Reaction Pathways in Nucleophilic Displacements with 1-Benzyl-Δ^2-tetrazoline-5-thione and 1,2,3,4-Thiatriazoline-5-thione

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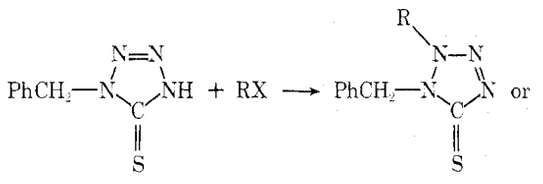
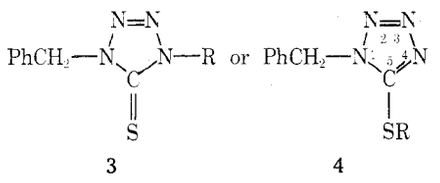
1-Benzyl-Δ^2-tetrazoline-5-thione (1) reacted with benzyl chloride, methyl iodide, benzoyl chloride, and arylsulfonyl chlorides to give S derivatives (4). Phenylacetyl chloride, on the contrary, furnished the N derivative **3c**. Structure elucidation was based on ^1H and ^{13}C nmr analysis and confirmed by ir in the cases of the acyl derivatives. The structure of the benzoylated product of sodium thiatriazolinethiolate, formulated by Lieber, *et al.*, as the N product **6c**, was reinvestigated by ^{13}C nmr spectroscopy and found to be the S product **7c** in agreement with the findings of Christophersen and Holm.

1-Benzyl-Δ^2-tetrazoline-5-thione (**1**), prepared from benzyl isothiocyanate and sodium azide,[1] is an ambident nucleophile, and substitution could lead to products **2, 3, or 4.** In fact, treatment of **1** with benzyl chloride, methyl iodide, phenylacetyl chloride, benzoyl chloride, and three different arylsulfonyl chlorides gave a single crystalline product in good yield in each case (see Table I). If substitution occurred at nitrogen, the more stable thiourea structure **3** would be favored over its azo homolog **2** in analogy with other systems.[2]



1 **2**



3 **4**

a b c d

R $PhCH_2$ CH_3 $PhCH_2CO$ PhCO

e f g

R $C_6H_5SO_2$ p-$ClC_6H_4SO_2$ p-$CH_3C_6H_4SO_2$

Although the structure of the alkylated product can be elucidated by ^1H nmr spectroscopy in some favorable cases (see below), we wanted to have at hand more general criteria based on the ^{13}C chemical shifts of the functional groups C=S and C=N occurring in structures **3** and **4.** Since it is well known that the carbonyl carbon atoms absorb over a wide range (*ca.* 40 ppm) in the ^{13}C nmr spectra depending on substituents,[3] we may expect the same situation for the C=S and C=N carbon atoms. To locate their absorptions in our cases, we have therefore utilized model compounds whose structures are unambigously settled by ^1H nmr analysis.

The starting material **1** showed in the ^1H nmr spectrum a broad absorption at δ 14.5 ppm (exchangeable with D_2O) which is indicative of an NH function rather than an SH function (structure **4,** R = H).[4] This is in agreement with the ir findings of Lieber, *et al.*,[5] for the solid state structure of other 1-substituted-Δ^2-tetrazoline-5-thiones. The formulation of Jensen and Pedersen[6] that these compounds have the tetrazole-5-thiol structure is incorrect. The C=S carbon absorption of **1** in the ^{13}C nmr spectrum ($CDCl_3$) was found at δ 164.4 while the methylene carbon absorbed at δ 50.9 ppm.

Treatment of **1** with benzyl chloride did not give the symmetrical structure **3a,** since the ^1H nmr spectrum exhibited two different methylene absorptions at δ 4.50 and 5.30 ppm. The ^{13}C spectrum showed, *inter alia,* an absorption peak at δ 153.9 ppm attributable to the C=N carbon atom of structure **4a.** This shift value is in good agreement with that reported by Weigert and Roberts[7] for the unsubstituted tetrazole (DMSO-d_6, δ 144 ppm), when the expected substituent effects are taken into account. Further evidence for this assignment is provided by the methylated product which exhibited carbon resonances at δ 155.1 (C=N), 51.1 (CH_2N), and 15.4 ppm (CH_3S). The 15.4-ppm peak cannot be attributed to a CH_3N carbon atom which is known to absorb at lower field (δ >20 ppm).[8] On the basis of these considerations we are able to reject structures **2** and **3** for the alkylated products studied in this work.

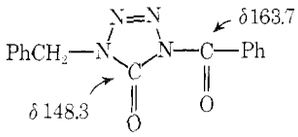
An inspection of the substituted products presented in Table I discloses that N substitution only occurred in one case, namely with phenylacetyl chloride. Indeed, product **3c** showed typical ^{13}C resonances at δ 164.7 (C=S) and

Table I
Reaction Products of 1 with Alkyl Halides, Acyl Chlorides, and Arylsulfonyl Chlorides

No.	R	Yield, %	Mp, °C	^1H nmr (δ values)[a,b]	^{13}C nmr (δ values in ppm from TMS)[b] C$_5$	$PhCH_2N$	Other shift values
4a	$PhCH_2$	99	62.5–63.5	4.50 (s, 2 H, CH_2S), 5.30 (s, 2 H, CH_2N)	153.9	51.1	$PhCH_2S$ at 38.1
4b	CH_3	88	37–38	2.73 (s, 3 H) 5.38 (s, 2 H)	155.1	51.1	CH_3S at 15.4
3c	$PhCH_2CO$	99	63–66	4.44 (s, 2 H, CH_2CO), 5.40 (s, 2 H, CH_2N)	164.7	50.8	$PhCH_2CON$ at 41.2 and 177.9
4d	PhCO	98	99–101	5.56 (s, 2 H)	146.4	52.3	PhCOS at 184.4
4e	$C_6H_5SO_2$	52	85–86	5.76 (s, 2 H)	146.65	52.5	
4f	p-$ClC_6H_4SO_2$	50	113.5–114.5	5.75 (s, 2 H)	146.5	52.6	
4g	p-$CH_3C_6H_4SO_2$	79	125.5–126.5	2.45 (s, 3 H), 5.73 (s, 2 H)	146.8	52.5	

[a] The aromatic proton absorptions are omitted. [b] All the spectra were recorded in $CDCl_3$.

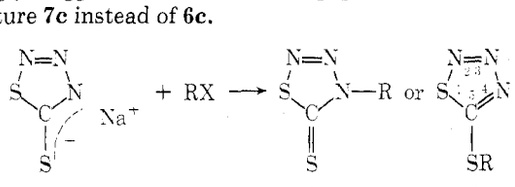
177.9 ppm (CON). The ir spectrum also confirms structure **3c**, showing a high C=O stretching absorption at 1770 cm^{-1} which is typical for azolides.[9] The benzoylated product, on the contrary, has structure **4d** as evidenced by the ^{13}C absorptions at δ 146.4 (C=N) and 184.4 (COS), in addition to the ir C=O thio ester vibration at 1705 cm^{-1} in the ir spectrum.[10] If benzoylation should have occurred at nitrogen, a carbonyl carbon absorption at about δ 165 ppm would be expected in analogy with that found for 1-benzyl-4-benzoyltetrazolin-5-one (**5**). This compound has been prepared in our laboratory[11] from 1-benzyl-4*H*-tetrazolin-5-one and benzoyl chloride (see Experimental Section).



5 (^{13}C nmr taken in C_6D_6)

The data listed in Table I also indicate that the reactions of **1** with arylsulfonyl chlorides have led to thiosulfonic esters **4e–g.** Indeed, the ^{13}C spectra were devoid of C=S peaks at about δ 165 but, instead, showed typical C=N peaks at δ 146–147 ppm.[12]

In view of these results, we are now in a position to reconsider by ^{13}C nmr spectroscopy the structure of the benzoylated product of sodium thiatriazolinethiolate. Lieber, *et al.*,[13] formulated this product as the *N*-benzoyl derivative **6c** because it decomposed to give benzoyl isothiocyanate instead of benzoyl thiocyanate which would result from **7c.** Jensen and Pedersen,[6] however, challenged the value of this argument, stating that an acyl thiocyanate is highly unstable and would easily rearrange to the corresponding acyl isothiocyanate during the degradation experiment. Christophersen and Holm[14] then investigated the thermal decomposition of the benzoylated product by ir techniques and reported the successive appearance and disappearance of an absorption peak at 2170 cm^{-1} which they attributed to the unstable benzoyl thiocyanate. This observation strongly suggests that the starting product would have structure **7c** instead of **6c.**



6 **7**

a b c

R $PhCH_2$ $PhCOCH_2$ PhCO

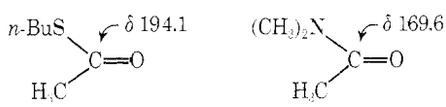
To solve the structure of the benzoylated product by ^{13}C nmr spectroscopy, we have prepared as a model compound for this series the benzyl derivative **7a,** whose structure was previously[13] proven by an unequivocal synthesis starting from benzyl dithiocarbazate ($PhCH_2SCSNHNH_2$) and nitrous acid. In analogy with structure **4a** this compound showed a CH_2S carbon absorption at δ 39.5 ppm. The C=N carbon resonance, however, was shifted to lower field (δ 179.8 ppm) compared with **4a,** due to a modification of the ring structure. Phenacyl chloride also furnished the S derivative **7b** as shown by the ^{13}C nmr values recorded in Table II.

Structure **6c,** formulated by Lieber, *et al.*,[13] for the benzoylated derivative of sodium thiatriazolinethiolate, is now decisively eliminated in favor of **7c** on the basis of ^{13}C nmr analysis. Indeed, the product showed a C=N absorption peak at δ 171.5 in addition to a COS absorption at 185.2 ppm which is comparable with that found for compound **4d.** The ir (KBr) C=O stretching vibration at 1670 cm^{-1} also points to this conclusion.

Table II
^{13}C Nmr Data ($CDCl_3$, δ Values) of the Substitution Products of Sodium Thiatriazolinethiolate

No.	R	C_5	Other shift values
7a	$PhCH_2$	179.8	$PhCH_2S$ at 39.5
7b	$PhCOCH_2$	179	$PhCOCH_2S$ at 191.9 and 43.5
7c	PhCO	171.5	PhCOS at 185.2

From the viewpoint of ^{13}C nmr spectroscopy, it is interesting to note the large difference in C=N shift values ($\Delta\delta$ = 25 ppm) between tetrazoles (δ 145–155) and thiatriazoles (δ 170–180), caused by a change of heteroatom (S *vs.* N) attached to the C=N carbon. This is not unexpected since the C=O carbon absorption undergoes a shift of the same magnitude ($\Delta\delta$ = 22–25 ppm) when a sulfur substituent is replaced by a nitrogen substituent as illustrated below with *n*-butyl thioacetate and *N,N*-dimethylacetamide.[15]



Experimental Section

The ir spectra were taken on a Perkin-Elmer Model 521 spectrometer. Proton nmr spectra were recorded with a Varian A-60 or XL-100 spectrometer using TMS as an internal reference. For ^{13}C nmr spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation.

The thiatriazole derivatives **7a–c** were prepared as described earlier.[13] 1-Benzyl-Δ^2-tetrazoline-5-thione (**1**), mp 143.5–144° ($CHCl_3$–pentane), was prepared in 47% yield by the procedure of Lieber and Ramachandran.[1]

Substitution Products of 1. These were obtained by combining equimolar amounts (0.01 mol) of **1,** triethylamine, and the electrophilic reagent in ether (50 ml) at reflux temperature for the appropriate reaction time (19 hr for benzyl chloride, 6 hr for methyl iodide and acyl chlorides, and 24 hr for arylsulfonyl chlorides). The precipitated NEt_3·HX was removed by filtration and the filtrates were evaporated partially or completely to give crude products which were crystallized from the appropriate solvents. In the case of **4b,** the ether solution of the crude product was first washed several times with a 5% solution of sodium thiosulfate and dried before allowing it to crystallize at low temperature. In the experiments with arylsulfonyl chlorides, the thiosulfonic esters **4e–f** partially precipitated together with NEt_3·HCl. They were dissolved by adding 100 ml of benzene with stirring prior to isolation of the salt. [Satisfactory analytical data (*m/e* for $M^{\cdot+}$ ±0.002 for **4a,b,d,e** and **3c;** ±0.3% for C, H, N for **4f** and **4g**) have been obtained for the new compounds (Editor).]

Synthesis of 1-Benzyl-4-benzoyltetrazolin-5-one (5). Equimolar amounts (0.02 mol) of benzyl azide and tosyl isocyanate were heated at 90° for 24 hr in the absence of solvent. The reaction mixture was dissolved in CH_2Cl_2 and cooled to give 1-benzyl-4-tosyltetrazolin-5-one in 80% yield; mp 115–117°; ir (KBr) 1760 cm^{-1}. This compound was hydrolyzed in methanol at reflux temperature for 4 days. After removal of the solvent, the crude mixture was crystallized from CH_2Cl_2 to give 1-benzyl-4-*H*-tetrazolin-5-one in 90% yield; mp 136–139°; ir (KBr) 1680–1720 cm^{-1}. This compound (0.01 mol) was dissolved in ether (60 ml) and treated with equimolar amounts of NEt_3 and benzoyl chloride at reflux temperature for 2 hr. The precipitated salt was removed by filtration and the mother liquor was allowed to cool. 1-Benzyl-4-benzoyltetrazolin-5-one (**5**) was thus obtained in 60% yield; mp 92–93°; ir (KBr) 1770 cm^{-1}.

Registry No.—**1,** 33898-72-5; **3c,** 53078-72-1; **4a,** 53078-73-2; **4b,** 53078-74-3; **4d,** 53078-75-4; **4e,** 53078-76-5; **4f,** 53078-77-6; **4g,** 53078-78-7; **5,** 53078-79-8; **7a,** 34930-32-0; **7b,** 53078-80-1; **7c,** 33125-49-4; benzyl chloride, 100-44-7; methyl iodide, 74-88-4; phenylacetyl chloride, 103-80-0; benzoyl chloride, 98-88-4; benzenesulfonyl chloride, 98-09-9; *p*-chlorobenzenesulfonyl chloride, 98-60-2; *p*-methylbenzenesulfonyl chloride, 98-59-9; phenacyl chloride, 532-27-4; sodium thiatriazolinethiolate, 53129-36-5.

References and Notes

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(12) After completion of our work, Stájer, *et al.*, reported the S-sulfinylation of 1-substituted tetrazoline-5-thiones and conversion of the resulting disulfides into thiosulfonic esters: G. Stájer, J. Pintye, F. Klivényi, and A. E. Szabó, *Acta Chim. (Budapest)*, **80**, 89 (1974); G. Stájer, E. A. Szabó, J. Pintye, F. Klivényi, and P. Sohár, *Chem. Ber.*, **107**, 299 (1974).
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(15) See ref 8, spectra 85 and 192.

Synthesis of *endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamates

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The synthesis and separation of *endo*- and *exo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamates *via* 5-(1-keto-2-hydroxyethyl)bicyclo[2.2.1]hept-2-enes are described. The imidazolyl derivatives have a rigid bicyclo[2.2.1]heptane structure; the endo compound was synthesized as a model for α-chymotrypsin and the exo compound was synthesized for purposes of comparison. The mode of 2,5 disubstitution of bicyclo[2.2.1]heptane was determined by a double resonance experiment using nmr.

Enzyme model studies are becoming increasingly important because of interest in enzyme mechanism and the design of synthetic catalysts with enzyme-like activity. However, a difficult problem has been the synthesis of model compounds that can mimic enzyme structure or mechanism, or both. The X-ray structure of α-chymotrypsin has been determined, indicating the spatial alignment of the important functionalities at the active site.[2] Enzyme mechanistic studies have clarified the roles of the functional groups, especially those of the histidine imidazolyl and serine hydroxyl groups in terms of organic reaction mechanisms.[3] Therefore, α-chymotrypsin could be the first enzyme whose catalytic efficiency can be approximated by a synthetic model.

We have approached the synthesis of an enzyme model which has a rigid structure with the correct spatial alignment of the imidazolyl and hydroxyl groups as in α-chymotrypsin (approximately 3 nm from one another). For this purpose we have chosen the bicyclo[2.2.1]heptane ring system as the framework that bears the two functional groups, because its internal free rotations are frozen and its endo-2-, endo-5-disubstituted structure assumes the alignment indicated above. With chymotrypsin, the reaction proceeds in two steps: an acylation of the enzyme on the serine hydroxyl group and a deacylation of the acyl enzyme, an ester.

In this report we describe the synthesis of the titled model compounds which simulate an acyl enzyme in the correct (endo) and incorrect (exo) stereochemistries. In another paper we will report their catalytic effectiveness. *trans*-Cinnamates were used because they are more readily available and have been used before.[3] The endo compound, as expected, was considerably faster than the exo compound, although the former does not have the reactivity of the cinnamoyl enzyme.

Results and Discussion

Hitherto, only one report concerning cyclic imidazole derivatives has appeared, namely the synthesis of 2- and 3-keto-*endo*-5-(2-imidazolyl)bicyclo[2.2.2]octane.[4a] The synthetic method used for this compound, however, cannot be applied to the present enzyme model, because it does not afford 4(5)-imidazolyl derivatives.

Our synthetic route is shown in Scheme I. At an early stage of this work, the methyl ketone was more easily available and stable than the corresponding hydroxymethyl ketone **1** and was tried as a precursor for the imidazole derivative **2**. But oxidation with selenium dioxide failed to give the glyoxal, which could be converted to **2**. The intermediate hydroxymethyl vinyl ketone is so easily polymerizable[4b] that it was allowed to react with cyclopentadiene without distillation from the reaction mixture, giving the crude Diels–Alder adduct **1** in 18% yield. Since this yield was nearly that reported by Reppe and coworkers for the hydroxymethyl ketone from 2-butyne-1,4-diol,[4b] the Diels–Alder reaction probably proceeded almost quantitatively.

For the determination of the endo:exo ratio, ketone **1** was fractionally distilled through a spinning band column, giving fractions of nearly 100% endo ketone and 85% exo ketone. The nmr spectrum of the endo ketone was consistent with that of methyl *endo*-2-norbornyl ketone.[5] In the spectrum of the exo ketone, a signal with four main peaks appeared at higher field than that of the exo C-5 proton ($\Delta\delta$ = 0.6) and was assigned to the endo C-5 proton.[5] Another important change was seen in the pattern of the olefinic protons. In the endo ketone they appeared as two symmetrical doublets centered at δ 6.16 and 5.81, but in the exo ketone the signal at higher field was diminished and was seen at lower field. Since this difference was adequate for quantitative treatment, this was used for determination of the