to indicate and O-2 to O-1 migration process which has not been reported previously. The rate of removal of the benzoate groups in sugar **20** is very rapid and similar to that of the nonanomeric acetates in **1** and **2**.

Further substantiation for the participation of a neighboring OH group in the solvolysis of an adjacent OAc group (either by polarization of the OAc or by *O*-acyl migration), is seen in the reaction of **15**, where the isolated 3-*O*-acetate group reacts ca. 10 times slower than the 2- and 3-*O*-acetate groups of compounds **12**-α and **12**-β. The reaction is selective to ester groups leaving the acetamido function intact.

The NMR kinetic data of galactose derivatives **8** and **18** indicate that (a) the anomeric acetate of **18** reacts initially (b) the $t_{1/2}$ of **18** is less than 1 min, which prevents the detection of partially deacetylated intermediates, and (c) compound **8**, in spite of the fact that it has an anomeric OMe group, undergoes deacetylation ($t_{1/2}$ ca. 7 min) much faster than compounds **1**, **3**, **5**, and **10**, probably due to the presence of primary acetate.

Experimental Section

General Remarks. Proton NMR spectra were recorded on a Bruker AM-300 spectrometer in deuteromethanol/Me_4Si, on a ca. 0.05-mol scale. All reactions were carried out under anhydrous conditions in flame-dried glass apparatus under nitrogen, in absolute methanol. The KCN (analytical grade Merck 4967) was dried under high vacuum for several hours. The starting sugars for which no reference is given are commerically available (Aldrich, Fluka). Polymer-bound cyanide used was Fluka 28490. Mixed ion-exchange resin Duolite MB-5113 was obtained from BDH. Progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum sheets precoated with silica gel (Merck, Art. 5554), and eluted with chloroform/methanol mixtures; the developing agent was 1% sulfuric acid in methanol, followed by heat.

General Procedure for Deacylation. To a stirred solution of KCN (0.5 mmol) in methanol was added in one portion a polyacylated sugar (1 mmol). The resulting mixture (solution or suspension) was stirred at room temperature until complete conversion to the polyhydroxy product took place, as indicated by TLC. The following illustrates alternative procedures used to purify the products.

Procedure A. To a stirred solution of KCN (45 mg, 0.7 mmol) in methanol (12 mL) was added β-galactose pentaacetate (**18**) (500 mg, 1.3 mmol), and the mixture was stirred for 20 min. The resulting clear solution was filtered through silica gel (Merck 7734), and the eluent was evaporated to dryness, affording a mixture of **19**-α and **19**-β (206 mg, 88% yield) as a white solid.

Procedure B. To a stirred mixture of polymer-supported cyanide (470 mg, 1.5 mmol of cyanide) in methanol (15 mL) was added β-4,6-*O*-ethylidene-1,2,3-tri-*O*-acetylglucose[9] (**12**-β) (500 mg, 1.5 mmol), and the mixture was stirred for 4 h. The polymer was filtered off and the filtrate evaporated to dryness, to give a mixture of **11**-α and **11**-β (284 mg, 92% yield), as a white solid.

Procedure C. 4,6-*O*-Ethylidene-2,3-di-*O*-acetyl-β-methoxyglucose (**1**)[9] (304 mg, 1 mmol) was added to a solution of KCN (42 mg, 0.65 mmol) in methanol (10 mL), an the mixture was stirred for 6 h. Evaporation of the solvent, followed by flash chromatography of the residue (silica gel, Merck 9385; eluted with 95:5 chloroform–methanol) gave **2** (210 mg, 95% yield).

Procedure D. To a stirred solution of KCN (200 mg, 3.1 mmol) in methanol (50 mL) was added sucrose octaacetate (6.3 g, 9.3 mmol), and the solution was stirred for 0.5 h. A precipitate formed, which was filtered, washed with methanol, and dried to give a solid (2.39 g, 75% yield), mp 185–193 °C (undepressed by admixture with an authentic sample of sucrose).

Procedure E. In addition to procedures A–D, the removal of the potassium cyanide catalyst could be carried out by adding at the end of the reaction an equilmolar amount of mixed ion-exchange resin. After stirring the mixture for several minutes, the resin was filtered off and evaporation of the filtrate provided KCN-free products.

Registry No. **1**, 100021-29-2; **2**, 27994-35-0; **3**, 34213-34-8; **4**, 18486-38-9; **5**, 4630-61-9; **6**, 55811-42-2; **7**, 100021-30-5; **8**, 5019-23-8; **9**, 1824-94-8; **10**, 100021-31-6; **11**, 13403-24-2; β-**12**, 27994-30-5; α-**12**, 29810-01-3; **13**, 100021-32-7; **14**, 100021-33-8; β-**15**, 73038-55-8; α-**15**, 100021-35-0; **16**, 100021-34-9; **17**, 22536-08-9; **18**, 4163-60-4; **19**, 59-23-4; **20**, 100101-51-7; **21**, 50-69-1; KCN, 151-50-8; sucrose octaacetate, 126-14-7; sucrose, 57-50-1.

(9) (a) Hall, D. M.; Stamm, O. A. *Carbohydr. Res.* **1970**, *12*, 421. (b) Helferich, B.; Appel, H. *Chem. Ber.* **1931**, *64B*, 184.

Notes

Studies in Ranitidine Chemistry: An Unusual O→N Methyl Migration

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Ranitidine (IV), an H_2-receptor antagonist, has been recently introduced in ulcer therapy as a powerful inhibitor of gastric acid secretion.[1] Its synthesis is described in serveral patents.[2–5] Some of the published procedures[2–3] involve the intermediacy of III, prepared by the reaction of I with II (Scheme I). Compound III has been reported to be isolated either as an oil[6] or as its oxalate salt.[7] We have recently been able to synthesize III as the free base and isolate it as a crystalline solid.

In the course of this work we became aware of the instability of III in methanolic solutions where it is completely transformed to another product upon standing at room temperature. This product, a very polar compound, was isolated and fully characterized. Spectral and analytical results confirmed its structure to be that of 1-oxo-1-[(2-(((((5-trimethylammonio)methyl)-2-furanyl)-methyl)thio)ethyl)amino]-2-nitroethene (V), indicating

(1) Daly, M. J.; Humphray, J. M.; Stables, R. *Br. J. Pharmacol.* **1981**, *72*, 49, 55.
(2) U.S. Patent 4 128 658, 1978. U.S. Patent 4 169 855, 1979.
(3) Eur. Pat. Appl. 55 625, 1981. Eur. Pat. Appl. 55 626, 1981.
(4) Toso, R.; Decorte, E.; Zonno, F.; Sunjic', V. *Acta Pharm. Jugosl.* **1981**, *31*, 117.
(5) U.K. Pat. Appl. 2 075 980, 1981.
(6) Eur. Pat. Appl. 57 981, 1982.
(7) Eur. Pat. Appl. 2930, 1979.

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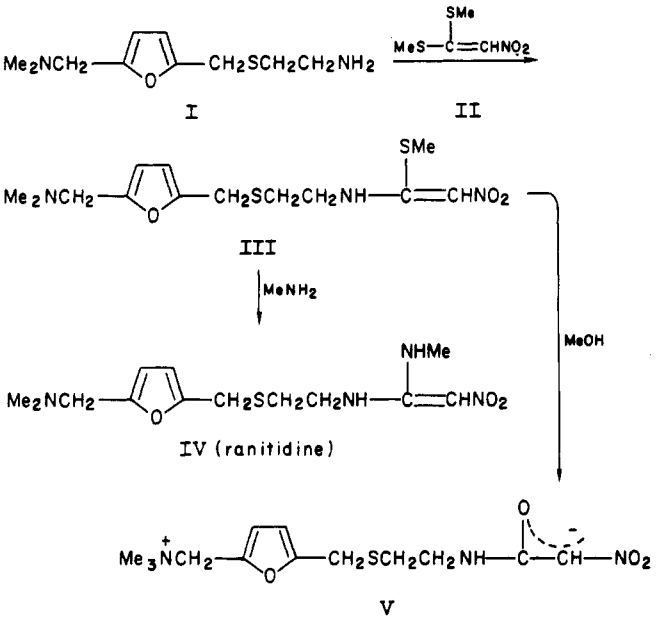
Table I. 300-MHz ^{1}H NMR Data (δ; J, Hz) for Compounds III and V in CD_3OD

	MeS	Me_2N	Me_3N^+	SCH_2CH_2	$ArCH_2$	$^+NCH_2$	CH_2ND	(a) (b)
III	2.54 (s)	2.27 (s)		2.85 (t, J = 6.6)	3.51 (s)	3.82 (s)	3.665 (t, J = 6.6)	(a + b) 6.25 (s)
V			3.14 (s)	2.73 (t, J = 6.3)	3.85 (s)	4.60 (s)	3.485 (t, J = 6.3)	(a) 6.775 (d, J = 3.6), (b) 6.43 (d, J = 3.6)

Scheme I



that the overall reaction involves a methyl transfer (Scheme I).

Whereas N→O alkyl migration processes are well established, i.e., nitrones to oxime *O*-ethers,[8] the corresponding O→N migration of a methyl group is a seldom encountered phenomenon. A thermally induced (300 °C) O→N intramolecular aryl migration has been described.[9]

In order to study the mechanism of the conversion of III to V a CD_3OD solution of III was monitored by ^{1}H NMR spectroscopy over a period of 7 weeks at room temperature. The transmethylation was found to be a rather complex process in which a relatively large number of intermediates are detected, but their plurality rendered their unequivocal identification rather difficult. However, the integration of the trialkylammonium signal of V showed that the transferred methyl group was a CD_3 and not a CH_3 group, clearly indicating that it stemmed from the solvent, e.g., O→N migration, and not from an S→N methyl shift which would have given a Me_3N^+ product.

In Table I are presented the ^{1}H NMR absorptions of the starting material III and the product V and in Figure 1 are described the time-dependent changes in concentrations of the various components of the reaction mixture.

The proposed mechanistic course of the reaction, based on interpretation and structure assignments of the species detected in the NMR spectra, is presented in Scheme II.

The initial step of the reaction is understood to involve a rapid H–D exchange, to give species A′. The next step involves an addition of CD_3OD and elimination of MeSD sequence, to give intermediate C. This intermediate may readily react either with another molecule of C to give the final product D or alternatively may react with A′ to give intermediates E and F, which may then continue under-

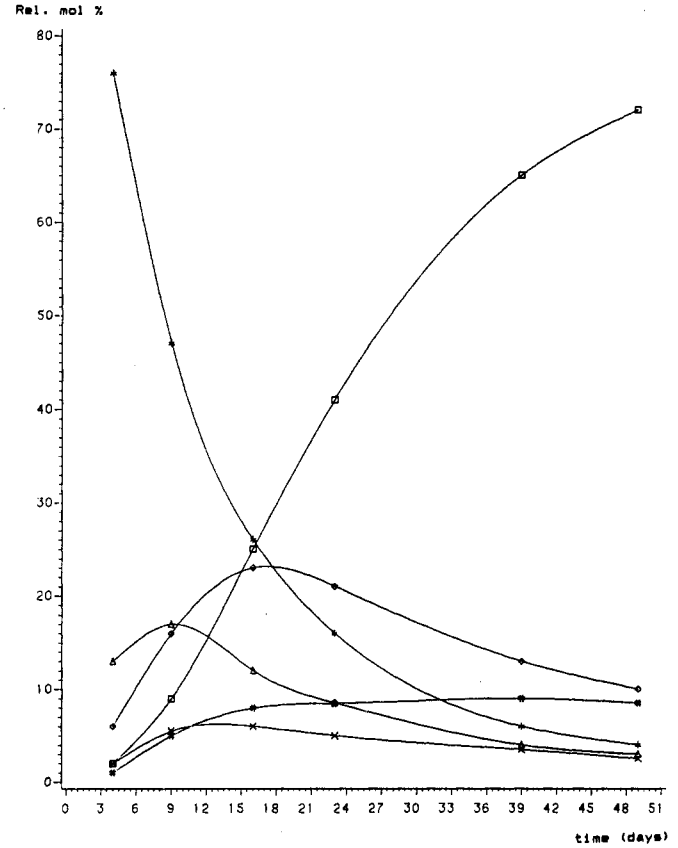
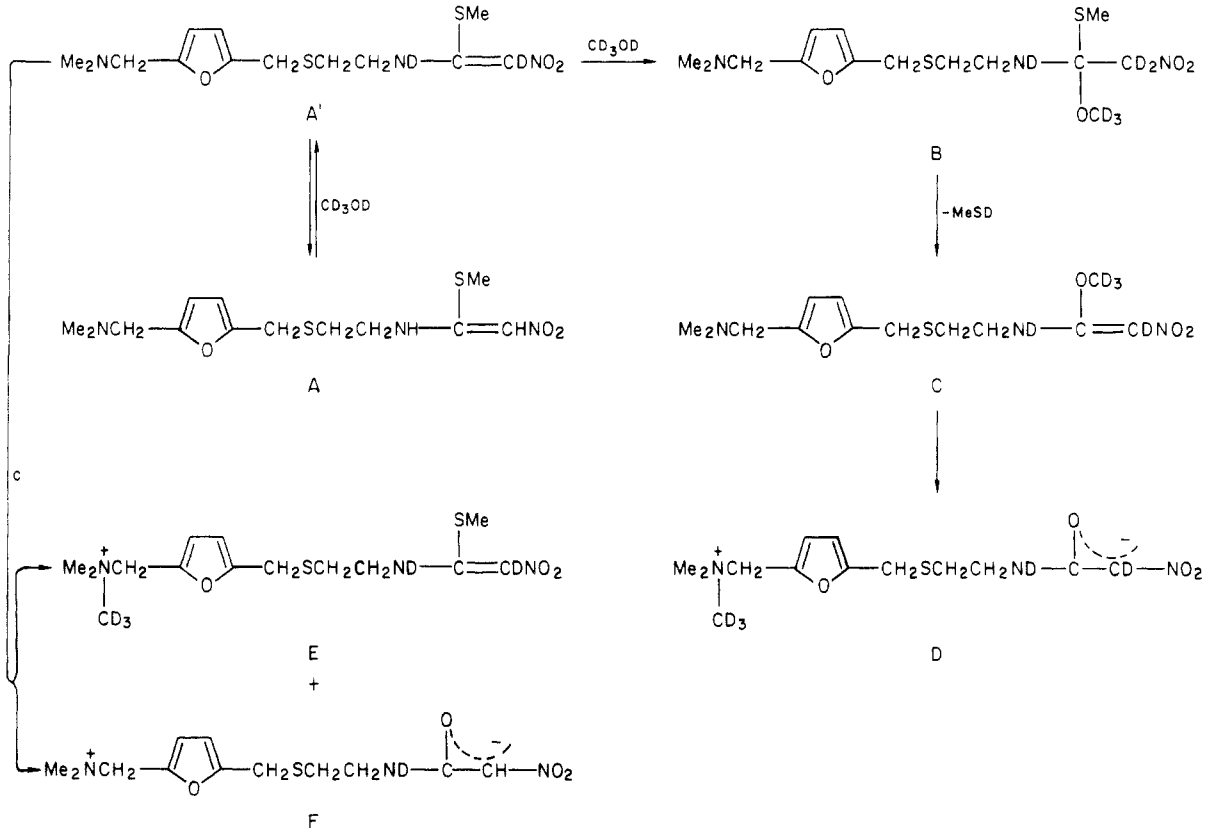


Figure 1. Time-dependent changes in concentrations of III and V and their intermediates in CD_3OD solution: (*) III; (□) V; (◇) tentatively assigned to E (Scheme II); (X, #, and △) unassigned structures (see text).

going similar addition, elimination, and methyl (or deuteromethyl) migration steps, eventually leading to the exclusive formation of the final product D. it has thus been assumed that a complete addition–elimination sequence A → B → C has taken place, in order to account for the number of species detected in the NMR spectra; however, a direct conversion of A′ → C via a vinylic substitution[10] is conceivable. It may be reasonable to suppose, that the methyl transfer proceeds from an entity (such as C) where the starting SMe has been replaced by the OCD_3 group, and the driving force for this process stems from the high degree of stability obtained upon delocalization of the anion in the product. In addition to the starting material (A) and the product (D) three intermediates which do not have and one which has a charged nitrogen are clearly detected in the kinetic NMR spectra. The major component other than the product D, the concentration of which reaches a maximum of ca. 25%, possesses a charged nitrogen. The structure of this intermediate is attributed to E, obtained initially in a relatively large amount due to the initial high concentration of A′. As the reaction progresses, the major component becomes the product D which, as indicated, may be formed either via C → D or from E and F by the stated sequential addition–elimina-

(8) Thyagarajan, B. S., Ed. "Mechanism of Molecular Migrations"; Intrascience: New York, 1968; pp 49–53.
(9) Scherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1972**, *37*, 1681.
(10) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7.

Scheme II



tion and/or migration steps.

Complete H–D exchange of the vinylic proton in both III and V in CD_3OD solution (see A–A′ in Scheme II) is clearly evident from the NMR spectrum. This type of exchange in aqueous media, over a range of pH values, for ranitidine and related model compounds, has been thoroughly investigated and was found to be of pseudo-first-order pH-dependent kinetics. It should be noted, however, that even at a pH of ca. 6, the rate of exchange was extremely small (virtually negligible after 24 h).[11] In our case the exchange is quite fast, and within less than 4 h complete H/D exchange is observed, suggesting that a rapid equilibrium between A and A′ exists. Moreover, the H→D exchange process in CD_3OD may contribute to the *E*/*Z* configurational instability of the nitro ethene functional group in both III and V. This is in agreement with the reported data for the inversion barriers around a double bond for some nitro ethylenes.[11]

An experiment conducted in two methanolic dilutions, where the concentration of III was in one case 10 times greater than in the other, indicated that the rate of formation of V was considerably faster in the concentrated solution. It may thus be concluded, that the O→N migration is an intermolecular and not an intramolecular process.

Experimental Section

1-Oxo-1-[(2-(((((5-trimethylammonio)methyl)-2-furanyl)methyl)thio)ethyl)amino]-2-nitroethene (*V*). A solution of III (5.0 g, 15 mmol), crystallized from toluene and recrystallized from acetone/water, mp 70–71 °C, in absolute methanol (50 mL) was set aside at room temperature for 7 weeks. The solvent was removed under reduced pressure, and the red brown solid residue was treated with a mixture of acetone/methanol (20:1). The yellow suspension was stirred at room temperature for 0.5 h, filtered, washed with acetone, and dried to give V (2.8 g, 8.8 mmol, 59% yield) as a cream colored solid: mp 168–169 °C; ^{13}C NMR ($CDCl_3$) 165.8 (CO^-), 155.8 (CCH_2S), 142.7 ($^+NCH_2C$), 118.4 (*C*HCH), 110.0 (CH*C*H), 109.4 ($CDNO_2$, t, $^1J_{CD}$ = 29 Hz), 62.3 ($^+NCH_2$), 53.1 (Me_3N^+), 38.5 (CH_2NH), 31.6 (SCH_2), 28.0 ppm (CCH_2S), [these assignments are confirmed by single-frequency off-resonance decoupled spectra, which provide signal multiplicity and ^{13}C–^1H correlation]; IR (KBr) 3430, 1600, 1530, 1460, 1215, 1025, 965, 880 cm^{-1}; MS (EI), *m*/*e* (relative intensity) 272 ($M^+ - Me_3 + H^+$) (5), 240 ($M^+ - Me_3NO$) (8), 169 (240 – CH_2=$CHNO_2$) (42), 137 (55), 125 (169 – $CH_2CH_2NH_2$) (49), 110 (74), 94 (2,5-$(CH_2)_2C_4H_2O$) (19).

Anal. Calcd for $C_{13}H_{21}N_3O_4S$: C, 49.49; H, 6.56; N, 13.38; S, 10.11. Found: C, 49.50; H, 6.71; N, 13.32; S, 10.17.

Registry No. III, 72115-14-1; V, 100045-25-8; MeOH, 67-56-1; H_2, 1333-74-0.

(11) Sega, A.; Toso, R.; Sunjic', V.; Klasinc, L.; Sablic', A.; Srzic', D. *Gazz. Chim. Ital.* **1981**, *111*, 217.

3-Imino-1,4,2-dioxazolidines by [1 + 2 + 2] Cycloaddition of an Isocyanide, 2-Methyl-2-nitrosopropane, and a Carbonyl Compound

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In a current study on the cycloaddition of 2-methyl-2-nitrosopropane (1) to *N*-aryl-*tert*-butylketeneimines such as **4** we observed that, under certain conditions, small amounts of the 3-imino-1,4,2-dioxazolidines **3e–g** were produced (Scheme I, eq 2).[1] These compounds—members of a novel class of 1,4,2-dioxazolidines— do not arise from the respective 3-imino-1,2-oxazetidines (i.e., the regular

(1) Yields range from below 5% (**3f,g**) to 15% (**3e**); the products did not form under N_2 or at higher temperatures (as exemplified for **3e**).

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