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The Mannich Reaction for 2,5-Dimercapto-1,3,4-thiadiazole

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The formation of Mannich bases with 2,5-dimercapto-1,3,4-thiadiazole (III) and some of its derivatives has been investigated. Depending on the amount of formaldehyde and a secondary amine used in the reaction, three different types of Mannich bases were prepared. With equimolecular amounts of both reagents a *mono*-Mannich base IV was obtained, but using formaldehyde in excess a *mono*-hydroxymethyl *mono*-Mannich base V was isolated. If both reagents were used in amounts corresponding to two equivalents, a *bis*-Mannich base VI was formed. Evidence for the structures of all these products was presented on the basis of chemical transformations and spectroscopic data. The *mono*-Mannich base IV was converted in its *S*-methyl derivative VIII which was prepared independently from IX in a Mannich reaction. Thus aminoalkylation proceeds first on the ring nitrogen and in a further reaction the *exo*-cyclic sulfur is substituted.

As part of a study of different reactions with heterocyclic compounds containing thioamide groups in the cyclic system we have recently investigated the Mannich reaction with different pyridazines[1]. Because of the similarities between their structural elements and those of pyridazines, 2,5-dimercapto-1,3,4-thiadiazole* and its derivatives seem to be of particular interest with regard to their structure and reactivity. Although the structure of 2,5-dimercapto-1,3,4-thiadiazole has been widely accepted as a dimercapto compound, it was recently shown[2,3] on the basis of its determined *p*K values and spectroscopic evidence that this compound exists in a monomercapto monothione form with an important contribution of the dipolar structure.

The Mannich reaction with mercaptans or thiophenols is known to proceed on the sulfur atom[4], but in the case of compounds with thioamide groups, in principle, two kinds of products can be expected, *i.e.* either nitrogen I or sulfur II substituted aminoalkylated derivatives.

Several cases of cyclic thioamides are known on which the Mannich reaction has been studied. In all of these cases, *e. g.* with benzoxazoline-2-thione[5, 6], thiazoline-2-thione and benzothiazoline-2-thione[7-9], or with benzimidazoline-2-thione[5, 10], the reaction proceeds only on the ring nitrogen.

2,5-Dimercapto-1, 3, 4-thiadiazole (III) possesses two reactive hydrogens which enables it to undergo reactions of the Mannich type in the presence of formaldehyde and amine. We now wish to describe three types of derivatives which were isolated and whose structures were examined. Using equimolecular

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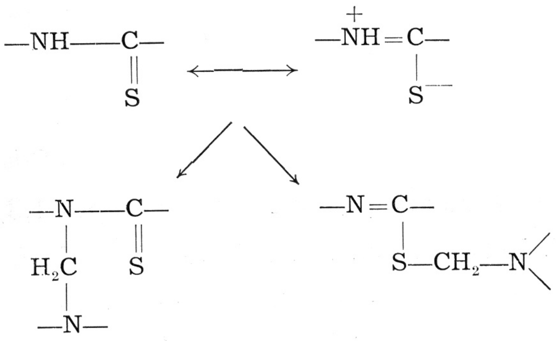
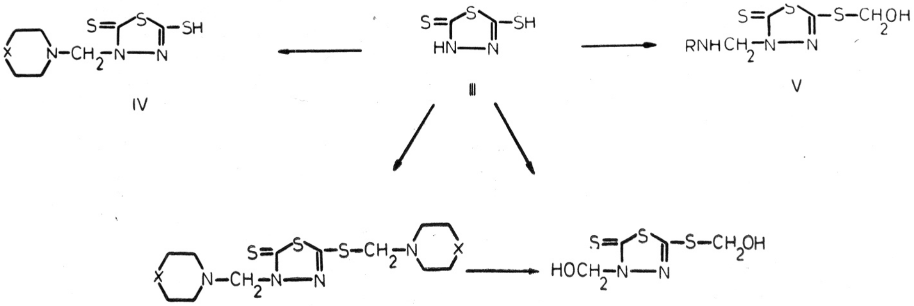
* The term "dimercapto" is used throughout this paper for the sake of simplicity.



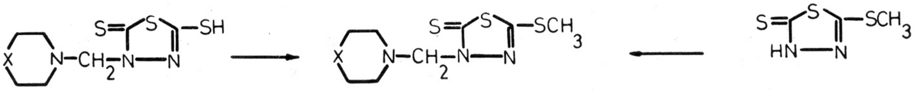
I II

amounts of reactants a *mono*-Mannich base IV could be obtained. From the infrared spectrum of IV the presence of a mercapto group is evident and its structure was proven as demonstrated in Chart II, *i. e.* an identical product VIII



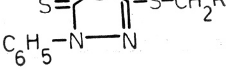
IV III V VI VII

was obtained by methylating IV or performing the Mannich reaction with IX. In addition, compounds IV and VIII gave a positive iodine-azide test[11] thus excluding the possibility of substitution on both *exo*-cyclic sulfur atoms. The reaction course can be interpreted in the following terms: the acidity of the

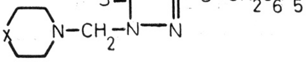


IV VIII IX

mercapto group allows the formation of stable ammonius salts which can be isolated. The monoaminoalkylation reaction, therefore, proceeds on the ring nitrogen and not on the *exo*-cyclic sulfur.



X

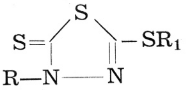
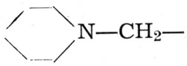
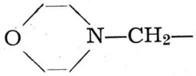
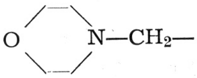
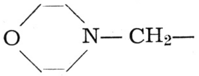
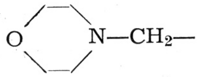
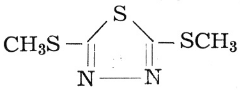


XI

Using the same proportion of amine, but excess formaldehyde, a mono-hydroxymethyl mono-Mannich base V was obtained. On the other hand, when using both formaldehyde and an amine in excess and performing the reaction in the absence of solvent, the bis-Mannich base VI was obtained. This was decomposed in acid solution into the *bis*-hydroxymethyl derivate VII which can otherwise be synthetized by the direct reaction of III with formaldehyde. Corroborative evidence for the above structural assignements of all the Mannich bases was provided by UV spectroscopy. The UV absorption maxima of Mannich bases or hydroxymethyl derivatives are very close to those of known *N, S*-disubstituted derivatives and different from *S, S*-disubstituted compounds as is evident from Table I.

TABLE I

UV spectra (in tetrahydrofurane)

		$\lambda_{max.}$ [Å]	ε
R	R$_1$		
H	H	3360 *infl.* 2600	13.500 a) 5.400
H	CH$_3$	3180 2350	log ε 4.04 b) log ε 3.67
C$_6$H$_5$	CH$_3$	3250	12.400 a)
	H	3240	6.390
CH$_2$OH	CH$_2$OH	3300	8.850
C$_6$H$_5$CH$_2$NHCH$_2$—	CH$_2$OH	3280	12.700
	CH$_3$	3260	12.050
		3300	7.570
	C$_6$H$_5$—CH$_2$—	3280	13.230
C$_6$H$_5$—	(*o*)Cl—C$_6$H$_4$—NH—CH$_2$—	3020 3350	7.700 8.820
		2880	log ε 4.01 b)

a) in ethanol (see ref. 2)
b) in ethanol (see ref. 3)

Additional evidence is provided by those Mannich bases which were prepared from starting materials where one of both thioamide groups is fixed. Thus

2-mercapto-4-phenyl-1, 3, 4-thiadiazoline-5-thione afforded X (R = OH, $-NH-C_6H_4$-Cl (*o*), or N $(CH_3)_2$ and the position of the long-wave-lenght maximum is very close to that of XI, prepared from 2-benzylmercapto-5-mercapto-1, 3, 4-thiadiazole with formaldehyde and a secondary amine in the conventional manner.

Most of the Mannich bases are not easily purified since recrystallization and heating cause progressive decomposition.

EXPERIMENTAL

All melting-points were observed on a Kofler heating microscope. The UV spectra were recorded on a Beckman DU Spectrophotometer and the infrared spectra on a Perkin-Elmer Model 21 Spectrophotometer, fitted with a sodium chloride prism. The samples were examined as mulls in Nujol or hexachlorobutadiene. Throughout this paper formaldehyde means 35% aqueous formaldehyde.

2,5-Dimercapto-1, 3, 4-thiadiazole III was prepared according to the procedure of Losanitch[12] and 2-mercapto-4-phenyl-1, 3, 4-thiadiazoline-5-thione was prepared in an analogous manner from phenylhydrazine[13].

2-Methylmercapto-1,3,4-thiadiazoline-5-thione (IX)

In an ethanolic solution of sodium ethylate prepared from 2.3 g. sodium and 100 ml. of absolute alcohol, 15 g. of III were dissolved followed by 14.2 g. of methyl iodide. The mixture was refluxed on a water bath for 10 min., cooled and poured into 300 ml. of water. The resulting yellow crystals were pure enough for further work. Yield: 13.2 g. (81%), m. p. 134—6°. The compound is identical with the product obtained by using the procedure of Busch and Biehler.[14]

2-Benzylmercapto-1, 3, 4-thiadiazoline-5-thione was obtained from a comparable reaction, but employing 12.6 g. of benzylchloride. Yield: 20.5 g. (85.5%), m. p. 130° lit.[16] gives m. p. 131°).

Salt formation of III with triethylamine — 1.5 g. of II were suspended in 50 ml. of sodium dry benzene and treated with 1.0 g. of triethylamine, which had been previously dried over potassium hydroxide. An exothermic reaction occured as the amine was added and the separated oil was left to crystallize at 0°C. The separated crystals were washed consecutively with benzene, a little ethanol and ether. The remaining colourless crystals had m. p. 132°: yield 2.45 g. The salt dissolves immediately in water, is soluble in ethanol and insoluble in benzene. With conc. hydrochloric acid the original thiadiazole III can be regenerated. A potentiometric determination of the molecular weight gave the value 245 (theoretically 251) and this is in agreement with the presumption that salt formation occurs in the ratio 1:1.

2-Mercapto-4-piperidinomethyl-1,3,4-thiadiazoline-5-thione (IV, X = CH_2)

Alter the vigorous reaction between a mixture of 1.5 g. of III, 1 ml. of piperidine and 1 ml. of formaldehyde had subsided, the product was left in an evacuated dessicator over conc. sulfuric acid for some days. The crude product was collected and recrystallized from a n-hexane-ethyl acetate mixture (1 : 1) whereby 1.5 g. (61%) of the pure compound separated, m. p. 161°. A mixed m. p. with III gave a m. p. depression of about 20°. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3240 Å, ε 6,390. The product has an IR absorption at 2250 cm^{-1} (SH).

Anal. $C_8H_{13}N_3S_3$ (247.21) calc'd.: C 38.87; H 5.30; S 38.83%
found: C 38.51; H 5.08; S 38.70%

In essentially the same way the following compounds were prepared:

2-Hydroxymethylmercapto-4-(2'-methoxyphenylamino)-methyl-1,3,4-thiadiazoline-5-thione (V, R = $-C_6H_4-OCH_3$ *(o)*)

To a suspension of 1.5 g. of III in 10 ml. of methanol, 1.4 ml. of *o*-anisidine and 2 ml. of formaldehyde were added. From the solution a crude yellow product separated and was crystallized twice from a mixture of 5 ml. of tetrahydrofurane and 50 ml. of methanol. Yield: 1.45 g. (46%). M. p. 93—5°.

Anal. $C_{11}H_{13}N_3O_2S_3$ (315.44) calc'd.: C 41.91; H 4.16; S 30.45%
found: C 42.38; H 4.25; S 30.98%

2-Hydroxymethylmercapto-4-(2'-chlorophenylamino)-methyl-1,3,4-thiadiazoline-5-thione (V, R = $-C_6H_4-Cl$ *(o)*)

Upon crystallization from tetrahydrofurane and thereafter from a tetrahydrofurane — methanol mixture (1 : 10) the following compound was obtained in 77% yield. M. p. 95—7°.

Anal. $C_{10}H_{10}ClN_3OS_3$ (319.86) calc'd.: N 13.14; S 30.08%
found: N 12.96; S 30.45%

2-Hydroxymethylmercapto-4-benzylaminomethyl-1,3,4-thiadiazoline-5-thione (V, R = $CH_2C_6H_5$)

Obtained in 95% yield. The crude product was washed with ether and dried. M. p. 98—100° (dec.). UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3280 Å, ε 12,700.

Anal. $C_{11}H_{13}N_3OS_3$ (299.44) calc'd.: N 14.04; S 32.08%
found: N 14.28; S 32.07%

2-Morpholinomethylmercapto-4-morpholinomethyl-1,3,4-thiadiazoline-5-thione (VI, X = O)

After the initial exothermic reaction between 1.5 g. of III, 1.8 g. of morpholine and 2 ml. of formaldehyde had subsided, unreacted III was filtered off and the residue was left in an evacuated dessicator over conc. sulfuric acid. After two days, crystallization started and after the oil has solidified, the crystals were collected and recrystallized from *n*-hexane and ethyl acetate mixture (3 : 1). 2.2 g. (63%) of the pure compound separated, m. p. 97—9°. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3300 Å, ε 7,570.

Anal. $C_{12}H_{20}N_4O_2S_3$ (348.31) calc'd.: C 41,38; H 5.79; N 16.09; S 27.56%
found: C 41.24; H 6.22; N 15.89; S 27.65%

2-Hydroxymethylmercapto-4-hydroxymethyl-1,3,4-thiadiazoline-5-thione (VII)

a) To a suspension of 3 g. of III in 20 ml. of methanol, 6 ml. of formaldehyde were added. The reaction mixture evolved heat, dissolution occured and thereafter colourless crystals began to separate. The methanol was evaporated *in vacuo* at room temperature and the crude bis-hydroxymethyl derivative remained as a yellow liquid. After the addition of 25 ml. of iced water a solid precipitated which was filtered and crystallized from water (70 ml.). From the cooled filtrate, crystals separated yielding 3.8 g. (90%) of the pure product with m. p. 106—8° (dec.). The compound gave a positive iodine-azide reaction. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3300 Å, ε 8,850.

Anal. $C_4H_6N_2O_2S_3$ (210.31) calc'd.: C 22.84; H 2.88; N 13.33; S 45.69%
found: C 22.97; H 2.99; N 13.21; S 45.60%

b) A suspension of the bis-Mannich base (VI, X = O) in water was treated with hydrogen chloride and almost colourless crystals separated. The product was crystallized twice from water. Yield 59%. The mixed m. p. with the compound obtained in a) gave no depression.

2-Methylmercapto-4-morpholinomethyl-1,3,4-thiadiazoline-5-thione (VIII, X = O)

a) To 1.64 g. of XI and 0.9 ml. of morpholine in 10 ml. of methanol 1 ml. of formaldehyde was added. The reaction mixture was shaken until a colourless precipitate separated. Recrystallization from a *n*-hexane and ethyl acetate mixture (1 : 1) gave a product with m. p. 85—7°. Yield 75%. The iodine-azide reaction was positive. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3260 Å, ε 12,050.

Anal. $C_8H_{13}N_3OS_3$ (263.21) calc'd.: N 15.97; S 37.30%
found: N 15.77; S 37.08%

b) 2-Mercapto-4-morpholinomethyl-1,3,4-thiadiazoline-5-thione was prepared in essentially the same way as the piperidino analogue (IV, X = CH_2). It was obtained as an oil which was used as such for further reactions. The resulting product (2.5 g.) was dissolved in a solution of sodium ethylate (0.23 g. of sodium in 20 ml. of absolute alcohol) and refluxed with 1.42 g. of methyl iodide on a water bath for 20 min. The cooled reaction mixture was poured into 30 ml. of water and the separated crystals were collected and crystallized from *n*-hexane and ethyl acetate (1 : 1), m. p. 85—7°. This sample, when mixed with the product obtained from a) gave no depression in m. p.

2-Hydroxymethylmercapto-4-phenyl-1,3,4-thiadiazoline-5-thione (X, R = OH)

To a suspension of 4.25 g. of 2-mercapto-4-phenyl-1,3,4-thiadiazoline-5-thione in 30 ml. of methanol, 6 ml. of formaldehyde were added. After the initial exothermic reaction a clear solution was obtained from which colourless crystals separated. The mixture was diluted with 150 ml. of water and after remaining at 0° C the voluminous precipitate was filtered and crystallized from aqueous methanol (1 : 1). 4.1 g. of colourless crystals were obtained with m. p. 54—5°. The compound gave a positive iodine-azide test.

Anal. $C_9H_8N_2OS_3$ (256.37) calc'd.: N 10.94; S 37.50%
found: N 11.02; S 37.83%

2-(2'-Chlorophenylamino)-methylmercapto-4-phenyl-1,3,4-thiadiazoline-5-thione (X, R = —NHC_6H_4—Cl(*o*))

A suspension of 2.26 g. of 2-mercapto-4-phenyl-1,3,4-thiadiazoline-5-thione in 15 ml. of methanol was treated successively with 1.4 g. of *o*-chloroaniline and 3.3 ml. of formaldehyde. The reaction mixture was left for some hours, filtered and the collected crystals purified from 7 ml. of tetrahydrofurane and a mixture of 5 ml. of tetrahydrofurane and 50 ml. of methanol respectively. The crystals were finally washed with ether yielding 2.82 g. (77%) of the product with m. p. 130—2°. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3020 and 3350 Å, ε 7,700 and 8,820.

Anal. $C_{15}H_{12}ClN_3S_3$ (365.83) calc'd.: C 49.21; H 3.30; N 11.48; S 26.29%
found: C 49.46; H 3.49; N 10.99; S 26.01%

2-Dimethylaminomethylmercapto-4-phenyl-1,3,4-thiadiazoline-5-thione (X, R = $N(CH_3)_2$)

The same procedure as above was used (1.4 ml. of a 33% aqueous solution of dimethylamine was used) and the crude oily Mannich base was left for 14 days at 0° C whereupon crystals commenced to separate. The product was crystallized from tetrahydrofurane and was obtained in 20% yield. M. p. 152—4°. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3360 Å, ε 7,980.

Anal. $C_{11}H_{13}N_3S_3$ (283.24) calc'd.: N 14.84; S 33.89%
found: N 14.58; S 33.60%

2-Benzylmercapto-4-morpholinomethyl-1,3,4-thiadiazoline-5-thione (XI, X = O)

A mixture of 2.4 g. of 2-benzylmercapto-1,3,4-thiadiazoline-5-thione, 0.9 ml. of morpholine and 1 ml. of formaldehyde was shaken at room temperature until colourless crystals separated. Crystallization from a *n*-hexane and ethyl acetate mixture (1 : 1) gave the Mannich base in 82% yield; m. p. 85—7° C. The iodine-azide reaction was positive. UV spectrum (in tetrahydrofurane): $\lambda_{max.}$ 3280 Å, ε 13,230.

Anal. $C_{14}H_{17}N_3OS_3$ (339.30) calc'd.: C 49.55; H 5.05; N 12.39; S 28.29%
found: C 49.99; H 5.07; N 12.22; S 27.80%

2-Benzylmercapto-4-piperidinomethyl-1,3,4-thiadiazoline-5-thione (XI, X = CH_2)

was prepared according to the above procedure in 74% yield. M. p. 82—4°.

Anal. $C_{15}H_{19}N_3S_3$ (337.53) calc'd.: C 53.40; H 5.68; N 12.46; S 28.46%
found: C 53.06; H 5.86; N 12.40; S 28.10%

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IZVLEČEK

Mannichova reakcija z 2,5-dimerkapto-1,3,4-tiadiazolom

J. Kobe, A. Pollak, B. Stanovnik in M. Tišler

Na 2,5-dimerkapto-1,3,4-tiadiazolu (III) smo raziskovali nastanek Mannichovih baz. V odvisnosti od količine uporabljenega formaldehida in sekundarnega amina nastanejo po Mannichovi reakciji tri vrste spojin. Pri uporabi ekvimolekularnih količin obeh reagentov nastanejo mono-Mannichove baze IV, dočim smo s prebitnim formaldehidom izolirali *mono*-hidroksimetil *mono*-Mannichovo bazo V. Kadar uporabimo oba reagenta v količini, ki ustreza dvema ekvivalentoma, nastane bis-Mannichova baza VI. Strukture omenjenih produktov smo ugotavljali s pomočjo kemičnih pretvorb in na osnovi spektroskopskih podatkov. *Mono*-Mannichovo bazo IV smo pretvorili v njen *S*-metil derivat VIII, katerega smo pripravili z neodvisno sintezo iz IX po Mannichovi reakciji. Na osnovi podatkov lahko zaključimo, da poteka aminoalkiliranje najprej na obročnem dušiku, v naslednji stopnji pa poteka reakcija na eksocikličnem žveplovem atomu.

ODDELEK ZA KEMIJO
FAKULTETA ZA NARAVOSLOVJE IN TEHNOLOGIJO
LJUBLJANA

Sprejeto 3 marca 1965.