An Investigation of the *ortho*-Claisen Rearrangement in Pyrimidines[1]

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ortho-Claisen rearrangement of a 4-crotoxypyrimidine has been shown to proceed with inversion of the migrating group. A cross-over experiment has demonstrated the rearrangement to be intramolecular. Rearrangement of a 4-alloxypyrimidine gives, in addition to the 5-allyl product, the corresponding 3-allyl-4-pyrimidone. Both products result from irreversible, competing rearrangements.

In a recent paper, Minnemeyer[2] reported the application of the Claisen rearrangement to the pyrimidine ring system. A number of 2-substituted 4-alloxypyrimidines were rearranged to give the corresponding 2-substituted 4-hydroxy-5-allylpyrimidines.[3]

While the thermal rearrangements of alkyl groups to adjacent nitrogen atoms in 2- and 4-pyrimidyl ethers have been reported many times,[4] the above reaction is unique in that rearrangement of an allyl group to an adjacent carbon atom takes place when the possibility for rearrangement to an *ortho*-nitrogen atom also exists. Yields of C-alkylated products varied widely with the substituent at the 2-position but were generally within the range 2–28%.

The *ortho*-Claisen rearrangement is generally believed to be an intramolecular reaction proceeding through a six-membered cyclic transition state.[5] Cross-over studies have shown that cleavage of allyl phenyl ethers into separate fragments does not take place when these compounds undergo *ortho*-Claisen rearrangement.[6,7]

The rearrangement of allyl pyrimidyl ethers appears to be formally analogous with the *ortho*-Claisen rearrangement of allyl phenyl ethers. However, reactions of the pyrimidine ring system differ sufficiently from those of the phenyl ring so that an *a priori* assumption that the same mechanism operates in the two reactions may not be justified.

It has been demonstrated that the *ortho*-Claisen rearrangement of allyl phenyl ethers proceeds with inversion of the migrating group.[8–10] To determine whether this inversion also takes place in allyl pyrimidyl ethers, 2-methylthio-4-crotoxypyrimidine (I) was synthesized. The infrared spectrum of I shows absorption at 1675 cm.$^{-1}$ due to the double bond stretching vibration of the —CH=CHCH$_3$ group and confirms the crotoxy structure of I.[11] In the corresponding alloxy ether[2] this absorption occurs at 1650 cm.$^{-1}$ and is consistent with the presence of the —CH=CH$_2$ group.[11]

Thermal rearrangement of I gave 2-methylthio-4-hydroxy-5-methallylpyrimidine (II). The identity of II was established by an unequivocal synthesis from 2-methylthio-2-pseudourea and ethyl 2-formyl-3-methyl-4-pentenoate (III). Croxall and Van Hook had established the methallyl structure of the formyl ester III by application of the reverse Claisen condensation to form ethyl 3-methyl-4-pentenoate which on hydrogenation yielded ethyl 3-methylpentanoate.[12] The pyrimidine from this condensation and that obtained by the rearrangement of I yielded identical infrared spectra. A mixed melting point gave no depression. It can therefore be concluded that inversion of the allyl group does take place during the *ortho*-Claisen rearrangement of allyl pyrimidyl ethers.

A cross-over experiment in which a mixture of 2-benzylthio-4-crotoxypyrimidine (IV) and 2-methylthio-4-alloxypyrimidine (V) were rearranged together gave no detectable intermolecular rearrangement products and indicated that the rearrangement proceeds by a normal intramolecular mechanism.[6,7] For this study IV was synthesized and rearranged to 2-benzylthio-4-hydroxy-5-methallylpyrimidine (VI). Pyrimidine V, 2-benzylthio-4-alloxypyrimidine (VII) and the corresponding rearranged 5-allylpyrimidines have been previously reported.[2]

Rearrangement of the crotoxypyrimidines, I and IV was found to take place readily at 245°. Markedly lower yields were obtained when these compounds were rearranged at higher temperatures. Since the rearrangements of V and VII had been conducted at 255°[2] these reactions were reinvestigated at 245°. Rearrangement was found to take place with no significant decrease in yield at the lower temperature. Yield data for the four rearrangements at 245° are summarized in Table I.

TABLE I

REARRANGEMENT OF ALLYL PYRIMIDYL ETHERS AT 245°

Reactant	Product	% Yield
VII	VIII	22–28
V	XV	20–25
IV	VI	26–38
I	II	28–32

Measurements of the rate of rearrangement of the ethers IV and V at 245° established that 25% of IV is converted to VI after two hours while 13% of V is rearranged to the corresponding 5-allylpyrimidine, XV, after the same time interval. After three hours at

(1) This investigation was supported by Grant CY-2857 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) H. J. Minnemeyer, J. A. Egger, J. F. Holland, and H. Tieckelmann, *J. Org. Chem.*, **26**, 4425 (1961).

(3) Throughout this paper compounds which can exist in either the lactim or lactam form will be called "hydroxypyrimidines." Compounds which are locked in the lactam form by the presence of substituents on nitrogen atoms will be called "pyrimidones."

(4) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 2001 (1930); H. J. Fisher, and T. B. Johnson, *ibid.*, **54**, 727 (1932); E. Bergmann and H. Heimhold, *J. Chem. Soc.*, 955 (1935).

(5) D. S. Tarbell, *Org. Reactions*, **II**, 22 (1944); E. S. Gould "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, pp. 644–649.

(6) C. J. Hurd and L. Schmerling, *J. Am. Chem. Soc.*, **59**, 107 (1937).

(7) N. L. Morse and J. F. Kincaid, Abstracts of the 102nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1941, p. M-11.

(8) L. Claisen and E. Tietze, *Ber.*, **58**, 275 (1925).

(9) C. J. Hurd and M. A. Pollak, *J. Org. Chem.*, **3**, 550 (1938).

(10) J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952).

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 36.

(12) W. J. Croxall and J. O. Van Hook, *J. Am. Chem. Soc.*, **72**, 803 (1950).

this temperature 35% of the crotyl ether, IV, has been converted to VI and 18% of the allyl ether, V, has been converted to XV, thus establishing that the two rearrangements occur simultaneously.

The composition of the rearrangement product of the mixture of IV and V was investigated using quantitative paper chromatography. This procedure established that less than 7% of IV could have been converted to the cross-over product, 2-benzylthio-4-hydroxy-5-allylpyrimidine (VIII) and that less than 3% of V could have been converted to the methylthio cross-over product, II, thus establishing that the rearrangement of IV and V proceeds without the formation of significant amounts of intermolecular products.[13]

It should be noted that while the result of the cross-over experiment rules out the formation of dissociated ions during rearrangement, it does not exclude the possibility that dissociation of the molecules into an intimate ion pair[14] within a single solvation shell could take place.

The rearrangement of allyl pyrimidyl ethers usually results in the formation of less than 40% of the 5-substituted product. To determine the composition of the remainder of the reaction mixture, the residue from a rearrangement of VII was investigated. Rearrangement of the allyl group of VII to the ring nitrogens would have given 2-benzylthio-3-allyl-4-pyrimidone (IX) and 2-benzylthio-1-allyl-4-pyrimidone (X).

For this work the N-allylpyrimidones IX and X were synthesized by treating 2-benzylthio-4-hydroxypyrimidine (XI) with allyl bromide in base. The reaction resulted in the formation of a tan, viscous oil which proved to be a mixture of IX, X, and the allyl pyrimidyl ether VII.[15]

Although assignment of N-1 and N-3 alkyl structures are commonly made in the pyrimidine literature without presenting supporting evidence,[16] the excellent work of Brown, Hoerger, and Mason,[17] Berson,[18] Cromwell,[19] and Mason,[20] provides a strong basis for the assignment of structures in N-alkylpyrimidones by investigation of their infrared and ultraviolet absorption spectra.[21]

A rearrangement of VII was carried out at 255° and a 24% yield of the 5-allyl rearrangement product, VIII, was filtered from solution. The filtrate was chromatographed on a neutral alumina column. The composition of the reaction mixture was found to be that shown in Table II.

No X was observed in the rearrangement mixture. It was found, however, that this material is unstable at temperatures above 230°. Attempts to distil an authentic sample under vacuum resulted in the formation of a white sublimable solid which tentatively has been identified as 1-allyl-2-thiouracil (XIV). The ultraviolet spectrum of XIV in neutral solution shows a single maximum at 270 mμ. In basic solution, two maxima are observed at 270 and 236 mμ, indicating the presence of an ionizable hydrogen. These spectra are identical with those reported by Shugar and Fox for 1-ethyl-2-thiouracil.[22] The infrared spectrum of XIV shows carbonyl absorption at 5.98 μ.[23] Careful chromatography of the reaction mixture failed to reveal the presence of even small amounts of XIV in fractions where this compound is known to be eluted. It can therefore be concluded that significant amounts of X are not formed during the rearrangement.

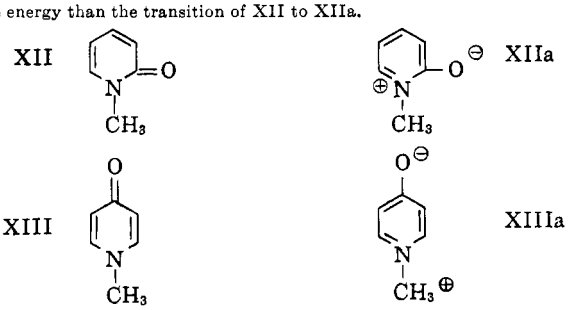
The possibility existed that the major products of the rearrangement of VII (*i.e.* VIII and IX) resulted from competing rearrangements to the 3 and 5 posi-

TABLE II

COMPOSITION OF REARRANGEMENT REACTION MIXTURE

2-Benzylthio-4-alloxypyrimidine	20%
2-Benzylthio-3-allyl-4-pyrimidone	30%
2-Benzylthio-4-hydroxy-5-allylpyrimidine[a]	24%
2-Benzylthio-4-hydroxy-5-allylpyrimidine[b]	10%
2-Benzylthio-4-hydroxypyrimidine	2%
Unidentified material	9%
Not eluted	5%
	100%

[a] Crystallized from solution on cooling and was removed by filtration. [b] Obtained by elution from the alumina column.



It has been observed that integrated intensity of the ultraviolet absorption is proportional to the charge separation involved in the limiting canonical form.[18] Thus, stronger absorption would be expected from the *para*-quinonoid structure of XIIIa than is observed in the *ortho*-quinonoid structure of XIIa.

In accord with these observations, the compound from allyl bromide and XI which has been assigned structure X shows a higher extinction coefficient and an absorption maximum at shorter wave length (ϵ = 23,400, λ_{max} = 236 mμ) than that compound which has been assigned structure IX (ϵ = 10,320, λ_{max} = 294 mμ).

Cromwell has observed that the carbonyl absorption band in α,β-unsaturated carbonyl compounds occurs at lower energy than the carbonyl band in α,β-α′,β′-unsaturated carbonyl compounds.[19] Carbonyl absorption is observed at 5.96 μ in the α,β-unsaturated compound IX, while this absorption occurs at 6.10 μ in the α,β-α′,β,′-unsaturated compound, X.

Shugar and Fox[22] have recorded the ultraviolet spectrum of 2-ethylthio-1-methyl-4-pyrimidone and 2-ethylthio-3-methyl-4-pyrimidone. The ultraviolet spectrum of the former is nearly identical with that of X while the spectrum of the latter is very similar to that of IX. This similarity would be expected since both the allylic double bond and the phenyl ring are insulated from the pyrimidine ring in IX and X and therefore act as isolated chromophores.

(13) The composition of the remainder of the cross-over rearrangement mixture was not investigated in the present work. Rearrangement of the allyl group to the *ortho* N atom will be the subject of a future investigation.

(14) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961); S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958); S. Winstein, E. Clippinger, A. H. Foinberg, and G. C. Robinson, *Chem. Ind.* (London), 664 (1954).

(15) The formation of ethers in reactions of this type has been previously reported. See T. B. Johnson and R. Moran, *J. Am. Chem. Soc.*, **37**, 2591 (1915).

(16) D. J. Brown, *Rev. Pure Appl. Chem.*, **3**, 115 (1953).

(17) D. J. Brown, C. Hoerger, and S. Mason, *J. Chem. Soc.*, 211 (1955).

(18) J. A. Berson, *J. Am. Chem. Soc.*, **75**, 3521 (1953).

(19) N. H. Cromwell, F. A. Miller, A. R. Jackson, R. L. Frank, and D. J. Wallace, *ibid.*, **71**, 3337 (1949).

(20) S. F. Mason, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," K. Schofield, ed., The Chemical Society, London, 1955.

(21) Berson[18] has measured the ultraviolet spectrum of 1-methyl-2-pyridone (XII) and 1-methyl-4-pyridone (XIII). The long wave length band associated with the *para*-quinonoid structure of XIII occurs at a shorter wave length than the long wave length band associated with the *ortho*-quinonoid structure of XII. Mason[20] explains that the transition from XIII to XIIIa brings about greater charge separation and therefore requires more energy than the transition of XII to XIIa.

(22) D. Shugar and J. J. Fox, *Bull. soc. chim. Belg.*, **61**, 293 (1952).

(23) An attempt was made to synthesize XIV by condensation of N-allylthiourea with the sodium salt of ethyl formylacetate. This reaction gave 3-allyl-2-thiouracil. The 1-allyl isomer was not formed.

tions or from an equilibrium between either or both of these positions and the 4 position.

A sample of IX was subjected to rearrangement conditions. Careful investigation of the reaction mixture failed to reveal the presence of any of the allyl pyrimidyl ether VII or the 5-allylpyrimidine, VIII. In a similar experiment, VIII was heated under conditions sufficient for the rearrangement of VII to VIII. No detectable amounts of VII or IX were formed. However, VIII did undergo slow decomposition to form the unidentified material which was observed in the mixture (9%) resulting from the rearrangement of VII.

The absence of VII when VIII and IX are subjected to rearrangement conditions rules out the possible existence of an equilibrium between the 4-position and the 3- and 5-positions and demonstrates the formation of VIII and IX from VII to result from irreversible, competing rearrangements of the allyl group from the 4 position to the 3 and 5 positions.

Experimental[24]

2-Methylthio-4-crotoxypyrimidine (I).—Sodium (1.84 g., 0.080 g.-atom) was dissolved in 20 ml. of crotyl alcohol and added to a solution of 12.8 g. (0.080 mole) of 2-methylthio-4-chloropyrimidine[25] dissolved in 20 ml. of crotyl alcohol. The mixture was allowed to stand at room temperature for 1 hr. Excess crotyl alcohol was removed at reduced pressure. The remaining oil was dissolved in ether and washed with water. After drying over magnesium sulfate, the ether was removed at reduced pressure and the resulting oil distilled to give 13.6 g. (86%) of product, b.p. 85° (1.3 mm.).

Anal. Calcd. for $C_9H_{12}N_2OS$: C, 55.07; H, 6.16; N, 14.27. Found: C, 55.47; H, 6.09; N, 14.44.

2-Benzylthio-4-crotoxypyrimidine (IV) was prepared in 78% yield by this procedure, b.p. 140° (0.04 mm.).

Anal. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.14; H, 5.92; N, 10.29. Found: C, 65.72; H, 5.92; N, 9.87.

2-Methylthio-4-hydroxy-5-methallylpyrimidine (II). A. By Rearrangement.—2-Methylthio-4-crotoxypyrimidine (I), 5.0 g., was dissolved in 15 ml. of N,N-diethyl-*m*-toluidine and refluxed at 245° for 6 hr. The residue was allowed to cool to room temperature and the product crystallized from solution after 1 hr. The crystals were collected on a Büchner funnel and washed with a small amount of ether. Removal of the solvent under reduced pressure gave a second crop of crystals for a total of 1.29 g. (26%). This material was recrystallized from 80% ethanol to give a white, crystalline solid, m.p. 131–132°.

Anal. Calcd. for $C_9H_{12}N_2OS$: C, 55.07; H, 6.16; N, 14.27. Found: C, 55.32; H, 6.23; N, 14.11.

2-Benzylthio-4-hydroxy-5-methallylpyrimidine (VI) was prepared in 32% crude yield by this procedure. Recrystallization from 80% ethanol gave a 24% yield of white crystalline solid m.p. 110–111°.

Anal. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.14; H, 5.92; N, 10.29. Found: C, 66.03; H, 5.80; N, 10.39.

B. From Ethyl 2-Formyl-3-methyl-4-pentenoate.—2-Methylthio-2-pseudourea sulfate (5.40 g., 0.0193 mole) was dissolved in 30 ml. of 10% sodium hydroxide. To this was added 6.55 g. (0.0385 mole) of ethyl 2-formyl-3-methyl-4-pentenoate[12] dissolved in 15 ml. of 95% ethanol. The resulting mixture was stirred at room temperature for several hours and allowed to stand overnight. The solvent was removed at reduced pressure and 70 ml. of water was added to the oily residue. The solution was acidified with glacial acetic acid. A white precipitate formed which was filtered, washed with water, collected, and dried, m.p. 130–132°.

A mixture melting point of products from methods A and B was not depressed. The infrared spectra of the two compounds are identical.

2-Benzylthio-1-allyl-4-pyrimidone (X).—2-Benzylthio-4-hydroxypyrimidine (18.1 g., 0.083 mole) was dissolved in 300 ml. of absolute ethanol. To this was added 6.5 g. (0.10 mole) of 85% potassium hydroxide followed by 12.7 g. (0.10 mole) of allyl bromide. The mixture was refluxed for 5 hr. and allowed to stand overnight. Potassium bromide was filtered from the solution. The solvent was removed under reduced pressure to yield a yellow-brown oil which was dissolved in 50 ml. of carbon tetrachloride and washed with 25 ml. of 10% sodium hydroxide. Three layers formed: (a) an upper, aqueous layer containing unchanged XI, (b) a dark brown middle layer, and (c) a lower carbon tetrachloride layer.

Layer b was dissolved in chloroform, washed with 10% sodium hydroxide and then with 10% sodium chloride solution. After drying, the chloroform was removed under reduced pressure to yield a yellow-brown oil. This was further purified on a column of neutral alumina.[26] Acetone was used as the eluent and 6.9 g. of 2-benzylthio-1-allyl-4-pyrimidone, a light yellow oil was obtained.

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.08; H, 5.46; N, 10.85. Found: C, 64.80; H, 5.30; N, 11.14.

Infrared data: carbonyl absorption at 6.10 μ. Ultraviolet data: single maximum at 236 mμ; $\lambda_{max}^{ethanol}$ (ϵ 23,400).

2-Benzylthio-3-allyl-4-pyrimidone (IX).—The carbon tetrachloride layer (c) from above was washed with 10% sodium hydroxide and then with 10% sodium chloride solution. The dried solvent was removed under reduced pressure to yield 11.9 g. of yellow-brown oil. This was chromatographed on neutral

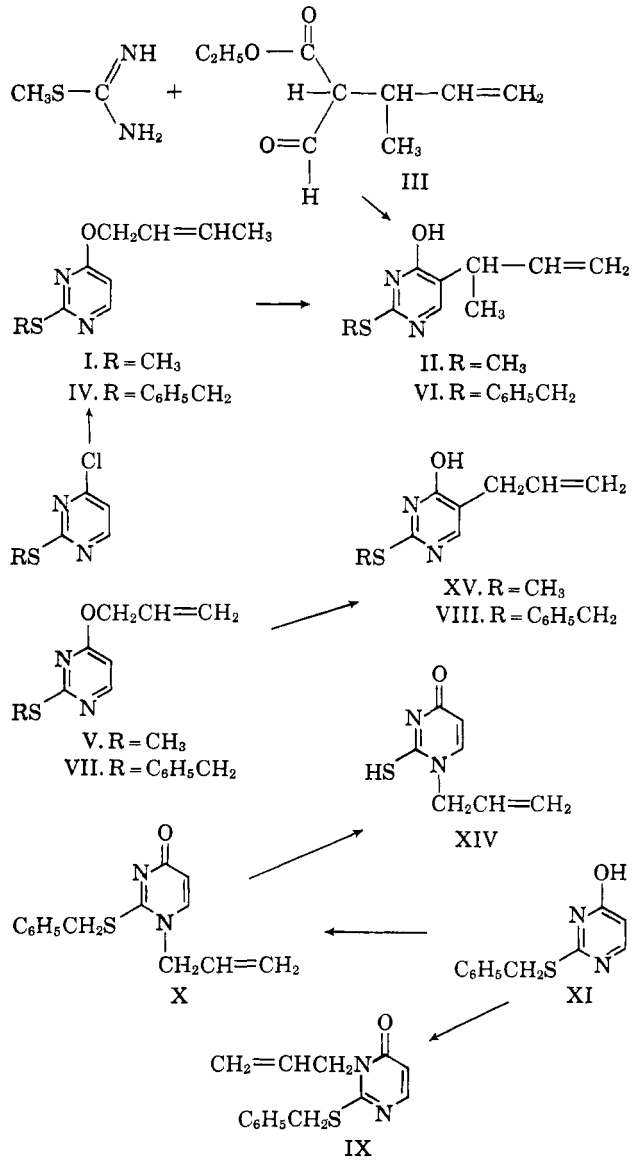


Figure 1

(24) All melting points and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(25) T. Matsukawa and B. Ohta, *J. Pharm. Soc., Japan*, **69**, 491 (1949).

(26) Woelm neutral alumina of activity grade I, 25 g. of alumina per gram of sample.

alumina.[26] Elution with methylene chloride yielded 6.0 g. of 2-benzylthio-4-alloxypyrimidine. The solvent was then changed to ethyl acetate and 4.1 g. of IX was eluted.

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.08; H, 5.46; N, 10.85. Found: C, 65.14; H, 5.37; N, 11.17.

Infrared data: carbonyl absorption at 5.96 μ. Ultraviolet data: single maximum in ethanol at 294 mμ; $\lambda_{max}^{ethanol}$ (ϵ 10,320).

1-Allyl-2-thiouracil.—2-Benzylthio-1-allyl-4-pyrimidone (6.6 g., 0.025 mole) was heated under vacuum (0.1 mm.). At a pot temperature of 230°, a mixture of liquid and white solid distilled. The solid was collected by filtration and recrystallized from aqueous ethanol to give 0.75 g. of white needles, m.p. 197–198°.

Anal. Calcd. for $C_7H_8N_2OS$: C, 49.97; H, 4.79; N, 16.66. Found: C, 50.44; H, 5.26; N, 16.02.

Infrared data: carbonyl absorption at 5.98 μ. Ultraviolet data: pH 7, single maximum at 270 mμ; pH 13, double maxima at 269 and 236 mμ.

Chromatography of Rearrangement Residue from 2-Benzylthio-4-alloxypyrimidine (VII).—Six and six-tenth grams of VII was rearranged by heating in N,N-diethyl-*m*-toluidine at 255° for 8 hr. The solvent was removed under reduced pressure and 1.6 g. of VIII crystallized from solution on cooling. This was removed by filtration and the residue, 5.0 g., chromatographed on alumina.[26] A graded series of solvents was used to elute the residue components from the column: benzene, methylene chloride, 1:1 (v./v.) methylene chloride–ethyl acetate, ethyl acetate, 1:1 (v./v.) ethyl acetate–acetone, acetone, 10:1 (v./v.) acetone–methanol, methanol. Semiquantitative ultraviolet spectra were run on alternate fractions. When like fractions were combined and solvents removed under reduced pressure, the residue was found to have the following composition with the components listed in order of elution (identifications are based on the comparison of infrared and ultraviolet absorption spectra with those of known compounds) (see Table III).

TABLE III

Fraction 1	2-Benzylthio-4-alloxypyrimidine (VII)	1.29 g.
Fraction 2	2-Benzylthio-3-allyl-4-pyrimidone (IX)	1.99 g.
Fraction 3	Unidentified material (believed polymeric)	0.58 g.
Fraction 4	2-Benzylthio-4-hydroxy-5-allylpyrimidine (VIII)	0.63 g.
Fraction 5	2-Benzylthio-4-hydroxypyrimidine (XI)	0.13 g.
		4.62 g.

Approximately 8% of the material which was placed on the column was not eluted by prolonged treatment with methanol.

Attempted Equilibration of 2-Benzylthio-3-allyl-4-pyrimidone (IX).—A 3.50-g. sample of IX in 10 ml. of N,N-diethyl-*m*-toluidine was heated at 255° for 8 hr. The solvent was removed under reduced pressure. Chromatography of the residue resulted in the recovery of 2.9 g. of unaltered IX. No VII or VIII was detected in the residue.

Attempted Equilibration of 2-Benzylthio-4-hydroxy-5-allylpyrimidine (VIII).—A 1.00-g. sample of VIII was dissolved in N,N-diethyl-*m*-toluidine and heated for 6 hr. at 255°. The solvent was removed under reduced pressure and upon cooling 0.65 g. of unaltered VIII crystallized from solution and was removed by filtration.

Chromatography of the filtrate showed that no VII or IX was present in the residue. The unidentified material observed in fraction 3 was present in this residue.

Cross-over Rearrangement of 2-Methylthio-4-crotoxypyrimidine (I) and 2-Benzylthio-4-alloxypyrimidine (VII). Experiment 1.—Equal molar quantities of I (2.50 g., 0.127 mole) and VII (3.28 g., 0.127 mole) were dissolved in 18 ml. of N,N-diethyl-*m*-toluidine. The solution was heated at 245° for 7 hr. After cooling, 25 ml. of ether was added and the solution was extracted four times with 20-ml. portions of Claisen's alkali.[27] Water, 40 ml., was added to the Claisen's alkali solution. The solution was washed with ether and acidified with hydrochloric acid. A precipitate formed on acidification. The mixture was extracted four times with 25-ml. portions of chloroform. The solvent was removed under reduced pressure at room temperature to give 1.9 g. of mixed product.

A portion of this solid, 0.400 g. was dissolved in 50 ml. of methanol and 20 λ of this solution was spotted on Whatman 3-mm. filter paper. An ascending chromatogram with water as the solvent was run; the methylthio compounds, II and 2-methylthio-4-hydroxy-5-allylpyrimidine (XV) move with an R_f of 0.9 while the benzylthio compounds, VI and VIII, remain at the origin. The methylthio spot was detected by its absorption under ultraviolet light and a wedge was cut out around it. A descending chromatogram was run on the wedge using a *t*-butyl alcohol, methyl ethyl ketone, water, ammonium hydroxide (4:3:2:1 v./v.) solvent system.[28] A control chromatogram on which both II and XV had been spotted was run at the same time. After development, the control chromatogram showed two ultraviolet absorbing spots; R_f = 0.96, II; and R_f = 0.91, XV. One ultraviolet absorbing spot was visible on the experimental chromatogram at R_f = 0.96, no absorption was visible at R_f = 0.91. The area at which the cross-over spot would appear as determined by the control chromatogram, was cut from the experimental chromatogram, extracted four times with 2-ml. portions of 10% sodium hydroxide, and diluted to 10 ml.

The ultraviolet absorption spectrum was determined using a Beckman DK-2 spectrophotometer. The reference beam contained the sodium hydroxide extract of a spot which had been cut from a non-ultraviolet absorbing area of the paper. An absorbance of less than 0.002 units was measured. Comparison of this absorbance to a previously prepared working curve shows that less than 3% of the rearranged material could be present as the methylthio cross-over compound, XV.

Experiment 2.—Equal molar quantities of 2-methylthio-4-crotoxypyrimidine (I) (2.50 g., 0.127 mole) and 2-benzylthio-4-alloxypyrimidine (VII) (3.28 g., 0.127 mole) were dissolved in 18 ml. of N,N-diethyl-*m*-toluidine. The solution was heated at 245° for 7 hr. After cooling, 25 ml. of ether was added to the reaction mixture which was then extracted four times with 25-ml. portions of Claisen's alkali. Distilled water, 25 ml., was added to the Claisen's alkali solution which was then washed with ether and acidified with 9 *N* hydrochloric acid. The resulting precipitate was collected to give 0.71 g. of the 2-benzythio compound(s) VI and VIII. The 2-methylthio compounds II and XV remain in solution in the acidified Claisen's alkali.

A portion of the precipitate, 0.3138 g. was dissolved in 50 ml. of methanol. Twenty λ of this solution was spotted on Whatman 3-mm. paper. Authentic samples of VI and VIII were spotted and run as a control. The papers were then coated with a 1:1 (v./v.) solution of acetone–formamide, air dried for 15 min., and then run as an ascending chromatogram with cyclohexane as the mobile phase.[29] After development of the control chromatogram, VI had moved with R_f = 0.90 and VIII had moved with R_f = 0.81. After development of the experimental chromatogram, one ultraviolet absorbing spot was visible at the R_f corresponding to the intramolecular rearrangement product, VIII. No spot was visible at the R_f at which the intermolecular product, VI would be formed. This area was cut from the paper, extracted, and the ultraviolet absorption spectrum of the extract measured as described above. An absorbance of less than 0.002 units was measured. Comparison of this absorbance to a previously prepared working curve shows that less than 7% of the rearranged material could be present as the 2-benzylthio cross-over product, VI.

Acknowledgment.—The authors are grateful to Mr. William Gorth for his technical assistance with the paper chromatographic procedures.

(27) L. Claisen, *Ann.*, **418**, 96 (1919); Claisen's alkali was prepared by dissolving 35 g. of potassium hydroxide in 25 ml. of water and adding 100 ml. of methanol.

(28) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

(29) J. Gasparic and J. Borechy, *J. Chromatog.*, **5**, 466 (1961).