The Base-catalyzed Condensation of α-Haloaldehydes with Dichloroacetates

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The reaction of aliphatic α-haloaldehydes with methyl dichloroacetate in the presence of sodium methoxide was carried out. α-Chloroaldehydes afforded 2,4-dichloro-2,3-epoxyalkanoates (**5**), whereas α-bromoaldehydes gave 2,2-dichloro-3,4-epoxyalkanoate (**7**). The attempted epoxy-carbonyl rearrangement of **5** with hydrogen chloride or thionyl chloride failed. The thermal decomposition of methyl 2,4-dichloro-2,3-epoxynonanoate (**5c**) at 300—400°C afforded methyl 3-chloro-2-oxo-3-nonenoate (**9c**), and the similar treatment of methyl 2,4-dichloro-4-methyl-2,3-epoxypentanoate (**5a**) afforded a mixture of methyl 3,4-dichloro-4-methyl-2-oxopentanoate (**6a**), methyl 3-chloro-4-methyl-2-oxo-3-pentenoate (**9a**), and methyl 3-chloro-4-methyl-2-oxo-4-pentenoate (**10**). The treatment of **5** with thiourea in methanol gave the thiazole derivative (**15**), but neither sodiomalonate nor sodioacetoacetate reacted with **5**.

The base-catalyzed condensation of aldehydes with the dichloroacetic ester has been reported by several authors.[1-4] It is known that the reaction affords α-chloroglycidic esters (**1**) and the α-chloropyruvic ester (**2**). Compound **2** is produced by the epoxy-carbonyl rearrangement of **1**:[4]

$$RCHO + Cl_2CHCO_2R' \longrightarrow R\text{-}\underset{\diagdown O \diagup}{CH\text{-}C}(Cl)\text{-}CO_2R' \quad \mathbf{1}$$

$$\longrightarrow R\text{-}CHCCO_2R' \quad (Cl,\ O) \quad \mathbf{2}$$

Aliphatic aldehydes with a longer chain, such as heptanal, hexanal, and nonanal, usually give rearranged products (**2**). On the contrary, acetaldehyde and propionaldehyde yield the corresponding α-chloroglycidates (**1**) predominantly. Furthermore, 2-chloro-2,3-epoxyisocaproate resists the epoxy-carbonyl rearrangement with hydrogen chloride.[4] As an extension of previous work,[4] we carried out the Darzens-type condensation of aliphatic α-haloaldehydes with methyl dichloroacetate in the presence of sodium methoxide in order to establish a synthetic route to obtain 2-chloro-4-halogeno-2,3-epoxyalkanoate (**5**) and 3-chloro-4-halogeno-2-oxoalkanoate (**6**). The present report will describe the results of this reaction and will discuss the chemical properties and the structural chacacterization of the products. The yields, boiling points, and analytical results of the products are listed in Table 1.

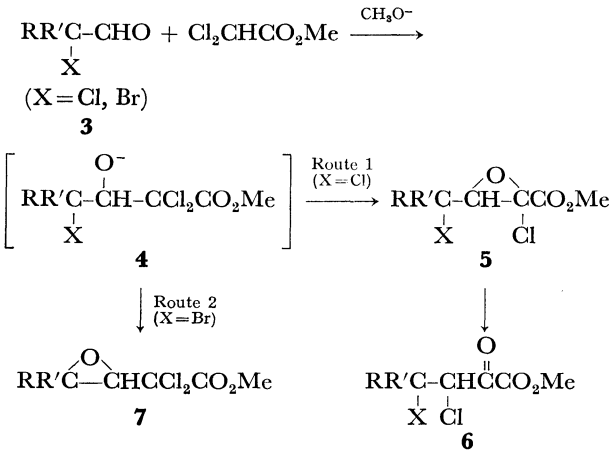
Two pathways can be postulated for the elimination of the halogen atom of the possible intermediate (**4**), as is shown in Scheme 1. One involves the formation of the glycidates, **5**, which might further undergo an epoxy-carbonyl rearrangement to **6** (Route 1). In the other, the halogen atom originating from α-haloaldehyde is eliminated to produce 2,2-dichloro-3,4-epoxyalkanoate (**7**) (Route 2).

TABLE 1. PRODUCTS FROM THE REACTION OF α-HALOALDEHYDES WITH METHYL DICHLOROACETATE

α-Haloaldehyde RR′C(X)-CHO			Products[a]		Yield, %	Bp, °C/mmHg	Found, %		Calcd, %	
R	R′	X	Code	Structure			C	H	C	H
CH_3	CH_3	Cl	**5a**	$(CH_3)_2CClCH(O)CHCClCO_2Me$	34	86—89/3	39.51	4.70	39.46	4.73
C_2H_5	H	Cl	**5b**	$C_2H_5CH(Cl)CH(O)CHCClCO_2Me$	56	94—97/4	39.65	5.01	39.46	4.73
n-C_5H_{11}	H	Cl	**5c**	$C_5H_{11}CH(Cl)CH(O)CHCClCO_2Me$	40[b]	119—126/3	47.34	6.46	47.07	6.32
C_2H_5	H	Br	**7b**	$C_2H_5CH(O)CHCHCl_2CO_2Me$	10	98— 99/7	39.28	4.57	39.45	4.73
n-C_5H_{11}	H	Br	**7c**	$C_5H_{11}CH(O)CHCHCl_2CO_2Me$	15	107—112/2	46.77	6.39	47.07	6.32

a) All the compounds listed here are new.
b) Obtained as the mixture of **5c** and **7c** (92: 8). See experimental part.

1) V. F. Martynov and M. I. Titov, *Zh. Obschch. Khim.*, **32**, 319 (1962); *Chem. Abstr.*, **57**, 12373c (1962).
2) R. N. McDonald and P. A. Schwab, *J. Org. Chem.*, **29**, 2459 (1964).
3) A. Takeda, S. Wada, and T. Uno, *Mem. School Eng., Okayama Univ.*, **2**, 80 (1967).
4) A. Takeda, S. Wada, M. Fujii, and H. Tanaka, This Bulletin, **43**, 2997 (1970).

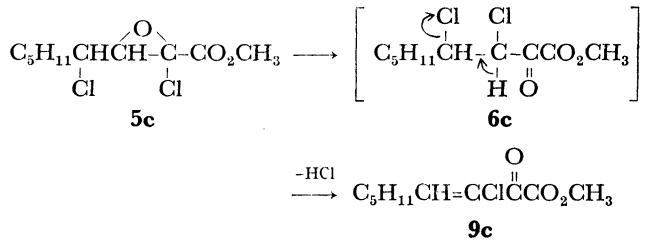


Scheme 1

The reaction of α-chloroaldehyde with dichloroacetates usually gave 2,4-dichloro-2,3-epoxyalkanoate (**5**) in a 30—55% yield. α-Chloroheptanal, however, gave a small amount (8% yield) of methyl 2,2-dichloro-3,4-epoxynonanoate (**7c**) in addition to methyl 2,4-dichloro-2,3-epoxynonanoate (**5c**). This indicates that the halogen atoms at the α and γ positions in the intermediacy (**4c**) compete as leaving groups. Indeed, α-bromoaldehydes afforded only 2,2-dichloro-3,4-epoxyalkanoate (**7**) under the same reaction conditions, even though in poor yields (10—15%), without the formation of **5**. Both compounds, **5** and **7**, were stable enough to be distillable under reduced pressure. For the structural assignment of these compounds, the NMR spectra, especially the multiplet (1H) at τ 5.8—6.2 (**5c**, C_4-methine proton) and the multiplet (1H) at τ 6.73 (**7c**, C_4-epoxide methine proton), were instructive.

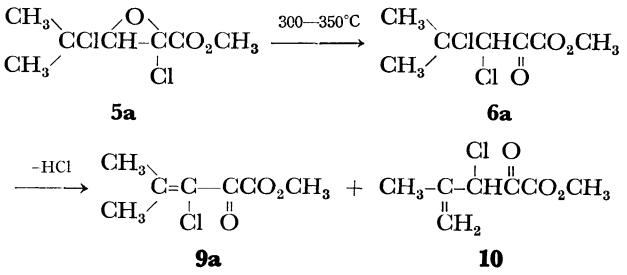
The esters **5** were treated with dry hydrogen chloride in ether at 0°C in order to investigate their facility at undergoing epoxy-carbonyl rearrangement, but the starting material was recovered unchanged, without any formation of pyruvates, **6**. Furthermore, the treatment of methyl 2,4-dichloro-2,3-epoxynonanoate (**5c**) with dry hydrogen chloride in ether at the reflux temperature, or even with excess thionyl chloride at the reflux temperature, still had no effect on its transformation to **6**. The hydrolysis of **5c** with 10% H_2SO_4 afforded only 2,4-dichloro-2,3-epoxynonanoic acid (**8**). Since the acidic hydrolysis of glycidate usually causes decarboxylative elmination thus producing ketone or aldehyde,[5,6] it is rather surprising that the acid **8** can be isolated as stable crystals. The acid **8** was again transformed to **5c** with diazomethane. The larger stability of the esters **5** as compared to α-monochloroglycidate (**1**) under treatment with hydrogen chloride or thionyl chloride may be accounted for by assuming that the migration of the chlorine atom at C_2 is hindered by the electrical repulsion which the chlorine atom attached to C_4 exerts.

The transformation of **5** to **6** was performed pyrolytically; it was usually accompanied by a secondary elimination of hydrogen chloride. The distillation of **5c** at 300—400°C (oven temperature) under an atmosphere of nitrogen gave only methyl 3-chloro-2-oxo-3-nonenoate (**9c**). The IR bands of **9c** at 1740, 1690, and 1610 cm^{-1} are characteristic of the α,β-unsaturated ketoester. The triplet at τ 2.8 (J=7 Hz) in the NMR spectrum of **9c** represents the signal from the C_4-vinyl proton. These data all support the structure of **9c**. For the formation of **9c**, the rearranged product, **6c**,

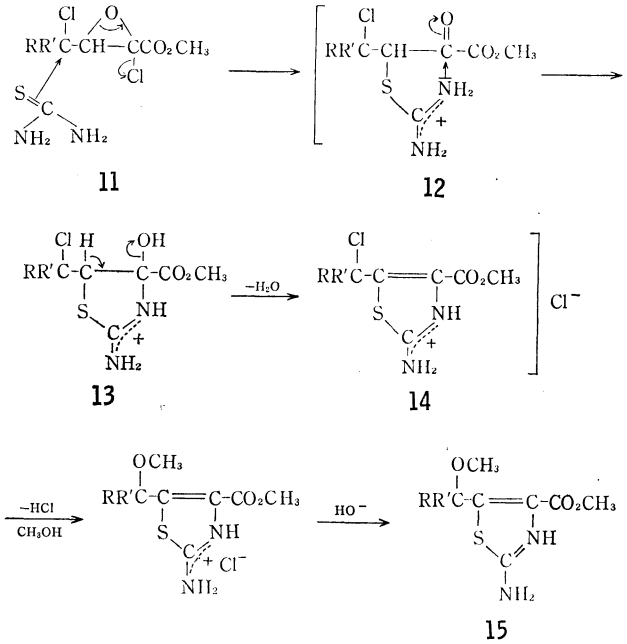


Scheme 2

might be the intermediate from which the more acidic hydrogen at C_3 is eliminated. This mechanism is supported by the pyrolysis of 4-methyl-2,4-dichloro-2,3-epoxypentanoate (**5a**), where the rearranged product **6a** has been isolated. The distillation of **5a** at 300—350°C gave a mixture of three components, methyl 3,4-dichloro-4-methyl-2-oxopentanoate (**6a**, 17%), methyl 3-chloro-4-methyl-2-oxo-3-pentenoate (**9a**, 9%), and methyl 3-chloro-4-methyl-2-oxo-4-pentenoate (**10**, 72%). The reaction sequence is shown in Scheme 3. The treatment of **6a** with triethylamine resulted in the formation of **9a** (37%).



Scheme 3



Scheme 4

5) M. Mousseron and R. Granger, *Compt. Rend.*, **218**, 358 (1944).
6) G. Darzens, *ibid.*, **195**, 884 (1932).

Although carbanions, such as sodiomalonate and sodioacetoacetate, were unreactive with **5** in methanol or dioxane, thiourea reacted with **5** in methanol to give the corresponding thiazole derivative (**15**). The possible pathway of the formation of **15** is shown in Scheme 4. Since 2-chloro-2,3-epoxyalkanoate has been known to produce the thiazole derivative readily,[4] it is reasonable to assume that the chlorinated thiazole derivative (**14**), which was formed intermediately, readily underwent solvolysis with methanol.

Experimental

The melting points and boiling points are uncorrected. The microanalyses were carried out by Mr. Eiichiro Amano of our laboratory. The analytical determinations by glpc were performed on a Hitachi K-53 model gas chromatograph (3 mm o.d.×1 m, 10% Apiezon Grease L on Chromosorb W), and the preparative isolations by glpc were performed on a Yanagimoto GCG-550T model gas chromatograph (3 mm o.d.×2.25 m, 10% Apiezon Grease L on Chromosorb W). We are indebted to Dr. Akira Suzuki and Mr. Shigezo Shimokawa, both of Hokkaido University, and to Mr. Hiroshi Ooyama, Hokko Chemical Industry Co., Ltd., for the NMR measurements.

The α-chloroaldehydes used in this experiment were prepared by the method of Stevens[7,8] by treating aldehydes with sulfuryl chloride: α-chloroisobutanal, bp 86—90°C (lit,[7] bp 86—88°C), yield 38%; α-chlorobutanal, bp 36—37°C/50 mmHg (lit,[8] bp 104—110°C), yield 27%; α-chloroheptanal, bp 76—79°C/24 mmHg (lit,[8] bp 36—38°C/2 mmHg), yield 78%. The α-bromoaldehydes were obtained by the direct bromination of aldehydes with bromine:[9,10] α-bromoheptanal, bp 75—78°C/4 mmHg (lit,[9] bp 81—82°C/3 mmHg), yield 40%; α-bromobutanal, bp 47—50°C/21 mmHg (lit,[10] bp 33°C/15 mmHg), yield 10%.

The following experiments are shown as typical runs.

Methyl 2,4-Dichloro-2,3-epoxy-4-methylpentanoate (5a). Powdered sodium methoxide (5.5 g, 0.1 mol) was added with caution to a mixture of freshly-distilled α-chloroisobutanal (10.6 g, 0.1 mol) and methyl dichloroacetate (14.3 g, 0.1 mol) dissolved in 60 m*l* of dry ether, at 5—10°C. After the addition had been completed, the heterogeneous reaction mixture was allowed to warm up to room temperature and then refluxed for 1.5 hr. The ethereal extract was washed several times with water and dried over Na_2SO_4. After the removal of the solvent, it was distilled to give 7.2 g (34%) of **5a**: bp 86—89°C/3 mmHg; IR (cm^{-1}, liquid) 1750 (ester C=O); NMR (τ, $CDCl_3$) 6.15 (s, 3H, $-COOCH_3$), 6.27 (s, 1H, $-\underset{\backslash O /}{CH}-CCl-$), 8.23 (s, 6H, $(CH_3)_2CCl-$).

Methyl 2,4-Dichloro-2,3-epoxynonanoate (5c). Powdered sodium methoxide (6.8 g, 0.125 mol) was added with caution to a mixture of freshly-distilled α-chloroheptanal (14.8 g, 0.1 mol) and methyl dichloroacetate (14.3 g, 0.1 mol) dissolved in dry ether (30 m*l*), at 0±1°C. The mixture was stirred for 1.5 hr at room temperature and then treated with water. The ethereal layer was separated, washed several times with water, and dried over Na_2SO_4. After the removal of the solvent, it was distilled giving 10.3 g (40% yield)[11] of the liquid, which was collected at 119—126°C/3 mmHg. Glpc analysis showed it to consist of two components. The peaks, retention times (min), and integrated percentages[12] are as follows: 1, 15.5, 8; 2, 17.1, 92. Component 1 was collected by preparative glpc and was identified as methyl 2,2-dichloro-3,4-epoxynonanoate (**7c**) by a comparison of its IR data and retention time with those of an authentic sample (see next section). Component 2 (**5c**) was purified similarly and analyzed: IR (cm^{-1}, liquid) 1760 (ester C=O); NMR (τ, $CDCl_3$) 6.08 (s, 3H, $-COOCH_3$), 5.8—6.2 (m, 1H, $-(CH_2)_4\underline{CH}Cl-$), 6.4 (d, 1H, $-\underset{\backslash O /}{CH}-\underset{\backslash Cl}{C}-$), 8.0—8.8 (m, 8H, $CH_3(C\underline{H}_2)_4-$), 9.03 (t, 3H, J=5 Hz, $C\underline{H}_3(CH_2)_4-$).

Methyl 2,2-Dichloro-3,4-epoxynonanoate (7c). Into a solution of α-bromoheptanal (15.0 g, 0.077 mol) and methyl dichloroacetate (11.0 g, 0.077 mol) in dry ether (30 m*l*), sodium methoxide (5.1 g, 0.096 mol) was stirred at 0±1°C. After the addition had been completed, the reaction mixture was allowed to warm up to room temperature. Stirring was continued for 1.5 hr. After the subsequent addition of water, the ethereal layer was separated, washed several times with water, dried over Na_2SO_4, and concentrated. A residual, thick yellow oil was distilled to give 3.0 g (15%) of **7c**: bp 107—112°C/2 mmHg; IR (cm^{-1}, liquid) 1750, 1760 (ester C=O); NMR (τ, $CDCl_3$) 6.1 (s, 3H, $-COOCH_3$), 6.52 (d, 1H, J=2.5 Hz, $-\underset{\backslash O /}{CH}-C\underline{H}CCl_2-$), 8.2—8.9 (m, 8H, $CH_3(C\underline{H}_2)_4-$), 9.09 (d, 3H, $C\underline{H}_3(CH_2)_4-$). A considerable amount of an undesirable resinous material was formed in this reaction and was discarded as a residue.

2,4-Dichloro-2,3-epoxynonanoic Acid (8). In a 50-m*l* three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser fitted with a drying tube, were placed dry methanol (20 m*l*) and sodium (0.46 g, 0.02 mol). While the mixture was being stirred at 0°C, 5.0 g (0.02 mol) of methyl 2,4-dichloro-2,3-epoxynonanoate (**5c**) and then 0.5 m*l* of water were added slowly. The solution was allowed to warm up to room temperature and then stirred for 3 hr. The sodium salt of the acid, **8**, precipitated in the solution was collected by filtration and washed with absolute methanol and ether. The salt was treated with a mixed solution of 2 m*l* of concentrated hydrochloric acid and 10 m*l* of water. The organic layer was extracted with ether, washed with water, and dried over Na_2SO_4. After the removal of the solvent, white needles were obtained. Recrystallization from *n*-hexane gave 1.5 g (31%) of white needles; mp 36—37°C; IR (cm^{-1}, liquid[13]) 2650 and 2500 (acid OH), 1738 (acid C=O).

Found: C, 44.43; H, 5.83%. Calcd for $C_9H_{14}Cl_2O_3$: C, 44.83; H, 5.83%.

The esterification of the above acid, **8** (1.7 g, 0.0071 mol), was carried out with diazomethane in ether. The removal of the solvent left a thick yellow liquid which, on distillation, gave 0.9 g of a clean oil: bp 126—127°C/5 mmHg. It was identified as **5c** by a comparison of IR and glpc with those of an authentic sample.

Thermal Decomposition of Methyl 2,4-Dichloro-2,3-epoxynonanoate (5c). The distillation of **5c** (2.5 g, 0.0098 mol) was carried out by heating it at 300—400°C with a mantle heater under an atmosphere of nitrogen. A thick yellow oil (2.0 g)

7) C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, **79**, 3448 (1957).
8) C. L. Stevens, E. Farkas, and B. Gillis, *ibid.*, **76**, 2695 (1954).
9) F. Ramiraz and A. F. Kirly, *ibid.*, **75**, 6026 (1953).
10) A. Kirrmann, *Compt. Rend.*, **184**, 525 (1927).
11) Estimated as compound **5c**.
12) Observed on a 1-m 10% Apiezon Grease L on Chromosorb W column. Column temp., 150°C; carrier gas, N_2 (0.5 kg/cm², 42 m*l*/min); detector, FID.
13) The IR spectrum of **8** was measured on warm NaCl prisms.

was distilled at 240—250°C under the evolution of hydrogen chloride. The glpc analysis of the oil showed two peaks.[12] The peaks, retention times (min), and integrated percentages are as follows: 1, 11.6, 62; 2, 17.2, 38. Component 1 (major constituent), collected by preparative glpc, was identified as methyl 3-chloro-2-oxo-3-nonenoate (**9c**): IR (cm^{-1}, liquid) 1740 (ester C=O), 1690 (conjugated keto C=O), 1610 (conjugated C=C).

Found: C, 54.89; H, 6.98%. Calcd for $C_{10}H_{15}ClO_3$: C, 54.92; H, 6.91%.

The spectral data of component 2 (minor constituent) were identical with those of **5c**.

Thermal Decomposition of Methyl 2,4-Dichloro-2,3-epoxy-4-methylpentanoate (5a). The distillation of **5a** (7 g, 0.033 mol) was carried out in the same manner as in the foregoing experiment on **5c**. A thick yellow oil (5.6 g) came out at 200—210°C under the evolution of hydrogen chloride. It gave a clean oil (5.1 g) on distillation under reduced pressure: bp 119—124°C/44 mmHg. Glpc analysis[14] showed three peaks, with retention times (min) of 4.5, 8.0, and 9.5 respectively, and in an area ratio of 72: 10: 18. The crude product was fractionated into components by preparative glpc. The spectral data and analyses of these components are as follows (components, retention times,[14] IR, NMR, analysis): Component 1: 4.0 min; IR (cm^{-1}, liquid) 1750 (ester C=O), 1735 (keto C=O), 1640, 1610 (C=C); NMR (τ, $CDCl_3$) 4.38 (s, 1H, $-\underset{\underset{H}{|}}{C}ClCOCO_2CH_3$), 4.78 (s, 2H, $CH_3-\overset{\overset{CH_2}{||}}{C}-$), 6.11 (s, 3H, $-COOCH_3$), 8.13 (s, 3H, $CH_3-\overset{\overset{CH_2}{||}}{C}-$). Found: C, 47.29; H, 4.95%. Calcd for $C_7H_9ClO_3$: C, 47.61; H, 5.14%. Component 2: 5.6 min; IR (cm^{-1}, liquid) 1740 (ester C=O), 1685 (conjugated keto C=O) and 1590 (conjugated C=C); NMR (τ, $CDCl_3$) 6.12 (s, 3H, $-COOCH_3$), 7.76 (s, 3H, $CH_3-\underset{\underset{CH_3}{|}}{C}=CCl-$) and 7.88 (s, 3H, $CH_3-\underset{\underset{CH_3}{|}}{C}=CCl-$). Found: C, 47.32; H, 5.24. Calcd for $C_7H_9ClO_3$: C, 47.61; H, 5.14. Component 3: 7.2 min; IR (cm^{-1}, liquid) 1760 (ester C=O) and 1740 (keto C=O); NMR (τ, $CDCl_3$) 3.98 (s, 1H, $-\underset{\underset{H}{|}}{C}Cl-CO-$), 6.12 (s, 3H, $-COOCH_3$), 8.35 (s, 3H, $CH_3-\underset{\underset{CH_3}{|}}{C}ClCHCl-$) and 8.48 (s, 3H, $CH_3-\underset{\underset{CH_3}{|}}{C}ClCHCl-$). Found: C, 39.80; H, 4.67%. Calcd for $C_7H_{10}Cl_2O_3$: C, 39.46; H, 4.73%. On the basis of these data, components 1, 2, and 3 are identified as methyl 3-chloro-4-methyl-2-oxo-4-pentenoate (**10**), methyl 3-chloro-4-methyl-2-oxo-3-pentenoate (**9a**), and methyl 3,4-dichloro-4-methyl-2-oxopentanoate (**6a**) respectively. The conjugation of the double bond with the keto carbonyl group is obvious in compound **9a**, while it is not in compound **11**. Compound **9a** has no double bond.

Dehydrochlorination of 6a with Triethylamine. To a solution of gas-chromatographically-pure sample of **6a** (12 mg, 5.6×10^{-5} mol) in dry ether (0.1 m*l*), was added triethyl amine (0.0145 g, 1.4×10^{-4} mol) at room temperature. After the solution had been shaken upon occasion for 30 min, the excess of triethylamine was removed by evaporation. The glpc analysis of the residual oil showed two peaks which corresponded to **9a** and **6a** in retention times, *i.e.*, 8.0 min and 9.5 min respectively. By referring to the peak areas it can be estimated that 37% of the starting material (**6a**) has been transformed to **9a**.

2-Amino-4-methoxycarbonyl-5-(1-methoxyhexyl)thiazole (15c). A solution of **5c** (1.2 g 0.0047 mol) and thiourea (0.36 g, 0.0047 mol) in methanol (10 m*l*) was refluxed for 18 hr. The mixture was diluted with water and made alkaline with aqueous ammonia. The organic layer was extracted with ether, washed with water, and dried over Na_2SO_4. After the removal of the solvent, 0.9 g of a brownish-green oil (**15c** of *ca.* 80% purity by thin layer chromatography[15]) was obtained. A pure sample of **15c** was collected by preparative tlc for microanalyses and spectra determinations: R_f 0.2; IR (cm^{-1}, liquid) 3400, 3300, 3110, 2920, 1707, 1620, 1540, 1220; NMR (τ, $CDCl_3$) 4.1 (s, 2H, $-NH_2$), 4.9 (t, 1H, $J=6$ Hz, $C_5H_{11}-C\underline{H}OCH_3-$), 6.18 (s, 3H, $-COOCH_3$), 6.71 (s, 3H, $-OCH_3$), 8.1—8.9 (m, 8H, $CH_3(C\underline{H}_2)_4-$), 9.1 (t, 3H, $J=4.5$ Hz, $C\underline{H}_3(CH_2)_4-$).

Found: C, 52.98; H, 7.32; N, 10.08%. Calcd for $C_{12}H_{20}N_2O_3S$: C, 52.92; H, 7.40; N, 10.28%.

2-Amino-4-methoxycarbonyl-5-(1-methoxyisopropyl)thiazole (15a) A solution of **5a** (2.1 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in methanol (15 m*l*) was refluxed for 15 hr. By treating the mixture in ways similar to those used in the case of **15c**, 0.9 g of a pale yellow oil (**15a** of *ca.* 80% purity by tlc[15]) was obtained. The analytical sample of **15a** was prepared by tlc: R_f 0.15; IR (cm^{-1}, liquid) 3400, 3320, 3120, 2960, 1610, 1620, 1540, 1215; NMR (τ, $CDCl_3$) 4.02 (s, 2H, $-NH_2$), 6.12 (s, 3H, $-COOCH_3$), 6.71 (s, 3H, $-OCH_3$,) 8.33 (s, 6H, $2CH_3-$).

Found: C, 46.84; H, 6.15; N, 11.84%. Calcd for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16%.

14) Column temp., 110°C.

15) On silica gel G (E. Merck AG, Darmstadt) with acetone–*n*-hexane (1: 3 v/v).