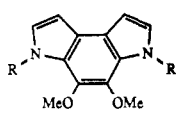
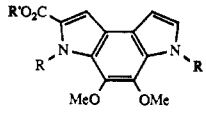
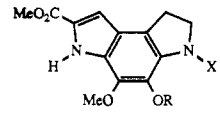
of fluoride sources, we were unable to remove both of the SEM groups from ester **8**. By contrast, removal of these groups from **7** proceeded smoothly in DMF at 85 °C using *n*-Bu_4NF, with ethylenediamine as the formaldehyde sponge (75%).[7b]



7: R=SEM
9: R=H
10: R=BOC



8: R=SEM; R'=Et
11: R=BOC; R'=Me
12: R=H; R'=Me



13: R=Me; X=H
14: R=Me; X=$CONH_2$
15: R=Me; X=$COCH_3$
16: R=H; X=$CONH_2$
17: R=H; X=$COCH_3$

To allow functionalization at the α-position, indole **9** mp 201-202 °C, was first blocked in quantitative yield with the *tert*-butyloxycarbonyl (BOC) group,[13] which is known to direct lithiation on indoles[14] and is easily removable under both acidic and basic conditions. The resulting protected indole **10**, mp 111-113 °C, was lithiated in THF with lithium 2,2,6,6-tetramethylpiperidide (-78 °C, 10 min) and, after cooling to -100 °C, treated with $ClCO_2Me$ to effect the desired homologation in 76% yield (88%, based on recovered starting material). Deprotection of the resulting ester **11** was accomplished most efficiently under thermolytic conditions (185 °C, oil bath temperature, 25 min),[15] affording **12** as a viscous liquid which slowly crystallized (mp 126-128 °C). As this substance was clean by both TLC and 250-MHz NMR, the next two steps were also carried out in the same flask. Thus reduction of **12** proceeded chemoselectively to indoline **13** (CH_3CO_2H, $NaCNBH_3$, 15-20 °C),[16] which upon quenching with aqueous KOCN and warming generated urea **14**, mp 186-188 °C (lit.[3a] 175-177 °C), in 92% yield from **11**.

Selective demethylation of **14**, on the side with the urea, was expected, since the resulting hydroxyl is strongly hydrogen bonded in both CC-1065 and the PDE's. By use of the dimethyl sulfide complex of BBr_3,[17] the demethylation was indeed selective but was accompanied by appreciable amounts of the didemethylated compound. The related BCl_3 complex[17] was milder and gave a good yield of urea **16** (85%, 70% conversion). An analogous sequence of reactions, using acetic anhydride instead of KOCN, afforded the amide **15**, which was demethylated to **17**.[18-20]

Since the deprotection, reduction, and acylation are all performed in one pot, our synthesis of the B and C units requires only 10 steps from pyrrole; the overall yield is in excess of 20% for both systems, making these compounds synthetically far more accessible than by the previous route.[21] Moreover, we are successfully applying this basic strategy to synthesize the A unit of CC-1065 as well as the thiophene analogues of both PDE-I and PDE-II.[22]

Acknowledgment. This work was supported by a grant from the National Institutes of Health (Grant NIH-CA 41995). V.H.R. thanks the University of Pennsylvania for partial support in the form of a Dean's Fellowship.

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(18) Spectral data of selected intermediates. ^1H NMR (250 MHz, $CDCl_3$): **7**, δ -0.056 (s, 9 H, $SiMe_3$), 0.89 (t, 2 H, J = 8.3 Hz, CH_2Si), 3.50 (t, 2 H, J = 8.3 Hz, OCH_2), 4.04 (s, 3 H, OCH_3), 5.72 (s, 2 H, NCH_2O), 6.57 (d, 1 H, J = 3.2 Hz, Ar H), 7.10 (d, 1 H, J = 3.2 Hz, Ar H); **9**, δ 4.06 (s, 3 H, OCH_3), 6.73 (dd, 1 H, J = 2.3, 2.9 Hz, Ar H), 7.18 (t, J = 2.7 Hz, 1 H, Ar H), 8.38 (br s, 1 H, NH); **10**, δ 1.65 (s, 9 H, *t*-Bu), 3.96 (s, 3 H, OCH_3), 6.68 (d, 1 H, J = 3.6 Hz, Ar H), 7.53 (d, 1 H, J = 3.6 Hz, Ar H); **11**, δ 1.65 (s, 9 H, *t*-Bu), 1.69 (s, 9 H, *t*-Bu), 3.92 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.71 (d, 1 H, J = 3.7 Hz, Ar H), 7.38 (s, 1 H, Ar H), 7.54 (d, 1 H, J = 3.7 Hz, Ar H); **12**, δ 3.94 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 6.73 (dd, 1 H, J = 2.2, 2.9 Hz, Ar H), 7.17 (t, 1 H, J = 2.9 Hz, Ar H), 7.42 (d, 1 H, J = 2.2 Hz, Ar H), 8.62 (br s, 1 H, NH), 9.21 (br s, 1 H, NH); **15**, δ 2.27 (s, 3 H, $COCH_3$), 3.10 (t, 2 H, J = 7.5 Hz, Ar CH_C), 3.83 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.34 (t, 2 H, J = 7.5 Hz, CH_2iN), 7.07 (d, 1 H, J = 2.1 Hz, Ar H), 9.00 (br s, 1 H, NH).

(19) Spectra (200 MHz NMR, IR, and MS) of compounds **14**, **16**, and **17** corresponded perfectly with those of the naturally derived materials.[3a,20]

(20) We thank Professor Umezawa for providing us spectra of PDE-I and PDE-II and some of their methyl derivatives.

(21) We had hoped to further shorten our synthesis by starting with the BOC analogue of diketone **4**. While this derivative is easily prepared, all attempts to convert it to the BOC analogue of the enol ether **6** led to loss of the BOC group. Details of these experiments and other variants in the synthesis will be described in the full publication.

(22) Jones, R. J.; Cava, M. P., unpublished results.

Alkali Metal Complexation by Thione Sulfur in *N*-Acyl Thioamides[1]

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Received August 29, 1985

Alkali-metal complexation by amide carbonyl oxygen is a well-established phenomenon which has been investigated by a number of techniques including NMR spectroscopy.[2-7] Complexation by thioamide sulfur, however, has not previously been investigated by these methods. This paper reports on experiments which demonstrate potassium ion chelation by *N*-acyl thioamides by monitoring perturbations in the equilibrium of diastereomers that differ in configuration (*E*,*Z*) at the thioamide partial double bond.

The *N*-acyl thioamides employed in this study, *N*-acetylthioacetamide (**1**, mp 59-61 °C, lit.[8] 61-62 °C), and *N*-propionylthiopropionamide (**2**, mp 42-45 °C), were prepared by treatment of the corresponding imides with Lawesson's reagent.[9] Although both mono- and dithiation have been reported for the reaction of Lawesson's reagent with cyclic imides,[10] the reaction of acyclic compounds, in our hands, produced only monothiated derivatives as isolable products. A similar observation has been noted for *N*-benzoylacetamide although *N*,*N*-diacetylaniline produced no isolable products other than thioacetanilide.[11]

The room temperature ^1H spectrum of *N*-acetylthioacetamide features two methyl singlets at δ 2.094 and 2.883 assigned to the acetyl and thioacetyl methyl groups, respectively. Similarly the ^{13}C spectrum features signals at δ 166.6 (carbonyl), 211.2

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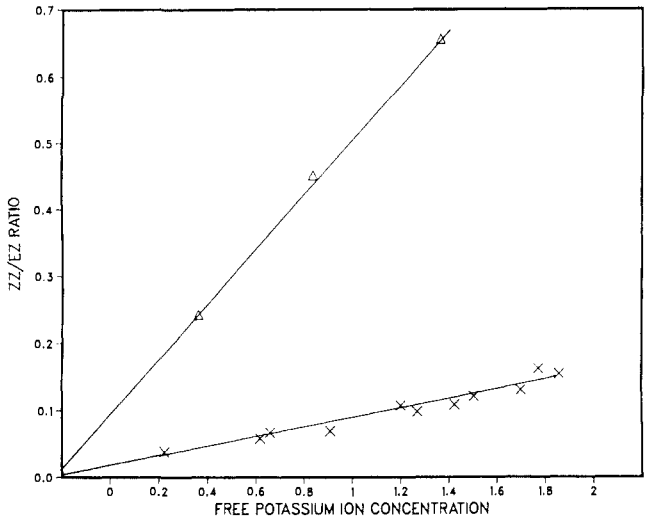
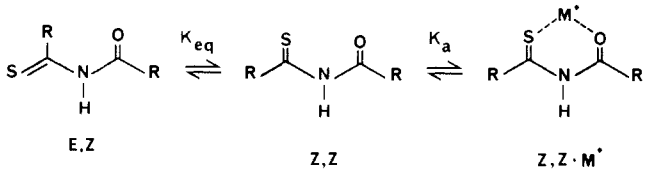


Figure 1. Configurational ratio as a function of free potassium ion concentration (eq 1, $M_{free} = M - RI(R + 1)$): (×) *N*-acetylthioacetamide (**1**); (△) *N*-propionylthiopropionamide (**2**).

(thiocarbonyl), 24.9 (acetylmethyl), and 34.5 [(thioacetyl)methyl]. Both spectra indicate the presence of a single diastereomer or a rapidly interconverting mixture. That only a single isomer is



1, R = CH_3
2, R = CH_2CH_3

present is indicated by the essential identity of room temperature spectra to those at −90 °C. At this temperature, rotation about amide and thioamide bonds should be slow on the NMR time scale.[12] Addition of KSCN to solutions of **1** at −90 °C resulted in the appearance of new signals in the ^1H NMR spectra at δ 2.58 and 2.23, which must be due to the thioacetyl and acetyl groups, respectively, in (*Z,Z*)-**1**·M^+. Since the chemical shift change for the thioacetyl group is substantial, while that for the acetyl group is negligible, we can conclude that the two species differ in configuration at the thioamide partial double bond and assign the *E,Z* configuration to the diastereomer that is present in the absence of alkali-metal cation.

The behavior of *N*-propionylthiopropionamide was similar except that a small signal (<5%) was observed for the methyl group in (*Z,Z*)-**2** (δ 2.63) even in the absence of added salt. This is in accord with the postulated assignments since the increased steric interactions between the ethyl group and acyl oxygen atom would be expected to destabilize the *E,Z* form relative to the *Z,Z* form.[14] Addition of salt led to more dramatic increases in the *Z,Z* isomer.

The effect of added metal ion on the configurational equilibrium is illustrated in Figure 1 in which the isomer ratios for **1** and **2** are plotted as a function of the unchelated metal ion concentration (eq 1, $M_{free} = [M - RI(1 + R)]$):

$$R = K_a'[M - RI(1 + R)] \quad (1)$$

$$K_a' = K_a K_{eq} \quad (2)$$

where R is the observed *Z,Z*/*E,Z* ratio, M is the concentration of added salt and I is the concentration of ligand. K_a', the equilibrium constant relating *E,Z*- and *Z,Z*-**1**·K^+ forms, is the product of K_{eq}, the equilibrium constant for *E,Z* and *Z,Z* isomers in the absence of metal ion, and K_a, the association equilibrium constant for the *Z,Z* isomer (eq 2). Linear least squares analysis furnished the equilibrium constant K_a', which is a measure of the complexing ability of the *N*-acylthioamide: **1**, $K_a' = 0.073$; **2**, $K_a' = 0.41$. The complexing ability of the *Z,Z* isomer (K_a), which is considerably larger, can be obtained if the equilibrium constant for *E,Z* and *Z,Z* forms (in the absence of metal ion) is known. While K_{eq} is too small for estimation in the case of **1**, integration of the low-temperature spectrum of **2** indicated that K_{eq} was about 0.05, corresponding to a value of 8.2 for K_a.

We attribute the major difference in complexing abilities of **1** and **2** to the greater ease with which **2** adopts the *Z,Z* form. This is likely due to increased steric interactions between the carbonyl oxygen and an ethyl group as opposed to a methyl group. The same factor is responsible for the preference of *N*-acetylpropionamide for the *E,Z* configuration as opposed to the *Z,E* configuration.[14]

In order to obtain an estimate of the difference in complexing ability between amide sulfur and amide oxygen we examined the complexing ability of *N*-acetylacetamide (**3**) under the same conditions. Since there is a substantial amount of the *Z,Z* isomer in equilibrium even in the absence of metal ion, eq 1 is not valid, and eq 3 was used: $K_a' = 20$, $K_a = 38$, $K_{eq} = 0.59$. We can

$$K_a = \frac{(R - K_{eq})(R + 1)}{K_{eq}[M(R + 1) - I(R - K_{eq})]} \quad (3)$$

compare the complexation abilities between **1** and **3** using either K_a or K_a'. On either basis it is clear that while the imide is better at complexation, thioamide sulfur does have significant ability to complex alkali metal cations.

Registry No. **1**, 3542-00-5; **2**, 99797-96-3; KSCN, 333-20-0; K^+, 24203-36-9.

(12) The coalescence temperature for interconversion of amide torsional isomers in *N*-acetylacetamide is well above temperature: $T_c = -60$ °C, $\Delta G_c^* = 10.8$ kcal/mol.[13]

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(15) This equation is valid when $M^+ >> I$. At low metal ion concentrations there is a considerable amount of triple ion[16] $((Z,Z)\text{-}3)_2\cdot M^+$ present. In order to obtain an estimate for K_a in this concentration range, we assumed that the second association constant, $K_a^2 = [(Z,Z)_2\cdot M^+]/[((Z,Z)\cdot M^+)(Z,Z)]$ was equal to the first (K_a). The value quoted is an average of four determinations which were in good agreement.

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Decyclization of Crown Ethers. Ring-Opening Reaction of 18-Crown-6 with $ZrCl_4$

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Received July 18, 1985

We have previously reported that $AlCl_3$ reacts with crown ethers in aromatic solvents to form [$AlCl_2$·crown ether][$AlCl_4$].[1] The ionic substance shows the two-phase effect (liquid clathrate) in an excess of aromatic.[2] Since it would be desirable to have access to liquid clathrates based on early-transition-metal ions, we have carried out the reaction of group IVB (group 4)[13] halides with 18-crown-6. $TiCl_4$ reacts to form the adduct, $TiCl_4$·18-crown-6, in which the crown ether functions as a bidentate ligand.[3] To our surprise, the reaction of $ZrCl_4$ with 18-crown-6 in toluene/THF (15% THF by volume) leads to the formation of an open-ring macrocyclic coordination product of formula [$ZrCl_2$·(OCH_2C-

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