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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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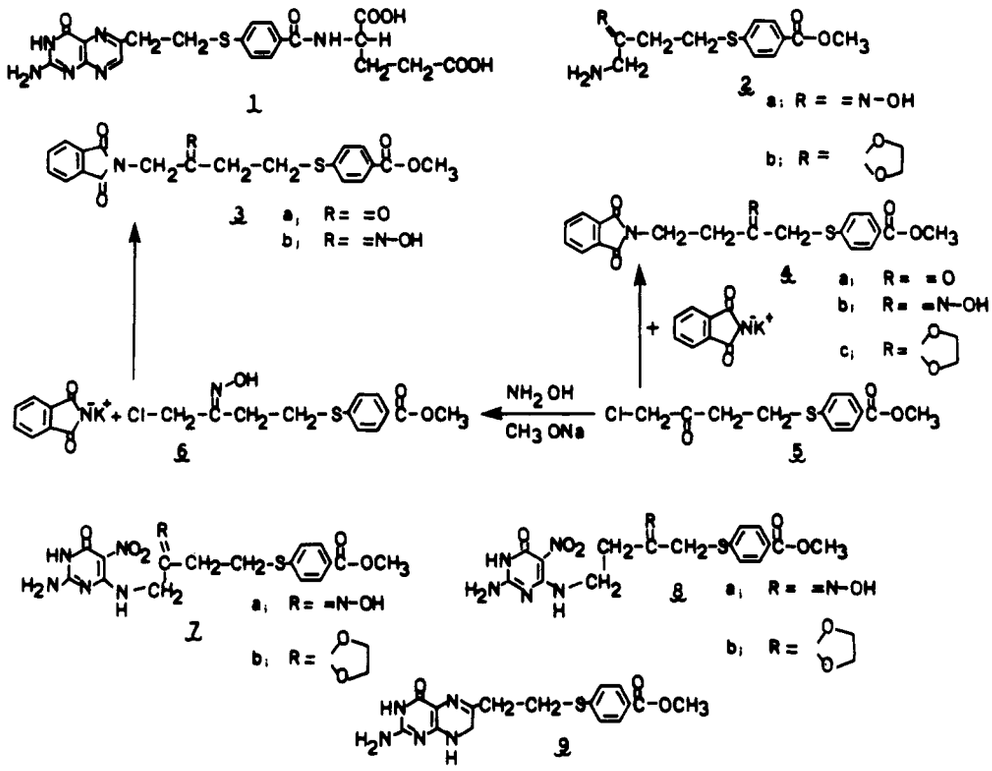
Scheme I

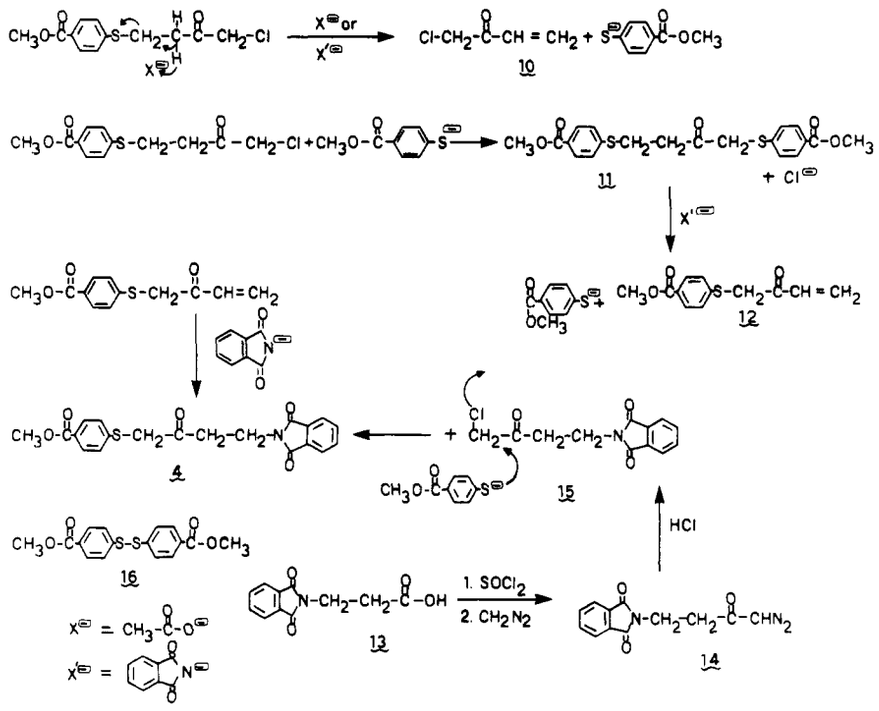


formed in the reaction mixture that was less polar than **4a**. Under these conditions, this product predominates; only very little **4a** is formed (~10%). However, addition of 1 equiv more of potassium phthalimide at this stage resulted in the complete disappearance of this material with the concomitant formation of **4a**. Therefore, it became clear that this reaction occurred in a stepwise fashion; **4a** is formed by reaction of potassium phthalimide with the less polar intermediate. In order to prove this assumption, conditions were optimized so that the less polar intermediate (hereto referred to as **11**) could be isolated and characterized. Compound **11** had a molecular weight of 404, as determined by mass spectrometry, and showed NMR resonances in TFA at 7.95 (d, 4 H), 7.4, 7.33 (d d, 4 H), 4.06 (s, 6 H), 3.93 (s, 2 H), and 3.25 (c, 4 H) ppm. The formation and isolation of **11** requires the formation of *p*-(carbomethoxy)thiophenolate anion in the reaction mixture, which in turn should result from a reverse Michael addition to chloro ketone **5** by potassium phthalimide. If this assumption was correct, then we reasoned that weak nucleophiles, such as sodium acetate, might be used to generate a phenolate anion from **5**, which on reaction with chloro ketone **5** should yield intermediate **11** in quantitative yield. This is because we had prior knowledge that intermediate **11** is stable to sodium acetate in boiling methanol. Thus, treatment of a solution of **5** in boiling methanol with excess sodium acetate gave intermediate **11** in quantitative yield, as required by the proposed mechanism. Next, the fate of 4-chloro-3-butenone, which is a compulsory co-product of the reaction between **5** and sodium acetate, was investigated. Evaporation of the reaction mixture, after removal of **11** by filtration, extraction of the residue with ether, and evaporation of the ether layer, yielded an oil that gave an NMR spectrum that was identical with 4-chloro-3-butenone. This compound, a sample of which was available, was found to be stable to sodium acetate under conditions of the above reaction. These experimental results clearly demonstrated the mechanism by which **11** was generated from **5** on treatment with potassium phthalimide.

Next, we examined the mechanism of the subsequent steps by which **11** was converted to **4a**. Treatment of **11** with potassium phthalimide in acetonitrile, with or without the presence of crown ether, resulted in the formation of two products, one of which was identical with **4a**. The other product, which was less polar than **4a**, was identified as **16** by isolation after workup and chromatography of the reaction mixture. This material was identical in all respects with an authentic sample[4] of **16**. On the other hand, by monitoring the reaction by TLC until all **11** had disappeared, evaporation and ether extraction of the reaction mixture resulted in the isolation of *p*-(carbomethoxy)thiophenol.[4] The isolation of *p*-(carbomethoxy)thiophenol and dimer **16** from the reaction mixture gave evidence for the mechanism of formation of **4a** from **11**. It is postulated that attack of potassium phthalimide on **11** resulted in the formation of an enolate that collapsed to an intermediate **12**; a retro Michael reaction and subsequent addition of phthalimide to **12** in a Michael addition resulted in the formation of **4a** with the liberation of the resonance-stabilized thiophenolate anion. The enhanced stability of **4a** toward potassium phthalimide, compared to **11**, together with the formation of a thermodynamically more stable intermediate (**12**) from **11** facilitates the formation of **4a**. A direct nucleophilic attack of phthalimide anion on **11** with concurrent displacement of the thiophenolate anion is unlikely because one would anticipate the production of both **4a** and **3a** by this mechanism.

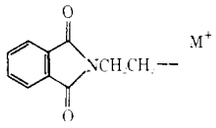
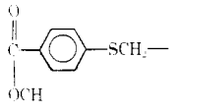
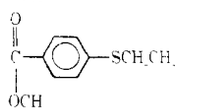
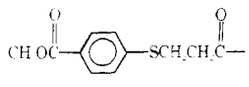
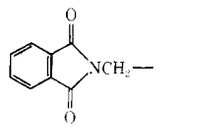
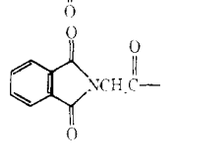
From the preceding discussion, it is apparent that the initial formation of the enolate from **5** leads to the formation of **11**. Due to the ease of formation of **12**, nucleophillic displacement reactions on **5** results in the formation of rearranged products. Therefore, any attempt involving direct displacement of chlorine of **5** by a nucleophile should be carried out under conditions which avoid enolate formation. On reaction of **5** with H_2NOH, chloro ketone **5** could be converted to the chloroacetonyl oxime **6** under carefully controlled conditions. Reaction of **6** with potassium phthalimide in acetonitrile or DMF resulted in the formation of an oxime **3b**, which was not identical with **4b**. Deprotection of the carbonyl group of **3b** with aqueous TFA resulted in the formation of a ketone, which was an isomer of **4a** but was not identical with it. The compound showed relevant NMR signals at 7.98 (m, phthalimido, 4 H), 7.84, 7.35 (d, d, arom, 4 H), 4.53 (s, methylene, 2 H), 3.93

Scheme II



(s, carbomethoxy, 3 H), and at 3.29 and 2.93 (t, t, ethylene, 4 H) ppm and had a different R_f value and melting point. Structure **3a** was assigned to this product after comparing its mass spectral fragmentation pattern with that of **4a.** The relevant fragments and their respective *m/e* values are presented in Table I. The presence of fragments representing *m/e* values of 188, 195, and 223 in the mass spectrum of **3a** and the total absence of these fragments in the spectrum of **4a** establishes the structure of **3a** as written. The mass spectrum of **4a** shows a fragment representing an *m/e* value of 174, which is completely absent in the spectrum of **3a.** Since this value of 174 represents the *N*-ethylphthalimide fragment, the structure of **4a** is also correct as written. In addition, fragments having *m/e* values of 160 and 181 are generated from both compounds, the former being nine times more intense and the latter five times less intense for **3a** compared to **4a.** These observations are in complete agreement with the proposed structures for both **3a** and **4a.**

Table I

fragment	mass to charge ratio (*m/e*) 4a	3a
	404 174	404 absent
	181	181
	absent	195
	absent	223
	160	160
	absent	188

Experimental Section

Melting points are uncorrected and were determined on a Fisher-Johns apparatus. NMR spectra were run in CF_3COOH or $CDCl_3$ on a 90-MHz Perkin Elmer R-32 spectrometer with Me_4Si as internal lock signal. Field strengths of the various proton resonances are expressed in parts per million and coupling constants in hertz. Peak multiplicity is depicted as usual: s, singlet; d, doublet; t, triplet; q, quartet; br, broadened singlet or unresolved miltiplet; and c, complex signal, the center of which is given. UV spectra were determined on a Beckman Model 25 spectrophotometer. Mass spectra were run at Research Triangle Institute in North Carolina. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Yields represent the actual amount of pure compound isolated, assuming 100% reaction.

1-Chloro-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone (5). A solution of *p*-(carbomethoxy)thiophenol, 3.36 g (20 mmol) in 10 mL of benzene, was added to a solution of 2.5 g (22 mmol) of chloromethyl vinyl ketone in 10 mL of benzene under nitrogen. To this mixture 5 drops of triethylamine was added and stirred for 30 min at 25 °C. The solution was then evaporated to dryness in vacuum and the residue was recrystallized from acetone and hexane: mp 94–95 °C; yield 5.15 g (94.5%); NMR ($CDCl_3$) 8.0, 7.3 (d, d arom, 4 H), 4.08 (s, chloromethyl, 2 H), 3.86 (s, carbomethoxy, 3 H), and at 3.21 and 3.0 (t, t, ethylene, 4 H) ppm. Anal. Calcd for $C_{12}H_{13}ClO_3S$: C, 52.85; H, 4.80; Cl, 13; S, 11.75. Found: C, 53.0; H, 4.77; Cl, 12.83; S, 11.86.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone (3a). A solution of 2.725 g (10 mmol) of **5** was made in 30 mL of THF and added to a solution prepared by dissolving successively 810 mg (15 mmol) of sodium methoxide and 1.4 g (20 mmol) of hydroxylamine hydrochloride in 200 mL of methanol. After stirring for 1 h, the solution was evaporated to dryness, and the residue thus obtained was suspended in 100 mL of water and extracted repeatedly three times with 100 mL each of chloroform. The combined chloroform layer was washed with water and dried with Na_2SO_4. The chloroform layer was evaporated to dryness to obtain **6:** NMR ($CDCl_3$) 7.86, 7.34 (d, d, J = 9 Hz, aromatic, 4 H); 4.23 (s, chloromethyl, 2 H), 3.80 (s, carbomethoxy, 3 H), 3.23 and 2.83 (t, t, ethylene, 4 H) ppm. Treatment of this compound with potassium phthalimide, as described for the preparation of **4a,** gave **3b:** 80% yield; mp of 145 °C; NMR ($CDCl_3$) 7.87 (c, phthalimido, arom, 6 H), 7.37 (d, J = 9 Hz, arom, 2 H), 4.47

(s, methylene, 2 H), 3.95 (s, carbomethoxy, 3 H), and at 3.2 and 2.7 (t, t, J = 8 Hz, 4 H) ppm. Deprotection of this oxime was accomplished at 55 °C with the use of a 1:1 (v/v) mixture of TFA/H_2O for 30 min. The desired compound **3a** was isolated after dilution and extraction of the reaction mixture with chloroform and was freed of minor impurities by column chromatography over silica gel CC_4. The compound was eluted in chloroform and crystallized from methanol as silky needles, mp 136–138 °C. The rearranged compound **4a** was found to be more polar than **3a** on silica gel CC_4 TLC plates using chloroform as the solvent. Anal. Calcd for $C_{20}H_{17}NO_5S$: C, 62.64; H, 4.47; N, 3.65; S, 8.36. Found: C, 62.48; H, 4.47; N, 3.58; S, 8.17.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone (4a). A solution of 2.73 g (10 mmol) of chloromethyl ketone **5** in 20 mL of acetonitrile was added dropwise to a suspension of 3.7 g (20 mmol) of potassium phthalimide in a solution of 2.64 g of 18-crown-6 ether in 80 mL of acetonitrile. This mixture was stirred at 25 °C for 6 h and filtered, and the filtrate was evaporated to dryness. The residue thus obtained was triturated with water, and the slightly yellow product was collected by filtration and recrystallized from methanol: mp 126–127 °C; yield 2.0 g. Anal. Calcd for $C_{20}H_{17}NO_5S$: C, 62.64; H, 4.47; N, 3.65; S, 8.36. Found C, 62.46; H, 4.30; N, 3.55; S, 8.43.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone Oxime (4b). Compound **4a**, 3.83 g (10 mmol), was dissolved in 70 mL of 1:1 mixture of pyridine and absolute alcohol (v/v). To this solution 695 mg (10 mmol) of hydroxylamine hydrochloride was added and the mixture was heated under reflux for 2 h and then evaporated to remove solvent. The resulting gum was triturated with water, and the solid thus formed was filtered and recrystallized form ethyl acetate/hexane: mp 152–153 °C; yield 3.56 g. This compound was not identical with **3b** in all respects (TLC, NMR, mp). For example, the methylene resonance of **4b** appeared as a singlet at 3.8, and the ethylene protons as two triplets as 4.0 and 2.9 ppm. Anal. Calcd for $C_{20}H_{18}N_2O_5S$: C, 60.29; H, 4.55; N, 7.03; S, 8.05. Found: C, 60.40; H, 4.58; N, 6.92; S, 8.07.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone Ethylene Ketal (4c). In a round-bottom flask 1.99 g (5 mmol) of **4a** was suspended, and 10 mL of ethylene glycol was added to it, followed by the addition of 200 mg of *p*-toluenesulfonic acid monohydrate. The mixture was heated to ~150 °C, when most of the ketone dissolved. To this hot solution, benzene was very carefully added, and the flask was attached to a Dean–Stark apparatus and refluxed with continuous removal of water for 8 h. After this period, benzene was removed by flash evaporation, and 3.0 g of solid potassium bicarbonate was added to the flask and diluted to 500 mL with a saturated solution of potassium bicarbonate in water. The precipitated solid was filtered and recrystallized from methanol: yield 1.5 g; mp 103 °C. Anal. Calcd for $C_{22}H_{21}NO_6S$: C, 61.83; H, 4.92; O, 22.48. Found: C, 61.67; H, 4.80; O, 22.31.

Hydrazinolysis of 3b and 4b: Preparation of 7a and 8a. The experimental procedures were carried out in an analogous fashion as previously reported from our laboratory.[4-6] As a typical example, 1 equiv of either **3b** or **4b** was dissolved in the minimum required amount of absolute ethanol, and exactly 1 equiv of 95% hydrazine hydrate was added to it under an atmosphere of N_2. The reaction was frequently monitored by TLC for the complete disappearance of the starting material. When complete, which usually takes about 72 h at 25 °C, the solution was treated with 1 molar equiv of 1 N HCl, evaporated to dryness, and extracted with water. The clear aqueous solution was basified to pH 8.0 by the addition of NH_4OH, and the gummy material thus obtained was isolated by extraction with ethyl acetate. The ethyl acetate layer was washed, dried with Na_2SO_4, filtered, and evaporated to a gum. The NMR spectrum did not exhibit resonances due to the phthalimide moiety, but was otherwise consistent with the required structures in both instances. An alcoholic solution of this amine was treated with a solution of 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine in absolute alcohol and refluxed for 1.5 h in the presence of 1 molar equiv of *N*-methylmorpholine. Both compounds **7a** and **8a** were precipitated during the reaction and were removed by filtration, washed, and dried to obtain analytical samples. The compounds were formed in ~60–70% yield based on the amine used for the reaction: mp 145–148 °C (**7a**) and 135–136 °C (**8a**). Only one of these two isomeric compounds (**7a**) could be converted to the pterdine structure **9** by subsequent synthetic procedures. Details of these reactions will be published elsewhere. Anal. Calcd for $C_{16}H_{18}N_6O_6S$: C, 45.5; H, 4.29; N, 19.89. Found for **8a**: C, 45.62; H, 4.18; N, 19.76. Found for **7a**: C, 45.27; H, 4.32; N, 20.07.

***N*-(4-Chloro-3-oxobutyl)phthalimide (15).** Treatment of *N*-(2-carboxyethyl)phthalimide with thionyl chloride according to the procedure of Viscontini[11] gave the corresponding acid chloride (mp 108 °C). A solution of 4.75 g (20 mmol) of this acid chloride in dry THF was treated with ethereal alcohol-free diazomethane prepared from 10 g of diazald at 0–5 °C. After 30 min, gaseous HCl was passed through the reaction mixture for 5 min. The solution was stirred for an additional 30 min and evaporated to dryness in vacuum. The residue thus obtained was crystallized from methanol: mp 109–110 °C; yield 4.2 g. The compound exhibited NMR resonances expected of the desired structure. Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.26; H, 3.98; Cl, 14.12; N, 5.57. Found: C, 57.31; H, 4.10; Cl, 14.16; N, 5.66.

Preparation of 4a from 15 and *p*-(Carbomethoxy)thiophenol. To a mixture of 503 mg (2 mmol) of **14**, 336 mg (2 mmol) of *p*-(carbomethoxy)thiophenol, and 212 mg (2 mmol) of anhydrous sodium carbonate, 10 mL of acetone was added and the mixture was stirred under nitrogen for 6 h. The white suspension thus obtained was evaporated to dryness, diluted with 50 mL of water, and extracted with ethyl acetate. The ethyl acetate layer was evaporated after washing and the residue was crystallized from methanol: mp 126–127 °C (undepressed by mixing with **4a**); yield 720 mg. This compound was identical in all respects with **4a** prepared by the crown ether reaction.

Reaction of Chloromethyl Ketone 5 with Sodium Acetate: Preparation of 11. A solution of 5.45 g (20 mmol) of **5** in 300 mL of hot methanol was treated with 10.88 g (80 mmol) of sodium acetate trihydrate. The clear solution thus obtained was heated to boiling on a hot plate and the volume was reduced to ~150 mL when white crystals of **11** began to separate. At this point, the reaction mixture was allowed to cool to 25 °C, and after 1 h the crystals were collected by filtration, washed with water, and recrystallized from methanol: yield 3.92 g (theoretical yield 4.04 g); mp 167 °C. Anal. Calcd for $C_{20}H_{20}O_5S_2$: C, 59.41; H, 4.95; S, 15.84. Found: C, 58.98; H, 4.94; S, 15.53.

The original filtrate prior to washings was evaporated at 25 °C, in vacuum, and the residue was extracted repeatedly with ether. The combined ether layer was dried over anhydrous Na_2SO_4 and evaporated. The NMR spectrum of the oily resudue thus obtained was identical with an authentic spectrum of 4-chloro-3-butenone.

Reaction of 11 with Potassium Phthalimide: Formation of 4a and Isolation of 16. To a mixture of equimolar amounts of **11** and potassium phthalimide (1 mmol each) 30 mL of acetonitrile was added, followed by the addition of 100 mg of 18-crown-6 ether. The mixture was allowed to stir at 25 °C, and the reaction was frequently monitored by TLC for the complete disappearance of **11**. When all of **11** had reacted, which took 2.5 h, the reaction mixture was evaporated to dryness at 25 °C. Ice was added to the residue and triturated, and the solid thus obtained was separated by filtration. The filtrate was acidified to pH 4.0 by glacial acetic acid and the solution was extracted with ether. The ether layer was washed, dried with Na_2SO_4, and on evaporation gave a solid residue that was identified as *p*-(carbomethoxy)thiophenol by comparison with an authentic sample. The solid residue was purified by chromatography over silica gel CC-7. Benzene eluted a crystalline material from the column that was identified as **16**. Chloroform eluted **4a**, which was identical in all respects with the material obtained by reaction of potassium phthalimide with **5**.

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Registry No.—**3a**, 67425-98-3; **3b**, 67425-99-4; **4a**, 67426-00-0; **4b**, 67426-01-1; **4c**, 67426-02-2; **5**, 67426-03-3; **6**, 67426-04-4; **7a**, 67416-04-4; **7a**, 67426-05-5; **8a**, 67426-06-6; **11**, 67426-07-7; **13**, 3339-73-9; **13** acid chloride, 17137-11-0; **14**, 7504-49-6; **15**, 65495-45-6; **16**, 35190-68-2; *p*-(carbomethoxy)thiophenol, 6302-65-4; chloromethyl vinyl ketone, 25476-89-5; potassium phthalimide, 1074-82-4; 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine, 1007-99-4.

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