THE REACTION OF DIMETHYL N-(1,2,4-TRIAZOL-5-YL)IMINODITHIOCARBONATES WITH DINUCLEOPHILES*

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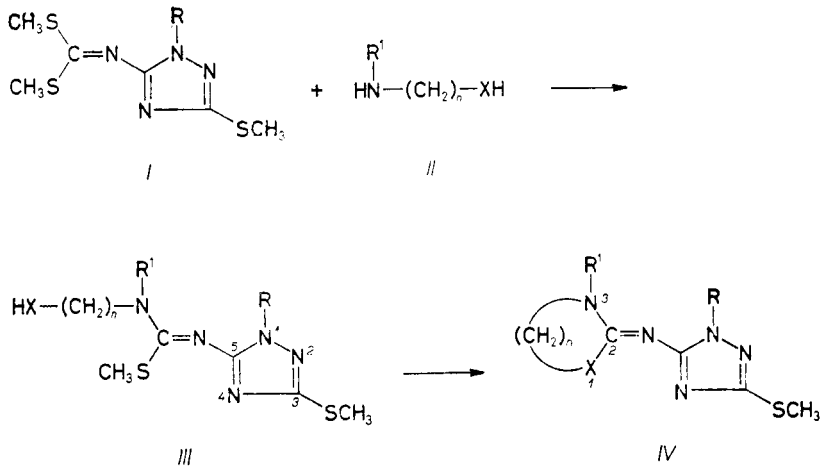
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

A series of N-(3-methylthio-1,2,4-triazol-5-yl) substituted carbamimidothioates (*III*), 2-iminoazolidines (*IV*, X = O, S, NH, $n = 2$), 2-iminohexahydro-1,3-oxazines (*IV*, X = O, $n = 3$), 2-iminohexahydropyrimidines (*IV*, X = NH, $n = 3$), and N,N′-alkylenebis(carbamimidothioates) (*V*) was prepared from dimethyl N-(3-methylthio-1,2,4-triazol-5-yl)iminodithiocarbonates (*I*). N-substituted azolidines *IV*, X = O, S, NH, $n = 2$, such as acetyl, methyl, (ethoxycarbonyl)-methyl, 1-(ethoxycarbonyl)ethyl, 2-chloroethylcarbamoyl, 2-cyano-2-(ethoxycarbonyl)ethenyl, and 2,2-dicyanoethenyl, were also prepared. The structure of isomers and tautomers of several compounds was determined using ^{1}H NMR, ^{13}C NMR, and UV data.

Recently we have described[2] the synthesis and structure elucidation of several dimethyl N-(3-methylthio-1,2,4-triazol-5-yl)iminodithiocarbonates (*I*). Biological



SCHEME 1

* Part XXVI in the series On Triazoles; Part XXV: see ref.[1].

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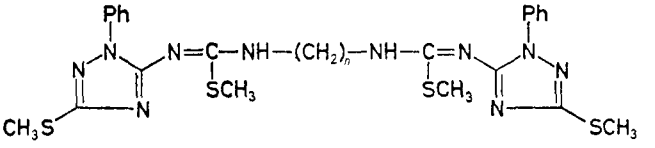
considerations led us to react them with ω-hydroxyalkylamines (*II*, X = O), ω-mercaptoalkylamines (*II*, X = S), and 1,ω-diaminoalkanes (*II*, X = NH) (ref.[3]) (Scheme 1).

The reaction of *I* with *II*, X = O led at 80–110°C to ω-hydroxyalkylisothiourea derivatives (*III*, X = O) that could be cyclized at 150–160°C to the corresponding 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]oxazolidines (*IV*, X = O, *n* = 2) and 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]perhydrooxazines (*IV*, X = O, *n* = 3) (Table I).

On the other hand, the reaction of *I* with *II*, X = S or NH led directly (most probably again through the corresponding isothiourea derivatives *III*) to 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]thiazolidines (*IV*, X = S, *n* = 2), 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]imidazolidines (*IV*, X = NH, *n* = 2) and 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]perhydropyrimidines (*IV*, X = NH, *n* = 3) (Scheme 1). Surprisingly, the reaction of *I*, R = Ph and *II*, X = NH, R^1 = H provided *V* which were probably formed by the reaction of the corresponding intermediates *III*, X = NH, R = Ph, R^1 = H with another molecule of *I*, R = Ph.



V, *n* = 2,3

The structure of the isothiourea derivatives *III* and also of compounds *IV*, X = O, S, NH was in good agreement with their spectral data (Tables II and III). The decision between the two possible tautomeric structures, the "imino" (*III*, R^1 = H) and the "amino" with NH group attached to the triazole ring, was based on the ^{1}H NMR spectra, where a direct coupling was observed between the NH and the methylene protons (see e.g. the $NHCH_2$ quartets of *IIIb*, *IIId*, and *IIIe*, Table II). This proves the tautomeric form *III*, R^1 = H to be predominant in dimethyl sulfoxide solution.

Also *IV*, X = O, S, NH, R^1 = H, may appear in two tautomeric forms. In case of imidazolidine and perhydropyrimidine derivatives *IV*, X = NH the decision between both tautomeric forms was made basing on the alkylation reactions of *IV*, X = NH, R = Ph, R^1 = H, *n* = 2 which yielded the corresponding mono (*VIa* – *VIc*) and dialkyl (*VII*) derivatives, the spectra of which were again in full accordance with those expected. The dialkyl derivative *VII* may exist in the "imino" form only. The UV spectra of *VIa* and *VII* in ethanol (Table IV) were very similar to those of the corresponding imidazolidine and perhydropyrimidine derivatives *IVb* and *IVd* (Table III). Hence, all these derivatives had to exist predominantly, at least in ethanolic solutions, in the *IV*-type, i.e. "imino" tautomeric form.

TABLE I

Synthesis of N-(3-methylthio-1,2,4-triazol-5-yl)-substituted carbamimidothioates (*III*), 2-iminoazolidines, 2-iminohexahydro-1,3-oxazines and 2-iminohexahydropyrimidines (*IV*), and N,N′-alkylenebis(carbamimidothioates) (*V*)

Compound	R	R^1	*n*	X	Method Solvent, ml	Yield %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found %C	%H	%N	%S
IIIa	H	H	3	O	—	82	120—121	$C_8H_{15}N_5OS_2$	36·76	5·78	26·79	24·54
					MeCN, 50		(EtOH)	(261·37)	36·91	5·88	26·66	24·32
IIIb	Ph	H	2	O	—	67	93—94·5	$C_{13}H_{17}N_5OS_2$	48·27	5·30	21·65	19·83
					dioxane, 40		(MeOH)	(323·45)	48·30	5·39	21·37	19·75
IIIc	Ph	H	3	O	—	69	66—68	$C_{14}H_{19}N_5OS_2$	49·83	5·68	20·75	19·00
					toluene, 40		(MeOH)	(337·47)	50·01	5·48	20·76	19·18
IIId	Ph	H	2[a]	O	—	47	88—90	$C_{14}H_{19}N_5OS_2$	49·83	5·68	20·75	19·00
					toluene, 40		(MeCN)	(337·47)	49·81	5·78	20·66	18·97
IIIe	Ph	H	2[b]	O	—	58	109—111	$C_{15}H_{21}N_5OS_2$	51·26	6·02	19·92	18·25
					dioxane, 40		(EtOH)	(351·49)	51·39	6·11	19·80	18·10
IIIf	DMP[c]	H	2	O	—	47	114—116	$C_{15}H_{21}N_5OS_2$	51·26	6·02	19·92	18·25
					dioxane, 40		(MeCN)	(351·49)	51·37	6·16	20·09	18·21
IIIg	DMP[c]	H	3	O	—	70	120—122	$C_{16}H_{23}N_5OS_2$	52·58	6·34	19·16	17·55
					dioxane, 40		(MeOH)	(365·52)	52·63	6·41	19·09	17·31
IVa	H	H	2	NH	*A*	79	197—199	$C_6H_{10}N_6S$	36·35	5·08	42·39	16·17
					BuOH, 30		(MeOH)	(198·25)	36·18	5·21	42·29	16·23
IVb	Ph	H	2	NH	*A*	85	127—128	$C_{12}H_{14}N_6S$	52·54	5·14	30·63	11·69
					BuOH, 30		(EtOH)	(274·35)	52·65	5·31	29·95	11·88
IVc	DMP[c]	H	2	NH	*A*	53	226—228	$C_{14}H_{18}N_6S$	55·61	6·00	27·79	10·60
					BuOH, 30		(PrOH)	(302·40)	55·87	6·08	27·81	10·46
IVd	Ph	H	3	NH	*A*	38	138—140	$C_{13}H_{16}N_6S$	54·15	5·59	29·14	11·12
					$CHCl_3$, 30		(EtOH)	(288·37)	54·32	5·71	28·93	11·31
IVe	Ph	2-HE[d]	2	NH	*A*	69	92—94	$C_{14}H_{18}N_6OS$	52·81	5·70	26·39	10·07
					EtOH, 40		(MeCN)	(318·40)	52·96	5·60	26·08	9·96

IVf	H	H	2	O	*A* DMF, 15	41	208–210 (DMF)	$C_6H_9N_5OS$ (199·23)	36·17 35·94	4·55 4·62	35·15 35·28	16·09 15·94
IVg	Ph	H	2	O	*B* DMF, 5	54	116–118 (MeCN)	$C_{12}H_{13}N_5OS$ (275·34)	52·35 52·49	4·76 4·81	25·44 25·29	11·65 11·61
IVh	Ph	H	2[e]	O	*A* DMF, 15	51	136–137 (MeOH)	$C_{14}H_{17}N_5OS$ (303·39)	55·43 55·51	5·65 5·70	23·08 23·14	10·57 10·62
IVi	H	H	3	O	*B* DMF, 10	58	194–196 (EtOH)	$C_7H_{11}N_5OS$ (213·26)	39·43 39·61	5·20 5·37	32·84 32·70	15·03 14·89
IVj	H	Me	2	O	*A* BuOH, 40	58	171–173 (MeCN)	$C_7H_{11}N_5OS$ (213·26)	39·42 39·65	5·20 5·31	32·84 22·67	15·04 14·87
IVk	Ph	Me	2	O	*A* DMF, 15	78	170–172 (EtOH)	$C_{13}H_{15}N_5OS$ (289·36)	53·96 54·10	5·23 5·47	24·20 24·23	11·08 10·97
IVl	Ph	Et	2	O	*A* DMF, 15	61	82–84 (*i*-PrOH)	$C_{14}H_{17}N_5OS$ (303·39)	55·43 55·32	5·65 5·55	23·08 22·94	10·57 10·46
IVm	Ph	Bu	2	O	*A* DMF, 15	71	78–80 (MeCN)	$C_{16}H_{21}N_5OS$ (331·44)	57·98 58·08	6·39 6·29	21·13 21·14	9·67 9·65
IVn	Ph	$PhCH_2$	2	O	*A* DMF, 15	72	148–150 (MeCN)	$C_{19}H_{19}N_5OS$ (365·46)	62·44 62·45	5·24 5·21	19·16 19·31	8·77 8·98
IVo	Ph	2-HE[d]	2	O	*A* DMF, 15	52	127–128 (MeCN)	$C_{14}H_{17}N_5O_2S$ (319·38)	52·65 52·81	5·37 5·44	21·93 21·71	10·02 9·88
IVp	Ph	H	2	S	*B*[f] DMF, 10 H_2O, 5	72	101–102 (EtOH)	$C_{12}H_{13}N_5S_2$ (291·40)	49·46 49·61	4·50 4·55	24·03 23·87	22·01 21·92
Va	—	—	2	—	*B* MeCN, 10	35	183–185 (DMF)	$C_{24}H_{28}N_{10}S_4$ (584·82)	49·29 49·51	4·83 4·97	23·95 23·70	21·93 21·68
Vb	—	—	3	—	*B* MeCN, 10	38	162–164 (DMF)	$C_{25}H_{30}N_{10}S_4$ (598·84)	50·14 49·95	5·05 5·07	23·39 23·12	21·42 21·20

[a] X—$CH(CH_3)CH_2$—N; [b] X—$CH_2CH(CH_2CH_3)$—N; [c] 2,6-dimethylphenyl; [d] 2-hydroxyethyl; [e] X—$CH_2C(CH_3)_2$—N; [f] 2-aminoethanethiol hydrochloride and Na_2CO_3 were used; work-up: dilution with 30 ml H_2O and trituration of the oily crystals.

TABLE II

^{1}H NMR and ^{13}C NMR data (δ, ppm; in CD_3SOCD_3) of N-(3-methylthio-1,2,4-triazol-5-yl)-substituted carbamimidothioates (*III*)

Compound	Triazole		Carbamimidothioate				Triazole				Carbamimidothioate		
	SCH_3	R	NCH_2 XCH_2	CCH_2C	XH	NH	SCH_3	C-3	C-5	SCH_3	R	C	NCH_2 XCH_2	CCH_2C
IIIa	2·49 s	13·0 b	3·38 q 3·51 q	1·74 qi	4·63 t	[a]	2·44 s	160·0	157·9	15·1 15·6	—	165·3	42·3 60·1	34.2
IIIb	2·58 s	7·31 t 7·48 t 7·90 d	3·40 q 3·60 q	—	5·05 t	9·90 t	2·44 s	158·5	156·8	15·1 15·3	123·8 127·9 130·8 139·3	166·5	47·6 61·0	—
IIIc	2·57 s	7·31 t 7·47 t 7·88 d	3·44 q 3·52 q	1·76 qi	4·65 t	9·73 t	2·43 s	158·4	156·4	15·1 15·2	123·8 128·0 130·2 139·2	166·8	42·2 59·8	33·7

IIId	2·57 s	7·31 t 7·47 t 7·90 d	3·4 m 3·9 m[c]	1·13[b]	5·08 d	10·0 b	2·44 s	158·5	156·8	15·2 15·3	123·7 127·0 130·0 139·4	167·1	52·5 66·3[c]	22·5[b]
IIIe	2·57 s	7·31 t 7·48 t 7·90 d	3·5 m[c] 3·7 m	0·93 t[d] 1·66 dq[d]	5·08 t	9·95 d	2·45 s	158·5	156·6	15·2 15·5	123·9 128·0 130·3 139·2	166·8	59·2[c] 63·7	11·2[d] 26·1[d]
IIIf	2·54 s	1·97 s 2·05 s 7·19 d 7·28 t	3·40 m 3·60 m	—	5·05 bs	9·65 bs	2·45 s	159·0	157·8	15·1 15·7	18·5 128·9 136·0 136·6 136·8	166·1	46·7 60·4	—
IIIg	2·53 s	1·96 s 2·02 s 7·19 d 7·28 t	3·40 m 3·55 m	1·75 m	4·7 bs	9·5 bs	2·42 s	158·9	157·8	15·0 15·6	19·4 129·8 131·0 137·5	166·4	42·6 60·1	34·2

[a] Not detected; [b] CH_3; [c] CH; [d] ethyl.

TABLE III

^{1}H NMR and ^{13}C NMR data (δ, ppm; in CD_3SOCD_3) of 2-(3-methylthio-5-amino-1,2,4-triazol-5-yl)-substituted iminoazolidines, iminohexahydro-1,3-oxazines, and iminohexahydropyrimidines (*IV*) and N,N′-alkylenebis(carbamimidothioates) (*V*)

Compound	Triazole		Heterocycle			Triazole				Heterocycle		
	SCH_3	R	NCH_2 XCH_2	NH	R^1	C-3	C-5	SCH_3	R	R^1	C-2	NCH_2 XCH_2
IVa	2·45 s	11·5 b[c]	3·47 s[a]	7·3 bs[b]	—	157·4 q	162·1 s	15·2 q	—	—	163·0 m	43·3 43·3
IVb[d]	2·54 s	7·23 t 7·42 t 7·96 d	3·53 s[a]	7·61 s[b]	—	158·4 q	160·2 s	15·2 q	123·0 127·3 130·5 140·3	—	163·5 m	43·6 43·6
IVc	2·50 s	1·97 s 7·15 7·30 m	3·60 s[a]	7·5 bs[b]	—	158·3 q	160·8 s	15·2	18·9 129·5 130·1 137·4 137·8	—	163·3 m	43·2 43·2
IVd[d]	2·60 s	7·18 t 7·37 t 7·96 d	3·08 t[a] 1·70 m[e]	7·8 b[b]	—	157·7	158·9 [f]	15·1	123·4 126·4 129·3 139·7	—	155·7	39·8 39·8 21·7[c]
IVe	2·58 s	7·21 t 7·38 t 7·84 d 7·85 b	3·64 t 3·38 t	8·1 bs	3·53 m[a] 3·80 t[g]	158·3	159·0 [f]	15·1	123·1 126·8 129·4 139·3	48·1 61·8	161·3	48·5 41·8

IVf	2·49 s		3·71 t 4·45 t	8·40 s 12·8 bs	—	158·1	160·7	15·4	—	—	163·5	44·3 67·7
IVg	2·60 s	7·31 t 7·48 t 7·88 d	3·80 t 4·52 t	8·7 bs	—	158·3	158·8	15·1	123·6 127·7 130·3 139·4	—	164·0	44·4 67·8
IVh	2·57 s	7·29 t 7·46 t 7·85 d	— 4·19 s 1·39 s[h]	8·7 bs	—	158·1	158·9	15·1	123·6 128·7 130·2 139·4	—	162·2	56·1[i] 69·0 28·1[k]
IVi	2·46 s		3·43 t 4·28 t 1·95[e]	9·1 bs 13·2 bs	—	157·2	160·5	15·4	—	—	158·1	40·0 67·0 22·5[e]
IVj	2·42 s		3·62 t 4·44 t	12·5 bs	2·89 s	157·4	158·9	15·4	—	33·2	158·8	49·1 67·1
IVk	2·51 s	7·27 t 7·45 t 7·83 d	3·65 t 4·46 t	—	2·93 s	159·2	159·6	15·0	123·3 127·6 130·3 139·6	33·1	156·7	48·9 67·4
IVl	2·51 s	7·28 t 7·45 t 7·79 d	3·66 t 4·47 t	—	1·13 t 3·38 q	158·5	159·8	15·1	123·4 127·7 130·3 139·7	13·5 40·8	156·9	46·3 67·5
IVm	2·59 s	7·23 t 7·37 t 7·84 d	3·57 t 4·50 t	—	0·92 t 1·33 m 1·56 qi 3·36 t	158·3	160·4[f]	15·0	123·8 127·5 129·8 139·9	15·6 21·3 30·5 47·0	156·6	46·2 67·1

TABLE III
(*Continued*)

Compound	Triazole		Heterocycle			Triazole				Heterocycle		
	SCH_3	R	NCH_2 XCH_2	NH	R^1	C-3	C-5	SCH_3	R	R^1	C-2	NCH_2 XCH_2
IVn	2·53 s	7·27 – 7·40 m[j] 7·77 d	3·60 t 4·51 t	–	4·56 s 7·40 m[j]	158·7	159·7	15·0	123·5 127·8 130·2 139·4	129·2 129·3 130·2 137·7	156·6	46·7 49·6 67·6
IVo	2·52 s	7·28 t 7·45 t 7·82 d	3·75 t* 4·48 t	–	3·42 t* 3·62 q 4·92 t[g]	158·8	159·7	15·1	123·3 127·6 130·3 139·6	–	156·8	47·8 48·8 60·0 67·6
IVp	2·57 s	7·30 t 7·46 t 7·85 d	3·37 t 3·68 t	8·85 bs	–	158·2	159·0	15·1	123·6 127·8 130·3 139·4	–	171·8	47·2 31·1
Va	2·51 s	7·30 t 7·50 t 7·85 d	3·65 bs[a]	9·80 bs	2·46 s[k]	–	–	–	–	–	–	–
VIb	2·54 s	7·30 t 7·45 t 7·85	3·48 t[a] 1·95[e]	9·75 bs	2·48 s[k]	–	–	–	–	–	–	–

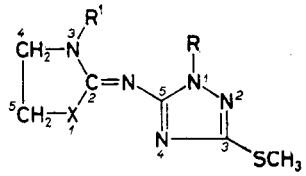
[a] 4 H; [b] 2 H; [c] UV (EtOH): λ_{max} ($\varepsilon \cdot 10^{-3}$) 233 nm (18·8) and 281 nm (14·5); [d] UV (EtOH): λ_{max} ($\varepsilon \cdot 10^{-3}$) 238 nm (18·8) and 290 nm (16·4); [e] CCH_2C; [f] in $CDCl_3$; [g] 1 H; [h] CH_3; [i] $NCCH_2$; [j] 2 H + 5 H; [k] SCH_3 (carbamimidothioate).

TABLE IV

UV, IR, and ^{1}H NMR data of 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]azolidine derivatives *VI*, *VII*, *XII*, *XIII*, and *XIV*

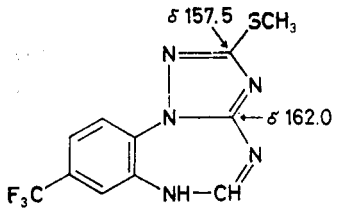
Compound	UV λ, nm ($\varepsilon \cdot 10^{-3}$)	IR ($\tilde{\nu}$, cm^{-1})			^{1}H NMR (δ, ppm; in CD_3SOCD_3)			
		NH	C=O	C=N	CH_3S NH	NCH_2 XCH_2	Ph *o*, *m*, *p*	R^1
VIa	236 (18·8) 284 (12·5)	3400 2850	—	1 610 1 589	2·57 s 7·92 bs	3·59 s 3·48 t	8·05 d 7·47 t 7·25 t	2·89 s
VIb	238 (22·1) 286 (17·2)	3380 3320	1750	1 615 1 590 1 540	2·55 s 7·50 bs	3·66 bs[a]	7·65 d 7·47 t 7·33 t	3·10 s[b] 4·20 q[c] 1·25 t[c]
VIc	242 (20·7) 288 (16·2)	3330	1750	1 610 1 600 1 510	2·54 s 7·35 bs	3·63 m[a]	7·65 d 7·45 t 7·28 t	4·73 q[d] 1·42 d[e] 4·11 q[c] 1·25 t[c]
VII	238 (18·5) 283 (14·3)	—	—	1 610 1 580	2·52 s —	3·48 s[a]	7·91 d 7·44 t 7·24 t	2·57 s[f]
XIIa	246 (20·5) 290 (14·6)	3260	1690	1 630 1 600 1 500	2·55 s 9·80 bs	3·58 t 3·32 t	7·72 — 7·22 m[g]	2·45 s
XIIb	241 (23·0) 288 (10·7)	—	1675	1 570 1 550	2·56 s —	4·01 t 4·55 t	7·70 d 7·52 t 7·40 t	2·42 s
XIIc	250 (23·3) 306 (10·7)	—	1675	1 570	2·61 s —	4·15 t 3·24 t	7·66 d 7·52 t 7·42 t	2·37 s
XIII	218 (19·4) 266 (14·0)	3340 3250	1670	1 640 1 550	2·56 s 8·60 bs 12·7 bs[h]	3·70 t 3·11 t	—	2·48 s
XIV	230 (23·1) 279 (13·6)	3250	1695	1 600 1 510	2·60 s 9·30 bs 8·70 bs[k]	3·44 t 3·70 t	7·64 d 7·48 t 7·35 t	3·60 t[i] 4·00[j]

[a] 4 H; [b] CH; [c] ethyl; [d] CH; [e] CH_3; [f] 6 H; [g] 5 H; [h] triazole NH; [i] CH_2N; [j] CH_2Cl; [k] NHCO.

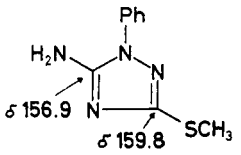


	X	R	R^1
VIa	NH	Ph	CH_3
VIb	NH	Ph	$CH_2COOC_2H_5$
VIc	NH	Ph	$CH(CH_3)COOC_2H_5$
VII	NCH_3	Ph	CH_3
XIIa	NH	Ph	$COCH_3$
XIIb	O	Ph	$COCH_3$
XIIc	S	Ph	$COCH_3$
XIII	NH	H	$COCH_3$
XIV	NH	Ph	$CONHCH_2CH_2Cl$

Structure of the imidazolidines and perhydropyrimidines (*IV*, X = NH, R^1 = H, n = 2 or 3) is in full agreement with their ^{13}C NMR spectra, too (Table III). It is known[4] that the chemical shifts of the triazole carbon atoms depend only on whether the nitrogen atoms attached are "pyrrole-like" or "pyridine-like" and are little influenced by the kind of the triazole substituents. Thus, if the tautomeric structure *IV* is correct the chemical shifts of the triazole carbon atoms 3 and 5 of all *IV*, X = = NH, R^1 = H have to be similar to those of *VIII* (ref.[5]) and should differ significantly from those of *IX* (ref.[4]) having the similar "imino" and "amino" structures, respectively. The chemical shifts of the triazole carbon atoms 3 and 5 of the imidazolidines *IVa–IVc* (X = NH, R^1 = H) and perhydropyrimidine *IVd* (X = NH, R^1 = H) appeared at 157·4–159·2 and 158·8–162·1 ppm, respectively (Table III), being similar to those of *VIII* (157·5 and 162·0 ppm, respectively) and differing from those of *IX* (159·8 and 156·9 ppm, respectively) thus pointing out to the predominant "imino" tautomer *IV* in dimethyl sulfoxide solution.



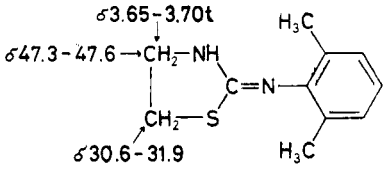
VIII



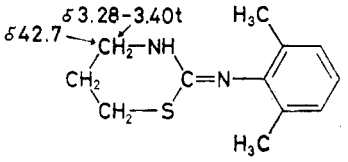
IX

In case of oxazolidines *IVf–IVh*, perhydrooxazine *IVi*, and thiazolidine *IVp*, no coupling was observed in the ^1H NMR spectra between the NH and the methylene

protons. This is the case observed in the aryliminothiazoline and -thiazine series[6,7], but, as proved, giving no information about the "imino" or "amino" tautomeric structure. On the other hand, the chemical shifts of the NCH_2 triplets of thiazolidine *IVp* and oxazolidines *IVf* and *IVg* (3·68 and 3·71–3·80 ppm, respectively) were similar to those of substituted phenyliminothiazolidines *X* (3·65–3·70 ppm). The same was the situation with the chemical shift of the NCH_2 triplet of perhydrooxazine *IVi* (3·43 ppm) which was similar to that of phenyliminoperhydrothiazines *XI* (3·28–3·40 ppm) to which *IV*-type structure was assigned[8] on the basis of ^{13}C NMR. These data support the *IV*-type predominant tautomeric structure of *IVp*, *IVf* and *IVg* in dimethyl sulfoxide solutions.



X

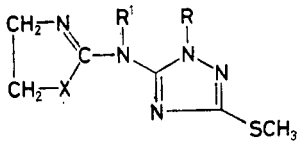


XI

The predominant tautomeric structure *IV* of thiazolidine *IVp* in dimethyl sulfoxide solution was also corroborated by its ^{13}C NMR spectra, where the NCH_2 and SCH_2 carbon atoms appeared with chemical shifts of 47·2 and 31·1 ppm, respectively, in excellent agreement with those of the corresponding phenyliminothiazolidines *X* (47·3–47·6 and 30·6–31·9 ppm, respectively).

It should be mentioned that in spite of the difference in heteroatom the chemical shifts of the NCH_2 carbon atoms of perhydrooxazine *IVi* (Table III) and the known perhydrothiazine *XI* proved to be also similar giving a further proof of the *IV*-type predominant tautomeric structure of our perhydrooxazine *IVi* in dimethyl sulfoxide solution.

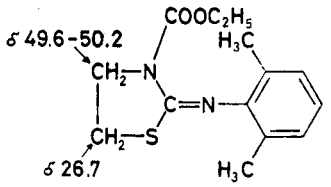
The *IV*-type predominant tautomeric structure of oxazolidines *IVf* and *IVg* and thiazolidine *IVp* is also corroborated by their UV spectra in ethanolic solution which are similar to those of their analogues *IVj–IVo* with $R^1 \neq H$ (see Table III).



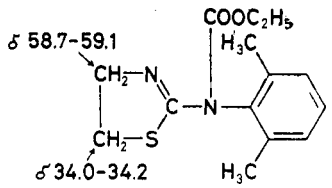
XV

In the acetylation or carbamoylation of *IV*, X = O, S, NH, R^1 = H, n = 2 both the "endo" (*XII*, *XIII*, *XIV*) and "exo" (*XV*) derivatives could be formed.

An easy decision between structures *XII* and *XV* was based on the comparison of the chemical shifts of the C-4 (NCH_2) and C-5 (SCH_2) carbon atoms of thiazolidine *XIIc* (50·2 and 27·5 ppm, respectively; Table V) with those of isomeric *XVI* (49·6 – 50·2 and 26·7 – 26·7 ppm, respectively) and *XVII* (58·7 – 59·1 and 34·0 – 34.2 ppm, respect-



XVI

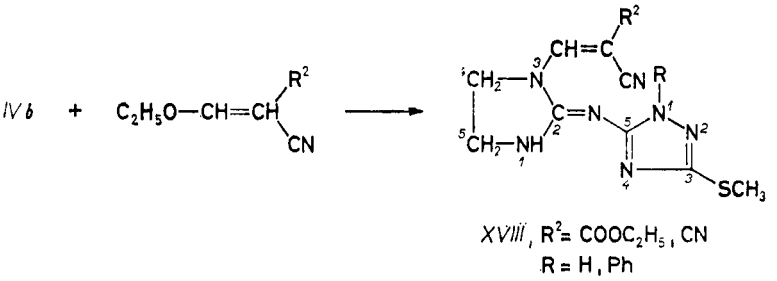


XVII

ively) described previously[8]. The similarity of the corresponding chemical shifts of acetylated *XIIc* and *XVI* proves the structure of the former unequivocally. As the changes of the chemical shifts of the C-2, C-4, and C-5 carbon atoms of the acetylated thiazolidine, oxazolidine, and imidazolidines *XIIc*, *XIIb*, and *XIIa* when compared to those of the starting materials *IV*, X = S, O, NH, n = 2, were in all cases similar, structure *XIIb* and *XIIa* could be assigned to the acetylated oxazolidine and thiazolidine derivatives, too. This is also in accordance with the UV spectra of *XIIa*, *XIIb*, and *XIIc*, which are in all cases similar to each other and show a slight bathochromic shift of the highest maxima when compared with *IV*, X = S, O, NH, *n* = 2 (Table IV).

The ^1H NMR, ^{13}C NMR, and UV spectra of the carbamoyl derivative *XIV* were similar to those of the corresponding acetyl derivative *XIIa*, thus again pointing out to the ring nitrogen being carbamoylated.

The reaction of *IVa* and *IVb* with ethyl 2-cyano-3-ethoxyacrylonitrile or ethyl 2-cyano-3-ethoxyacrylate led to *XVIII*, R^2 = CN or COOEt (Scheme 2), the spectra of which were again in accordance with those expected (Tables VI, VII). However, in case of R^2 = COOEt both *Z* and *E* isomers could be formed. The decision between



XVIII, R^2 = $COOC_2H_5$, CN
R = H, Ph

SCHEME 2

TABLE V

^{13}C NMR data (δ, ppm; in CD_3SOCD_3) of 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]azolidine derivatives *VI*, *VII*, *XII*, *XIII*, and *XIV*

Compound	Azolidine		Triazole		Ph	R^1		
	C-2	C-3 C-5	C-3 C-5	CH_3S	*i*, *o*, *m*, *p*	CO	CH_3	CH_2
VIa	161·5	43·2 49·3	158·4 159·5	15·0	140·0 122·6 130·1 126·8	—	33·0	—
VIb	160·7 m	41·9 47·5	158·4 q 158·9 s	15·1	139·6 122·9 129·3 126·5	170·3	15·2[a]	46·9 62·1[a]
VIc	160·9 m	42·8 44·3	158·7 q 159·2 s	15·2	140·0 122·8 130·2 127·1	173·5	15·7[a] 16·4[b]	52·8[c] 63·3[a]
VII	161·0	49·3	157·6 159·3	15·0	140·3 122·4 130·2 126·9	—	35·6	—
XIIa	158·0	44·9 40·9	155·8 158·9	15·1	139·1 124·8 130·2 128·4	170·8	26·4	—
XIIb	154·4*	45·4 67·6	154·8* 160·3	15·1	138·7 124·6 130·5 128·9	170·6	25·9	—
XIIc	166·8	50·2 27·7	156·3 160·2	15·3	138·4 125·5 130·4 129·4	171·0	27·2	—
XIII	158·0 m	44·0 41·0	155·0 s 160·0 q	15·3	—	171·1	26·3	—
XIV	155·8	43·1 39·4	156·2 159·0	15·1	138·7 124·8 129·3 128·4	153·0	—	42·0[c] 43·0[c]

[a] Ethyl; [b] $CHCH_3$; [c] $NHCH_2$ and $ClCH_2$.

TABLE VI
UV, IR, and ^{1}H NMR data of *XVIII*

R	R^2	UV	IR ($\tilde{\nu}$, cm^{-1})			^{1}H NMR (δ, ppm; in CD_3SOCD_3)				
		λ, nm ($\varepsilon \cdot 10^{-3}$)	NH	C=N C=O	C=N	CH_3S NH	4-CH_2 5-CH_2	Ph *o*, *m*, *p*	CH	Et
Ph	CN	220 (17·4) 280 (23·4) 320sh (12·6)	3 280	2 230 —	1 670 1 600	2·59 s 9·0 bs	4·30 t 3·80 t	7·80dd 7·50dt 7·35 t	8·13 s	—
H	COOEt	228 (11·4) 308 (22·7)	3 325	2 222 1 699	1 636 1 589	2·50 s 11·5 b	4·21 t 3·76 t	—	8·65 s	4·28 q 1·26 t
Ph	COOEt	218 (17·2) 280 (26·8) 318 (18·0)	3 280	2 230 1 720	1 670 1 600 1 530	2·66 s [a]	4·58 t 3·12 t	7·20 — 7·6 m[b]	8·71 s	4·38 q 1·41 q

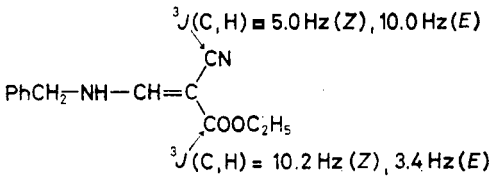
[a] Not detected; [b] 5 H.

TABLE VII
^{13}C NMR data (δ, ppm; in CD_3SOCD_3) of *XVIII*

R	R^2	Azolidine		Triazole		Ph *i*, *o*, *m*, *p*	=C(CN)	CH	CN	COOEt
		NCH_2 $NHCH_2$	C-2	C-3 C-5	CH_3S					
Ph	CN	43·6 45·1	153·5	156·4 159·4	15·4	139·0 124·2 130·5 128·5	58·5	151·3	115·4[a] 117·1[b]	—
H	COOEt	42·8 45·1	153·9	157·9 159·5	15·3	—	79·7	148·0	117·4[c]	15·7[d] 62·8[d] 165·7[e]
Ph	COOEt	42·7 45·0	154·2	156·9 159·2	15·1	139·0 123·7 130·3 128·1	80·4	148·1	117·2[f]	15·7[d] 62·8[d] 165·3[g]

[a] "*E*"; [b] "*Z*"; [c] ^3J(C, H) = 10·1 Hz; [d] ethyl; [e] ^3J(C, H) = 3·8 Hz; [f] ^3J(C, H) = 10·0 Hz; [g] ^3J(C, H) = 3·7 Hz.

these two isomers was made using the proton coupled ^{13}C NMR spectra. The comparison of the published[9] ^3J(C, H) coupling constants of the CN and CO carbon atoms and the vinyl protons in *Z*- and *E*-*XIX* with those in *XVIII*, R^2 = COOEt, R = H and *XVIII*, R^2 = COOEt, R = Ph (10·1 and 3·8 Hz, and 10·0 and 3·7 Hz, respectively) proved the *E* structure of the last two compounds unequivocally.



XIX

EXPERIMENTAL

Melting points were determined on a Kofler–Boëtius microapparatus and are uncorrected IR spectra (KBr) were obtained using a Perkin–Elmer 577 spectrophotometer. UV spectra in ethanol were obtained with a Varian Cary 118 and a Pye Unicam SP 8-150 instruments. ^1H NMR and ^{13}C NMR spectra, in $CDCl_3$, and CD_3SOCD_3, with TMS and DDS, were recorded on Varian XL-100, Bruker WM-250, and Bruker WP-80 SY instruments (^1H at 100, 250, and 80 MHz, respectively, in the CW or FT mode, ^{13}C at 25·14, 62·89, and 20·15 MHz, respectively).

General Method for the Preparation of *III*

To a solution of 0·01 mol of dimethyl N-(3-methylthio-1,2,4-triazole-5-yl)iminodithiocarbonate[3] *I* in an appropriate solvent 0·012 mol of alkanolamine *II*, X = O was added and the solution boiled for 2 h. The solvent was evaporated in vacuo to dryness, the residue was triturated with ether, the crystalline precipitate was filtered off and recrystallized from an appropriate solvent (Table I).

General Method for the Preparation of *IV* (Method *A*)

A solution of 0·01 mol of carbamimidothioate *III* in 5 ml of an appropriate solvent was refluxed for 1 h. The solvent was evaporated in vacuo to dryness, the residue was triturated with acetone, the precipitated crystals were filtered off and recrystallized from an appropriate solvent (Table I).

General Method for the Direct Preparation of *IV* and *V* (Method *B*)

To a solution of 0·01 mol of dimethyl N-(3-methylthio-1,2,4-triazole-5-yl)iminodithiocarbonate[3] *I* in an appropriate solvent 0·012 mol of alkanolamine *II*, X = O, thioalkanolamine *II*, X = S or 1,ω-diaminoalkane *II*, X = NH was added and the solution refluxed with stirring for 2 h. Further work-up was the same as in Method *A* except for trituration with methanol (Table I).

1-Methyl-2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*VIa*) and 1,3-Dimethyl-2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*VII*)

To a suspension of 0·6 g (0·02 mol) of sodium hydride (80% suspension in paraffin oil) in 30 ml of dry dimethylformamide 4·6 g (0·016 mol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*IVb*) was added in small portions with stirring below 20°C. The stirring was continued at room temperature for 15 min, then 2·4 g (0·016 mol) of methyl iodide was added to the reaction mixture and stirred at 60°C for further 2 h. After cooling 50 ml of water was added, the mixture was extracted with chloroform (3 × 30 ml), the chloroform solution was washed with water, dried over sodium sulfate and evaporated in vacuo to dryness. The oily residue was chromatographed on silica gel (eluent C_6H_6–AcOEt 1 : 2) to yield 1·1 g (24%) of *VIa*, m.p. 145–147°C (ethanol) and 2·8 g (58%) of *VII*, m.p. 116–117°C (EtOH).

VIa: For $C_{13}H_{16}N_6S$ (288.37) calculated: 54·15% C, 5·60% H, 29·14% N, 11·12% S; found 54·06% C, 5·18% H, 29·26% N, 11·08% S.

VII: For $C_{14}H_{18}N_6S$ (302·40) calculated: 55·61% C, 6·00% H, 27·79% N, 10·60% S; found: 55·78% C, 6·07% H, 27·61% N, 10·49% S.

Ethyl {2-[(3-Methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine-1-yl}acetate (*VIb*)

To a suspension of 0·6 g (0·02 mol) of sodium hydride (80% suspension in paraffin oil) in 30 ml of dry dimethylformamide 4·6 g (0·016 mol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*IVb*) was added in small portions with stirring below 20°C. The stirring was continued at room temperature for 15 min, then 1·96 g (0·016 mol) of ethyl chloroacetate was added dropwise at room temperature followed by heating of the reaction mixture to 90–100°C for 3 h. After cooling the reaction mixture was quenched with 50 ml of water, the product was filtered off and recrystallized from methanol. Yield 3·4 g (59%), m.p. 112–114°C. For $C_{16}H_{20}N_6O_2S$ (360·44) calculated: 53·32% C, 5·59% H, 23·32% N, 8·88% S; found: 53·49% C, 5·75% H, 23·22% N, 8·76% S.

Ethyl 2-{2-[(3-Methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine-1-yl}propionate (*VIc*)

Prepared as *VIb*, using 2·9 g (0·016 mol) of ethyl 2-bromopropionate. Yield 4·5 g (75%), m.p. 77–78°C (MeOH). For $C_{17}H_{22}N_6O_2S$ (374·46) calculated: 54·53% C, 5·92% H, 22·44% N, 8·56% S; found: 54·63% C, 6·10% H, 22·48% N, 8·41% S.

1-Acetyl-2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*XIII*)

To a solution of 1·98 g (0·01 mol) of 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*IVa*) in 15 ml of pyridine 0·94 g (0·012 mol) of acetyl chloride was added dropwise at room temperature. The reaction mixture was then stirred at 70°C for 1 h. After cooling 30 ml of water was added to the reaction mixture, the crystals were filtered off and recrystallized from 1-butanol. Yield 1·46 g (61%), m.p. 209–211°C. For $C_8H_{12}N_6OS$ (240·29) calculated: 39·99% C, 5·03% H, 34·98% N, 13·34% S; found: 40·12% C, 5·17% H, 34·79% N, 13·29% S.

1-Acetyl-2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*XIIa*)

Prepared as *XIII* using 2·74 g (0·01 mol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]-imidazolidine (*IVb*) instead of *IVa*. Yield 1·67 g (53%), m.p. 185–186°C (dioxane). For

$C_{14}H_{16}N_6OS$ (316·38) calculated: 53·15% C, 5·10% H, 26·56% N, 10·13% S; found: 53·08% C, 5·21% H, 26·32% N, 10·01% S.

1-Acetyl-2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]oxazolidine (*XIIb*)

A solution of 0·47 g (0·0017 mol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl]imino]oxazolidine (*IVg*) in 5 ml of acetic anhydride was refluxed for 30 min. After cooling 10 ml of water was added with stirring. An oily product crystallized upon further stirring. It was filtered off, washed with water, and recrystallized from 2-propanol. Yield 0·28 g (47%), m.p. 166–168°C. For $C_{14}H_{15}N_5OS_2$ (317·37) calculated: 52·98% C, 4·76% H, 22·07% N, 10·10% S; found: 53·12% C, 4·79% H, 21·95% N, 10·02% S.

1-Acetyl-2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]thiazolidine (*XIIc*)

Prepared as *XIIb* using 0·6 g (2·06 mmol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazole-5-yl)-imino]thiazolidine (*IVp*) instead of *IVg*. Yield 0·64 g (93%), m.p. 137–138°C (methanol). For $C_{14}H_{15}N_5OS_2$ (333·43) calculated: 50·43% C, 4·53% H, 21·00% N, 19·23% S; found: 50·49% C, 4·55% H, 20·87% N, 19·16% S.

1-(2-Chloroethylcarbamoyl)-2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*XIV*)

To a solution of 1·0 g (0·005 mol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*IVb*) in 10 ml of dioxane 0·54 g (0·0051 mol) of 2-chloroethyl isocyanate was added and the mixture was refluxed with stirring for 30 min. After cooling the solution was evaporated in vacuo to dryness and the residue was recrystallized from dioxane. Yield 1·1 g (58%) m.p. 148–149°C. For $C_{15}H_{18}ClN_7OS$ (379·87) calculated: 47·42% C, 4·77% H, 9·33% Cl, 25·81% N, 8·44% S; found: 47·56% C, 4·85% H, 9·21% Cl, 25·70% N, 8·36% S.

3-{2-[(3-Methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidin-1-yl}-2-cyanoacrylonitrile (*XVIII*, R = Ph, R^2 = CN)

To a solution of 2 g (0·0073 mol) of 2-[(3-methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*IVb*) in 10 ml of dioxane 0·9 g (0·0073 mol) of 2-cyano-3-ethoxyacrylonitrile[10] was added and the mixture refluxed for 5 h. After cooling it was evaporated in vacuo to dryness and the residue was recrystallized from dimethylformamide. Yield 1·9 g (74%), m.p. 254–256°C. For $C_{16}H_{14}N_8S$ (350·41) calculated 54·84% C, 4·03% H, 31·98% N, 9·15% S; found: 54·96% C, 4·19% H, 31·80% N, 9·03% S.

Ethyl *E*-3-{2-[(3-Methylthio-1*H*-1,2,4-triazol-5-yl)imino]imidazolidin-1-yl}-2-cyanoacrylate (*XVIII*, R = H, R^2 = COOEt)

Prepared as *XVIII*, R = Ph, R^2 = CN using 1·0 g (0·005 mol) of 2-[(3-methylthio-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine (*IVa*) instead of *IVb* and 0·85 g (0·005 mol) of ethyl 2-cyano-3-ethoxyacrylate[11] instead of 2-cyano-3-ethoxyacrylonitrile. Yield 1·4 g (87%), m.p. 243–245°C (DMF). For $C_{12}H_{15}N_7O_2S$ (321·41) calculated: 44·84% C, 4·72% H, 30·51% N, 9·97% S; found: 45·01% C, 4.81% H, 30·42% N, 9·83% S.

Ethyl *E*-3-{2-[(3-Methylthio-1-phenyl-1*H*-1,2,4-triazol-5-yl)imino]imidazolidine-1-yl}-2-cyanoacrylate (*XVIII*, R = Ph, R^2 = COOEt)

Prepared as *XVIII*, R = Ph, R^2 = CN using 1·2 g (0·0073 mol) of ethyl 2-cyano-3-ethoxyacrylate[10] instead of 2-cyano-3-ethoxyacrylonitrile. Yield 2·3 g (79%), m.p. 234–235°C (DMF). For $C_{18}H_{19}N_7O_2S$ (397·46) calculated: 54·39% C, 4·82% H, 24·67% N, 8·07% S; found: 54·51% C, 5·00% H, 24·48% N, 8·02% S.

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