While 6-A and -B could be separated by preparative HPLC, both A and B equilibrated back to the original mixture (1:1).[13] This behavior seemed difficult to rationalize based on structure 6. The isolation of A and B and equilibration back to the original mixture was somewhat like that observed for syn and anti isomerisms of oximes and nitrosamines. Another explanation would be the possible interconversions via the intermediates shown in Scheme I which are also the presumed intermediates formed in the synthesis of 6 from 3 and formaldehyde/formic acid.[4] Addition of 7 to 3 could explain the conversions between 6-A and -B since both the (+) and (−) forms of 7 and 3 would be present.

Synthesis of 6 from both (+)- and (−)-primaquine was accomplished by using the same procedure as for the (±) form.[4] HPLC analyses of the products from both showed only one peak (6-B) even after standing in solution at room temperature for several days. This result rules out any explanation invoking syn–anti-type isomerism. By mixing equal quantities of 6 prepared from (+)-primaquine with that prepared from (−)-primaquine, the formation of peak 6-A could be followed by HPLC and was complete after 3 days. This last experiment provides convincing evidence that 6-A and -B[14] are interconverted as shown in Scheme I.

The formation of the novel dimeric compounds 5 and 6 from microbial enzyme systems may have implications for the complete understanding of the metabolism of primaquine. In addition, the stereochemical studies described here show that dimers like 5 do show atropisomerism and that 6-A and -B can accomplish epimerization without direct involvement of the asymmetric carbon atoms.[15]

Experimental Section

General HPLC Methods. For the quantitative analysis of the three isomers of 5 and the two isomers of 6, a C-18 reversed-phase, 5 μm-particle size HPLC system (Whatman PXS 5/25 ODS column) was utilized. The mobile phase (1.0 mL/min) was prepared by using 8.4 g of KH_2PO_4, 6.6 g of K_2HPO_4, 4.0 g of *N,N*-dimethyloctylamine, 2.8 L of CH_3OH, and 1.2 L of water. The chromatographic peaks were detected by using a dual wavelength unit (Waters Assoc. Model 440) operating at 254 and 280 nm in conjunction with a dual-pen strip chart recorder. Identifications of the components of the mixtures were based on a comparison of the retention time and the A_{254}/A_{280} ratio of each component.

Equilibration Studies for 5-I, -II, and -III. The isomers I, II, and III (retention times 6.5, 8.7, 11.8 min, respectively) obtained in pure form as described previously[3] were dissolved in 1-octanol (a few μg per 20 μL) in separate capillary tubes which were then sealed. The sealed tubes were placed in a sand bath at 192 °C. The capillary was removed at the specified times and broken, a few microliters withdrawn, resealed and then replaced in the sand bath. The initial solution ($t = 0$) and samples at $t = 60$, 150, and 210 min were analyzed by HPLC. The conversion of 5-I to a 1:1 equilibrium mixture of 5-I and 5-III was found to follow simple first-order kinetics. Linear regression analysis of the data gave a half-life of 132 min. Essentially the same results were found from following the conversion of 5-III to the equilibrium mixture of the two isomers.

HPLC Separation of 6-A and -B and Determination of Half-Life. A 1:1 mixture of 6-A and 6-B was injected onto a 10 μm, C-18, reversed-phase column (Waters, μ-Bondapak C-18) by using the same mobile phase; however, a 1.5 mL/min flow rate was used. The chromatographic experiment showed base-line separation of 6-A and 6-B (retention times 29.1, 35.2 min, respectively). The pure fractions were stored at room temperature in the mobile phase. A second C-18 reversed-phase HPLC system was then used to follow the kinetics of the conversion of 6-A to the 1:1 equilibrium mixture of 6-A and 6-B. A least-squares regression analysis of the data showed a half-life of 10.6 h for the interconversion at room temperature in the methanol–phosphate buffer system.

Synthesis of 6 from Optically Active Primaquine (1) and Equilibration of 6-A and -B. A 5-mg sample each of (+)- and (−)-primaquine (1) diphosphate was acetylated by using acetic anhydride–pyridine at room temperature for 0.5 h (no starting material, TLC). The evaporated residue was then converted to 6 by using the same procedure as previously described.[4] The evaporated residues from this reaction were purified by flash chromatography over alumina (Woelm, N, III) using ethyl acetate–*n*-hexane (1:1). About 1 mg of purified 6 was obtained from each isomer. These were then analyzed by HPLC. Samples of 6 prepared from (+)- and (−)-primaquine were then mixed (equal quantities) and allowed to stand at room temperature in methanol and the equilibration followed by HPLC.

Synthesis of 5 from (−)-Primaquine (1). (−)-Primaquine (1) diphosphate (4 mg) was acetylated as described previously for 6 and converted to 5 by using the procedure outlined previously.[3] The HPLC analysis was performed on the residue after workup.

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(12) The peaks would be expected to have the same area ratios since one peak would represent the pair of enantiomers (RCH_2R and SCH_2S) while the other one would represent the meso form (RCH_2S) which could form in two ways.

(13) The $t_{1/2}$ for interconversion was 10.6 h at room temperature in the mobile phase used for HPLC.

(14) Peak A thus represents the RCH_2S dimer while peak B is an enantiomeric mixture of RCH_2R and SCH_2S.

(15) In some related studies using chiral HPLC stationary phases, details of which will be published later, we have now separated 5 into its six stereoisomers and 6 into its three stereoisomers.

Synthesis of *N*-(3-(Dimethylamino)-2-(substituted thio)-2-propenylidene)-*N*-methylmethanaminium Salts via 2-(Alkylthio)- and 2-(Arylthio)-3-(dimethylamino)acroleins

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Derivatives of *N*-(3-(dimethylamino)-2-propenylidene)-*N*-methylmethanaminium salts (4) are well-known in the literature as intermediates for the synthesis of 5-substituted pyrimidines and other heterocyclic systems.[1] Although 2-aryl, alkyl, alkoxy, and alkylamino derivatives are known, the 2-substituted thio derivatives have not been reported. Our initial attempts at preparing these 2-thio analogues using standard literature procedures[2] for known methanaminium derivatives were unsuccessful.

We report herein a novel two-step synthetic procedure (Scheme I) to these compounds based on the known addition of sulfenyl halides to enamines.[3] The sulfenyl

(1) (a) Wagner, R. M.; Jutz, C. *Chem. Ber.* **1971**, *104*, 2975. (b) Zaschke, H. *Z. Chem.* **1977**, *17*, 63. (c) Jutz, C.; Kuchlechnes, R.; Seidel, H. J. *Chem. Ber.* **1969**, *102*, 2301. (d) Lloyd, D.; Tucker, K. S. *J. Chem. Soc., Perkin Trans. 1* **1981**, *3*, 726.

(2) (a) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1963**, *78*, 869. (b) Jutz, C.; Lobering, H.; Trinkel, K. *Synthesis* **1977**, 332. (c) Kucera, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3793.

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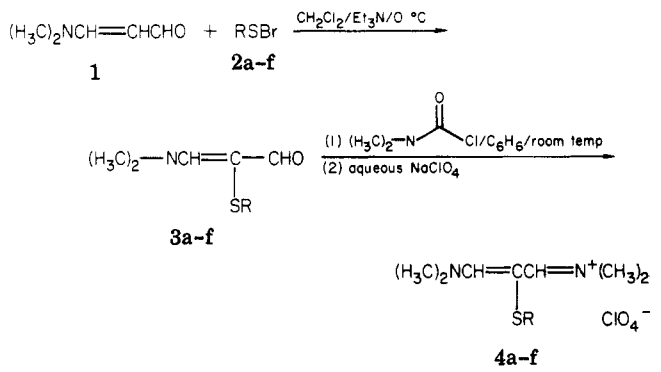
Table I

	3			4		
R	mp, °C	% yield	^{1}H NMR ($CDCl_3$/Me_4Si), δ H_a/H_b	mp, °C	% yield	^{1}H NMR ($CDCl_3$/Me_4Si), δ H_c
CH_3	oil	30.3	7.07/8.96	84.5–85.5	30	7.85
$CH_2CH_2CH_3$	oil	63	7.25/9.08	73–74	57	7.93
C_6H_{11}	oil	10	7.17/8.95	130–132	21	7.90[b]
C_6H_5	90–92	39	7.48/9.11	134–136	33	8.24
4-$CH_3C_6H_4$	112–113	55	7.10/9.17	112–113	12	8.09[b]
$CH_2C_6H_5$	oil	22.6	7.15/9.05	175–177	32	7.78[b]

[a] Satisfactory analyses (±0.4 for C,H,N) were obtained for 3d,3e and 4a-f. NMR and mass spectra (MN^+ peaks) consistent with the desired structure were obtained for all compounds. [b] DMSO-d_6.

Scheme I



a, R = CH_3; b, R = $CH_2CH_2CH_3$; c, R = C_6H_{11}; d, R = C_6H_5; e, R = 4-$CH_3C_6H_4$; f, R = $CH_2C_6H_5$

bromides **2** were conveniently prepared in situ from the appropriate disulfide and bromine. At 0 °C, these sulfenyl bromides were reacted with 3-(dimethylamino)acrolein to give novel 2-(substituted thio)-3-(dimethylamino)acroleins **3** that can be readily converted to 2-(substituted thio) methanaminium salts **4** by stirring with dimethylcarbamyl chloride in benzene for 3 days.[4]

Experimental Section

All melting points were determined on a Thomas-Hoover "Uni-Melt" capillary melting apparatus and are uncorrected. NMR spectra were recorded on either a Varian EM 360A spectrometer at 60 MHz or a Perkin-Elmer R-32 spectrometer at 90 MHz with Me_4Si as an internal standard. Low-resolution mass spectra were recorded on a Finnigan 4023 GC/MS/DS instrument (chemical ionization, methane). Microanalyses were performed by the Analytical Laboratories of The Dow Chemical Co., Midland, MI. No attempt was made to optimize yields.

3-(Dimethylamino)-2-(phenylthio)-2-propenal (3d). Under nitrogen, a CH_2Cl_2 solution of 32.75 g (0.15 mol) of phenyl disulfide was cooled to 0 °C. Bromine, 23.9 g (0.15 mol), was added neat. After 10 min, a CH_2Cl_2 solution of 25 g (0.25 mol) of 3-(dimethylamino)acrolein (Fluka Chemical Co.) and 50 mL of Et_3N was added dropwise while the temperature was held at 0 °C. After being stirred overnight at room temperature, the reaction was shaken with water (200 mL × 2). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated to give 49.5 g of crude **3d** as a dark oil. The aldehyde was purified by preparative HPLC (EtOAc) to give 20.2 g (39%) of pure **3d** as light tan crystals: mp 90–92 °C; NMR ($CDCl_3$) δ 3.22 (s, 6 H), 7.13 (s, 5 H), 7.48 (s, 1 H), 9.11 (s, 1 H); mass spectrum, m/z 208 (MH^+).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.79; H, 6.33; N, 6.76. Found: C, 63.54; H, 6.41; N, 6.70.

In a similar manner, aldehydes **3a**, **3b**, **3c**, **3e**, and **3f** were prepared.

***N*-(3-(Dimethylamino)-2-(phenylthio)-2-propenylidene)-*N*-methylmethanaminium Perchlorate (4d).** A 17.5-g (0.085-mol) sample of **3d** was mixed with 10.7 g (0.1 mol) of dimethylcarbamyl chloride and 60 mL of benzene. The reaction was stirred at room temperature for 3 days and then extracted with 100 mL of water. The aqueous layer was treated with 15 g of $NaClO_4 \cdot H_2O$. The solid was collected and after recrystallization (1/1 CH_3OH/C_2H_5OH) yielded 9.5 g (33%) of **4d** as a light orange solid: mp 134–136 °C; NMR ($CDCl_3$) δ 3.39 (s, 6 H), 3.48 (s, 6 H), 7.05–7.48 (m, 5 H), 8.24 (s, 2 H); mass spectrum, m/z 235 (M^+).

Anal. Calcd for $C_{13}H_{19}ClN_2O_4S$: C, 46.64; H, 5.72; N, 8.36. Found: C, 47.0; H, 5.82, N, 8.46.

Using a similar procedure, compounds **4a**, **4c**, **4e**, and **4f** were prepared.

Conversion of Perchlorate 4b to the Iodide Salt. A 25.0-g (0.083-mol) sample of the perchlorate salt **4b** was dissolved in CH_2Cl_2 and shaken vigorously with 75 g of KI/200 mL of water (2×). The CH_2Cl_2 layer was dried (Na_2SO_4) and then concentrated to give a white solid. Recrystallization (2-propanol) gave 16.5 g (61%) of the iodide salt as white crystals: mp 168–171 °C; NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 8 Hz), 1.58 (m, 2 H), 2.48 (t, 2 H, J = 8 Hz), 3.52 (s, 6 H), 3.72 (s, 6 H), 8.88 (s, 2 H); mass spectrum, m/z 201 (M^+).

Anal. Calcd for $C_{10}H_{21}IN_2S$: C, 36.60; H, 6.45; N, 8.53. Found: C, 36.80; H, 6.35; N, 8.35.

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Registry No. **3a**, 90584-65-9; **3b**, 90584-66-0; **3c**, 90584-67-1; **3d**, 74093-76-8; **3e**, 74093-77-9; **3f**, 90584-68-2; **4a**, 90584-70-6; **4b**, 90584-72-8; **4b** iodide salt, 90584-81-9; **4c**, 90584-74-0; **4d**, 90584-76-2; **4e**, 90584-78-4; **4f**, 90584-80-8; $(MeS)_2$, 624-92-0; $(PrS)_2$, 629-19-6; $(c\text{-}HxS)_2$, 2550-40-5; $(PhS)_2$, 882-33-7; $(p\text{-}MeC_6H_4S)_2$, 103-19-5; $(PhCH_2S)_2$, 150-60-7; dimethylcarbamyl chloride, 79-44-7; 3-(dimethylamino)acrolein, 927-63-9.

(3) Cook, G. A. "Enamines: Synthesis, Structure and Reactions"; Marcel Dekker: New York, 1969; pp 148–149.
(4) Arnold, Z. *Collect. Czech. Chem. Commun.* **1974**, *24*, 760.

Self-Condensation of 3*H*-Pyrrol-3-one 1-Oxides

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Whereas the parent 3-aza- and 3,4,-diazacyclopentadienones are unknown, phenyl-substituted derivatives **1**[1,2] and **2**[3,4] have been detected despite their relative lability

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