α-(6-nitroveratrylidene)-γ-butyrolactones were studied.

Triethyl phosphite reduction of lactone (13) at 160 - 170° gave a cyclized carbonyl containing product, which was, therefore, not the anticipated 4-methoxyfuro[2,3-b]-quinoline (14). Instead, a 45 % yield of 3,4-dihydro-5-methoxy[1,3]oxazino[3,4-a]-

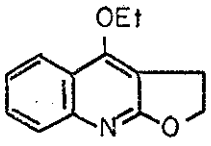


(13) (92)

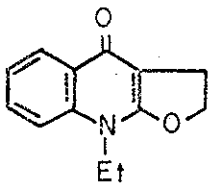
(91) (93)

indol-4-one (91) was obtained.[38] Since there is much evidence for the intermediacy of nitrenes in the triethyl phosphite reduction, the formation of (91) by lactone ring expansion to the indole nitrogen could involve a nitrene (92). Addition of the nitrene to the lactone carbonyl and olefinic carbons with the formation of an aziridine (93), followed by rearrangement would lead to (91).

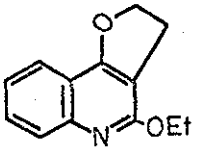
A mixture of three cyclic products was obtained from the reduction of the benzoyl-lactone (12).[38] Chromatographic separation yielded a trace of one solid which was tentatively identified as a furoquinoline. Spectral data indicated that deoxygenation and ethylation had occurred to produce one of four possible structures: two linear, (94a) and (94b), and two angular, (94c) and (94d), furoquinolines. Strong absorption at 1640 cm^{-1} in the infrared suggests a furoquinol-2-one structure (94d).



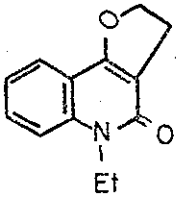
(94a)



(94b)



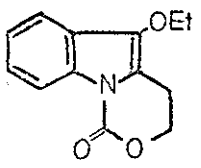
(94c)



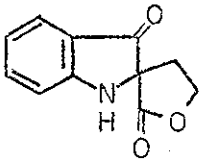
(94d)

The second product was identified as the 5-ethoxy (95; 0.7 %) analogue of oxazinoindole (91). Formation of (95) may also involve an aziridine intermediate similar to (93) followed by rearrangement and O-ethylation. The major product was the highly fluorescent spiro-indolinone (96; 12.5 %), formed by nitrene insertion in the α-position of the lactone. Hydrolysis of (96) with dilute sodium hydroxide solution produced the corresponding alcohol, 1,2-dihydro-2-(2-hydroxy-

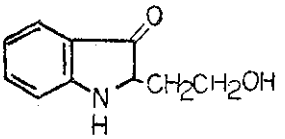
ethyl)indol-3-one (97) in 42 % yield.



(95)



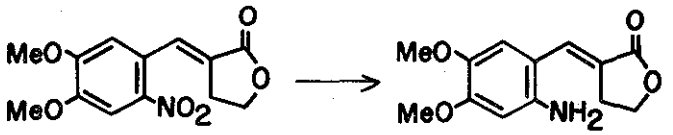
(96)



(97)

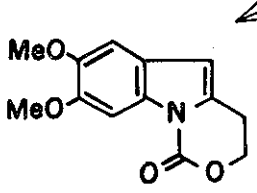
Reduction of α-(6-nitroveratrylidene)-γ-butyrolactone (98) with triethyl phosphite at 160 - 165° afforded low yields of 3,4-dihydro-7,8-dimethoxy[1,3]oxazino-[3,4-a]indole-1-one (99), ethyl 5,6-dimethoxyindole-2-carboxylate (100), and 2,3-dihydro-6,7-dimethoxyfuro[2,3-b]quinoline (101).[39] Again, nitrene addition reactions involving the lactone carbonyl and the olefinic bond are indicated.

Catalytic hydrogenation of (98) in methanolic hydrochloric acid over 5 % palladium on carbon, the same procedure used to convert the methoxybenzylidene-lactone (13) to the furoquinoline (14),[12] gave only α-(6-aminoveratrylidene)-γ-butyrolactone (102). Nmr spectral analysis of (98) and (102) indicated a trans-configuration of the carbonyl and phenyl groups. Photolysis of an ethanolic solution of (102) caused isomerization and cyclization to the furoquinoline (101) in 15 % yield.[39]

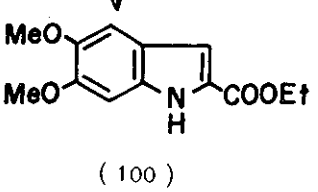


(98)

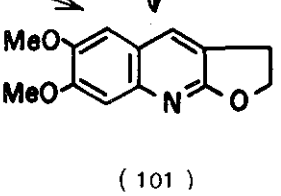
(102)



(99)



(100)



(101)

Conclusions

Chemical modifications within the 5-nitro-2-substituted furan series have demonstrated that a variety of changes can be made while retaining or improving antimicrobial activity. Most of the modifications involve compounds derived from 5-nitro-2-furaldehyde in which the aldehyde function is part of a substituted hydrazone, which in turn may be part of an linear or cyclic groupling. However, it was also demonstrated that activity is retained when the hydrazone or azomethine (-CH=N-) group in furazolidone (5) is replaced by a thiazole ring, as in nitrofuran (30).

The importance of the 5-nitro-2-furyl moiety was further demonstrated by the synthesis and evaluation of 5-aminofurans. Although this work ultimately contributed to the identification of nitrofuran metabolites (75) and (81), and to a clarification of reductive pathways, the resulting aminofuran derivatives are devoid of significant antibacterial activity.

From these studies, it is concluded that although aminofurans and ring opened nitriles may be products of chemical and bacterial reduction, aminofurans are not intermediates in this process, as had been proposed by other workers. A proposed pathway, involving cis- and trans-oximes (84), to account for the independent formation of aminofuran (85) and nitrile (88) was presented.

It was also found that aminofurans, especially those wherein the hydrazone nitrogen is part of a ring (type B), are relatively stable, reactive compounds. This was demonstrated by their ability to form hydrochlorides (64), acetamides (68), Schiff bases (77) and aminomethylenemalonates (89). High temperature cyclization of (89) produced the furo[2,3-b]pyridine (90).

Triethyl phosphite reduction of o-nitrobenzoyl- (12), o-nitro-α-methoxybenzylidene- (13), and 6-nitroveratrylidene- (98) γ-butyrolactones yields predominantly indole derivatives. A trace amount of a deoxygenated product was obtained from lactone (12), which was tentatively assigned an N-ethylfuroquinolone (94d) structure

on the basis of spectral data. Reduction of lactone (98) also produced a furoquinoline (101), in addition to the indoles (99) and (100). The intermediacy of nitrenes was postulated to account for the reduction products.

It may be concluded from these results that indoles are the preferred products when the lactone ring is saturated. Rearrangements involving breaking bonds in such a ring are more likely than in the resonance stabilized oxazolone ring (23). The formation of the aromatic oxazolo[5,4-b]quinoline (25) system from (23) is therefore favored.

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