Regioselective Syntheses of 2-Amino-4,5-dialkylthiophene-3-carboxylates and Their Conversion to 3,4-Dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylates

Gary D. Madding*, and Michael D. Thompson

Department of Chemical Process Development, Bristol-Myers Company,
Evansville, Indiana 47721

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The synthesis of 3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylates *via* acid catalyzed reactions of various 2-aminothiophene-3-carboxylates with activated nitriles is presented. The requisite thiophenes were prepared regioselectively by methods which represent improvements over previously published procedures.

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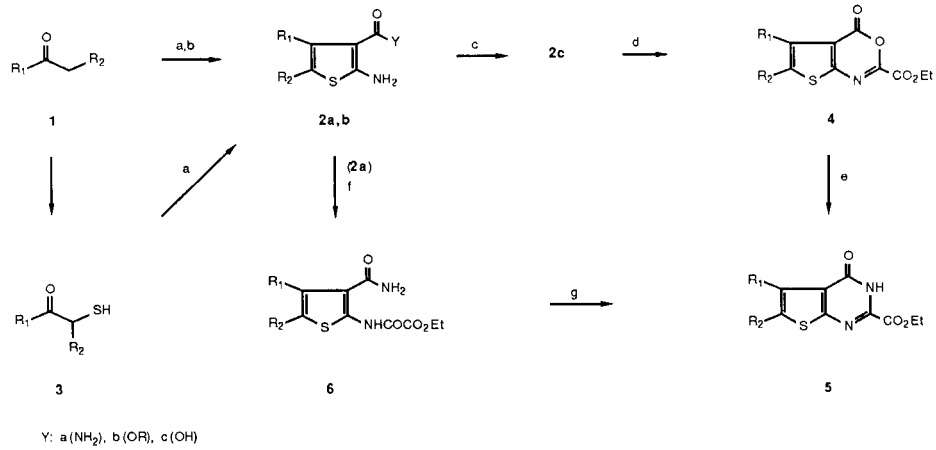
The synthesis of a series of 3,4-dihydro-4-oxothieno-[2,3-*d*]pyrimidine-2-carboxylates, which are useful as orally active antiallergy agents, has been described [1]. We would like to report a further study of the chemistry of these compounds and several improvements in the synthetic approach to them. The main focus of our work has been the synthesis of tiprinast, 3,4-dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-carboxylic acid (**15d**), a compound which has shown effective clinical activity in the relief of allergy symptoms.

The basic approach to these compounds has been to construct the pyrimidinone ring on a 2-amino-3-carboxy substituted thiophene (**2**) [1], which in turn was available from procedures published by Gewald and coworkers [2], see Scheme 1. Either **2c** was converted to the oxazine **4** with two equivalents of ethyl oxalyl chloride and then to **5** with ammonium acetate, or **2a** was first acylated to the oxamate **6** and then pyrrolyzed to **5**. Generally, the yields in these processes were moderate, but acceptable; however, there are several practical limitations to these processes which must be addressed if one is to consider a commercial synthesis of these compounds. The 2-aminothiophene-3-carboxamides **2a** are crystalline compounds and easily purified by crystallization, but they are produced in good yields only from cyclic ketones. The corresponding esters **2b** are available in moderate yields from acyclic ketones, but they are generally obtained as crude, high-boiling oils which are not easily purified. In addition, unsymmetrical ketones having α- and α'-methylenes available give a mixture of products differing in the substitution at the 4 and 5-positions. The difference in regiochemistry is dependent upon the activity (electronic and/or steric) differences of the two methylene groups, see Scheme 2.

For example, when R_1 is H and R_2 is isobutyl the ratio of **9:10** has been estimated to be 70:30. Originally Gewald had avoided the regiochemistry problem by starting with the α-mercapto ketones **3**. However, he abandoned that approach (along with any concern about regiochemistry) in favor of the "improved" approach starting with symmetric ketones and sulfur because of the undesirability of preparing the α-mercaptoketones.

In addition to the difficulties associated with the synthesis of the thiophene ring, two problem areas exist with the construction of the pyrimidinone. Ethyl oxalyl chloride, as

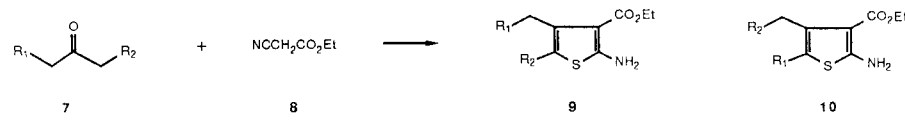
Scheme 1 [a]



Y: a (NH_2), b (OR), c (OH)

[a] a. $NCCH_2COY$, EtN, b. S_8. c. KOH, EtOH; HCl. d. 2 eq $ClCOCO_2Et$, pyr. b. NH_4OAc. f. 1 eq $ClCOCO_2Et$, pyr. g. 260°C.

Scheme 2

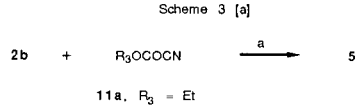


7 8 9 10

with most mixed derivatives of oxalic acid, is relatively expensive. Secondly, the ring closure of **6** was conducted at 260° for a short time, and the energy and equipment requirements to accomplish this on a large scale could be expensive. We chose to address these two problems first.

The work of Sugiyama and coworkers, in which they converted *o*-aminobenzoates into 2-carboxyquinazolones by treatment with a cyanoformate and acid [3], suggested the possibility of fusing the pyrimidinone ring to the aminothiophenecarboxyalate in a single step. Indeed, at the time we were doing our work, Shisoo and coworkers followed this approach, and they successfully converted **2b** into **5** (R_1, R_2 = -$(CH_2)_4$-) in moderate yield [4].

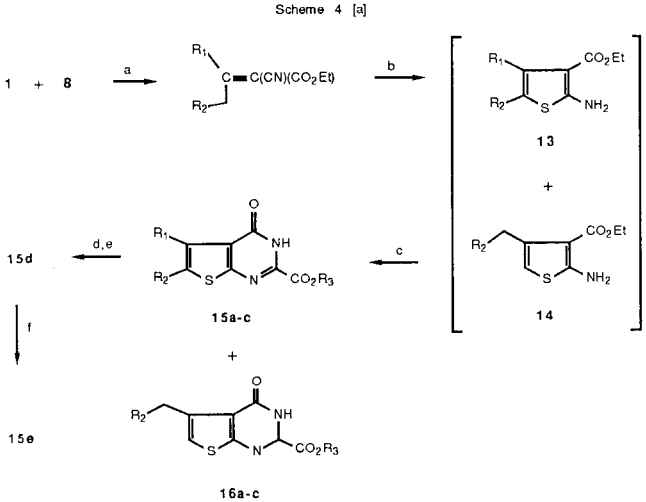
Scheme 3 [a]



[a] a. anhydrous HCl.

In the particular case of tiprinast (**15e**), these combined synthetic processes worked well as shown in Scheme 4. The initial Knoevenagel condensation product between

Scheme 4 [a]



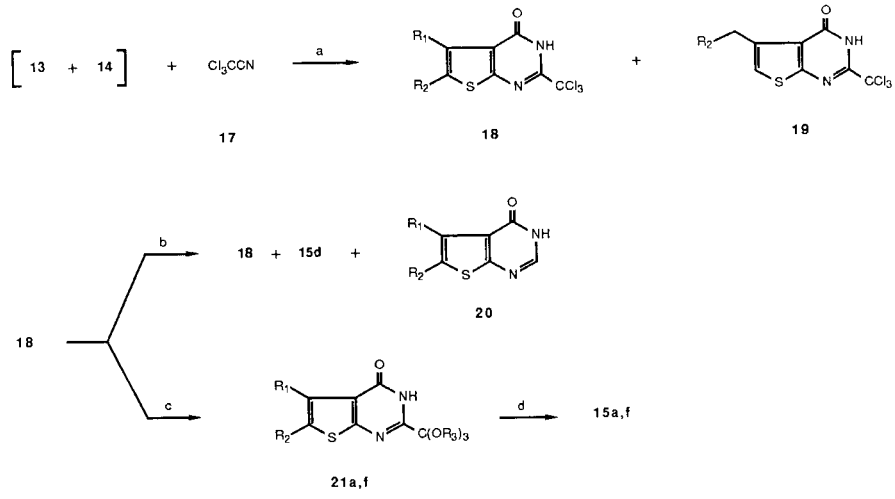
R_1 CH_3-
R_2 $(CH_3)_2CHCH_2$-
R_3 a, Et; b, *i*-Pr; c, *n*-Bu; d, H; e, [(N-Methyl-D-glucamine)·H]; f, Me

[a] a. NH_4OAc, HOAc, toluene, Δ. b. S_8, Et_3N. c. **11a-c**, HCl, HOAc. d. KOH, EtOH. e. HCl. f. N-Metheyl-D-glucamine.

the ketone **1** (R_1 = methyl, R_2 = isobutyl) and ethyl cyanoacetate (**8**) was purified by intermediate conversion to a water-soluble bisulfite addition product, extraction, and reconversion to the cyanoacrylate **12**. Treatment of **12** under the usual Gewald conditions gave a mixture of the 2-aminothiophene-3-carboxylates **13** and **14** as a dark, crude oil in 75% yield from **1** [2]. Those compounds were not easily separated, and so the mixture was allowed to react with an alkyl cyanoformate to give a mixture of the thienopyrimidinones **15a-c** and **16a-c** in moderate yield. The desired product **15a-c** comprised approximately 70% of the mixture, and it was easily isolated by multiple recrystallizations. The purified ester **15a-c** was then hydrolyzed to the carboxylic acid, **15d** which was then converted to a water soluble salt, such as the salt with *N*-methyl-D-glucamine **15a** [5].

To our knowledge, the alkyl cyanoformates are available in significant quantities only through laboratory synthesis [6], and we would prefer to use commercially available starting materials. Since Abdelrazek successfully used trichloroacetonitrile with *o*-aminobenzoates under base catalysis to prepare 2-trichloromethylquinazolines [7], we attempted the same type of reaction with trichloroacetonitrile and the substituted mixture of 2-aminothiophene-3-carboxylates **13** and **14**. However, we were unable to obtain the desired reaction under their conditions. When the same reaction was attempted using anhydrous hydrochloric acid as in our previous pyrimidinone syntheses, 2-trichloromethylthienopyrimidinone **18** was obtained in 48% yield, see Scheme 5. The isolated product appeared to be free from isomer **19**, which, if it was present, was lost during work-up. Typically, trichloromethyl moieties are hydrolyzed to carboxylic acids under strongly acidic conditions [8]. However, when **18** was treated with 100% sulfuric acid at 100°, followed by ethanolic quench, the desired ethyl ester was obtained as a mixture consisting of 50% starting material **18** and 50% product **15a**. As more vigorous conditions were employed, increasing amounts of decarboxylated material **20** were obtained. Alternatively, aqueous base hydrolysis gave significant degradation along with a low yield of the dipotassium salt of **15d**. This result suggested that nucleophilic displacement of the chlorines could give a triethyl orthoester, which in turn could be converted to the ethyl ester **15a**. When **18** was refluxed with excess sodium ethoxide, the orthoester **21a** was obtained. This intermediate was not isolated. Instead, it was immediately mixed with dilute aqueous acid giving ethyl ester **15a** in 51% yield. This product contained no

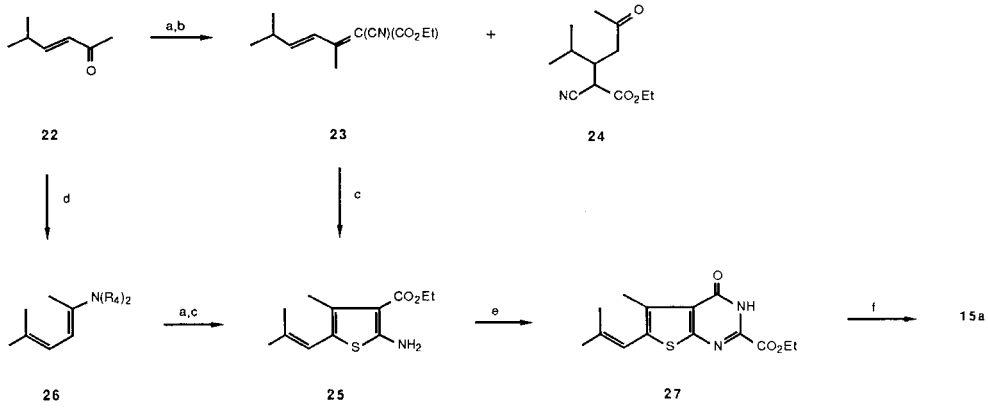
Scheme 5 [a]



R_1, CH_3-, R_2, $(CH_3)_2CHCH_2$-, R_3, a, Et; f, Me

[a] a. HCl, HOAc. b. 100% H_2SO_4, EtOH. c. NaOR. d. 10% HCl.

Scheme 6 [a]



R_4, $-(CH_2)_5-$ or $-CH_2CH_2OCH_2CH_2-$

[a] a. **8**. b. NH_4OAc, HOAc, toluene, Δ. c. S_8, Et_3N. d. $(R_4)NH$. e. **11a**, HCl, HOAc. f. H_2, Pd/C.

detectable **16a**. Since this reaction should be general to any alkoxide nucleophile, trichloromethyl intermediate **18** was treated with methoxide. This gave the trimethyl orthoester **21f**. When this intermediate was treated with dilute aqueous acid, the ester **15f** was obtained in 67% yield from **18**. These results clearly display the usefulness of **18** as an intermediate in the preparation of esters of **15** which in turn give tiprinast **15d** on hydrolysis.

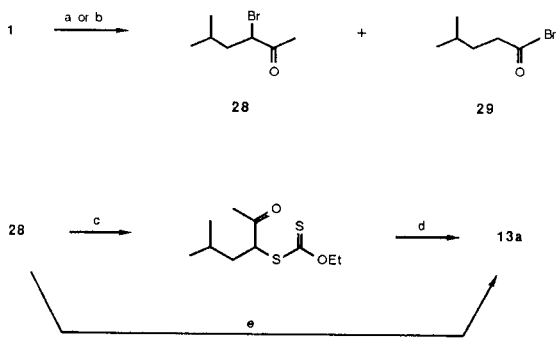
We next turned our attention to the major problem of this synthesis, that of the regiospecific synthesis of the intermediate thiophene. The simplicity of the Gewald approach was appealing, and we preferred to stay with it if the selectivity for reaction at the desired center could be improved. Ideally, it seemed that functionalization at the desired α-position of the ketone was the best course. To achieve this, two substrates were used, one being 5-methyl-3-hexen-2-one (**22**), and the other 3-bromo-5-methylhexan-2-one (**28**). The first reagent was readily available, and it seemed reasonable that the double bond would aid the ring closure in the proper direction. The small amount of **23** obtained from **22** and **8** did give the expected isobutenylthiophene **25** under the Gewald conditions; unfortunately, Knovenagel condensation did not compete well with Michael addition of the cyanoacetate to the unsaturated ketone. Therefore, **22** was converted to the dienamine **26**, which in turn gave the desired product **25** upon treatment with ethyl cyanoacetate, sulfur, and triethylamine. This was treated with ethyl cyanoformate giving **27**. Final-

ly, the double bond was reduced using hydrogen and 5% palladium on carbon. Although the reaction was slow, **15a** was obtained in high purity, and no **16a** was detected. Unfortunately, **15a** was obtained in low overall yield (8%) from **22**. Attempts at a similar preparation of **27** using trichloroacetonitrile instead of ethyl cyanoformate for pyrimidinone formation were unsuccessful.

At this point attention was turned to the use of the alternate substrate, 3-bromo-5-methylhexan-2-one (**28**), which was also an α-functionalized ketone. Since this α-bromoketone was not available commercially, it had to be prepared. In a brief study it was found that 5-methylhexan-2-one (**1**) could be preferentially brominated in the 3-position with copper(II) bromide [9] in a ratio of approximately 70 to 1 compared to the 1-position. Acid catalyzed bromination with elemental bromine gave the products in a ratio of about 75 to 1.

The literature teaches that conversion of α-haloketones directly to the corresponding mercapto compounds with sodium hydrosulfide is often not a useful procedure [10], principally because the compounds, once formed, undergo further reaction with additional haloketone, with the air, or with themselves. Therefore, it occurred to us to prepare the mercaptoketone in the presence of the necessary components to trap the reactive intermediate as the desired thiophene. Two methods were discovered to accomplish this, see Scheme 7. In the first, the bromoketone **28** was converted to the ethyl xanthogenate **30**. The conditions required for conversion of a xanthogenate to the free thiol, treatment with a primary or secondary amine, are also sufficient conditions to affect the condensation of the liberated mercaptoketone with ethyl cyanoacetate. Indeed, treatment of **28** with diethylamine, followed by addition of **8** and triethylamine produced **13a** in good yield, as indicated by vpc; see Scheme 7.

Scheme 7 [a]



[a] a. $CuBr_2$, EtOAc, Δ. b. HBr, HOAc, Br_2, c. $EtOCS_2K$, acetone. d. Et_2NH, EtOH, **8**, Et_3N. e. $NaSH(H_2O)_x$, EtOH, **8**, Et_3N.

The second method was even simpler, in that the bromoketone was used directly, without conversion to an intermediate product. A mixture of sodium hydrosulfide hydrate, ethyl cyanoacetate, triethylamine, and 3-bromo-5-methylhexan-2-one was heated together in ethanol for five hours, and **13a** was obtained from this reaction in over 40% yield. As mentioned earlier, **13a** and related esters are generally oils which are difficult to purify, and, therefore, reported yields are really only estimates. The crude product was converted to **15a** as in Scheme 4, and after a single recrystallization the content of **16a** in **15a** was 0.9 wt%. The product **15a** was obtained in 19% overall yield from **1**; this may be compared to 18% from **1** as obtained in the route shown in Scheme 4, and 18% from **1** through the intermediate trichloromethyl pyrimidinone **18**.

In summary, we have reported procedures for the regioselective synthesis of 4,5-disubstituted-2-aminothiophene-3-carboxylates. The first process utilizes the *in situ* formation and trapping of α-mercaptoketones, and the second relies on the directing influence of a dienamine in the Gewald approach to these thiophenes. The compounds so prepared were then converted to 2-carboxy substituted thienopyrimidinones by acid catalyzed reaction with several activated nitriles.

EXPERIMENTAL

Melting points were determined using a Buchi 510 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MX1 spectrophotometer. Proton magnetic resonance spectra were recorded on a Perkin-Elmer R32 instrument. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane as an internal standard (00.0). High performance liquid chromatography was done using an HP 1080 series chromatograph with a 25 μl injection loop, Varian Autosampler, 320 nanometers detection and an HP 1084 microprocessor.

Ethyl 3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**15a**).

Method A.

A solution of 38.0 g (1.04 mole) anhydrous hydrogen chloride in 300 ml glacial acetic acid at 10° was added to a solution of 230.4 g (0.96 mole) of the crude thiophenes **13** and **14** [1] and 104.1 g (1.05 mole) ethyl cyanoformate (**11a**) in 1000 ml of glacial acetic acid. The dark solution was stirred and heated at 90° for 4 hours. The solution was then added over 1 hour with vigorous stirring to 3 kilograms ice/water. The resulting solid was collected on a filter, rinsed with water and dried to give 256.8 g of crude material. It was first recrystallized from 2-propanol and then toluene and then acetone. The final yield was 137.2 g (49% of theory); mp 175-176°; ir (0.5% potassium bromide): 3100, 2960, 2880, 1740, 1680, 1305 and 1195 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (d, $(CH_3)_2$, 6H, J = 6.4 Hz), 1.49 (t, O-C-CH_3, 3H, J = 7.2 Hz), 1.95 (m, CH, 1H), 2.56 (s, CH_3-thiophene, 2H), 2.70 (d, CH_2, 2H, J = 7.0 Hz), 4.54 (q, OCH_2, 2H, J = 7.2 Hz), and 10.55 (bs, NH, 1H).

Anal. Calcd. for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52; S, 10.89. Found: C, 57.23; H, 6.28; N, 9.50; S, 10.98.

The isomeric composition of this material was monitored by hplc (4 millimeter inside diameter × 30 centimeter μ Bondapak C_{18} Column, 1 ml/minute 40 THF: 60 H_2O, 320 nanometer uv detection, 25 microliter sample of 0.05% compound in mobile phase, typical retention times -**15a** 19 minutes, **16a** 27 minutes). The crude material was typically 70% **15a** and 30% **16a**. After recrystallization from 2-propanol **15a** contained about 10% **16a**, and the purity was increased to $\geq$ 99.9% by further recrystallizations from toluene and acetone.

Method B, *via* **30**.

Preparation of *S*-(2-Oxo-5-methyl-3-hexyl) Ethyl Xanthogenate (**30**).

A mixture of 130.0 g (0.811 mole) potassium ethyl xanthate and 1.0 liter acetone was stirred as 105.8 g (0.548 mole, based on 130.8 g, 81% crude material) 3-bromo-5-methylhexan-2-one (**28**) was added over 0.5 hours. The temperature rose to 42°. The mixture was stirred another 0.5 hours, and then it was heated to 55°. The heat was turned off and the mixture was stirred an additional 4 hours. It was filtered, and the filtrate was distilled to dryness *in vacuo*. The residue was washed with water (2 × 500 ml), and the remaining oil was dried over anhydrous magnesium sulfate. The product weighed 120.0 g (86% of theory). Gc (6 feet OV-1 column, 175° isothermal, 40 ml nitrogen/minute) showed a major peak at 3.53 minutes. The oil was used in the next step without purification.

Ethyl 2-Amino-4-methyl-5-(2-methylpropyl)thiophene-3-carboxylate (**13**) from **30**.

A solution of the crude xanthate **30** (23.4 g, a maximum of 0.1 mole) and 8.0 g (0.11 mole) diethylamine in 50 ml 95% ethanol was stirred; the temperature rose from 23° to 30° and then slowly fell. After 1 hour, 11.3 g (0.1 mole) ethyl cyanoacetate was added, followed by 2.0 g (0.02 mole) triethylamine. The temperature rose to 30° and stayed for 2 hours and then slowly fell to 25°. After standing for 20 hours, the solution was concentrated *in vacuo*, and the residual oil was washed with 200 ml water. The oil was dried over anhydrous magnesium sulfate. Gc (6 feet OV-1 column, 40 ml nitrogen/minute, 175° isothermal) revealed that the starting material (retention time 3.53 minutes) was essentially gone, and **13** at 10.32 minutes was present.

An analytical sample of **13** was prepared by flash-chromatography on a silica gel (32-65 micron) column using toluene as eluant, R_f = 0.4. Fractions containing the desired material were combined, and the solvent was removed under reduced pressure. The resulting amber oil gave the following analytical data; ir (0.5% potassium bromide): 3440, 3325, 2950, 1660, 1575, 1475, 1400, and 1260 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.92 (t, O-C-CH_3, 3H, J = 6.5 Hz), 1.34 (d, $(CH_3)_2$, 6H, J = 6.4 Hz), 1.75 (nine lines, CH, 1H, J = 7.0 Hz), 2.17 (s, thiophene-CH_3, 3H), 2.40 (d, thiophene-CH_2, 2H, J = 7.0 Hz), 4.27 (q, OCH_2, 2H, J = 6.5 Hz), and 5.96 (s, NH_2, 2H).

Anal. Calcd. for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.94; N, 5.80; S, 13.29. Found: C, 59.74; H, 8.06; N, 5.87; S, 13.23.

Preparation of **15a**.

When the resulting crude **13** was treated with **11a** as in Method A, the **15a** obtained after crystallization from 2-propanol contained 0.9 weight percent **16a**, and had mp 173.5-176°.

Method C, *via* Sodium Hydrosulfide.

Ethyl 2-Amino-4-methyl-5-(2-methylpropyl)thiophene-3-carboxylate (**13**).

Sodium hydrosulfide hydrate (assumed to be dihydrate, 315.0 g, 3.42 moles) was stirred in 1.5 liters of 95% ethanol under nitrogen as 193.5 g (1.71 moles) ethyl cyanoacetate (**11a**) and 173.0 g (1.71 moles) triethylamine were added. The mixture was stirred 15 minutes, and then 330.2 g (1.71 moles) crude 3-bromo-5-methyl-2-hexanone (**28**) was added over 20 minutes. The mixture was stirred and heated at gentle reflux for 5 hours. It was cooled to 20° and filtered. The filtrate was concentrated *in vacuo*, and the dark residue was stirred with 1 liter of water. The mixture was extracted with methylene chloride (3 × 300 ml, brine added to promote separation). The combined extracts were stripped *in vacuo* to give 268 g dark oil. The oil was taken up in 500 ml toluene and stripped *in vacuo* to remove remaining water to return 247 g (60% of theory) dark oil. Treatment of the crude **13** so obtained gave results essentially the same as in Method B.

Ethyl 3,4-Dihydro-5-(3-methylbutyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**16a**).

This compound was isolated by medium pressure column chromatography (25 millimeter inside diameter × 30 centimeter column; E. Merck Silica Gel 60, 230-240 mesh; 100 pounds per square inch; 30 ethyl acetate: 70 hexane) from residues from the isolation of **15a** in Method A. Compound **16a** eluted before **15a**; the tlc (7.6 centimeter glass plates coated with Silica GF254, uv detection, 30 ethyl acetate: 70 hexane) R_f's were 0.23 for **15a** and 0.30 for **16a**, mp 133-136°; ir (0.5% potassium bromide): 3100, 2960, 2870, 1735, 1680 and 1305 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.98 (d, $(CH_3)_2$, 6H, J = 6.0 Hz), 1.98 (t, OCCH_3, 3H, J = 7.2 Hz), 1.62 (m, CH-CH_2, 3H), 3.08 (m, -CH_2-thiophene, 2H), 4.55 (q, OCH_2, 2H, J = 7.2 Hz), 7.06 (s, -CH=, 1H) and 10.50 (bs, NH, 1H).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found: C, 57.15; H, 6.28; N, 9.58.

2-Propyl 3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**15b**).

This compound was prepared in the same manner as **15a** in Method A above, mp 179-182°; ir (0.5% potassium bromide): 3250, 2960, 2870, 1700, 1315 and 1180 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.98 (d, $(CH_3)_2$, 6H, J = 6.5 Hz), 1.46 (d, $(CH_3)_2$CO, 6H, J = 6.3 Hz), 1.96 (m, CH, 1H), 2.55 (s, CH_3-thiophene, 3H), 2.71 (d, CH_2-thiophene, 2H, J = 7.0 Hz), 5.37 (sextet, OCH, 1H, J = 6.3 Hz), and 10.41 (bs, NH, 1H).

Anal. Calcd. for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08; S, 10.40. Found: C, 58.12; H, 6.47; N, 9.44; S, 10.53.

1-Butyl 3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**15c**).

This compound was prepared in the same manner as **15a** in Method A above, mp 143.5-164°; ir (0.5% potassium bromide): 3090, 2960-2870, 1740, 1670, 1300 and 1185 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 (t, CH_3, 3H, J = 7.0 Hz), 0.98 (t, $(CH_3)_2$, 6H, J = 6.5 Hz), 1.45 (m, CH_2, 2H), 1.82 (m, CH_2, 2H), 2.56 (s, CH_3-thiophene, 3H), 2.71 (d, CH_2-thiophene, 2H, J = 7.1 Hz), 4.48 (t, OCH_2, 2H, J = 6.6 Hz), and 10.83 (bs, NH, 1H).

3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxo-2-(trichloromethyl)thieno-[2,3-*d*]pyrimidine (**18**).

Gaseous hydrochloric acid (1.45 moles) was bubbled into 437.5 ml (7.6 moles) of glacial acetic acid at 10° (±2°). After 30 minutes, the bubbling was stopped, and nitrogen was swept across the solution for 30 minutes at 10° (±2°). This solution was added to a mixture of 350.0 g (4.55 moles, a mixture of isomers) of thiophene **13** + **14** and 291.2 ml (2.02 moles) of trichloroacetonitrile in 350 ml of acetic acid. The resulting mixture was heated with stirring on a steam bath overnight. The solvent was removed under reduced pressure and 1 liter of 2-propanol was added. This mixture was warmed on a steam bath to reflux and then was cooled to room temperature with stirring. After cooling in a refrigerator overnight, the mixture was filtered and rinsed with cold isopropanol giving a tan solid, which when dry weighed 198.0 g (0.58 mole, 40% yield), mp 189-192°. This was used without further purification. An analytical sample was prepared by successive recrystallization with acetone (1:35), toluene (1:6), and 2-propanol (1:30) giving white crystals, mp 192-193.5°; ir (0.5% potassium bromide): 3400 (br), 2960, 2875, 1675(s), 1580, 1470, 1310, 1210, 850, 780 and 675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.85 (d, CH$(CH_3)_2$, 6H, J = 6 Hz), 1.8 (m, CH, 1H), 2.45 (s, ArCH_3, 3H), 2.65 (d, ArCH_2, 3H, J = 6 Hz), and 12.6 (s, NH, 1H).

Anal. Calcd. for $C_{12}H_{13}Cl_3N_2OS$: C, 42.43; H, 3.86; N, 8.25; S, 9.44; Cl, 31.31. Found: C, 42.45; H, 3.81; N, 8.36; S, 9.56; Cl, 31.16.

3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxo-2-(triethoxymethyl)thieno-[2,3-*d*]pyrimidine (**21a**).

To a mixture of sodium ethoxide in ethanol, generated from 1.0 g (43 mmoles) of sodium in 200 ml of ethanol, a mixture of 3.0 g (8.8 mmoles) of trichloromethyl intermediate **18** in 50 ml of toluene was added. This was heated to reflux for 18 hours. After cooling and solvent removal under reduced pressure, the residue was taken up in 25 ml of ethanol and poured into 50 ml of 5% aqeuous sodium bicarbonate solution. This was extracted with 3 × 25 ml of toluene. The combined organic layer was dried with anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the remaining solid was recrystalliz-

ed with absolute ethanol (1:5) giving 1.2 g (3.2 mmoles, 36% yield) of white needles, mp 135.5-137°; ir (0.5% potassium bromide): 3400 (br), 3175, 3100, 2995, 1660, 1270, 1210, 1140, 1125, 1080, 1000, and 900 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (d, $CH(CH_3)_2$, 6H, J = 6 Hz), 1.33 (s, OCH_2CH_3, 9H, J = 6 Hz), 1.9 (m, CH, 1H), 2.56 (s, $ArCH_3$, 3H), 2.71 (d, $ArCH_2$, 2H, J = 6 Hz), 3.67 (q, OCH_2, 6H, J = 6 Hz), 9.8 (s, NH, 1H).

Anal. Calcd. for $C_{16}H_{26}N_2O_4S$: C, 58.67; H, 7.66; N, 7.60; S, 8.70. Found: C, 58.85; H, 7.81; N, 7.75; S, 8.74.

Ethyl 3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**15a**).

To a solution of sodium ethoxide in ethanol, generated from 95 g (4.0 moles) of sodium and 1500 ml of ethanol, 275 g (0.809 mole) of trichloromethyl intermediate (**18**) was added. This mixture was heated to reflux 8 hours. After cooling, the mixture was filtered. The dark solution was stirred with 1 liter of water while 250 ml of 10% aqueous hydrochloric acid solution was added. The *p*H was acidic to litmus. After 1 hour of stirring at room temperature, this mixture was filtered and dried giving 150 g of tan solid. Recrystallization with toluene (1:5) gave 122 g (0.415 mole, 51% yield) of off-white solid, mp 175.5-177°; spectral data was consistent with an authentic sample of **15a**.

3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxo-2-(trimethoxymethyl)-thieno[2,3-*d*]pyrimidine (**21f**).

To a mixture of sodium methoxide in methanol, generated from 12.8 g (0.56 g-atom) of sodium in 250 ml of methanol, 34.0 g (0.10 mole) of trichloromethyl intermediate **18** was added. This was heated to reflux for 2 hours. After cooling, the mixture was poured into 250 ml of 5% aqueous sodium bicarbonate solution and extracted with 3 × 100 ml of methylene chloride. The combined organic layer was dried with anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the remaining solid was recrystallized with methanol giving 11.1 g (0.034 mole, 34% yield) of white crystals, mp 152-154°; ir (0.5% potassium bromide): 3440 (br), 3110, 2950, 1650, 1575, 1490, 1460, 1440, 1270, 1205, 1100 and 990 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (d, $CH(CH_3)_2$, 6H, J = 7 Hz), 1.66 (s, $ArCH_3$, 3H), 1.78 (d, $ArCH_2$, 2H, J = 7 Hz), 1.94 (m, CH, 1H), 3.52 (s, OCH_3), and 10.87 (brs, NH, 1H).

Anal. Calcd. for $C_{15}H_{22}N_2O_4S$: C, 55.20; H, 6.79; N, 8.58. Found: C, 55.13; H, 6.70; N, 8.54.

Methyl 3,4-Dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**15f**).

To a solution of sodium methoxide in methanol, generated from 9 g (4.0 mole) of sodium and 125 ml of methanol 15.0 g (0.809 mole) of trichloromethyl intermediate **18** was added. This mixture was heated to reflux for 2 hours. After cooling, the mixture was filtered and rinsed with 200 ml of methanol. The resulting solution was stirred with 325 ml of water, then 75 ml of 10% hydrochloric acid solution was added. The *p*H was acidic to litmus. This was warmed with stirring to 50°, then cooled to 0°. Filtration followed by recrystallization with toluene (1:5) gave 8.3 g (0.030 mole, 67% yield) of white solid, mp 173-175°; ir (0.5% potassium bromide): 3440 (br), 3090, 3040, 2950, 1740, 1670, 1560, 1490, 1460, 1440, 1300, 1200, and 1050 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.75 (d, $CH(CH_3)_2$, 6H, J = 7 Hz), 1.75 (m, CH, 1H), 2.50 (s, $ArCH_3$, 3H), 2.56 (d, $ArCH_2$, 2H, J = 7 Hz), 4.0 (s, OCH_3, 3H), and 10.2 (brs, NH, 1H).

Anal. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found: C, 55.74; H, 5.82; N, 10.07.

Ethyl 2-Cyano-3,6-dimethylhepta-2,4-dienoate (**23**).

A mixture of 117 g (1.04 mole) of 5-methyl-3-hexene-2-one, 113 g (1.00 mole) of ethyl cyanoacetate, 77 g (1.00 mole) of ammonium acetate and 9 ml of morpholine (catalytic) in 300 ml of toluene was heated to reflux, and water was removed by azetropic distillation. After the water was completely removed (4 hours), this was extracted with 250 ml of water, and the organic layer was dried with anhydrous magnesium sulfate. Filtration followed by removal of solvent under reduced pressure gave an oil. This was stirred on a steam bath for 2 hours with a solution of 75 g of sodium bisulfite in 350 ml of water. After cooling, the organic layer was removed, and a solution of 29 g of sodium hydroxide in 100 ml of water was added. This was extracted with 3 × 150 ml of water. After cooling, the organic layer was removed, and a solution of 29 g of sodium hydroxide in 100 ml of water was added. This was extracted with 3 × 150 ml of toluene. The combined organics were dried with anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure giving 18.5 g (8.9 mole, 9% yield) of thick liquid, ^1H nmr (deuteriochloroform): δ 1.07 (s, $CHCH_3$, 3H), 2.4 (two singlets (isomers), vinyl CH_3, 3H), 4.30 (q, OCH_2, 2H, J = 8 Hz), and 6.2-7.9 (m, vinyl H, 2H).

Ethyl 2-Amino-4-methyl-5-isobutenylthiophene-3-carboxylate (**25**, from **23**).

A mixture of 5.0 g (0.024 mole) of diene **23**, 0.8 g (0.025 mole) of sulfur and 3.5 ml (0.025 mole) of triethylamine in 50 ml of absolute ethanol was heated to reflux. After 10 hours, the mixture was cooled, poured into 100 ml of water and extracted with 3 × 100 ml of methylene chloride. The combined organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure giving a dark oil (quantitative; spectra shows impurities; gc, 6 feet OV-1 column, 40 ml nitrogen per minute, 175° isothermal, 43% of desired isomer) which was used without further purification.

5-Methyl-2-morpholino-2,4-hexadiene (**26a**).

A mixture of 561 g (5.00 moles) of 5-methyl-3-hexene-2-one, 450 g (5.20 moles) of morpholine, and 3.2 g of *p*-toluenesulfonic acid monohydrate in 2 liters of toluene was heated to reflux, and water was azeotroped out. After 22 hours, 110 ml of water had been removed. The solution was cooled to room temperature and extracted with 250 ml of saturated sodium bicarbonate solution, 250 ml of water, then dried with anhydrous magnesium sulfate. Filtration, followed by removal of solvent under reduced pressure gave a dark oil which was distilled giving 610 g (3.36 moles, 67% yield) of pale yellow liquid, bp 90-95° @ 0.20-0.25 millimeters of mercury; ^1H nmr (deuteriochloroform): δ 1.70 (s, vinyl CH_3, 3H), 2.86 (t, NCH_2, 4H, J = 4 Hz), 3.72 (t, OCH_2, 4H, J = 4 Hz), and 5.2-6.2 (dd, vinyl H, 2H, J = 12, 12 Hz) [11].

An analytical sample was prepared using three consecutive bulb to bulb distillations (100-130° @ 0.40 mm Hg). This gave a pale yellow liquid; all analytical data was collected within 3 hours [12]; ^1H nmr (deuteriochloroform): as above; ir (neat): 2950, 2905, 2850, 2810, 1600, 1445, 1260, 1225, 1180, 1125, 1000, and 905 cm^{-1}.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.45; H, 10.36; N, 7.45 [12].

Ethyl 2-Amino-4-methyl-5-isobutenylthiophene-3-carboxylate (**25**, from **26a**).

A mixture of 544 g (3.00 moles) of enamine **26a**, 96 g (3.00 moles) of sulfur, and 340 g (3.01 moles) of ethyl cyanoacetate in 1400 ml of absolute ethanol was warmed to reflux for 72 hours. The mixture was cooled and diluted with 5 liters of water. This was extracted with 3 × 1 liters of methylene chloride. The combined organic was dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure giving a dark oil (quantitative; spectra shows impurities; gc, 6 feet OV-1 column, 40 ml nitrogen per minute, 175° isothermal, 70% of desired isomer, similar to gc of **25** which was prepared from **23**) which was used without further purification. The preparation of analytically pure sample is the same as that described in the experimental for **25** from **26b**.

5-Methyl-2-piperidine-2,4-hexadiene (**26b**).

A mixture of 112 g (1.00 mole) of 5-methyl-3-hexene-2-one, 90 g (1.06 moles) of piperidine, and 0.5 g of *p*-toluenesulfonic acid monohydrate in 500 ml of toluene was heated to reflux, and water was removed by azeotropic distillation. After 18 hours, the mixture was cooled to room temperature and the solvent was removed under reduced pressure. Distillation of the remaining liquid gave 104 g (0.58 mole, 58% yield) of pale liquid, bp 88-89° @ 0.3 millimeters of mercury; ^1H nmr (deuteriochloroform): δ 1.53 (br s, $CH_2CH_2CH_2CH_2CH_2$, 6H), 1.70 (s, vinyl CH_3, 3H), 1.78

(s, vinyl CH_3, 3H), 1.86 (s, vinyl CH_3, 3H), 2.9 (brm, NCH_2, 4H), and 5.2-6.3 (dd, vinyl *H*, 2H, J = 12, 12 Hz) [11].

An analytical sample was prepared using three consecutive bulb to bulb distillations (100-120° @ 0.40 mm Hg). This gave pale yellow liquid; ^{1}H nmr (deuteriochloroform): as above; ir (neat): 2925, 2850, 2790, 1640, 1595, 1440, 1375, 1230, 1220, 1180, 1125, 1055, 990, 900 and 845 cm^{-1}.

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 11.80; N, 7.81. Found: C, 80.31; H, 11.48; N, 7.60.

Ethyl 2-Amino-4-methyl-5-isobutenylthiophene-3-carboxylate (**25**, from **26b**).

A mixture of 102 g (0.57 mole) of enamine **26b**, 18 g (0.57 mole) of sulfur, and 65 g (0.57 mole) of ethyl caynoacetate in 200 ml of absolute ethanol was heated to reflux for 6 hours. This was poured into 500 ml of water and extracted with 3 × 100 ml of methylene chloride. The combined organic layers were dried with anhydrous magneisum sulfate and filtered. The solvent was removed under reduced pressure giving a dark liquid (quantitative; spectra shows impurities; gc, 6 feet OV-1 column, 40 ml nitrogen per minute, 175° isothermal, 65% of desired isomer, similar to gc of **25** which prepared from **23**) which was used without further purification.

An analytical sample was prepared by using flash chromatography on a portion of crude (toluene as eluant), R_f = 0.4. The clean fractions were collected together, solvent was removed under reduced pressure, and the residue was dissolved in boiling hexane. This cooled at room temperature giving a solid. Filtration and rinsing with hexane gave a tan solid, mp 79-82°; ir (0.5% potassium bromide): 3440, 3325, 1650, 1590, 1495, and 1275 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.34 (t, CH_2CH_3, 3H), 1.79 (s, vinyl CH_3, 3H), 1.86 (s, vinyl CH_3, 3H), 2.18 (s, thiophenyl CH_3, 3H), 4.27 (q, CH_2CH$_3$, 2H), and 6.09 ppm (brs, NH_2,vinyl *H*, 3H).

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.05; H, 7.52; N, 5.80.

Ethyl 3,4-Dihydro-6-α-isobutenyl-5-methyl-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**27**).

A solution of 109 g (3.00 mole) of anhydrous hydrochloric acid in 900 ml of acetic acid at 10° was poured into a solution of 3 mmoles of crude thiophene **25**, and 925 g (60% pure, 5.60 moles) of ethyl cyanoformate in 2.5 liters of acetic acid. The resulting mixture was heated on a steam bath for 6 hours. After cooling to room temperature, this was poured slowly into 10 liters of water giving a gummy solid which was slurried with 500 ml of 2-propanol. Filtration followed by air drying gave 102 g (0.35 mole, 12% yield) of yellow solid. This was recrystallized from 3 liters of toluene. Filtration and air drying gave 74 g (0.25 mole, 8% yield) of yellow solid, mp 235.5-237.5°; ir (0.5% potassium bromide): 3400 (br), 3000 (br), 1745, 1680, 1495, 1390, 1310, 1200, and 1040 cm^{-1}; nmr (hexadeuteriodimethylsulfoxide): δ 1.50 (t, OCH_2CH_3, 3H, J = 5 Hz), 1.94 (s, vinyl CH_3, 3H), 2.00 (s, vinyl CH_3, 3H), 2.52 (s, ArCH_3, 3H), 4.46 (q, OCH_2, 2H, J = 5 Hz), 6.22 (s, vinyl *H*, 1H), and 11.8 (s, N*H*, 1H).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 57.67; H, 5.48; N, 9.57; S, 11.01.

Ethyl 3,4-Dihydro-6-isobutyl-5-methyl-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylate (**15a**).

A mixture of 49.3 g of (0.17 mole) of **27** and 7 g of 5% palladium on carbon in 4 liters of toluene was stirred vigorously in a hydrogen atmosphere for 24 hours. The catalyst was removed and replaced with fresh catalyst (7 g). The hydrogenation was continued for 48 hours. The catalyst was removed by filtration and the solvent was concentrated to 500 ml. This was cooled to 0° and the resulting solid was filtered giving 45.3 g (0.15 mole, 91% yield) of off-white needles, mp 175-177°; ir (0.5% potassium bromide): 3100, 2960, 2880, 1740, 1680, 1305 and 1195 cm^{-1}; nmr (deuteriochloroform): ß 1.00 (d, $(CH_3)_2$, 6H, J = 6.4 Hz), 1.49 (t, O-C-CH_3, 3H, J = 7.2 Hz, 1.95 (m, C*H*, 1H), 2.56 (s, Ar CH_3, 3H), 2.70 (d, CH_2, 2H, J = 7.0 Hz), 4.54 (q, OCH_2, 2H, J = 7.2 Hz), and 10.55 (bs, N*H*, 1H).

Anal. Calcd. for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52; S, 10.89. Found: C, 57.23; H, 6.28; N, 9.50; S, 10.98.

3-Bromo-5-methylhexan-2-one.

Method A.

A mixture of 57.5 g (0.504 mole) 5-methylhexan-2-one (**1**, R_1 = methyl, R_2 = isobutyl), 225.0 g (1.007 moles) copper(II) bromide and 250 ml ethyl acetate was stirred under nitrogen as it was gently heated on a steam bath for 1.5 hours. Most of the dark copper(II) bromide was changed to white copper(I) bromide, and the supernatant was emerald green. The mixture was cooled and filtered. The filtrate was washed with water (2 × 200 ml) and again filtered to remove a new precipitate. The filtrate was washed with 5% aqueous sodium bicarbonate (2 × 100 ml) and then with 100 ml 1% aqueous ethylenediaminetetraacetic acid solution. The organic layer was dried over anhydrous potassium carbonate. The solvent was slowly distilled (20 centimeter Vigreaux column) at 15 millimeters of mercury at less than or equal to 35°. The residual oil weighed 91.2 g. It was distilled *in vacuo*, and after a small forerun, fractions bp 52-59°/8 millimeters of mercury (36.5 g) and 59-64°/8 millimeters of mercury (31.9 g) were collected. The fractions were analyzed by gc (6 feet OV-1 column, 100° isothermal, 40 ml nitrogen per minute). The first fraction contained 12.5 area % starting ketone **1** (retention time 1.54 minutes), 84.9% 3-bromo **28** (retention time 3.52 minutes), and 1.2% 1-bromo **29** (retention time 4.79 minutes). Ratio **28**:**29** = 70:8.

Method B.

A solution of 218.2 g (1.91 moles) **1** (R_1 = methyl, R_2 = isobutyl) in 500 ml acetic acid was stirred in an ice bath at 10-15°; 6 drops 48% hydrobromic acid were added and the solution was stirred for 10 minutes. Then 290.5 g (1.82 moles) bromine was added over 1.5 hours at 15°. After the addition was complete, the solution was diluted with 800 ml ice-water. The layers were separated, and the organic layer was washed with portions of 5% aqueous sodium bicarbonate until the wash was *p*H 8. The material was dried over anhydrous potassium carbonate to give 330.2 g (94% of theory) lightly colored oil. The crude material could be used without purification provided allowance was made for unreacted ketone content by vpc assay. Distillation as above provided material which had a ratio of **28**:**29** = 76:5.

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[12] This compound appeared to rapidly decompose. Within a few minutes in air, a very dark viscous oil would form. The best CHN data obtained is shown in the experimental section. When used immediately, satisfactory products were obtained.