FORMATION OF DIHYDROAZA-AZULANONES POSSESSING SPIROCYCLIC MOIETIES: [8+2] TYPE CYCLOADDITION REACTIONS OF IMINOTROPONES TO AN EXOCYCLIC DOUBLE BOND OF 8-OXOHEPTAFULVENE

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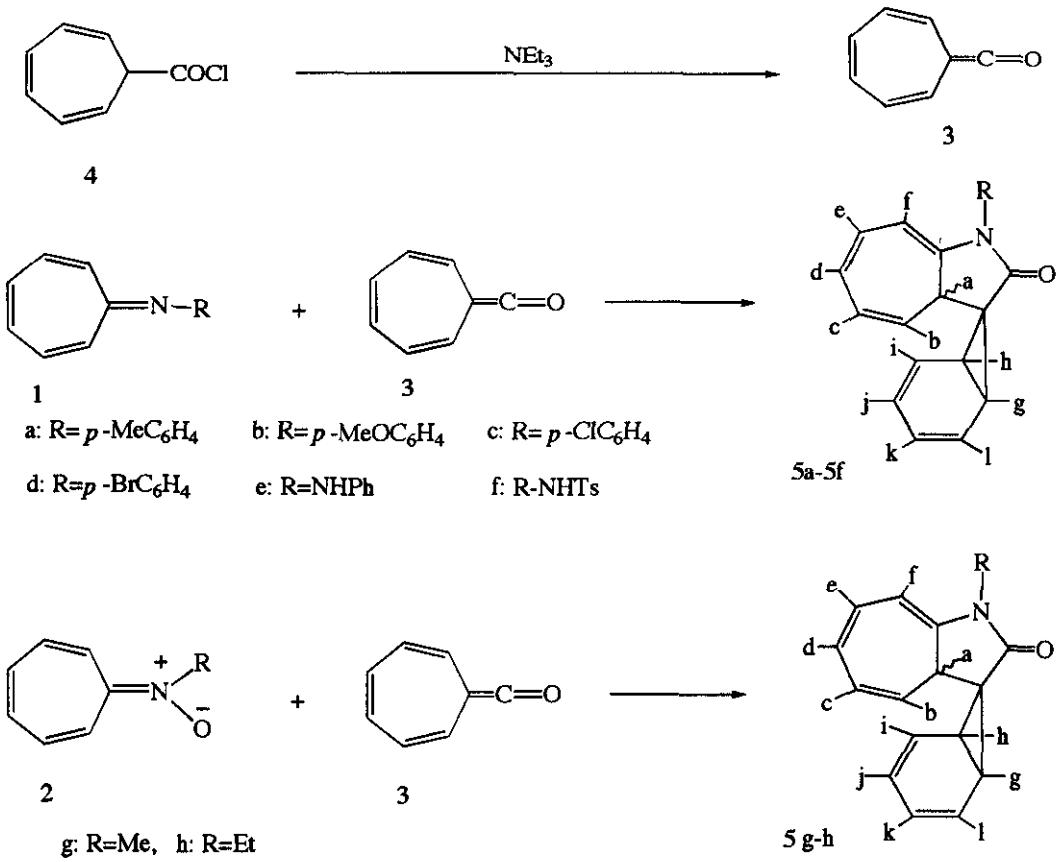
Abstract—— Reactions of *N*-(*p*-substituted phenyl)iminotropones with 8-oxoheptafulvene proceeded through [8+2] type cycloadditions to form dihydroaza-azulanones possessing spirocyclic and norcaradiene moieties. Reactions of 8-oxoheptafulvene with phenyl- or tosylhydrazones of tropone gave the same type of dihydroaza-azulanones. Analogous reactions with *N*-alkyliminotropone *N*-oxides also gave the same type of adducts *via* the corresponding *N*-alkyliminotropones, which were derived from reactions of the iminotropone *N*-oxides with 8-oxoheptafulvene.

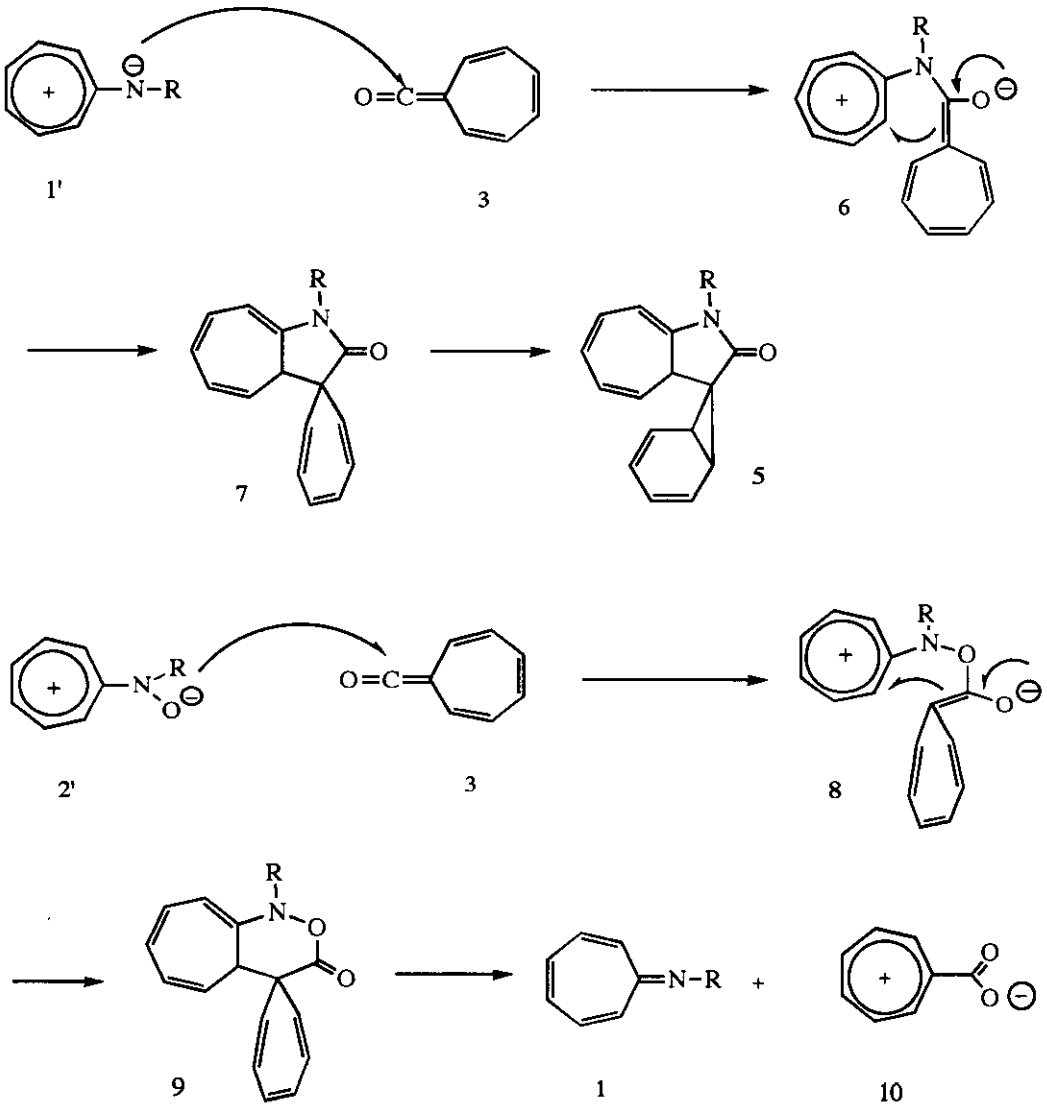
As a result of the stabilities of 6 π electrons aromatic structures, tropone derivatives such as tropone, thiotropone, or iminotropones (1a-1d) have zwitter ionic structures with cationic seven-membered ring parts.[1] The same is the case with tropone hydrazones (1e-1f), iminotropone *N*-oxides (2g-2h), or 8-oxoheptafulvene (3).[2] Iminotropone *N*-oxides (2) can be regarded as both tropone derivatives and nitrone derivatives. In fact, 2 are known to react as tropone derivatives with triazoline-2,5-diones and as nitrone derivatives with several kinds of isocyanates.[3] 8-Oxoheptafulvene (3) can also be considered to be both a tropone derivative and a ketene derivative.

Cycloaddition reactions of tropones with 2 π components are known to proceed through mainly two kinds of pathes; i.e., a [8+2] type addition rout and a [4+2] type addition path.[4] The former route has been adopted as a synthetically useful method to form various types of heterocyclic compounds fused with seven-membered ring moieties. Thus it is of interest to investigate the reaction mode of the cycloadditions of iminotropone derivatives (1a-f and 2g-h) with 8-oxoheptafulvene (3). As a series of our research on the reactions of iminotropones to form dihydroaza-azulanones and azulanones, we studied reactions of the several types of iminotropones with 8-oxoheptafulvene.[5] The results are reported here.

8-Oxoheptafulvene (3) was generated from 2,4,6-cycloheptatriene-1-carbonyl chloride (4) with triethylamine in the presence of three equimollar amount of *N*-(*p*-methylphenyl)iminotropone (1a) in ether at -15°C.[2] After stirring at room temperature for 45 h, the resulted reaction mixture was column chromatographed to give a dihydroaza-azulanone derivative (5a) in 58% yield. The analogous reactions with *N*-(*p*-methoxyphenyl)iminotropone (1b), *N*-(*p*-chlorophenyl)iminotropone (1c), *N*-(*p*-bromophenyl)iminotropone (1d), tropone phenylhydrazone (1e), and tropone tosylhydrazone (1f) afforded the corresponding dihydroaza-azulanones 5b (57%), 5c (57%), 5d (69%), 5e (13%), and 5f (11%), respectively.



Reactions of 8-oxoheptafulvene (3) with iminotropone *N*-oxides (2) gave the same type of adducts as those of the reactions of iminotropones (1). Thus, reactions of 3 with *N*-methyliminotropone *N*-oxide (2g) and *N*-ethyliminotropone *N*-oxide (2h) afforded 5g and 5h in 45 and 51% yields, respectively.



The structures of the adducts were deduced to be dihydroaza-azulanones possessing spirocyclic moieties on the basis of their spectral, especially nmr spectral, properties and confirmed by good resemblaneces of these properties to those of the analogous compounds.[2,6]

The reactions of iminotropones (1a-1f) with 3 are considered to proceed as follows. A nucleophilic attack of the nitrogen atom of 1 at the exocyclic carbon atom of 3 forms the ionic intermediate (6), which then cyclizes to a tropilidene type adduct (7). It is known that a spiro[4.6]undecatriene system tautomerizes to a norcaradiene system,[7] thus, in the present case too, 7 rearranges to the final product (5).

An ionic intermediate (8) is considered to be formed by a nucleophilic attack of the oxygen atom of 2. Subsequent cyclization gave an intermediate (9), which then generated a zwitter ionic compound (10)[8] and an iminotropone derivative (1),[3] which then reacts with 3 through the path mentioned above to form 5.

Thus it was made clear that iminotropones (1) and iminotropone *N*-oxides (2) reacted through formally a [8+2] type cycloaddition route, which was rather common in the reactions of tropone derivatives. On the other hand, 8-oxoheptafulvene (3) played a role of a ketene derivative. The nucleophilicities of the nitrogen and the oxygen atoms of 1 and 2, respectively, are considered to be strengthened by the contributions of 6 π electrons aromatic structures of the seven-membered ring parts as shown in the Figure as 1' and 2'.

EXPERIMENTS

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus and were not corrected. Nmr spectra were recorded with Hitachi R-90 or Varian XL-200 spectrometer with tetramethylsilane as an internal standard. Ir spectra were taken with a JASCO FT/IR 5300 spectrophotometer. Mass spectra were measured with a Hitachi M 2000S spectrometer. Wako gel C-200 or Wako gel B5F were used for column and thin-layer chromatography, respectively.

Reaction of 1a with 3. To a solution of 1a (520 mg, 2.7 mmol) and 4 (150 mg, 1 mmol) in anhydrous ether (10 ml) was slowly added triethylamine (150 mg, 1.5 mmol) under a nitrogen stream at -15°C. After stirring at room temperature for 45 h, the reaction solution was diluted with ether, washed with water, and dried over anhydrous sodium sulfate. After filtration, the solvent was removed on a rotary evaporator to give an orange tar, which was then separated with column chromatography on silica gel to give yellow crystals 5a (180 mg, 58%) with n-hexane-ethyl acetate 9:1 as an eluent.

5a: mp 183.0–184.0°C. Hrms m/z: 313.1447. Calcd for $C_{22}H_{19}NO$ m/z: 313.1465. Ms m/z (rel intensity): 313 (M^+, 77), 207 (26), 195 (100). Ir (KBr): 3030, 2980, 1716 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.73 (d, H_a), 2.38 (s, 3H, Me), 3.28 (m, H_g or H_h), 3.52 (m, H_h or H_g), 4.79 (dd, H_b), 5.49 (d, H_f), 5.9–6.5 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l), 7.16–7.32 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=5.0, J_{bc}=8.5, J_{ef}=6.4. Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.38; H, 6.03; N, 4.31.

Reaction of 1b with 3. Triethylamine (150 mg, 1.5 mmol) was added to a solution of 1b (660 mg, 3 mmol) and 4 (150 mg, 1 mmol) in dry ether (5 ml) at −15°C. After the same treatment as above the reaction mixture was chromatographed on silica gel to give pale brown crystals 5b (190 mg, 57%, hexane–ethyl acetate 8:2).

5b: mp 183.5–185.0°C. Hrms m/z: 329.1417. Calcd for $C_{22}H_{19}NO_2$ m/z: 329.1414. Ms m/z (rel intensity): 329 (M^+, 66), 211 (100), 133 (96). Ir (KBr): 3427, 1717, 1250 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.76 (d, H_a), 3.29 (m, H_g or H_h), 3.53 (m, H_h or H_g), 3.85 (s, 3H, Me), 4.80 (dd, H_b), 5.50 (d, H_f), 5.8–6.6 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l), 7.00–7.26 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=5.0, J_{bc}=8.0, J_{ef}=6.4.

Reaction of 1c with 3. Triethylamine (150 mg, 1.5 mmol) was added to a solution of 1c (620 mg, 3 mmol) and 4 (150 mg, 1 mmol) in dry ether (5m l) at −15°C. After the same treatment as above the reaction mixture was chromatographed on silica gel to give brown crystals 5c (190 mg, 57%, n–hexane–ethyle acetate 9:1).

5c: mp 160.0–161.5°C. Hrms m/z: 333.0933. Calcd for $C_{21}H_{16}NOCl$ m/z: 333.0919. Ms m/z (rel intensity): 333 (M^+, 85), 227 (32), 215 (58), 118 (100). Ir (KBr): 3042, 2924, 1721 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.72 (d, H_a), 3.24 (m, H_g or H_h), 3.46 (m, H_h or H_g), 4.80 (dd, H_b), 5.53 (d, H_f), 5.9–6.6 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l), 7.30–7.47 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=4.6, J_{bc}=8.8, J_{ef}=6.7. Anal. Calcd for $C_{21}H_{16}NOCl$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.62; H, 4.94; N, 4.47.

Reaction of 1d with 3. Triethylamine (150 mg, 1.5 mmol) was added to a solution of 1d (720 mg, 2.8 mmol) and 4 (150 mg, 1 mmol) in dry ether (5 ml) at −15°C. After the same treatment as above the reaction mixture was chromatographed on silica gel to give yellow crystals 5d (260 mg, 69%, n–hexane–ethyle acetate 9:1).

5d: mp 165.0–166.0°C. Hrms m/z: 377.0396. Calcd for $C_{21}H_{16}NOBr$ m/z: 377.0414. Ms m/z (rel intensity): 378 (M^+, 86), 271 (26), 259 (46), 118 (100). Ir (KBr): 3043, 1723 cm^{-1}. ^1H Nmr ($CDCl_3$), δ: 1.76 (d, H_a), 3.23 (m, H_g or H_h), 3.46 (m, H_h or H_g), 4.80 (d, H_b), 5.53 (d, H_f), 5.9–6.5 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l), 7.24–7.61 (m, 4H, aromatic protons). Coupling conatants in Hz: J_{ab}=5.5, J_{ef}=6.1. Anal. Calcd for $C_{21}H_{16}NOBr$: C, 66.68; H, 4.26; N, 3.70. Found: C, 66.46; H, 4.16; N, 3.64.

Reaction of 1e with 3. Triethylamine (150 mg, 1.5 mmol) was added to a solution of 1e (590 mg, 3.0 mmol) and 4 (150 mg, 1 mmol) in dry ether (10 ml) at −15°C. After the same

treatment as above the reaction mixture was chromatographed on silica gel to give yellow crystals 5e (41 mg, 13%, n-hexane–ethyl acetate 7:3).

5e: mp 145.0–146.0°C. Hrms m/z: 314.1401. Calcd for $C_{21}H_{18}N_2O$ m/z: 314.1417. Ms m/z (rel intensity): 314 (M^+, 20), 222 (17), 209 (9), 196 (100). Ir (KBr): 3017, 1723, 1644 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.80 (d, H_a), 3.33 (m, H_g or H_h), 3.58 (m, H_h or H_g), 4.75 (dd, H_b), 5.85 (d, H_f), 5.9–6.6 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l), 6.78–7.25 (m, 5H, aromatic protons). Coupling constants in Hz: J_{ab}=4.1, J_{bc}=8.6.

Reaction of 1f with 3. Triethylamine (150 mg, 1.5 mmol) was added to a solution of 1f (820 mg, 3.0 mmol) and 4 (150 mg, 1 mmol) in tetrahydrofuran (10 ml) at −15°C. After the same treatment as above the reaction mixture was chromatographed on silica gel to give yellow crystals 5f (43 mg, 11%, hexane–ethyl acetate 7:3).

5f: mp 172–173°C. Hrms m/z: 392.1196. Calcd for $C_{22}H_{20}N_2O_3S$ m/z: 392.1190. Ms m/z (rel intensity): 392 (M^+, 49), 237 (59), 221 (30), 118 (100). Ir (KBr): 3017, 1723, 1644 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.67 (d, H_a), 2.45 (s, 3H, Me), 3.06 (m, H_g or H_h), 3.55 (m, H_h or H_g), 4.83 (dd, H_b), 5.68 (d, H_f), 5.9–6.6 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l), 7.37 (d, 2H, aomatic protons), 8.06 (d, 2H, aromatic protons). Coupling constants in Hz: J_{ab}=5.0, J_{ef}=6.5.

Reaction of 2g with 3. To a solution of 2g (400 mg, 3.0 mmol) and triethylamine (150 mg, 1.5 mmol) in dry ether (10 ml) was slowly added 4 (150 mg, 1 mmol) under a nitrogen stream at room temperature. After stirring for 2 h, the reaction solution was diluted with ether, washed with water, and dried over anhydrous sodium sulfate. After filtration, the solvent was removed on a rotary evaporator to give a brown tar, which was then separated with thin layer chromatography on silica gel to give an orange oil 5g (53 mg, 45 %, n-hexane–ethyl acetate 10:1).

5g: Hrms m/z: 237.1151. Calcd for $C_{16}H_{15}NO$ m/z: 237.1152. Ms m/z (rel intensity): 237 (M^+, 60), 236 (100), 220 (4). Ir (oil): 3443, 1716, 1633, 1529 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.70 (d, H_a), 3.10 (s, Me), 3.30 (m, H_h or H_g), 3.61 (m, H_h or H_g), 4.69 (dd, H_b), 5.55 (d, H_f), 5.9–6.5 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l). Coupling constants in Hz: J_{ab}=4.3, J_{bc}=8.4.

Reaction of 2h with 3. 4 (150 mg, 1.0 mmol) was added to a solution of 1h (450 mg, 2 mmol) and triethylamine (150 mg, 1.5 mmol) in dry ether (10 ml) at r.t. After the same treatment as above the reaction mixture was separated with thin layer chromatography to give an orange oil 5h (64 mg, 51 %, n-hexane–ethyl acetate 4:1)

5h: Hrms m/z: 251.1283. Calcd for $C_{17}H_{17}NO$ m/z: 251.1308. Ms m/z (rel intensity): 251 (M^+, 64), 250 (100), 222 (11). Ir (oil): 3427, 1712, 1628, 1531 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.28 (t, CH_3), 1.65 (d, H_a), 3.30 (m, H_g or H_h), 3.61 (m, 3H, H_g or H_h and CH_2), 4.62 (dd, H_b), 5.60 (d, H_f), 5.9–6.6 (m, 7H, H_c, H_d, H_e, H_i, H_j, H_k, H_l). Coupling constants in Hz: J_{ab}=4.3, J_{bc}=8.7.

REFERENCES

1. Y. Kurita, S. Seto, T. Nozoe, and M. Kubo, *Bull. Chem. Soc. Jpn.*, 1953, 26, 272; W. E. Truce and J. P. Shepherd, *J. Am. Chem. Soc.*, 1977, 99, 6453; B. D. Dean and W. E. Truce, *J. Org. Chem.*, 1980, 45, 5429; Y. Fukazawa, S. Usui, Y. Kurata, Y. Takeda, and N. Saito, *ibid.*, 1989, 54, 708; K. Saito, T. Watanabe, and K. Takahashi, *Chem. Lett.*, 1989, 101; T. Machiguchi and S. Yamabe, *ibid.*, 1990, 1511; K. Ito, K. Saito, S. Takeuchi, and K. Takahashi, *Heterocycles*, 1992, 34, 1415; K. Ito, K. Saito, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, 1992, 65, 812.
2. T. Asao, N. Morita, and K. Kitahara, *J. Am. Chem. Soc.*, 1972, 94, 3655; N. Morita, Y. Kitahara, and T. Asao, *Tetrahedron Lett.*, 1972, 869; T. Asao, N. Morita, C. Kabuto, and Y. Kitahara, *ibid.*, 1972, 4382; N. Morita, T. Asao, W. Iwagame, and Y. Kitahara, *Chem. Lett.*, 1973, 67; N. Morita and T. Asao, *Tetrahedron Lett.*, 1974, 2083; K. Kato, Y. Kitahara, N. Morita, and T. Asao, *Chem. Lett.*, 1977, 873; K. Saito, *Bull. Chem. Soc. Jpn.*, 1987, 60, 2105; K. Saito, K. Ito, C. Kabuto, and K. Takahashi, *ibid.*, 1991, 64, 2383; K. Saito, M. Hattori, T. Sato, and K. Takahashi, *Heterocycles*, 1992, 34, 129.
3. D. Mukherjee, L. N. Domelsmith, and K. N. Houk, *J. Am. Chem. Soc.*, 1978, 100, 1954; S. Kajigaeshi, S. Matsuoka, S. Kanemasa, and M. Noguchi, *Heterocycles*, 1984, 22, 461; K. Ito, K. Saito, and K. Takahashi, *ibid.*, 1993, 36, 1459.
4. C. Jutz, I. Rommel, I. Lengyel, and J. Feeney, *Tetrtahedron*, 1966, 22, 1809; L. A. Paquette and N. Harton, *Tetrahedron Lett.*, 1968, 2289; G. R. Tian, S. Sugiyama, A. Mori, and H. Takeshita, *Bull. Chem. Soc. Jpn.*, 1988, 61, 2393; R. P. Gandhi and M. P. S. Ishar, *Chem. Lett.*, 1989, 101.
5. K. Ito, K. Saito, and K. Takahashi, *Heterocycles*, 1991, 32, 1117; *idem, Bull. Chem. Soc. Jpn.*, 1992, 65, 812; *idem, Heterocycles*, 1992, 34, 2339; *idem, ibid.*, 1993, 36, 21.
6. The orientation of the cyclohexadiene moiety of the norcaradiene part was confirmed by the same method employed by Asao *et al.*, i.e., the drifts of the chemical shifts of the nmr signals of protons in the presence of shift reagent, tris(dipivaloylmethanate)eulopium, $Eu(DPM)_3$, were measured as shown in the following table with the case of 5b.

Table. Effect of Shift Reagent on the Chemical Shifts (δ ppm)

		H_a	H_b	H_f	$H_{g,\ h}$
chemical		1.76	4.80	5.50	3.29, 3.53
shifts	$Eu(DPM)_3$	2.57	5.47	6.17	4.43, 4.94
drift		0.81	0.67	0.67	1.14, 1.41

The drifts of H_g and H_h were larger than those of the other protons suggesting that H_g and H_h are located closely to the carbonyl group to which the shift reagent was coordinated.[2]

Taking into account sp^2 hybridizations of the nitrogen atoms in the lactam rings, 5 are considered to exist as racemic mixtures concerning the orientations of methine protons H_a.

7. H. Durr and H. Kober, *Chem. Ber.*, 1973, 106, 1565; W. Adam, H. Reballo, H. D. Urr, J. H. Pauly, K. Peters, E. M. Peters, and H. G. von Scheneiring, *Tetrahedron Lett,*, 1982, 23, 923.
8. The compound (10) is at now a speculated product and efforts to isolate or trapp 10 are now in progress.

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