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N-Quaternary Compounds

Part X. Further Syntheses of Pyridinium-3-oxide Derivatives from Amino Acids

KJELL UNDHEIM and MICHEL GACEK

Chemical Institute, University of Oslo, Oslo 3, Norway

N-Furfurylamino acids have been synthesized by reductive alkylation using furfural, and the products oxidized either electrolytically to 2,5-dimethoxy-2,5-dihydrofurans or by sodium hypochlorite. The oxidation products were rearranged in acid solution to pyridinium-3-oxide derivatives of the corresponding amino acids. NMR data are used in configurational and conformational assignments.

Optically active pyridinium-3-oxides have been synthesized by acid catalyzed rearrangement of *N*-5-hydroxymethylfurfurylamino acids.[1] Pyridinium derivatives available by this method must carry an alkyl or aralkyl substituent in the 6-position since the right oxidation level for rearrangement of the furan is reached by oxidation of the α-carbon of the 5-alkyl or aralkyl group in the furan. We here report on a general method in which *N*-furfurylamino acids are oxidized by alkoxylation to *N*-2,5-dialkoxy-2,5-dihydrofurfurylamino acids, cyclic ketals, which then are subjected to acid catalysed rearrangement. The alkoxylation of furan derivatives is mainly due to Clauson-Kaas and coworkers,[2] who used this technique for the synthesis of various 3-pyridinols. Alkoxylation can also be carried out by the addition of bromine or chlorine to a methanolic solution of the furan in the presence of a weak base.[3] Bromine or chlorine oxidation of furfural in aqueous solution yields a highly reactive oxidation product which is further transformed without prior isolation.[4] In a similar way we have found that *N*-furfurylamino acids are oxidized in the furan ring by hypochlorite and that the oxidation products rearrange to pyridinium derivatives. Acetate oxidation on the other hand, requires the presence of unsubstituted ortho positions.[5] The furfurylamino acid derivatives (IV) were prepared by reductive alkylation of the methyl esters of amino acids in methanol using catalytic hydrogenation over 5 % palladium on charcoal or Raney-Ni at atmospheric pressure. Alternatively the intermediate Schiff bases were first prepared by condensation between the amino acid methyl esters and furfural in the presence of anhydrous sodium sulphate.

The methyl esters of the amino acids were liberated from their hydrochlorides by treatment with ammonia in chloroform or with magnesium oxide in water-chloroform mixture.[6]

The Schiff bases (III) were optically stable on distillation. They were reduced catalytically as above or by the use of sodium borohydride in methanol. Catalytic hydrogenation at 3.5 atmospheres yielded the corresponding tetrahydrofurans. A new asymmetric center has been introduced into these compounds (V) at the C_2-carbon in the furan ring. NMR showed that both diastereomers were formed in equal amounts.

The esters of furfurylamino acids (IV) were oily materials which could be distilled without racemisation. The electrolytic oxidation of these compounds was carried out in methanol at −30° in the presence of ammonium bromide using the apparatus described by Clauson-Kaas.[2] The optical rotation of the reaction product fell sharply on distillation. The pyridinium derivative from the crude dimethoxy derivative showed a substantially higher rotation than the same product from the distilled dimethoxy derivative. The decreased optical rotation on distillation can be attributed, at least partially, to epimerisation at the amino acid asymmetric carbon and not mainly to any fractionation of the isomers arising from the two asymmetric centers introduced into the furan ring. The highest optical purity of the pyridinium derivatives were thus obtained by using the crude material from the electrolytical oxidation. This was subjected to rearrangement in warm acid solution. The reaction should be conducted in a nitrogen atmosphere in order to obtain the pyridinium derivative in a higher yield. Without nitrogen the reaction mixture becomes very dark and gives large amounts of polymeric materials. In a second approach the furfurylamine (IV) in acid solution was oxidized by the addition of sodium hypochlorite solution and the transformation of the oxidation product to a

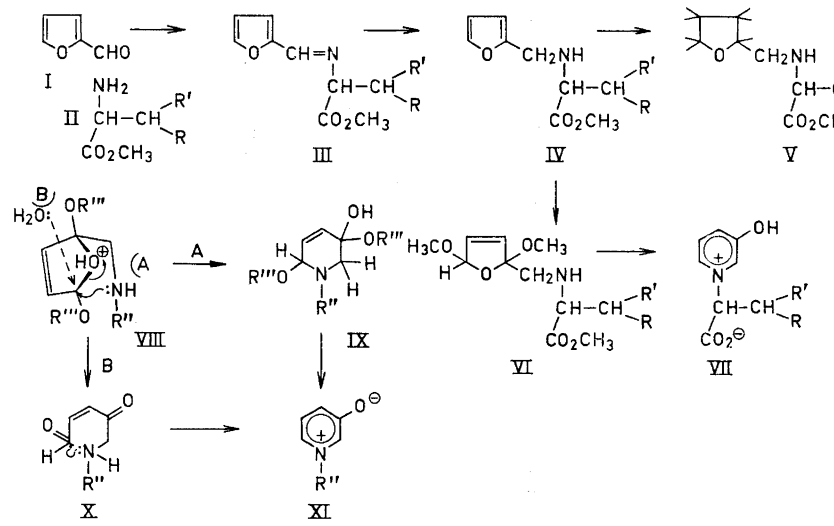
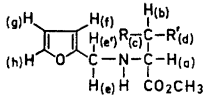


Table 1. NMR data in CCl_4.

Substituents		Chemical shift in τ values									Coupling constants in cps							
R	R^1	$H_{(h)}$	$H_{(g)}$	$H_{(f)}$	$H_{(e)}$	$H_{(a)}$	$H_{(b)}$	$R_{(c)}$	$R_{(d)}$[1]	OCH_3	J_{ab}	J_{ac}	J_{ad}	J_{bc}	J_{bd}	J_{gh}	J_{gf}	J_{hf}
H	H	2.50	3.60	3.20	1.90	5.99	8.57	8.57	8.57	6.32	7.0	7.0	7.0	—	—	1.7	3.5	0.9
CH_3	CH_3	2.51	3.56	3.15	1.95	6.48	7.68	9.07	9.07	6.36	6.9	—	—	6.9	6.9	1.7	3.5	0.9
H	C_6H_5	2.59	3.61	3.24	2.25	6.00	6.72	7.00	2.87	6.3	5.5	8.2	—	13.5	—	1.7	3.5	0.9

Table 2. NMR data in CCl_4.



Substituents		Chemical shift in τ values										Coupling constants in cps								
R	R^1	$H_{(h)}$	$H_{(g)}$	$H_{(f)}$	$H_{(e)}$	$H_{(e')}$	$H_{(a)}$	$H_{(b)}$	$R_{(c)}$	$R_{(d)}$[1]	OCH_3	J_{ab}	J_{ac}	J_{ad}	J_{bc}	J_{bd}	J_{gh}	J_{gf}	J_{hf}	$J_{ee'}$
H	H	2.74	3.79	3.94	6.27	6.40	6.72	8.77	8.77	8.77	6.36	7.0	7.0	7.0	—	—	1.9	3.0	1.0	14.0
CH_3	CH_3	2.74	3.76	3.92	6.32	6.48	7.06	8.18	9.10	9.10	6.36	6.0	—	—	6.5	6.5	1.9	3.2	1.0	14.0
H	C_6H_5	2.80	3.81	4.00	6.28	6.45	6.6	7.2		2.86	6.48						1.9	3.0	1.0	11.0

Table 3. NMR data in NaOD.

Comp. VII	Substituents		Chemical shift in τ values							Coupling constants in cps			
	R	R^1	H_2	H_6	H_4	H_5	$H_{(a)}$	$H_{(b)}$	$R_{(c)}$	$R_{(d)}{}^1$	J_{ab}	J_{ac}	J_{bc}	J_{bd}
a	H	H	2.2		2.4		4.91	8.18	8.18	8.18	7.0	7.0	—	—
b	CH_3	CH_3	2.1		2.4		5.54	7.46	8.87	9.20	10.0	—	6.5	6.5
c	H	C_6H_5	2.4		2.7		4.88	6.25	6.72	2.80	4.5	11.0	14.5	—

pyridinium derivative completed by warming the acid solution. These experiments were run on a small scale without isolation of the products since the electrolytic oxidation method seemed to give the better products. However, the authenticity of the pyridinium derivatives formed was ascertained by chromatography and UV measurements on the reaction mixture. The pyridinium derivatives (VII) absorb at 295 and 325 mμ in HCl aq and NaOH aq, respectively, and are blue fluorescent in UV light.

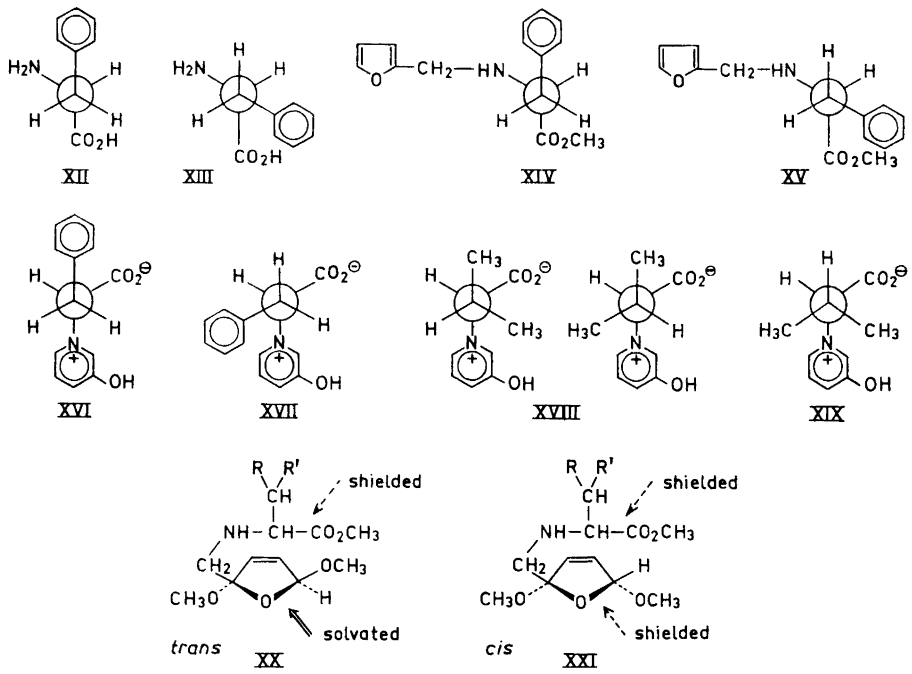
The desired product (VII) was isolated from the reaction mixture by phenol extraction at pH 3.5 and was further purified by passage of an aqueous solution through a DEAE-Sephadex column from which the pyridinium acid was eluted with aqueous formic acid.

The suggested mechanism for the formation of pyridinium derivatives from oxidized furfurylamines is shown above. First the cyclic ether oxygen is protonated. The amino acid nitrogen, in a position to form a five-membered ring, then attacks the electrophilic C-5 carbon (VIII) resulting in breakage of the cyclic carbon-oxygen bond and formation of a six-membered ring (IX). In the isomer with the 5-methoxy group *cis* to the amino function competition between this mechanism and water-induced opening of the ring could very well occur due to steric repulsion between the methoxy group and the approaching amino group. The open intermediate (X) then must recyclise to a pyridine (XI).

The NMR spectra of the Schiff bases (Table 1) are as expected. In the spectra of the furfurylamines (Table 2) the nonequivalence of the furfurylmethylene protons ($H_{e-e'}$) can be seen. But in the spectra recorded at 60 Mc the chemical shifts are so close that the satellite tops are very weak. The nonequivalent methylene protons (H_{b-c}) in the phenylalanine moiety have very similar chemical shifts, so that they appear as a broad doublet due to the coupling with the vicinal methine proton. The two methyl groups in the valine derivative also have about the same chemical shifts and therefore appear as a doublet. However, the parent amino acids have the expected ABX system which is also found in the quaternary derivatives (Table 3). In our previous paper,[1] we have tried to explain such findings by conformational preferences. The Newman projections are shown below.

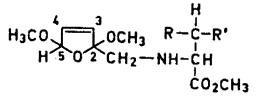
The two largest groups in phenylalanine must be the phenyl group and the carboxyl group. The molecule should therefore prefer a conformation in which these groups are *anti* (XII) instead of a *gauche* conformation (XIII). In the furfurylamine the furan ring is three bond lengths away from the vicinal α-carbon and therefore not so space demanding. If this part of the molecule is assumed to exert a similar sterical repulsion as the carbomethoxy group on the substituents on the β-carbon no special conformation is preferred (XIV, XV). The chemical shifts of the methylene protons therefore become nearly the same. In the quaternary structure, however, the two aromatic rings on the vicinal carbons, being the largest groups, will assume an *anti* conformation (XVI) rather than *gauche* (XVII). In the valine derivative the two conformations XVIII should be preferred rather than XIX.

The methoxy groups in the methoxylated product (VI) can be either *cis* or *trans* with respect to each other. The NMR spectra are complex due to extensive overlapping of the signals. The C-5 methine protons appear in



broad singlets at 4.4 and 4.6 τ and are therefore weakly coupled to the vinyl protons. The proton at the lower field can be ascribed to the *trans* isomer because of paramagnetic shielding from the 2-methoxy group located 1,3 and *cis* to this methine proton.[7,8] The signal intensities of both these protons are the same. Therefore the *cis* and *trans* isomers are formed in equal amounts. The methoxy groups are found as closely spaced doublets around 6.6 and 6.9 τ. The signals from the methoxy groups in both *cis* and *trans* 2,5-dimethoxy-2,5-dihydrofuran appear at 6.67 τ.[8] Therefore the lower field absorption can be ascribed to the 5-methoxy group in both the *cis* and *trans* isomers in agreement with the expected shielding effect on the 2-methoxy group from the side-chain in the 2-position. In hexadeuterobenzene the signals from the vinyl protons are spread out from the same low field as in carbon tetrachloride towards a higher field (Table 4). The low field C-5 methine proton is also shifted upfield while the other C-5 proton signal is not affected. This is best explained by assuming that the substituted aminomethylene group exerts a larger shielding effect, by virtue of its size, than a methoxy group to solvation of the furan ring by benzene molecules. The furan ring in the *cis* isomer (XXI), therefore, is more effectively shielded towards solvation than the *trans* isomer (XX) in which the diamagnetic shielding effect of the benzene molecule causes an upfield shift.

Table 4. NMR data in CCl_4 and C_6H_6-d_6.



Substituents		Chemical shift in τ values							
		CCl_4					C_6H_6-d_6		
R	R^1	$H_{(5)}$ *trans*	$H_{(5)}$ *cis*	$H_{(3)}-H_{(4)}$	$OCH_{3(5)}$	$OCH_{3(2)}$	$H_{(5)}$ *trans*	$H_{(5)}$ *cis*	$H_{(3)}-H_{(4)}$
H	H	4.35	4.64	3.8—4.1	6.6	7.0	4.45	4.67	3.8—4.3
CH_3	CH_3	4.35	4.64	3.8—4.1	6.6	7.0	4.45	4.67	3.8—4.3
H	C_6H_5	4.40	4.80	4.0—4.3	6.6	7.0	4.51	4.82	3.9—4.4

EXPERIMENTAL

Paper chromatography or TLC in silica gel in the systems BuOH:EtOH:NH:H_2O (4:1:2:1) and BuOH:HOAc:H_2O (100:22:50) have been used in this work. The NMR spectra were recorded on a Varian A-60A spectrophotometer and the UV-data on a Perkin-Elmer model 137 UV spectrophotometer.

N-Furfurylidine-amino acid methyl esters (III). Freshly distilled furfural (0.22 mole) was added dropwise to a stirred mixture of the amino acid methyl ester and anhydrous sodium sulphate (7.0 g) in a nitrogen atmosphere. The rate of furfural addition was such that the temperature did not rise above 40°. After 2 h the reaction mixture was heated to 60° and stirred at this temperature under nitrogen atmosphere for 10 h. The sodium sulphate was then filtered off and the filtrate fractionally distilled to give the title compounds as colourless liquids.

Table 5.

Substituents		B.p. °C/mm Hg	Yield %	Molecular formula	Found			Calc.		
R	R'				C	H	N	C	H	N
H	H	87–88°/0.4	67	$C_9H_{11}NO_3$	59.45	6.20	7.50	59.65	6.12	7.73
CH_3	CH_3	82–83°/0.1	82	$C_{11}H_{15}NO_3$	63.39	7.27	7.00	63.16	7.23	6.69
H	C_6H_5	136–38°/0.01	66	$C_{15}H_{15}NO_3$	70.08	5.77	5.39	70.01	5.87	5.44

N-Furfurylamino acid methyl esters (IV). a) The amino acid methyl ester hydrochloride (0.05 mole) was dissolved in methanol (150 ml), the pH adjusted to 8 by addition of alcoholic sodium hydroxide, the precipitated sodium chloride filtered off, furfural (4.8 g, 0.05 mole) and 5 % palladium on charcoal (10 g) added to the filtrate and the mixture hydrogenated at atmospheric pressure until the hydrogen uptake had ceased. The catalyst was then removed by filtration through a bed of Celite 535, the filtrate evaporated, the residual oil dissolved in ether (100 ml), the ether washed with saturated aqueous $NaHSO_3$ to remove any furfural, the ether dried and evaporated. This material was pure enough for further work. The yields were of the order 40–60 %.

Table 6.

Substituents		B.p. °C/mm Hg	Yield %	Molecular formula	Found			Calc.		
R	R'				C	H	N	C	H	N
H	H	62–64/0.15	21	$C_9H_{13}NO_3$	58.76	7.07	7.69	58.99	7.15	7.64
CH_3	CH_3	66–67/0.2	66	$C_{11}H_{17}NO_3$	62.86	8.04	6.80	62.55	8.11	6.63
H	C_6H_5	138–40/0.2	43	$C_{15}H_{17}NO_3$	68.99	6.56	5.61	69.47	6.61	5.40

b) *N*-Furfurylidene-amino acid methyl ester (0.05 mole) was hydrogenated over 5 % Pd/C in methanol (150 ml), and the reaction mixture worked up as above.

c) *N*-Furfurylidene-amino acid methyl ester (0.10 mole) was added dropwise over 10 min to a stirred ice-cold solution of sodium borohydride (0.075 mole) in methanol (150 ml). The reaction was stopped after 4 h, the excess hydride destroyed by slow addition of acetone (30 ml), the solution evaporated, the residue extracted with carbon tetrachloride (3 × 50 ml), the organic extracts washed with water (3 × 15 ml), dried over sodium sulphate, the solvent evaporated and the residue distilled.

N-*Tetrahydrofurfurylamino acid methyl esters (V).* The *N*-furfurylidene-amino acid methyl ester (0.05 mole) dissolved in methanol (150 ml) was hydrogenated over 5 % Pd/C (10 g) at 3.5 atm. until the hydrogen uptake had ceased. The catalyst was then removed by filtration through Celite 535, the filtrate evaporated and the residual oil fractionally distilled to give a colourless liquid.

Table 7.

Substituents		B.p. °C/mm Hg	Yield %	Molecular formula	Found			Calc.		
R	R′				C	H	N	C	H	N
H	H	68–70/0.2	55	$C_9H_{17}NO_3$	57.17	8.97	7.50	57.75	9.15	7.48
CH_3	CH_3	76–77/0.15	40	$C_{11}H_{21}NO_3$	61.53	9.75	6.60	61.37	9.83	6.50
H	C_6H_5	137–39/0.35	45	$C_{15}H_{21}NO_3$	68.05	7.91	5.33	68.41	8.04	5.32

N-*(2,5-Dimethoxy-2,5-dihydrofurfuryl)amino acid methyl esters (VI).* Ammonium bromide (5.0 g) was dissolved in methanol (260 ml), the furfurylamino acid ester (0.05 mole) added, the solution cooled to −30° and electrolyzed at this temperature using 4 A. The theoretical number of coulombs were used. Methanolic sodium methoxide (20 ml, from 1.2 g of sodium) was then added, the reaction mixture evaporated, the residue extracted with ether (150 ml), the ether solution washed with water (2 × 15 ml), dried and evaporated. The residual oil was then distilled or used as such in the next step. The yield of crude product was of the order 60–80 %.

Table 8.

Substituents		B.p. °C/mm Hg	Yield %	Molecular formula	Found			Calc.		
R	R′				C	H	N	C	H	N
H	H	96–98/0.35	29	$C_{11}H_{15}NO_5$	54.01	8.00	5.58	53.86	7.81	5.71
CH_3	CH_3	100–102/0.2	55	$C_{13}H_{23}NO_5$	57.28	8.21	5.17	57.12	8.48	5.12
H	C_6H_5	164–66/0.15	37	$C_{17}H_{23}NO_5$	63.36	7.40	4.25	63.53	7.21	4.36

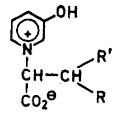
2-(3-Hydroxypyridinium)propionates (VII). a) The above esters (VI, 0.0075 mole) in 2 N HCl (25 ml) were heated to boiling in a nitrogen atmosphere. The heating was stopped after 50 min when the solution had become yellowish in colour. If an inert nitrogen atmosphere is not used the reaction mixture becomes very darkly coloured and the yield is decreased.

The cold solution was extracted with ether (2 × 10 ml), the pH of the aqueous solution adjusted to 3.5 with 5 N NaOH, extracted with aqueous phenol (3 × 15 ml), the phenol extracts washed with water (2 × 10 ml), ether (135 ml) added, the separated aqueous phase collected, the phenol-ether layer washed with water (2 × 25 ml), the combined aqueous extracts washed with ether to remove any phenol and the solution chromatographed on a DEAE-Sephadex A-25 column in the amine form. Elution with water removed any decarboxylated material. The desired material was eluted with 0.02 N formic acid and was isolated by freeze-drying.

Table 9.

Substituents		M.p. °C	Solvent for recrystallisation	Yield %	Molecular formula	Found			Calc.		
R	R′					C	H	N	C	H	N
H	H	156–57	MeOH/Ether	36	$C_8H_9NO_3$	56.96	5.55	8.20	57.49	5.43	8.38
CH_3	CH_3	158–59	iPrOH/Ether	68	$C_{10}H_{13}NO_3$	60.84	6.64	7.19	61.54	6.71	7.17
H	C_6H_5	141–42	MeOH/Acetone	70	$C_{14}H_{13}NO_3$	68.95	5.40	7.74	69.13	3.38	5.75

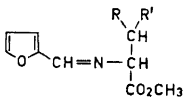
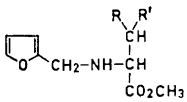
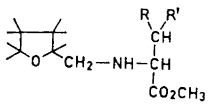
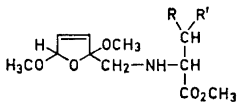
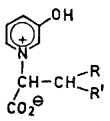
Table 10. UV absorption.



Comp.	Substituents		N HCl aq.		N NaOH aq.			
VII	R	R′	λ	log ε	λ	log ε	λ	log ε
a	H	H	295	3.48	325	3.72	250	3.88
b	CH_3	CH_3	295	3.72	325	3.67	250	3.92
c	H	C_6H_5	295	3.61	325	3.60	250	3.85

b) Aqueous sodium hypochlorite (0.8 ml, 10 %) was added dropwise to *N*-furfuryl-amino acid methyl ester (10^{-3} mole) dissolved in N HCl (2 ml) at 0°. 6 N HCl (5 ml) was added after 50 min and the solution heated under reflux for 45 min. Chromatography and UV spectra of the reaction mixture showed that the title compound was formed, but in lower yield than under procedure a).

Table 11. Optical rotations measured at 25°.

Formulae	R	R′	$[\alpha]_D$	$[\alpha]_{546}$	g/100 ml	Solvent
	H	H	−17.6	−18.7	1.2	$CHCl_3$
	CH_3	CH_3	−116	−142	1.0	»
	H	C_6H_5	−53.1	−63.8	1.0	»
	H	H	− 6.0	− 6.8	1.0	»
	CH_3	CH_3	−31.7	−34.6	0.9	»
	H	C_6H_5	−17.3	−16.1	0.9	»
	H	H	− 1.9	− 1.4	0.9	»
	CH_3	CH_3	− 9.1	−10.2	1.1	»
	H	C_6H_5	+0.7	+1.3	1.0	»
	H	H	− 2.5	− 2.9	1.7	»
	CH_3	CH_3	− 5.6	− 5.8	1.5	»
	H	C_6H_5	− 1.0	− 1.0	1.1	»
	H	H	+5.0	+4.7	0.7	0.1 N HCl
	CH_3	CH_3	+10.7	+11.2	0.8	»
	H	C_6H_5	−81.6	−89.6	0.4	»

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