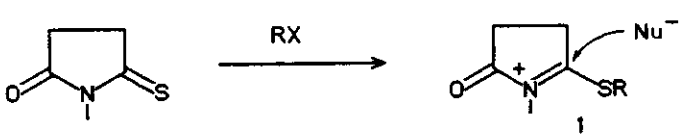
SYNTHESIS OF 2,2-DISUBSTITUTED SUCCINIMIDES AND THEIR REGIOSELECTIVE THIOCARBONYLATION REACTION

Yoshiyuki Kosugi,* Masako Kosugi, and Fumiko Hamaguchi
Tokyo College of Pharmacy, Horinouchi 1432-1, Hachioji,
Tokyo 192-03, Japan

Abstract —— 2,2-Dialkoxy- and 2,2-bis(alkylthio)succinimide (3a-c and 3g) were prepared from 2,3-dibromosuccinimide by the reaction with alkoxide or thiolate anion. In contrast to most 2,2-disubstituted succinimides, thiocarbonylation reaction of the imides bearing ethylenedioxy group with Lawesson reagent occurred at the more hindered carbonyl group to give monothioimides (6c and 6d) as major products.

New methods for activating the α-position in nitrogen heterocycles, including generations of N-acyliminium and thioiminium intermediates, have been developed in recent years.[1] In relation to those activating methods, the reaction of N-acylthioiminium salts (1) with nucleophiles is of interest as a promising method for the introduction of C-functional group to the α-position in pyrrolidine or piperidine ring since 1 seemed to be more stable than N-acyliminium and more reactive than thioiminium analogues. The intermediates (1) are easily accessible from cyclic imides by thiocarbonylation and subsequent S-alkylation. However, generation of two isomers would be observed during the thiocarbonylation reaction, when unsymmetrically substituted cyclic imides were used as starting materials, just like a situation as the metal hydride reduction of substituted cyclic imides[2] and anhydrides.[3] In order to examine the selectivity between two carbonyl groups



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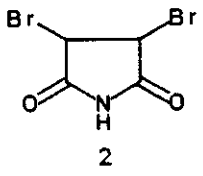
in the imides, we have synthesized a series of geminally disubstituted succinimides by newly developed method or in part according to a known procedure, and investigated their thiocarbonylation reaction with Lawesson reagent.

In the same way as we have demonstrated the introduction of methoxy group to 3-halo-5-hydroxy-2(5H)-furanones,[4] 2-bromomaleimide obtained from maleimide by bromination followed by dehydrobromination was found to undergo conversion to 2,2-dimethoxysuccinimide (**3a**) by treatment with 2 equivalent of sodium methoxide in methanol at 5 ℃ for 48 h. Thus, the reaction of 2,3-dibromosuccinimide (**2**) with 3 equivalent of sodium methoxide in methanol [-15 ℃ → 5 ℃, 48 h then HCl/MeOH workup] gave **3a** as a crude oil which on purification by flash column chromatography (SiO_2, hexane/acetone) afforded crystalline solid (mp 76-77 ℃, lit.[5] 77-79 ℃) in 70% yield. Since thiolate anion is more nucleophilic than methoxide ion, dithioketal (**3b**)[6] was successfully obtained as pale yellow crystals by dissolving the dibromide (**2**) in methanol solution containing sodium methoxide (3 eq.) and 1,2-ethanedithiol (1 eq.) [-15 ℃ → 5 ℃, 24 h then HCl/MeOH workup] in 67% yield. In the presence of 1,3-propanedithiol, however, the above procedure did not give any desired product, but furnished the maleimide derivative (**4**) instead. The cyclization of **4** to the dithioketal (**3g**) could finally be achieved by refluxing the reaction mixture for 2 h (62% yield from **2**). Ketal (**3c**), the oxygen analogue of **3b**, was similarly obtained by treating **2** with ethylene glycol sodium salt prepared from sodium (3 eq.) in ethylene glycol [0 ℃ → rt, 48 h then HCl/MeOH workup]. Subsequent N-alkylation of **3c** with methyl bromoacetate in the presence of sodium hydride in THF gave **3d** in 72% yield. In addition, 2,2-dimethyl- (**3e**) and 2,2-diphenylsuccinimide (**3f**) were also prepared from the corresponding succinic acids by thermal cyclocondensation <u>via</u> ammonium salts or for more convenience by heating with formamide [150 ℃, overnight]. Physical data of the imides are listed in Table II.



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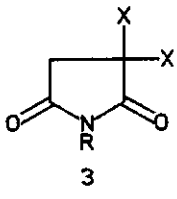

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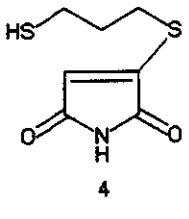
a: X=OMe, R=H
b: X=SCH_2CH_2S, R=H
c: X=OCH_2CH_2O, R=H
d: X=OCH_2CH_2O, R=CH_2CO_2Me
e: X=Me, R=H
f: X=Ph, R=H
g: X=$S(CH_2)_3S$, R=H



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Thiocarbonylation reactions were carried out by heating the solution of imides (3a-f) in appropriate solvent using 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide[7] (Lawesson reagent). After removal of solvent, the remaining mixtures were separated by flash column chromatography (SiO_2, hexane/chloroform) to give monothioimides (5 and 6) and dithioimides (7) as yellow crystalline solids, respectively (Table I and Table III). The structures of products were confirmed by their ir, ^{1}H-nmr and ms spectra. The characteristic downfield shift of the methylene protons (0.32-0.39 ppm) as a result of the electron withdrawing effect of the neighbouring C=S group clearly suggested the structure of monothioimides (5). In most cases, thiocarbonylation occurred at the

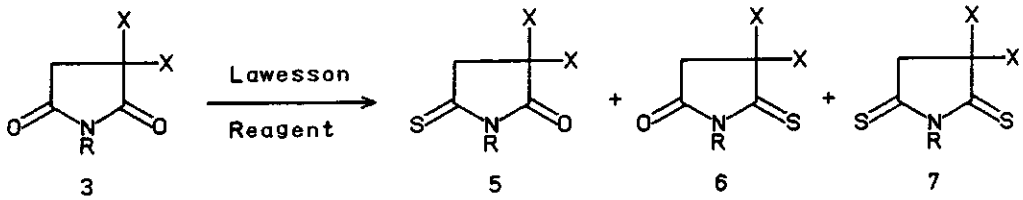

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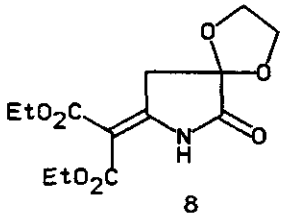
Table I. Thiocarbonylation Reaction of 2,2-Disubstituted Succinimides (3a-f).

Compound	(Reaction Conditions)	Yield (%) 5	6	7	3
3a X=OMe, R=H	(dioxane, 95 ℃, 30 min)	58	1	-	40
3b X=SCH_2CH_2S, R=H	(dioxane, reflux, 30 min)	89	4	5	-
3c X=OCH_2CH_2O, R=H	(THF, reflux, 1 h)	9	28	3	58
	(C_6H_6, reflux, 3 h)	13	38	18	21
	(dioxane, reflux, 20 min)	19	33	26	15
	(dioxane, reflux, 3 h)	8	24	59	-
3d X=OCH_2CH_2O, R=CH_2CO_2Me	(dioxane, reflux, 2 h)	15	30	5	49
3e X=Me, R=H	(dioxane, reflux, 30 min)	70	4	7	18
3f X=Ph, R=H	(dioxane, reflux, 30 min)	68	-	-	30

less hindered side to afford 5 predominantly. However, ethylendioxy group dramatically changed the selectivity, yielding 6c and 5c in the ratio of 3 : 1. This reversal of regioselectivity was also observed in the reaction of the N-substituted derivative (3d). As it was difficult to separate the isomeric mixture (6c and 5c) especially in a large scale synthesis, the mixture was subsequently condensed with ethyl bromomalonate in the presense of sodium ethoxide in ethanol to give a readily separable mixture of alkylidene compounds[8] (9 and 8, 73% yield) in the same ratio as 6c : 5c.



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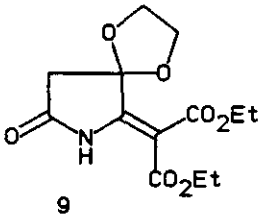

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It is well known that hydride reduction of cyclic imides[2] and anhydrides[3] preferentially occurred at the sterically more hindered carbonyl group. Although such regioselectivity has been explained mainly by steric effect of substituent, electronic interaction between a imide carbonyl and a neighbouring heteroatom is still likely to rationalize the selectivity in the case of 2-acetoxysuccinimide where the reduction was completely regioselective.[9] Thus, alkoxy group may also affect the selectivity even in the preparation of thioimides. However, the fact that methoxy group which seemed to occupy larger space than ethylenedioxy group by means of free rotation did not cause any irregular reactivity again suggested finely sensitive of steric factor. Where as the steric effect and the electronic perturbation may activate the same carbonyl group in hydride reductions, each influence may work independently to the opposite direction in the case of thiocarbonylation reactions since the approach of relatively large sulfur reagent to the more hindered carbonyl is disadvantageous. That is probably the reason why the regioselectivity is reversible.

Table II. Physical Data of 2,2-Disubstituted Succinimides (3a-g).

Compound	Mp (°C) and Spectral Data [ir (KBr, ν, cm^{-1}); ^{1}H-nmr ($CDCl_3$, δ, ppm); ms (m/z)]
3a	mp 76-77; ir 3225 (NH), 2975 and 2950 (CH), 1795, 1720 (C=O); nmr 9.35 (1H, br s, NH), 3.43 (6H, s, 2×OCH_3), 2.85 (2H, s, CH_2).
3b	mp 118-120; ir 3180 (NH), 2940 (CH), 1785, 1710 (C=O), 1350, 1200; nmr 9.00 (1H, br s, NH), 3.85-3.40 (4H, m, SCH_2CH_2S), 3.28 (2H, s, CH_2); m/z 189 (M^+).
3c	mp 175-176; ir 3250 (NH), 2900 (CH), 1780, 1740, 1715 (C=O), 1210, 1060; nmr 8.00 (1H, br s, NH), 4.40-4.10 (4H, m, OCH_2CH_2O), 2.97 (2H, s, CH_2); m/z 157 (M^+).
3d	mp 88-89; ir 2930 (CH), 1735 and 1715 (C=O), 1415, 1305, 1215, 1010; nmr 4.47-4.05 (4H, m, OCH_2CH_2O), 4.23 (2H, s, NCH_2), 3.73 (3H, s, OCH_3), 3.00 (2H, s, CH_2); m/z 229 (M^+).
3e	mp 107-109; ir 3170 (NH), 3075, 2980 (CH), 1780, 1710 (C=O), 1395, 1240, 1150, 845; nmr 8.95 (1H, br s, NH), 2.58 (2H, s, CH_2), 1.32 (6H, s, 2×CH_3).
3f	mp 142-144; ir 3170 (NH), 3060, 3000 (CH), 2780, 1785, 1705 (C=O), 700; nmr 8.50-7.20 (1H, br s, NH), 7.33 (10H, m, 2×Ph), 3.47 (2H, s, CH_2).
3g	mp 177-182; ir 3180 (NH), 3075, 2950 and 2910 (CH), 2790, 1780, 1705 (C=O), 1350, 1200, 810; nmr 8.75 (1H, br s, NH), 3.93-3.60 (2H, m, SCH_2), 2.78 (2H, s, CH_2), 2.80-2.53 (2H, m, SCH_2), 2.40-1.65 (2H, m, CH_2); m/z 203 (M^+).

Table III. Physical Data of 2,2-Disubstituted Thiosuccinimides (5, 6 and 7).

Compound	Mp (°C) and Spectral Data [ir (KBr, ν, cm^{-1}); ^1H-nmr ($CDCl_3$, δ, ppm); ms (m/z, %)]
5a	mp 78-80; ir 3200 and 3140 (NH), 3000 and 2920 (CH), 1740 (C=O), 1450, 1295, 1250, 1100; nmr 9.66 (1H, br s, NH), 3.42 (6H, s, 2×OCH_3), 3.18 (2H, s, CH_2); m/z 175 (M^+, 50), 147 (48), 88 (100).
5b	mp 210-217 (dec.); ir 3100 (NH), 2925 (CH), 1720 (C=O), 1455, 1220; nmr 9.10 (1H, br s, NH), 3.85-3.40 (4H, m, SCH_2CH_2S), 3.60 (2H, s, CH_2); m/z 205 (M^+, 96), 189 (34), 146 (24), 118 (100).
5c	mp 155-156; ir 3150 (NH), 2900 (CH), 1755 (C=O), 1460, 1285, 1250, 1200, 1060; nmr 9.30 (1H, br s, NH), 4.47-4.05 (4H, m, OCH_2CH_2O), 3.29 (2H, s, CH_2); m/z 173 (M^+, 32), 145 (21), 112 (10), 86 (100).
5d	mp 74-76; ir 2950 (CH), 1765 and 1745 (C=O), 1355, 1205; nmr 4.63 (2H, s, NCH2), 4.50-4.07 (4H, m, OCH_2CH_2O), 3.73 (3H, s, OCH_3), 3.35 (2H, s, CH_2); m/z 245 (M^+, 100), 217 (56), 184 (69), 129 (88).
5e	mp 143-146; ir 3200 and 3140 (NH), 2980 and 2930 (CH), 1740 (C=O), 1440, 1240, 1140; nmr 9.75 (1H, br s, NH), 2.97 (2H, s, CH_2), 1.32 (6H, s, 2×CH_3); m/z 143 (M^+, 100), 56 (41).
5f	mp 156-157; ir 3190 and 3130 (NH), 2900 (CH), 1730 (C=O), 1460, 1230, 700; nmr 9.50 (1H, br s, NH), 7.33 (10H, m, 2×Ph), 3.83 (2H, s, CH_2); m/z 267 (M^+, 70), 223 (10), 194 (19), 165 (28), 78 (100).
6a	mp 127-128; ir 3200 and 3110 (NH), 2940 (CH), 1785, 1735 (C=O), 1440, 1220, 1200; nmr 9.40 (1H, br s, NH), 3.43 (6H, s, 2×OCH_3), 2.90 (2H, s, CH_2); m/z 175 (M^+, 13), 145 (99), 115 (100).
6b	mp 180-183 (dec.); ir 3100 (NH), 2925 (CH), 1760, 1735 (C=O), 1460, 1215; nmr 9.57 (1H, br s, NH), 3.93-3.43 (4H, m, SCH_2CH_2S), 3.40 (2H, s, CH_2); m/z 205 (M^+, 100), 172 (24), 146 (55), 118 (70).
6c	mp 138-140; ir 3100 (NH), 2900 (CH), 1750 (C=O), 1455, 1205, 1035; nmr 9.67 (1H, br s, NH), 4.67-4.00 (4H, m, OCH_2CH_2O), 3.01 (2H, s, CH_2); m/z 173 (M^+, 61), 130 (46), 114 (63), 86 (100).
6d	mp 74-76; ir 2995, 2955 and 2895 (CH), 1765 and 1735 (C=O), 1330, 1185, 1170; nmr 4.60 (2H, s, NCH_2), 4.60-4.10 (4H, m, OCH_2CH_2O), 3.73 (3H, s, OCH_3), 3.04 (2H, s, CH_2); m/z 245 (M^+, 78), 202 (98), 170 (46), 142 (52), 113 (100).
6e	mp 135-136; ir 3120 (NH), 2975 (CH), 1730 (C=O), 1445, 1210, 1195; nmr 9.60 (1H, br s, NH), 2.65 (2H, s, CH_2), 1.40 (6H, s, 2×CH_3); m/z 143 (M^+, 100), 128 (56), 100 (10), 56 (56).
7a	mp 110-112; ir 3150 (NH), 2950, 2925 and 2900 (CH), 1470, 1215, 1110; nmr 10.05 (1H, br s, NH), 3.41 (6H, s, 2×OCH_3), 3.25 (2H, s, CH_2); m/z 191 (M^+, 43), 176 (27), 161 (100), 144 (45), 131 (49).
7b	mp 169-172 (dec.); ir 3180 (NH), 2900 (CH), 1465, 1205; nmr 10.20 (1H, br s, NH), 3.92-3.43 (4H, m, SCH_2CH_2S), 3.73 (2H, s, CH_2); m/z 221 (M^+, 100), 162 (64).
7c	mp 112-114; ir 3140 (NH), 2900 (CH), 1465, 1230, 1200, 1105, 1030; nmr 10.50 (1H, br s, NH), 4.60-4.08 (4H, m, OCH_2CH_2O), 3.37 (2H, s, CH_2); m/z 189 (M^+, 100), 161 (14), 146 (32), 129 (37).
7d	mp 71-72; ir 1980 and 1900 (CH), 1740 (C=O), 1375, 1335, 1180; nmr 5.06 (2H, s, NCH_2), 4.67-4.10 (4H, m, OCH_2CH_2O), 3.73 (3H, s, OCH_3), 3.42 (2H, s, CH_2); m/z 261(M^+, 100), 218 (56), 186 (38), 129(81).
7e	mp 77-78; ir 3130 (NH), 3970 and 3900 (CH), 1470, 1455, 1210, 1135, 1080; nmr 10.20 (1H, br s, NH), 3.07 (2H, s, CH_2), 1.38 (6H, s, 2×CH_3); m/z 159 (M^+, 100), 144 (33), 126 (20), 85 (31).

The investigations described here demonstrate that the isomeric monothioimides can be obtained complementally by choosing dimethoxy or ethylenedioxy group as a ring substituent and will become useful intermediates for more complicated pyrrolidines. Further synthetic studies on this line are in progress.

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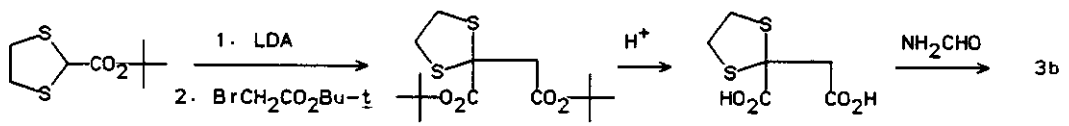
6. In order to identify the structure of **3b**, an alternative synthesis was carried out by the route as shown below.



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8. **8**: mp 108-110 °C; ir (KBr, ν, cm^{-1}) 3270 (NH), 2975 and 2900 (CH), 1750 and 1700 (C=O), 1640 and 1600 (C=C), 1265, 1245, 1210, 1030; nmr ($CDCl_3$, δ, ppm) 10.40 (1H, br s, NH), 4.45-4.03 (4H, m, OCH_2CH_2O), 4.25 (4H, q, J=7.5Hz, $2\times OCH_2CH_3$), 3.33 (2H, s, CH_2), 1.30 (6H, t, J=7.5Hz, $2\times OCH_2CH_3$); ms (m/z, %) 299 (M^+, 34), 254 (33), 226 (39), 199 (36), 127 (66), 86 (100).
9: mp 74-75 °C; ir (KBr, ν, cm^{-1}) 3300 (NH), 3000 (CH), 1740 and 1695 (C=O), 1645 (C=C), 1210; nmr ($CDCl_3$, δ, ppm) 9.95 (1H, br s, NH), 4.25 (2H, q, J=6.5 Hz, OCH_2CH_3), 4.23 (2H, q, J=6.5Hz, OCH_2CH_3), 4.23-3.87 (4H, m, OCH_2CH_2O), 2.68 (2H, s, CH_2), 1.32 (3H, t, J=6.5Hz, OCH_2CH_3), 1.27 (3H, t, J=6.5Hz, OCH_2CH_3); ms (m/z, %) 299 (M^+, 62), 254 (97), 210 (100), 138 (61).
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