^{13}C NMR Spectra and Anomerization of *cis*- and *trans*-5-Arylamino-3-isopropyl-1,2,4-trioxanes

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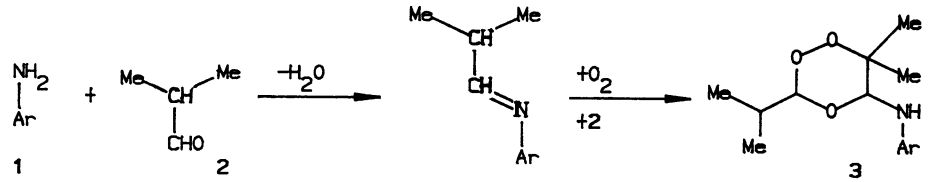
(Received December 4, 1987)

Synopsis. The cis and trans isomers of 3-isopropyl-6,6-dimethyl-5-arylamino-1,2,4-trioxanes have been clearly identified and the anomerization of arylaminotrioxanes has been detected by the ^{13}C NMR spectra in chloroform-*d*.

The 1,2,4-trioxanes have interested researchers since they play the active role in Arteannuin (Qinghosu),[1] an antimalarial remedy. Several methods for synthesizing 1,2,4-trioxanes have been reported;[2] recentry we obtained 5-arylamino-3-isopropyl-1,2,4-trioxanes (**3**) from one-pot reactions of arylamines (**1a—p**) and 2-methylpropanal (**2**) (molar ratio 1 : 3) in the presence of oxygen.[3] (Scheme 1) After purification by column chromatography, the liquid trioxanes were found by NMR spectra to be a mixture of two isomers. From a hexane, or occasionally a hexane–ethyl acetate, solution of the liquid, one of the isomers of **3** slowly crystallized into colorless prisms. Based on X-ray crystal-structure analyses of the prisms, the structures of the trioxane ring in **3a**[4] and **3k**[5] were found to be different from each other. The structure of **3a** was the chair conformation of the trioxane ring with the naphthylamino group bonding at an equatorial position (cis isomer), while that of **3k** bonded to the 2-chloroanilino group occupying an axial position (trans isomer). We now report on the distinction between these cis and trans isomers of **3** on the basis of ^{13}C NMR spectra.

Results and Discussion

The sixteen synthesized trioxanes (**3**) were divided into three groups according to ^{13}C NMR chemical shifts (Table 1). The *gem*-dimethyl groups at C-6 of **3** were assigned by comparing their NMR signals with those of other trioxanes having one methyl at C-6 (5-arylamino-6-methyl-6-phenyl-3-(1-phenylethyl)-1,2,4-trioxanes[6]). The trioxanes of group 1, including **3a**, exhibited the C-3 signals at a lower field (δ 107.3—107.1) than those of the group 2, including **3k** (δ 99.7—99.4), whereas axial methyl signals at C-6 of group 1 appeared at higher fields (δ 17.7—17.4) than those of group 2 (δ 23.8—23.6). Since the C-3 and axial methyl carbons are in the γ-position relative to the nitrogen, the difference between these chemical shifts may be interpreted according to the suggestion that the γ-gauche-effect is stronger than the γ-trans-effect for nitrogen.[7] When the $CDCl_3$ solutions of group 1 were allowed to stand at room temperature for a long time, new ^{13}C signals appeared in the higher fields where the trioxanes of group 2 had shown signals. Similarly, when the $CDCl_3$ solutions of group 2 were allowed to stand, new ^{13}C signals were observed in the lower fields where those of group 1 had appeared. (These new signals are shown in parentheses in Table 1.) These changes in the spectra can be explained in terms of the establishment of an equilibrium between cis and trans isomers: the change is caused by an anomerization at C-5 of the 1,2,4-trioxane ring. Since the intensity ratio of the two isomers reached a constant value within about two days, it may be reasonable to assume that these two isomers reached equilibrium during this period. Molar fractions of cis isomer (x_{cis} were derived from average intensities of distinguishable ^{13}C signals at



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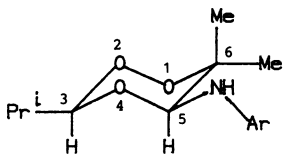
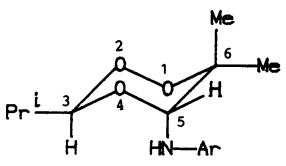


3 (cis)



3 (trans)

Ar=a; 1-naphthyl b; 2-methyl-4-chlorophenyl c; 2,4-xylyl d; 2,5-xylyl e; 4-chlorophenyl f; 4-bromophenyl g; 4-ethoxycarbonylphenyl h; 4-acetylphenyl i; 3-acetylphenyl j; 2-methyl-3-chlorophenyl k; 2-chlorophenyl l; *o*-tolyl m; phenyl n; 9-anthryl o; mesityl p; 2,6-xylyl

Scheme 1.

Table 1. ^{13}C NMR Chemical Shifts of 5-Arylamino-1,2,4-trioxanes (**3**) in $CDCl_3$ at 25 °C (δ/ppm from Me_4Si)[a]

	C-3	CH	Me	Me	C-5	eq. Me	C-6	ax. Me
Group 1								
3a-cis	107.1	31.0	16.9, 16.7		86.7	22.0	80.0	17.6
trans	(99.5)	(30.6)			(81.6)	(22.7)		(23.6)
3b-cis	107.1	31.0	16.9, 16.8		86.5	22.0	79.8	17.5
trans	(99.4)	(30.6)			(81.3)	(22.7)		(23.6)
3c-cis	107.3	31.1	17.0		87.1	22.2	80.2	17.5
trans	(99.5)	(30.8)			(81.8)	(22.9)		(23.8)
3d-cis	107.3	31.1	17.0		86.6	22.1	80.1	17.7
trans	(99.5)	(30.8)			(81.5)	(22.9)		(23.8)
3e-cis	107.2	31.0	16.8		86.4	21.8	79.8	17.4
trans	(99.5)	(30.6)			(81.2)	(22.4)	(79.7)	(23.6)
3f-cis	107.2	31.0	16.8		86.2	21.8	79.8	17.5
trans	(99.5)	(30.6)			(81.1)	(22.4)		(23.6)
3g-cis	107.3	31.0	16.9, 16.8		85.5	21.9	79.7	17.5
trans	(99.7)	(30.6)			(80.4)	(22.3)		(23.2)
3h-cis	107.1	31.0	16.8, 16.7		85.5	21.8	79.7	17.5
trans	(99.7)	(30.6)			(80.5)	(22.3)		(23.6)
3i-cis	107.2	31.0	16.8		86,2	21.8	79.9	17.5
trans	(99.6)	(30.5)			(81.0)	(22.4)	(79.8)	(23.7)
Group 2								
3j-trans	99.5	30.6	16.8		81.4	22.8	79.9	23.6
cis	(107.2)	(31.0)			(86.5)	(22.0)		(17.6)
3k-trans	99.5	30.6	16.8, 16.6		81.1	22.5	79.6	23.6
cis	(107.1)	(31.0)			(85.8)	(21.9)	(79.7)	(17.5)
3l-trans	99.4	30.6	16.8		81.4	22.7	79.9	23.6
cis	(107.1)	(31.0)			(86.5)	(22.0)		(17.5)
3m-trans	99.7	30.7	17.0		81.4	22.6	80.0	23.8
cis	(107.4)	(31.1)			(86.5)	(22.0)		(17.6)
Group 3								
3n-cis	107.0	31.0	16.9, 16.5		92.1	22.6	81.2	17.6
3o-cis	106.9	31.2	16.7		90.7	22.2	81.0	17.2
3p-cis	106.9	31.2	16.8		90.4	22.2	81.0	17.2

a) Newly appeared signals in solution are given in parentheses.

equilibrium. Thus, the free-energy difference of this change ($G°_{cis}-G°_{trans}$) was evaluated from x_{cis} by the equation $G°_{cis}-G°_{trans}=RT\ln(1-x_{cis})/x_{cis}$ at 25 °C (Table 2). These $G°_{cis}-G°_{trans}$ values were very close to those of 2-(arylamino)tetrahydropyrans.[8] Thus, there would be no appreciable dipole interaction between arylamino substituent and the three oxygen atoms of the trioxane ring.

When the $CDCl_3$ solutions of the trioxanes of group 3 were allowed to stand at room temperature, no ^{13}C signal of another isomer (corresponding to trans) was observed in solution, and only signals of the prducts of trioxane decomposition (acetone and 2-methylpropanal) were observed. The observed spectra of group 3 were very similar to those of group 1 except for the C-5 signal which shifted to a lower field. All trioxanes of group 3 are bonded with a 2,6-disubstituted arylamino group at C-5. These low-field shifts in ^{13}C NMR spectra, having the above similarity, have been recognized in the methyl signal of *N*-methylaniline derivatives having two substituents at ortho positions (Table 3). Therefore, it is considered that in group 3 there exists only a cis isomer with an arylamino group rotated along the N–C bond.

Table 2. Equilibration of 5-Arylamino-3-isopropyl-1,2,4-trioxanes (**3**) in $CDCl_3$ at 25 °C

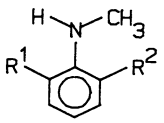
Trioxane	cis isomer, %	$G°_{cis}-G°_{trans}$/kJ mol^{-1}
3a	78±2	3.1±0.1
3b	80±1	3.4±0.1
3c	82±1	3.8±0.1
3d	82±1	3.8±0.1
3e	80±5	3.4±0.2
3f	87±3	5.1±0.1
3g	93±2	6.4±0.1
3h	91±1	5.7±0.1
3i	80±2	3.4±0.1
3j	80±3	3.4±0.1
3k	75±3	2.7±0.1
3l	79±2	3.3±0.1
3m	79±3	3.3±0.1

Experimental

Melting points are all uncorrected. Spectral characterization was carried out with the following instruments. ^{13}C NMR: JEOL JNM-FX100 and Varian CFT-20 spectrometers using tetramethylsilane as an internal standard;

Table 3. Chemical Shifts of Methyl-Carbon of *N*-Methylanilines in $CDCl_3$ (δ/ppm from Me_4Si)

Compd	$R^1=R^2=H$[9]	$R^1=H, R^2=Me$[9]	$R^1=R^2=Me$[10]
$\underline{C}H_3$-N	30.4	30.4	35.3



^1H NMR: Hitachi R-20A spectrometer; MS: JEOL JMS-DX300 mass spectrometer using a direct insertion probe at 20 eV and 100 μA of ionization energy; IR: Hitachi 215 spectrometer.

Materials. The general preparation of 5-arylamino-1,2,4-trioxanes has recently been reported and trioxanes **3a,3c—d** and **3k—p** have been described.[3]

5-(4-Chloro-2-methylanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane (3b): prisms from hexane–ethyl acetate (yield 38%), mp 103—104 °C (decomp); IR (Nujol) 3440, 1300, 1255, 1150, and 1050 cm^{-1}; ^1H NMR of cis isomer ($CDCl_3$) δ=0.95 (6H, d, J=6.5 Hz), 1.19 (3H, s), 1.52 (3H, s), ca. 1.9 (1H, m), 2.12 (3H, s), 3.71 (1H, d, J=10 Hz), 4.77 (1H, d, J=10 Hz), 5.06 (1H, d, J=5.5 Hz), and 6.5—7.2 (3H, m) DI-MS (20 eV) m/z (%) 301, 299 (M^+, 7:23), 172, 170 (24:100); Found: C,60.34; H,7.39; N, 4.63%. Calcd for $C_{15}H_{22}NO_3Cl$: C, 60.09; H, 7.39; N, 4.67%.

5-(4-Chloroanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane (3e): prisms from hexane (yield 17%), mp 54—55 °C (decomp); IR(Nujol) 3410, 1310, 1250, 1155, and 1070 cm^{-1}; ^1H NMR of cis isomer ($CDCl_3$) δ=0.92 (6H, d, J=7 Hz), 1.15 (3H, s), 1.46 (3H, s), ca. 1.8 (1H, m), 3.92 (1H, d, J=10 Hz), 4.75 (1H, d, J=10 Hz), 5.02 (1H, d, J=5.5 Hz), and 6.5—7.3 (4H, m); DI-MS (20 eV) m/z (%) 287, 285 (M, 6:17), 158, 156 (33:100); Found: C, 58.94; H, 7.09; N, 4.85%. Calcd for $C_{14}H_{20}NO_3Cl$: C, 58.84 H, 7.05; N, 4.90%.

5-(4-Bromoanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane (3f): prisms from hexane (yield 31%), mp 49—51 °C (decomp); IR (Nujol) 3420, 1290, 1250, 1155, 1140, and 1070 cm^{-1}; ^1H NMR of cis isomer ($CDCl_3$) δ=0.95 (6H, d, J=7 Hz), 1.17 (3H, s), 1.49 (3H, s), ca. 1.9 (1H, m), 3.95 (1H, d, J=10 Hz), 4.79 (1H, d, J=10 Hz), 5.04 (1H, d, J=5.5 Hz), and 6.4—7.4 (4H, m); DI-MS (20 eV) m/z (%) 331, 329 (M^+, 23:23), 202, 200 (94:100); Found: C, 50.95; H, 6.18; N, 4.21%. Calcd for $C_{14}H_{20}NO_3Br$: C, 50.92; H, 6.10 N, 4.24%.

5-(4-Ethoxycarbonylanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane(3g): prisms from hexane (yield 17%), mp 99—101 °C (decomp); IR (Nujol) 3420, 1680, 1290, 1270, 1180, 1150, and 1060 cm^{-1}; ^1H NMR of cis isomer ($CDCl_3$) δ=0.93 (6H, d, J=6.5 Hz), 1.15 (3H, s), 1.32 (3H, t, J=7 Hz) 1.49 (3H, s), ca. 1.8 (1H, m), 4.24 (2H, q, J=7 Hz), 4.37 (1H, d, J=10 Hz), 4.78 (1H, d, J=10 Hz), 5.04 (1H, d, J=5.5 Hz), and 6.5—7.9 (4H, m); DI-MS (20 eV) m/z (%) 323 (M^+ ,8), 194 (100); Found: C, 63.22; H, 7.85; N, 4.40%. Calcd for $C_{17}H_{25}NO_5$: C, 63.13; H, 7.79; N, 4.33%.

5-(4-Acetylanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane (3h): prisms from hexane–ethyl acetate (yield 35%), mp 105—106 °C (decomp); IR (Nujol) 3430, 1670, 1280, 1265, 1150, and 1060 cm^{-1}; ^1H NMR of cis isomer ($CDCl_3$) δ=0.96 (6H, d, J=6.5 Hz), 1.20 (3H, s), 1.53 (3H, s), ca. 1.9 (1H, m), 2.51 (3H, s), 4.50 (1H, d, J=10 Hz), 4.96 (1H, d, J=10 Hz), 5.13 (1H, d, J=5.5 Hz), and 6.7—8.0 (4H, m); DI-MS (20 eV) m/z (%) 293 (M^+ ,10), 164 (100); Found: C, 65.41; H, 7.91; N, 4.65%. Calcd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77%.

5-(3-Acetylanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane (3i): prisms from hexane–ethyl acetate (yield 42%), mp 82—84 °C (decomp); IR (Nujol) 3440, 1680, 1295 (w), 1270, 1150, and 1050 cm^{-1}; ^1H NMR of cis isomer ($CDCl_3$) δ=0.96 (6H, d, J=6.5 Hz), 1.21 (3H, s), 1.53 (3H, s), ca. 1.8 (1H, m), 2.58 (3H, s), 4.21 (1H, d, J=10 Hz), 4.96 (1H, d, J=10 Hz), 5.16 (1H, d, J=5.5 Hz), and 6.6—7.5 (4H, m); DI-MS (20 eV) m/z (%) 293(M^+ ,8), 164 (100); Found: C, 65.31; H, 8.05; N, 4.65%. Calcd for $C_{16}N_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77%.

5-(3-Chloro-2-methylanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane (3j): prisms from hexane (yield 4.2%, yield of crude liquid 41%), mp 37—38 °C (decomp); IR (Nujol) 3450, 1300, 1250, 1155, 1130, and 1050 cm^{-1}; ^1H NMR of trans isomer ($CDCl_3$) δ=0.95 (6H, d, J=7 Hz), 1.19 (3H, s), 1.52 (3H, s), ca. 1.9 (1H, m), 2.20 (3H, s), 4.84 (1H, d, J=10 Hz), 4.80 (1H, d, J=10 Hz), 5.11 (1H, d, J=5.5 Hz), and 6.5—7.3 (3H, m); DI-MS (20 eV) m/z (%) 301, 299 (M^+, 5:14), 172, 170 (31:100); Found: C, 60.08; H, 7.47; N, 4.72%. Calcd for $C_{15}H_{22}NO_3Cl$: C, 60.09; H, 7.39; N ,4.67%.

We are indebted to Mr. Mamoru Sekine of the Department of Chemistry, Ibaraki University, and Mr. Hideto Suzuki of the Analytical Center, the University of Tsukuba, for obtaining the ^1H and ^{13}C NMR spectra. This research was partially supported by a Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture (Ibaraki University, 1986).

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6) Preparation of these trioxanes were reported in ref 3), but their ^{13}C NMR spectra have been unpublished. In 5-arylamino-6-methyl-6-phenyl-3-(1-phenylethyl)-1,2,4-trioxanes, the axial methyl signals at C-6 appeared at δ 15.5—15.8 in the cis isomer and at δ 25.7—26.7 in the trans isomer.

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