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Acyl Migrations in Diacyl Derivatives of 2-Methylmercaptobenzimidazole
A Model of Biotin

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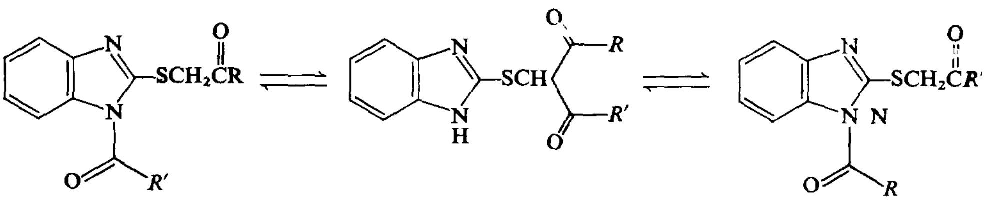
Diacyl derivatives of 2-methylmercaptobenzimidazole undergo the tautomerization **2** ⇌ **1** ⇌ **2′**. Thermodynamic predominancy of one isomer over the others depends on the substituents on carbonyl groups. It has been found that electron-withdrawing substituents tend to favor **2**-type compounds, whereas electron-releasing substituents make **1**-type compounds more stable. The migration has been extended to include the carboethoxy group, and the results are discussed in relation to the mechanism of biotin-dependent enzymic carboxylation.

INTRODUCTION

In a previous communication we reported that some diacyl derivatives of 2-methylmercaptobenzimidazole (**a–c**) undergo acyl migration under quite mild conditions (*1*).



2   **1**   **2′**

a: $R = \text{Ph}$, $R' = CH_3$ **d:** $R = p\text{-}CH_3C_6H_4\text{–}$, $R' = p\text{-}ClC_6H_4\text{–}$

b: $R = R' = \text{Ph}$ **e:** $R = CF_3$, $R' = p\text{-}CH_3C_6H_4\text{–}$

c: $R = R' = CH_3$ **f:** $R = CH_3$, $R' = OC_2H_5$

The thermodynamic predominancy among the diacyl derivatives depends on the substituents *R* and *R′*. Namely, the C → N rearrangement of 1-phenyl-2-(2′-mercaptobenzimidazolyl)butane-1,3-dione (**1a**) affords a mixture of *S*-phenacyl-*N*-acetyl-2-mercaptobenzimidazole (**2a**) and *S*-acetonyl-*N*-benzoyl-2-mercaptobenzimidazole (**2′a**). Slower acyl exchange then converts **2′a** into **2a**; 1,3-diphenyl-2-(2′-mercaptobenzimidazolyl)propane-1,3-dione (**1b**) is too unstable to be isolated. Irreversible N → C conversion of *S*-acetonyl-*N*-acetyl-2-mercaptobenzimidazole (**2c**) to 3-(2′-mercaptobenzimidazolyl)pentane-2,4-dione (**1c**) takes place in the presence of a weak base such as pyridine. The reaction may serve as a model for biotin-dependent carboxylation (*1–3*), and it is interesting to obtain an insight into the relation between the nature of the substituents and the direction of migration.

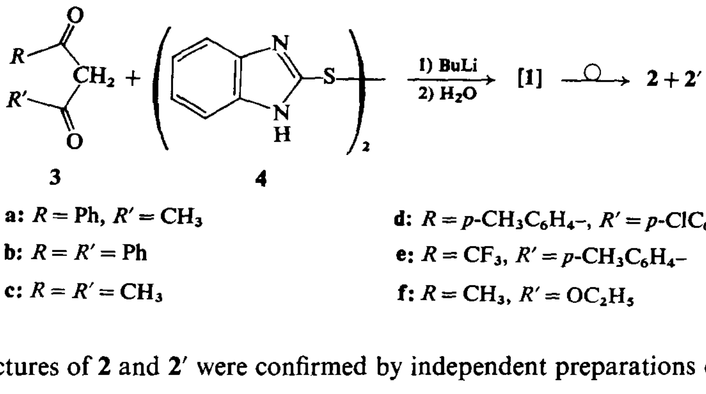
The present paper concerns the electronic effect of substituents that governs relative stability of isomers. In the latter part of the paper the discussion will be focused on the mechanism of biotin-dependent carboxylation.

RESULTS AND DISCUSSION

All migration reactions were carried out at room temperature, about 23°C.

Products

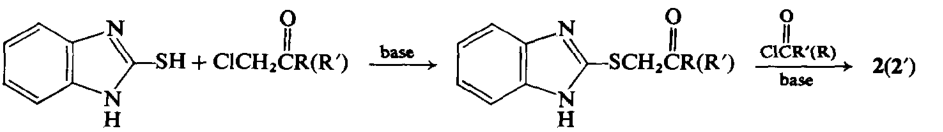
When a 3 M excess of the lithium salt of *p*-chloro-*p*′-methyldibenzoylmethane (**3d**) was allowed to react with 2,2′-dibenzimidazolyl disulfide (**4**) in a tetrahydrofuran (THF)–dimethylsulfoxide (DMSO) mixture, there were isolated 1-*p*-chlorobenzoyl-2-*p*-methylphenacylthiobenzimidazole (**2d**), 1-*p*-methylbenzoyl-2-*p*-chlorophenacylthiobenzimidazole (**2′d**), and 2-mercaptobenzimidazole in 20, 45, and 85% yields, respectively.



3 **4**

a: *R* = Ph, *R*′ = CH_3
b: *R* = *R*′ = Ph
c: *R* = *R*′ = CH_3
d: *R* = *p*-$CH_3C_6H_4$–, *R*′ = *p*-ClC_6H_4–
e: *R* = CF_3, *R*′ = *p*-$CH_3C_6H_4$–
f: *R* = CH_3, *R*′ = OC_2H_5

The structures of **2** and **2′** were confirmed by independent preparations of these compounds.



5(5′)

a: *R* = Ph, *R*′ = CH_3
b: *R* = *R*′ = Ph
c: *R* = *R*′ = CH_3
d: *R* = *p*-$CH_3C_6H_4$–, *R*′ = *p*-ClC_6H_4–
e: *R* = CF_3, *R*′ = *p*-$CH_3C_6H_4$–
f: *R* = CH_3, *R*′ = OC_2H_5

The equilibrium between the *C*-*p*-methylbenzoyl-*N*-*p*-chlorobenzoyl derivative, **2d**, and its counterpart, **2′d**, in chloroform-*d* was followed by nmr spectroscopy. A pair of singlets due to methyl and methylene protons in **2d** (δ 2.43 and 4.87) or in **2′d** (δ 2.48 and 4.83) changed to a set of four singlets after an appropriate time interval. A new pair of singlets was found to coincide with that from **2′d** or that from **2d**, respectively. Relative amounts of **2d** and **2′d** in the solution were calculated from relative peak heights of signals. The results summarized in Table 1 reveal that the equilibrium composition, **2d**/**2′d**, is slightly larger than unity.

TABLE 1

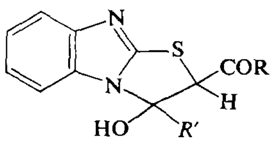
EQUILIBRIUM BETWEEN 1-*p*-CHLOROBENZOYL-2-*p*-METHYLPHENACYLTHIOBENZIMIDAZOLE (**2d**) AND 1-*p*-METHYLBENZOYL-2-*p*-CHLOROPHENACYLTHIOBENZIMIDAZOLE (**2′d**) IN CHLOROFORM-*d* AT ROOM TEMPERATURE (~23°C)

Starting material	Time (days)								
	0	1	2	3	4	5	6	7	8
2d	100[a]	78	72	—	63	62	—	52	57
2′d	100	77	68	58	51	—	49	47	48

[a] All values are percentages.

C → N Acyl Migration

There is no doubt that a cyclic carbinolamine (**6** or **6′**) is involved as a common intermediate of C → N and N → C acyl migrations (*1*, *5–7*). Alper and co-workers (*6*) have



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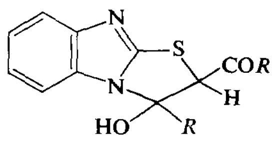


6′

proposed that the substituent effect in the ring chain tautomerism of **5**-type compounds can be attributed to electronic and steric properties; the more electron-withdrawing and the smaller the *R*, the more favorable the cyclic tautomer. The electronic effect of substituents is understandable from susceptibilities of various carbonyl groups toward nucleophilic attack (*8*). Slight dominance of the *N*-*p*-chlorobenzoyl derivative, **2d**, over the *N*-*p*-methylbenzoyl derivative, **2′d**, in the equilibrium mixture and the fact that the sole product from the reaction of 1,1,1-trifluoro-4-*p*-methylphenylbutane-2,4-dione (**3e**) with the disulfide, **4**, was 1-trifluoroacetyl-2-*p*-methylphenacylthiobenzimidazole (**2′e**) are in accord with reported substituent effects. However, previously reported results on the C → N and N → C migrations of the acetyl group (**1a** → **2a**; **1c** ↛ **2c**) (*1*) cannot be explained by the proposed substituent effects. Relative stabilities of the *C*,*C*-diacyl derivatives, **1a**, **1b**, and **1c**, also are in contradiction to the susceptibilities of acetyl and benzoyl groups toward a nucleophilic attack (*9*). It should be noted that the substituent effect discussed above is that for the ring-chain tautomerism and, in order to understand the effect for the overall rearrangement, one has to take into account the effect for the N → C acyl migration.

N → C Acyl Migration

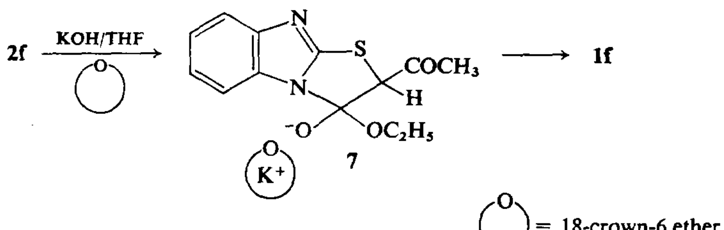
As mentioned above, the N → C acyl migration involves a cyclic intermediate, **6** or **6′**, and it is apparent that the facility of the migration depends on the basicity of amide oxygen and the acidity of methylene protons. The reported trend for basicities

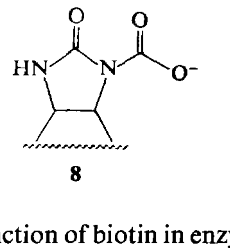
(*10*) and acidities (*11*) of these groups coincides with the presently observed results. That the *C,N*-diacetyl derivative, **2c**, can rearrange to the *C,C*-diacetylated compound, **1c**, only under basic conditions and that the *N*-trifluoroacetyl derivative, **2'e**, cannot undergo the N → C acyl migration even under strongly basic conditions support the idea that proton abstraction is the most important process for this rearrangement.

Consequently, the *C,N*-diacylated compound **2** (or **2'**) resists the rearrangement when *R'* (or *R*) is electron-withdrawing and *R* (or *R'*) is electron-releasing.

A Model Reaction

The above conclusion suggests that the carboalkoxy group on a ring nitrogen might have a greater migrating aptitude than an acyl group, because an alkoxy group is more electron-releasing than an alkyl group. We then attempted the rearrangement of 1-ethoxycarbonyl-2-acetonylthiobenzimidazole (**2f**) into ethyl 2-(2'benzimidazolylthio)-3-oxobutanoate (**1f**). This compound did not undergo the rearrangement in THF with or without a weak base such as pyridine. However, when **2f** was treated with sodium hydroxide in a THF–water mixture, the migration of ethoxycarbonyl group took place, and **1f** was isolated in 57% yield based on consumed **2f**. It is interesting to note that, even under such hydrolytic conditions as those presently employed, the migration proceeds much faster than the hydrolysis of the carboethoxy group (*12*). The use of 18-crown-6 ether made it possible to isolate the cyclic intermediate (**7**): When **2f** was added to a solution of 18-crown-6 ether and potassium hydroxide in THF, a white precipitate of **7** appeared immediately. The structure of **7** was elucidated from uv, nmr, and mass spectral data. The mass spectrum of **7** exhibits the highest peak at *m/e* 260 (M^+-H_2O), which represents a remarkable difference from mass spectra of **1**- or **2**-type compounds.





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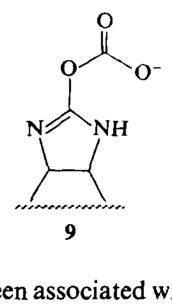

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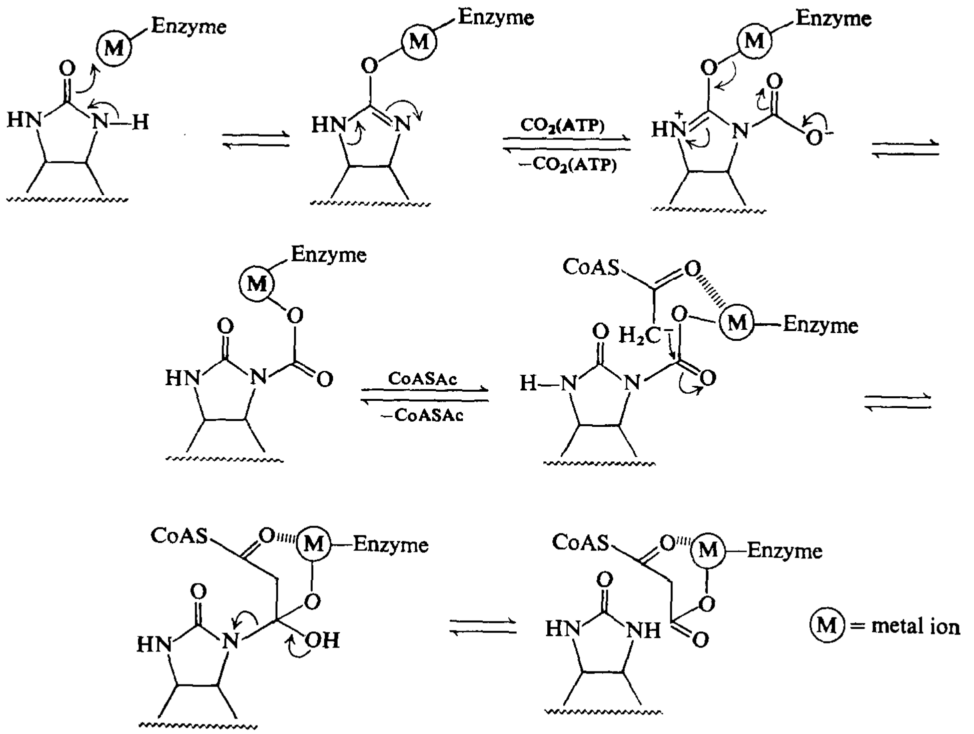
The function of biotin in enzymic carboxylation has long been associated with activation of carbon dioxide through bonding to a ring nitrogen (**8**) (*2, 13*). The most impressive support for this mechanism is the isolation of the dimethyl ester of *N'*-carboxybiotin from enzymic systems (*14*). Guchhait and co-workers have witnessed enzymic activity of *N*′-carboxybiotin (*15*).

Bruice and co-workers, on the other hand, argued against Lynen's mechanism and proposed oxygen-bonded carbon dioxide (**9**) for the active species (*3*). These authors found by the aid of model reactions that the **9**-type compound has a large susceptibility toward nucleophilic attack (*3b*).



Although the present results do not provide evidence, which justifies discussion of the structure of active carboxybiotin itself, they supply the first organo-chemical evidence that the carboxy group in **8** has the ability to be transferred into acyl-CoA or an acyl-enzyme moiety under certain conditions.

A revised mechanism for enzymic reaction, based on the mechanism of N → C acyl migration, may be represented by Scheme 1. In the present mechanism, carbon dioxide is attacked by an imidazole nitrogen instead of an imidazolidone nitrogen. The large nucleophilicity of the former nitrogen has been proven (*3a*, *16*).

EXPERIMENTAL

2,2′-Dibenzimidazolyl disulfide (**4**). Fifteen grams of 2-mercaptobenzimidazole was dissolved in 1.5 liters of an aqueous solution of potassium hydroxide (5.6 g) at 75–85°C, after which an ethanol solution of iodine (12.9 g) at 50–60°C was added.

The yellow precipitate was washed successively with aqueous sodium thiosulfate, ethanol, and ether. The solid (14.1 g, 95% yield) was obtained and used without further purification.

1-Benzyl-2-acetonylthiobenzimidazole (**2'a**). A mixture of THF (5 ml) and benzoyl chloride (6 ml) was added dropwise to an ice-cooled and stirred THF (30 ml) solution containing 4.12 g of 2-acetonylthiobenzimidazole (*5*) and 6 ml of pyridine. The solution was stirred for 45 min in an ice bath and then for 1.5 hr at room temperature. Benzene (70 ml) was added to the reaction mixture, and the benzene layer was washed successively with dilute hydrochloric acid, dilute aqueous ammonium chloride, and water and then dried over Drierite. Benzene was evaporated *in vacuo*, and the residue was solidified by adding ether. Solids were recrystallized from a hexane–benzene mixture to give 3.4 g (55% yield) of the product; mp 105–107°C; ir (KBr) 1733, 1695, 1476, 1448, 1352, 1323, 748, and 702 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.40 (*s*, 3H), 4.15 (*s*, 2H), and 6.5–7.9 (*m*, 9H); mass spectrum (70 eV) *m/e* 310 (M^+), 282, 281, 151, 150, 122, 118, 106, 105 (base), 77, 69, 51, and 43.

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.80; H, 4.55; N, 9.03; S, 10.31. Found: C, 65.51; H, 4.40; N, 8.99; S, 10.49.

1-Acetyl-2-phenacylthiobenzimidazole (**2a**). 2-Phenacylthiobenzimidazole (*17*) (2.68 g) in THF (60 ml)–pyridine (10 ml) was reacted with acetyl chloride (4 g) in THF (10 ml) as described above and 2.07 g (67% yield) of **2a** was obtained after recrystallizations from benzene: mp 158–159°C (literature (*4*): mp 155–156°C).

1-Benzolyl-2-phenacylthiobenzimidazole (**2b**). Starting from 1.34 g of 2-phenacylthiobenzimidazole and 0.7 g of benzoyl chloride, 1.5 g (81% yield) of **2b** was isolated after recrystallizations from a hexane–chloroform mixture: mp 134–136°C; ir (KBr) 1698, 1678, 1445, 1333, 1296, 1192, 947, 745, and 702 cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.90 (*s*, 2H), 6.50–7.90, and 7.92–8.23 (*m*, 14H); mass spectrum (70 eV) *m/e* 372 (M^+), 354, 151, 150, 105 (base), and 77.

Anal. Calcd for $C_{22}H_{16}N_2O_2S$: C, 70.97, H, 4.30; N, 7.53; S, 8.60. Found: C, 70.86 H, 4.32; N, 7.61; S, 8.70.

1-Acetyl-2-acetonylthiobenzimidazole (**2c**). This compound was prepared according to Alper and Taurins (*5*): mp 116–118°C (literature (*5*). mp 115.5–118°C).

1-p-Methylbenzoyl-2-p-chlorophenacylthiobenzimidazole (**2'd**). The reaction with 1.51 g of 2-*p*-chlorophenacylthiobenzimidazole and 0.8 g of *p*-methylbenzoyl chloride gave 1.66 g (79% yield) of **2'd** after recrystallizations from a hexane–chloroform mixture: mp 143.5–145°C; ir (KBr) 1690, 1606, 1588, 1444, 1322, 901, 803, 758, and 747 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.48 (*s*, 3H), 4.83 (*s*, 2H), and 6.64–8.07 (*m*, 12H); mass spectrum (70 eV) *m/e* 420 (M^+), 402, 272, 271, 181, 161, 150, 139, 119 (base), 111, and 91.

Anal. Calcd for $C_{23}H_{17}ClN_2O_2S$: C, 65.63; H, 4.08; N, 6.66. Found: C, 65.74; H, 3.80; N 6.55.

1-p-Chlorobenzoyl-2-p-methylphenacylthiobenzimidazole (**2d**). The reaction with 1.5 g of 2-*p*-methylphenacylthiobenzimidazole and 1.75 g of *p*-chlorobenzoyl chloride gave 1.3 g (59% yield) of **2d** after recrystallizations from a chloroform–ether mixture: mp 161–162°C; ir (KBr) 1703, 1680, 1607, 1590, 803, 753, and 740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.43 (*s*, 3H), 4.87 (*s*, 2H), and 6.67–8.02 (*m*, 12H).

Anal. Calcd for $C_{23}H_{17}ClN_2O_2S$: C, 65.63; H, 4.08; N, 6.66. Found: C, 65.81; H, 3.93; N, 6.68.

1-Trifluoroacetyl-2-p-methylphenacylthiobenzimidazole **(2'e)**. 2-*p*-Methylphenacylthiobenzimidazole (1.38 g) and trifluoroacetic anhydride[1] (25 g) were mixed and stirred for 40 hr at room temperature. The reaction mixture was poured into 200 ml of cold water, and the precipitate was collected and dissolved in THF. The solution was dried over Drierite, and THF was evaporated *in vacuo*. The residue was recrystallized from THF to give 0.33 g (33% yield) of **2'e**: mp 165–168°C; ir (KBr) 1680, 1645, 1613, 1530, 1455, 1428, 1215, 1200, 1178, 1130, 1002, 742, and 720 cm^{-1}; ^1H nmr ($CDCl_3$–DMSO-d_6) δ 2.43 (*s*, 3H), 5.19 (*s*, 2H), and 7.10–8.30 (*m*, 8H); ^{19}F nmr ($CDCl_3$–DMSO-d_6) $\delta^{CF_3CO_2H}$ 3.88 (*s*); mass spectrum (70 eV) *m/e* 284, 283, 264, 254, 240, 163, 149, 119 (base), and 91.

Anal. Calcd for $C_{18}H_{13}F_3N_2O_2S$: C, 57.12; H, 3.46; N, 7.41. Found: C, 57.15; H, 3.41; N, 7.72.

1-Acetyl-2-carboethoxymethylthiobenzimidazole **(2'f)**. 2-Carboethoxymethylthiobenzimidazole (*18*) (2.36 g) was reacted with acetyl chloride (2 ml) to give 0.39 g (14% yield) of **2'f** after recrystallization from acetonitrile: mp 117.5–118.5°C; ir (KBr) 1740, 1720, 1475, 1457, 1372, 1303, 1178, 1160, 762, and 754 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.28 (*t*, 3H), 2.76 (*s*, 3H), 4.07 (*s*, 2H), 4.23 (*q*, 2H), and 7.10–7.70 (*m*, 4H); mass spectrum (70 eV) *m/e* 278 (M^+), 236, 223, 205, 163, and 149.

Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.07. Found: C, 55.91; H, 5.15; N, 10.03.

1-Ethoxycarbonyl-2-acetonylthiobenzimidazole **(2f)**. From 2.1 g of 2-acetonylthiobenzimidazole (*5*) and 2 ml of ethyl monochloroacetate was obtained 2.3 g (80% yield) of **2f** after recrystallization from a benzene–hexane mixture: mp 104–105°C; ir (KBr) 1745, 1713, 1450, 1330, 1208, 1080, 1010, 759, and 748 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.53 (*t*, 3H), 2.40 (*s*, 3H), 4.15 (*s*, 2H), 4.57 (*q*, 2H), and 7.10–7.90 (*m*, 4H); mass spectrum (70 eV) *m/e* 278 (M^+), 263, 235, 191, 163, 149, 131, and 119.

Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.05; H, 5.11; N, 10.05.

1-Phenyl-2-(2'-benzimidazolylthio)butane-1,3-dione **(1a)**. A THF (20 ml) solution of 1-phenylbutane-1,3-dione (3.24 g) was added dropwise to an ice-cooled and stirred suspension of sodium hydride (50% purity, 0.96 g) in THF (30 ml). The mixture was stirred for 20 min at room temperature, then 3 g of **4** was added. After stirring for 30 min at room temperature, the mixture was neutralized with aqueous hydrochloric acid–ammonium chloride. Low-boiling materials were evaporated *in vacuo*, and the residue was solidified in benzene. The solid was recrystallized from a benzene–hexane mixture to give 2.13 g (69% yield) of **1a**: mp 117–119°C; ir (KBr) 1600, 1583, 1480, 1441, 1408, 1358, 1263, 740, and 677 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.93–2.40 (*m*), 2.48 (*s*) (total 3H), and 7.08–7.76 (*m*, 9H); mass spectrum (70 eV) *m/e* 310 (M^+), 292, 291, 250, 224, 223, 192, 188, 162, 161, 147, 105 (base), and 77.

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.80; H, 4.55; N, 9.03; S, 10.31. Found: C, 65.96; H, 4.62; N, 8.90; S, 10.31.

3-(2'Benzimidazolylthio)pentane-2,4-dione **(1c)**. Starting with 2 g of acetylacetone, 0.96 g of sodium hydride (50% purity), and 3 g of **4**, 2.15 g (87% yield) of **1c** was isolated: mp 196–198°C (literature (*5*, *18*): mp 178–179, 185–186°C).

[1] In order to prevent base-catalyzed rearrangement, acetic anhydride was employed in place of acetyl chloride and pyridine (*4*).

Ethyl 2-(2'-benzimidazolylthio)-3-oxo-butanoate (**1f**). Ethyl acetoacetate (1.5 ml) was reacted with **4** (1.5 g) to give 1.15 g (83 % yield) of **1f** after recrystallization from benzene: mp 149–150°C; ir (KBr) 1640, 1595, 1415, 1393, 1260, 749, and 740 cm^{-1}; ^1H nmr ($CDCl_3$-DMSO-d_6) δ 1.12 (*t*), 1.29 (*t*) (total 3H), 1.84 (*s*), 2.20 (*s*), 2.36 (*s*), 2.45 (*s*) (total 3H), 4.13 (*q*), 4.20 (*q*) (total 2H), 5.05 (*s*), 5.31 (*s*), 5.78 (*s*) (total 0.5H), and 6.90–7.70 (*m*, 4.5H); mass spectrum (70 eV) *m/e* 278 (M^+), 235, 216, 190, 149, and 107; uv (EtOH + 18-crown-6 ether) λ_{max} 224, 250, 284, and 291 nm.

Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.06; H, 5.34; N, 10.04.

Reactions of **3b**, **3d**, *and* **3e** *with* **4**. These compounds were reacted with **4** under the same conditions as described for preparations of **1a** and **1c** to give **2b**, **2'd**, **2d**, and **2'e** in 57, 45, 20, and 38 % yields, respectively.

Rearrangement of **2f**. *Method A*. Into a THF (15 ml) solution of **4f** (0.5 g) were added 3 ml of water and 35 mg of sodium metal, successively. The solution was stirred for 12 hr at room temperature, and volatile materials were removed *in vacuo*. The residue was extracted with chloroform, and the chloroform layer was dried over Drierite. The solvent was removed *in vacuo*, and residual solids were fractionally recrystallized from acetonitrile yielding 0.2 g (39 % yield) of **2f** and 0.17 g (57.5 % yield) of **1f**.

Method B. Into a THF solution (5 ml) suspending 0.12 g of potassium hydroxide (85 % purity), 5.09 g of 18-crown-6 ether in 30 ml of THF was added. The solution became clear. Into this solution, 0.5 g of **2f** in 7 ml of THF was added dropwise. The white precipitate (0.75 g, 71 % yield) that immediately appeared was filtered off. The precipitate was recrystallized from acetonitrile to give **7**; mp 153.5–155°C; ir (KBr) 3270, 1627, 1552, 1410, 1368, 1325, 1065, 768, and 750 cm^{-1} and (from 18-crown-6 ether) 2900, 1350, 1243, 1110, 965, and 846 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.19 (*t*, 3H), 2.48 (*s*, 3H), 4.08 (*q*, 2H), 6.77–7.53 (*m*, 4H), and (from 18-crown-6 ether) 3.52 (*s*, 24H); mass spectrum (70 eV) *m/e* 260 (M^+–H_2O), 232, 190, 177, 133, 101, 89, and 73; uv (EtOH) λ_{max} 217, 247, 284, and 291 nm.

Anal. Calcd for $C_{25}H_{37}N_2O_9SK$: C, 51.71; H, 6.42; N, 4.82. Found: C, 51.56; H, 6.51; N, 5.62.

The salt, **7**, was dissolved in a small amount of chloroform and was subjected to column chromatography on silica gel with ether eluent. The rearranged product, **1f**, was isolated in 65.5 % yield (36 mg).

Spectroscopy. The nmr spectra were recorded on a Varian T-60 or HA-100 spectrometer. The ir and uv spectra were recorded on Hitachi EPI-S2 and Union Giken SM-401 spectrophotometers, respectively. The mass spectra were obtained from a Hitachi RMU-6E mass spectrometer.

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REFERENCES

1. Y. Akasaki and A. Ohno, *J. Amer. Chem. Soc.* **96**, 1957 (1974).
2. F. Lynen, *Biochem. J.* **102**, 381 (1967).

3. (a) A. F. Hegarty, T. C. Bruice, and S. J. Benkovic, *Chem. Commun.*, 1173 (1969); (b) R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.* **94**, 2823 (1972); (c) T. C. Bruice and A. F. Hegarty, *Proc. Nat. Acad. Sci. USA* **65**, 805 (1970).
4. A. N. Krasovskii, P. M. Kochergin, and T. E. Kozlovskaya, *Khim. Geterotsikl. Soedin*, **7**, 393 (1971); *Chem. Abstr.* **76**, 14433z (1972).
5. A. E. Alper and A. Taurins, *Canad. J. Chem.* **45**, 2904 (1967).
6. H. Alper, E. C. H. Keung, and R. A. Partis, *J. Org. Chem.* **36**, 1352 (1971).
7. (a) H. Singh and S. Singh, *Indian J. Chem.* **11**, 311 (1973); (b) H. Singh and S. Singh, *Indian J. Chem.* **9**, 918 (1971).
8. B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.* **82**, 1773 (1960).
9. For example, M. A. Gubareva, *Zh. Obshch. Khim.* **17**, 2259 (1947).
10. R. B. Homer and C. D. Johnson, "The Chemistry of the Amides" (J. Zabicky, Ed.), pp. 187–243. Interscience Publishers, New York, 1970.
11. D. J. Cram, "Fundamentals of Cerbanion Chemistry," pp. 1–20. Academic Press, New York, 1965.
12. Cf. M. Caplow and M. Yager. *J. Amer. Chem. Soc.* **89**, 4513 (1967).
13. T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, pp. 380–388. W. A. Benjamin, New York, 1966.
14. J. Knappe, E. Ringelmann, and F. Lynen, *Biochem. Z.* **335**, 168 (1961).
15. R. B. Guchhait, S. E. Polakis, D. Hollis, C. Fenselau, and M. D. Lane, *J. Biol. Chem.* **249**, 6646 (1974).
16. (a) M. Caplow, *J. Amer. Chem. Soc.* **87**, 5774 (1965); (b) M. Caplow, *J. Amer. Chem. Soc.* **90**, 6795 (1968); (c) M. Caplow, *Biochemistry*, **8**, 2656 (1969).
17. S. Nakajima, I. Tanaka, T. Seki, and T. Anmo, *Yakugaku Zasshi* **78**, 1378 (1958).
18. J. J. D'Amico, R. N. Campbell, and E. C. Guinn, *J. Org. Chem.* **29**, 865 (1964).