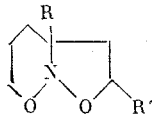
REACTION OF 2,9-DIOXA-1-AZABICYCLO[4.3.0]NONANE DERIVATIVES WITH BORON FLUORIDE ETHERATE

I. E. Chlenov, Yu. B. Salamonov,
B. N. Khasapov, N. F. Karpenko,
O. S. Chizhov, and V. A. Tartakovskii

UDC 542.91:547.728

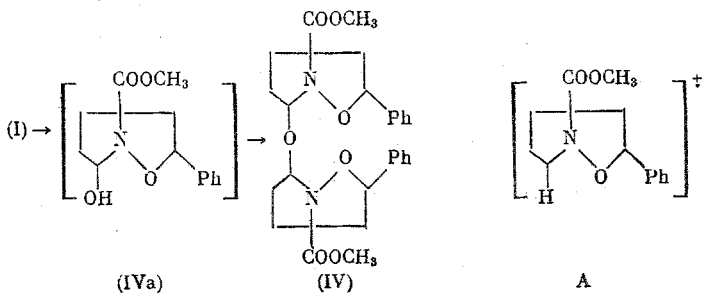
Previously it was shown [1] that when reacted with BF_3 etherate (BFE) the 8-phenyl- and 8-carbomethoxy-6-methyl-2,9-dioxa-1-azabicyclo [4.3.0]nonanes respectively rearrange to the 3-phenyl- and 3-carbomethoxy-8-hydroxy-5-methyl-2-oxa-1-azabicyclo[4.3.0]octanes. The reaction of BFE with other 2,9-dioxa-1-azabicyclo-[4.3.0]nonane derivatives (I)-(III) was studied in the present paper.



(I)—(III)

R = $COOCH_3$, R′ = cis-Ph (I); R = Ph, R′ = trans-$COOCH_3$ (IIa);
R = Ph, R′ = cis-$COOCH_3$ (IIb); R = OCH_3, R′ = trans-Ph (III)

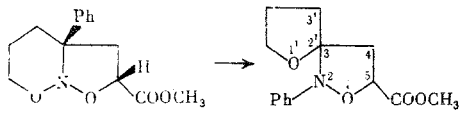
The reaction of BFE with (I) leads to compound (IV).



(IVa) (IV) A

The structure of (IV) was assigned on the basis of the elemental analysis, IR, PMR, and ^{13}C NMR spectral data. The mass spectrum of (IV) has the peak of the molecular ion (MI) with m/e 508, while the most intense peak is that of the ion with m/e 246, which corresponds to fragment A. Compound (IV) is evidently formed via the cleavage of water from two molecules of the intermediately formed 8-hydroxy-2-oxa-1-azabicyclo[3.3.0]octane derivative (IVa).

The reaction of BFE and (IIa) leads to a mixture of two steric isomers of the spiro(isoxazolidine-3,2′-tetrahydrofuran) derivative (Va, b).



(IIa) (Va, b)

The PMR spectral data are given in Table 1. The protons of the isoxazolidine ring appear as the ABX system, whose parameters were determined by the INDOR method. The ^{13}C NMR spectral data are given in Table 2. The C^4 signal was assigned using the selective monochromatic decoupling from the protons at C^4 (~ 274 Hz from HMDS in the PMR spectrum, in $CHCl_3$ solution). The characteristics of the high-resolution mass spectrum of (Va, b) do not contradict the proposed structure. The most intense peak is that of the

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2830-2833, December, 1977. Original article submitted May 30, 1977.

0568-5230/77/2612-2619$07.50

TABLE 1. PMR Spectral Data for (Va, b) (δ, ppm from HMDS, toluene-d_8)

Compound	H_X	H_A	H_B	J_{AX}	J_{BX}	J_{AB} (Hz)	CH_3	CH_2O	H_2C-CH_2
(Va) *	4,74	2,78	2,56	6,7	8,6	12,7	3,63s	3,15–3,80 m	1,04–1,64m
(Vb)	4,58	2,79	2,50	4,5	9,6	12,7	3,68s		1,64–2,39 m

TABLE 2. ^{13}C NMR Spectral Data for (Va, b) (δ, ppm from TMS, $CHCl_3$ solution)

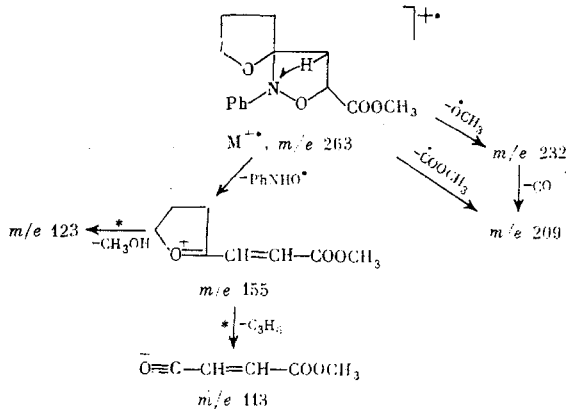
Compound	C=O	CH_3	C_3	C_5	C_4	$C_{5'}$	$C_{3'}$, $C_{4'}$	Ph_s	Ph
(Va)	171,7s	51,7 q	102,0 s	73,0 d	44,8t	68,1 t	31,6 t 24,3 t	143,9s	127,6 125,6
(Vb)	171,1s	51,7 q	101,2 s	73,2 d	44,2 t	68,1 t	31,3 t 24,3 t	144,4s	123,4

TABLE 3. ^{13}C NMR Spectral Data for (VIa, b) (δ, ppm from TMS, $CHCl_3$ solution)

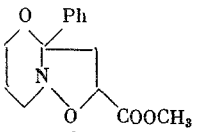
Compound	C=O	CH_3	O–C–N	CH–O	CH_2O	N–CH_2	$2CH_2$	Ph_s	Ph
(VIa) *	171,8 s	51,4 q	92,4 s	72,7d	61,0t	44,3t	30,3 t; 17,9t	136,6s	128,0 127,3
(VIb)	170,9 s	51,1 q	91,0 s	72,7 d	62,3t	44,7t		136,5s	126,0 124,9

*Predominant isomer.

$C_8H_{11}O_3$ ion (experimental m/e 155.0757; calculated m/e, 155.0708), which is formed by the cleavage of the [Ph – NHO·] grouping from the MI. This type of fragmentation of (Va, b) is given in the following scheme:



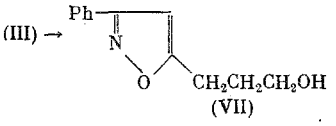
The reaction of BFE with a mixture of (IIb) (80%) and (IIa) (20%) leads to the formation of (Va, b) in an amount that corresponds to the amount of (IIa) in the starting mixture. In addition, product B was isolated, which, based on the TLC, differs from (Va, b) and is not a pure compound. The predominant component (70-80%) in B is a compound that evidently represents a mixture of two steric isomers (VIa, b). The high-resolution mass spectrum of B has a peak of composition $C_{14}H_{17}NO_4$ (experimental m/e 263.1137; calculated m/e 263.1157), which apparently corresponds to the MI of (VIa, b). The most intense peak in the mass spectrum is that of the ion of composition C_7H_5O (experimental m/e 105.0339; calculated m/e 105.0340), which corresponds to the benzoyl cation. From the mass and ^{13}C NMR spectral (Table 3) data it may be concluded that (VIa, b) is a rearrangement product and contains the fragments O–C–N and O–C–Ph. Taking this into account, the following probable structure can be proposed for (VIa, b):



(VIa, b)

Although this structure is in agreement with the spectral data, it must be regarded as being hypothetical. Nevertheless, it can be assumed as proven that the reaction of BFE with (IIa) and (IIb) leads to different products,* and consequently the mutual arrangement of the substituents can exert a decisive effect on the direction of the reaction of BFE with 6,8-disubstituted 2-9-dioxa-1-azabicyclo[4.3.0]nonanes.

The reaction of BFE with (III) leads to the formation of 3-phenyl-5-γ-hydroxypropylisoxazole (VII).



(VII)

The structure of (VII) was proved by identification with an authentic specmien [3].

EXPERIMENTAL

The PMR spectra were taken on Perkin–Elmer R-12, Varian DA-60, and JEOL NMH-100 instruments, while the ^{13}C NMR spectra were taken on a Varian XL-100 instrument (25.15 MHz). The mass spectra were obtained on Varian MS-30 AEI and CH-6 instruments, and the IR spectra were obtained on a UR-10 instrument. We used silica gel LSL 5/40 and a luminescent indicator for the chromatography.

Preparation of (IV). To a solution of 0.8 g of (I) [4] in 25 ml of abs. benzene at 5-6°C was added in drops 0.56 ml of BFE in 6 ml of abs. benzene, and the mixture was stirred for 1 h at ~ 20°, neutralized with a solution of 0.78 g of Na_2CO_3 in 40 ml of H_2O, extracted with ether, and dried over $MgSO_4$. After distilling off the solvents we obtained 0.38 g (48%) of (IV), mp 170-173° (ethanol). Found: C 66.12; H 6.36; N 5.56%. $C_{28}H_{32}N_2O_7$. Calculated: C 66.14; H 6.30; N 5.51%. Infrared spectrum (ν, cm^{-1}): 1740 (C=O). PMR spectrum (δ, ppm from HMDS, $CDCl_3$): 3.74 s (OCH_3); 4.90 q (O–CH–Ph); 5.38 m (O–CH–N); 1.4-2.93 m ($3CH_2$). ^{13}C NMR spectrum (δ, ppm from TMS, $CHCl_3$): 173.9 s (C=O); 52.6 q (OCH_3); 75.8 s (–C–N); 80.2 d (O–CH–Ph); 95.0 d (O–CH–N); 48.3 t (CH_2); 32.6 t (CH_2); 29.3 t (CH_2); 136.8 s, 128.0 d, 126.8 (Ph).

Preparation of Va, b). To a solution of 0.32 g of (IIa) [4] in 10 ml of abs. benzene at 6-8° was added in drops 0.26 ml of BFE in 2 ml of abs. benzene, and the mixture was stirred for 1.5 h at ~ 20°, neutralized with a solution of 0.28 g of Na_2CO_3 in 30 ml of H_2O, extracted with ether, and dried over $MgSO_4$. After distilling off the solvents, the residue was subjected to preparative TLC (eluant = 1:1 $CHCl_3$–ether) to give 0.21 g (66%) of (Va, b), R_f 0.63, mp 59-61° (hexane). Found: C 63.90; H 6.53; N 5.28%. $C_{14}H_{17}NO_4$. Calculated: C 63.88; H 6.46; N 5.32%. Infrared spectrum (ν, cm^{-1}): 1755 (C=O).

Preparation of (VIa, b). To a solution of 1 g of mixed (IIa) and (IIb) (1:4) in 40 ml of abs. benzene at 5-7° was added in drops 1.62 ml of BFE in 5 ml of abs. benzene, and the mixture was stirred for 2 h at ~ 20°, neutralized with a solution of 1.74 g of Na_2CO_3 in 50 ml of H_2O, and extracted with ether. The residue from distilling off the solvents was subjected to preparative TLC (eluant = 2:1 benzene–ether) to give 0.12 g of (Va, b) (60%, when based on (IIa)), R_f 0.32, and 0.25 g of product B, R_f 0.4, which contained 70-80% of (VIa, b).

Preparation of (VII). To a solution of 0.49 g of (III) [5] in 10 ml of abs. benzene at 5-8° was added in drops 0.3 ml of BFE in 2 ml of abs. benzene, and the mixture was stirred for 40 min at ~ 20°, refluxed in benzene for 8 h, neutralized with a solution of 0.33 g of Na_2CO_3 in 30 ml of H_2O, extracted with ether, and dried over $MgSO_4$. The residue from distilling off the solvents was subjected to preparative TLC (eluant = 2:1 benzene-ether) to give 0.07 g (15%) of (VII), R_f 0.12.

CONCLUSIONS

1. The direction of the reaction of boron fluoride etherate with 6,8-disubstituted 2,9-dioxa-1-azabicyclo-[4.3.0]nonanes depends on the nature and spatial arrangement of the substitutnts.

2. The first member of a new heterocyclic system was obtained, namely a spiro(isoxazolidine-3,2'-tetrahydrofuran) derivative.

*The formation of (VIa, b) is not observed when BFE is reacted with (IIa).

LITERATURE CITED

1. I. E. Chlenov, L. N. Kolymagina, and V. A. Tartakovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1972, 893.
2. F. Caruso, G. Cum, and N. Ucella, Tetrahedron Lett., 1971, 3711.
3. I. E. Chlenov, I. M. Petrova, and V. A. Tartakovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1974, 2651.
4. I. E. Chlenov, V. I. Khudak, L. N. Kolymagina, N. S. Morozova, and V. A. Tartakovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1970, 4867.
5. I. E. Chlenov, I. M. Petrova, V. M. Shitkin, and V. A. Tartakovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1976, 1405.

METHYLATION OF CARBOHYDRATES WITH METHYL IODIDE IN PRESENCE OF DIMSILPOTASSIUM

N. V. Bovin, V. A. Nesmeyanov, and A. Ya. Khorlin

UDC 542.91:547.455:547.226

A procedure that has found wide use in the structural chemistry of carbohydrates is the Hakomori methylation method [1], the reaction of methyl iodide with the alkoxide groupings of sugars in DMSO. The latter are generated by treatment with dimethylsulfinyl anion (dimsilsodium), which is obtained from DMSO and NaH.

The efficiency and reproducibility of methylation by this method are determined to a large degree by the purity of the NaH.

A compound that is widely used in synthetic organic chemistry to generate the dimsil anion is potassium tert-butoxide (KtB) [2], which is not only a readily available commercial product but can also be easily obtained under laboratory conditions. Dimsilpotassium is not explosive, whereas the reaction of NaH with DMSO at times led to explosion [3, 4]. However, dimsilpotassium has not been used for the methylation of carbohydrates. A modification of the Hakomori method is proposed in the present paper, which includes the generation of methylsulfinyl anion using KtB.

The methylation process under these conditions can be depicted by the following series of transformations:

$$t\text{-BuO}^-\text{K}^+ + \text{CH}_3\text{S(O)CH}_3 \rightleftarrows \text{CH}_3\text{S(O)CH}_2^-\text{K}^+ + t\text{-BuOH} \quad (1)$$

$$\text{CH}_3\text{S(O)CH}_2^- + \text{ROH} \rightleftarrows \text{CH}_3\text{S(O)CH}_3 + \text{RO}^- \quad (2)$$

$$\text{RO}^- + \text{CH}_3\text{I} \rightarrow \text{ROCH}_3 + \text{I}^- \quad (3)$$

R — R = sugar moiety

Actually, methylation took place under these conditions, but not in a single experiment were we able to obtain complete methylation, most probably because of the competing methylation of the tert-butanol and the inadequate concentration of methylsulfinyl anion. The removal of the tert-butanol from the reaction sphere by evaporation in vacuo made it possible to shift the equilibrium of reaction (2) toward the formation of alkoxide anion, the subsequent treatment of which with CH_3I (reaction (3)) led to the completely methylated sugar in high yield.

The efficiency of the method was checked on the examples of methylating cellobiose, cellobiitol, 2-acetamido-2-desoxy-D-glucose, 2-acetamido-2-desoxy-D-glucitol, and glycogen. Complete methylation of the mono- and oligosaccharides was achieved by a single treatment, in which connection the aminosugars underwent N,O-methylation. To obtain the completely methylated glycogen required a double treatment of the polysaccharide. In all cases, independent of the amounts of starting saccharides (from 1 to 500 mg) the completely methylated derivatives were obtained in over 90% yield. Their R_f values (TLC) and retention times relative to hexa-O-acetylmannitol (GLC) are given in Table 1.

M. M. Shemyakin Institute of Bioorganic Chemistry, Academy of Sciences of the USSR, Moscow.

Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2834-2836, December, 1977. Original article submitted June 8, 1977.

0568-5230/77/2612-2622$07.50