Chem. Pharm. Bull. 21(8)1683—1691(1973)

UDC 547.895.03 : 543.422.25 : 543.51

Studies on Diphenyl Ether Derivatives. VIII.[1] NMR Spectra and Conformational Structure of Dibenz[*b*,*g*][1,5]oxazocine and Thiazocine Derivatives and Their Mass Spectra

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(Received November 27, 1972)

The NMR spectra of 6-substituted 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine and thiazocine derivatives (**1**) and the sulfoxides or sulfones (**6**) and the bimolecular sixteen membered ring compounds (**2**) were reported. The methylene protons at 5 and 7-position of the ring of **6** appeared as a AB system quartet. All ring methylene protons in **2** gave a singlet. The temperature dependent coalescence and splitting of the singals was observed in **1**. At low temperature the 5,7-methylene protons in thr ring of **1** gave a AB quartet and a singlet. From these facts it was suggested that **1** was a mixture of the conformational isomer A and B in Fig. 8 and they could not freely rotate each other even at room temperature. **6** existed only as the structure A. The Mass spectra of them were also reported.

We have synthesized the dibenz[*b*,*g*][1,5]oxazocine and thiazocine derivatives which furnish a new 6,6,8-tricyclic ring system to check their pharmacological activities, comparing with the well-known 6,6,6-phenothiazines and 6,6,7-dibenzothiazepines *etc.*[1,3,4,5] As shown in Chart 1 the condensation of bis(2-bromomethylphenyl)ether or sulfide (**3**) with primary amine (**4**) gave the 6-substituted 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocines or thiazocines (**1**) and the sixteen membered ring compounds, 5,13-disubstituted 2,3-, 7,8-, 10,11-, 15,16-tetrabenzo-1,9-dioxa(thia)-5,13-diaza-cyclohexadeca-2,7,10,15-tetraenes (**2**) as by-product. The latter compounds are also a new ring system and considered a kind of orthocyclophane containing four benzene rings. The product ratio of **1** and **2** in the condensation of **3** with **4** was found to vary according to the reaction conditions such as the solvent and the existence of acid-removing agents *etc.* On the other hand an intresting fact was observed that the condensation reaction of bis(2-bromomethylphenyl) sulfoxide or sulfone (**5**) with **4** gave only dibenz[*b*,*g*][1,5]thiazocine-12-oxide or 12,12-dioxide (**6**) in better yield and none of bimolecular by-product. Pala, *et al.*[6,7] synthesized 6-benzyl-6,7-dihydro-5H,12H-dibenz[*c*,*f*]azocine (**8**) by the condensation of 2,2-dibromomethyldiphenylmethane (**7**) with benzylamine in high yield but reported none of by-product. **1**, **2** and **6** obtained by the above method exhibited the characteristic nuclear magnetic resonance (NMR) spectra suggesting their conformational structure. In this paper we shall discuss the NMR spectra and their conformational structure of **1**, **2** and **6** and also refer to their Mass spectra.

NMR Spectra at Room Temperature

The most characteristic NMR absorption signals of dibenz[*b*,*g*][1,5]oxazocine and thiazocine derivatives are derived from four benzylic protons at 5 and 7 positions in the oxazocine

1) Part VII: S. Tanaka and Y. Ogata, *Yakugaku Zasshi*, **93**, 1003 (1973).
2) Location: *4 Koishikawa, Bunkyo-ku, Tokyo.*
3) Part IV: S. Tanaka and K. Hashimoto, *Yakugaku Zasshi*, **93**, 982 (1973).
4) Part V: S. Tanaka, K. Hashimoto and H. Watanabe, *Yakugaku Zasshi*, **93**, 991 (1973).
5) Part VI: S. Tanaka, H. Watanabe and Y. Ogata, *Yakugaku Zasshi*, **93**, 997 (1973).
6) S. Casadio, G. Pala, E. Crescenzi, E. Marazzi-Uberti, G. Coppi and C. Turba, *J. Med. Chem.*, **11**, 97 (1968).
7) G. Pala, A. Mantegani and E. Zugna, *Tetrahedron*, **26**, 1275 (1970).

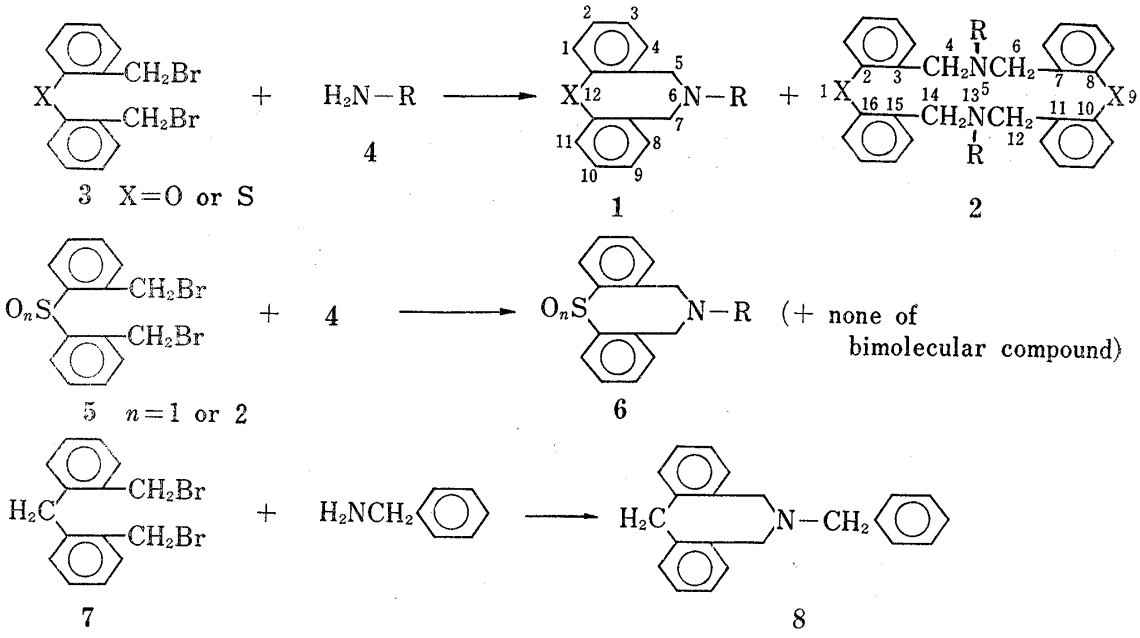


Chart 1

and thiazocine nucleus. Each NMR spectrum measured at room temperature for 6-benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine (**9**), 6-benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine (**10**), 6-benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine-12-oxide (**11**), 6-benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine-12,12-dioxide (**12**), 5,13-dibenzyl-2,3-, 7,8-, 10,11-, 15,16-tetrabenzo-1,9-dioxa-5,13-diazacyclohexadeca-2,7,10,15-tetraene (**13**) and 5,13-dibenzyl-2,3-,7,8-,10,11-,15,16-tetrabenzo-1,9-dithia-5,13-diaza-cyclohexadeca-2,7,10,15-tetraene (**14**) was shown in Fig. 1 to Fig. 6 respectively. As shown in Fig. 1 the benzylic protons at side chain of (**9**) absorbed at 3.35 ppm and four 5,7-benzylic protons in the oxazocine nucleus appeared as a very asymmetrically broad absorption at about 3.8 ppm with a long and gentle slope to the lower field, up to about 5 ppm. Most oxazocine derivatives showed such similar shape of the absorption peak for the 5,7-benzylic protons. The thiazocine homolog (**10**) also gave a broad peak at about 3.5 to 6 ppm for the benzylic protons at 5 and 7 position in the thiazocine nucleus. The sulfoxides (**11**) and the sulfones (**12**) exhibited the clear AB system quartet for four 5,7-benzylic protons in the nucleus as shown in Fig. 3 and Fig. 4. The AB system absorption was appeared at 3.85 and 4.14 ppm with J=15 Hz in **11** and at 4.07 and

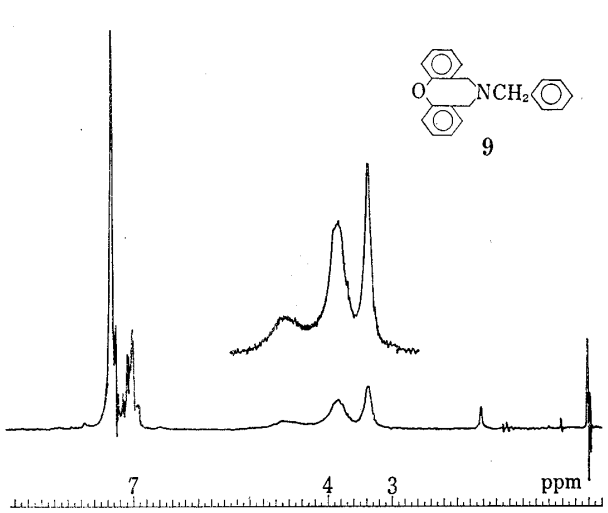


Fig. 1. NMR Spectrum of **9**

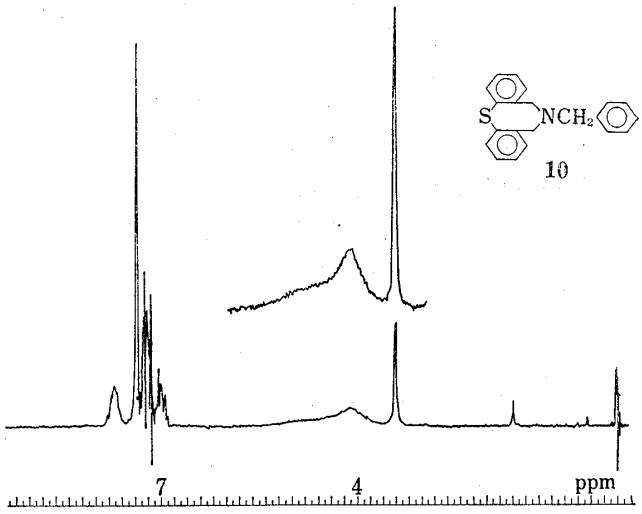


Fig. 2. NMR Spectrum of **10**

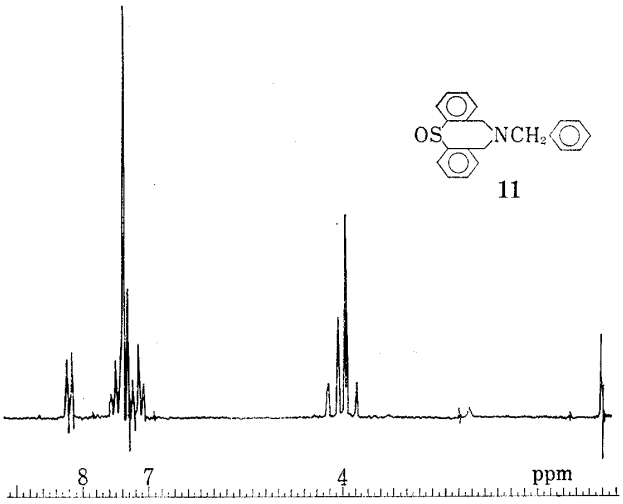


Fig. 3. NMR Spectrum of **11**

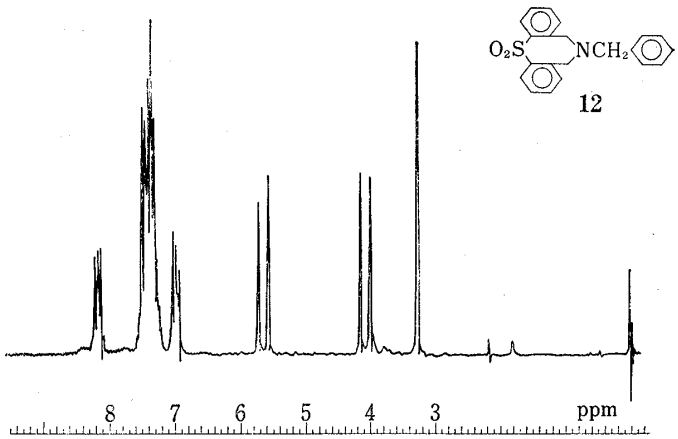


Fig. 4. NMR Spectrum of **12**

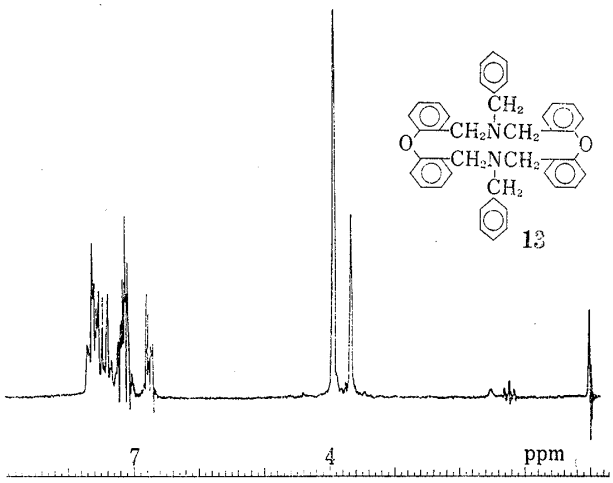


Fig. 5. NMR Spectrum of **13**

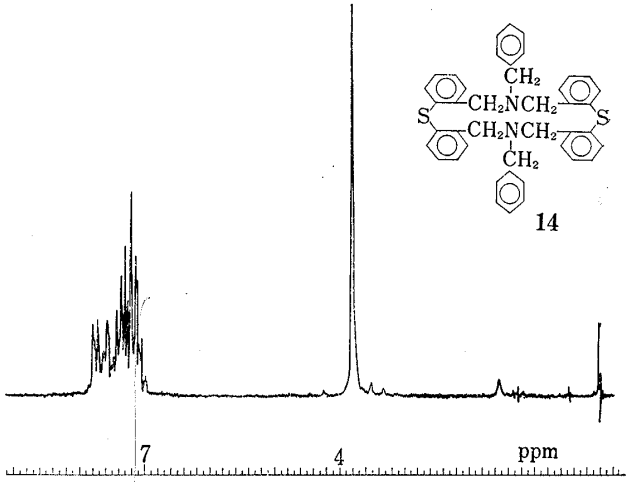


Fig. 6. NMR Spectrum of **14**

5.64 ppm with $J=15$ Hz in **12**. The absorption of the side chain benzylic protons was appeared at 3.95 ppm in **11** and at 3.26 ppm in **12** respectively. Sixteen membered ring oxa-compound **13** had a singlet at 3.92 ppm for eight nucleus benzylic protons and a singlet at 3.66 ppm for four side chain benzylic protons as shown in Fig. 5. Thia-homolog (**14**) had a singlet at 3.78 ppm for all benzylic protons as shown in Fig. 6.

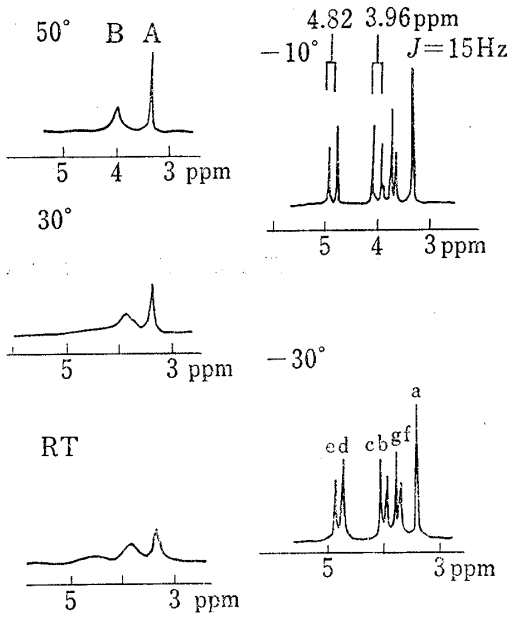
It was known that the NMR spectra of the methylene protons of some cyclic compounds gave the AB system quartet if two protons were not magnetically equivalent and the ring system was restricted the free rotation.[8-10] Pala, *et al.*[6] also reported the benzylic protons at 5,7-positions and 12-position in **8** exhibited the AB system absorption at the measurement at −30° respectively. They suggested that the tricyclic system in **8** had some rigidity even at room temperature. We have also measured the NMR spectra of several compounds of **1** and **2** at various temperature. The results would be described and discussed at the following sections.

NMR Spectra at Various Temperature and the Conformational Structure of Dibenz[*b*,*g*][1,5]-oxazocine Derivatives

The NMR spectra of 6-benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine (**9**) at 50°, 30°, room temperature (r.t.), −10°, −30° were shown in Fig. 7. The broad and asymmetrical

8) K. Mislow, M. Glass, H. Hoppo, E. Simon and G. Wahl, *J. Am. Chem. Soc.*, **86**, 1710 (1964).
9) W. Meyerand and R. Meyer, *J. Am. Chem. Soc.*, **85**, 2170 (1963).
10) K. Tori, Y. Hamashima and A. Takamizawa, *Chem. Pharm. Bull.* (Tokyo), **12**, 924 (1964).

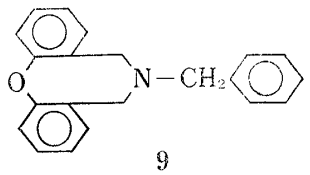
absorption, signal B became relatively sharp and symmetrical at 4.04 ppm at 50°. The signal B splitted clearly below −10°. Four 5- and 7-benzylic protons in the oxazocine nucleus appeared as the typical AB system quartet, signal b, c, d, e in Fig. 7, at 3.96 and 4.82 ppm with J=15 Hz below −10°. Signal a was assigned to the benzylic protons at the side chain. Besides these signals two new signals, f and g, appeared at 3.61 and 3.68 ppm and their integral ratio was 1:2 as shown in Fig. 7. There are two possible conformational structures, structure



Estimated area of each signals

No.	Area	W.P.C.
50°		
A	4562	38.011
B	7439	61.988
30°		
A	2671	33.493
B	5303	66.506
r.t.		
A	2865	32.617
B	5917	67.381
−10°		
a	3671	25.046
f	1372	9.367
g	2830	19.312
b	1408	9.612
c	1915	13.066
d	2005	13.660
e	1455	9.933

Fig. 7. NMR Spectrum of **9**



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A and structure B as shown in Fig. 8, for the 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine and thiazocine derivatives. Structure A was considered to have a high rigidity and the two pairs of the ring methylene protons, Ha and Hb, were considerably fixed and could not freely rotate. Therfore, Ha and Hb became nonequivalent and appeared as the AB system absorptions. Structure B, on the other hand, was so flexible that the ring methylene protons, Ha and Hb, could freely rotate and appeared as a singlet absorption even at −30°. Thus signal a was assigned to two benzylic protons at side chain and signal b, c, d, e were assigned to four nucleus benzylic protons in the structure A. Signal f and g were assigned to the side chain benzylic proton and the nucleus benzylic protons in the structure B respectively. The integral data showed that the area of signal f plus signal g was about 29% of all the benzylic protons. Therefore **9** was considered to exist as a mixture of about 71% conformational isomer A and about 29% conformational isomer B below −10°. The characteristic asymmetric broad absorption of 5,7-methylene protons of **9** at room temperature was considered as the result of some mixing of structure A with structure B and of considerable restriction on their mutual inversion. Increasing temperature to 50° caused the coalescence of the signal. The broad asymmetrical signal became symmetrical and rather steep showing that the mutual inversion of each methylene proton became more possible. It was also observed that as increasing temperature the integral ratio of signal A to signal B became bigger as shown in Fig. 7; the ratio was 33: 67 at room temperature and 38: 62 at 50°. The fact would mean that at high temperature some amounts of the benzylic protons at side chain and the nucleus would make a singlet signal. In other words it was suggested that the structure which had the equivalent side chain and nucleus benzylic protons increased at high temperature.

The NMR spectra of 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine (**15**) at various temperature were given inFig. 9. The 5,7-benzylic protons appeared as a sharp singlet at room temperature. The fact suggested that four 5,7-benzylic protons in the oxazocine nucleus could

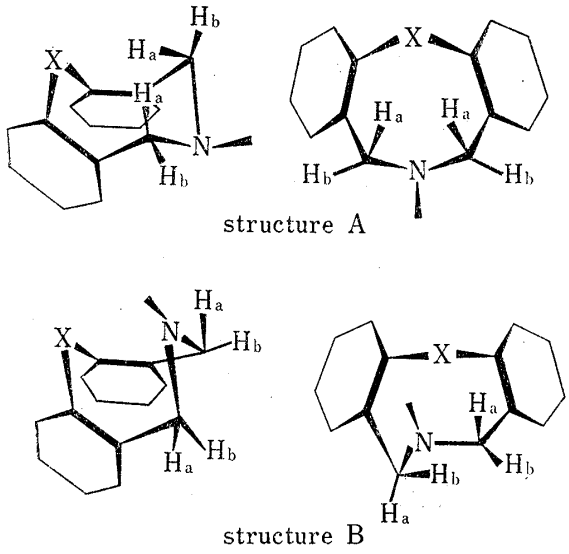


Fig. 8. Conformational Structures of 6,7-Dihydro-5H-dibenz[*b*,*g*][1, 5] oxazocine and thiazocines

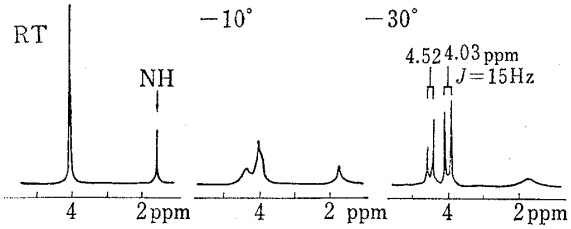
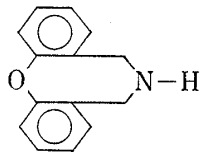


Fig. 9. NMR Spectra of **15**



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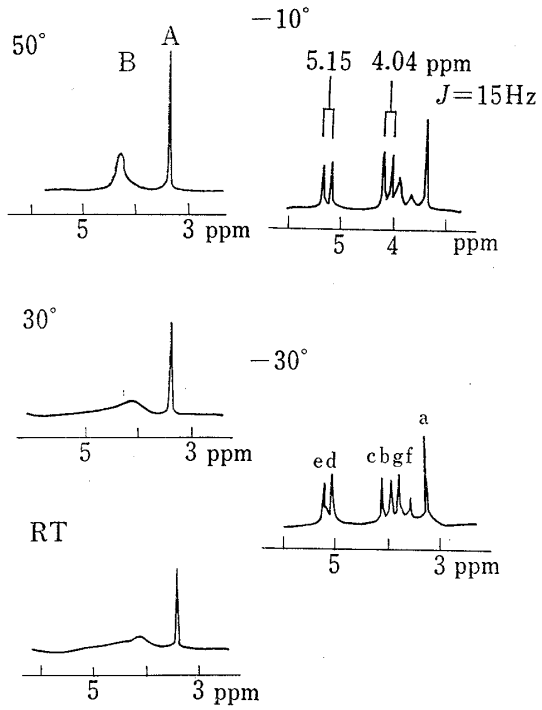
freely rotate at room temperature unless any 6-substituent was present. But the singlet became broad and asymmetrical at −10° which shape was observed for **7** at room temperature. At −30° the absorption splitted to the AB system and a singlet as expected. The AB system quartet occured at 4.52 and 4.03 ppm with J=15 Hz and were assigned to the benzylic protons of structure A in Fig. 8. The singlet derived from structure B was overlapped with a signal of the quartet at 3.95 ppm. The existence ratio of structure A to structure B for (**15**) at −30° was estimated to be about 3: 1.

NMR Spectra at Various Temperature and the Conformational Structure of Dibenz[*b*,*g*][1,5]-thiazocine Derivatives

Dibenz[*b*,*g*][1,5]thiazocines exhibited almost the same NMR spectra as oxazocines in which a typical temperature dependent coalescence and splitting was observed. The NMR spectra of 6-benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine (**10**) were given in Fig. 10. The 5,7-benzylic protons in the thiazocine nucleus appeared as a broad absorption peak with a gentle slope to the lower field and did not show such extreme asymmetry as oxazocine (**9**) did. The broad absorption became considerable sharp at 50°. Measurement below −10° led to the clear splitting. The AB system quartet, signal b, c, d, e, appeared at 4.04 and 5.15 ppm with J=15 Hz, and the signal a, appeared at 3.31 ppm, were assigned to the 5,7-benzylic protons in the nucleus and the side chain benzylic protons of structure A respectively. Signal f and g, appeared at 3.50 and 3.81 ppm, were assigned to the side chain benzylic protons and the 5,7- ring benzylic protons of structure B respectively. The existence ratio of structure B in **10** was 18% at −10°. The less value compared with 29% in **9** would be the reason for the more symmetrical absorption for the 5,7-benzylic protons of the thiazocine series at room temperature than the absorption of the oxazocine series. The integral ratio of signal A to signal B was increased as temperature was raised. The ratio was 37: 63 at room temperature, 47: 53 at 30° and 46: 54 at 50°. It was the same phenomena that were observed in the Oxazocine series. It was considered that most benzylic protons in structure B at higher temperature than 30° could freely rotate to make a singlet absorption which had the same δ value as the side chain benzylic protons.

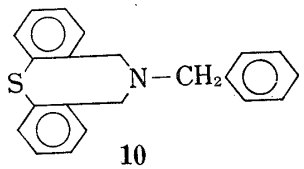
The NMR spectra of 6-methyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine (**16**) were shown in Fig. 11. The temperature dependence was observed as the above mentioned compounds. The spectra showed a temperature coalescence at 50° and a clear splitting below −10°. The



Estimated area of each signals

No.	Area	W.P.C.
50°		
A	3337	46.373
B	3859	53.626
30°		
A	2807	47.136
B	3148	52.863
r.t.		
A	3177	36.573
B	5509	63.426
−10°		
a	3504	28.947
f	610	5.040
g	1561	12.901
b	1545	12.764
c	1502	12.415
d	1772	14.644
e	1608	13.284

Fig. 10. NMR Spectra of **10**



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methyl protons and four nucleus benzylic protons of the structure A appeared as signal a at 2.12 ppm and signal b, c, d, e, typical AB system quartet at 4.06 and 5.30 ppm with J=15 Hz respectively. Signal f at 2.46 ppm and signal g at 3.87 ppm were assigned to the methyl protons and the ring benzylic protons in structure B respectively. The existence ratio of structure A and structure B at −30° was about 71: 29.

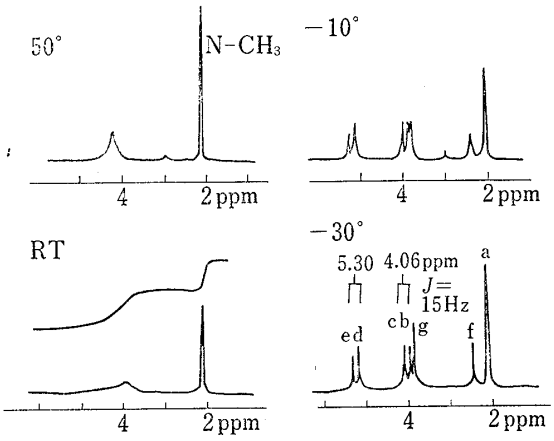
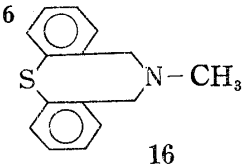


Fig. 11. NMR Spectra of **16**



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Discussion on the NMR Spectra

As mentioned before 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine and thiazocine derivatives (**1**) exist as a mixture of structure A and structure B. On the other hand the sulfoxide and sulfone compounds (**2**) seemed to exist only as the conformational structure A, because the ring methylene protons of **2** appeared only as the AB system and the spectra did not show any change at 50° and −30°. As described in Fig. 8 structure A was regarded as the "pseudo-chair" form and structure B as the "pseudo-boat" form. If the perturbation of the oxygen or sulfur bonding in structure A occured the ring system would become the structure B, that is "pseudo-boat" form. It was not clear that the mutual inversion of structure A and structure B was attributed to whether the perturbation of the oxygen or sulfur bond or to the perturbation of the -C-N-C- bond. But we could point the difficulty of the perturbation of the oxygen or sulfur bond in the sulfoxide and sulfone compounds. And it was also unable to assign the cause of the difference between the spectra of the oxazocine or thiazocines (**1**) and the spectra of dibenz[*c*,*f*]azocines (**8**) at this time. No occurrence of the sixteen membered ring compounds in the condensation reaction of **4** with **5** could be attributed to the configurational difficulty to set up the ring because of the bulkiness of the sulfoxide and sulfone

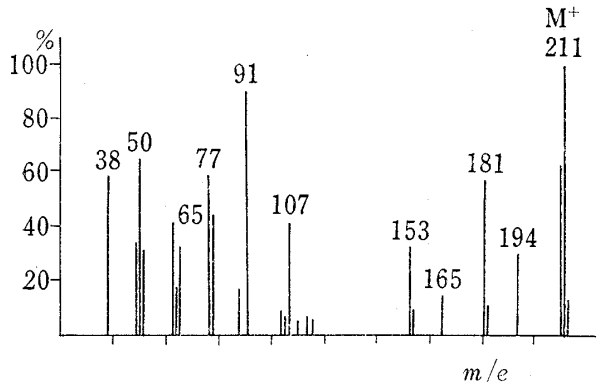
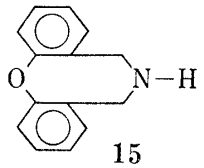


Fig. 12. Mass Spectrum of **15**



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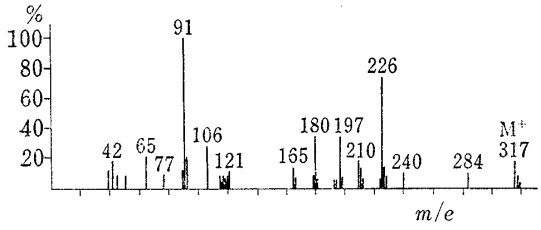
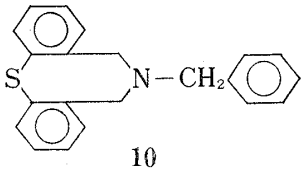


Fig. 14. Mass Spectrum of **10**



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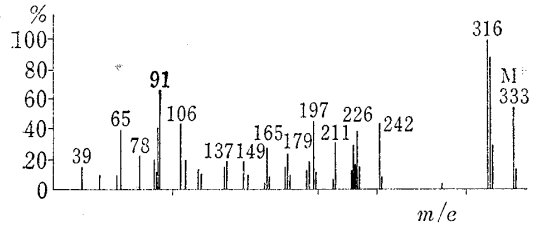
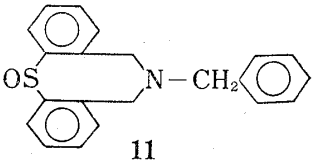


Fig. 16. Mass Spectrum of **11**



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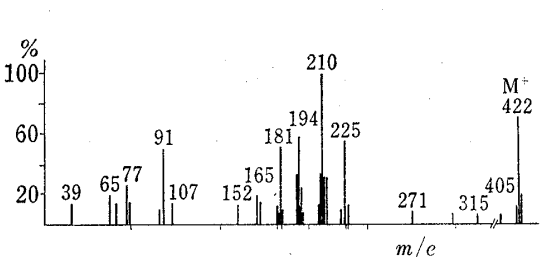
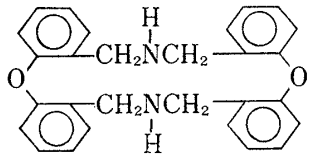


Fig. 13 Mass Spectrum of **18**



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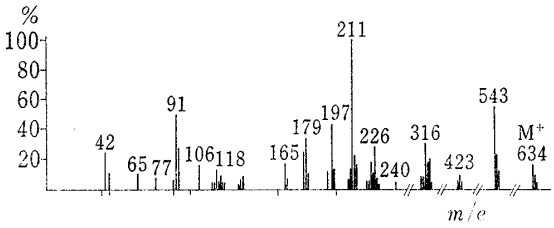
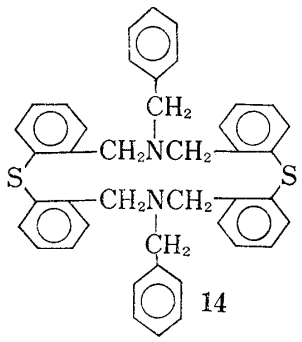


Fig. 15. Mass Spectrum of **14**



14

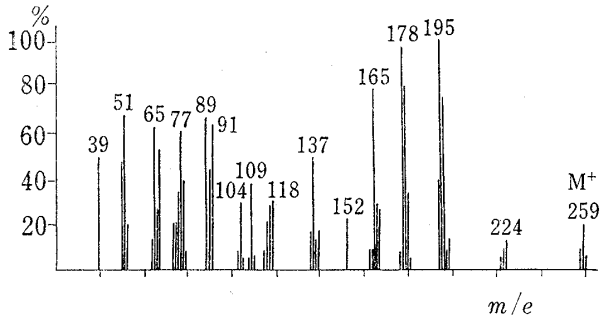
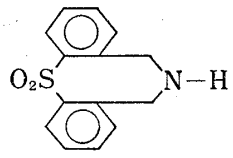


Fig. 17. Mass Spectrum of **17**



17

group. In fact it was difficult to set up the sixteen membered ring structure for the sulfoxide and sulfone series using with the Steuart molecular model.

Mass Spectra of 6,7-Dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine and Thiazocine Derivatives and the Sixteen Membered Ring Compounds

Each Mass spectrum of **15**, **18**, **10**, **14**, **11** and 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine-12,12-dioxide (**17**) was shown in Fig. 12 to Fig. 17 respectively. Each series exhibited their own characteristic fragmentation patterns. Each mother ring system of each series made the stable molecular ion. Therefore all compounds of one series gave the common fragmentation patterns after exhibiting the normal fragmentation of each substituents. Thus 6,7-dihydro-5H-dibenz[*b*,*g*][1,5]oxazocine series gave the series of *m/e* 210, 194, 181, 165, 152, 107, 91, 77 and 65 as the common fragment ions as shown in Fig. 15. The basic peak was

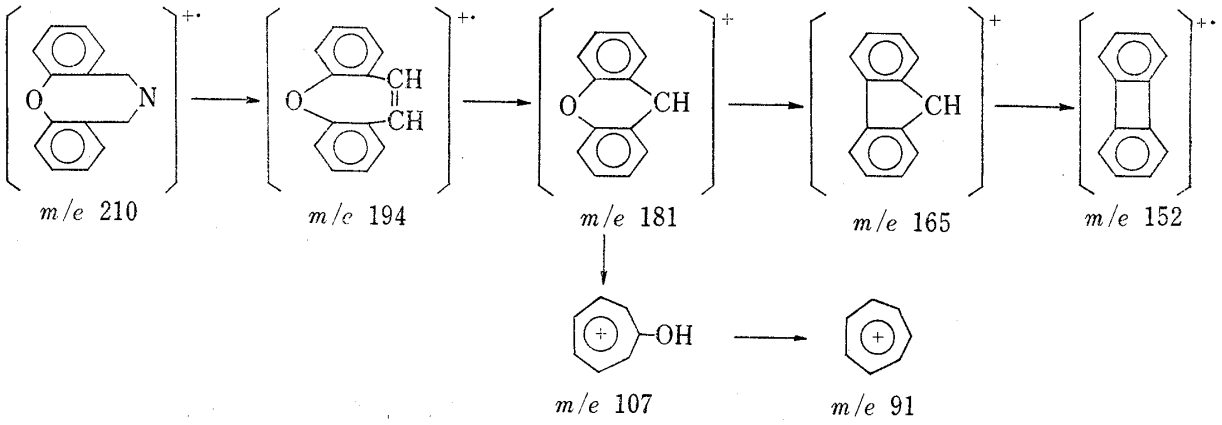


Chart 2

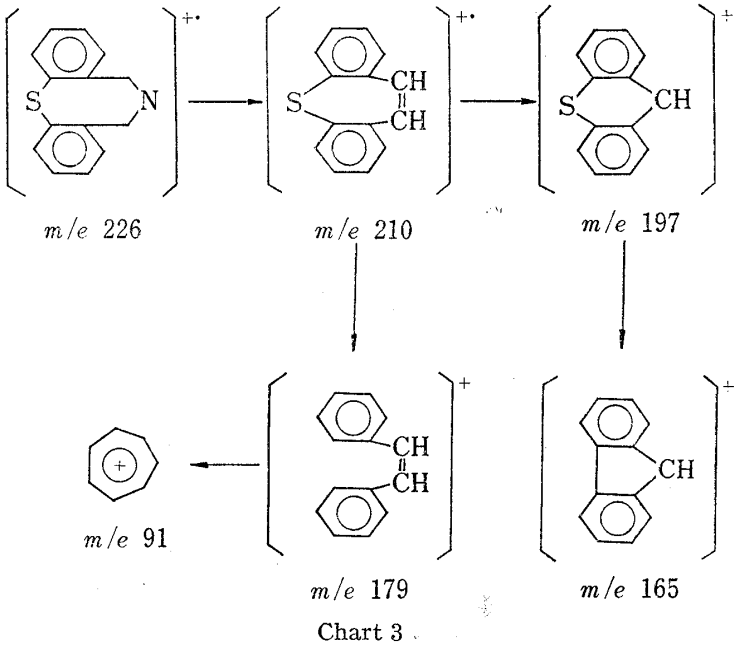


Chart 3

m/e 210 or 91. As the results of the measurements of the high resolution Mass each fragment ion and the fragmentation pathway were estimated as shown in Chart 2. Sixteen membered oxa-homologs exhibited the very similar spectra as the oxazocines at less than *m/e* 210 as shown in Fig. 13. The molecular ion peak appeared clearly but there were a few strong peaks at more than *m/e* 210. 6,7-Dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine derivatives gave the series of *m/e*: 226, 210, 197, 179, 165, 91, 77, 65, as the common fragment ions for the series as shown in Fig. 14. Each ion and the fragmentation pathway were estimated as shown in Chart 3. The sixteen membered ring thia homolog exhibited very similar fragmentation pattern as the thiazocines at less than *m/e* 226 as shown in Fig. 15. The molecular ion appeared clearly but there were few intensive peaks at more than *m/e* 226. The sulfoxide derivatives gave the almost same spectra as the thiazocines except the clear molecular ion, which spectrum was given in Fig. 16. It was

suggested the deoxygenation of the sulfoxide group occured at first. The sulfone compounds also exhibited the similar spectra as the thiazocine series as shown in Fig. 17.

Experimental

NMR Spectra Measurement——The NMR spectra were recorded on a JNM-PS100 (JEOL). Chemical shifts (δ value) were recorded as ppm with tetramethylsilane as the internal standard. Deuterochloroform was used as the solvent. The integral area given in Fig. 7 and Fig. 10 were estimated with the Chart Reader CR-114 (JEOL).

Mass Spectra Measurement——The Mass spectra were recorded on a JMS-O1SG-2 (JEOL). The ionizing voltage was set to 75 eV and the sample heating temperature varied between about 30° and about 200°.

Mass Spectrum of 6,7-Dibenz[*b*,*g*][1,5]oxazocine (15)——Refer Fig. 12. Sample temperature (S.T.), 30°. *m/e*; 211 (M^+, Basic Peak): Obsd. 211.0968. Calcd. 211.0997 for $C_{14}H_{13}O$. Error, −0.0029. 194: Obsd. 194.0770. Calcd. 194.0731 for $C_{14}H_{10}O$. E., +0.0039. 181: Obsd. 181.0667. Calcd. 181.0653 for $C_{13}H_9O$. E., +0.0014. 165: Obsd. 165.0675. Calcd. 165.0704 for $C_{13}H_9$. E., −0.0028. 153: Obsd. 153.0658. Calcd. 153.0704 for $C_{12}H_9$. E., −0.0046. 107: Obsd. 107.0548. Calcd. 107.0496 for C_7H_7O. E., +0.0048. 91: Obsd. 91.0535. Calcd. 91.0547 for C_7H_7. E., −0.0012.

Mass Spectrum of 6-Benzyl-6,7-dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine (10)——Refer Fig. 14. S.T. 80°. *m/e*; 317 (M^+): Obsd. 317.1240. Calcd. 317.1238 for $C_{21}H_{19}NS$. E., +0.0002. 284: Obsd. 284.1439. Calcd. 284.1439 for $C_{21}H_{18}N$. E., ±0.0000. 226: Obsd. 226.0697. Calcd. 226.0690 for $C_{14}H_{12}NS$. E., +0.0007. 210: Obsd. 210.0494. Calcd. 210.0503 for $C_{14}H_{10}S$. E., −0.0008. 197: Obsd. 197.0421. Calcd. 197.0424 for $C_{13}H_9S$. E., −0.0003. 179: Obsd. 179.0855. Calcd. 179.0860 for $C_{14}H_{11}$. E., −0.0004. 165: Obsd. 165.0702. Calcd. 165.0704 for $C_{13}H_9$. E., −0.0002. 91 (Basic Peak): Obsd. 91.0533. Calcd. 91.0547 for C_7H_7. E., −0.0002.

Mass Spectrum of 6,7-Dihydro-5H-dibenz[*b*,*g*][1,5]thiazocine-12,12-dioxide (17)——*m/e*; 259 (M^+): Obsd. 259.0658. Calcd. 259.0667 for $C_{14}H_{13}NO_2S$. E., −0.0008. 224: Obsd. 224.0533. Calcd. 224.0533 for $C_{14}H_{10}NS$. E., +0.0000. 195 (Basic Peak): Obsd. 195.1075. Calcd. 195.1048 for $C_{14}H_{13}N$. E., +0.0027. 178: Obsd. 178.0827. Calcd. 178.0782 for $C_{14}H_{10}$. E., +0.0045. 165: Obsd. 165.0706. Calcd. 165.0704 for $C_{13}H_9$. E., +0.0002. 152: Obsd. 152.0630. Calcd. 152.0625 for $C_{12}H_8$. E., +0.0004. 137: Obsd. 137.0086. Calcd. 137.0061 for C_7H_5OS. E., +0.0024.

Acknowledgement The authors are grateful to Mr. T. Naito, Director of the Research and Development Department of Eisai Co., Ltd., Mr. H. Arie, Director of the Research Laboratory, for their kind encouragements. Thanks are also due to Mr. M. Nezu for NMR measurements and to Mrs. H. Saito for mass spectra measurements.