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Synthesis and Conformation of 1-Methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]nonane 7-Oxide

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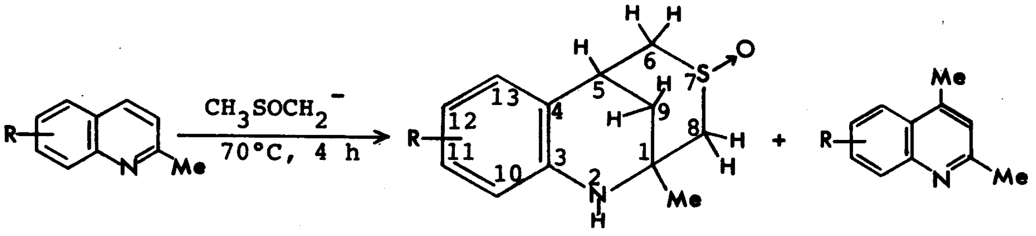
1-Methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]nonane 7-oxide has been synthesized by the reaction of quinaldine with methylsulfinylmethyl carbanion, and its structure has been elucidated on the basis of spectral data and some chemical evidence. The conformation of the product has been further investigated by means of proton and carbon-13 nuclear magnetic resonance spectroscopy together with molecular mechanics calculations. The molecular mechanics calculations indicate that the stable conformer has a chair thiane ring with an equatorial sulfoxy group.

Keywords——methylsulfinylmethyl carbanion; quinaldine; 3,4-benzo-7-thia-2-azabicyclononane 7-oxide; ring formation; conformational analysis; ^{1}H-NMR; ^{13}C-NMR; molecular mechanics calculation

The methylsulfinylmethyl carbanion ($CH_3SOCH_2^-$) is an extremely useful methylating agent in syntheses.[1] In the course of a search for new antispasmodic agents, we found an interesting reaction of quinaldine (**1a**) with this carbanion, giving a novel tricyclic compound (**2a**),[2,3] in addition to a small amount of the expected methylation product (**3a**), as shown in Chart 1.

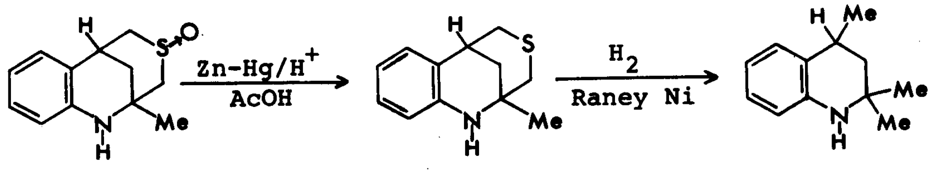


1a—e **2a—e** **3a—d**

a: R=H
b: R=12-CH_3
c: R=10-CH_3
d: R=10-OCH_3
e: R=12-F

Chart 1

The structure of this novel compound was determined to be **2a** as follows. In association with the molecular ion peak (*m*/*z* 221) in the mass spectrum (MS), elemental analysis revealed the product to be a 1:1 adduct of **1a** and dimethylsulfoxide (DMSO). The presence of a secondary amine and a sulfoxy group was indicated by the infrared (IR) absorption bands at 3460 and 1010 cm^{-1}. Furthermore, the proton nuclear magnetic resonance spectrum suggested a tentative structure (**2a**) together with the probable stable conformation in solution.[2] Finally, the structure (**2a**) was confirmed by chemical transformation of **2a** to the known trimethyl tetrahydroquinoline (**5**),[4] in two steps (desulfurization with Raney nickel after



2a 4 5

Chart 2

TABLE I. Reaction Products of Quinaldines (1a—e) and Methylsulfinylmethyl Carbanion

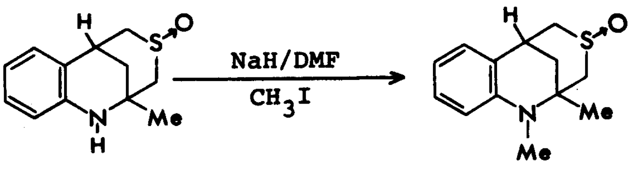
Compd. No.	Yield (%)	Appearance	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	MS m/z	Yield of methylation product (3a—d) (%)
2a	60	Colorless needles	216—218	$C_{12}H_{15}NOS$	65.12 (64.96	6.83 6.89	6.33 6.26)	221 (M^+), 158, 144, 131	11
2b	67	Colorless needles	204—206	$C_{13}H_{17}NOS$	66.35 (66.57	7.28 7.15	5.95 5.66)	235 (M^+), 172, 158, 145	8
2c	13	Colorless needles	154—156	$C_{13}H_{17}NOS$	66.35 (66.27	7.28 7.41	5.95 5.83)	235 (M^+), 172, 158, 145	—
2d	29	Colorless needles	204—206	$C_{13}H_{17}NO_2S$	62.12 (62.04	6.87 6.94	5.57 5.52)	251 (M^+), 188, 174, 161	2
2e	7	Colorless needles	200—202	$C_{12}H_{14}FNOS$	60.23 (60.03	5.90 6.17	5.85 5.80)	239 (M^+), 176, 162, 149	—

treatment with zinc amalgam and hydrogen chloride), as shown in Chart 2.

Some quinaldine derivatives (**1b**—**e**) were reacted with the carbanion under the same conditions and the corresponding tricyclic products (**2b**—**e**) were also obtained, as summarized in Table I.[5] All the compounds afforded elemental analysis results as well as spectral data in reasonable agreement with the assigned structures.

The identification and estimation of the methylated minor products (**3a**—**d**) were done by gas chromatography, by comparing the retention times and peak areas with those of authentic specimens.[6]

As shown in Chart 3, compound **2a** was further methylated with methyliodide to give 1,2-dimethyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]nonane 7-oxide (**6**),[5] which has antispasmodic activity.[3]



2a 6

Chart 3

Conformations of 2a—e and 6

The stable conformation of **2a**—**e** and **6** in solution were investigated by means of proton and carbon-13 nuclear magnetic resonance (^1H- and ^{13}C-NMR) spectroscopy. Except for the aromatic ring carbons, the ^{13}C-NMR signals were easily assignable on the basis of the multiplicity in the ^1H off-resonance spectra. As shown in Table II, the corresponding sp^3 carbons in **2a**—**e** were observed at almost the same positions, whereas the signals of **6** appeared at slightly different positions from those of **2a**—**e**. These assignments were

Table II. ^{13}C-NMR Chemical Shifts (δ) of **2a**—**e** and **6** (Multiplicities Observed in Off-Resonance Spectra in Parenthesis)

Compd. No.	C(1)	C(1)-Me	C(5)	C(6), C(8)	C(9)	C(3)
	(s)	(q)	(d)	(t) (t)	(t)	(s)
2a	51.15	29.65	33.46	60.02, 67.73	35.45	142.73
2b	51.27	29.82	33.57	60.12, 67.91	35.74	140.45
2c	51.56	30.23	33.80	60.23, 68.03	35.62	140.43
2d	51.08	29.88	33.39	60.09, 68.23	35.68	145.14
2e	51.47	29.83	33.63	59.75, 68.04	35.33	139.39
6	55.32	28.07	34.12	60.00, 62.43	37.97	145.53

Compd. No.	C(4)	C(10)	C(11)	C(12)	C(13)	Me
	(s)	(d)	(d)	(d)	(d)	(q)
2a	120.58	127.29	116.83	127.29	113.03	
2b	120.03	128.61[a]	128.43[a]	126.03	113.26	20.33
2c	120.23[a]	120.41[a]	126.03	129.02	116.89	17.17
2d	121.01	132.76	116.53	120.33	108.44	55.37
2e	121.82	113.9—115.6		155.30[b]	113.9—115.6	
6	123.55	127.84	116.63	128.57	111.20	31.29

a) Assignment may be reversed. *b*) $J_{\text{C-F}}=236$ Hz.

confirmed by the ^{1}H selective decoupling experiments, but two carbons C(6) and C(8) could not be definitively assigned because they have the same multiplicities and similar chemical shift values. The signals of the axial and equatorial protons on C(6) and C(8) are separated by more than 0.8 ppm, because of the different susceptibilities to the magnetic anisotropy of the sulfoxy group. Therefore, these protons could not be decoupled simultaneously. Unfortunately, the aromatic carbons are superimposed on each other and show the same multiplicities in the off-resonance spectra, so precise assignments could not be achieved.

Chemical shifts and coupling constants in the ^{1}H-NMR spectra are summarized in Table III. Again, the assignments of the aromatic protons were difficult because of the complex overlapping signals. The aliphatic region of the ^{1}H-NMR spectra of **2a**—**e** resemble each other, and the signals were assignable by means of ^{1}H–^{1}H homospin decoupling experiments. As seen in the case of the ^{13}C-NMR spectra, the ^{1}H-NMR spectrum of **6** was somewhat different from those of **2a**—**e**. Two protons at C(9) in **6** were observed at 2.0 ppm as a broad doublet ($J=3$ Hz), indicating that these two protons were coupled with the proton at C(5) as well as with the equatorial protons at C(6) and C(8). Namely, on irradiation of the doublet at 2.0 ppm, the broad multiplets at 3.63 and 3.87 ppm were changed to a sharp doublet of double doublets ($J=2.5$, 4.5, and 11 Hz) and a doublet of doublets ($J=2.5$ and 12 Hz), respectively, whereas the corresponding protons at C(9) in **2a**—**e** appeared as an AB quartet ($^{2}J=12$ or 13 Hz) which further exhibited vicinal and long-range couplings (^{3}J or $^{4}J=2$, 3, or 4 Hz) with the protons at C(5), C(6), and C(8). On the other hand, while the axial proton at C(6) in **6** was observed as a doublet of doublets ($^{2}J=11$ Hz and $^{3}J=3$ Hz), the corresponding proton in **2a**—**e** appeared as a doublet ($^{2}J=11$ Hz) in consequence of coincidental overlap on the doublet of the axial proton at C(8).[7] As shown in Tables II and III, the features of the ^{1}H-

Table III. ^{1}H-NMR Chemical Shifts (δ) and ^{1}H–^{1}H Coupling Constants (Hz) of **2a**—**e** and **6**

Compd. No.	C(1)-Me	C(5)-H	*N*-H	C(6)-H		C(8)-H		C(9)-H		C(10)-H	C(11)-H	C(12)-H	C(13)-H		
				axial	equatorial	axial	equatorial	axial	equatorial						
2a	1.42 s	3.40 m	4.24 br s	2.76 d *J*=11	3.56 td *J*=2, 11	2.78 d *J*=11	3.72 br d *J*=11	2.03 dd *J*=2, 13	1.79 tdd *J*=2, 4, 13	6.92—7.16 m		6.64 t *J*=8	6.42 d *J*=8		
2b	1.38 s	3.32 m	3.96 br s	2.72 d *J*=11	3.54 td *J*=2, 11	2.76 d *J*=11	3.69 dd *J*=2, 11	1.99 dd *J*=2, 13	1.77 tdd *J*=2, 4, 13	6.80 m		—	6.38 d *J*=9	C(12)-Me	2.21 s
2c	1.46 s	3.40 m	3.76 br s	2.76 d *J*=12	3.57 td *J*=2, 12	2.79 d *J*=12	3.71 br d *J*=12	2.04 br d *J*=13	1.80 tdd *J*=2, 4, 13	—	6.92 d *J*=8	6.60 t *J*=8	6.92 d *J*=8	C(10)-Me	2.08 s
2d	1.46 s	3.39 m	4.41 br s	2.73 d *J*=11	3.48 td *J*=2, 11	2.74 d *J*=11	3.67 dd *J*=2, 11	2.00 dd *J*=2, 12	1.78 tdd *J*=2, 4, 12	—		6.65 m		C(10)-OMe	3.81 s
2e	1.39 s	3.33 m	4.29 br s	2.75 d *J*=11	3.56 td *J*=2, 11	2.76 d *J*=11	3.55 br d *J*=11	1.98 dd *J*=3, 13	1.74 tdd *J*=2, 4, 13	6.73 m		—	6.36 dd *J*=5, 10		
6	1.43 s	3.32 quintet *J*=3—4.5	—	2.79 dd *J*=3, 11	3.63 br ddd *J*=2.5, 4.5, 11	2.63 d *J*=12	3.87 br dd *J*=2.5, 12	2.00 br d *J*=3		6.77 dd *J*=2, 7.5	6.62 dt *J*=1, 7.5	7.11 ddd *J*=2, 7.5, 8	6.53 d *J*=8	*N*-Me	2.91 s

and ^{13}C-NMR spectra of **2a**—**e** are all similar to each other, so the conformations of these molecules should be virtually identical. On the other hand, the ^{1}H-NMR coupling constants are not very different between **6** and **2a**—**e**, but the ^{1}H- and ^{13}C-NMR chemical shifts of **6** are slightly different from those of the corresponding signals of **2a**—**e**.

The thia-azabicyclo[3.3.1]nonane oxide system can take both chair and twist-boat conformations at the 6-membered thiane ring. Moreover, each of them may have various configurations concerning the direction of the N–H and S–O bonds. Consequently, four chair and four twist-boat conformations are conceivable. Inspection of a molecular model revealed that the conformation with the chair thiane ring is in good agreement with the NMR spectral data of **2a**—**e** as well as **6**, although the boat form was proposed for **2a** on the basis of a ^{1}H-NMR shift reagent experiment.$^{2)}$

Thus, molecular mechanics calculations were performed to investigate the conformations

TABLE IV. Calculated Steric Energies (kcal mol^{-1}) of Stable Conformations of the Compounds with and without the *N*-Methyl Group

	Chair	Twist-boat
N-H compound (**2a**)	19.6250	27.2022
N-Me compound (**6**)	30.8025	36.4398

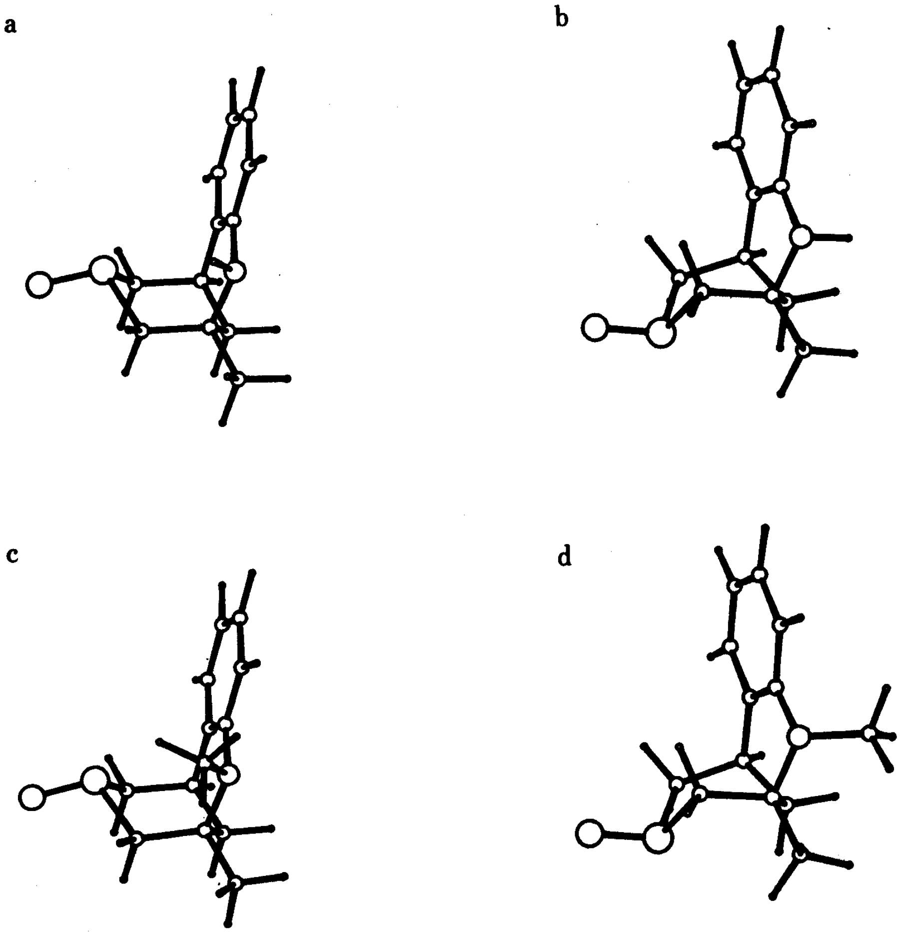


Fig. 1. ORTEP Drawings of the Calculated Stable Conformers of Chair (a) and Twist-Boat (b) Forms of *N*-H Compound (**2a**), and Chair (c) and Twist-Boat (d) Forms of *N*-CH_3Compound (**6**)

of **2a**—**e** and **6**. In the cases with and without an *N*-methyl group, the approximate coordinates were calculated by means of the program COORD[8)] for every possible structure mentioned above. Then iterative calculations were carried out to minimize the steric energy of each structure by means of the molecular mechanics program MMI.[9)]

The steric energies of the most stable conformers of the chair and the twist-boat forms are listed in Table IV, and ORTEP drawings[10)] of these stable conformers are shown in Fig. 1. For both compounds (with and without the *N*-methyl substituent), the chair conformer is more than 5 kcal/mol more stable than the twist-boat one.

The calculated dihedral angles of the chair conformer of the *N*-H and *N*-methyl compounds were consistent with the ^{1}H-NMR spectra of **2a**—**e** and **6**, respectively. All dihedral angles between C(5)-H and the two protons at C(6) as well as at C(9) were approximately 60 °, which explained the observed coupling constants ($^3J = 3$ Hz) very well. The calculated structures also show that the three equatorial protons at C(6), C(8), and C(9) exist nearly on a single plane in "W" configurations, in accordance with the observed long range couplings. Moreover, as shown in Fig. 1, the calculated stable chair conformer of both the *N*-H and *N*-methyl compounds has an equatorial sulfoxy group. This is also consistent with the finding that although the thiane oxide ring prefers the chair conformation with the axial sulfoxy group, the configuration of the sulfoxy group is sensitive to the substituent at the β-position, so 3,3-dimethyl thiane 1-oxide has a preference for the equatorial sulfoxy group.[11)] The equatorial sulfoxy structures of **2a**—**e** together with **6** were confirmed by the data in Table III, since the chemical shift differences (more than 0.8 ppm) and the geminal coupling constants (*ca.* 11 Hz) between the two protons at C(6) as well as C(8), agree well with the reported values.[11)]

On the other hand, the calculated twist-boat conformation with or without the *N*-methyl group is not consistent with the observed ^{1}H-NMR coupling constants, namely, the proton at C(5) does not bisect the H–C–H angles at C(6) or C(9), and the equatorial protons at C(6), C(8), and C(9) do not constitute a "W" configuration. Furthermore, the rather large calculated energy difference between the chair and the twist-boat forms tends to rule out the existence of the twist-boat form. Although the small but distinct chemical shift differences between **2a**—**e** and **6** could not be explained, it is concluded that the stable conformations of **2a**—**e** and **6** in solution are the chair conformations with the equatorial sulfoxy goup.

Experimental

All the melting points are uncorrected. The ^{13}C-NMR spectra were taken on a JEOL JNM FX-100 Fourier transform NMR spectrometer at 25.0 MHz, and the ^{1}H-NMR spectra were recorded using JEOL JNM PS-100 and JEOL JNM FX-100 spectrometers at 100 MHz. Samples were prepared as approximately 10% (w/v) solutions in $CDCl_3$. Chemical shifts are given in ppm from tetramethylsilane (TMS) as an internal standard, and coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). The IR spectra were recorded on a JASCO IRA-I spectrometer. MS were taken with a Hitachi GC-MS M-52 spectrometer with a direct inlet system for electron impact (70 eV) mass spectroscopy. Gas chromatography was carried out on a JGC 20 KEP gas chromatographic analyzer equipped with an FID detector, using a 3 mm × 1 m stainless steel column packed with 10% SE-30 on Chromosorb W-AW-DMCS (60—80 mesh). The column temperature was gradually raised from 50 to 150 °C, and N_2 was passed at the flow rate of 50 ml/min. The sample was prepared as an approximately 1% solution in acetone.

All the calculations were carried out on a FACOM M-382 computer at Nagoya University Computation Center.

1-Methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]nonane 7-Oxide (2a—e)——Under an N_2 atmosphere, quinaldine or a derivative (**1a**—**e**) (0.02 mol) was added to a DMSO solution of methylsulfinylmethyl carbanion, prepared from NaH (2.64 g, 0.11 mol) and 100 ml of DMSO. After being maintained at 70 °C for 3.5 h (except in the case of **1e**, where the reaction was halted at 30 min to prevent polymerization), the reaction mixture was poured into an excess of water, then extracted with CH_2Cl_2 to afford colorless needles (from benzene) of the tricyclic compound (**2a**—**e**). The results are summarized in Table I.

Reduction of the Thiane Oxide (2a)——Zinc amalgam (prepared from 5 g of Zn powder, 0.5 g of $HgCl_2$ and

0.5 ml of conc. HCl) was added to a solution of 0.5 g (2.3 mmol) of **2a** in AcOH (30 ml). After addition of 30 ml of conc. HCl, the reaction mixture was heated on a water bath (95 °C) for 1 h, then basified with NH_4OH, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on a silica gel column with benzene–$CHCl_3$ (1 : 1). The collected fraction was evaporated, and the residue was recrystallized from cyclohexane to give 1-methyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]nonane (**4**), mp 95—96.5 °C in 72% yield. *Anal.* Calcd for $C_{12}H_{15}NS$: C, 70.22; H, 7.31; N, 6.82. Found: C, 69.99; H, 7.35; N, 6.75. IR ($CHCl_3$): 3460 (NH), 1270 (–S–) cm^{-1}. ^1H-NMR δ: 1.30 (3H, s, CH_3), 1.77 (2H, d, $J=3$ Hz, C(9)-H_2), 2.40 (1H, br d, $J=12$ Hz, C(8)-equatorial H), 2.48 (1H, br dd, $J=3$, 12 Hz, C(6)-equatorial H), 2.96 (1H, d, $J=12$ Hz, C(8)-axial H), 3.12 (1H, dd, $J=3$, 12 Hz, C(6)-axial H), 3.29 (1H, m, C(5)-H), 3.84 (1H, br s, NH), 6.5—7.2 (4H, complex, aromatic H). MS m/z: 205 (M^+).

Desulfurization of the Thiane (4)——A mixture of a solution of 0.3 g (1.5 mmol) of **4** in 25 ml of EtOH and 2 g of Raney Ni (T-1) was stirred at 100 °C for 62 h in an autoclave under an H_2 pressure of 3 atm. After cooling, the reaction mixture was filtered, the filtrate was evaporated, and the residue was chromatographed on a silica gel column with cyclohexane to give 2,4,4-trimethyl-1,2,3,4-tetrahydroquinoline (**5**), mp 40—41 °C in 58% yield. *Anal.* Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 81.77; H, 9.84; N, 7.79. IR ($CHCl_3$): 3440 (NH) cm^{-1}. ^1H-NMR δ: 1.16 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.33 (3H, d, $J=7$ Hz, CH–$\underline{CH_3}$), 1.48 (1H, d, $J=12$ Hz, CH–$\underline{H}$), 1.73 (1H, dd, $J=6$, 12 Hz, CH–$\underline{H}$), 2.90 (1H, m, CH–), 6.30—7.18 (4H, complex, aromatic H). MS m/z: 175 (M^+). The product (**5**) was identical with an authentic sample[4] in terms of mp, IR, and NMR data.

1,2-Dimethyl-3,4-benzo-7-thia-2-azabicyclo[3.3.1]nonane 7-Oxide (6)——A dimethylformamide (DMF) solution of **1a** (4.42 g, 0.019 mol) was added to a mixture of NaH (2.4 g, 0.1 mol) and 50 ml of DMF. To this reaction mixture, MeI (14.2 g, 0.1 mol) was added at 55—60 °C within 30 min. The mixture was stirred for 2 h at this temperature, cooled, poured into ice water (200 ml), and extracted with CH_2Cl_2. After evaporation of the solvent, the residue was washed with benzene–cyclohexane (1 : 3), and recrystallized from EtOAc to afford the *N*-methyl compound (**6**) as colorless needles, mp 138—140 °C, in 77% yield. *Anal.* Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.23; H, 7.43; N, 5.93. MS m/z: 235 (M^+), 173, 158, 145.

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