2(3H)- AND 2(5H)-FURANONES. III.[1]

AN EFFICIENT SYNTHESIS AND THE ESCHENMOSER-MANNICH REACTION OF N-SUBSTITUTED 4-AMINO-2(5H)-FURANONES

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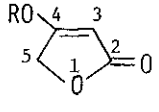
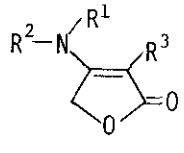
Abstract- A series of N-substituted 4-amino-2(5H)-furanones (II) was derived from β-tetronic acid (I) by direct action of several aliphatic and aromatic amines. The Eschenmoser-Mannich reaction of II readily gave the corresponding Mannich bases (VI) quantitatively.

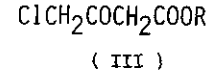
The Mannich reaction of dihydro-2(3H)-furanones serves as a tool for the α-methylenation of γ-lactones.[2] However, no example of the Mannich reaction involving 4-hydroxy- or 4-alkoxy-2(5H)-furanones (I) is known to date,[3] much less any device for the α-homologation of 2(5H)-furanones despite their wide use for the preparation of biologically active substances or as a building block for heterocyclic compounds.[4] The only example of the Mannich-fashioned homologation at C_3 of the 4-oxyganated system is the reaction between β-tetronic acid (I; R=H) and dimethylformamide diethyl acetal.[3d] The reaction involving 4-amino-2(5H)-furanone, a nitrogenous congener of I, has not been examined either to date. In the study to examine the reactivity of a series of β-tetronic acid congeners, we have investigated the Eschenmoser-Mannich reaction of N-substituted 4-amino-2(5H)-furanones (II) which can be readily derived from I (R=H).



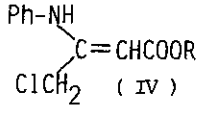
(I) R=H, Me, Bn



(II) R^3=H
(VI) R^3=CH_2NMe_2



(III)



(IV)

4-Amino-2(5H)-furanones (II) have been prepared from 4-methoxy-2(5H)-furanone (I; R=Me) via the initial addition of several aliphatic amines to I (R=Me), but the method has been found unsuccessful with aromatic amines.[5] On the other hand, Gelin and Pollet[6] reported that phenyl- and benzylhydrazines failed to react with methyl β-tetronate (I; R=Me) but reacted smoothly with I (R=H) to give 4-hydrazino compounds.

We conducted the direct condensation of I (R=H) with a variety of aliphatic and aromatic amines and obtained the corresponding enamines (II) in good yield as shown in Table I.

Table I. N-SUBSTITUTED 4-AMINO-2(5H)-FURANONES

Compound (II)	Yield (%)	mp (°C)	(recrystallizatn. solvent)	Exact Mass Found	Exact Mass Calcd.	
R^1=R^2=tetramethylene[a]	93	121-123	(benzene)	153.0792;	153.0789	for $C_8H_{11}O_2N$
R^1=R^2=pentamethylene[b]	66.5	103-105	(benzene)	167.0954;	167.0947	for $C_9H_{13}O_2N$
R^1=R^2=Me	78	84-85	(benzene)	127.0624;	127.0633	for $C_6H_9O_2N$
R^1=H, R^2=Me[c]	78	180-182	(ethanol)	113.0447;	113.0477	for $C_5H_7O_2N$
R^1=H, R^2=Ph[d]	80	220-222	(ethanol)	175.0624;	175.0633	for $C_{10}H_9O_2N$
R^1=Me, R^2=Ph	84	107-108	(benzene)	189.0782;	189.0789	for $C_{11}H_{11}O_2N$
R^1=H, R^2=benzyl (Bn)[e]	83	152-154	(ethanol)	189.0794;	189.0789	for $C_{11}H_{11}O_2N$

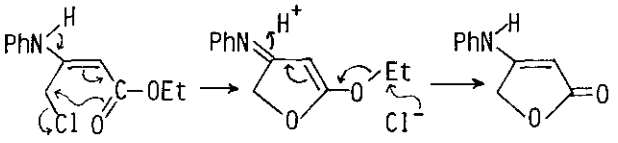
a) Lit.,[5] yield 72%, mp 83-85°C.
b) Lit.,[6] yield 65%, mp 85-88°C.
c) Lit.,[6] yield 85%, mp 180-182°C.
d) Lit.,[7] mp 220°C; lit.,[8] yield 86.9%, mp 222-223°C; lit.,[9] mp 218°C.
e) Lit.,[6] yield 60%, mp 137-139°C.

The 4-anilino compound (II, R^1=H, R^2=Ph) was obtained with no practical difficulty as was described by Wolff and Schimpff.[7] Boosen[8] reported the ready formation of II (R^1=H, R^2=Ph) from γ-chloroacetoacetic esters (III) and aniline and mentioned that in the reaction course a possibility of initial formation of tetronic acid (I; R=H) and subsequent condensation with aniline into II (R^1=H, R^2=Ph) could not be excluded, while Böhme[9] characterized the intermediate β-anilino-γ-chlorocrotonate (IV) in the same reaction.

We conducted the reaction of N-methylaniline with ethyl γ-chloroacetoacetate and obtained no trace amount of N-methylanilino compound (II; R^1=Me, R^2=Ph), the result suggesting the absence of the initial formation of I (R=H) in the reaction, because the direct condensation of N-methylaniline with I (R=H) gave smoothly the desired enamine II (R^1=Me, R^2=Ph) in good yield.

The difference between the reaction of III with aniline and that with N-methylaniline would be explained in terms of the participation of a phenylimino intermediate (V) in the transition of the former, and the mechanism of the lactonization would be postulated as illustrated in the following. The formation of the intermediary ketene acetal could be facilitated and stabilized by the conjugated phenylimino

group. The reaction of monoalkylamines with III also gave II (R^1=H) though in low yield, and the N-H in II (R^1=H) was readily methylated with methyl iodide without any methylation at C_3.



(IV) (V) (II)

One of the spectroscopic feature of II is a marked upfield shift of the proton or carbon resonance for position 3 in nmr spectra as compared with that of I as summarized in Table II. The improved reactivity of this position was found to be well associated with this feature as evidenced by the following electrophilic substitution discussed below.

Table II. NMR DATA FOR POSITION 3 IN 4-OXYGENATED AND 4-NITROGENATED 2(5H)-FURANONES

Compound	C_3-Proton (δ; ppm)	C_3-Carbon (δ; ppm)	Solvent
I; R=H[a)]	5.20	89.8	DMSO-d_6
I; R=Bn[b)]	4.90	87.6	$CDCl_3$
I; R=Me[c)]	5.11	88.7	$CDCl_3$
II; R^1=R^2=tetramethylene	4.55	80.1	$CDCl_3$
II; R^1=R^2=pentamethylene	4.60	80.9	$CDCl_3$
II; R^1=R^2=Me	4.57	80.7	$CDCl_3$
II; R^1=H, R^2=Me	4.48	78.2	DMSO-d_6
II; R^1=H, R^2=Ph	5.25[d)]	83.7	DMSO-d_6
II; R^1=Me, R^2=Ph	4.80	84.2	$CDCl_3$
II; R^1=H, R^2=Bn	4.56	79.3	DMSO-d_6

a) Prepared from ethyl acetoacetate according to our 'one pot'-fashioned procedure[1] with partial modification: ether was added as a Lewis base on the bromination.

b) Prepared from I (R=H) according to the method described by Pollet and Gelin.[10] A partial modification by use of a Soxhlet apparatus packed with anhydrous $MgSO_4$, instead of a Dean-Stark water separator, resulted in marked improvement of the yield and notable reduction of the reaction period (11h vs. 80h).

c) Prepared from I (R=H) according to the method described by Gelin and Pollet.[11]

d) The exceptional downfield shift is due to the delocalization of enamino electrons resulting the conjugation of the furanone with the phenyl across the less crowded nitrogen.

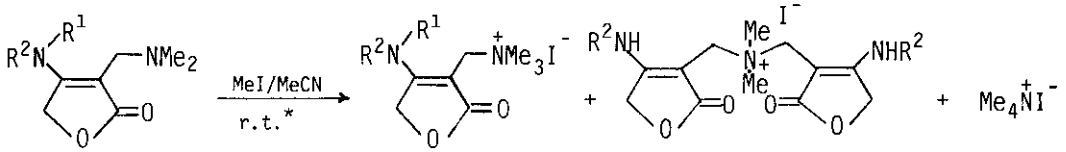
The enamines (II) reacted smoothly with Eschenmoser's salt under mild conditions to give hydriodides of the corresponding Mannich bases (VI) quantitatively as summarized in Table III.

Table III. MANNICH BASES (VI) FROM II

Compound	Yield (%)*	mp (°C)	Exact Mass Found	Exact Mass Calcd.
R^1=R^2=tetramethylene	quant.	64-65	210.1355	210.1368 for $C_{11}H_{18}N_2O_2$
R^1=R^2=pentamethylene	89.0	105-106	224.1519	224.1525 for $C_{12}H_{20}N_2O_2$
R^1=R^2=Me	quant.	113-115	184.1215	184.1212 for $C_9H_{16}N_2O_2$
R^1=H, R^2=Me	quant.	38-42	170.1050	170.1055 for $C_8H_{14}N_2O_2$
R^1=H, R^2=Ph	98.5	(oil)	232.1199	232.1211 for $C_{13}H_{16}N_2O_2$
R^1=Me, R^2=Ph	92.3	(oil)	246.1346	246.1368 for $C_{14}H_{18}N_2O_2$
R^1=H, R^2=Bn	93.8	(oil)	246.1347	246.1368 for $C_{14}H_{18}N_2O_2$

*) quant. : quantitative

The Mannich bases (VI) from N,N-disubstituted 4-amino-2(5H)-furanones reacted with methyl iodide to give the corresponding quaternary salts. On the other hand, N-monosubstituted Mannich bases (VI; R^1=H) gave a mixture of normal quaternary salts, intermolecular quaternary salts (VII), and tetramethylammonium iodide.



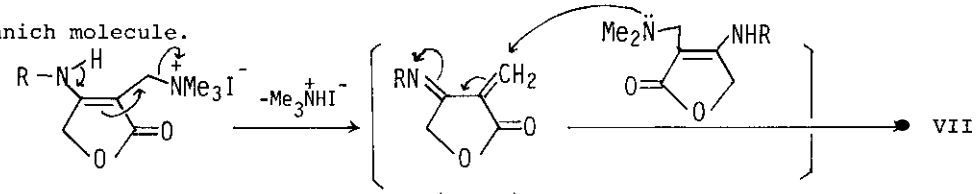
(VI) (VII)

* r.t.: room temperature

When the reaction temperature for quaternization was kept at -8∿-10°C, no intermolecular quaternary salt was obtained from VI (R^1=H) exclusive of the N-phenyl system, but the normal quaternary salt was the only product.

In the case of the 4-anilinofuranone (VI, R^2=Ph), however, the mixture was again obtained as a glassy solid even under the condition at -8∿-10°C.

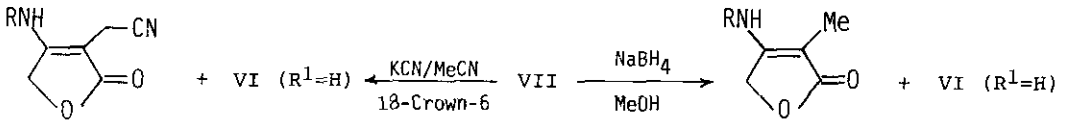
In the initial stage of investigation, we assumed that the normal quaternary salt from N-monosubstituted furanones (VI, R^1=H) could be transformed into a 4-imino-3-methylenefuranone (VIII). The furanone (VIII), however, failed to be isolated nor characterized because of its instability. The furanone (VIII) is presumed to be transformed immediately into the twin furanone ammonium (VII) by action of another Mannich molecule.



R=Me, Bn, Ph (VIII)

The extra ease of formation of the twin furanone ammonium (VII, R^2=Ph) from 4-anilinofuranone Mannich base (VI; R^1=H, R^2=Ph) can be rationalized in terms of the facilitation in formation of and the stabilization of the transient 4-phenyliminofuranone system by conjugation of the phenyl with the ene-imine system.

The structure of the twin furanone ammoniums was evidenced by the fact that the sodium borohydride reduction or cyanation with potassium cyanide of the salts gave a mixture of the starting Mannich base and the corresponding α-methyl- (IX) or α-cyanomethyl-furanone (X) while the same treatment of the normal ammoniums gave no Mannich amines.



(X)
R=Me, Bn, Ph

(IX)
R=Me, Bn, Ph

In the cyanation of the 4-anilinofuranone compound (VII, R^2=Ph), the resulting Mannich base (VI; R^1=H, R^2=Ph) itself also suffered from cyanation possibly *via* intermediate VIII, and thus the nitrile (X) was the only product, the situation being evidenced by the independent cyanation of VI (R^1=H, R^2=Ph) where the nitrile (X, R=Ph) and bis[4-anilino-2(5H)-furanon-3-yl]methane were isolated.[12]

EXPERIMENTAL

Mps were determined on a Yanaco hot-stage melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Shimadzu IR-435 grating IR spectrometer, and nuclear magnetic resonance (nmr) spectra were recorded at 200 MHz (JEOL JNM-FX 200 spectrometer) and 50 MHz with tetramethylsilane or sodium 4,4-dimethyl-4-sila-1-pentanesulfonate as an internal standard. High-resolution mass (ms) spectra were recorded on a JEOL JMS-HX 100 spectrometer. Preparative thin-layer chromatography (PTLC) was performed on Merck kieselgel 60 F_{254}.

General Procedure for the Preparation of N-Substituted 4-Amino-2(5H)-furanones (II)

a) From β-tetronic acid (I, R=H): Amine (10 mmol) was added to a solution of I (0.2 g, 2 mmol) in glacial acetic acid (5 ml), and the resulting mixture was heated at 115-120° for 3 hr and followed by azeotropic distillation by adding dry benzene dropwise to the reaction mixture at 115-120°C. After additional heating for 2 h, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in

chloroform (100 ml), and to the solution was added anhydrous potassium carbonate (5 g). The resulting suspension was stirred until any acid was completely consumed. On filtration of the suspension and subsequent evaporation of the filtrate was obtained the aminofuranone (II).

4-Dimethylamino-2(5H)-furanone (II, R^1=R^2=Me): Dimethylamine hydrochloride (10 mmol) and anhydrous potassium acetate (10 mmol) were used in place of the free amine described in the general procedure. Ir ν_{max}^{KBr} cm^{-1}: 1800(m), 1712(s), 1610(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.94(6H, s, NMe_2), 4.57(1H, s, C_3-H), 4.70(2H, s, C_5-H). ^{13}C-Nmr($CDCl_3$, 60°C)[13] δ: 39.4(q), 66.9(t), 81.1(d), 169.3(s), 175.3(s). Ms m/z(%): 128(M^++1, 8.4), 127(M^+, 100), 126(4.0), 99(7.5), 98(8.4), 70(16.6), 69(26.2).

4-Methylamino-2(5H)-furanone (II; R^1=H, R^2=Me): Methylamine hydrochloride (10 mmol) and anhydrous potassium acetate (10 mmol) were used in place of the free amine described in the general procedure. Ir ν_{max}^{KBr} cm^{-1}: 3260, 1775(m), 1700(s), 1600(s). ^{1}H-Nmr(DMSO-d_6, 50°C) δ: 2.71(3H, d, J=5 Hz, NMe), 4.48(1H, s, C_3-H), 4.59(2H, s, C_5-H), 7.26(1H, NH, exchangeable with D_2O). ^{13}C-Nmr(DMSO-d_6, 50°C) δ: 30.5(q), 66.6(t), 78.2(d), 169.7(s), 174.6(s). Ms m/z(%): 114(M^++1, 7.4), 113(M^+, 100), 112(10.3), 85(9.2), 84(13.4), 55(27.8).

4-Pyrrolidino-2(5H)-furanone (II, R^1=R^2=tetramethylene):
Ir ν_{max}^{KBr} cm^{-1}: 1770(m), 1715(s), 1608(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.04(4H, t-like, J=7 Hz, N-C-CH_2), 3.30(4H, t-like, J=7 Hz, N-CH_2-C), 4.55(1H, s, C_3-H), 4.70(2H, s, C_5-H). ^{13}C-Nmr($CDCl_3$, 25°C)[13] δ: 24.7 & 25.5(each t), 47.2 & 49.1(each t), 66.9(t), 80.1(d), 166.1(s), 175.5(s). Ms m/z(%): 154(M^++1, 10.7), 153(M^+, 100), 152(17.9), 125(8.6), 96(10.4), 95(17.3).

4-Piperidino-2(5H)-furanone (II, R^1=R^2=pentamethylene):
Ir ν_{max}^{KBr} cm^{-1}: 1788(m), 1705(s), 1600(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.67(6H, m, N-C-CH_2-CH_2CH_2), 3.18(4H, m, NCH_2), 4.60(1H, s, C_3-H), 4.69(2H, s, C_5-H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 23.6(t), 25.1(t), 48.2(t), 66.9(t), 80.9(d), 168.1(s), 175.6(s).
Ms m/z(%): 168(M^++1, 12.3), 167(M^+, 100), 166(31.8), 138(15.9), 109(22.7), 83(23.3), 55(19.3), 41(24.5).

4-Benzylamino-2(5H)-furanone (II; R^1=H, R^2=Bn): Insoluble in chloroform.[14]
Ir ν_{max}^{KBr} cm^{-1}: 3210, 1780(m), 1699(s), 1605(s). ^{1}H-Nmr(DMSO-d_6, 50°C) δ: 4.26(2H, d, J=5.9 Hz, $PhCH_2$), 4.56(1H, s, C_3-H), 4.64(2H, s, C_5-H), 7.30(5H, s, Ph), 7.82(1H, NH, exchangeable with D_2O). ^{13}C-Nmr(DMSO-d_6, 50°C) δ: 47.7(t), 67.0(t), 79.3(d), 127.2(d), 127.4(d), 128.5(d), 137.6(s), 168.9(s), 175.1(s). Ms m/z(%): 190(M^++1, 14.0), 189(M^+, 98.0), 145(3.0), 113(10.6), 92(10.2), 91(100).

4-(N-Methylanilino)-2(5H)-furanone (II; R^1=Me, R^2=Ph): The excess N-methylaniline was removed in the last stage of work-up by washing the chloroform solution of the product with 5% hydrochloric acid (3 ml × 3) and with water (3 ml).
Ir ν_{max}^{KBr} cm^{-1}: 1772(m), 1715(s), 1575(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 3.30(3H, s, NMe), 4.55(2H, s, C_5-H), 4.79(1H, s, C_3-H), 7.12-7.24(2H, m, aromatic H), 7.26-7.45(3H, m, aromatic H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 40.9(q), 67.5(t), 84.2(d), 125.3(d), 127.8(d), 130.1(d), 144.0(s). Ms m/z(%): 190(M^++1, 13.7), 189(M^+, 100), 188(2.8), 144(15.5), 132(16.5), 131(5.7), 82(18.4).

4-Anilino-2(5H)-furanone (II; R^1=H, R^2=Ph): Insoluble in chloroform.[14]
Ir ν_{max}^{KBr} cm^{-1}: 3250, 3200, 3120, 3080, 1800(w), 1685(s), 1580(s). ^{1}H-Nmr(DMSO-d_6, 50°C) δ: 4.84(2H, s, C_5-H), 5.25(1H, s, C_3-H), 7.07(1H, t, J=7 Hz, aromatic C_p-H), 7.18(2H, d, J=7 Hz, aromatic C_o-H), 7.36(2H, t, J=7 Hz, aromatic C_m-H), 9.58(1H, NH, exchangeable with D_2O). ^{13}C-Nmr(DMSO-d_6, 50°C) δ: 68.0(t), 83.7(d), 118.7(d), 123.0(d), 129.4(d), 140.2(s), 162.9(s), 174.7(s). Ms m/z(%): 176(M^++1, 13.6), 175(M^+, 100), 174(6.8), 146(6.0), 144(6.8), 130(7.0), 118(18.5), 117(8.0).

b) From ethyl γ-chloroacetoacetate (III): Amine (33 mmol) and glacial acetic acid (6 mmol) were added to a solution of III (5 g, 30 mmol) in dry benzene (40 ml), and the resulting mixture was heated under reflux for 5 h by use of a Soxhlet apparatus packed with anhydrous magnesium sulfate and dry benzene (50 ml). After cooling, the solid deposited was collected, washed with benzene and triturated with ethanol to give II.

4-Methylamino-2(5H)-furanone (II; R^1=H, R^2=Me): Methanolic methylamine was used as a starting material, and the product was washed with water in the final stage of work-up. Yield: 40%.

4-Benzylamino-2(5H)-furanone (II; R^1=H, R^2=Bn): Yield: 49%.

4-Anilino-2(5H)-furanone (II; R^1=H, R^2=Ph): Yield: 79%.

c) From N-monosubstituted 4-amino-2(5H)-furanones (II, R^1=H): A suspension consisting of II (R^2=Me: 4.3 mmol, R^2=Bn: 2.6 mmol, R^2=Ph: 2.9 mmol), anhydrous potassium carbonate (5 g), methyl iodide (10 ml), DME (8 ml), and acetone (15 ml) was stirred at room temperature for 3 days. After removal of the inorganic material by filtration, the filtrate was evaporated, and the resulting residue was taken in chloroform (50 ml). The chloroform layer was evaporated to give the corresponding N,N-disubstituted 4-amino-2(5H)-furanone (II, R^1=Me).

4-Dimethylamino-2(5H)-furanone (II, R^1=R^2=Me): Yield: 62%.

4-(N-Methylanilino)-2(5H)-furanone (II; R^1=Me, R^2=Ph): Yield: 97%.

4-(N-Methylbenzylamino)-2(5H)-furanone (II, R^1=Me, R^2=Bn): Yield: quantitative. Mp 87.5-88°C (colorless prisms from ether/benzene). Ir ν_{max}^{KBr} cm^{-1}: 1784(m), 1715(s), 1590(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ:2.89(3H, s), 4.32(2H, s), 4.67(1H, s), 4.73(2H, s), 7.10-7.36(5H, m). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 37.6(q, non-sharp), 55.8(t, non-sharp), 66.9(t), 81.6(d), 126.8(d), 127.9(d), 128.9(d), 135.1(s), 168.9(s), 175.1(s). Ms m/z(%): 204(M^++1, 8.0), 203(M^+, 53.8), 202(M^+-1, 13.0), 92(9.9), 65(8.1). Exact Mass: Calcd for $C_{12}H_{13}NO_2$: 203.0946; Found: 203.0923.

General Procedure for the Eschenmoser-Mannich Reaction of 4-Amino-2(5H)-furanones (II): Finely ground Eschenmoser's salt (0.85 mmol) was added to a mixture of II (0.6 mmol) and dry dimethoxyethane (DME, 5 ml), and the resulting suspension was stirred at room temperature for 3 h. The solvent was removed by decantation, and the deposited hydriodide of Mannich base was washed with dry ether. The hydriodic salt was dissolved in a saturated potassium carbonate solution, and the solution was extracted with methylene chloride (10 ml × 5). The extract was dried over anhydrous sodium sulfate and evaporated to give free Mannich base (VI).

3-(N,N-Dimethylaminomethyl)-4-pyrrolidino-2(5H)-furanone (VI, R^1=R^2=tetramethylene): Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 2810, 2770, 1720(s), 1605(s), 1459, 1361, 1338, 1062, 1039, 1000. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.99(4H, t-like, J=7 Hz, C_4-N-C-CH_2), 2.20(6H, s, NMe_2), 3.08 (2H, s, NCH_2-C_3), 3.28-3.80(4H, m, C_4-NCH_2), 4.57(2H, s, C_5-H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 25.1(t), 44.6(q), 48.2(t), 51.4(t, N$\underline{C}H_2$-C_3), 65.9(t), 89.5(s), 162.8(s), 176.7(s). Ms m/z(%): 211(M^++1, 1.7), 210(M^+, 52.8), 209(M^+-1, 1.2), 195(M^+-15, 23.9), 167(30.4), 166(M^+-44, 94.4), 165(100).

3-(N,N-Dimethylaminomethyl)-4-piperidino-2(5H)-furanone (VI, R^1=R^2=pentamethylene): Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 2810, 2770, 1719(s), 1600(s), 1460, 1440, 1340, 1320, 1270, 1062, 1040, 1002. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.52-1.74(6H, m, C_4-N-C-$CH_2CH_2CH_2$), 2.17(6H, s, NMe_2), 3.04(2H, s, NCH_2-C_3), 3.40-3.52(4H, m, C_4-NCH_2), 4.58(2H, s, C_5-H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 24.2(t), 26.2(t), 44.6(q), 49.1(t), 52.7(t, N$\underline{C}H_2$-C_3), 66.0(t), 89.8(s), 163.2(s), 177.1(s). Ms m/z(%): 225(M^++1, 2.9), 224(M^+, 20.5), 209(M^+-15, 20.1), 181(21.5), 180(100), 179(72.1), 136(18.3), 41(17.8).

4-Dimethylamino-3-(N,N-dimethylaminomethyl)-2(5H)-furanone (VI, R^1=R^2=Me): Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2770, 1720(s), 1618(s), 1450, 1410, 1340, 1061, 1040, 1000. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.20(6H, s, NMe), 3.06(2H, s, NCH_2), 3.16(6H, s, C_4-NMe), 4.58(2H, s, C_5-H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 40.1(q), 44.5(q), 52.1(t), 66.0(d), 90.2(s), 164.9(s), 176.8(s). Ms m/z(%): 185(M^++1, 2.6), 184(M^+, 21.1), 169(27.7), 141(27.2), 140(100), 139(22.4), 96(18.7), 86(19.1), 44(15.3).

3-(N,N-Dimethylaminomethyl)-4-(N-methylamino)-2(5H)-furanone (VI; R^1=H, R^2=Me):
Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3210(NH), 2810, 2770, 1725(s), 1639(s), 1410, 1361, 1330, 1060, 1002. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.16(6H, s, NMe), 2.87(3H, d, J=5 Hz, convertible to a singlet on treatment with D_2O, C_4-NMe), 3.13(2H, broad s, NCH_2-C_3), 4.64(2H, t, J=2 Hz, homoallylic coupling with NCH_2-C_3; C_5-H), 6.50(1H, broad signal, NH, exchangeable with D_2O). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 30.1(q, C_4-NCH_3), 45.1(q), 53.5(t), 64.6(t), 89.5(s), 166.4(s), 175.2(s). Ms m/z(%): 171(M^++1, 9.3), 170(M^+, 51.9), 169(3.9), 155(96.4), 140(46.8), 126(74.4), 72(50.7), 55(40.5), 44(100).

4-Anilino-3-(N,N-dimethylaminomethyl)-2(5H)-furanone (VI; R^1=H, R^2=Ph):
Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3190(NH), 2810, 2780, 1725(s), 1640(s), 1598(s), 1498, 1440, 1420, 1361, 1322, 1312, 1099, 1039, 1003. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.29(6H, s, NMe), 3.30(2H, broad s, NCH_2-C_3), 4.91(2H, t, J=1 Hz, C_5-H), 6.91(2H, dq, J=8, 1.5 Hz, aromatic C_o-H), 7.08(1H, tt, J=8, 1.5 Hz, aromatic C_p-H), 7.32(2H, tt, J=8, 1.5 Hz, aromatic C_m-H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 45.2(q), 54.2(t), 65.8(t), 93.4(s), 119.5(d), 124.1(d), 129.8(d), 139.3(s), 162.0(s), 173.9(s). Ms m/z(%): 233(M^++1, 3.9), 232(M^+, 23.9), 231(2.1), 187(40.0), 143(40.1), 140(31.2), 129(100), 128(22.9), 59(22.5), 45(38.8), 44(70.3).

3-(N,N-Dimethylaminomethyl)-4-(N-methylanilino)-2(5H)-furanone (VI; R^1=Me, R^2=Ph):
Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 2810, 2775, 1720(s), 1618(s), 1588(s), 1490, 1460, 1400, 1340, 1080, 1045, 1030, 1000. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.16(6H, s, NMe), 3.02(2H, s, NCH_2-C_3), 3.61(3H, s, C_4-NMe), 4.35(2H, s, C_5-H), 7.18-7.48(5H, m, aromatic H). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 41.5(q, C_4-NMe), 44.7(q), 51.7(t), 66.7(t), 93.0(s), 126.4(d), 127.9(d), 129.9(d), 144.9(s), 163.7(s), 176.7(s). Ms m/z(%): 247(M^++1, 10.1), 246(M^+, 47.8), 245(6.0), 232(17.6), 231(M^+-15, 100), 203(70.6), 202(93.8), 201(31.1).

4-(N-Benzylamino)-3-(N,N-dimethylaminomethyl)-2(5H)-furanone (VI: R^1=H, R^2=Bn):
Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3270(NH), 2810, 2775, 1725(s), 1640(s), 1450, 1360, 1322, 1059, 1003. ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.20(6H, s, NMe), 3.16(2H, s, NCH_2-C_3), 4.31(2H, broad s, convertible to a singlet on treatment with D_2O, $PhCH_2N$), 4.57(2H, s, C_5-H), 7.02-7.18(1H, exchangeable with D_2O, NH), 7.20-7.40(5H, m, Ph). ^{13}C-Nmr($CDCl_3$, 25°C) δ: 45.1(q), 47.6(t, $PhCH_2N$), 53.6(t, NCH_2-C_3), 64.7(t), 90.3(s), 126.6(d), 127.9(d), 129.0(d), 137.6(s), 165.6(s), 175.0(s). Ms m/z(%): 247(M^++1, 1.3), 246(M^+, 8.1), 202(12.3), 201(25.7), 158(8.2), 92(9.8), 91(100), 46(23.6), 45(11.4), 44(28.2).

Quaternization of the Mannich Bases (VI)

General Procedure for the Methylation of 4-(N,N-Disubstituted Amino)-3-(N,N-dimethylaminomethyl)-2(5H)-furanones: To a stirred solution of Mannich base (0.5 mmol) in acetonitrile (1 ml) was added methyl iodide (10 mmol), and the resulting mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the resulting residue was washed with dry ether to give the corresponding quaternary salt quantitatively.

Trimethyl[4-pyrrolidino-2(5H)-furanon-3-ylmethyl]ammonium Iodide :
Ir ν_{max}^{Nujol} cm^{-1}: 1720(s), 1600(s), 1272, 1212, 1121, 1062, 1045, 975, 915, 881, 781, 761, 719, 695. ^{1}H-Nmr(D_2O, 25°C) δ: 2.10(4H, m), 3.15(9H, s), 3.52(2H, m), 3.76(2H, m), 4.34(2H, s, $\overset{+}{N}CH_2$-C_3), 5.04(2H, s, C_5-H). ^{13}C-Nmr(D_2O, 25°C) δ:23.7(t), 25.1(t), 49.9(t), 52.1(q, $\overset{+}{N}$Me), 60.1(t, $\overset{+}{N}CH_2$), 67.9(t), 79.1(s), 167.8(s), 178.5(t).

Trimethyl[4-piperidino-2(5H)-furanon-3-ylmethyl]ammonium Iodide:
Ir ν_{max}^{Nujol} cm^{-1}: 1720(s), 1599(s), 1295, 1202, 1119, 1064, 1060, 1045, 1020, 1010, 979, 966, 864, 781, 695. ^{1}H-Nmr(D_2O, 50°C) δ: 1.70(6H, broad signal), 3.07(9H, s), 3.51(4H, broad signal), 4.34(2H, s), 5.02(2H, s). ^{13}C-Nmr(D_2O, 50°C) δ: 23.5(t), 26.0(t), 50.5(t), 53.0(q, $\overset{+}{N}$Me), 61.7(t, $\overset{+}{N}CH_2$), 68.9(t), 79.6(s), 168.7(s), 180.0(s).

[4-Dimethylamino-2(5H)-furanon-3-ylmethyl]trimethylammonium Iodide:
Ir ν_{max}^{Nujol} cm^{-1}: 1735(s), 1620(s), 1055, 970, 860, 700. ^{1}H-Nmr(D_2O, 25°C) δ: 3.08 (9H, s), 3.19(6H, s), 4.36(2H, s), 5.00(2H, s). ^{13}C-Nmr(D_2O, 25°C) δ: 41.9(q), 53.1(q, $\overset{+}{N}$Me), 61.3(t, $\overset{+}{N}CH_2$), 69.0(t), 80.5(s), 171.0(s), 179.8(s).

Trimethyl[4-(N-methylanilino)-2(5H)-furanon-3-ylmethyl]ammonium Iodide:
Ir ν_{max}^{Nujol} cm^{-1}: 1733(s), 1605(s), 1580(s), 1285, 1201, 1060, 878, 682, 619, 600. ^{1}H-Nmr(D_2O, 50°C) δ: 2.70(9H, s), 3.44(3H, s), 3.62(2H, s), 5.16(2H, s), 7.38-7.47 (2H, m), 7.50-7.64(3H, m). ^{13}C-Nmr(D_2O, 50°C) δ: 43.2(q), 53.2(q, $\overset{+}{N}$Me), 61.0(t, $\overset{+}{N}CH_2$), 69.3(t), 83.3(s), 127.3(d), 129.8(d), 131.0(d), 143.4(s), 170.2(s), 179.0(s).

General Procedure for the Methylation of 4-(N-Monosubstituted Amino)-3-(N,N-dimethylaminomethyl)-2(5H)-furanones: To a stirred solution of Mannich base in acetonitrile was added dropwise methyl iodide in acetonitrile at -10°C (bath temperature), and the resulting mixture was stirred at -10°C for 30 min and subsequently at room temperature for 1 h. Filtration or evaporation of the reaction mixture followed by washing the residue with dry ether gave the corresponding quaternary salt.

Trimethyl[4-(N-methylamino)-2(5H)-furanon-3-ylmethyl]ammonium Iodide: Yield: 94%.
Ir ν_{max}^{Nujol} cm^{-1}: 3200, 1722(s), 1620(s). ^{1}H-Nmr(D_2O, 25°C) δ: 2.94(3H, s), 3.08(9H, s), 4.04(2H, s), 5.04(2H, s). ^{13}C-Nmr(D_2O, 25°C) δ: 30.7(q), 52.7(q), 59.6(t),

67.4(t), 80.5(s), 174.0(s), 178.6(s).

[4-(N-Benzylamino)-2(5H)-furanon-3-ylmethyl]trimethylammonium Iodide: Yield: quantitative. Ir ν_{max}^{Nujol} cm^{-1}: 3160, 1720(s), 1618(s). ^{1}H-Nmr(CD_3CN, 25°C) δ: 3.09(9H, s), 4.35(2H, s), 4.36(2H, d, J=6 Hz, convertible to a singlet on treatment with D_2O, C_4-NCH_2Ph), 4.72(2H, s), 7.24-7.38(5H, m), 8.51(1H, broad signal, exchangeable with D_2O).

Sodium Borohydride Reduction of Quaternary Salts;

i) General Procedure for the Normal Salt: To a solution of the quaternary salt in methanol was added sodium borohydride (8 molar equivalents) at 0 °C, and the resulting mixture was stirred for 3 h at room temperature. The solvent was removed under reduced pressure, and the residue was extracted with methylene chloride. The extract was evaporated, and the residue was subjected to preparative thin-layer chromatography (PTLC) on silica gel (eluent: benzene/acetone = 3 : 1).

The Reduction of the Ammonium from an N(C_4)-Monomethylfuranone (VI; R^1=H, R^2=Me): Two products were isolated: a) 3-Methyl-4-(N-methylamino)-2(5H)-furanone in 29% yield as colorless rhombs (from ethyl acetate), mp 160-162°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1720(s), 1640(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.69(3H, broad s), 2.94(3H, d, J=5 Hz, convertible to a singlet on treatment with D_2O), 4.54(1H, broad signal, exchangeable with D_2O), 4.63(2H, broad s). Ms m/z(%): 128(M^++1, 10.4), 127(M^+, 100), 126(M^+-1, 22.9), 98(27.8), 82(52.4), 69(24.2), 54(35.3), 42(21.1). Exact mass: Calcd. for $C_6H_9NO_2$: 127.0633; Found: 127.0657. b) 3-Methoxymethyl-4-(N-methylamino)-2(5H)-furanone in 9% yield as colorless microneedles (from benzene), mp 100.5-101.5°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1720(s), 1638(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.91(3H, d, J=5 Hz, convertible to a singlet on treatment with D_2O), 3.32(3H, s), 4.19(2H, broad s), 4.65(2H, broad s), 5.57(1H, broad signal, exchangeable with D_2O). Ms m/z(%): 158 (M^++1, 8.2), 157(M^+, 86.3), 156(M^+-1, 9.9), 127(98.3), 113(32.8), 72(64.0), 67(31.7), 55(38.7). Exact mass: Calcd for $C_7H_{11}NO_3$: 157.0739; Found: 157.0748.

The Reduction of the Ammonium from an N(C_4)-Benzylfuranone (VI; R^1=H, R^2=Bn): Two products were isolated: a) 4-Benzylamino-3-methyl-2(5H)-furanone in 28% yield as colorless plates (from benzene), mp 112-113°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1721(s), 1640(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.69(3H, t, J=1 Hz), 4.34(2H, d, J=6 Hz, convertible to a singlet on treatment with D_2O), 4.57(2H, t, J=1 Hz), 4.92(1H, broad signal, exchangeable with D_2O), 7.20-7.36(5H, m). Ms m/z(%): 204(M^++1, 6.1), 203(M^+, 40.3), 202(M^+-1, 0.7), 92(9.7), 91(100). Exact mass: Calcd for $C_{12}H_{13}NO_2$: 203.0946; Found: 203.0963. b) 4-Benzylamino-3-methoxymethyl-2(5H)-furanone in 27% yield as

a colorless paste. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1730(s), 1640(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 3.32(3H, s), 4.20(2H, broad s), 4.33(2H, d, J=6 Hz), 4.60(2H, broad s), 5.96(1H, broad signal, exchangeable with D_2O), 7.20-7.36(5H, m). Ms m/z(%): 234(M^++1, 2.2), 233(M^+, 13.9), 232(M^+-1, 1.5), 203(21.8), 202(17.8), 201(31.7), 92(10.5), 91(100), 65(12.5). Exact mass: Calcd for $C_{13}H_{15}NO_3$: 233.1052; Found: 233.1023.

The Reduction of the Ammonium from an N(C_4)-Dimethylfuranone (VI; R^1=R^2=Me): Two products were isolated: a) 4-(N,N-Dimethylamino)-3-methyl-2(5H)-furanone in 11.5% yield as colorless plates (from benzene-ether), mp 91-92.5°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (s), 1620(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.96(3H, s), 3.03(6H, s), 4.53(2H, s). Ms m/z(%): 142(M^++1, 9.9), 141(M^+, 100), 140(M^+-1, 25.7), 96(50.7), 86(20.1), 83(16.3), 68(22.1), 56(10.2), 42(15.4). Exact mass: Calcd for $C_7H_{11}NO_2$: 141.0790; Found: 141.0817. b) 4-(N,N-Dimethylamino)-3-methoxymethyl-2(5H)-furanone in 19% yield as colorless prisms (from benzene-ether), mp 112-113°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (s), 1618(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 3.09(6H, s), 3.32(3H, s), 4.16(2H, s), 4.57 (2H, s). Ms m/z(%): 172(M^++1, 5.6), 171(M^+, 50.8), 170(M^+-1, 3.1), 141(44.6), 96(16.3), 86(67.6). Exact mass: Calcd for $C_8H_{13}NO_3$: 171.0895; Found: 171.0907.

The Reduction of the Ammonium from a 4-(N-Methylanilino)furanone (VI; R^1=Me, R^2=Ph): *The only product isolated was 3-methyl-4-(N-methylanilino)-2(5H)-furanone.* Yield: 27.8%. A colorless paste. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722(s), 1621(s), 1590(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.21(3H, t-like, J=1 Hz), 3.36(3H, s), 4.59(2H, q-like, J=1 Hz), 7.12-7.41(5H, m). Ms m/z(%): 204(M^++1, 17.1), 203(M^+, 100), 202(M^+-1, 15.2), 158(16.8), 156(14.6), 146(13.1), 144(13.2), 112(30.7), 77(16.4). Exact mass: Calcd for $C_{12}H_{13}NO_2$: 203.0946; Found: 203.0968.

ii) General Procedure for the Abnormal Salt: To a stirred solution of the Mannich base in acetonitrile (3 ml) was added dropwise methyl iodide (20 molar equivalents) in acetonitrile (1 ml) at room temperature, and the mixture was stirred at room temperature for 5 h. The deposited tetramethylammonium iodide was collected by filtration, and the filtrate was evaporated under reduced pressure to give the quaternary salt as a glassy solid. The glassy solid was dissolved in methanol (3 ml), and to this was added sodium borohydride (8 molar equivalents) at 0°C. After stirring for 3 h at room temperature, the solvent was removed under reduced pressure, and the resulting residue was subjected to PTLC on silica gel (eluent: benzene/acetone = 3 : 1). The quaternization step was monitored by TLC prior to the reduction.

The Reduction of the Ammonium from a 4-Anilinofuranone (VI; R^1=H, R^2=Ph): The tetramethylammonium iodide collected on quaternization was of 46.4% yield, and two

products were isolated: a) 4-Anilino-3-(N,N-dimethylaminomethyl)-2(5H)-furanone (VI; R^1=H, R^2=Ph) in 26% yield, identified with an authentic specimen by spectral comparison. b) 4-Anilino-3-methyl-2(5H)-furanone in 49% yield (based on the starting Mannich base) as colorless microcrystals (from ethyl acetate), mp 190-192°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1732(s), 1640(s), 1598(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 1.78(3H, broad s), 4.83(2H, broad s), 6.36(1H, broad signal, exchangeable with D_2O), 7.02(2H, d-like, J=7 Hz), 7.16(1H, t-like, J=7 Hz), 7.36(2H, t-like, J=7 Hz). Ms m/z(%): 190(M^++1, 14.8), 189(M^+, 100), 188(M^+-1, 13.3), 160(15.5), 144(17.8), 143(11.4), 142(13.7), 132(17.8), 130(14.4), 117(11.2), 93(12.4), 77(26.3), 51(16.0). Exact mass: Calcd for $C_{11}H_{11}NO_2$: 189.0790; Found: 189.0797.

The Reduction of the Ammonium from a 4-(N-Methylamino)furanone (VI; R^1=H, R^2=Me): The tetramethylammonium iodide collected on quaternization was of 28.1% yield, and three products were isolated: a) 3-(N,N-Dimethylaminomethyl)-4-(N-methylamino)-2(5H)-furanone (VI; R^1=H, R^2=Me) in 21% yield, identified with an authentic specimen by spectral comparison. b) 3-Methyl-4-(N-methylamino)-2(5H)-furanone in 23% yield (based on the starting Mannich base), identified with an authentic specimen by spectral comparison. c) 3-Methoxymethyl-4-(N-methylamino)-2(5H)-furanone in 14% yield, identified with an authentic specimen by spectral comparison.

The Reduction of the Ammonium from a 4-(N-Benzylamino)furanone (VI; R^1=H, R^2=Bn): The tetramethylammonium iodide collected on quaternization was of 32.8% yield, and three products were isolated: a) 4-(N-Benzylamino)-3-(N,N-dimethylaminomethyl)-2(5H)-furanone (VI; R^1=H, R^2=Bn) in 11% yield, identified with an authentic specimen by spectral comparison. b) 4-(N-Benzylamino)-3-methyl-2(5H)-furanone in 25% yield (based on the starting Mannich base), identified with an authentic specimen by spectral comparison. c) 4-(N-Benzylamino)-3-methoxymethyl-2(5H)-furanone in 19% yield (based on the starting Mannich base), identified with an authentic specimen by spectral comparison.

Cyanation of Quaternary Salts;

i) General Procedure for the Normal Salt: To a solution of the quaternary salt in acetonitrile were added potassium cyanide (4 molar equivalents) and 18-Crown-6 (5 mg), and the resulting mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure, and the residue was extracted with methylene chloride. The extract was evaporated, and the residue was subjected to PTLC on silica gel (eluent: chloroform/ethanol = 10 : 1).

The Cyanation of the Ammonium from an N(C_4)-Monomethylfuranone (VI; R^1=H, R^2=Me):

3-Cyanomethyl-4-(N-methylamino)-2(5H)-furanone was obtained in 90.5% yield as colorless plates (from ethyl acetate), mp 125-126.5°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300, 2250, 1738(s), 1650(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.98(3H, d, J=5 Hz, convertible to a singlet on treatment with D_2O), 3.29(2H, broad s), 4.71(2H, t, J=1 Hz), 5.26(1H, broad signal, exchangeable with D_2O). Ms m/z(%): 153(M^++1, 10.5), 152(M^+, 100), 151(M^+-1, 7.2), 107(38.5), 106(25.5), 80(12.8), 79(24.3), 72(10.1), 68(13.2), 67(12.6), 66(11.7), 42(10.6). Exact mass: Calcd for $C_7H_8N_2O_2$: 152.0586; Found: 152.0598.

The Cyanation of the Ammonium from an N(C_4)-Dimethylfuranone (VI; R^1=R^2=Me): 3-Cyanomethyl-4-(N,N-dimethylamino)-2(5H)-furanone was obtained in 68.6% yield as colorless prisms (from benzene-ether), mp 77-78.5°C. Ir ν_{max}^{Nujol} cm^{-1}: 2230, 1738(s), 1722(s), 1625(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 3.15(6H, s), 3.47(2H, s), 4.62(2H, s). Ms m/z(%): 167(M^++1, 11.5), 166(M^+, 100), 165(M^+-1, 13.5), 122(11.4), 121(75.9), 108(14.3), 94(17.7), 93(31.7), 56(19.2), 42(11.1). Exact mass: Calcd for $C_8H_{10}N_2O_2$: 166.0743; Found: 166.0734.

The Cyanation of the Ammonium from an N(C_4)-Benzylfuranone (VI; R^1=H, R^2=Bn): 4-(N-Benzylamino)-3-cyanomethyl-2(5H)-furanone was obtained in 58% yield as colorless needles (from benzene), mp 143.5-145°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300, 2250, 1739(s), 1645(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 3.28(2H, broad s), 4.38(2H, d, J=6 Hz, convertible to a singlet on treatment with D_2O), 4.65(2H, broad s), 5.91(1H, broad signal, exchangeable with D_2O), 7.26-7.37(5H, m). Ms m/z(%): 229(M^++1, 6.0), 228(M^+, 35.3), 227(M^+-1, 1.1), 92(9.6), 91(100), 65(8.7). Exact mass: Calcd for $C_{13}H_{12}N_2O_2$: 228.0899; Found: 228.0909.

The Cyanation of the Ammonium from a 4-(N-Methylanilino)furanone (VI; R^1=Me, R^2=Ph): 3-Cyanomethyl-4-(N-methylanilino)-2(5H)-furanone was obtained in 61.3% yield as colorless prisms (from benzene-ether), mp 161.5-162.5°C. Ir ν_{max}^{Nujol} cm^{-1}: 2240, 1721(s), 1622(s), 1588(s). ^{1}H-Nmr($CDCl_3$, 25°C) δ: 2.67(2H, s), 3.39(3H, s), 4.72(2H, s), 7.24-7.29(2H, m), 7.38-7.50(3H, m). Ms m/z(%): 229(M^++1, 16.7), 228(M^+, 100), 227(M^+-1, 19.2), 183(17.6), 144(15.0), 137(30.9). Exact mass: Calcd for $C_{13}H_{12}N_2O_2$: 228.0898; Found: 228.0896.

ii) General Procedure for the Abnormal Salt: The crude quaternary salt was prepared according to the procedure described for the sodium borohydride reduction of the abnormal salt and dissolved in acetonitrile (2 ml). To this solution were added potassium cyanide (4 molar equivalents) and 18-Crown-6 (5 mg), and the resulting mixture was heated under reflux for 3 h. After cooling, the solvent was removed under reduced pressure, and the residue was extracted with chloroform. The extract was

evaporated, and the resulting residue was triturated to give crystalline products, otherwise was subjected to PTLC on silica gel (eluent: chloroform/ethanol = 10 : 1).

The Cyanation of the Ammonium from an N(C_4)-Monomethylfuranone (VI; R^1=H, R^2=Me): Two products were isolated: a) 3-(N,N-Dimethylaminomethyl)-4-(N-methylamino)-2(5H)-furanone (VI; R^1=H, R^2=Me) in 11% yield, identified with an authentic specimen by spectral comparison. b) 3-Cyanomethyl-4-(N-methylamino)-2(5H)-furanone in 49% yield (based on the starting Mannich base), identified with an authentic specimen by spectral comparison.

The Cyanation of the Ammonium from an N(C_4)-Benzylfuranone (VI; R^1=H, R^2=Bn): Two products were isolated: a) 4-(N-Benzylamino)-3-(N,N-dimethylaminomethyl)-2(5H)-furanone (VI; R^1=H, R^2=Bn) in 4.4% yield, identified with an authentic specimen by spectral comparison. b) 4-Benzylamino-3-cyanomethyl-2(5H)-furanone in 55% yield (based on the starting Mannich base), identified with an authentic specimen by spectral comparison.

The Cyanation of the Ammonium from a 4-Anilinofuranone (VI; R^1=H, R^2=Ph): The only product isolated was 4-anilino-3-cyanomethyl-2(5H)-furanone. Yield: 55.1% based on the starting Mannich base. Colorless prisms from ethanol, mp 229.5-230°C. Ir ν_{max}^{Nujol} cm^{-1}: 3300, 3230, 3200, 3100, 2240, 1705(s), 1638(s), 1588(s). ^{1}H-Nmr(DMSO-d_6, 50°C) δ: 3.40(2H, s), 5.00(2H, s), 7.10-7.20(3H, m), 7.32-7.40(2H, m), 9.50(1H, broad signal, exchangeable with D_2O). Ms m/z(%): 215(M^++1, 15.9), 214(M^+, 100), 213(M^+-1, 21.8), 169(29.5), 168(17.9), 130(12.9), 129(22.8), 77(22.4), 51(12.5). Exact mass: Calcd for $C_{12}H_{10}N_2O_2$: 214.0742; Found: 214.0747.

The Cyanation of the 4-Anilinofuranone Mannich Base (VI; R^1=H, R^2=Ph): To a stirred solution of the Mannich base (100 mg) in CH_3CN (2 ml) were added potassium cyanide (100 mg) and 18-Crown-6 (5 mg), and the resulting suspension was heated under reflux for 5.5 h. After cooling and subsequent filtration, the reaction mixture was evaporated, and the resulting residue was subjected to PTLC on silica gel (eluent: benzene/ethanol = 20 : 1) to give two products: a) 4-Anilino-3-cyanomethyl-2(5H)-furanone in 13% yield, identified with an authentic specimen by spectral comparison. b) Bis[4-anilino-2(5H)-furanon-3-yl]methane in 7% yield as colorless microneedles (from benzene), mp 228-229°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1720, 1640, 1598. ^{1}H-Nmr($CDCl_3$) δ: 3.23(2H, s), 4.96(4H, s), 6.99(4H, d, J=7 Hz), 7.08(2H, t, J=7 Hz), 7.32(4H, t, J=7 Hz), 8.34(2H, broad signal, exchangeable with D_2O). Ms m/z(%): 363(M^++1, 25.7), 362(M^+, 100), 270(55.4), 226(8.0), 188(11.7), 129(8.9). Exact mass: Calcd for $C_{21}H_{18}N_2O_4$: 362.1267; Found: 362.1237.

NOTES AND REFERENCES

1. The previous paper entitled "A Laboratory Synthesis of 4-Hydroxy-2(5H)-furanone (β-Tetronic Acid)" [T. Momose, N. Toyooka, and Y. Takeuchi, Heterocycles, 1986, 24, 1429] constitutes Part II of this series. The paper entitled "Syntheses of *Dihydroactinidiolide and* Actinidiolide, and Partial Synthesis of Dihydrosecurinine" [Z. Horii, M. Ito, I. Minami, M. Yamauchi, M. Hanaoka, and T. Momose, Chem. Pharm. Bull., 1970, 18, 1967] constitutes Part I of this series.
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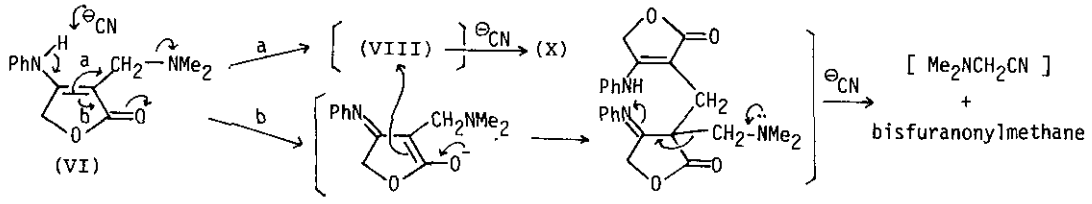
12. The pathway to the products was tentatively postulated as depicted below.



13. At room temperature was observed some broadening or splitting of the signals due to the restricted rotation around the N-C_4 bond in the vinylogous urethane system.

14. The product crystallized on evaporation of the solvent acetic acid, and the procedure of work-up was partially modified: the dissolution in chloroform was omitted. Direct washing of the crystals with water (3 ml × 3) resulted in removal of the acid and excess amine.

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