Synthesis and Rearrangement of Glycidic Thiol Esters. Migratory Aptitudes[1]

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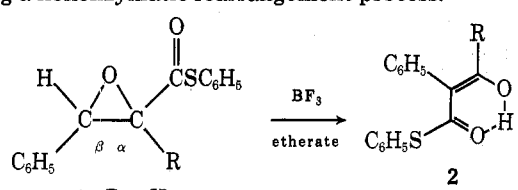
The boron trifluoride etherate induced rearrangement of glycidic thiol esters has been studied. Migration of an α substituent occurs in those cases where at least one phenyl or two methyl groups are attached to the β position of the thiolglycidate allowing for stabilization of positive charge at the β position when the epoxide ring is opened by the Lewis acid. 3-Phenylthiolglycidates (**4a** and **4c**) undergo rearrangement with thiol ester group migration in preference to migration of the α-hydrogen atom to give the corresponding β-oxo thiol esters (**5a** and **5c**), respectively. However, the α-phenyl group migrates in preference to the thiol ester function in the rearrangement of *S*-phenyl 3,3-dimethyl-2-phenylthiolglycidate (**4d**) to give thiolpyruvate (**14**) as the major product. In one example involving the rearrangement of *S*-phenyl 2-phenylthiolglycidate (**4e**) to form β-oxo thiol ester (**2a**), a β hydrogen serves as the migrating group. The rearrangement of **4e** also gives a smaller amount of β-lactone **16**, formed in a novel ring expansion reaction involving the shift of the phenylthio group to the α position.

Intramolecular Wagner–Meerwein rearrangement processes involving a 1,2 migration to an electron-deficient center have been studied extensively. It is well known that aryl groups, alkyl groups, and hydrogen atoms may serve as migrating groups in this reaction. More recently a large variety of electron-withdrawing substituents have been observed to function as migrating groups, including ketone,[2] ester,[3] amide,[4] amidate,[5] nitrile,[6] phosphonate ester,[7] phosphinyl,[8] sulfoxide,[9] sulfone,[9] nitro,[10] and halogen groups.[11] In this connection the rearrangement of epoxides substituted with electron-withdrawing groups has received the greatest attention. We have been interested in the synthesis and chemistry of glycidic thiol esters (**1**). These compounds undergo boron trifluoride induced rearrangement with thiol ester group migration to give the enol tautomer (**2**) of the corresponding β-oxo thiol ester.[12] This is the first reported example of migration of the thiol ester function during a nonenzymatic rearrangement process.[13]



1a, R = H
b, R = CH_3

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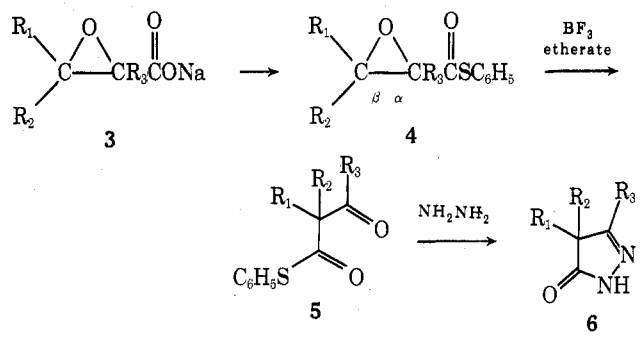
We wish to report here on the migratory aptitude of the thiol ester group relative to other groups such as methyl, phenyl, hydrogen, and carbethoxy. Similar studies on the migratory aptitude of ketone[2b] and carbethoxy groups[3a] in related epoxide rearrangement processes have been reported. Also with the recent development of a high-yield procedure for the preparation of thiolglycidates,[14] the BF_3-induced rearrangement of glycidic thiol esters provides a convenient synthetic route to β-oxo thiol esters and also certain α-keto thiol esters. Despite the importance of these functional groups in biological systems, relatively few methods have been found for their preparation.[15,16]

Results and Discussion

Initially we synthesized glycidic thiol esters from the corresponding salts using thionyl chloride or oxalyl chloride Schotten–Baumann procedures. The oxalyl chloride method that we used is similar to that developed by Speziale and Frazier[17] for the synthesis of glycidamides. Thus, for example, glycidic thiol esters **4a** and **4b** were prepared by allowing glycidate salts **3a** and **3b** to react with oxalyl chloride in benzene followed by treatment with benzenethiol and pyridine in ether solvent. Glycidic thiol ester **4c** was prepared by treatment of **3c** with *S*-phenyl thiolchlorocarbonate in tetrahydrofuran at 0°.



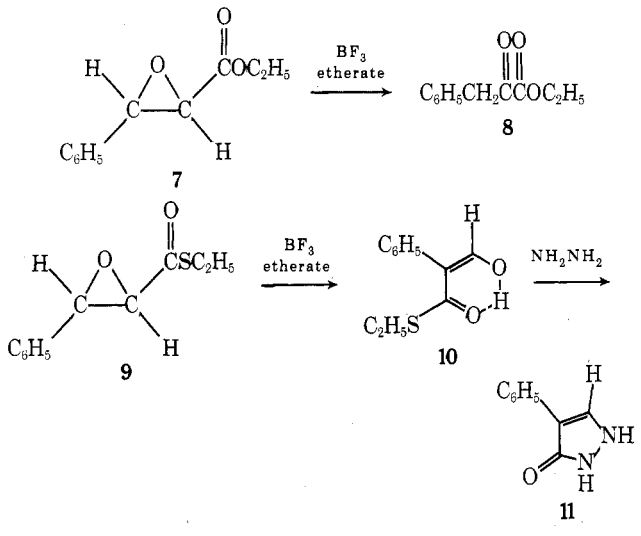
a, $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = H$
b, $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = CH_3$
c, $R_1 = C_6H_5$; $R_2 = C_6H_5$; $R_3 = H$

All of the BF_3-induced rearrangements of glycidic thiol esters that we have studied were found to proceed rapidly (within 30 min or less) when the glycidic thiol esters (**4**) were treated with excess boron trifluoride etherate (4 equiv) in ether solvent at room temperature. These conditions were used by House[2] in the rearrangement of α,β-epoxy ketones, although stronger conditions were needed in some cases. Somewhat more severe conditions involving BF_3 gas in benzene solvent were used by Kagan and Singh[3a] in the rearrangement of glycidic (oxygen) esters. The rearrangement products obtained in our study were isolated in high yield by evaporation of the ether solvent followed by direct column chromatography on silica gel.

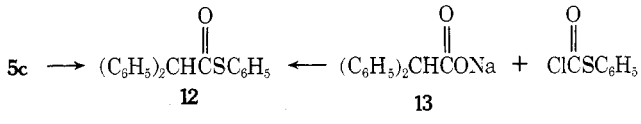
The BF_3-induced rearrangement of *S*-phenyl 3-methyl-3-phenylthiolglycidate (**4a**) gave *S*-phenyl 2-methyl-2-phenyl-3-oxopropanethioate (**5a**) as the major product (87%). In a similar way thiolglycidate **4b** gave β-keto thiol ester **5b** in 91% yield. The structure of the rearrangement products, **5a** and **5b**, were established on the basis of spectral data and by conversion to the corresponding 2-pyrazoline-5-ones, **6a** and **6b**, by treatment with hydrazine hydrate in ethanol. The formation of **5a** from **4a** may be explained by assuming initial opening of the epoxide ring by the Lewis acid followed by 1,2 migration of the thiol ester function from the α to the electron-deficient β carbon atom.[18] We have reported earlier that **1a** and **1b** undergo rearrangement to give **2a** and **2b** involving migration of the thiol ester function.[12] These results together with the results presented here suggest that the *S*-phenyl thiol ester function has higher migratory aptitude than methyl or hydro-

gen in the BF_3-induced rearrangement of glycidic thiol esters. A similar preference for carbonyl group migration has been observed in the rearrangement of chalcone epoxides.[2b] In the case of glycidic esters the carbethoxy group migrates in preference to methyl in the BF_3-induced rearrangement of ethyl 2-methyl-3-phenylglycidate.[3a,19]

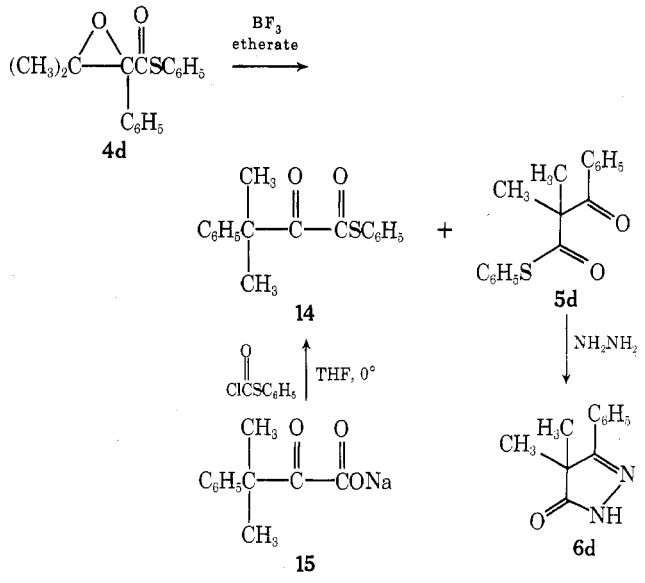
Interestingly the rearrangement of ethyl 3-phenylglycidate (**7**) has been reported to give ethyl 3-phenylpyruvate (**8**) involving apparent migration of the α hydrogen.[3a] In this connection we have examined the rearrangement of *S*-ethyl 3-phenylthiolglycidate (**9**). Rearrangement of **9** gave primarily the enol tautomer of *S*-ethyl 2-phenyl-3-oxopropanethioate (**10**). It is probable that the thiol ester group migrates in the conversion of **9** to **10** in view of the fact that we have already shown with a ^{14}C labeling study[12b] that the thiol ester group and not the β-phenyl group migrates in the corresponding conversion of *S*-phenyl ester **1a** to **2a.** In any case, when these results are compared to those obtained by Kagan and Singh[3a] they suggest that the presence of the sulfur atom has a major influence on the migratory aptitude of the thiol ester function in this system.



Furthermore, these results support the conclusion that the thiol ester group has higher migratory aptitude than the normal (oxygen) ester in these rearrangement reactions. In agreement with this interpretation we find that *S*-phenyl 3,3-diphenylthiolglycidate (**4c**) underwent BF_3-induced rearrangement with thiol ester group migration to give *S*-phenyl 2,2-diphenyl-3-oxopropanethioate (**5c**) in 85% yield. In contrast, ethyl 3,3-diphenylglycidate rearranges in the presence of HCl at 200° to give ethyl diphenylpyruvate involving migration of a hydrogen atom.[20] The structure of **5c** was established by deformylation using the method of House[2a] to give *S*-phenyl diphenylethanethioate (**12**). **12** was synthesized independently from sodium diphenylacetate (**13**) and *S*-phenyl thiolchlorocarbonate.

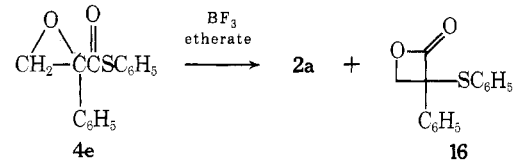


Also in this connection we have examined the rearrangement of *S*-phenyl 3,3-dimethyl-2-phenylthioglycidate (**4d**). Two products, thiolpyruvate **14** (80% yield) and β-keto thiol ester **5d** (10% yield), were obtained. The structure of **14** was established by independent synthesis involving treatment of sodium 3,3-dimethyl-3-phenylpyruvate (**15**) with *S*-phenyl thiolchlorocarbonate in THF at 0°. The BF_3-induced rearrangement of **4d** to **5d** would appear to involve migration of the thiol ester function. This is noteworthy[3d] in view of the fact that it is the first reported case where a carbonyl group has been found to compete with phenyl as the migrating group in the rearrangement of α,β-epoxy carbonyl systems. In contrast only the phenyl group has been observed to migrate in the BF_3-induced rearrangement of ethyl 2-phenyl-3,3-dimethylglycidate.[3a] The major product obtained from the rearrangement of **4d** is thiolpyruvate **14,** which would result from migration of the α-phenyl. This suggests that the α-phenyl group has higher migratory aptitude than the thiol ester function in the rearrangement of α-phenyl glycidic thiol esters.



In summary, in the BF_3-induced rearrangement of *S*-phenyl glycidic thiol esters involving shifts from the α position to the electron-deficient β carbon atom, the relative migratory aptitudes would be as follows: phenyl > *S*-phenyl thiol ester > methyl or hydrogen. A similar order has been found for the benzoyl group in the rearrangement of chalcone epoxides[2b] and for the carbethoxy group in the rearrangement of glycidic esters.[3a] We have also obtained results that suggest that the thiol ester group has higher migratory aptitude than the carbethoxy group in these rearrangement reactions.

House[2c] has shown that the BF_3-induced rearrangement of 2,3-epoxy-2-phenylpropiophenone leads to initial generation of positive charge at the α position owing to resonance stabilization by the α-phenyl substituent. One of the β hydrogen atoms then migrates to the α position (or alternatively the hydrogen is lost as a proton) to give after work-up with phenylhydrazine the corresponding pyrazole derivative of α-formyldeoxybenzoin. In a similar manner ethyl 2-phenylglycidate is converted into ethyl 2-phenyl-3-oxopropanoate, although in low yield.[3a] We have found that the rearrangement of *S*-phenyl 2-phenylthiolglycidate (**4e**) provides a similar rearrangement product, **2a,** in 55% yield. We also isolated from this rearrangement reaction β-lactone **16** in about 20% yield. The structure assignment



for **16** is based on elemental analysis and spectral data. The ir spectrum shows a β-lactone carbonyl at 1815 cm^{-1} while the NMR spectrum shows an AB quartet at δ 4.47 and 4.61 (J_{AB} = 5.5 Hz). In the mass spectrum the molecular ion oc-

curs at *m/e* 256 while the base peak is at *m/e* 212 ($M^{\cdot+} - CO_2$). We would rationalize the formation of **16** by initial attachment of the BF_3 catalyst to the thiol ester carbonyl oxygen atom followed by intramolecular coordination of the electrophilic carbonyl carbon with the epoxide oxygen atom resulting in opening of the epoxide ring and formation of the four-membered ring. A 1,2 shift of the phenylthio group to the α-carbon position would generate β-lactone **16**. Migration of the phenylthio group and formation of the four-membered ring may occur simultaneously. The conversion of **4e** to **16** represents a novel ring expansion reaction not previously observed in the Lewis acid induced rearrangement of other α,β-epoxy carbonyl systems.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A spectrometer using tetramethylsilane (Me_4Si) as an internal standard except where otherwise noted. Mass spectral analysis was performed on a Varian MAT CH-5 instrument. THF was dried over sodium metal–anthracene complex and distilled prior to use. Benzene was dried over sodium metal while ether was dried over $LiAlH_4$. Both were distilled prior to use. The petroleum ether had a boiling point range of 60–110°. The silica gel used for column chromatography was Baker reagent grade (60–200 mesh). Merck silica gel GF-254 was used for preparative thin layer chromatography. Melting points and boiling points are uncorrected. The elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. *S*-Phenyl thiolchlorocarbonate was purchased from Columbia Organic Chemicals Co.

Sodium 2,3-dimethyl-3-phenylglycidate (3b), believed to be the trans (*E*) isomer, was obtained from a mixture of sodium (*E*)- and (*Z*)-2,3-dimethyl-3-phenylglycidate[21] by fractional crystallization from ethanol and water as colorless plates: mp 314–316° dec; NMR (D_2O, Me_4Si external standard) δ 7.30 (s, 5 H), 1.53 (s, 3 H), 1.10 (s, 3 H).

***S*-Phenyl 3-Methyl-3-phenylthiolglycidate (4a).** Sodium 3-methyl-3-phenylglycidate (**3a**,[22] 2.25 g, 0.011 mol) was suspended in anhydrous benzene (25 ml) under nitrogen at 0°. This was treated with pyridine (3–5 drops) followed by the dropwise addition over a period of 1 hr of freshly distilled oxalyl chloride (2.22 g, 0.0175 mol) in benzene (5 ml). The reaction mixture was stirred at 0° for 30 min and the benzene was removed by evaporation under reduced pressure maintaining the temperature below 15°. Fresh benzene (20 ml) and pyridine (3–5 drops) were added and then evaporated under reduced pressure. Anhydrous ether was added to the residue and the temperature was lowered to −40 to −50°. Benzenethiol (1.00 g, 0.0091 mol) in ether (5 ml) and pyridine (0.92 g, 0.012 mol) in ether (5 ml) were added dropwise separately and simultaneously over a period of 20 min. The reaction mixture was stirred at −40 to −50° for an additional 2 hr and then warmed to room temperature before water (25 ml) was added. The ether layer was separated and the water was reextracted with ether (25 ml). The combined ether extracts were dried (Na_2SO_4) and concentrated and the crude product was subjected to column chromatography on silica gel eluting with petroleum ether followed by benzene–petroleum ether, which upon evaporation gave what is believed to be the trans (*E*) isomer of **4a** (1.16 g, 4.3 mmol, 38%). Recrystallization (*n*-hexane and benzene) gave colorless needles: mp 68–69°; NMR (CCl_4) δ 7.33 (s) and 7.27 (s) (10 H), 3.48 (s, 1 H), 1.83 (s, 3 H); ir (KBr) 1690 cm^{-1} (broad).

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 71.33; H, 5.14; S, 11.69.

***S*-Phenyl 2,3-dimethyl-3-phenylthiolglycidate (4b),** believed to be the trans (*E*) isomer, was obtained using a similar procedure from sodium 2,3-dimethyl-3-phenylglycidate (**3b**), oxalyl chloride, benzenethiol, and pyridine in 17% yield. Recrystallization (*n*-hexane and benzene) gave colorless needles: mp 61–62°; NMR (CCl_4) δ 7.33 (s) and 7.26 (s) (10 H), 1.78 (s, 3 H), 1.18 (s, 3 H); ir (KBr) 1690 cm^{-1} (broad).

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.66; H, 5.40; S, 11.13.

***S*-Phenyl 2-phenylthiolglycidate (4e)** was obtained using a similar procedure from sodium 2-phenylglycidate,[23] oxalyl chloride, benzenethiol, and pyridine in 35% yield. Recrystallization (*n*-hexane and benzene) gave colorless plates: mp 55.5–57°; NMR (CCl_4) δ 7.42 (s) superimposed on a multiplet 7.80–7.20 (10 H), 3.35 (d, 1 H, J = 6.5 Hz), 2.97 (d, 1 H, J = 6.5 Hz); ir (KBr) 1690 cm^{-1} (broad).

Anal. Calcd for $C_{15}H_{12}O_2S$: 70.29; H, 4.72; S, 12.51. Found: C, 70.11; H, 4.84; S, 12.32.

***S*-Phenyl 3,3-Diphenylthiolglycidate (4c).** Sodium 3,3-diphenylglycidate (**3c**,[20] 2.62 g, 0.010 mol) was suspended in dry THF (30 ml) under nitrogen atmosphere at 0°. It was treated with pyridine (3–5 drops) followed by the dropwise addition over a period of 30 min of *S*-phenyl thiolchlorocarbonate (1.72 g, 0.010 mol) in dry THF (5–10 ml). The reaction mixture was stirred for 30 min at 0° and then at room temperature for an additional 60 min before it was poured into cold water (200 ml) and ether (200 ml). The ether layer was separated and the water layer was extracted again with ether (100 ml). The combined ether extracts were dried (Na_2SO_4) and concentrated to give an oil which was subjected to column chromatography on silica gel eluting with petroleum ether followed by benzene–petroleum ether (1:1) to collect the product (2.4 g, 0.0072 mol, 72%). Recrystallization (*n*-hexane and benzene) gave pure **4c** as colorless plates: mp 93–95°; NMR (CCl_4) δ 7.22 (s) superimposed on multiplet 7.60–6.70 (15 H), 3.90 (s, 1 H); ir (KBr) 1675 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_2S$: C, 75.87; H, 4.85; S, 9.65. Found: C, 75.67; H, 4.58; S, 9.51.

***S*-Phenyl 2-phenyl-3,3-dimethylthiolglycidate (4d)** was obtained in a similar manner from sodium 2-phenyl-3,3-dimethylglycidate[21] and *S*-phenyl thiolchlorocarbonate in 72% yield. Recrystallization (*n*-hexane and benzene) gave colorless needles: mp 66–67°; NMR ($CDCl_3$) δ 7.28 (s) superimposed on multiplet at 7.65–7.10 (10 H), 1.62 (s, 3 H), 1.07 (s, 3 H); ir (KBr) 1700 cm^{-1} (broad).

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; H, 11.28. Found: C, 72.01; H, 5.65; S, 11.11.

Rearrangement of 4a. Boron trifluoride etherate (0.55 ml, 4.4 mmol) was added to **4a** (0.298 g, 1.1 mmol) in dry ether (15 ml) under nitrogen atmosphere and the reaction was stirred at room temperature for 30 min before concentrating under reduced pressure. The residual oil was subjected to column chromatography on silica gel eluting with benzene. Concentration of the benzene eluent containing the product gave *S*-phenyl 2-methyl-2-phenyl-3-oxopropanethioate (**5a**) as a faint yellow oil (0.260 g, 0.96 mmol, 87%): NMR (CCl_4) δ 10.00 (s, 1 H), 7.42 (s) and 7.25 (s) (10 H), 1.83 (s, 3 H); ir (thin film) 1725, 1685 cm^{-1}.

The product (0.260 g, 0.96 mmol) in ethanol (3 ml) was treated with hydrazine hydrate (0.20 g, 4.0 mmol) and the solution was refluxed for 20 min and then allowed to stand at room temperature. Crystals began to form after approximately 1 day. After 3 days the crystalline derivative was washed with warm hexane (to remove diphenyl disulfide) and recrystallized from ethanol and water to give 4-methyl-4-phenyl-2-pyrazolin-5-one (**6a**), mp 101–102° (lit. mp 99–101°,[24] 107–110°[25]).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.20; H, 5.61; N, 15.89.

Rearrangement of 4b. Using the same general procedure **4b** was converted to *S*-phenyl 2-methyl-2-phenyl-3-oxobutanethioate (**5b**), which was obtained as a faint yellow oil in 91% yield. **5b** crystallized after trituration with ether. Recrystallization from *n*-hexane gave pure **5b**: mp 65–66°; NMR (CCl_4) δ 7.32 (s) and 7.28 (s) (10 H), 2.07 (s, 3 H), and 1.85 (s, 3 H); ir (thin film) 1715, 1685 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.73; H, 5.78; S, 11.22.

5b was converted to 3,4-dimethyl-4-phenyl-2-pyrazolin-5-one (**6b**) on treatment with hydrazine hydrate in ethanol. Recrystallization from ethanol and water gave colorless plates, mp 156–158° (reported[26] mp 158–159°). The mixture melting point with an authentic sample (mp 156–158°) prepared from hydrazine hydrate and ethyl 2-methyl-2-phenyl-3-oxobutanoate[3a] in ethanol was not depressed.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.99; H, 6.66; N, 14.80.

Rearrangement of 9. Using the same general procedure **9**[14] was converted to the *Z* enol tautomer of *S*-ethyl 2-phenyl-3-oxopropanethioate (**10**). It was necessary to purify this product further by a second column chromatography on silica gel eluting with benzene–petroleum ether (1:1) followed by short-path distillation (bath temperature 115–120°, 0.4 mm) to give the product as a faint yellow oil in 53% yield: NMR (CCl_4) δ 12.30 (d, 1 H, J = 12.0 Hz), 7.22 (s, 5 H), 6.90 (d, 1 H, J = 12.0 Hz), 2.88 (q, 2 H, J = 7.0 Hz), 1.24 (t, 3 H, J = 7.0 Hz); ir (thin film) 1725 (m), 1670 (shoulder), 1625 cm^{-1} (s). The structure of the rearrangement product was

confirmed by conversion of the chromatographed material to 4-phenylpyrazolone (11) (mp 221–223°) using hydrazine hydrate in ethanol. The mixture melting point of this pyrazolone with an authentic sample was not depressed.[27]

Rearrangement of 4c. In a similar way **4c** was converted to *S*-phenyl 2,2-diphenyl-3-oxopropanethioate (**5c**) which was obtained as a light yellow oil in 85% yield: NMR ($CDCl_3$) δ 10.02 (s, 1 H), 7.28 (s, 15 H); ir (thin film) 1730, 1685 cm^{-1}.

The rearrangement product was deformylated using the procedure of House.[2a] A solution of the rearrangement product (1.0 g) and sodium acetate (1.2 g) in ethanol (150 ml) was allowed to reflux for 3 hr. The reaction mixture was cooled to room temperature before adding ether (150 ml). The ether was extracted with 20% sodium chloride solution (3 × 150 ml), dried (Na_2SO_4), and concentrated to give an oil which solidified on standing. The NMR of this product suggested that it was a mixture of ethyl diphenylacetate and *S*-phenyl diphenylethanethioate (**12**). Recrystallization from hexane and benzene gave pure **12** as colorless needles: mp 81–83°; NMR (CCl_4) δ 7.28 (s) and 7.23 (s) (15 H), 5.13 (s, 1 H); ir (KBr) 1690 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 78.54; H, 5.11; S, 10.31.

The mixture melting point of this compound with an authentic sample (prepared as described below) was not depressed. In a later attempt to purify **5c** by preparative thin layer chromatography on silica gel **12** was obtained instead, mp 80–82°. The mixture melting point of this material with authentic **12** (described below) was also not depressed.

***S*-Phenyl Diphenylethanethioate (12).** Using the same *S*-phenyl thiolchlorocarbonate procedure described for the synthesis of *S*-phenyl 3,3-diphenylthiolglycidate (**4c**), sodium diphenylacetate was converted to **12** in 64% yield after column chromatography. Recrystallization (*n*-hexane and benzene) gave colorless needles, mp 81–83°.

In a separate experiment the rearrangement product **5c** was converted to 4,4-diphenyl-2-pyrazolin-5-one (**6c**) on treatment with hydrazine hydrate in ethanol. The crystals were washed with *n*-hexane followed by recrystallization from ethanol and water to give colorless plates: mp 204–206°; ir (KBr) 3320 (sharp), 1705, 1725 cm^{-1} (shoulder).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.03; H, 5.12; N, 11.84.

Rearrangement of 4d. Using the same procedure **4d** was converted to *S*-phenyl 3,3-dimethyl-3-phenylthiolpyruvate (**14**), which was obtained as a thick yellow oil that crystallized on standing. Recrystallization (*n*-hexane and benzene) gave the pure thiolpyruvate **14** as yellow plates in 70% yield: mp 47–48°; NMR (CCl_4) δ 7.18 (s, 10 H), 1.58 (s, 6 H); ir (KBr) 1715, 1695 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.67; H, 5.54; S, 11.31.

The mother liquors obtained from the recrystallization of **14** on concentration gave a mixture of **14** (10%) along with *S*-phenyl 2,2-dimethyl-3-phenyl-3-oxopropanethioate (**5d**, 10%) which were separated by careful column chromatography on silica gel eluting with benzene–petroleum ether (1:9). **5d** was obtained as a colorless oil: NMR (CCl_4) δ 8.1–7.8 (m, 2 H), 7.35 (s) superimposed on a multiplet at 7.6–7.2 (8 H), 1.62 (s, 6 H); ir (thin film) 1695, 1675 cm^{-1}. This was converted to 4,4-dimethyl-3-phenyl-2-pyrazolin-5-one (**6d**) on treatment with hydrazine hydrate in ethanol. The product was purified by chromatography on a silica gel column eluting with 2% ethanol in benzene. Recrystallization from benzene–*n*-hexane followed by a second recrystallization from ethanol and water gave the pure pyrazolone **6d**, mp 117–118° (lit.[28] mp 118°). The mixture melting point with an authentic sample (mp 117–118°) prepared from ethyl 2,2-dimethyl-3-phenyl-3-oxopropionate[29] and hydrazine hydrate in ethanol was not depressed. An analytical sample was obtained after two recrystallizations from ethanol and water.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.08; H, 6.61; N, 15.16.

Sodium Phenyldimethylpyruvate (15). Ethyl phenyldimethylpyruvate[3a] was converted to **15** in 56% yield using Claisen's method.[30] The salt was obtained as an amorphous, faint yellow powder: NMR (D_2O, Me_4Si external standard) δ 7.38 (s, 5 H), 1.55 (s, 6 H).

***S*-Phenyl 3,3-Dimethyl-3-phenylthiolpyruvate (14).** Using the *S*-phenyl thiolchlorocarbonate procedure described for the synthesis of *S*-phenyl 3,3-diphenylthiolglycidate (**4c**), pyruvate salt **15** was converted to thiolpyruvate **14** in 59% yield after column chromatography. Recrystallization (*n*-hexane and benzene) gave **14** as yellow plates, mp 47–48°. The NMR and ir spectra of this compound were identical with the NMR and ir spectra of **14** obtained from the rearrangement of **4d**. The mixture melting point was not depressed.

Rearrangement of 4e. Using the same general rearrangement procedure, **4e** was converted to a mixture of products containing the *Z* enol tautomer of *S*-phenyl 2-phenyl-3-oxopropanethioate (**2a**) and a second compound, β-lactone **16**. The mixture was separated by a second column chromatography on silica gel eluting with benzene–petroleum ether (1:4). The β-lactone **16** was eluted first (20% yield). Recrystallization (*n*-hexane and benzene) gave colorless plates: mp 99–100°; NMR ($CDCl_3$) δ 7.32 (s) superimposed on a multiplet at 7.60–7.15 (10 H), 4.47 and 4.61 (AB quartet, 2 H, J = 5.5 Hz); ir (KBr) 1815 cm^{-1} (strong); mass spectrum (92°, 70 eV) *m/e* (rel intensity) 256 ($M\cdot^+$, 15), 212 ($M\cdot^+ - CO_2$, 100), 211 (31), 165 (10), 147 ($M\cdot^+ - C_6H_5S$, 17), 110 (57).

Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72; S, 12.51. Found: C, 70.21; H, 4.78; S, 12.70.

Further elution of the silica gel column with benzene–petroleum ether (1:4) gave the *Z* enol tautomer of *S*-phenyl 2-phenyl-3-oxopropanethioate (**2a**) (55% yield): NMR (CCl_4) δ 12.35 (d, 1 H, J = 12.5 Hz), 7.23 (s, 10 H), 6.85 (d, 1 H, J = 12.5 Hz); ir (neat) 1700, 1625 cm^{-1}. The structure of this rearrangement product was established by conversion to 4-phenylpyrazolone (**11**) (mp 223–224°) using hydrazine hydrate in ethanol. The mixture melting point with an authentic sample[12a,27] was not depressed.

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Registry No.—**2a**, 30031-66-4; **3a**, 54984-42-8; *trans*-**3b**, 54934-18-8; *cis*-**3b**, 54934-35-9; **3c**, 54934-19-9; **4a**, 54934-20-2; **4b**, 54934-21-3; **4c**, 54934-22-4; **4d**, 54934-23-5; **4e**, 54934-24-6; **5a**, 54934-25-7; **5b**, 54934-26-8; **5c**, 54934-27-9; **5d**, 54934-28-0; **6a**, 941-18-4; **6b**, 18182-57-5; **6c**, 40110-22-3; **6d**, 24979-47-3; **9**, 54885-09-5; **10**, 54934-29-1; **11**, 54934-30-4; **12**, 54934-31-5; **14**, 54934-32-6; **15**, 54934-33-7; **16**, 54934-34-8; benzenethiol, 108-98-5; sodium 2-phenylglycidate, 24568-17-0; *S*-phenyl thiolchlorocarbonate, 13464-19-2; sodium 2-phenyl-3,3-dimethylglycidate, 24568-18-1; sodium diphenylacetate, 1716-11-6; ethyl phenyldimethylpyruvate, 54934-36-0.

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Synthesis of 10-Thiofolic Acid. A Potential Antibacterial and Antitumor Agent[1a]

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An unambiguous synthesis of 10-thiofolic acid has been carried out in good yield starting from *p*-carbomethoxy thiophenol. Methods have been developed for the quantitative conversion of **6** to the bromo ketone **8**. *p*-Carbomethoxy thiophenol (**3**) and the acid (**2**) were found to be unstable in organic solvents in the presence of oxygen and were converted to the corresponding disulfides (**4** and **5**). A reduction procedure has been developed for the rapid and clean conversion of **14** to **15**, and a procedure for the simultaneous cyclization–oxidation of **15** to **16**. 10-Thiofolic acid (**1**) has been tested for its ability to inhibit the growth of two folate-requiring organisms and showed good antifolate activity. It has also shown moderate activity in preliminary screening against L-1210 leukemia in mice.[23]

The synthesis and biological evaluation of homofolic acid[1b] and its reduced derivatives (**20**)[2,3] have given impetus to the search for folic acid analogs which are altered in the region corresponding to the C^9–N^{10} bridge in folic acid. A number of analogs in this class have been reported recently.[4–10] It appeared to us that the replacement of the 10-amino group of folic acid by a heteroatom would result in folate analogs whose tetrahydro forms[2,3] could contribute interference to the thymidylate synthesis reaction owing to their inability to form cyclic one-carbon intermediates through positions 5 and 10. This paper details the synthesis and preliminary antifolate activity of such a compound, 10-thiofolic acid (**1**).

At the outset, a convenient procedure for the preparation of *p*-carbomethoxythiophenol (**3**) was required. This was accomplished by a route previously described by Wiley,[11] and the disulfide **4** was also isolated from the reaction mixture. Hydrolysis of **3** gave *p*-carboxythiophenol (**2**), which was converted to the disulfide **5** during crystallization. The quantitative conversion of *N*-(2,3-epoxypropyl)phthalimide to the bromo ketone **8** was carried out by modifications of the original literature procedures.[12–14] Reaction of **3** with **8** in pyridine produced **9** in 75% yield, which was subsequently converted to the oxime **10**. This compound was isolated as a 1:1 mixture of the syn and anti isomers as evidenced by NMR spectroscopy and thin layer chromatography. Since the eventual removal of this carbonyl protective group was required at a later step, no attempt was made to separate and identify the individual isomers.

The NMR spectral observations also excluded a possibility that the product might be a thioketal formed by the reaction of 2 mol of thio ester with the carbonyl moiety of **8** in preference to the nucleophilic displacement of the bromide by **3**.

Although several methods are described in the literature for the cleavage of the phthalimide function for compounds similar to **10**, including treatment with strong acids and bases, the use of hydrazine[15] was preferred because of its ability to cleave such systems under mild conditions. This was accomplished smoothly and in high yield. These reactions are summarized in Scheme I. Several attempts were

Scheme I