sively washed with aqueous 2 N HCl (15 mL) and H_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2). The major product from the reaction was eluted from the column by using 20% EtOH–EtOAc as the eluent and was identified as **14** (R_f 0.22, EtOAc); 46% yield (0.50 g); mp 202–205 °C; IR (KBr) 3220, 1715, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3 H), 1.29 (s, 3 H), 1.75–2.06 (m, 2 H), 2.25–2.94 (m, 5 H), 3.25 (dd, 1 H, J = 10, 5 Hz), 4.13 (ddd, 1 H, J = 12, 3, 2 Hz), 5.12 (br s, 1H); ^{13}C NMR ($CDCl_3$) 23.1 (t, J = 130 Hz), 23.2 (q, J = 120 Hz), 28.0 (q, J = 120 Hz), 43.4 (t, J = 130 Hz), 44.1 (t, J = 130 Hz), 45.4 (t, J = 130 Hz), 55.1 (s), 63.3 (d, J = 140 Hz), 160.8 (s), 210.1 (s) ppm; MS, *m/e* (relative intensity) 196 (92), 181 (100), 153 (36).

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.02; H, 8.12; N, 14.38.

Preparation of 3,3,6,6-Tetramethyl-4-oxa-1,7-diazabicyclo[3.3.0]octan-8-one (15). A solution of 1.50 g (8 mmol) of **7e**, 0.20 mL (2.5 mmol) of trifluoroacetic anhydride, and 0.18 mL (1.5 mmol) of anhydrous $SnCl_4$ in CH_2Cl_2 (100 mL) was heated to reflux (3 days). A 5% aqueous HCl solution (20 mL) was then added to the solution which was allowed to stir for 10 min at room temperature. The mixture was neutralized with 15% aqueous NaOH, and the organic layer was separated and then washed with H_2O (20 mL), dried (Na_2SO_4) and concentrated in vacuo. Thin-layer and ^{13}C NMR spectral analyses of the crude product showed the presence of both a major (R_f 0.64, EtOAc) and a minor (R_f 0.30, EtOAc) reaction product. The crude product was purified by flash chromatography (SiO_2, EtOAc). The major product (R_f 0.64, EtOAc) was isolated and identified as **15**: 30% yield (0.50 g); mp 128–130 °C; IR (KBr) 3200, 1690, 1300, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.30 (s, 9 H), 3.00 (d, 1 H, J = 12 Hz), 3.90 (d, 1 H, J = 12 Hz), 4.83 (s, 1 H), 6.00 (br s, 1 H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) 22.1 (q, J = 120 Hz), 26.8 (q, J = 120 Hz), 28.0 (q, J = 120 Hz), 28.3 (q, J = 120 Hz), 55.5 (s), 57.0 (t, J = 140 Hz), 88.0 (s), 96.5 (d, J = 170 Hz), 163.7 (s) ppm; MS, *m/e* (relative intensity) 184 (37), 169 (80), 156 (28), 126 (64), 111 (14), 100 (100), 83 (59), 82 (38), 68 (16).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.61; H, 8.78; N, 15.07.

Acknowledgment. We thank the Robert A. Welch Foundation and the National Institutes of Health (Grant No. NS15604) for their support of this research.

Registry No. **4a**, 763-32-6; **4b**, 7515-62-0; **4c**, 928-97-2; **4d**, 928-96-1; **4e**, 513-42-8; **4f**, 5390-04-5; **5**, 77-71-4; **6a**, 91466-51-2; **6b**, 91445-24-8; **6c**, 91445-21-5; **6d**, 91445-22-6; **6e**, 59004-93-2; **6f**, 91445-23-7; **7a**, 91445-25-9; **7b**, 91445-26-0; **7c**, 91445-27-1; **7d**, 91445-28-2; **7e**, 91445-29-3; **7f**, 91445-30-6; **8a**, 91445-31-7; **8b**, 91445-33-9; **9a**, 91445-32-8; **9b**, 91445-34-0; **10**, 91445-35-1; **11**, 91445-36-2; **12**, 91547-55-6; **13**, 91547-56-7; **14**, 91445-37-3; **15**, 91445-38-4.

Reactions of α-Oxo Ketene Dithioacetals with Dimethylsulfonium Methylide: A New Versatile Synthesis of Furans and Butenolides

Renji Okazaki,* Yoshio Negishi, and Naoki Inamoto

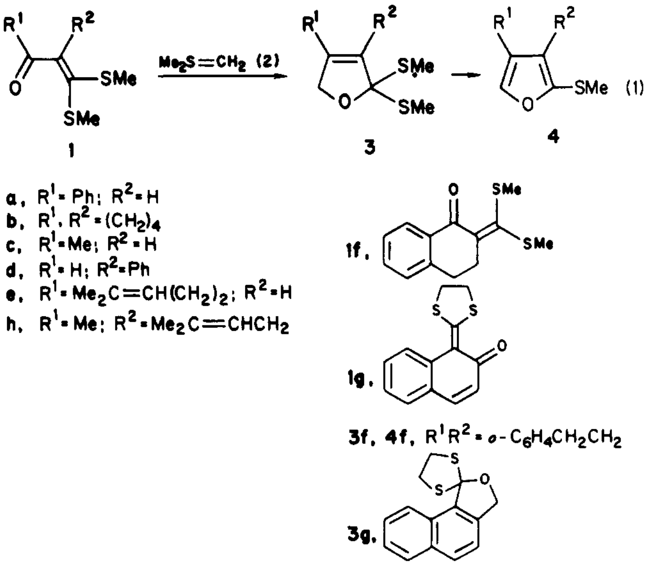
Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Tokyo 113, Japan

Received April 13, 1984

The reaction of 1-mono- and 1,2-disubstituted 3,3-bis(methylthio)-2-propen-1-ones **1** with dimethylsulfonium methylide (**2**) affords 2,2-bis(methylthio)-2,5-dihydrofurans **3** via epoxide **8** which can be isolated in a special case. A couple of methods including acid treatment effected the conversion of **3** to 2-(methylthio)furans **4**, which are found to be useful synthons of a variety of furans and butenolides. Two naturally occurring furans, perillene and rosefuran, were synthesized by this method.

Since many furans and butenolides exist in nature and some of them exhibit interesting biological activities, a number of synthetic methods have been developed.[1] There is a continuing need, however, for simple, versatile synthetic methods for this important class of compounds.

During our study of conjugated ketene dithioacetals,[2] we have found that the reaction of α-oxo ketene dithioacetals **1**, readily available from ketones (or aldehydes) and carbon disulfide,[3] react with dimethylsulfonium methylide (**2**) to give **3**, which is then converted into 2-(methylthio)furans **4** (eq 1). Since one of the α-positions of **4** is masked by a methylthio group which can be substituted by Grignard reagents, removed by Raney nickel, or hydrolyzed into a carbonyl group, **4** was found to be a very



---

[1] Sargent, M. V.; Cresp, T. M. "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds; Pergamon Press: New York, 1978; Vol. 4, p 693, "Terpenoids and Steroids": The Chemical Society: London; Vols. 1 to current.

[2] O-oka, M.; Kitamura, A.; Okazaki, R.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 301. Okazaki, R.; Ishii, F.; Inamoto, N. *Ibid.* **1978**, *51*, 309. Okazaki, R.; Sunagawa, K.; Kang, K.-T.; Inamoto, N. *Ibid.* **1979**, *52*, 496. Okazaki, R.; Sunagawa, K.: Kotera, M.; Kang, K.-T.; Inamoto, N. *Ibid.* **1982**, *55*, 243.

[3] (a) Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1959**, 1398. (b) Thuillier, A.; Vialle, J. *Ibid.* **1962**, 2182, 2187, 2194. Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779. (c) Saquet, M.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1966**, 1582. (d) Gompper, R.; Schmidt, R. R.; Kutter, E. *Liebigs Ann. Chem.* **1965**, *684*, 37. (e) Thuillier, A.; Vialle, J. *Bull Soc. Chim. Fr.* **1962**, 2194. (f) Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, 3817. (g) Shahak, I.; Sasson, Y. *Ibid.* **1973**, 4207. (h) Dieter, R. K. *J. Org. Chem.* **1981**, *46*, 5031.

Table I. Syntheses of Dihydrofurans 3 and Furans 4 from 1,2-Disubstituted 3,3-Bis(methylthio)-2-propen-1-ones 1 and Dimethylsulfonium Methylide (2)[a]

	product yield,[b] %		
substrate	3 (from 1)	4 (from 3)	method[c] (3 → 4)
1a	92	91	A
1b	97	72	B
1c	*d*	35[e]	B
1d	*d*	51[e]	B
1e	83	61	A
1f	92	89	C
1g	71		
1h		81[f]	

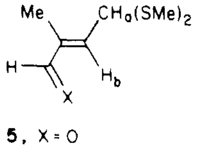
[a] The reactions of 1 with 2 were carried out in THF at −70 °C (10 min) and then at room temperature (1 h). [b] Isolated yield of pure materials. [c] Reaction conditions for 3 → 4. A: catalytic H_3O^+, room temperature, 1 h; B: Florisil column chromatography; C: $MeI-H_2O$, 56 °C, 6 h. [d] Not determined. [e] Yield from 1. [f] The compound (4h) was obtained via epoxide 7 (see text).

useful synthon of a variety of furans and butenolides.[4]

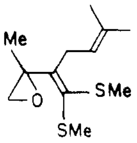
Results and Discussion

Synthesis of 2,2-Bis(methylthio)-2,5-dihydrofurans 3 and 2-(Methylthio)furans 4. The reaction of α-oxo ketene dithioacetal **1a** (1.0 equiv) with dimethylsulfonium methylide (**2**) (1.2 equiv) in tetrahydrofuran (THF) at room temperature afforded dihydrofuran **3a** in 92% yield. THF is the solvent of choice in this reaction since use of 1,2-dimethoxyethane (DME) resulted in a complex mixture containing 2-(methylthio)-4-phenylfuran (**4a**) (21%)[5] and use of ether gave 33% of **3a** along with recovered **1** (33%) probably because of low solubility of **1** in this solvent. Use of excess **2** must be avoided since it leads to a considerable decrease in the yield.

The reactions with some other α-oxo ketene dithioacetals (**1b–g**) under similar conditions to those described above also gave the corresponding **3**, and the results are listed in Table I along with those for conversion of **3** into (methylthio)furans **4**. Although compounds **3** were obtained in good to excellent yields, they could not be purified because of high liability to lose methanethiol, giving furans **4**. Indeed **3** was converted into **4** quite readily by several methods, e.g., (i) catalytic aqueous HCl, (ii) chromatography on Florisil column, and (iii) methyl iodide in aqueous acetone. In Table I are listed the highest yields obtained by the three methods. In the cases of **3c** and **3d** the crude products were directly purified by Florisil column chromatography to give **4c** and **4d**. The structures of **3** and **4** were established by spectral and analytical data, and the mass spectra of **3** are very similar to those of **4** probably because of facile conversion of **3** into **4** by electron impact. In the reaction with **1c**, aldehyde **5** was also obtained, and the ratio of **4c** to **5** was dependent on the reaction conditions. Thus the yields of **4c** and **5** were (i) 19% and 12% at room temperature in the absense of triethylamine, (ii) 29% and 25% at room temperature in the presence of triethylamine (7 equiv), and (iii) 35% and trace at −20 °C in the presence of triethylamine (2 equiv). The configuration of **5** was determined to be *E* by NOE for ^1H NMR spectrum of the corresponding 2,4-dinitrophenylhydrazone **6**; irradiation of C-Me protons increased the intensity of H_a by 25%, whereas no essential change was observed for that of H_b.

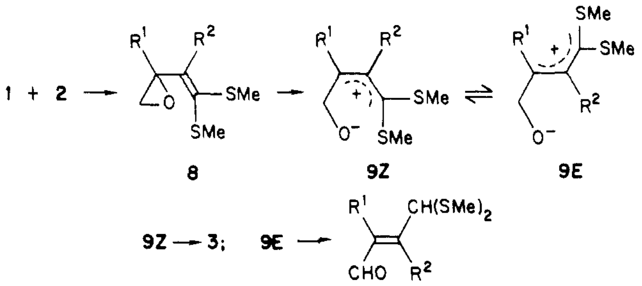


5, X = O
6, X = $NNHC_6H_3(NO_2)_2$



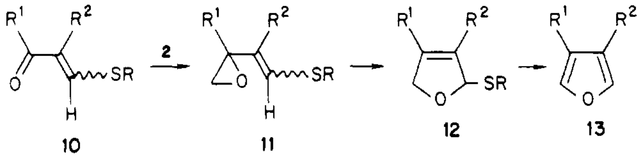
7

Scheme I



In contrast to **1a–g** the reaction of ketene dithioacetal **1h** with the ylide **2** gave epoxide **7** in 81% yield. Treatment of **7** with boron trifluoride etherate in ether or hydrogen chloride in aqueous methanol afforded **4h** almost quantitatively.

Isolation of the aldehyde **5** and the epoxide **7** provides important information for understanding of the mechanism for the formation of **3** from **1**. The reaction most probably proceeds as described in Scheme I. The initial product is thought to be epoxide **8** but in most cases these are converted into dihydrofurans **3** via zwitterionic intermediate **9Z** as they are formed since **9Z** is a tertiary, allylic carbonium ion highly stabilized by two methylthio groups. In the case of **1h** the presence of a relatively large 3-methyl-2-butenyl (prenyl) group diminishes the planarity and hence the electron-donating ability of the ketene dithioacetal group, thus making the isolation of **7** possible. In this connection it is interesting to compare the present reaction with that of vinyl sulfide **10** and **2** reported by Garst and Spencer.[6] The present reaction seems to proceed faster than the reaction of **10** since in the reaction with **10** even the use of 5 M excess of **2** has been reported to result in the recovery of unreacted **10** (20–30%), whereas the use of 1.2 molar equiv of **2** was enough to complete the present reaction. The elimination of **3** to **4** is also much easier than that of **12** → **13** as expected from higher carbonium ion stabilizing effect by the two alkylthio groups. Thus the conversion of **3** into **4** can be carried out under much milder conditions (i.e., weakly acidic conditions) than that of **12** into **13** which requires treatment with mercuric salts.



Since **3** would be formed from **9Z**, the yield of **3** seems to depend on the relative stability of **9Z** and **9E**. When R^1R^2 is cyclic (e.g., **1b**, **1f**, **1g**) only **9Z** is possible and therefore the high yield of **3** results. When R^1 is larger than CH_2O^- group and R^2 is smaller than $C(SMe)_2$ group (e.g., **1a**, **1e**), **9Z** becomes more favorable than **9E** to give a good yield of **3**. When the size of R^1 and CH_2O^- or that of R^2

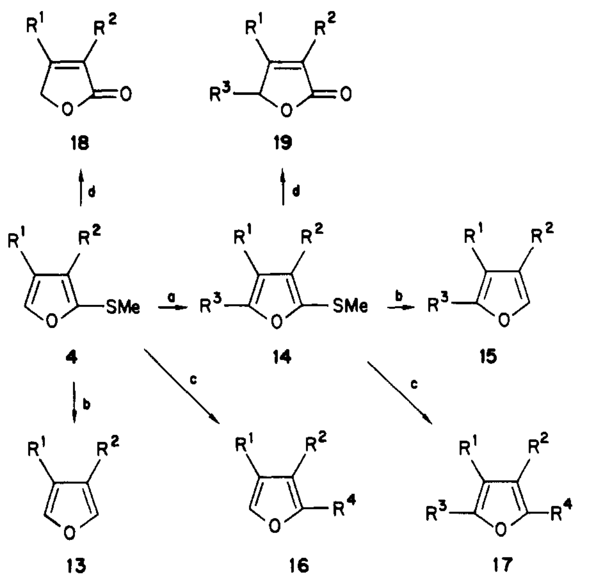
---

[4] Part of this work was published in a preliminary form: Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1055.

[5] The complexity of the reaction products is partly due to the relatively high boiling point of DME compared with that of THF which necessitates a longer time and somewhat higher temperatures in evaporation of the solvent.

[6] Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250.

Scheme II[a]



[a] (a) (1) BuLi, (2) R^3X; (b) Raney Ni; (c) $R^4MgX-NiCl_2(PhCH_2CH_2CH_2PPh_2)$; (c) $R^4MgX-NiCl_2-(Ph_2PCH_2CH_2CH_2PPh_2)$. (d) H_3O^+-MeOH. Series **a**: R^1 = Ph, R^2 = H, R^3 = R^4 = Me. Series **b**: R^1R^2 = $(CH_2)_4$, R^3 = R^4 = Me. **4** → **14**: **a**, 93%; **b**, 84%. **14** → **15**: **a**, 54%. **4** → **13**: **a**, 42%; **b**, 71%. **4** → **16**: **a**, 61%. **14** → **17**: **b**, 63%. For **4** → **18** and **14** → **19**, see Table II.

and $C(SMe)_2$ is similar, reactions resulting from **9E** such as the formation of the aldehyde **5** also take place, thus lowering the yield of **3**.[7]

Synthesis of Variously Substituted Furans and Butenolides from 2-(Methylthio)furans 4. With 3- (or 4-) substituted and 3,4-disubstituted 2-(methylthio)furans in hand, the introduction of an alkyl group into 2- and/or 5-positions of the furan ring was next attempted. In view of the known transformations, i.e., (i) Raney nickel desulfurization of the SMe group, (ii) facile lithiation of α-position of the furan ring,[8] and (iii) coupling reactions of the Grignard reagents with the SMe group on the furan ring,[9] 2-(methylthio)furans **4** are considered to be very useful for the synthesis of variously substituted furans as illustrated in Scheme II. Furans **14a** (R^1 = Ph, R^2 = H, R^3 = Me) and **14b** [R^1R^2 = $(CH_2)_4$, R^3 = Me] were synthesized from **4a** and **4b** by lithiation–alkylation sequence (with methyl iodide) in 93% and 84% yields, respectively. The (methylthio)furans **14a**, **4a**, and **4b** were converted into 2,3-disubstituted **15a** (54%), 3-substituted **13a** (42%), and 3,4-disubstituted **13b** (71%), respectively, by Raney nickel desulfurization. The methylthio group in **4** and **14** can be replaced by appropriate substituents when nickel-catalyzed Grignard coupling reactions are used. For example, **16a** (R^1 = Ph, R^2 = H, R^4 = Me) and **17b** (R^1R^2 = $(CH_2)_4$, R^3 = R^4 = Me) were obtained in 61% and 63% yields from **4a** and **14b**, respectively. In these conversions it should be noted that both of isomeric 2-methyl-3-phenylfuran (**15a**) and 2-methyl-4-phenylfuran (**16a**) can be prepared from **4a**.

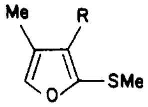
Table II. Syntheses of Butenolides 18 and 19 by Acid Hydrolysis of 4 and 14[a]

	(methylthio)furan			reaction	
	R^1	R^2	R^3 or R^4	time, h	yield, %
4a	Ph	H		1.5	52
4b	$(CH_2)_4$			15[b]	62
4c	Me	H		1.6	64
4d	H	Ph		8	97
4e	$Me_2C{=}CH(CH_2)_2$	H		1	70
14a	Ph	H	Me	5	15
14b	$(CH_2)_4$		Me	1	72

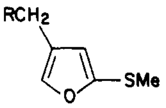
[a] Hydrolysis was carried out with excess dilute H_2SO_4 in refluxing methanol except for **4b**. [b] The reaction was done with a catalytic amount of dilute HCl at room temperature.

A variety of substituted butenolides can also be prepared from the (methylthio)furans **4** and **14**. Thus, acid hydrolysis of **4a–e** and **14a,b** afforded **18a–e** and **19a,b**, respectively, mostly in good yields. The results are shown in Table II. Although the butenolides are known to be alkylated at the 4-position by lithiation with lithium diisopropylamide (LDA) followed by quenching with alkyl halides, the selectivity is poor to give side products such as 2-alkylated and 2,2- and 2,4-dialkylated butenolides.[10] In contrast, the present method provides a selective synthetic route to 4-alkylated butenolides since the regioselective alkylation of the (methylthio)furans **4** is possible. Recently, a similar route to butenolides has been reported as a key step in the total synthesis of triptonide and triptolide.[11]

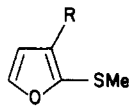
Some comments on the scope and limitation of the present method are in order. Since α-oxo ketene dithioacetals **1** are readily synthesized from the reaction of ketones (or aldehydes) with a base and carbon disulfides,[3] R^1 and R^2 can be introduced by choosing appropriate starting carbonyl compounds. Since priority sequence, $ArCH_2{\sim}C{=}C{\cdot}CH_2 > RCH_2 > CH_3$, is known[3a] for the position of introduction of a bis(methylthio)methylidene group for asymmetrical ketones, methyl ketones RCH_2COCH_3 (R = alkyl) will give only (methylthio)furan **20**. When one desires furans of type **21** and hence α-oxo ketene dithioacetals $RCH_2COCH{=}C(SMe)_2$, the following route (eq 2) from **1c** is employable as exemplified for the synthesis of **1e** which is later used in perillene synthesis.[12] Although one can obtain furans of type **22** from an aldehyde RCH_2CHO, the yield of α-oxo ketene dithioacetals **23** is reported to be usually low except when R is aryl because of competitive aldol reactions.[3c] However, this drawback can be overcome because most of substituted furans derived from **22** can also be derived from **4** (R^1 =



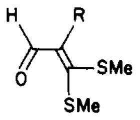
20



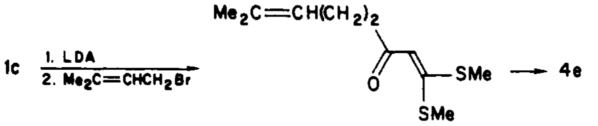
21



22



23



(2)

---

(7) Although in the case of **1h** the size of $C(SMe)_2$ group is larger than a prenyl group and hence **9E** seems more favorable than **9Z**, **4h** is obtained in a good yield from the epoxide **7**. This suggests that the isolation of the epoxide is important to obtain a good yield of **4** probably because the intermediate **9** reacts with **2** in the reaction mixture to give unidentified byproducts, consistent with the fact that excess use of **2** diminishes the yield of **3** from **1**.

(8) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216. Ziegler, K.; Hammond, G. S. *J. Am. Chem. Soc.* **1968**, *90*, 513.

(9) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447.

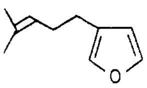
(10) Gedge, D. R.; Pattenden, G. *Tetrahedron Lett.* **1977**, 4443.

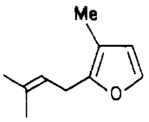
(11) Garver, L. C.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 867.

(12) An attempt to obtain **1h** by quenching the kinetic enolate of $Me_2C{=}CH(CH_2)_2C({=}O)Me$ with carbon disulfide at −78 °C resulted in no reaction. The reaction at room temperature gave **1h** derived from the thermodynamic enolate.

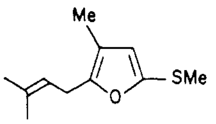
R, R^2 = H) which is obtainable from **1c** as shown above for **1c** → **4e** (eq 2).

Synthesis of Perillene and Rosefuran. The abovementioned methodology of furan synthesis starting from α-oxo ketene dithioacetals was applied to the synthesis of the naturally occurring isomeric furans, perillene (**24**) and rosefuran (**25**).[13,14] (Methylthio)furan **4e** was desulfurized by Raney nickel to give perillene in 80% yield. Rosefuran was synthesized in 68% yield by desulfurization of (methylthio)furan **26** which was obtained from **4c** by lithiation–prenylation in 55% yield. It is worth noting in these syntheses that the isomeric furans **24** and **25** were both synthesized from a single starting material (**1c**) and that this represents the first synthesis of rosefuran starting from a nonfuranoid compound.


24



25



26

Experimental Section

All reactions were carried out under an argon atmosphere. Melting points and boiling points are uncorrected. IR spectra were obtained by using a Hitachi infrared spectrophotometer Model 260-30. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained by using a Hitachi R-20B and a JOEL EX-90Q spectrometer with tetramethylsilane as an internal standard, respectively, and the solvent was carbon tetrachloride for the former and deuteriochloroform for the latter unless otherwise stated. Mass spectral analyses were obtained on a Hitachi RMU-6 spectrometer. High-resolution mass spectra were measured with a JOEL JMS-D300 spectrometer. The ether and tetrahydrofuran used were distilled from benzophenone ketyl.

All chemicals used were commercial samples unless reference is given to their purification or preparation.

Syntheses of α-Oxo Ketene Dithioacetals 1. The compounds **1a**,[3a] **1b**,[3b] **1c**,[3b] **1d**,[3c] **1f**,[3b] and **1g**[3d] were synthesized by the reported method.

1h was prepared by a similar method[3a,b] and purified by chromatography (neutral alumina, hexane–ether, 5:1): a pale yellow oil, 85%; IR (neat) 1690 cm^{-1}; NMR δ 1.62 (3 H, br s), 1.69 (3 H, br s), 2.22 (3 H, s), 2.24 (3 H, s), 2.29 (3 H, s), 3.21 (2 H, br d, J = 7.5 Hz), 4.96 (1 H, m); MS, m/e (relative intensity) 215 (8), 183 (12), 43 (100). Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.35, H, 7.87; S, 27.83. Found: C, 57.07; H, 7.69; S, 27.55. **1e** was synthesized from **1c**. To a THF (5 mL) solution of lithium diisopropylamide (LDA) (3.1 mmol) was added 4,4-bis(methylthio)-3-buten-2-one (**1c**, 0.483 g, 3.0 mmol) in THF (10 mL) at −78 °C. After stirring for 15 min, 1-bromo-3-methyl-2-butene (prenyl bromide, 0.38 mL, 3.2 mmol) was added, and the temperature of the reaction mixture was raised to room temperature, where stirring was continued for 1 h. After usual workup and chromatography (neutral alumina, hexane–ether, 1:1), **1e** was obtained in 70% yield (0.477 g) as a pale yellow oil along with recovered **1c** (0.094 g, 20%): IR (neat) 1640 cm^{-1}; NMR δ 1.59 (3 H, br s), 1.63 (3 H, br s), 2.1–2.4 (4 H, m), 2.35 (3 H, s), 2.37 (3 H, s), 5.03 (1 H, m), 5.89 (1 H, s); MS, m/e 215 (100), 147 (99), 75 (84), 69 (72). Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.35; H, 7.87; S, 27.83. Found: C, 57.05; H, 7.67; S, 27.38.

General Procedure for the Synthesis of Bis(methylthio)dihydrofurans 3 from 1. To trimethylsulfonium tetrafluoroborate (2.4 mmol, 400 mg)[15] in THF (13 mL) was added butyllithium in hexane (2.4 mmol) at −10 °C, and the mixture was stirred for 15 min at this temperature to produce **2**. To the solution cooled to −70 °C was added a THF solution (7 mL) of **1** (2.0 mmol) and stirred for 10 min at this temperature and then for 1 h at room temperature. The reaction was quenched with water (0.5 mL) and the THF was evaporated below 30 °C. After addition of brine (40 mL) and extraction with ether or dichloromethane, the organic layer was dried ($MgSO_4$) and concentrated. The dihydrofurans thus obtained were stored in a refrigerator below −10 °C. It was difficult to obtain analytically pure specimen of **3** (except **3g**, vide infra) since purification by bulb-to-bulb distillation or by chromatography (even with Florisil) always resulted in partial or complete conversion to (methylthio)furans **4**.

General Procedure for the Conversion of 3 to (Methylthio)furans 4. Method A. To a methanol solution (5 mL) of **3** (1 mmol) was added 0.2 mL of 2 M hydrochloric acid and the solution was stirred for 1 h at room temperature. The solution was neutralized with aqueous sodium carbonate and extracted with ether. The combined ethereal solution was washed with brine, dried ($MgSO_4$), and concentrated.

Method A′. To a methanol solution (5 mL) of **3** was added 10% of acetic acid (0.2 mL), and the solution was stirred for 3 h at 30 °C and subjected to a similar workup to method A.

Method B. Chromatography of **3** using Florisil with pentane or pentane–ether (5:1) as eluent directly afforded **4**.

Method C. To an aqueous solution (0.6 mL) of sodium carbonate (0.32 g, 3 mmol) was added an acetone solution (3 mL) of **3** and then methyl iodide (0.3 mL, 4.8 mmol). The reaction mixture was stirred for 3 h (6 h for **3g**) and then worked up similarly to method A.

The (methylthio)furans **4** thus obtained were stored in a refrigerator under an argon or nitrogen atmosphere.

2,2-Bis(methylthio)-4-phenyl-2,5-dihydrofuran (3a) and 2-(Methylthio)-4-phenylfuran (4a). **3a**: a yellow oil (92%); NMR δ 2.09 (6 H, s), 5.04 (2 H, d, J = 1.8 Hz), 6.06 (1 H, t, J = 1.8 Hz), 7.27 (5 H, s); MS, m/e (relative intensity) 190 (100), 147 (34), 115 (30). **4a** was obtained by method A or C in a quantitative yield (by NMR) and purified by Florisil chromatography: colorless crystals (91%), mp 32–34 °C, bp 60 °C (0.02 mmHg); NMR δ 2.37 (3 H, s), 6.59 (1 H, d, J = 0.9 Hz), 7.1–7.4 (5 H, m), 7.63 (1 H, d, J = 0.9 Hz); MS, m/e (relative intensity) 190 (100), 147 (49), 115 (42). Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85. Found: C, 69.56; H, 5.42; S, 16.71.

1,1-Bis(methylthio)-1,3,4,5,6,7-hexahydroisobenzofuran (3b) and 1-(Methylthio)-4,5,6,7-tetrahydroisobenzofuran (4b). **3b**: a yellow oil (97%); NMR δ 1.5–1.9 (4 H, m), 1.99 (6 H, s), 1.9–2.5 (4 H, m) 4.99 (2 H, br s); MS, m/e (relative intensity) 168 (100), 125 (79), 91 (57). **4b** was obtained by method A′ or C quantitatively (by NMR) and purified by Florisil chromatography: a colorless oil (63%). **3b** was also converted to **4b** by method B (72%): bp 50 °C (0.3 mmHg); NMR δ 1.5–1.8 (4 H, m), 2.23 (3 H, s), 2.3–2.7 (4 H, m), 7.10 (1 H, br s); MS, m/e (relative intensity) 168 (100), 125 (69), 91 (62). Anal. Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 63.75; H, 7.35.

2,2-Bis(methylthio)-4-methyl-2,5-dihydrofuran (3c) and 4-Methyl-2-(methylthio)furan (4c). The reaction of **1c** with **2** under the conditions described in the general procedure for the synthesis of **3** gave a mixture of **3c** [NMR δ 1.85 (3 H, m), 2.03 (6 H, s), 4.54 (2 H, m), 5.40 (1 H, m)] and 4,4-bis(methylthio)-2-methyl-2-butenal (**5**). When the crude reaction mixture was chromatographed on Florisil, **4c** (19%) (eluted with pentane) and **5** (eluted with ether) were obtained. Further purification of **5** by silica gel chromatography gave a pure yellow oil (12%): IR (neat) 2725, 1690 cm^{-1}; NMR δ 1.77 (3 H, d, J = 1.2 Hz), 2.13 (6 H, s), 4.56 (1 H, d, J = 10.5 Hz), 6.24 (1 H, dq, J = 10.5 Hz, 1.2 Hz), 9.43 (1 H, s); MS, m/e 176 (17), 129 (100), 61 (85). 2,4-Dinitrophenylhydrazone (relative intensity) (**6**): red orange crystals, mp 162–163 °C (ether); IR (KBr) 3280, 1615, 1510, 1330 cm^{-1}; NMR ($CDCl_3$) δ 2.06 (3 H, d, J = 1.2 Hz), 2.19 (6 H, s), 4.70

---

[13] Reported syntheses of perillene. From furan derivatives: Thomas, A. F.; Ozainne, M. *J. Chem. Soc. C* **1970**, 220. Tanis, S. P. *Tetrahedron Lett.* **1982**, *23*, 3115. From nonfuranoid compounds: ref, 6; Kondo, K.; Matsumoto, M. *Chem. Lett.* **1974**, 701; Tetrahedron *Lett.* **1976**, 391. Harirchian, B.; Magnus, P. D. *Synth. Commun.* 1977, *7*, 119. Takahashi, S. *Ibid.* **1976**, *6*, 331.

[14] Reported syntheses of rosefuran (all from furan derivatives). Buchi, G.; Kovats, E. Sz.; Enggist, P.; Uhde, G. *J. Org. Chem.* **1968**, *33*, 1227. Vig, O. P.; Vig, A. K.; Handa, V. K.; Sharma, S. D. *J. Indian Chem. Soc.* **1974**, *51*, 900 (*Chem. Abstr.* **1975**, *82*, 156499y). Birch, A. J.; Slobbe, J. *Tetrahedron Lett.* **1976**, 2079. Takeda, A.; Shinhama, K.; Tsuboi, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1903. Ly, N. D.; Schlosser, M. *Helv. Chim. Acta* 1977, *60*, 2085.

[15] Hashimoto, T.; Kitano, H.; Fukui, K. *Nippon Kagaku Zasshi* **1968**, *89*, 810.

(1 H, d, J = 10.8 Hz), 5.93 (1 H, dq, J = 10.8 Hz, 1.2 Hz), 7.83 (1 H, s), 7.99 (1 H, d, J = 10.2 Hz), 8.34 (1 H, dd, J = 10.2 Hz, 2.4 Hz), 9.14 (1 H, d, J = 2.4 Hz), 11.26 (1 H, br s); MS, m/e (relative intensity) 356 (1.5), 309 (81), 127 (100). Anal. Calcd for $C_{13}H_{16}N_4O_4S_2$: C, 43.81; H, 4.52; N, 15.72; S, 17.79. Found: C, 43.75; H, 4.44; N, 15.87; S, 17.63.

The yields of **3c** and **5** were dependent on the reaction temperature and the quantity of triethylamine added. The reactions were carried out in a similar manner to that of the general procedure except that the ylide **2** was added to a mixture of **1** and triethylamine and the results were as follows (the reaction temperature, the molar equivalent of triethylamine, the yields of **3c** and **5**): (a) room temperature, 7 equiv, 29%, 25%; (b) −10 °C, none, 28%, 15%; (c) −20 °C, 2 equiv, 35%, trace.

4c: colorless oil; NMR δ 1.97 (3 H, d, J = 1.2 Hz), 2.32 (3 H, s), 6.18 (1 H, s), 7.16 (1 H, q, J = 1.2 Hz); MS, m/e (relative intensity) 128 (46), 85 (100); exact mass calcd for C_6H_8OS 128.1886, found 128.1858. **4c** was oxidized by m-chloroperbenzoic acid at −78 °C in dichloromethane to give the corresponding sulfoxide (79%); a colorless oil, bp 50 °C (0.25 mmHg); NMR ($CDCl_3$) δ 2.06 (3 H, d, J = 0.9 Hz), 2.90 (3 H, s), 6.80 (1 H, s), 7.42 (1 H, m). Anal. Calcd for $C_6H_8O_2S$: C, 49.98; H, 5.59. Found: C, 49.59; H, 5.59.

2,2-Bis(methylthio)-3-phenyl-2,5-dihydrofuran (3d) and 2-(Methylthio)-3-phenylfuran (4d). The reaction of **1d** with **2** gave a complex mixture containing **3d** as judged by ^{1}H NMR. The mixture was chromatographed on Florisil (elution with pentane) to give **4d**: a colorless oil (22%); NMR δ 2.31 (3 H, s), 6.54 (1 H, d, J = 2.2 Hz), 7.1–7.7 (6 H, m); MS, m/e (relative intensity) 190 (20), 147 (100). Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85. Found: C, 68.89; H, 4.95; S, 16.64.

When the reaction was conducted in the presence of a 7-equiv excess of triethylamine, the yield of **4d**, after purification by Florisil chromatography, was 51%.

2,2-Bis(methylthio)-4-(4-methyl-3-pentenyl)-2,5-dihydrofuran (3e) and 2-(Methylthio)-4-(4-methyl-3-pentenyl)furan (4e). **3e**: a pale yellow oil (83%); NMR δ 1.60 (3 H, br s), 1.66 (3 H, br s), 2.02 (6 H, s), 2.1–2.4 (4 H, m), 4.53 (2 H, br d, J = 2.2 Hz), 5.04 (1 H, tm, J = 7.2 Hz), 5.36 (1 H, br t, J = 2.2 Hz).

4e was obtained quantitatively (by NMR) from **3e** by method A and purified by Florisil chromatography: a colorless oil (61%); NMR δ 1.59 (3 H, br s), 1.68 (3 H, br s), 2.33 (3 H, s), 1.95–2.60 (4 H, m), 5.08 (1 H, m), 6.21 (1 H, m), 7.16 (1 H, m); MS, m/e (relative intensity) 196 (5), 149 (100), 99 (44); exact mass calcd for $C_{11}H_{16}OS$ 196.3060, found 196.3068.

Method B also gave **4e** (43%).

3,3-Bis(methylthio)-1,3,4,5-tetrahydronaphtho[1,2-*c*]furan (3f) and 3-(Methylthio)-4,5-dihydronaphtho[1,2-*c*]furan (4f). **3f**: a yellow oil (92%); NMR δ 2.02 (6 H, s), 2.70–3.15 (4 H, m), 4.90 (2 H, t, J = 2.7 Hz), 6.9–7.2 (4 H, m); MS, m/e (relative intensity) 216 (37), 201 (20), 173 (53), 141 (42), 45 (100).

4f was obtained by method B in 91% yield: a pale yellow oil; NMR δ 2.31 (3 H, s), 2.6–3.0 (4 H, m), 6.90–7.45 (4 H, m), 7.65 (1 H, s); MS, m/e (relative intensity) 216 (100), 201 (47), 173 (52), 115 (27); exact mass calcd for $C_{13}H_{12}OS$ 216.2972, found 216.2985.

1,1-(Ethylenedithio)-1,3-dihydronaphtho[1,2-*c*]furan (3g). The reaction mixture obtained from **1g** and **2** was chromatographed on neutral alumina (elution with ether) to give **3g** in 71% yield: pale yellow crystals; mp 156–159 °C; IR (KBr) 1620, 1245, 985, 825, 810, 755 cm^{-1}; NMR ($CDCl_3$) δ 3.15–3.80 (4 H, m), 4.83 (2 H, s), 7.03 (1 H, d, J = 9.0 Hz), 7.05–7.90 (4 H, m), 8.36 (1 H, m); MS, m/e (relative intensity) 260 (47), 200 (100), 171 (58). Anal. Calcd for $C_{14}H_{12}OS_2$: C, 64.58; H, 4.65; S, 24.63. Found: C, 64.84; H, 4.77, S, 24.15.

An attempt to convert **3g** to **4g** by method C resulted in the quantitative recovery of **3g**.

2-(1,2-Epoxy-1-methylethyl)-5-methyl-1,1-bis(methylthio)-1,4-hexadiene (7) and 4-Methyl-3-(3-methyl-2-butenyl)-2-(methylthio)furan (4h). The reaction of **1h** with **2** under conditions described for the general synthesis of **3** afforded **7** (81%): a pale yellow liquid; NMR δ 1.36 (3 H, s), 1.70 (6 H, br s), 2.20 (3 H, s), 2.22 (3 H, s), 2.60 (1 H, d, J = 6.0 Hz), 2.71 (1 H, d, J = 6.0 Hz), 3.0–3.3 (2 H, m), 5.06 (1 H, m); MS, m/e (relative intensity) 244 (0.8), 229 (2), 196 (74), 181 (29).

The epoxide **7** was converted to **4h** by the following three methods: (a) method A (96%), (b) adsorption on silica gel for 30 min followed by elution with ether (92%), (c) treatment of the ether solution with a trace amount of boron trifluoride etherate for 2 h at room temperature (quantitative). **4h**: a pale yellow oil; NMR δ 1.73 (6 H, br s), 1.90 (3 H, m), 2.25 (3 H, s), 3.12 (2 H, br d, J = 7.2 Hz), 5.05 (1 H, m), 7.11 (1 H, br s); MS, m/e (relative intensity) 196 (100), 181 (38), 105 (35), 69 (35); exact mass calcd for $C_{11}H_{16}OS$ 196.3060, found 196.3030.

2-Methyl-5-(methylthio)-3-phenylfuran (14a). To a THF solution (20 mL) of **4a** (483 mg, 2.54 mmol) was added butyllithium in hexane (3.07 mmol) at −10 °C. After stirring for 30 min at this temperature, methyl iodide (0.24 mL, 3.8 mmol) was added. The solution was kept at −10 °C for 10 min and then at room temperature for 1 h. Usual workup and chromatography on Florisil (elution with hexane–ether, 5:1) gave **14a** (483 mg, 2.36 mmol, 93%): a colorless oil, bp 70 °C (0.7 mmHg); NMR δ 2.36 (3 H, s), 2.40 (3 H, s), 6.45 (1 H, s), 7.24 (5 H, br s); MS, m/e (relative intensity) 204 (100), 189 (30), 161 (38), 128 (33). Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92; S, 15.69. Found: C, 70.30; H, 6.13; S, 15.36.

1-Methyl-3-(methylthio)-4,5,6,7-tetrahydroisobenzofuran (14b). Similar treatment of **4b** (530 mg, 3.07 mmol) with butyllithium (3.8 mmol) followed by quenching with methyl iodide (0.29 mL, 4.6 mmol) gave **14b** (468 mg, 2.57 mmol, 84%): a colorless oil, bp 50 °C (0.5 mmHg); NMR δ 1.5–1.9 (4 H, m), 2.12 (3 H, s), 2.19 (3 H, s), 2.2–2.6 (4 H, m); MS, m/e (relative intensity) 182 (61), 167 (76), 43 (100). Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74; S, 17.59. Found: C, 66.03; H, 7.86; S, 17.11.

3-Phenylfuran (13a). To an acetone solution (6 mL) of the (methylthio)furan **4a** (190 mg, 1 mmol) was added Raney Ni W-7[16] in ethanol (12 mL) (prepared from 1 g of Raney Ni alloy), and the solution was stirred for 30 min at room temperature. After filtration and washing (ethanol) of the Raney Ni, the filtrate was concentrated in vacuo. To the residue was added brine (20 mL), and the solution was extracted with ether. The combined ethereal solution was dried ($MgSO_4$), concentrated, and subjected to chromatography on Florisil (elution with pentane) to give **13a** (42%): colorless crystals, mp 51–57 °C (lit.[17] mp 50–54 °C); NMR δ 6.61 (1 H, m), 7.1–7.5 (6 H, m), 7.65 (1 H, m); MS, m/e (relative intensity) 144 (91), 115 (100).

4,5,6,7-Tetrahydroisobenzofuran (13b). Treatment of **4b** with Raney Ni as described above for **4a** gave **13b** (71%): a colorless oil; NMR δ 1.55–1.90 (4 H, m), 2.35–2.65 (4 H, m), 6.99 (2 H, s). The reaction of **13b** with maleic anhydride at 90 °C for 5 min afforded a Diels–Alder adduct in 79% yield: pale yellow crystals, mp 147–150 °C (benzene–hexane); IR (KBr) 1860, 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.4–1.8 (4 H, m), 1.95–2.30 (4 H, m), 3.15 (2 H, s), 5.17 (2 H, s); MS, m/e (relative intensity) 220 (1.2), 122 (100), 94 (50). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.55; H, 5.75.

2-Methyl-3-phenylfuran (15a). Similarly to **4a**, **14a** was desulfurized to give **15a** (54%) as a colorless oil. The ^{1}H NMR spectrum was in complete agreement with that reported.[18]

2-Methyl-4-phenylfuran (16a). To **4a** (196 mg, 1.03 mmol) and $NiCl_2(Ph_2PCH_2CH_2CH_2PPh_2)$[19] (31.5 mg, 0.058 mmol) in ether (10 mL) was added methylmagnesium iodide (2.2 mmol) in ether, and the solution was refluxed for 8 h. Usual workup and chromatography (Florisil, pentane) gave **16a** (100 mg, 0.63 mmol, 61%): colorless crystals, mp 64–68 °C (lit.[17] mp 63–67 °C). The NMR spectrum was identical with that reported.[17]

1,3-Dimethyl-4,5,6,7-tetrahydroisobenzofuran (17b). **17b** was obtained from **14b** (63%) in a similar manner to that described above for **4a**: a colorless oil; NMR δ 1.50–1.75 (4 H, m), 2.05 (6 H, s), 2.2–2.5 (4 H, m).[20]

Hydrolysis of (Methylthio)furans 4 to Butenolides 18 and 19. General Procedure. To a methanol solution (5 mL) of **4** (0.5–1.0 mmol) was added aqueous H_2SO_4 (6 M, 0.5–1.0 mL), and the solution was refluxed for indicated time in Table II. Brine (30 mL) containing sodium carbonate (0.6 g) was added, and the

---

[16] Adkins, H.; Billica, H. R. *J. Am. Chem. Soc.* **1948**, *70*, 695.

[17] Miller, D. *J. Chem. Soc. C* **1969**, 12.

[18] Sharf, H.-D.; Wolters, E. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 682; *Chem. Ber.* **1978**, *111*, 639.

[19] Van Hecke, G. R.; Horrocks, W. D., Jr. *Inorg. Chem.* **1966**, *5*, 1968.

[20] Treibs, W. *Ber.* **1937**, *70*, 85. Morel, T.; Verkade, P. E. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 35.

solution was extracted with dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on neutral alumina (elution with hexane–ether). In the case of **4b**, the hydrolysis was carried out by using aqueous HCl (2 M, 0.3 mL) instead of aqueous H_2SO_4. The structures of **18a** (mp 95–97 °C),[21] **18c**,[22] **18d** (mp 81–84 °C),[23] **18e**,[24] **19a** (mp 57–58 °C),[25] and **19b**[26] were identified by comparison of their IR and NMR spectra with the reported ones. **18b**: pale yellow crystals, mp 55–56 °C; IR (KBr) 1740 cm^{-1}; NMR δ 1.6–1.9 (4 H, m), 2.0–2.5 (4 H, m), 4.56 (2 H, br s); MS, *m/e* (relative intensity) 138 (28), 109 (100), 81 (80). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.29. Found: 69.40; H, 6.99.

Perillene (24). **4e** (116 mg, 0.59 mmol) was desulfurized by Raney Ni in a similar manner to that described for the synthesis of **13a** to give **24** (71 mg, 0.47 mmol, 80%). The NMR and MS spectra were in agreement with those reported.[13]

Rosefuran (25). 3-Methyl-2-(3-methyl-2-butenyl)furan (**26**) (165 mg, 0.84 mmol, 87%) was obtained from **4c** (124 mg, 0.97 mmol) in a similar manner to that described for **14a**; a colorless oil, bp 50 °C (0.2 mmHg); NMR δ 1.70 (6 H, br s), 1.89 (3 H, s), 2.20 (3 H, s), 3.20 (2 H, br d), 5.21 (1 H, m); MS, *m/e* (relative intensity) 196 (62), 181 (63), 128 (59), 41 (100). **26** (107 mg, 0.55 mmol) was desulfurized in a similar manner to that described for the synthesis of **13a** to give **25** (56 mg, 0.37 mmol, 68%). The NMR spectrum was in agreement with the reported one.[14]

Registry No. **1a**, 13636-88-9; **1b**, 17649-90-0; **1c**, 17649-86-4; **1d**, 4254-65-3; **1e**, 84735-54-6; **1f**, 57663-21-5; **1g**, 3275-23-8; **1h**, 91003-02-0; **2**, 6814-64-8; **3a**, 84735-55-7; **3b**, 84735-56-8; **3c**, 84735-58-0; **3d**, 91632-63-2; **3e**, 84735-57-9; **3f**, 91632-64-3; **3g**, 91632-65-4; **4a**, 84735-60-4; **4b**, 91632-66-5; **4c**, 84735-62-6; **4d**, 91632-67-6; **4e**, 84735-64-8; **4f**, 91632-68-7; **4h**, 91632-70-1; (*E*)-**5**, 84735-59-1; **7**, 91632-69-8; **13a**, 13679-41-9; **13b**, 91632-72-3; **14a**, 84735-61-5; **14b**, 91632-71-2; **15a**, 50552-26-6; **16a**, 21433-91-0; **17b**, 91632-73-4; **18a**, 1575-47-9; **18b**, 66309-76-0; **18c**, 6124-79-4; **18d**, 57200-23-4; **18e**, 61315-75-1; **19a**, 74528-46-4; **19b**, 68965-57-1; **24**, 539-52-6; **25**, 15186-51-3; **26**, 84735-63-7; prenyl bromide, 870-63-3.

---

(21) Krauser, S. F.; Watterson, A. C., Jr. *J. Org. Chem.* **1978**, *43*, 3400.

(22) Johnson, A. W.; Gowda, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razavi, Z.; Rosebery, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1734.

(23) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1980**, *58*, 2484.

(24) Poulter, C. D.; Wiggins, P. L.; Plummer, T. L. *J. Org. Chem.* **1981**, *46*, 1532.

(25) Metz, G.; Schwenker, G. *Synthesis* **1980**, 394.

(26) Baker, W. R.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 1022.

Syn–Anti Isomerism in the Opiate Hydrazones and Azines Derived from Naloxone, Naltrexone, and Oxymorphone

Vera M. Kolb* and Duy H. Hua[1]

Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, Illinois 62901, and Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

Received April 6, 1984

Very recently we demonstrated by a ^{13}C NMR study that the long acting opiate drugs naloxone hydrazone, naltrexone hydrazone, and oxymorphone hydrazone exist as mixtures of their anti and syn isomers (*Life Sci., Suppl. 1* **1983**, *33*, 419–422). That finding indicated that the corresponding opiate azines, which are formed from the above hydrazones, and which are much longer acting than these hydrazones, may exist theoretically as three possible isomers—anti–anti, anti–syn, and syn–syn. In this study samples of naloxone azine, naltrexone azine, and oxymorphone azine have been analyzed by ^{13}C NMR and high-resolution ^{1}H NMR. The presence of all three isomers has been observed.

Introduction

Long lasting opiate antagonist naloxazone (I), which is the hydrazone of naloxone, drew considerable attention because of its ability to inhibit selectively the high affinity, or μ_1, binding sites and to block opiate analgesia with little effect on other classes of binding sites or on opiate-induced lethality.[2] Similarly, the hydrazone derivatives of naltrexone (II) and oxymorphone (III) are shown to be long acting opiate antagonist and agonist, respectively, both in vivo and in vitro[3] (Figure 1). The mechanism through which these hydrazones exert their long acting effects remains unknown. A possibility that covalent binding of these hydrazones to the opiate receptor sites occurs was considered.[3] Also, it was suggested that the long lasting action of these hydrazones may be due to the presence of the corresponding azines in the preparations of hydrazones.[2] These azines were found to irreversibly block opiate binding in vitro 20- to 40-fold more potently than the corresponding hydrazones.[2,4]

The mechanism through which the opiate azines exert their ultra long lasting effects has not been elucidated so far. Originally it was suggested that since the azines are dimeric opiates they may simultaneously occupy two binding sites at the receptor.[2] Recently, it was suggested that an irreversible chemical reaction between the receptor and the azine might be going on at the azine functional group.[5] In either mechanism, the knowledge of the exact stereochemistry of the azine opiates is of great importance for a proper mapping of the opiate receptor.

In a recent preliminary communication we have demonstrated by a ^{13}C NMR study that the long acting opiate hydrazones naloxazone (I), naltrexazone (II), and oxymorphazone (III) exist as mixtures of their anti and syn isomers[6] (Scheme I). The less crowded anti isomer was found to be the major product in all cases (Table I). No equilibration of the syn and anti isomers was observed

---

(1) Department of Chemistry, Kansas State University, Manhattan, KS 66506.

(2) Hahn, E. F.; Carroll-Buatti, M.; and Pasternak, G. W. *J. Neurosci.* **1982**, *2*, 572 and the references cited therein.

(3) Pasternak, G. W.; Hahn, E. F. *J. Med. Chem.* **1980**, *23*, 674.

(4) Gintzler, A. R.; Pasternak, G. W. *Neurosci. Lett.* **1983**, *39*, 51.

(5) Pasternak, G. W., private communication.

(6) Kolb, V. M.; Gober, J. R. *Life Sci. Suppl. 1* **1983**, *33*, 419.

0022-3263/84/1949-3824$01.50/0