SYNTHESIS OF MACROCYCLES HAVING TRÖGER BASE SKELETONS[1)]
"[2.2]CYCLIC TRÖGER BASE"[2,3)]

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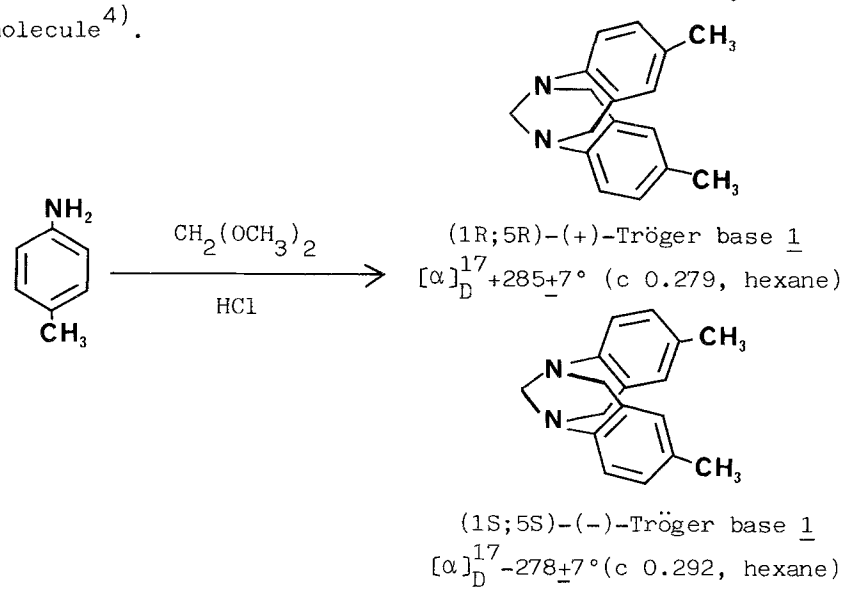
ABSTRACT: [2.2]Cyclic Tröger base 2 was synthesized by the condensation of 1,2-bis(4-aminophenyl)ethane with paraformaldehyde under acidic condition in 43.8% yield. [2.2]Cyclic Tröger base 2 was separated into meso form and racemate by fractional crystallization or using HPLC. Resolution of the racemate into its optical antipodes by passing the racemate through an activated D-(+)-lactose column was partially succeeded.

1. INTRODUCTION

In order to enable the recognition of a chiral guest molecule, a macrocyclic host molecule must have a suitable cavity for inclusion and only one of two enantiomeric guest molecules must undergo the energetically favorable interactions with the macrocyclic host molecule[4)].



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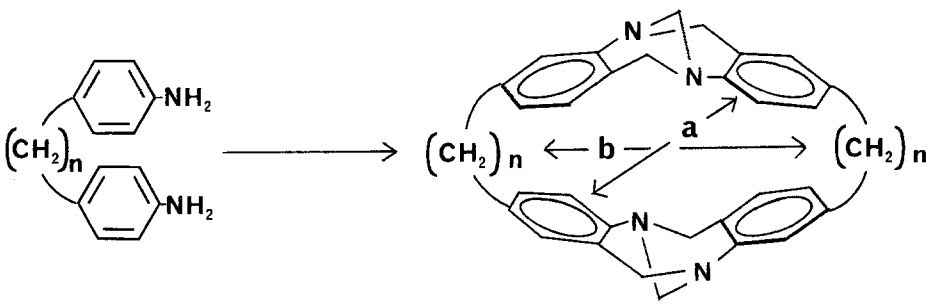
With the hope of obtaining such macrocycles, we tried to synthesize macrocyclic compounds having Tröger base skeletons as chiral host molecules.

In Tröger base 1[5,6,7,8] in which two nitrogen atoms are at bridgeheads, the configurational inversion is prevented. Tröger base 1 having only C_2 axis was resolved into its optical antipodes by passing it through an activated D-(+)-lactose column as described by Prelog and Wieland[9,10,11a,11b]. This was the first classical demonstration that optical activity was due to an asymmetric trivalent nitrogen atom. Cyclophanes 2 in Fig. 1 consisting of two Tröger base skeletons may be resolvable into optical antipodes which have an appropriate cavity for inclusion. Size of the cavity may be variable by adjusting lengths of the methylene groups intervening Tröger base skeletons as shown in Scheme 1.



Based on CPK model

	a	b
		(Å)
n=1	4.6	5.8
n=2	5.9	6.5
n=3	7.1	7.9

[n.n]Cyclic Tröger base

Scheme 1.

In this paper we report a simple method to construct macrocyclic compounds which can be easily transformed to many other optically active macrocyclic derivatives. [2.2]Cyclic Tröger base 2 was prepared by the condensation of 1,2-bis(4-aminophenyl)ethane with paraformaldehyde under acidic condition in one step as shown in Scheme 1.

2. RESULTS AND DISCUSSION

[2.2]Cyclic Tröger base 2 was obtained by the condensation of 1,2-bis(4-aminophenyl)ethane with paraformaldehyde under acidic condition in one step in unexpectedly high yield as shown in Scheme 1. According to the combination of (1R;5R)- and (1S;5S)-Tröger base units as shown in Fig. 1, there exist three possible isomers: namely, the meso form (1R;5R,1'S;5'S)cyclic Tröger base, and optically active forms (1R;5R,1'R;5'R)- and (1S;5S,1'S;5'S)cyclic Tröger base. The separation of [2.2]cyclic Tröger base 2 into the meso form 2a and the racemate 2b was accomplished by repeated fractional recrystallization from 2-propanol and CH_2Cl_2 or preparative HPLC. The racemate 2b was further resolved into the optical antipodes according to the classical method of Prelog and Wieland[9] by using D-(+)-lactose column with petroleum ether as an elutant.

Because of the rigidity and limited size of the cavity, all attempts to obtain inclusion compounds of the [2.2]cyclic Tröger base 2 and other small organic molecules have resulted in failure thus far. But, with the rather flexible [n.n]cyclic Tröger base ($n \geq 3$) with a suitable cavity in it, it may still be possible to obtain inclusion compounds of [n.n]cyclic Tröger base.
Further, the methano bridges $N-CH_2-N$ are very easily removable under acidic conditions to give cyclic tetrahydrodibenzo[b,f][1,5]diazocine derivatives, i.e. cyclic diaza analogs of 1,2,5,6-dibenzocyclooctane derivatives.

Because of their cyclic structures, many N substituted cyclic diazocine derivatives may be obtainable without racemization.

This synthetic method has been successfully applied to other systems, such as [1.1]- (<10% yield) and [3.3]cyclic Tröger base (13% yield). In order to make these macrocycles flexible, further studies on the synthesis of several derivatives of 2 are in progress.

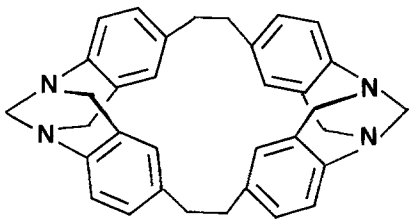
3. EXPERIMENTAL

3.1. Synthesis

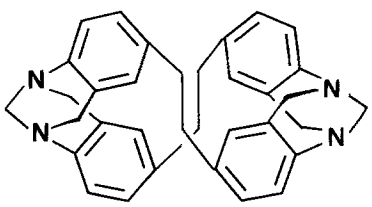
Synthesis of [2.2]cyclic Tröger base 2:n=2 in Scheme 1.

To a solution of 1,2-bis(4-aminophenyl)ethane (2.0 g, 9.4 mmole) in 500 ml of acetic acid was added 250 ml of conc HCl below 10°C. To this mixture was added paraformaldehyde (10.0 g, 330 mmole) at 0°C, and the flask being shaken occasionally. After 1h, the mixture was allowed to warm to room temperature and left standing for 5 to 7 days. The solution was evaporated to dryness in vacuo and the residue was neutralized with 2N NaOH solution. The mixture was extracted with benzene. After the usual work-up, the pale yellow powder was chromatographed on alumina with CH_2Cl_2 to give crude [2.2]cyclic Tröger

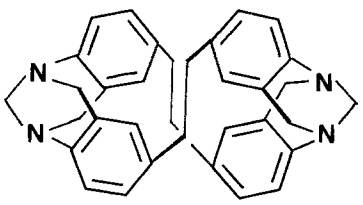
base 2. Recrystallization from 2-propanol and CH_2Cl_2 afforded 1.02 g (43.8%) of white crystals.



(1R;5R,1'S;5'S)
meso form 2a



(1R;5R,1'R;5'R)



(1S;5S,1'S;5'S)

racemate 2b

Fig. 1.

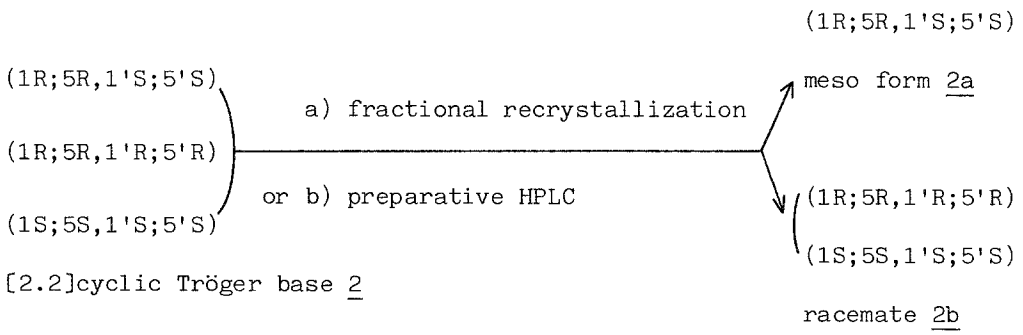
3.2. Separation

The separation of 2 into the meso form 2a and the racemate 2b.

The separation of [2.2]cyclic Tröger base 2 into the meso form 2a and the racemate 2b is shown in Scheme 2.

a) Repeated fractional recrystallization of 2 (2 g, 2a:2b=5:1 based on HPLC analysis) from 2-propanol and CH_2Cl_2 gave the chromatographically pure meso form 2a(730 mg) and the racemate 2b(120 mg).
Meso form 2a: colorless prisms from 2-propanol, mp > 242°C(dec); MS(m/z)M^+ 496(calcd 496). Anal. Found: C, 81.72; H, 6.46; N, 11.34%. Calcd for $C_{34}H_{32}N_4$: C, 82.22; H, 6.49; N, 11.28%. Racemate 2b: colorless granules from 2-propanol, mp > 226°C(dec); MS(m/z)M^+ 496 (calcd 496). Anal. Found: C, 81.80; H, 6.54; N, 11.15%.

b) Preparative HPLC. [2.2]Cyclic Tröger base 2 (6 mg) was separated into 2a (4 mg) and 2b (0.8 mg) by using Waters Radial Pak 5μ silica cartridge with ethyl acetate as an elutant.



Scheme 2.

3.3. Spectral Properties

^{1}H-NMR spectra. The data of nmr spectra are shown in Table 1.

IR spectra(KBr disk). The Tröger bases 1, 2a and 2b show no marked differences in IR spectra except for the absorptions due to CH_3 groups in 1. $\nu_{\phi-H}$ 3040, 3005, $\nu_{arom\ C=C}$ 1610, 1570, 1490, 1460, $\delta_{\phi-Hop}$ 895, 830, $\nu_{C-H}(-CH_2-N-)$ 2920, 2830, ν_{C-N} 1210, 1190, δ_{CH_2} 1440, $\nu_{\phi-N}$ 1350, 1325 cm^{-1}.

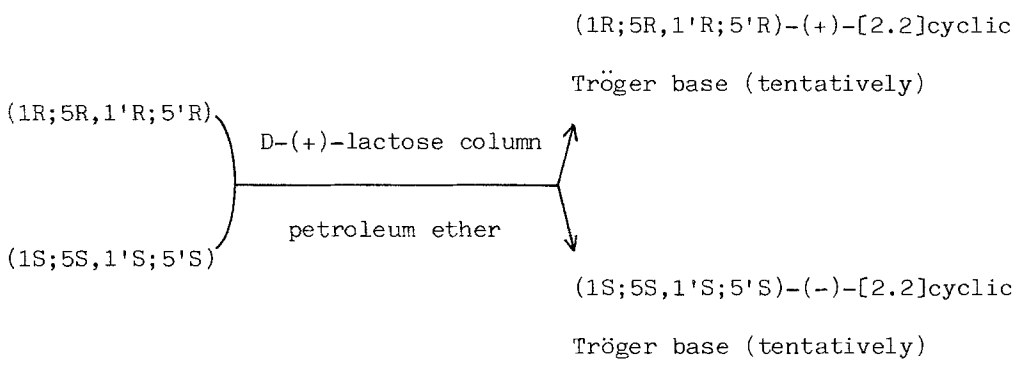
Electronic Spectra (in C_2H_5OH). The UV spectrum of 2 shows very similar absorption to that of the Tröger base 1. Tröger base 1: 215(ε, 16,490), 240 (ε, 8,660), 285 nm(ε, 2,100). [2.2]Cyclic Tröger base 2: 215(ε, 32,100), 240 (ε, 16,100), 285 nm(ε, 3,400).

3.4. Resolution

The partial resolution of the racemate 2b using D-(+)-lactose column.

The resolution of racemic [2.2]cyclic Tröger base 2b was performed according to the method of Prelog and Wieland[9]. The racemate 2b (40.8 mg) was chromatographed on an activated D-(+)-lactose (4.8 50 cm) with petroleum ether (bp 50-60°C). The first eluent (1900 ml) contained the base (25 mg) enriched in the (+)-isomer. Following eluent contained the base (13 mg) enriched in the (-)-isomer. The resolution was repeated for the (-)-isomer under the same conditions as described above.

(1R;5R,1'R;5'R)-[2.2]cyclic Tröger base (tentatively assigned on the analogy of (+)-Tröger base 1):$[\alpha]_D^{25}$=+134±18° (c 0.112 in ethanol). (1S;5S,1'S;5'S)-[2.2]cyclic Tröger base (tentatively assigned on the analogy of (-)-Tröger base 1):$[\alpha]_D^{25}$=-96±19.2°(c 0.052 in ethanol).



racemate 2b

Scheme 3.

Table. ^{1}H-NMR spectra (δ in $CDCl_3$)

	aromatic			methylene			CH_3 (1)
	Ha	Hb	Hx	endo	benzylic		CH_2-CH_2(2)
1	6.8 - 7.2m		6.7bs	4.29s	4.08d[a]	4.67d[a]	2.23s
2a	6.9bd	7.04d	6.44bs	4.17s	3.82d[a]	4.48d[a]	3.1-2.7m
2b	6.8 - 7.0bm		6.5bs	4.35s	3.90d[b]	4.55d[b]	2.98s

a) J_{gem}=16.5Hz; b) J_{gem}=16.4Hz: b=broad, d=doublet, m=multiplet, s=singlet.

Acknowledgment. We thank Mr. Masahiko Suenaga in our laboratory for nomenclature assistance.

References and Notes

1) Presented at the 15th Symposium on Structural Organic Chemistry, Kyoto, October, 1982.
2) The trivial name "[2.2]cyclic Tröger base" is used because of the cumbersome nomenclature.
3) 10,12,25,32-Tetraazanonacyclo[19.7.7.1.^{4,8}1.^{14,18}1.^{25,32}0.^{7,12}0.^{10,15}-0.^{24,34}0^{27,31}]octatriaconta-1(29),4,6,8(36),14,16,18(37),21,23,27,-30,34-dodecaene.
4) For reviews of host-guest chemistry; a) "Host Guest Complex Chemistry I" ed. by F. Vögtle, Springer-Verlag, Berlin Heidelberg, 1981. b) "Host Guest Complex Chemistry II" ed. by F. Vögtle, Springer-Verlag, Berlin Heidelberg 1982. c) D. J. Cram, Science, **219**, 1177 (1983).
5) J. Tröger, J. prakt. Chem., [2]36, 227 (1887).
6) 1,2'-Methylene-3-(4'-tolyl)-6-methyl-1,2,3,4-tetrahydroquinazoline.
7) Tröger base can be prepared merely by allowing a mixture of formaldehyde, p-toluidine and concentrated HCl in acetic acid to stand for several days. Structures proposed by Tröger and by later workers was incorrect, but Spielman[8] established the structure by an unequivocal synthesis.
8) M. A.Spielman, J. Am. Chem. Soc., **57**, 583 (1935).
9) V. Prelog and P. Wieland, Helv. Chim. Acta, **27**, 1127 (1944).
10) O. Červinka, A. Fábryová, and V. Novák, Tetrahedron Lett., 5375 (1966). Červinka et al. deduced from the empirical comparison of the ORD spectra of (+)-Tröger base and (-)-argemonine that the absolute configuration in it was 1S,5S, but later Mason[11a, 11b] et al. analyzed the CD curve of (+)- and (-)-Tröger base and reversed the configuration as shown in Scheme 1.
11a) S. F. Mason, G. W. Vane, K. Schofield, R. J. Wells, and J. S. Whitehurst, J. Chem. Soc., (B), 553 (1967).
11b) S. F. Mason, K. Schofield, R. J. Wells, J. S. Whitehurst, and G. W. Vane, Tetrahedron Lett., 137 (1967).