# SYNTHESIS OF PYRIDINIUM AND PICOLINIUM SALTS OF 5-NITRO-2-VINYLFURAN HAVING ANTIBACTERIAL PROPERTIES*

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Quaternization of pyridine, 2-, 3-, or 4-picoline with (*Z*)-, or (*E*)-5-nitro-2-furylvinyl bromide is described and the addition–elimination mechanism of the nucleophilic substitution to yield the respective (*Z*)-, or (*E*)-vinylammonium salts is discussed.

The majority of compounds related to 5-nitro-2-furan belongs to the ethylene derivatives of the panfuran type[1]; some of them are used as chemotherapeutics[2], other as preservatives[3], antibacterial preparations[4] *etc.* A high antibacterial activity and a broad application possibilities were found with derivatives having the 5-nitro-2-furan ring linked to the heterocyclic moiety through an ethylene bridge with a heterocyclic substitution. As found[5–10], the linkage of the pyridine molecule in position 2-, 3-, or 4- with a 5-nitro-2-furyl residue through an ethylene bridge results in good antibacterial[7], fungicidal[7], tuberculostatic[10], and antitrichomodal[10] properties of these preparations. 5-Nitro-2-furylvinyl bromide[11] (*I*) was ascertained to be responsible for the high activation power of 5-nitro-2-furan residue. The easy substitution of the halogen atom of *I* makes it possible to link in one step the 5-nitro-2-furylethylene residue to pyridine in position 1 to furnish the pyridinium salt having a considerable biologic activity[12,13].

This paper deals with the course of quaternization of pyridine with the respective (*Z*)- and (*E*)-5-nitro-2-furylvinyl bromide in benzene, toluene, acetonitrile, and dimethylformamide at 80° to 100°C. The 3- to 5-day reaction time was shortened to approximately 2 to 10 h, when using tertiary amine as the solvent, Table I.

Whereas quaternization of trimethylamine ($pK_a = 11{\cdot}01$) with bromide *I* takes already place at the boiling point of trimethylamine (5 to 7°C), pyridine ($pK_a = 5{\cdot}25$),

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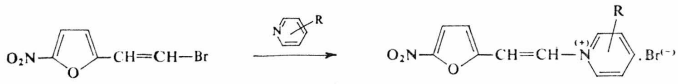


*Ia,b* *II–Va,b*

R = H (*II*); 2-$CH_3$ (*III*); 3-$CH_3$ (*IV*); 4-$CH_3$ (*V*) *a* = *Z*-isomer; *b* = *E*-isomer.

SCHEME 1

2-picoline ($pK_a$ = 5·92), 3-picoline ($pK_a$ = 5·52), and 4-picoline ($pK_a$ = 6·08) react after a long-lasting heating only. Attempts to quaternize the substituted cyanopyridines (2-CN, $pK_a$ = −0·26; 3-CN, $pK_a$ = 1·35 and 4-CN, $pK_a$ = 1·86) failed.

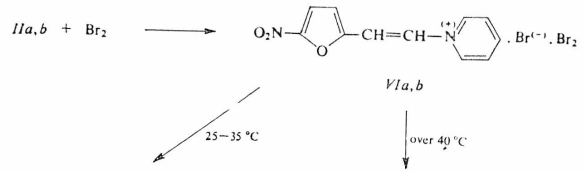
Mechanism of the reaction and the reaction course of the activated vinyl compounds with nucleophiles are compiled in several review articles[14,15–18]; for reactions, where the configuration of products remains unaltered, as shown by analysis of the reaction mixture and kinetic data, an addition–elimination mechanism is considered. Our $^1$H NMR data evidenced that configuration of the starting bromide *I* remained unaltered within 60 to 110°C upon reaction with pyridine, 2-, 3-, and 4-picoline. On the other hand, mixtures of isomers were obtained when using highly polar solvents as dimethylformamide, dimethyl sulfoxide and sulfolane. Considering the kinetic measurements of the reaction of *I* (Scheme 1) with secondary and tertiary amines[19–22], and also the maintenance of configuration of the ammonium salts *IIa,b*–*Va,b* we pre- sumed the addition–elimination course of quaternization of the six-membered ring.

TABLE I

Solvent effect on quaternization of *Ia,b* with pyridine

| Solvent | Temperature °C | Time h | Yield, % | |
|---|---|---|---|---|
| | | | *Ia* | *Ib* |
| Benzene | 80 | 24 | 7·0 | 12·0 |
| Toluene | 100 | 24 | 8·5 | 13·0 |
| Ethanol | 80 | 24 | 18·5 | 20·0 |
| Acetonitrile | 80 | 24 | 36·0 | 43·0 |
| Dimethylformamide | 80 | 10 | 27·0 | 40·0 |
| Pyridine | 80 | 2 | 68·0 | 70·0 |

Isomerization of the individual isomers does not occur in non-polar solvents up to 100°C. A *cis-trans* isomerization of these ammonium salts does take place in polar protic solvents. We investigated a new type of the *cis-trans* isomerization of vinylammonium derivatives induced by bromide. Bromination of *IIa,b* gave complex compounds of vinylpyridinium salts *VIa,b* at room temperature. Addition of bromine to the ethylenic bond did not occur up to 60–80°C. Compound *VIa* is little stable in the light, turns yellow, *i.e.* to *trans*-5-nitro-2-furylvinylpyridinium bromide (*IIb*, m.p. 275–280°C). The analogical compound *VIb* was obtained by reaction of *cis IIa* and bromine in $CHCl_3$; at the boiling point of the solvent, it turns to *IIb*. Pyridinium bromide dibromides *VIa,b* are highly reactive bromination reagents: with acetone they afford *IIa*, and *IIb* in high purity at 25–35°C, *IIb* at higher temperatures, and bromo acetone in a quantitative yield (Scheme 2).




SCHEME 2

To be easy identified, their solubility and biological activity investigated, the ammonium salts were transformed into iodides, perchlorates and picrates. Their activity was tested against selected bacterial, yeast and mildew strains using the plate diffuse method. Pyridinium salts *II* reveal strong antibacterial activity against Gram-positive (*Bacillus subtilis* 50 μg/disc), Gram-negative (*Pseudomonas aeruginosa* 12·5 μg/disc), as well as against microscopic fungi, as *Candida pseudotropicalis* (12 μg/disc). Also a high biological activity against *Salmonella enteritis* (3·1 μg/disc), *S. typhimurium* (1·125 μg/disc) was observed. Introduction of a substituent into the pyridine molecule (compounds *III*, *IV*, *V*) is of no positive effect on bacterial properties of preparations. A decrease of Gram-positive and disappearance of Gram-negative activity was estimated.

## EXPERIMENTAL

Melting points were measured on a Kofler hot stage, ultraviolet spectra were recorded with a UV-VIS (Zeiss, Jena) spectrophotometer, and $^1$H NMR spectra with a Tesla BS 487 C (Czechoslovakia) apparatus operating at 80 MHz, internal standard tetramethylsilane. (*Z*)-5-Nitro-2-furylvinyl bromide (*Ia*, m.p. 39–40°C, methanol) was prepared according to[11].

(*E*)-5-Nitro-2-furylvinyl Bromide (*Ib*)

Sodium 3-(5-nitro-2-furyl)acrylate (41 g, 0·2 mol) was suspended in $CHCl_3$ (500 ml) and brominated with bromine (12 ml) in $CHCl_3$ (200 ml) with stirring under reflux. After 4 h the mixture was filtered and chloroform was removed under reduced pressure. The distillation residue was suspended in benzene (50 ml), the insoluble 2,3-dibromo-3-(5-nitro-2-furyl)propionic acid[11] (20—22 g, 30%) was filtered off and washed twice with benzene (10—20 ml). The combined benzene solutions were concentrated to 10—20 ml and purified chromatographically through a silica gel (150—250 mesh, eluent benzene) column. Yield 1·45 g (7%), m.p. 62—64°C (methanol).

(*Z*)-5-Nitro-2-furylvinylpyridinium Bromide (*IIIa*)

Compound *Ia* (11 g, 0·05 mol) dissolved in pyridine (50 ml) was heated at 80°C for 2 h, the precipitate (12·5 g) was filtered off and recrystallized from ethanol with addition of ether. Yield 10·5 g (70%), m.p. 204—205°C. For $C_{11}H_9BrN_2O_3$ (296·9) calculated: 44·40% C, 3·05% H, 26·90% Br, 9·43% N, found: 43·96% C, 3·27% H, 27·10% Br, 9·28% N. The UV and $^1H$ NMR spectral data are listed in Tables II and III.

*Iodide*: Sodium iodide (0·75 g) in ethanol (10 ml) was added with stirring to *IIa* (1·5 g, 5 mmol) in a 80% ethanol (50 ml) and the orange precipitate was filtered off. Yield 1·6 g, m.p. 187—188°C. For $C_{11}H_9IN_2O_3$ (343·9) calculated: 36·66% I; found: 36·11% I. UV spectrum $\lambda_{max}^{MeOH}$, nm (log $\varepsilon$): 225 (3·27), 261 (3·01), 337 (3·05).

*Picrate*: Picric acid (1·14 g) in water was added to *IIa* (1·5 g, 6 mmol) in water (30 ml) under stirring, and the yellow precipitate was filtered off. Yield 2 g (95%), m.p. 126—127°C. For $C_{17}H_{11}N_5O_{10}$ (445·0) calculated: 15·73% N; found: 15·35% N. UV spectrum $\lambda_{max}^{MeOH}$, nm (log $\varepsilon$): 223 (3·53), 351 (3·48).

*Perchlorate*: $NaClO_4$ (0·6 g) in 80% ethanol) 10 ml) was added to *IIa* (1·5 g, 5 mmol) and the precipitate was filtered off. Yield 1·4 g (88%), m.p. 194—195°C. For $C_{11}H_9ClN_2O_7$ (316·6) calculated: 11·20% Cl; found: 11·20% Cl. UV spectrum $\lambda_{max}^{MeOH}$, nm (log $\varepsilon$): 226 (3·20), 263 (2·86), 341 (2·97).

(*E*)-5-Nitro-2-furylvinylpyridinium Bromide (*IIb*)

This compound was obtained in an analogous way from *Ib* as described for *IIa*. Yield 75%, m.p. 270—272°C (decomposition). For $C_{11}H_9BrN_2O_3$ (296·9) calculated: 44·40% C, 3·05% H, 26·90% Br, 9·43% N; found: 44·10% C, 3·12% H, 27·00% Br, 9·30% N. The UV and $^1H$ NMR data are listed in Tables II and III.

(*Z*)-5-Nitro-2-furylvinyl-2-picolinium Bromide (*IIIa*)

2-Picoline (10 ml) was added to *IIa* (2·18 g, 10 mmol (30 l) in $CH_3CN$ (30 ml) and the solution was heated at 60°C for 100 h. The solvent was distilled off *in vacuo*, and the residue was crystallized from ethanol–ether. Yield 2 g (64%) of brown *IIIa*, m.p. 227—22 °C. For $C_{12}H_{11}BrN_2O_3$ (311·1) calculated: 46·32% C, 3·56% H, 25·68% Br; 9·00% N, found: 46·04% C, 3·62% H, 24·94% Br. The UV and $^1H$ NMR data are listed in Tables II and III.

*Iodide*: brown, m.p. 227—229°C. UV spectrum $\lambda_{max}$ nm (log $\varepsilon$): 223 (3·61), 270 (3·13), 336 (3·16 )

*Picrate*: yellow-orange, m.p. 166—167°C. UV spectrum $\lambda_{max}$, nm (log $\varepsilon$): 225 (3·27), 261 (3·01), 351 (4·52).

*Perchlorate*: m.p. 117—119°C. UV spectrum $\lambda_{max}$, nm (log $\varepsilon$): 225 nm (3·25), 269 (2·99), 338 (3·06).

(*E*)-5-Nitro-2-furylvinyl-2-picolinium Bromide (*IIIb*)

A solution of *Ib* (2·18 g, 10 mmol) and 2-picoline (5 ml) in nitrobenzene (10 ml) was left to stand at room temperature for 200 h. The precipitated compound was filtered off and crystallized from ethanol–ether. Yield 0·4 g (13%) of yellow *IIIb*, m.p. 248–250°C (decomposition). For $C_{12}H_{11}BrN_2O_3$ (311·1) calculated: 46·32% C, 3·56% H, 25·68% Br, 9·00% N; found: 46·11% C, 3·60% H, 25·00% Br, 9·10% N. The UV and $^1$H NMR data are listed in Tables II and III.

TABLE II

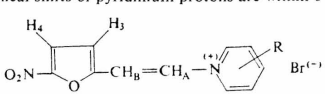
UV spectral data of methanolic solutions of 5-nitro-2-furylvinylpyridinium salts *II*–*V*

| Compound | $\lambda_{max}$, nm | log $\varepsilon^a$ | $\lambda_{max}$, nm | log $\varepsilon^a$ | $\lambda_{max}$, nm | log $\varepsilon^a$ |
|---|---|---|---|---|---|---|
| *IIa* | 225 | 3·27 | 261 | 3·01 | 340 | 3·05 |
| *IIb* | 227 | 3·37 | — | — | 362 | 3·63 |
| *IIIa* | 224 | 3·27 | 268 | 2·92 | 333 | 3·06 |
| *IIIb* | 227 | 3·20 | 268 | 2·91 | 348 | 3·26 |
| *IVa* | 223 | 3·25 | 268 | 3·00 | 334 | 3·05 |
| *IVb* | 223 | 3·32 | 267 | 3·00 | 361 | 3·35 |
| *Va* | 223 | 3·25 | 263 | 2·93 | 351 | 3·04 |
| *Vb* | 223 | 3·22 | — | — | 360 | 3·41 |

[a] $\varepsilon$ in m$^2$ mol$^{-1}$.

TABLE III

$^1$H NMR spectral data ($\delta$, ppm) of 5-nitro-2-furylvinylpyridinium salts *II*–*V* in hexadeuteriodimethyl sulfoxide. Chemical shifts of pyridinium protons are within 8·1–9·5 ppm




| Compound | $H_3$ | $H_4$ | $J^a_{3,4}$ | $H_B$ | $H_A$ | $J^a_{A,B}$ | $CH_3$ |
|---|---|---|---|---|---|---|---|
| *IIa* | 7·13 | 7·66 | 4·0 | 7·32 | 7·73 | 9·0 | — |
| *IIb* | 7·30 | 7·83 | 4·0 | 7·93 | 8·48 | 14·0 | — |
| *IIIa* | 7·11 | 7·67 | 4·0 | 7·36 | 7·64 | 9·0 | 2·50 |
| *IIIb* | 7·30 | 7·83 | 4·0 | 7·95 | 8·47 | 15·0 | 2·45 |
| *IVa* | 7·20 | 7·68 | 4·0 | 7·37 | 7·77 | 9·2 | 2·47 |
| *IVb* | 7·26 | 7·84 | 4·0 | 8·01 | 8·41 | 14·0 | 2·50 |
| *Va* | 7·18 | 7·68 | 4·0 | 7·35 | 7·80 | 9·2 | 2·45 |
| *Vb* | 7·28 | 7·80 | 4·0 | 7·89 | 8·50 | 13·9 | 2·46 |

[a] Hz.

(*Z*)-5-Nitro-2-furylvinyl-3-picolinium Bromide (*IVa*)

A solution of *Ia* (2·18 g, 10 mmol) in 3-picoline (30 ml) was heated at 100°C for 10 h and the precipitate was crystallized from ethanol–ether. Yield 2·1 g (65%), m.p. 197—199°C. For $C_{12}H_{11}$. $.BrN_2O_3$ (311·1) calculated: 46·32% C, 3·56% H, 25·68% Br, 9·00% N; found: 45·96% C, 3·44% H, 25·80% Br, 8·91% N. The UV and H NMR data are listed in Tables II and III.

*Iodide*: red, m.p. 200—201°C. UV spectrum $\lambda_{max}$, nm (log $\varepsilon$): 222 v3·50), 356 (3·29).

*Picrate*: green, m.p. 189—191°C. UV spectrum $\lambda_{max}$, nm (log $\varepsilon$): 216 (3·46), 360 (3·72).

*Perchlorate*: m.p. 131—133°C. UV spectrum $\lambda_{max}$, nm (log $\varepsilon$): 223 (3·25), 356 (3·30).

(*E*)-5-Nitro-2-furylvinyl-3-picolinium Bromide (*IVb*)

This compound was prepared as *IVa* in a 70% yield. M.p. 254—256°C (decomposition). For $C_{12}H_{11}BrN_2O_3$ (311·1) calculated: 46·32% C, 3·56% H, 25·68% Br, 9·00% N; found: 46·07% C, 3·55% H, 25·10% Br, 9·10% N. The UV and $^1$H NMR data are listed in Tables II and III.

(*Z*)-5-Nitro-2-furfurylvinyl-4-picolinium Bromide (*Va*)

A solution of *Ia* (2·18 g, 10 mmol) in 4-picoline (30 ml) was heated at 80°C for 50 h. Yield 2·3 g of a crude product, 1·5 g (48%) of ethanol–ether crystallized *Va*, m.p. 205—207°C (decomposition). For $C_{12}H_{11}BrN_2O_3$ (311·1) calculated: 46·32% C, 3·56% H, 25·68% Br, 9·00% N; found: 45·88% C, 3·67% H, 25·92% Br, 9·07% N. The UV and $^1$H NMR data are listed in Tables II and III.

(*E*)-5-Nitro-2-furylvinyl-4-picolinium Bromide (*Vb*)

The same procedure applied to *Va* gave from 1·7 g (5·5 mmol) *Ib* 1·05 g (43%) of yellow-brown *Vb*, m.p. 224—225°C (decomposition). The UV and $^1$H NMR data are listed in Tables II and III.

(*Z*)-5-Nitro-2-furylvinylpyridinium Bromide Dibromide (*VIa*)

A suspension of *IIa* (15 g, 50 mmol) in $CHCl_3$ (200 ml) was stirred with bromine (8 g) in $CHCl_3$ (100 ml) at 0°C. After a 5 h-stirring at room temperature the precipitate was filtered off. Yield 22 g (96%) of orange needles, m.p. 100°C (decomposition). For $C_{11}H_9Br_3N_2O_3$ (456·7) calculated: 28·91% C, 1·98% H, 52·46% Br, 6·13% N; found: 28·11% C, 1·92% H, 52·51% Br, 6·17% N. The UV and $^1$H NMR spectral data are identical with those of *IIa*.

(*E*)-5-Nitro-2-furylvinylpyridinium Bromide Dibromide (*VIb*)

*a*) From *IIb* in a 95% yield. Orange crystals, m.p. 111—113°C (decomposition).

*b*) The bromide *IIa* (3 g, 10 mmol) was suspended in chloroform (150 ml) and brominated with bromine (1·8 g, 0·6 ml) in chloroform (20 ml) at a reflux temperature for 3 h. The separated crystals were filtered off; yield 95%, m.p. 113°C (decomposition).

Reaction of *VI* and *VIb* with Acetone

The respective compound *VIa* or *VIb* (1·8 g, 5 mmol) was dissolved in acetone (50 ml) and stirred for 1 h. The pyridinium salt *IIa*, or *IIb* was filtered off. Yield 86%. 1-Bromopropanone remained after removal of acetone in a 99% yield, b.p. 138—140°C.

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