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RING EXPANSION IN THE ISOTHIAZOLE AND 1,2,5-THIADIAZOLE RING SYSTEMS. PREPARATION OF NOVEL HETEROCYCLES.

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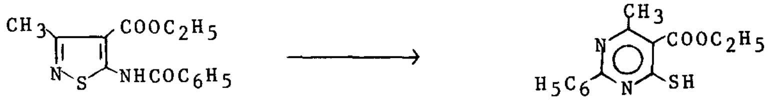
The chemistry of the relatively recent isothiazole and the related 1,2,5-thiadiazole ring systems has been expanding rapidly (1).

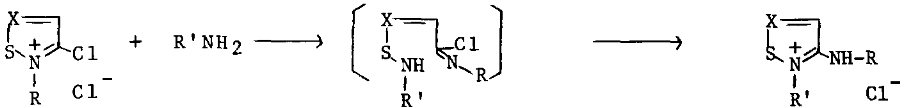
Ring expansion in those systems is, however, largely unknown and only recently has a report (2) appeared on the transformation of 3-methyl-4-carboethoxy-5-benzamidoisothiazole to a pyrimidine ring system on treatment with hydrazine.



We wish to report on a novel and general ring expansion reaction in the isothiazole and 1,2,5-thiadiazole ring systems which led to new heterocycles.

We have recently reported (3) on a general method of preparation of compounds of Type II by reacting quaternary salts I with amines, in which the attack of the nucleophile occurs mainly on sulfur (Scheme I).

Scheme I



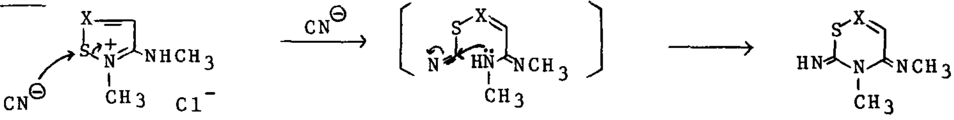
X=CH,N

I

II

We thought that by reacting compounds II with the appropriate nucleophile, attack would occur on the sulfur to yield an intermediate open chain amidine which would recyclize back to yield ring expanded compounds. Cyanide seemed to be an obvious first choice, and in fact treatment of IIa and IIb with 1 mole of cyanide in water led to an immediate reaction. The compounds were extracted into $CHCl_3$ and on evaporation, high yields of the ring expanded compounds IIIa and IIIb, respectively, were obtained (Scheme II).

Scheme II



IIa X=CH

IIb X=N

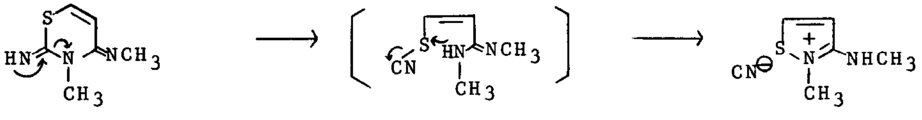
IIIa X=CH

IIIb X=N

The table contains the relevant physical data.

In the case of IIa one can use excess cyanide with no effect on the outcome of the reaction. Compounds IIIa and IIIb decompose slowly on standing for several days at room temperature, but are stable in the cold. From the decomposition products of IIIa we could isolate in 10% yield a compound (m.p. 235-238°C dec.) which has been shown to be the ring contracted product IIc. The IR spectrum of IIc shows a cyano band at 2060 cm^{-1}; the NMR spectrum is identical with that of IIa. The compound passed through a Cl$^-$ ion exchange resin led to IIa. This compound must have been formed by a reversal of the ring expansion reaction (Scheme III).

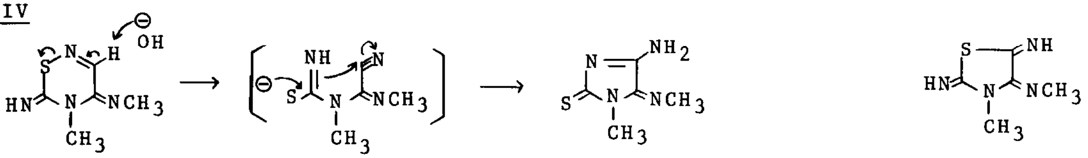
Scheme III



IIc

When IIb is treated with excess cyanide, an exothermic reaction occurs and a new compound V precipitates from the reaction mixture (80% yield). When IIIb is treated with traces of cyanide or NaOH, the same rearranged compound is obtained in quantitative yield (Scheme IV).

Scheme IV

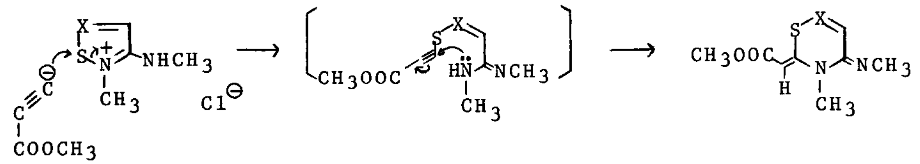


IIIb IV V VI

Compound V analyzes correctly and its mass spectrum shows the expected molecular ion (M$^+$156); the NMR spectrum shows the lack of vinyl proton. However, complete structure proof is not yet available and one cannot exclude the possibility that cyclization of intermediate IV has occurred on the sulfur to yield the thiazole compound VI.

To further illustrate the generality of the ring expansion, methyl propiolate was used as nucleophile. Here again the ring expanded products were obtained (Scheme V). Thus IIa and/or IIb was suspended in CH_2Cl_2; one equivalent of triethylamine and excess methyl propiolate were added. The reaction was stirred at room temperature until complete dissolution of starting material occurred (several hours). The solution was extracted with water and the organic layer evaporated to dryness to yield VIIa and VIIb, respectively.

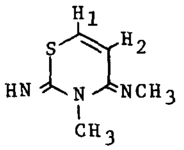
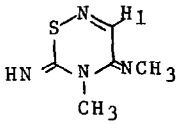
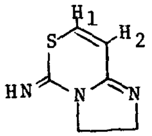
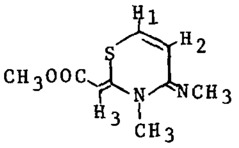
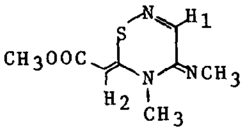
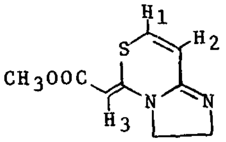
Scheme V



IIa X=CH
IIb X=N

VIIa X=CH
VIIb X=N

TABLE[a]

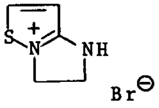
		M.P. °C	Yield %	NMR[b] δ ($CDCl_3$)
IIIa		71-73	100	3.30 (3H, s, $>NCH_3$) 3.56 (3H, s, $=NCH_3$) 6.78 (1H, d, H_2) 7.06 (1H, d, H_1) $J_{H_1-H_2}=5.5$ Hz
IIIb		83-84	70	3.57 (6H, s, $=NCH_3$ and $>NCH_3$) 8.80 (1H, s, H_1)
IX		128-30	95	4.17 (4H, s, $-CH_2CH_2-$) 6.75 (1H, d, H_2) 7.10 (1H, d, H_1) $J_{H_1-H_2}=5$ Hz
VIIa		oil 167 (dec.) (oxalate)	100	3.17 (3H, s, $>NCH_3$) 3.40 (3H, s, $=NCH_3$) 3.67 (3H, s, $-OCH_3$) 5.36 (1H, s, H_3) 6.50 (1H, d, H_2) 6.89 (1H, d, H_1) $J_{H_1-H_2}=5.5$ Hz
VIIb		96-97	45	3.34 (3H, s, $>NCH_3$) 3.40 (3H, s, $=NCH_3$) 3.70 (3H, s, $-OCH_3$) 5.10 (1H, s, H_2) 8.37 (1H, s, H_1)
X		230 (dec.)	94	3.90 (4H, m, $-CH_2CH_2-$) 3.70 (3H, s, $-OCH_3$) 5.00 (1H, s, H_3) 6.37 (1H, d, H_2) 6.80 (1H, d, H_1) $J_{H_1-H_2}=5$ Hz

[a] All compounds gave correct molecular ions and analyses.

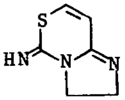
[b] Of the two methyl groups, we have assigned the lower chemical shift to the methyl attached to the imino nitrogen.

Only one isomer is formed to which we have tentatively assigned the structure resulting from the <u>cis</u> addition product in the ring closure step. Secondary amines are reported to yield, on addition to conjugated acetylenes, the <u>cis</u> addition product (4). Furthermore, it can be expected that in the transition state the carbomethoxy group would prefer to assume the least hindered position with respect to the N-methyl group.

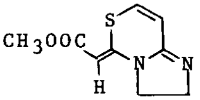
An interesting application of this ring expansion was effected on the bicyclic system VIII described previously by us (3b). Reaction with cyanide and methyl propiolate yielded in near quantitative yield the novel bicyclic compounds IX and X, respectively.



VIII



IX



X

In contrast with IIIa and IIIb, compounds VIIa, VIIb, IX, X are stable at room temperature. Their physical properties are reported in the table.

Work is in progress to evaluate the scope of the reaction.

ACKNOWLEDGMENT

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