S-butyl-N,S-dimethylsulfoximine, 67087-39-2; S,S-dibutyl-N-methylsulfoximine, 35362-76-6; S-benzyl-S-methyl-N-tosylsulfoximine, 38401-39-7; benzyl methyl sulfoxide, 824-86-2; p-toluenesulfonyl azide, 941-55-9; S-benzyl-N-[(p-bromomethyl)phenylsulfonyl]-S-methylsulfoximine, 67087-53-0; N-chloro-S-dichloromethyl-S-phenylsulfoximine, 67087-47-2; S-butyl-S-(1-chlorobutyl)-N-(p-tolysulfonyl)sulfoximine, 67070-02-4; S-(1-chloropropyl)-S-propyl-N-(p-tolylsulfonyl)sulfoximine, 67070-01-3; propyl 1-chloropropyl sulfoxide, 67087-41-6; butyl 1-chlorobutyl sulfoximine, 21128-90-5; phenyl chloromethyl sulfoxide, 7205-94-9; phenyl bromomethyl sulfoxide, 31268-20-9.

Supplementary Material Available: Analytical and spectral data of the compounds discussed in this paper (9 pages). Ordering information is given on any current masthead page.

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Alkenes from Base-Promoted Eliminations of α-Halo Sulfoximines

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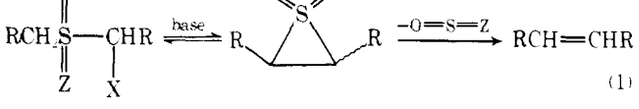
Upon treatment with base α-halo N-(p-tolylsulfonyl)sulfoximines bearing α hydrogens undergo 1,3 eliminations to yield alkenes in analogy to the Ramberg–Bäcklund reaction of α-halo sulfones. Treatment of benzylic α-bromo N-(p-tolylsulfonyl)sulfoximines with refluxing methanolic potassium hydroxide gave *cis*-alkenes as the major product, whereas under the same conditions α-chloro dialkylsulfoximines gave largely *trans*-alkenes. Neither NH nor N-methyl sulfoximines gave alkenes under the above conditions.

α-Halo sulfones undergo an interesting and facile 1,3 elimination which has occupied the attention of chemical laboratories since its discovery by Ramberg and Bäcklund in 1940.[1] (eq 1, Z = O). The question may then be asked as to



(1)

whether halo sulfoximines undergo a similar transformation (eq 1, Z = NR'). If so, how do various nitrogen substituents effect the reaction?

The stereochemistry observed in the alkene produced upon 1,3 elimination of α-halo dialkyl sulfones may vary from predominantly cis to equal amounts of isomeric alkenes.[2] If indeed, a similar 1,3 elimination may be made to occur with α-halo sulfoximines, bulky nitrogen substituents may promote the formation of *cis*-alkenes.

A series of N-substituted α-halo sulfoximines were prepared[3] and treated with base in order to determine to what extent the reaction occurs. Refluxing diastereomerically pure α-chloro sulfoximines in methanolic potassium hydroxide (6 equiv) gave the results shown in Scheme I.

The differences in the reactions of the various N-substituted sulfoximines in Scheme I with methanolic potassium hydroxide is curious. The production of 1-butanesulfinamide in reaction a can be rationalized in a number of ways, including the transient production of a three-membered S–N heterocycle. At this time, we have insufficient data to justify further speculation. The failure of the N-methyl derivative to undergo 1,3 elimination under the conditions of methanolic potassium hydroxide is surprising, since the leaving group, N-sulfinylmethylamine, is a stable compound. When the reaction is carried out with potassium deuterioxide in methanol-*O*-*d*, recovered starting material shows complete exchange of the α and α' protons with deuterium. Thus, the anion is capable of being formed, but apparently the elimination is slow under these conditions. A similar situation has been noted in the literature. 2-Bromothiacyclohexane 1,1-dioxide was initially reported not to undergo elimination after prolonged heating in a sodium hydroxide–dioxane solution, but later was found to give cyclopentene in 82% yield when exposed to potassium *tert*-butoxide in THF at 0 °C (eq 18).[4] It may very well turn out that elimination in the present case will occur under other conditions.

The isolation of 4-octene when the N-tosyl derivative (Scheme I) was treated with potassium hydroxide suggests that a reaction analogous to the Ramberg–Bäcklund reaction is operative. Several α-halo N-tosylsulfoximines were prepared and treated with potassium hydroxide. The cis–trans ratios of the alkenes produced were determined by gas chromatography. The compounds studied can be separated into two structural groups, the benzylic α-bromo and the α-chloro dialkylsulfoximines. The results are summarized in Table I.

In the reactions of the α-bromo sulfoximines **1c–e** and potassium hydroxide approximately 80% of the starting sulfoximines can be accounted for by two reaction pathways. One involves the desired 1,3-dehydrobromination leading to alkene, sulfonamide, and potassium sulfite, while the other is a reduction of the bromo sulfoximines to **4c–e**. The stereochemistry of the alkene produced from **1d** and **1e** is found to be predominately cis. From the α-chloro dialkylsulfoximines **1a** and **1b** only elimination to the alkene was observed. The

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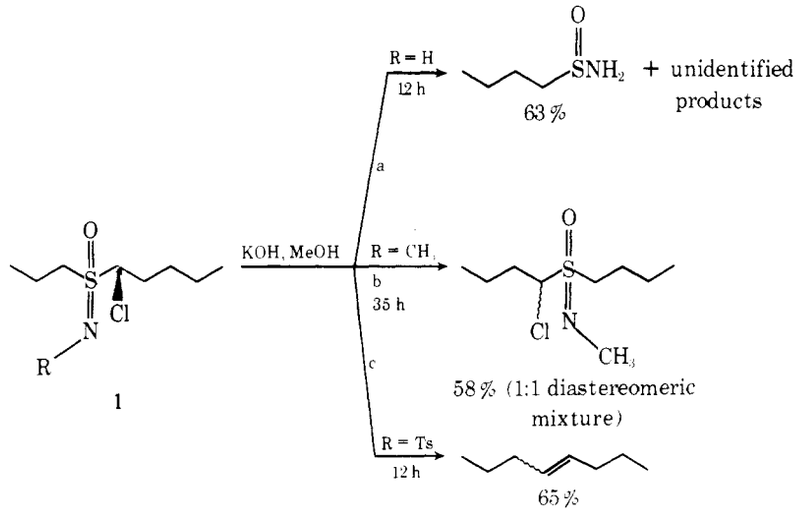
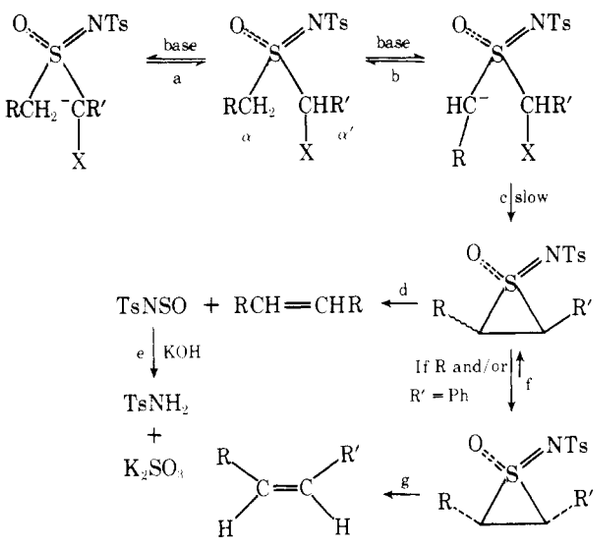
Scheme I



Scheme II

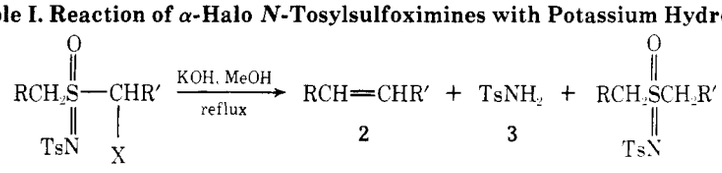


stereochemistry in these cases is found to be about a 1:1 mixture of *cis*- and *trans*-alkenes.

Scheme II rationalizes our results and is compatible with current thinking concerning the Ramberg–Bäcklund reaction. Perhaps the first step (a) is the reversible generation of the α′ anion resulting in epimerization at the α′ carbon. The α anion (formed in step b) can participate in a rate-determining internal nucleophilic displacement of the halide at the α′ position to give an "episulfoximine" intermediate (step c). A double inversion process analogous to that proposed in halo sulfone chemistry[5] is assumed. The stereochemical distribution of the episulfoximines will be controlled by an array of rate constants interlinking both the various configurational combinations at the α′-halo carbon and the α carbanion and the corresponding episulfoximines. Expulsion of the *N*-sulfinyl-*p*-toluenesulfonamide, assumed to occur stereospecifically, will result in alkene formation (step d). (The expulsion of SO_2 from episulfones is known to be stereospecific.) The distribution of diastereomeric alkenes is then determined by the distribution of the diastereomeric episulfoximines.

The benzylic systems, **1d** and **1c**, which yield predominantly *cis*-alkenes, may be special cases. Due to the enhanced acidity episulfoximines with benzylic protons may equilibrate (Scheme II, step f) in favor of an episulfoximine with R and R′ cis to one another and trans to the bulky *N*-Ts group prior to expulsion of TsNSO. Treatment of *cis*-2,3-diphenylthiirane 1,1-dioxide with base results in the exclusive production of *trans*-1,2-diphenylethene, indicating that epimerization (in

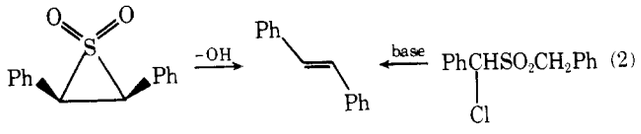
Table I. Reaction of α-Halo *N*-Tosylsulfoximines with Potassium Hydroxide



	R	R′	X	isomer composition of 1[a]	2, % yield (cis/trans)	registry no.	3, % yield[b]	4, % yield	registry no.
a	*n*-Pr	*n*-Pr	Cl	pure[e]	65 (48/52)	7642-15-1 (cis) 14850-23-8 (trans)	81	0	
b	Et	Et	Cl	pure[f]	*c* (51/49)	7642-09-3	59	0	
c	H	Ph	Br	1:1	34	13269-52-8 (cis) 100-42-5 (trans)	49	37	38401-39-7
d	CH_3	Ph	Br	1:1	49 (92/8)	766-90-5 (trans) 873-66-5 (trans)	76	19	67069-94-7
e[d]	Ph	Ph	Br	1:3	94 (96/4)	645-49-8 (cis) 103-30-0 (trans)	68	2	67-69-93-6

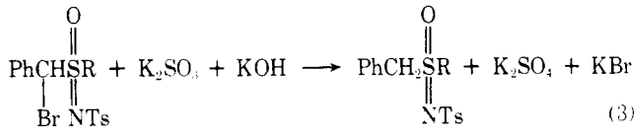
[a] Determined by NMR. [b] Control experiments on the isolation of 3 revealed mechanical loses of 10–20%. [c] Because of volatility the yield was not determined. [d] The reaction was run in aqueous dioxane/KOH. [e] Registry no.: 67070-02-4. [f] Registry no.: 67070-01-3.

this case, the isomer with the aryl groups trans is more stable) occurs prior to loss of SO_2 (eq 2).[6]



(2)

There remains the need for clarification of the mode of production of **4** (Table I). It is believed that potassium sulfite produced in the 1,3-elimination process (Scheme II) may be the agent responsible for the reduction of the bromo sulfoximines to sulfoximines (eq 3). Apparently α-chloro sulfoximines are not as readily reduced with sulfite.[7]



(3)

Experimental Section

The preparation of the following compounds has been reported in an earlier paper:[3] *S*-butyl-*S*-(1-chlorobutyl)sulfoximine; *S*-butyl-*S*-(1-chlorobutyl)-*N*-(*p*-tolylsulfonyl)sulfoximine; *S*-(1-chloropropyl)-*S*-propyl-*N*-(*p*-tolylsulfonyl)sulfoximines.

S-Butyl-S-(1-chlorobutyl)-N-methylsulfoximine. To 0.807 g (3.81 mmol) of diastereomerically pure *S*-butyl-*S*-(1-chlorobutyl)-sulfoximine dissolved in 25 mL of dichloromethane and cooled to 0 °C was added 0.5 g of anhydrous potassium carbonate and 0.586 g (3.86 mmol) of trimethyloxonium fluoroborate. The mixture was stirred at 0 °C for 30 min and then at room temperature for 18 h. After filtering, anhydrous ammonia was bubbled through the dichloromethane solution. A white precipitate of ammonium fluoroborate was formed and removed by filtration. The filtrate was washed with two 25-mL portions of water, dried ($MgSO_4$), and concentrated by rotary evaporation to give 0.649 g of a colorless oil. Column chromatography gave 0.566 g (57%) of the desired *N*-methyl derivative. By NMR only one diastereomer was present.

Amination of Sulfoxides with Mesitylsulfonyloxyamine.[8] Several unsubstituted sulfoximines were obtained by the method of Tamura and co-workers. Treatment of a dichloromethane solution of the sulfoxide with mesitylsulfonyloxyamine followed by a basic workup gave the following sulfoximines: *S*-benzyl-*S*-methylsulfoximine (95% yield; fine white needles from benzene–pentane; mp 81–82 °C); *S,S*-dibenzylsulfoximine (84% yield; white needles from methanol; mp 169–170 °C); *S,S*-dibutylsulfoximine (71.9%; colorless oil).

S-Benzyl-S-methyl-N-(p-tolylsulfonyl)sulfoximine was prepared by reaction of *S*-benzyl-*S*-methylsulfoximine with *p*-toluenesulfonyl chloride in pyridine in 73% yield as a white solid, mp 128–129 °C (pentane–ether).

S-Benzyl-S-ethyl-N-(p-tolylsulfonyl)sulfoximine. This material was isolated in 20.8% yield as a white crystalline solid, mp 102.5–103 °C, by reacting the corresponding sulfoxide with *p*-toluenesulfonyl azide in the presence of Raney–copper catalyst.[9]

S,S-Dibenzyl-N-(p-tolylsulfonyl)sulfoximine. Method A. This material was isolated in 27.6% yield as a white crystalline solid, mp 166–167 °C, by reacting the corresponding sulfoxide with *p*-toluenesulfonyl azide in the presence of Raney–copper catalyst. **Method B.** Treatment of *S,S*-dibenzylsulfoximine with 1 equiv of *p*-toluenesulfonyl chloride in pyridine gave the derivative in 43.4% yield, mp 166–167 °C (pentane–ether).

Bromination of S-Alkyl-S-benzyl-N-(p-tolylsulfonyl)sulfoximines. A flame-dried reaction vessel was charged with sodium hydride (6.2 mmol). While maintaining a nitrogen atmosphere, the oil from the sodium hydride dispersion was removed by washing with several small portions of pentane. The last traces of pentane were evaporated in a stream of nitrogen. After adding 5 mL of dimethylformamide (DMF) (distilled from CaH_2), the stirring mixture was cooled in an ice bath. The addition of the sulfoximine (6.0 mmol) in DMF (5 mL) was made slowly via syringe. Hydrogen evolved smoothly for about 40 min, producing a bright red solution of the anion. This solution was added in one portion to a cold (0 °C) solution of bromine (7.0 mmol) in DMF (7 mL). The addition was made by immersing the tip of the syringe beneath the stirring bromine solution. After stirring at room temperature for 30 min the orange solution was poured into 50 mL of saturated ammonium chloride and extracted with three 75-mL portions of chloroform. The extracts were then washed with 50 mL of 1 M Na_2SO_3 solution and concentrated by rotary evaporation. The residual oil was redissolved in a mixture of 300 mL of diethyl ether and 40 mL of chloroform and washed with water. The crude bromo sulfoximines were obtained by drying and concentration of the extracts.

S-(1-Bromo-1-phenylmethyl)-S-methyl-N-(p-tolylsulfonyl)sulfoximine (1c). The crude oil obtained by the general procedure was subjected to thick-layer chromatography (silica gel/ether, developed twice). A 26.5% yield of a diastereomeric mixture (1:1) of the bromo sulfoximines was obtained. Fractional crystallization effected partial separation of the diastereomers. One diastereomer was a white solid, mp 143–145 °C dec, while the other was an oil.

S-(1-Bromo-1-phenylmethyl)-S-ethyl-N-(p-tolylsulfonyl)sulfoximine (1d). A diastereomeric mixture of the bromo sulfoximines was isolated in 26.9% yield by thick-layer chromatography (silica gel/diethyl ether–cyclohexane (4:1), developed three times). A dichloromethane solution of the oil obtained from the chromatography was decolorized with activated charcoal. Addition of anhydrous ether precipitated the bromo sulfoximines as white solid, mp 118–124 °C dec. An NMR spectrum of the crystals obtained prior to the chromatography showed a diastereomeric ratio of 1:1.

S-Benzyl-S-(1-bromo-1-phenylmethyl)-N-(p-tolylsulfonyl)sulfoximine (1e). A diastereomeric mixture of the bromo sulfoximines was isolated as a white crystalline solid, mp 162–166 °C (ether), by thick-layer chromatography (silica gel/30% ether–cyclohexane, developed 12 times). Based on the weight and NMR spectrum of the crude yellow crystals obtained from the general procedure a yield of 61.8% was obtained. The diastereomeric ratio was 1:3.

Reaction of α-Halo Sulfoximines with Potassium Hydroxide. To the halo sulfoximine (1.0 mmol) in 10 mL of methanol was added 6 mL of 1 N KOH. The mixture was refluxed. The disappearance of sulfoximine was monitored by TLC (silica gel/ether). The reaction mixture was cooled, saturated with sodium chloride, and extracted with pentane. The pentane extracts were analyzed for alkene content by gas chromatography using a silver nitrate–ethylene glycol column. The basic solution was extracted with chloroform; the extract was washed with water, dried, and concentrated to give recovered sulfoximine and/or sulfinamide. The basic aqueous phase was made acidic to litmus with 3 M sulfuric acid and extracted with chloroform; the extract was washed, dried, and concentrated to give *p*-toluenesulfonamide when present.

Reaction of S-Benzyl-S-bromobenzyl-N-(p-tolylsulfonyl)-sulfoximine (1c) with Potassium Hydroxide. To 0.085 g (0.18 mmol) of a diasteromeric mixture (1:3) of bromo sulfoximines **1c** in 8.0 mL of aqueous dioxane (67% by volume) was added 0.6 mL of 0.1 N KOH (6 equiv). The mixture was refluxed 30 min. The loss of bromo sulfoximine was monitored by TLC (silica gel/ether). After cooling, 5 mL of saturated sodium chloride was added and the solution was acidified with 10% HCl. The solution was extracted with chloroform. The extracts were dried ($MgSO_4$) and concentrated to give 0.052 g of a mixture of *cis*- and *trans*-stilbene (93.5%), *S*-dibenzyl-*N*-(*p*-tolylsulfonyl)sulfoximine (1.7%), and *p*-toluenesulfonamide (67.5%) (mp 136–138 °C). These compounds were identified by GLC, NMR, IR, and TLC. VPC analysis (Apiezon L) showed 96.3% *cis*- and 3.7% *trans*-stilbene. On this column the cis isomer elutes first and then the trans.

Acknowledgment. This research was supported by a grant from the National Science Foundation.

Registry No.—**1c** isomer 1, 67070-00-2; **1c** isomer 2, 67069-99-2; **1d** isomer 1, 67069-98-1; **1d** isomer 2, 67069-97-0; **1e** isomer 1, 67113-89-7; **1e** isomer 2, 67113-90-0; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximinie isomer 1, 67069-96-9; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine isomer 2, 67113-99-9; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine-d_3 isomer 1, 67069-92-5; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine-d_3 isomer 2, 67069-89-0; *S*-butyl-*S*-(1-chlorobutyl)sulfoximine, 67069-95-8; mesitylsulfonyloxyamine, 36016-40-7; $MeSOCH_2Ph$, 824-86-2; *S*-benzyl-*S*-methylsulfoximine, 38401-38-6; $PhCH_2SOCH_2Ph$, 621-08-9; *S,S*-dibenzylsulfoximine, 67113-91-1; BuSOBu, 2168-93-6; *S,S*-dibutylsulfoximine, 22133-03-5; $EtSOCH_2Ph$, 2843-92-7; 1-butanesulfinamide, 67069-88-9.

Supplementary Material Available: Analytical and spectral data of the compounds discussed in this paper (3 pages). Ordering information is given on any current masthead page.

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(7) In an experiment performed by Dr. Susan Goff it was found that *S*-(bromomethyl)-*S*-methyl-*N*-tosylsulfoximine was reduced to *S,S*-dimethyl-*N*-tosylsulfoximine by potassium sulfite in refluxing methanol.
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Rearrangement Reaction of 1-Chloro-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone with Potassium Phthalimide

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Treatment of 1-chloro-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone with potassium phthalimide in acetonitrile resulted in skeletal rearrangement with the formation of 1-phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone. The structure of the rearrangement product was established by independent synthesis and mass spectrometry. The isolation of some intermediates from the reaction mixture gave evidence for the mechanism of this reaction; these mechanistic considerations guided the successful synthesis of 1-phthalimido-4-[*p*-(carbomethoxy)-thiophenoxy]-2-butanone.

As part of a continuing program[1-6] aimed at developing folate analogues that are altered at the C^9–N^{10} bridge region for possible use as anticancer agents,[7] we were interested in the synthesis of 11-thiohomofolic acid, which is an analogue of homofolic acid.[8] At the outset, we explored methods for the construction of the partial side chain **2**, which could eventually be elaborated to the title compound **1**. In this regard, we investigated the reaction between chloro ketone **5** and potassium phthalimide. Chloro ketone **5** was conveniently prepared by the nucleophilic addition of *p*-carbomethoxythiophenol[4] to hydroxymethyl vinyl ketone[9] and subsequent treatment of the resulting addition product with thionyl chloride.

Treatment of 1 equiv of chloro ketone **5** with a solution of 2 equiv of potassium phthalimide in acetonitrile containing crown ether for 4 h at ambient temperature and subsequent workup of the reaction mixture gave a product that displayed NMR resonances at 7.9 (d, J = 9 Hz, 2 H), 7.8 (c, 4 H), 7.3 (d, J = 9, 2 H), 3.97 (t, J = 7, 2 H), 3.9 (s, 3 H), 3.8 (s, 2 H), and 3.09 (t, J = 7, 2 H) ppm. These resonances, although they appeared to be consistent with the expected structure **3a**, were proved to be due to the alternate structure **4a**. This compound, on reaction with hydroxylamine, gave an oxime and on ketalization with ethylene glycol gave a crystalline ketal. Treatment of the oxime with hydrazine, in a standard hydrazinolysis reaction, liberated an aminoacetonyl oxime, which was different from **2a**, but reacted with 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine[4] to obtain an intermediate (**7a**). This reaction product, possessing spectral characteristics and giving analytical data consistent with either structure **7a** or **8a**, was deprotected at the carbonyl function using trifluoroacetic acid and 1 N HCl, as previously described.[5] The deprotected nitro ketone thus obtained was subjected to the dithionite reduction and one-step cyclization oxidation technique to generate the homopteroic acid analogue **9**.[4,5,10] Although the dithionite reduction of the nitro group to the amino group worked well, the subsequent cyclization of the pyrimidine to the dihydropteridine did not occur. Repetition of the same reaction sequence using a ketal protective group also resulted in complete failure of its transformation to the pteridine. Since several analogous amino ketones were readily cyclized to the pteridines, and no failures were reported in literature in using such an approach to the general synthesis of pteridines, it became apparent that the crown ether reaction product between chloro ketone **5** and potassium phthalimide did not have the expected structure **3a**. Since this product was a ketone, which could easily be converted to an oxime and an ethylene ketal, the alternate structure **4a** was proposed for this product. Indeed, if this product had structure **4a** rather than **3a**, then the failure to construct the pteridine ring using this material can easily be understood. These expectations were proved correct (vide infra). The transformations are summarized in Scheme I.

In order to prove that the crown ether reaction product has structure **4a**, an unambiguous synthesis of this material was undertaken. Reaction of phthalic anhydride with β-alanine gave *N*-(3-carboxypropyl)phthalimide (**13**), which was converted to an acid chloride by reaction with thionyl chloride. Treatment of the acid chloride with ethereal diazomethane gave the diazo ketone **14**, which was converted to the corresponding chloromethyl ketone **15** by standard procedures.[11] Reaction of *p*-(carbomethoxy)thiophenol[4] with **15** was carried out in acetone using 1 molar equiv of anhydrous sodium carbonate; subsequent workup of the reaction mixture gave a product that was identical with the crown ether reaction product in all respects (TLC, NMR, mp). Thus, the structure of the product obtained by reaction of chloromethyl ketone **5** with potassium phthalimide was unequivocally established as **4a**.

Mechanism of the Reaction

When equimolar amounts of chloromethyl ketone **5** and potassium phthalimide were allowed to react in the presence of crown ether using acetonitrile as a solvent, it was observed by monitoring the reaction by TLC that a product was being

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