Synthesis and Four Isomers of 5-Arylamino-3-isopropyl-6-methyl-6-phenyl-1,2,4-trioxanes

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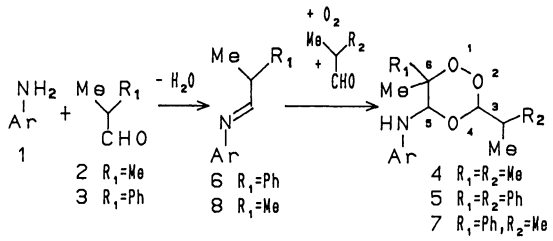
Synopsis. 5-Arylamino-3-isopropyl-6-methyl-6-phenyl-1,2,4-trioxanes were synthesized by autoxidation of imines in the presence of isobutyraldehyde. Their four isomers have been identified and the anomerization of 5-arylamino-1,2,4-trioxanes has been detected by the ^{13}C NMR spectra in chloroform-*d*.

The 1,2,4-trioxanes have attracted the attention of researchers since they play an active role in sesquiterpene Arteannuin,[1] an antimalarial remedy. Several methods for the synthesis of 1,2,4-trioxanes have been reported,[2] while we obtained 5-arylamino-1,2,4-trioxanes **4** and **5** through reactions of arylamines **1** and aldehydes **2** and **3** in the presence of oxygen (Scheme 1).[3] The structures of both the cis($3R^*,5S^*$) and trans ($3R^*,5R^*$) isomers of **4** became apparent based on X-ray crystal-structure analyses;[4] the distinction between these two isomers were established on the basis of ^{13}C NMR chemical shifts.[5] Trioxanes **4** and **5** are composed of an arylamine and two molecules of aldehyde incorporated in the same ring. We now report on the synthesis of trioxanes in which two different kinds of aldehydes are incorporated. The structures of four isomers of trioxanes, thus produced, are characterized.



Ar = a; *p*-tolyl b; *o*-tolyl c; phenyl d; 2-chlorophenyl e; 2,4-xylyl f; 4-chlorophenyl g; *m*-tolyl h; 2,6-xylyl i; mesityl.

Scheme 1.

Results and Discussion

Imines **6**, easily obtained from **1** and **3**, were autoxidized in the presence of **2** for a few days (Scheme 1). After the resulting mixture was separated into five products by HPLC (high-performance liquid chromatography), products were characterized by the use of a mass spectrometer. In the case of **6a**, the product corresponding to the first peak was assigned to be trioxane **4a** (*m/z* 265, M^+) in which two molecules of isobutyraldehyde are incorporated. The other four products showed the same parent ion peaks for new trioxane (*m/z* 327, M^+). A similar tendency in the reaction of imines **6b—g** was also observed by means of HPLC. On the other hand, imines **6h,i** bearing a 2,6-disubstituted phenyl moiety gave only one product. From these mixtures, colorless crystallines of trioxanes **7a—i** were obtained by column chromatography and recrystallization from hexane; they gave satisfactory spectral data (NMR, IR, MS).

Since imine **8** was partly interconverted into imine **6** during autoxidation with **3**, the oxidation of imines **8** in the presence of **3** gave a number of products. In the case of **8a**, these products consisted of **4a**, two isomers of **5a** and four isomers of **7a** on the basis of HPLC and mass spectra. We could not isolate any pure crystallines from these reaction mixtures.

Four isomers of **7** ($3R^*,5S^*,6R^*$, $3R^*,5R^*,6R^*$, $3R^*,5S^*,6S^*$, $3R^*,5R^*,6S^*$) and another four equatorial-axial interconversion conformers are expected by analogy with the case of 1,2,4-trisubstituted cyclohexanes.[6] Since a previous X-ray analysis of **4** suggested that the isopropyl group at C-3 is bonded at an equatorial position, **7** may exists in four isomers which have an isopropyl group bonding at an equatorial position (Fig. 1). ^{13}C NMR was the established method for the conformational analysis of **4**. Therefore, a conformational analysis of **7** was attempted by ^{13}C NMR.

Since the ^{13}C signal of C-3 of **7e,f** appeared at δ 99.8—99.9, the anilino nitrogen at C-5 is located γ-gauche to C-3 and the conformation at C-5 has been determined to be R^*. Since the methyl at C-6 is γ-

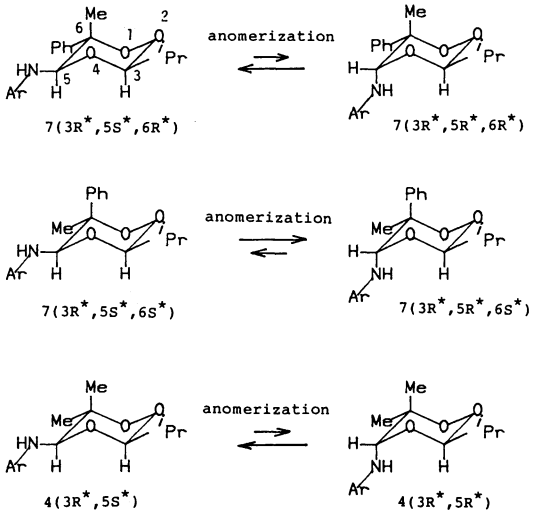


Fig. 1. Four possible isomers of **7** and two isomers of **4**.

Table 1. ^{13}C NMR Chemical Shifts of **7** in $CDCl_3$ at 25 °C (δ/ppm from Me_4Si)[a]

	C-3	CH	Me	Me	C-5	C-6	Me	Me-Ar
7a(3*R**,5*S**,6*R**)	107.2	31.1	17.0		86.8	82.6	16.3	20.4
(3*R**,5*R**,6*R**)	(99.9)	(30.6)			(83.0)		(25.7)	
7b(3*R**,5*S**,6*R**)	107.1	31.1	16.9		87.0	82.7	16.3	17.0
(3*R**,5*R**,6*R**)	(99.9)	(30.7)			(83.4)		(24.9)	
7c(3*R**,5*S**,6*R**)	107.2	31.0	17.0		86.4	82.6	16.3	—
(3*R**,5*R**,6*R**)	(99.9)	(30.6)			(82.6)		(25.6)	
7d(3*R**,5*S**,6*R**)	107.1	31.0	17.0		86.1	82.5	16.2	
(3*R**,5*R**,6*R**)	(99.6)	(30.6)			(83.7)		(25.2)	
7e(3*R**,5*R**,6*R**)	99.8	30.7	16.9		83.6	82.8	25.0	16.5, 20.4
(3*R**,5*S**,6*R**)	(107.1)	(31.1)			(87.5)		(16.3)	
7f(3*R**,5*R**,6*R**)	99.9	30.6	16.9		82.4_9	82.5_2	25.6	
(3*R**,5*S**,6*R**)	(107.2)	(31.1)			(86.5)		(16.2)	
7g(3*R**,5*R**,6*S**)	99.5	30.4	16.6		79.7	84.1	25.8	21.6
(3*R**,5*S**,6*S**)	(107.6)	(31.1)			(87.6)		(22.9)	
7h(3*R**,5*S**,6*R**)	106.9	31.1	16.7, 16.6		90.9	83.6	14.7	18.0
7i(3*R**,5*S**,6*R**)	106.7	31.2	16.7		91.1	83.6	14.6	17.9, 20.5
	C-3	CH	Me	Me	C-5	eq. Me	C-6	ax. Me
4f(3*R**,5*S**)[b]	107.2	31.0	16.8		86.4	21.8	79.8	17.4
(3*R**,5*R**)	(99.5)	(30.6)			(81.2)	(22.4)	(79.7)	(23.6)

a) Newly appeared signals in solution are given in parenthese. b) Typical trioxane of **4**, (3*R**,5*S**)-5-(4-chloroanilino)-3-isopropyl-6,6-dimethyl-1,2,4-trioxane, from Ref. 5).

trans to the nitrogen, from the ^{13}C shift value for this carbon at δ 25.0—25.6, the conformation at C-6 has been determined to be *R**. It may, therefore, be considered that the structure of **7e,f** is **7** (3*R**,5*R**,6*R**). When $CDCl_3$ solutions of **7e,f** were allowed to stand for a few days new ^{13}C signals appeared in lower fields where trioxanes of **7a—d** had shown signals. Similarly, when $CDCl_3$ solutions of **7a—d** were allowed to stand new ^{13}C signals were observed in the higher fields, where those of **7e,f** had appeared. These new signals are shown in parentheses in Table 1. Since these spectral changes can be ascribed to anomerization at C-5 of the 1,2,4-trioxane ring between **7** (3*R**,5*R**,6*R**) and **7** (3*R**,5*S**,6*R**), by analogy with the case of **4**[5] the structure of **7a—d** seems to be **7** (3*R**,5*S**,6*R**). The ^{13}C chemical shifts of C-3 (δ 107.1—107.2) and the methyl carbon (δ 16.2—16.3) support this conformation.

The ^{13}C NMR signals for **7g** were notable for C-5 and C-6 at δ 79.7 (the highest field) and at δ 84.1 (the lowest field), respectively. Since the nitrogen is located γ-gauche to C-3 from its value δ 99.5, the conformation of C-5 has been determined to be *R**. The ^{13}C signal for the methyl carbon at C-6 of this isomer (δ 25.8) was close to that of the anomeric isomer (δ 22.9). This may suggest that the methyl group in each isomer occupies an equatorial position of the trioxane ring and that the conformation of C-6 is *S**. Therefore, the structure of **7g** seems to be **7** (3*R**,5*R**,6*S**) and the anomeric isomer to be **7** (3*R**,5*S**,6*S**). Attempts to analyze **7g** by X-rays were unsuccessful because of the rapid intensity decrease of the reflections during measurement. However, an analysis with a technically insufficient number of reflections may support the 3*R**,5*R**,6*S** conformation of **7g**.[7]

Table 2. Equilibration of **7** in $CDCl_3$ at 25 °C

3*R**,5*S**,6*R** isomer/%		$\Delta G^{\circ a)}$/kJ mol^{-1}
7a	62±1	1.2±0.1
7b	62±2	1.2±0.2
7c	61±3	1.1±0.3
7d	71±1	2.2±0.1
7e	62±1	1.2±0.1
7f	57±1	0.7±0.1
3*R**,5*R**,6*S** isomer/%		$\Delta G^{\circ b)}$/kJ mol^{-1}
7g	81±5	3.7±0.8

a) $\Delta G^\circ = G^\circ_{3R^*,5R^*,6R^*} - G^\circ_{3R^*,5S^*,6R^*}$. b) $\Delta G^\circ = G^\circ_{3R^*,5S^*,6S^*} - G^\circ_{3R^*,5R^*,6S^*}$.

The ^{13}C NMR spectra of **7h,i** were very similar to those of **7a—d**, except for the C-5 signal which shifted to lower field (δ 90.9—91.1). It may, thus, be considered that the structure of **7h,i** is **7** (3*R**,5*S**,6*R**) and that the C-5 signal appeared at a low field owing to an anisotropic effect of the twisted aryl group.

The free-energy difference of anomerization was evaluated from the molar fractions of isomers derived from the average intensity of ^{13}C signals at equilibrium (Table 2). These values were smaller than those of trioxane **4**. The phenyl substitution of the ring causes a smaller free-energy differences between the anomeric isomers.

Experimental

Melting points are all uncorrected. Spectral characterizations were carried out with the following instruments: ^{13}C NMR, JEOL JNM-GSX400 spectrometer; ^{1}H NMR,

Hitachi R-20A spectrometer; MS, JEOL JMS-DX300 mass spectrometer; and IR, Hitachi 215 spectrometer. HPLC was performed by using a JASCO 800 liquid chromatograph with a SIL C18T column (7.2×250 mm, 90% methanol aq as eluent).

General Preparation of Trioxanes 7. The mixture of arylamine **1** (15 mmol) and 2-phenylpropionaldehyde (**3**) (15.5 mmol) was heated in an oil bath (110 °C) under nitrogen for 30 min. A solution of the crude imine **6** and isobutyraldehyde (**2**) (30 mmol) in hexane (25 ml) was autoxidized in a 100 ml Erlenmyer flask at room temperature. After about 2 to 4 days, the solvent and excess **2** were removed under reduced pressure and the residue was chromatographed on silica gel to give the corresponding trioxane **7**.

(3*R,5*S**,6*R**)-3-Isopropyl-6-methyl-6-phenyl-5-(*p*-toluidino)-1,2,4-trioxane (7a):** prisms from hexane (yield 13%), mp 83—85 °C (decomp); IR(Nujol) 3450, 1300, 1255, 1145, and 1055 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.99 (6H, d, J=6.5 Hz), 1.87 (3H, s), 2.19 (3H, s), ca. 1.9 (1H, m), 3.87 (1H, d, J=10 Hz), 5.14 (1H, d, J=10 Hz), 5.18 (1H, d, J=5.5 Hz), and 6.3—7.5 (9H, m); DI-MS m/z (%) 327 (M^+, 0.3), 136 (90), and 135 (100); Found: C, 73.27; H, 7.74; N, 4.26%. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.69; N, 4.27%.

(3*R,5*S**,6*R**)-3-Isopropyl-6-methyl-6-phenyl-5-(*o*-toluidino)-1,2,4-trioxane (7b):** prisms from hexane (yield 10%), mp 111—115 °C (decomp); IR (Nujol) 3460, 1300, 1260, 1175, 1145, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.04 (6H, d, J=6.5 Hz), 1.93 (3H, s), 2.05 (3H, s), ca. 2.0 (1H, m), 3.88 (1H, d, J=9 Hz), 5.14 (1H, d, J=9 Hz), 5.26 (1H, d, J=5.5 Hz), and 6.5—7.6 (9H, m); DI-MS m/z (%) 327 (M^+, 0.2), 136 (100), and 135 (63); Found: C, 73.44; H, 7.70; N, 4.24%. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.69; N, 4.27%.

(3*R,5*S**,6*R**)-5-Anilino-3-isopropyl-6-methyl-6-phenyl-1,2,4-trioxane (7c):** prisms from hexane (yield 13%), mp 97—98 °C (decomp); IR (Nujol) 3450, 1305, 1250, 1155, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (6H, d, J=6.5 Hz), 1.88 (3H, s), ca. 1.9 (1H, m), 4.00 (1H, d, J=9.5 Hz), 5.16 (1H, d, J=9.5 Hz), 5.20 (1H, d, J=5.5 Hz), and 6.5—7.8 (10H, m); DI-MS m/z (%) 313 (M^+, 1.5), 122 (83), and 121 (100); Found: C, 72.58; H, 7.40; N, 4.48%. Calcd for $C_{19}H_{23}NO_3$: C, 72.81; H, 7.39; N, 4.46%.

(3*R,5*S**,6*R**)-5-(2-Chloroanilino)-3-isopropyl-6-methyl-6-phenyl-1,2,4-trioxane (7d):** prisms from hexane (yield 6%), mp 116—118 °C (decomp); IR (Nujol) 3460, 1325, 1255, 1175, 1120, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.01 (6H, d, J=6.5 Hz), 1.87 (3H, s), ca. 2.0 (1H, m), 4.79 (1H, d, J=9.5 Hz), 5.19 (1H, d, J=9.5 Hz), 5.28 (1H, d, J=5.0 Hz), and 6.5—7.6 (9H, m); DI-MS m/z (%) 349, 347 (M^+, —, 0.2), 156 (49), 155 (25), and 120 (100); Found: C, 65.44; H, 6.45; N, 4.02%. Calcd for $C_{19}H_{22}NO_3Cl$: C, 65.60; H, 6.37; N, 4.02%.

(3*R,5*R**,6*R**)-3-Isopropyl-6-methyl-6-phenyl-5-(2,4-xylidino)-1,2,4-trioxane (7e):** prisms from hexane (yield 7%), mp 103—105 °C (decomp); IR (Nujol) 3450, 1295, 1265, 1150, and 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.97 (6H, d, J=6.5 Hz), 1.54 (3H, s), 1.96 (3H, s), ca. 1.9 (1H, m), 2.19 (3H, s), 3.95 (1H, d, J=6 Hz), 5.13 (1H, d, J=6 Hz), 5.47 (1H, d, J=5.5 Hz), and 6.7—7.4 (8H, m); DI-MS m/z (%) 341 (M^+, 0.2), 150 (24), 151 (56), and 105 (100); Found: C, 73.84; H, 8.09; N, 4.06%. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10%.

(3*R,5*R**,6*R**)-5-(4-Chloroanilino)-3-isopropyl-6-methyl-6-phenyl-1,2,4-trioxane (7f):** prisms from hexane (yield 2.2%), mp 69—70 °C (decomp); IR (Nujol) 3440, 1310, 1290, 1250, 1150, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (6H, d, J=6.5 Hz), 1.91 (3H, s), ca. 1.9 (1H, m), 4.18 (1H, d, J=6.5 Hz), 5.15 (1H, d, J=6.5 Hz), 5.32 (1H, d, J=5.5 Hz), and 6.3—7.4 (9H, m); DI-MS m/z (%) 349, 347 (M^+, —, 3.6), 156 (61), and 155 (100); Found: C, 65.60; H, 6.41; N, 4.05%. Calcd for $C_{19}H_{22}NO_3Cl$: C, 65.60; H, 6.37; N, 4.02%.

(3*R,5*R**,6*S**)-3-Isopropyl-6-methyl-6-phenyl-5-(*m*-toluidino)-1,2,4-trioxane (7g):** prisms from hexane (yield 4.7%), mp 84—85 °C (decomp); IR (Nujol) 3430, 1320, 1260, 1210, 1170, 1150, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67 (6H, d, J=6.5 Hz), 1.38 (3H, s), ca. 1.7 (1H, m), 2.29 (3H, s), 4.90 (1H, d, J=10 Hz), 5.66 (1H, d, J=10 Hz), 5.26 (1H, d, J=4.5 Hz), and 6.5—7.3 (9H, m); DI-MS m/z (%) 327 (M^+, 0.4), 134 (37), 135 (67), and 105 (100); Found: C, 73.28; H, 7.67; N, 4.28%. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.69; N, 4.27%.

(3*R,5*S**,6*R**)-3-Isopropyl-6-methyl-6-phenyl-5-(2,6-xylidino)-1,2,4-trioxane (7h):** prisms from hexane (yield 27%), mp 86—88 °C (decomp); IR (Nujol) 3390, 1285, 1260, 1215, 1065, and 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.96 (6H, d, J=6.5 Hz), 1.89 (6H, s), 1.94 (3H, s), ca. 1.95 (1H, m), 3.32 (1H, d, J=10 Hz), 4.58 (1H, d, J=10 Hz), 5.05 (1H, d, J=5.0 Hz), and 6.7—7.6 (8H, m); DI-MS m/z (%) 341 (M^+, 0.05), 150 (100), and 149 (83); Found: C, 74.00; H, 7.90; N, 4.12%. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10%.

(3*R,5*S**,6*R**)-3-Isopropyl-5-mesitylamino-6-methyl-6-phenyl-1,2,4-trioxane (7i):** prisms from hexane (yield 41%), mp 116—117 °C (decomp); IR (Nujol) 3410, 1230, 1165, 1070, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.94 (6H, d, J=6.5 Hz), 1.83 (6H, s), 1.93 (3H, s), ca. 1.9 (1H, m), 2.14 (3H, s), 3.23 (1H, d, J=11 Hz), 4.54 (1H, d, J=11 Hz), 5.03 (1H, d, J=4.5 Hz), and 6.6—7.6 (7H, m); DI-MS m/z (%) 355 (M^+, 0.07), 164 (100), and 163 (68); Found: C, 74.36; H, 8.22; N, 3.92%. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94%.

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7) The structure with non-hydrogen atoms was obtained, though at R=0.14, and showed both the phenyl and *m*-toluidino groups occupying and axial position.