Synthesis and Stereochemistry of 11-Amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepines and -oxepines

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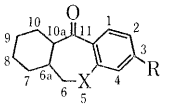
11-Amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepines (6a—d) and -oxepines (7a—d) were synthesized by the Leuckart reaction of 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepines (1a, b) and -oxepines (2a, b) followed by hydrolysis of the reaction products 4a—d and 5a—d, respectively. The four diastereomers, *cis*(6a-H, 10a-H)-*cis*(10a-H, 11-H) 6a and 7a, *cis*(6a-H, 10a-H)-*trans*(10a-H, 11-H) 6b and 7b, *trans*(6a-H, 10a-H)-*trans*(10a-H, 11-H) 6c and 7c, and *trans*(6a-H, 10a-H)-*cis*(10a-H, 11-H) 6d and 7d, were isolated and their configurations and conformations were elucidated by chemical methods together with ^{1}H-nuclear magnetic resonance spectroscopic and X-ray crystallographic analyses.

Keywords 11-amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepine; 11-amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]oxepine; stereochemistry; spectroscopic (NMR, X-ray) analysis

We have previously reported the synthesis of new tricyclic ring compounds, 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepines (**1a**, **b**), the corresponding oxepines (**2a**, **b**),[1] and the antiinflammatory aectic acid derivatives **3**,[2] and defined their stereochemistry at C-6a and C-10a (Fig. 1). Subsequently, several fundamental reactions of **1a**, **b** and **2a**, **b** were described.[3]

As an extension of those studies, we planned to prepare 11-amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]-thiepine (**6**) and -oxepine (**7**). Both compounds contain, in common, three asymmetric carbons (C-6a, C-10a and C-11) in their nuclei, and accordingly four diastereomers can exist, *cis*(6a-H, 10a-H)-*cis*(10a-H, 11-H) **6a** and **7a**, *cis*(6a-H, 10a-H)-*trans*(10a-H, 11-H) **6b** and **7b**, *trans*(6a-H, 10a-H)-*trans*(10a-H, 11-H) **6c** and **7c**, and *trans*(6a-H, 10a-H)-*cis*(10a-H, 11-H) **6d** and **7d**. Since the 11-amino derivatives **6a—d** and **7a—d** consist of a 6-7-6 membered ring system with two saturated rings, *i.e.*, the tetrahydrothiepine or tetrahydrooxepine ring and the cyclohexane ring (Chart 1), their conformations are expected to be quite flexible. It would be of interest to know the configuration and conformation of these compounds having the new tricyclic ring system. This paper deals with a synthesis of the 11-amino compounds, **6a—d** and **7a—d**, and elucidation of their configuration and conformation by means of chemical methods together with ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopic and X-ray crystallographic analyses.

Synthesis of 11-Amino Compounds The Leuckart reactions of both (C-6a and C-10a)-isomeric 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepines (**1a**, **b**) with ammonium formate at 220 °C for 5 h gave a mixture of four stereoisomeric 11-formylamino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepines (**4a—d**) as an oil in approximately 85% yield (Chart 1). Analysis by high-performance liquid chromatography (HPLC) showed that the mixture consisted of **4a**, **4b**, **4c**, and **4d** in a 7 : 10 : 6 : 77 ratio. Each isomer **4a—d** was isolated from the mixture by preparative HPLC (Table I). In this reaction, epimerization at C-10a had occurred, thus providing two pairs of stereoisomers, *cis*(6a-H, 10a-H)-*cis*(10a-H, 11-H)/*cis*-(6a-H, 10a-H)-*trans*(10a-H, 11-H) and *trans*(6a-H, 10a-



1a : X=S, R=H, *trans* (6a-H, 10a-H)
1b : X=S, R=H, *cis* (6a-H, 10a-H)
2a : X=O, R=H, *trans* (6a-H, 10a-H)
2b : X=O, R=H, *cis* (6a-H, 10a-H)
3 : X=S, O, R=CH(Me)CO_2H, *trans* (6a-H, 10a-H)

Fig. 1

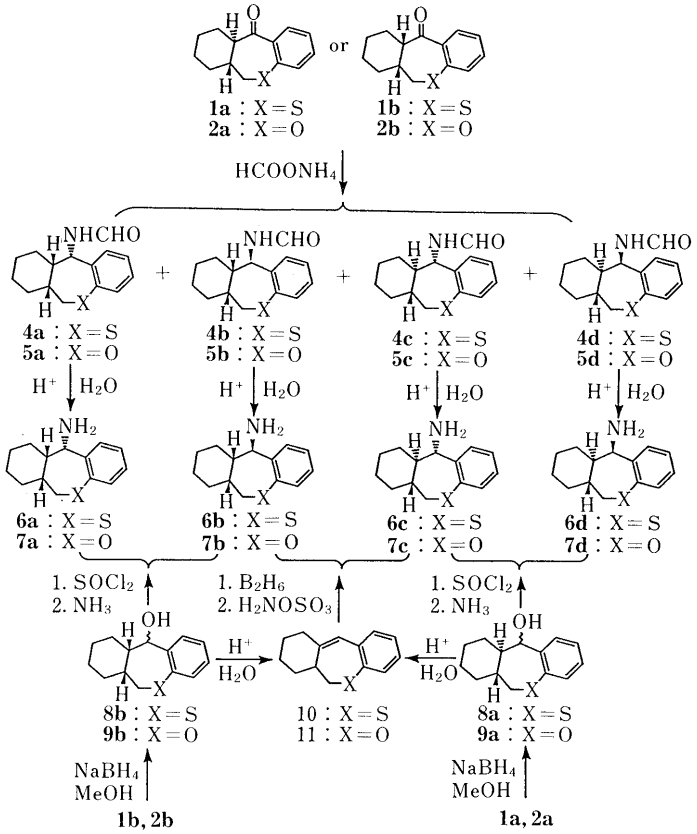


Chart 1

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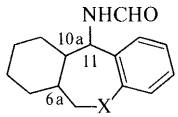
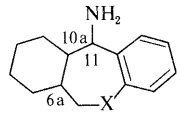
TABLE I. Physical Data for the Formamides **4a—d** and **5a—d**



Compd. No.	X	Yield (%)	Recrystn. solvent	mp (°C)	t_R[a] (min)	Formula	Analysis (%) Calcd C	H	N	S	Found C	H	N	S
4a	S	6	AcOEt	223—224	12.5	$C_{15}H_{19}NOS$	68.93	7.33	5.36	12.27	69.03	7.46	5.38	12.26
4b	S	8	Et_2O	154—157	13.2	$C_{15}H_{19}NOS$	68.93	7.33	5.36	12.27	68.80	7.49	5.33	12.61
4c	S	4	AcOEt	202—204	13.9	$C_{15}H_{19}NOS$	68.93	7.33	5.36	12.27	68.96	7.42	5.35	12.45
4d	S	60	AcOEt	111—113	16.0	$C_{15}H_{19}NOS$	68.93	7.33	5.36	12.27	69.21	7.55	5.35	12.43
5a	O	17	AcOEt	170—173	12.1[b]	$C_{15}H_{19}NO_2$	73.44	7.81	5.71		73.24	7.96	5.54	
5b	O	6	Et_2O	114—115	14.6[b]	$C_{15}H_{19}NO_2$	73.44	7.81	5.71		73.46	7.77	5.51	
5c	O	10	AcOEt	220—223	12.8[b]	$C_{15}H_{19}NO_2$	73.44	7.81	5.71		73.15	7.55	5.53	
5d	O	46	Et_2O	115—116	16.0[b]	$C_{15}H_{19}NO_2$	73.44	7.81	5.71		73.49	7.90	5.45	

a) HPLC: YMC-Pack A-312 column, 6 × 150 mm i.d.; 1% AcOH (containing PIC-B)–CH_3CN (50 : 50); flow rate 1 ml/min at 35 °C. *b*) 1% AcOH (containing PIC-B)–CH_3CN (58 : 42).

TABLE II. Physical Data for the Amine Hydrochlorides **6a—d**·HCl and **7a—d**·HCl



Compd. No.	X	Yield (%)	Recrystn. solvent	mp (°C) (dec.)	t_R[a] (min)	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
6a·HCl	S	86	EtOH	(270—280)	13.4	$C_{14}H_{19}NS$·HCl	62.32	7.47	13.14	5.19	11.88
							(62.29	7.47	13.34	5.11	11.82)
6b·HCl	S	83	EtOH	(>300)	14.9	$C_{14}H_{19}NS$·HCl	62.32	7.47	13.14	5.19	11.88
							(62.11	7.62	13.03	5.10	11.58)
6c·HCl	S	86	EtOH	(285—300)	14.0	$C_{14}H_{19}NS$·HCl	62.32	7.47	13.14	5.19	11.88
							(62.15	7.65	13.05	5.23	11.75)
6d·HCl	S	92	EtOH	(265—270)	13.5	$C_{14}H_{19}NS$·HCl	62.32	7.47	13.14	5.19	11.88
							(62.02	7.69	13.01	5.43	11.78)
7a·HCl	O	83	EtOH	(250—289)	9.5	$C_{14}H_{19}NO$·HCl	66.26	7.94	13.97	5.52	
							(65.99	8.17	14.06	5.36)	
7b·HCl	O	81	EtOH	(250—260)	10.3	$C_{14}H_{19}NO$·HCl	66.26	7.94	13.97	5.52	
							(66.10	7.88	14.11	5.50)	
7c·HCl	O	82	EtOH	(250—292)	10.6	$C_{14}H_{19}NO$·HCl	66.26	7.94	13.97	5.52	
							(65.96	7.96	13.85	5.41)	
7d·HCl	O	90	EtOH	(210—213)	9.9	$C_{14}H_{19}NO$·HCl	66.26	7.94	13.97	5.52	
							(66.05	7.73	13.76	5.47)	

a) HPLC: YMC-Pack A-312 column, 6 × 150 mm i.d.; 1% AcOH (containing PIC-B)–CH_3CN (70 : 30); flow rate 1 ml/min at 35 °C.

H)–*trans*(10a-H, 11-H)/*trans*(6a-H, 10a-H)–*cis*(10a-H, 11-H). The analogous reactions of the tetrahydrooxepines **2a** and **2b** gave a mixture of **5a**, **5b**, **5c**, and **5d** in a ratio of 21 : 8 : 14 : 57 as an oil in approximately 70% yield. Each isomer **5a—d** was isolated from the mixture by preparative HPLC.

Hydrolysis of **4a—d** and **5a—d** with dilute hydrochloric acid gave 11-amino-6,7,8,9,10,10a,11-octahydrodibenzo-[*b*,*e*]thiepines (**6a—d**) and -oxepines (**7a—d**) respectively (Chart 1 and Table II). The relative configurations at C-6a, C-10a and C-11 of compounds **6a—d** and **7a—d** were determined by the following chemical methods.

Determination of Configuration for 6a—d and 7a—d The *trans*(6a-H, 10a-H)-alcohols **8a** and **9a** and the *cis*-(6a-H, 10a-H)-alcohols **8b** and **9b**[3] were prepared by reduction of the corresponding *trans*(6a-H, 10a-H)-ketones **1a** and **2a** and *cis*(6a-H, 10a-H)-ketones **1b** and **2b** with sodium borohydride. Chlorination of the *trans*(6a-H, 10a-H)-alcohols **8a** and **9a** with thionyl chloride, followed by treatment with ammonia in a sealed tube, afforded isomeric pairs of the *trans*(6a-H, 10a-H)-amines **6c**/**6d** and **7c**/**7d**, respectively (Chart 1). Each isomer of the *trans*(6a-H, 10a-H)-amines was separated by preparative HPLC. Similarly, the C-11 isomeric pairs of the *cis*(6a-H, 10a-H)-amines **6a**/**6b** and **7a**/**7b** were obtained by the same treatment of the *cis*(6a-H, 10a-H)-alcohols **8b** and **9b**. The hydrochlorides of the amines were identical with the hydrochlorides of the foregoing products resulting from **1a**, **b** and **2a**, **b** *via* **4a—d** and **5a—d**, respectively, based on a comparison of their melting points and spectral data.

Rathke *et al.*[4] have reported that the hydroboration–amination reaction of 1-methylcyclohexene proceed-

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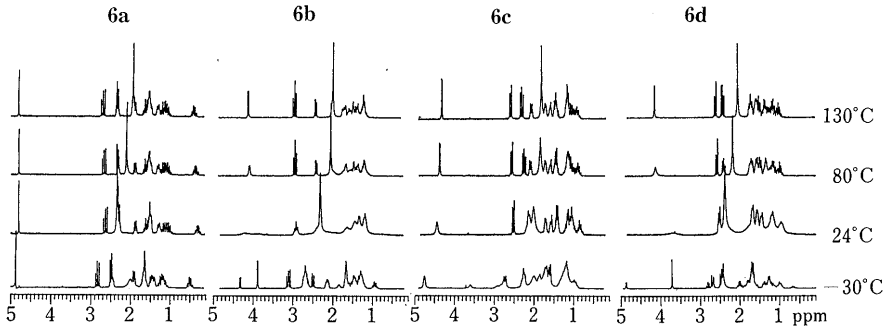

Fig. 2. ^{1}H-NMR Spectra of the Tetrahydrothiepine Amines **6a—d** at 24—130 °C in Nitrobenzene-d_5 or at −30 °C in $CDCl_3$

TABLE III. NMR Spectral Data for the Amines **6a—d** and **7a—d**

Compound No.	^{1}H-NMR[a] Chemical shifts (δ)		^{1}H-NMR[a] Coupling constants (J, Hz)		^{13}C-NMR[a] Chemical shifts (δ)		
	6a-H	10-H[b]	10a-H	11-H	C-6a	C-10a	C-11
6a	2.30 (m, 2.9[c])	0.41 (m)	1.85 (m, 2.9, 1[d])	4.76 (d, 1[e])	43.18 (d)	46.77 (d)	57.15 (d)
6b	1.98 (m, 1.5[c])	1.08—1.80 (m)	1.54 (m, 1.5, 8.1[d])	4.10 (d, 8.1[e])	35.15 (d)	46.29 (d)	60.58 (d)
6c	1.46 (m, 11.8[c])	0.82—1.26 (m)	1.16 (m, 11.8, 6.1[d])	4.31 (d, 6.1[e])	46.29 (d)	49.94 (d)	58.83 (d)
6d	1.50 (m, 12.0[c])	0.93—1.79 (m)	1.36 (m, 12.0, 2.2[d])	4.12 (d, 2.2[e])	41.45 (d)	48.66 (d)	62.11 (d)
7a[f]	2.37 (m, 3.5[c])	0.62 (m)	1.89 (m, 3.5, 2.2[d])	4.40 (d, 2.2[e])	40.96 (d)	46.27 (d)	55.30 (d)
7b[f]	2.52 (m, 3.8[c])	0.98—1.64 (m)	1.86 (m, 3.8, 5.5[d])	3.72 (d, 5.5[e])	35.55 (d)	44.42 (d)	60.91 (d)
7c[f]	1.55 (m, 11.1[c])	0.77 (m)	1.09 (m, 11.1, 7.3[d])	3.89 (d, 7.3[e])	45.21 (d)	49.12 (d)	57.21 (d)
7d[f]	2.02 (m, 12.0[c])	0.80 (m)	1.28 (m, 12.0, 1.9[d])	3.55 (d, 1.9[e])	39.65 (d)	47.52 (d)	62.95 (d)

a) In nitrobenzene-d_5 at 130 °C, 300 MHz. *b*) Axial proton. *c*) $J_{6a,10a}$. *d*) $J_{6a,10a}$, $J_{10a,11}$. *e*) $J_{10a,11}$. *f*) In nitrobenzene-d_5 at 100 °C.

ed stereospecifically to afford *trans*-2-methylcyclohexylamine. 6,6a,7,8,9,10-Hexahydrodibenzo[*b*,*e*]thiepine (**10**) and -oxepine (**11**),[3] on similar reaction, were successfully converted to the C-6a isomeric *trans*(10a-H, 11-H)-amines **6b**/**6c** and **7b**/**7c**, respectively (Chart 1). Each isomer of the *trans*(10a-H, 11-H)-amines was separated by preparative HPLC. The separated amine hydrochlorides were identical with the Leuckart reaction products **6b**·HCl, **6c**·HCl, **7b**·HCl and **7c**·HCl, based on a comparison of their melting points and spectral data. Consequently, the other amines **6a**, **6d**, **7a**, and **7d** were assignable as the *cis*(10a-H, 11-H)-isomers. From the above experiments, it follows that the relative configurations of the 11-amino derivatives are as shown by the structures **6a—d** and **7a—d**.

In the ^{1}H-NMR spectra of the tetrahydrooxepine amines **7b—d**, some signals were observed as rather broad peaks in $CDCl_3$ or nitrobenzene-d_5 at room temperature. On the other hand, the tetrahydrothiepine amines **6b—d** gave ^{1}H-NMR spectra (taken in $CDCl_3$ or nitrobenzene-d_5) in which many signals were abnormally broad over a wide range of the temperature (80——30 °C), so that the chemical shifts of 6-H, 6a-H, 10-H, 10a-H and 11-H, and hence J values, were not available (Fig. 2). Elevation of the temperature to 130 °C in nitrobenzene-d_5 sharpened those broad signals. This behavior implies the existence of many preferred conformations, of which interconversion can occur rapidly at high temperature.

Compounds **6a** and **7a**, in contrast, afforded normal ^{1}H-NMR spectra unaffected by changes of solvent and temperature. The ^{13}C-NMR spectra of **6a—d** and **7a—d** were taken in nitrobenzene-d_5 at 100—130 °C (Table III). However, contrary to our expectation, these spectra provided not useful information concerning the stereochemistry.

Assignment of the stereochemistry of the isomeric amines **6a—d** and **7a—d** was finally accomplished by the analysis of their H–H coupling constants in the NMR spectra taken at 100—130 °C in nitrobenzene-d_5 (Table III). Four compounds, **6b**, **6c**, **7b** and **7c**, showed a doublet signal due to 11-H at around δ 3.72—4.31 and the coupling constants between 10a-H and 11-H were in a range of 5.5—8.1 Hz, which data indicated 10a-H and 11-H to be *trans*. The other compounds **6a**, **6d**, **7a** and **7d** with small coupling constants (J=1—2.2 Hz) between 10a-H and 11-H were assigned as the *cis*(10a-H, 11-H)-isomers. Irradiation of 11-H of **6a—d** and **7a—d** permitted the assignment of the double doublets to 10a-H, which coupled to both 11-H and 6a-H. The 10a-H's of four compounds, **6c**, **6d**, **7c** and **7d**, appeared at δ 1.09—1.36 with coupling constants of 11.1—12.0 Hz between 6a-H and 10a-H; this indicates that 6a-H and 10a-H are in the *trans* configuration. Compounds **6a**, **6b**, **7a** and **7b** were similarly assigned as the *cis*(6a-H, 10a-H)-isomers, on the basis of their coupling constants (J=1.5—3.8 Hz) between 6a-H and 10a-H.

The relative configurations of compounds **6a** and **7a—d** were confirmed by nuclear Overhauser effect (NOE) experiments (Table IV). Irradiation of 6a-H's of **6a** and **7a** resulted in enhancement of 4.8 and 5.4% for 10a-H, respectively, and 11.5 and 10.8% for 11-H, respectively. This shows that 6a-H, 10a-H and 11-H are on the same side of the seven membered ring and, accordingly, the configuration of **6a** and **7a** is *cis*(6a-H, 10a-H)-*cis*(10a-H, 11-H) (Figs. 3 and 4). Compound **7c** was assigned as *trans*(6a-H, 10a-H)-*trans*(10a-H, 11-H) because of the existence of the NOE between 6a-H abd 11-H and the absence

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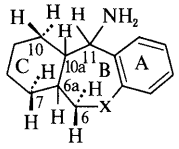
TABLE IV. NOE Difference Data for **6a** and **7a—d** in Nitrobenzene-d_5 at Room Temperature

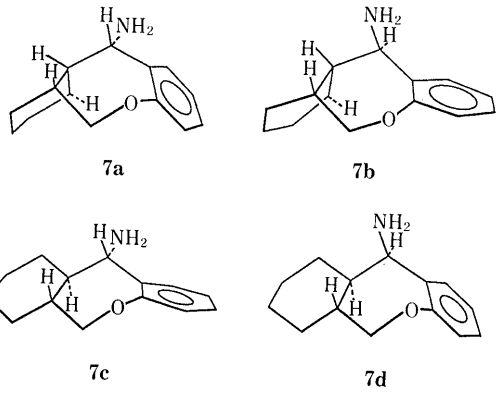


Compd. No.	Proton irradiated	Proton affected (%)
6a (X=S)	6-H_α	6-H_β (26.4), 6a-H (—[a]), 7-H_β (5.6)
	6-H_β	6-H_α (23.4), 10-H_β (2.7)
	6a-H	6-H_α (—[a]), 7-H_β (5.8), 10a-H (4.8), 11-H (11.5)
	10a-H	6a-H (3.5), 10-H_α (—[a]), 11-H (8.5)
	11-H	6a-H (8.7), 10a-H (3.5)
	11-NH_2	11-H (8.3)
7a (X=O)	6-H_α	6-H_β (21.0), 6a-H (8.4), 7-H_β (11.1)
	6-H_β	6-H_α (20.0), 10-H_β (2.3)
	6a-H	6-H_α (5.0), 10a-H (5.4), 11-H (10.8)
	10a-H	6a-H (6.2), 10-H_α (5.4), 11-H (9.4)
	11-H	6a-H (9.4), 10a-H (6.9)
	11-NH_2	10-H_α (7.2), 11-H (7.5)
7b (X=O)	6-H_α,H_β	6a-H (8.4), 7-H_β (5.0)
	6a-H	6-H_α (3.8), 7-H_β (5.0), 10a-H (5.7)
	10a-H	6a-H (5.2), 11-H (5.3)
	11-H	10a-H (5.5)
	11-NH_2	6a-H (6.3), 11-H (2.5)
7c (X=O)	6-H_α	6-H_β (25.8), 6a-H (7.9), 7-H_α (6.3)
	6-H_β	6-H_α (23.6), 7-H_β (2.0), 10a-H (1.2)
	6a-H	6-H_α (4.5), 11-H (9.1)
	10a-H	6-H_β (5.0)
	11-H	6a-H (7.9)
	11-NH_2	10a-H (3.3), 11-H (4.1)
7d (X=O)	6-H_α	6-H_β (25.5), 6a-H (7.6), 7-H_α (4.1)
	6-H_β	6-H_α (24.3), 7-H_β (3.4), 10a-H (6.3)
	6a-H	6-H_α (5.0)
	10a-H	11-H (4.7)
	11-H	10-H_β (5.8), 10a-H (5.3)
	11-NH_2	11-H (3.3)

a) NOE difference could not be determined because of overlap of the signals.

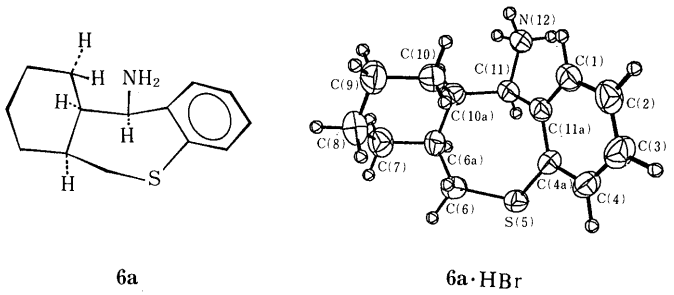
of NOE's between 6a-H and 10a-H, and 10a-H and 11-H. Similarly, compound **7d** was assigned as *trans*(6a-H, 10a-H)–*cis*(10a-H, 11-H) owing to the absence of NOE's between 6a-H and 10a-H, and 6a-H and 11-H and the existence of the NOE between 10a-H and 11-H. The *cis*(6a-H, 10a-H)– *trans*(10a-H, 11-H) configuration of **7b** was assigned based on the observation of the NOE between 6a-H and 10a-H, and the absence of NOE between 6a-H and 11-H. However, in the case of the tetrahydrothiepine compounds **6b—d**, which may have more flexible conformations seemed than the corresponding tetrahydrooxepines, the assignment by NOE experiments was unsuccessful.

The chemical shift of the axial 10-H in the ^{1}H-NMR spectra of the 11-amino compounds **6a—d** and **7a—d** is indicative of the molecular folding (the A/B/C ring stereochemistry). In the *cis*(6a-H, 10a-H)–*cis*(10a-H, 11-H)-isomers **6a** and **7a**, the 10-H's appear at δ 0.41 and 0.62, respectively, whereas the 10-H's are found at δ 0.77—1.08 in other isomers **6b—d** and **7b—d** (Table III). This large difference in the chemical shifts can be understood from an inspection of the Dreiding models. In the *cis*(6a-H, 10a-H)–*cis*(10a-H, 11-H)-isomers, the axial proton of the C-10 methylene group lies over the aromatic ring and should be subjected to an upfield shift owing to the ring current. In other isomers no shielding due to the aromatic ring anisotropy was observed. A similar conformational influence on chemical shifts has been observed for anthrasteroids.[5]



7a 7b 7c 7d

Fig. 3. The Solution-State Conformations of **7a—d**



6a 6a·HBr

Fig. 4. The Solution-State Conformations of **6a** and the Solid-State Conformation of One of the Enantiomers of **6a**·HBr

X-Ray Crystallographic Study The high field shift of approximately 1 ppm for the axial 10-H signal was important, as discussed above, for the configurational assignment of the *cis*(6a-H, 10a-H)–*cis*(10a-H, 11-H)-isomers **6a** and **7a**, in which the protons were assumed to be located above the aromatic ring, exhibiting an anisotropic effect. In order to confirm this assumption, the hydrobromide of **6a** was subjected to a single crystal X-ray analysis.

The X-ray crystal structure of **6a**·HBr, shown in Fig. 4, indicates that one hydrogen atom at C-10 in the concave site is close to the center of the aromatic ring and the cyclohexyl ring exist in the chair form. Thus solid-state conformation of **6a**·HBr established by X-ray analysis is practically identical with the preferred conformation (in solution) assigned by ^{1}H-NMR analysis of **6a** (Fig. 4).

Conclusion

Configurations and conformations of the 11-amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepines (**6a—d**) and -oxepines (**7a—d**) synthesized were elucidated by chemical methods and ^{1}H-NMR spectoscopic and X-ray crystallographic analyses. The tetrahydrothiepines **6b—d** were revealed to be conformationally more flexible, owing to the large sulfur atom, than the tetrahydrooxepines **7b—d**.

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Experimental

All melting points were determined with a Yanagimoto micro melting point apparatus, and are uncorrected. The ^{1}H-NMR and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra were obtained on a Varian XL-300 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s, singlet; d, doublet; m, multiplet; t, triplet; dd, double doublet; dt, double triplet; ddd, double double doublet. Infrared (IR) spectra were recorded on a Hitachi 260—10 grating infrared spectrophotometer and mass spectra (MS) on a JEOL D-300 mass spectrometer. HPLC was carried out on a Shimadzu LC-4A system. Organic extracts were dried over Na_2SO_4 and the solvent was removed with a rotary evaporater under reduced pressure.

The Leuckart Reaction of 6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepines (1a, b) and -oxepines (2a, b) A mixture of the ketone **1**[1] or **2**[1] (0.026 mol) and ammonium formate (33 g, 0.52 mol) was heated at 220 °C for 5 h and then poured into water. The solution was extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a mixture of the formamides **4a**—**d** or **5a**—**d**. Analysis of this mixture by HPLC using YMC-Pack A-312 column showed that (a) the Leuckart reaction of **1a** or **1b** gave a mixture of 11- formylamino-6,6a,7,8,9,10a,11-octahydrodibenzo[*b*,*e*]thiepine **4a**/**4b**/**4c**/**4d** in *ca.* 85% yield in a ratio of 7/10/6/77, and (b) the Leuckart reaction of **2a** or **2b** gave a mixture of 11-formylamino-6,6a,7,8,9,10,10a,11-octahydrodibenz[*b*,*e*]oxepine **5a**/**5b**/**5c**/**5d** in *ca.* 70% yield in a ratio of 21/8/14/57. The separation of these isomers was achieved by preparative HPLC using YMC-Pack ODS-A column.

Yield, melting point, t_R, IR and analytical data are summarized in Table I.

11-Amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepines (6a—d) and -oxepines (7a—d) General Procedure for the Hydrolysis of **4a**—**d** and **5a**—**d**: A solution of the formamide **4** or **5** (0.0004 mol) in a mixture of ethanol (5 ml) and 36% hydrochloric acid (2 ml) was refluxed for 0.5 h. The solvent was removed and the residue was crystallized from ethanol to give the corresponding amine hydrochloride, **6a**—**d**·HCl or **7a**—**d**·HCl. Yield, melting point, t_R and analytical data are summarized in Table II; ^{1}H-, ^{13}C-NMR and NOE data are summarized in Tables III, IV and V.

General Procedure for the Amination of 11-Hydroxy-6,6a,7,8,9,10,-10a,11-octahydrodibenzo[*b*,*e*]thiepines (**8a**, **b**) and -oxepines (**9a**, **b**): A mixture of the alcohol **8**[3] or **9**[3] (0.010 mol), dichloromethane (20 ml), and thionyl chloride (2.4 g, 0.020 mol) was heated at 60°C for 1.5 h. After evaporation of the solvent, the residual 11-chloro compounds was dissolved in dichloromethane (30 ml). Then liquid ammonia (50 ml) was added while the solution was cooled at −60 °C. The solution was placed in a sealed tube and allowed to stand for 3 d at room temperature. The excess ammonia was removed by evaporation and the residue was dissolved in dichloromethane. The solution was washed with a dilute K_2CO_3 solution, dried and concentrated. The residue was chromatographed on a silica gel column with chloroform–methanol (95 : 5, v/v) as an eluent to give a mixture of the amine isomers as an oil. This mixture was separated by preparative HPLC using a YMC-Pack ODS-A column. The starting alcohol and the products (with their yields) were as follows: **8a**, **6c** (25%) and **6d** (21%); **8b**, **6a** (18%) and **6b** (27%); **9a**, **7c** (11%) and **7d** (5%); **9b**, **7a** (1%) and **7b** (7%).

The hydrochlorides of the amines were identical in their NMR and IR spectra, and melting point with those of the Leuckart reaction products.

General Procedure for the Amination of 6,6a,7,8,9,10-Hexahydrodibenzo[*b*,*e*]thiepine (**10**) and -oxepine (**11**): Boron–tetrahydrofuran complex (1 M solution in tetrahydrofuran, 15 ml, 0.015 mol) was added to a solution of the hexahydro compound **10**[3] or **11**[3] (0.010 mol) in tetrahydrofuran (15 ml) under a nitrogen atmosphere at room temperature. The mixture was allowed to stand for 3 d, then a solution of hydroxylamine-*O*-sulfonic acid (3 g, 0.026 mol) in diglyme (30 ml) was added. The resulting mixture was heated at 140 °C for 2 h, then cooled and poured into a cold dilute potassium carbonate solution. The mixture was extracted with ethyl acetate. The organic layer was washed with water, drid and concentrated. The redidue was chromatographed on a silica gel column with chloroform–methanol (95 : 5, v/v) as an eluent to give a mixture of amines as an oil. Separation of this mixture was carried out by preparative HPLC. The starting material and the products (with their yields) were as follows: **10**, **6b** (3%) and **6c** (5%); **11**, **7b** (3%) and **7c** (1%).

The hydrochlorides of the amines were identical in their NMR and IR spectra, and melting point with those of the Leuckart reaction products.

Crystal Data for Compound 6a·HBr A colorless, prism shaped crystal was formed from aqueous ethanol, mp 294—300 °C (dec.) (uncorrected). *Anal.* Calcd for $C_{14}H_{19}NS \cdot HBr$: C, 53.50; H, 6.41; Br, 25.42; N, 4.46; S, 10.20. Found: C, 53.55; H, 6.45; Br, 25.65; N, 4.45; S, 10.16. Molecular weight = 314.29. ^{1}H-NMR (DMSO-d_6) δ: 0.40 (1H, m, 10-H), 1.06—1.67 (7H, m), 2.11 (1H, m), 2.36 (1H, m), 2.64 (1H, dd, J = 14.6, 3.2 Hz, 6-H), 2.78 (1H, dd, J = 14.6, 12.4 Hz, 6-H), 5.00 (1H, s, 11-H), 7.31 (1H, ddd, J = 7.4, 7.3, 1.5 Hz, 3-H), 7.33 (1H, ddd, J = 7.3, 1.5, 0.6 Hz, 4-H), 7.48 (1H, ddd, J = 7.5, 7.4, 1.5 Hz, 2-H), 7.65 (1H, ddd, J = 7.5, 1.5, 0.6 Hz, 1-H), 8.52 (2H, s, NH_2). Monoclinic, space group $P2_1/c$; a = 14.210(3) Å, b = 10.622(1) Å, c = 10.041(2) Å, α = 90.0°, β = 104.18(2)°, γ = 90.0°; V = 1469(1) Å; Z = 4; D_X = 1.42 g cm^{-3}; μ (CuK_α) = 49.74 cm^{-1}; crystal dimensions = 0.15 × 0.15 × 0.5 mm.

Data Collection and Processing The unit-cell dimensions were determined by a least-squares fit of 16 reflections in the range of $57° < 2\theta < 61°$. Data were collected at 20°C using a Rigaku-AFC5 diffractometer with CuK_α radiation (λ = 1.5418 Å); collection range, h −0/15, k 0/11, l −10/11; 2θ limits, $4° < 2\theta < 112°$; scan type, θ–2θ; scan width, $1.6 + 0.15° \tan\theta$; scan speed, 6°/min in θ; background time/scan time, 3.5 s; unique reflections = 1962.

The structure was solved by the heavy atom method. All atoms were refined by the block-diagonal least squares method.[6] The weighting scheme $w = 1.0/(\sigma_{F_O}^2 + 0.07086F_O + 0.0026F_O^2)$ gave good convergency of the refinement. The final R value is 0.057 for 1750 reflections ($F_O > 3\sigma_{F_O}$). Atomic scattering factors were taken from International Tables for X-Ray Crystallography (1974).[7]

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