On Triazoles. V [1,2]. Synthesis of 1- and 2-R¹-3-R²,R³-Amino-5-amino-1,2,4-triazoles

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The correct isomeric and tautomeric structure of different 1- and 2-R¹-3-R²,R³-amino-5-amino-1,2,4-triazole derivatives prepared from the corresponding *N*-cyano-*N'*-R²,R³-*S*-methyl-isothioureas and the corresponding hydrazines was proved with the help of their ir, uv, ^{1}H-nmr and ^{13}C-nmr spectra as well as the uv spectra of the Schiff bases of an isomeric pair.

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Recently we have described the reaction of *N*-cyanocarbonimidodithioic acid dialkyl esters with different substituted hydrazines to yield 1-substituted-3-alkylthio-5-amino-1*H*-1,2,4-triazoles and 2-substituted 3-alkylthio-5-amino-2*H*-1,2,4-triazoles [3]. The structure of the isomeric products obtained was proven on the basis of the different splitting scheme of the triazole carbon atoms in the proton coupled ^{13}C-nmr [3].

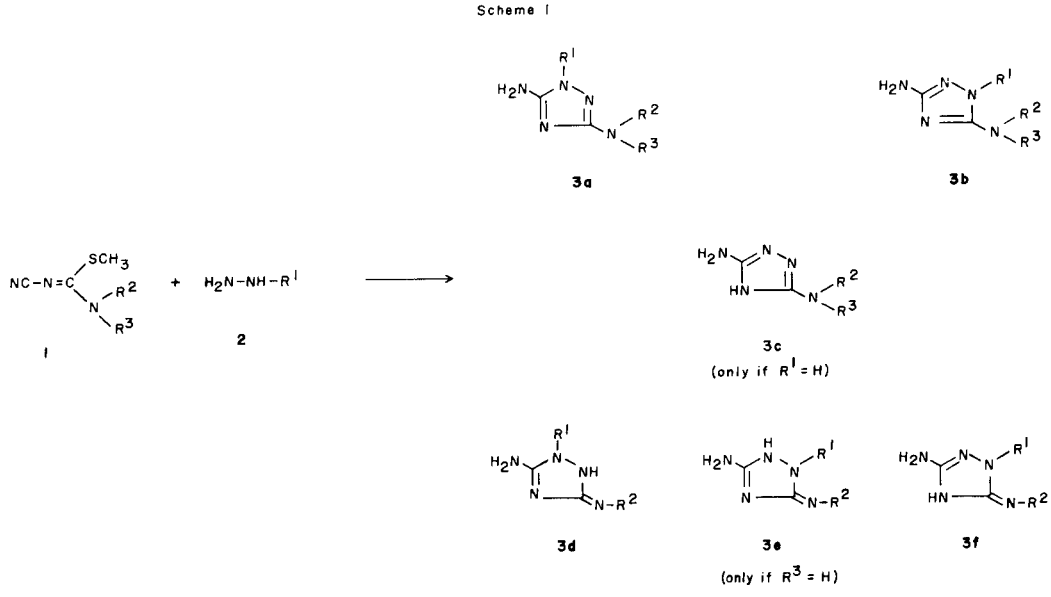
If instead of the *N*-cyanocarbonimidodithioic acid dialkyl esters **1** type *N*-cyano-*N'*-R²,R³-*S*-methylisothioureas **1** prepared by the known method [4] from the *N*-cyanocarbonimidodithioic acid dimethyl ester and the corresponding amines were used in the above reaction **3** type 3-R²,R³-amino-5-amino-1,2,4-triazole derivatives were obtained (Scheme 1). In this reaction if all (R¹, R² and R³) substituents are different from a hydrogen atom only **3a** and **3b** type isomers can form. These derivatives may, in principle, appear in different tautomeric forms arising from the 5-amino-, 5-imino-tautomerism, but as it will be shown the 5-imino-tautomeric forms could be excluded on the basis of pmr in all cases. On the other hand, if R¹ = H then the tautomeric forms **3a** (R¹ = H), **3b** (R¹ = H) and **3c** have to be taken in account. Furthermore, if R³ = H then besides the tautomeric forms **3a-3c** (R³ = H) the tautomers **3d-3f** have to be also taken into account (Scheme 1).

1. Structural Study of Derivatives **3** (R¹, R², R³ ≠ H) (Derivatives **3/1-3/3**, Table I).

1. Structural Study of Derivatives **3** (R¹, R², R³ ≠ H) (Derivatives **3/1-3/3**, Table I).

To prove the structure of derivatives **3** obtained first, the corresponding spectra of those derivatives were compared, where all substituents R¹, R² and R³ were different

Scheme I



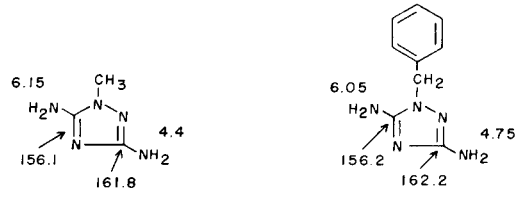
from a hydrogen atom.

These derivatives could be separated into two groups on the basis of the ν C=N bands in the ir spectra appearing between 1660-1653 cm^{-1} and 1643-1635 cm^{-1}, respectively (Table II). Nevertheless, no decision could be made as to which one corresponded to which structure. Moreover the two ν C=N regions were too close to each other to make safe differentiation between the two groups.

The uv spectra of the above derivatives could be again separated into two groups one characterised with a shoulder at about 215 nm which did not change in acidic or alkaline media, and the other one characterised by a maximum at about 230 nm which underwent a 10 nm batochromic shift in acidic media, but again no decision could be made as to which one corresponded to which structure.

In the pmr spectra of these derivatives taken in DMSO-d_6 solution the two NH_2 groups appeared as broad singlets, respectively, corresponding to two protons excluding all those tautomeric forms arising from the possible 5-imino-tautomerism. On the basis of the chemical shifts of the NH_2 groups these derivatives could be again separated into two groups, one characterised with the chemical shift of about 6 ppm and the other one with the chemical shift of about 5 ppm. Comparing these data with the chemical shifts of the NH_2 singlets of the 1-methyl- and 1-benzyl-3,5-diamino-1,2,4-triazole (**3/39** and **3/40**, respectively, Scheme 2, Table II) prepared as model compounds (**3/39**: δ NH_2 (3) = 4.4 ppm, δ NH_2 (5) = 6.15 ppm; **3/40**: δ NH_2 (3) = 4.75 ppm, δ NH_2 (5) = 6.05 ppm) having analogous chemical surroundings of the NH_2 groups it could be predicted that the derivatives with the NH_2 groups appearing

Scheme 2



3/39 3/40

at about 6 ppm corresponded to structure **3a**, while those with the NH_2 groups appearing at about 5 ppm would have to correspond to structure **3b**. Nevertheless, as the

Table I

Compound No.	R^1	R^2	R^3	Method	Yield (%)	mp (°C) (Cryst from)	Molecular formula (MW) or Reference mp (°C)	ANALYSIS Calculated/Found C	H	N	mp of the starting Isothiourea Derivative (Cryst from) or Reference
3b/1	Methyl	Morpholino		A	55	216-217 (H_2O)	$C_7H_{13}N_5O$ (183.21)	45.89 45.83	7.15 7.11	38.23 38.34	126-127 (2-PrOH) Lit [12] [a]
3a/2	2-Hydroxy-ethyl	Morpholino		A	43	168-170 (EtOH)	$C_8H_{15}N_5O_2$ (213.24)	45.06 45.12	7.09 7.13	32.85 32.90	see **3b/1**
3a/3	Benzyl	Morpholino		B	39	180-181 (MeOH)	$C_{13}H_{17}N_5O$ (259.31)	60.21 60.35	6.61 6.87	27.01 26.98	see **3b/1**
3b/3	Benzyl	Morpholino			13 [b]	148-149 (MeOH)	$C_{13}H_{17}N_5O$ (259.31)	60.21 60.18	6.61 6.76	27.01 27.13	see **3b/1**
3a-b/4	H	Methyl	Methyl	C	58	186-188 (2-PrOH)	Lit [13-14][a]				30-31.5 (2-PrOH)
3a-b/5	H	2-Hydroxy-ethyl	Methyl	C	14	147-149 (EtOH)	$C_5H_{11}N_5O$ (157.18)	38.20 38.41	7.05 7.21	44.56 44.48	
3a-b/6	H	Piperidino		C	93	158-160 (2-PrOH)	Lit [13-14][a]				58-59 (EtOAc)
3a-b/7	H	Morpholino		C	95	167-168 (2-PrOH)	Lit [13-14][a]				see **3b/1**
3a-b/8	H	4-Methyl-piperazino		C	88	89-91 (MeOH)	$C_7H_{14}N_6$ (182.23)	46.13 46.22	7.74 7.91	46.12 45.99	64-66 (2-PrOH)
3a-b/9	H	4-(2-Hydroxy-ethyl)-piperazino		C	61	214-216 (H_2O + MeOH)	$C_9H_{16}N_6O$ (212.26)	45.27 45.44	7.60 7.73	39.60 39.68	83-85 (2-PrOH)
3b/10	Methyl	2-Hydroxy-ethyl	H	A	31	161-163 (MeOH)	$C_5H_{11}N_5O$ (157.18)	38.20 38.33	7.05 7.11	44.56 44.42	131-133 (2-PrOH)
3b/11	Methyl	3-Hydroxy-propyl	H	A	72	134-135 (2-PrOH)	$C_6H_{13}N_5O$ (171.20)	42.09 42.23	7.65 7.77	40.91 41.03	91-93 (2-PrOH)
3b/12	Methyl	Cyclopropyl	H	A	39	188-189 (MeOH)	$C_6H_{11}N_5$ (153.19)	47.04 47.11	7.24 7.43	45.72 45.65	129-131 (2-PrOH)
3b/13	Methyl	Benzyl	H	A	82	159-161 (2-PrOH)	$C_{10}H_{13}N_5$ (203.24)	59.09 59.12	6.45 6.50	34.46 34.41	160-161 (2-PrOH) Lit. [15] 157-158
3a/14	Methyl	Phenyl	H	D	25	215-217 (2-PrOH)	$C_9H_{11}N_5$ (189.22)	57.12 57.13	5.86 5.88	37.02 37.14	190-192 (DMF) Lit. [15] 191-192
3b/14	Methyl	Phenyl	H	A	53	179-181 (2-PrOH)	$C_9H_{11}N_5$ (189.22)	57.12 57.06	5.86 5.92	37.02 36.96	see **3a/14**

[a] Mp not given. [b] Isolated from the mother liquor of **3a/3** by column chromatography.

Table I Continued

Compound No.	R^1	R^2	R^3	Method	Yield (%)	mp (°C) (Cryst from)	Molecular formula (MW) or Reference mp (C°)	ANALYSIS Calculated/Found C	H	N	mp of the starting Isothiourea Derivative (Cryst from) or Reference
3b/15	Methyl	2-Methyl-phenyl	H	A	43	160-162 (2-PrOH)	$C_{10}H_{13}N_5$ (203.24)	59.09 59.21	6.45 6.55	34.46 34.53	149-151 (2-PrOH)
3b/16	Methyl	4-Methyl-phenyl	H	A	51	186-188 (2-PrOH)	$C_{10}H_{13}N_5$ (203.24)	59.09 58.98	6.45 6.41	34.46 34.33	146-148 (2-PrOH) Lit [16] 148-149
3a-b/17	H	Methyl	H	C	78	166-168 (EtOH)	$C_3H_7N_5$ (113.13)	31.85 31.76	6.24 6.36	61.91 61.85	202-204 Lit [15] 203-204
3a-b/18	H	Propyl	H	B	75	148-150 (H_2O)	$C_5H_{11}N_5$ (141.18)	42.53 42.55	7.85 7.96	49.61 49.58	115-117 (2-PrOH)
3a-b/19	H	1-Methyl-ethyl	H	C	68	157-159 (H_2O)	$C_5H_{11}N_5$ (141.18)	42.53 42.67	7.85 7.90	49.61 49.55	117-119 (2-PrOH) Lit [12] [a]
3a-b/20	H	1,1-Dimethyl-ethyl	H	C	42	116-118 (MeOH)	$C_6H_{13}N_5$ (155.20)	46.43 46.34	8.44 7.69	45.13 45.10	honey
3a-b/21	H	3-Methyl-butyl	H	C	50	136-138 (EtOAc)	$C_7H_{15}N_5$ (169.23)	49.68 49.73	8.93 8.99	41.39 41.40	120-121 (MeOH)
3a-b/22	H	Allyl	H	C	70	114-115 (2-PrOH)	$C_5H_9N_5$ (139.16)	43.15 43.23	6.52 6.65	50.33 50.13	109-111 (EtOAc)
3a-b/23	H	Benzyl	H	C	97	151-153 (2-PrOH)	Lit [11] 150-151				see **3b/13**
3a-b/24	H	4-Chloro-benzyl	H	C	60	206-207 (2-PrOH)	$C_9H_{10}ClN_5$ (223.67)	48.33 48.31	4.51 4.63	31.31 31.28	183-185 (MeOH)
3a-b/25	H	1-(4-Chlorophenyl)-ethyl	H	C	76	73-75 (2-PrOH)	$C_{10}H_{12}ClN_5$ (237.69)	50.53 50.66	5.09 5.23	29.47 29.31	146-147 (2-PrOH)
3a-b/26	H	2-(3,4-Diethoxy-phenyl)-ethyl	H	C	82	183-184 (MeOH)	$C_{14}H_{21}N_5O_2$ (291.35)	57.71 57.78	7.27 7.43	24.04 24.11	117-118 (EtOH)
3a-b/27	H	2-(2,6-Dimethyl-phenoxy)-ethyl	H	C	86	105-107 (2-PrOH)	$C_{12}H_{17}N_5O$ (247.30)	58.28 58.09	6.93 7.02	28.32 28.40	164-165 (EtOH)
3a-b/28	H	2-(2,6-Dichloro-phenoxy)-ethyl	H	C	43	125-126 (EtOAc)	$C_{10}H_{11}Cl_2N_5O$ (288.14)	41.68 41.77	3.85 3.96	24.31 24.40	153-154 (EtOH)
3a-b/29	H	2-Diethylamino-ethyl	H	C	76	107-109 (Me_2CO)	$C_8H_{18}N_6$ (198.27)	48.46 48.55	9.15 9.32	42.39 42.41	88-90 [Hexane: EtOAc (1:1)]
3a-b/30	H	3-(2,6-Dimethyl-phenoxy)-propyl	H	C	58	141-142 (2-PrOH)	$C_{13}H_{19}N_5O$ (261.32)	59.75 59.63	7.33 7.21	26.80 26.71	111-112 (EtOH)
3a-b/31	H	Pyridine-2-yl-methyl	H	C	77	194-196 (H_2O)	$C_8H_{10}N_6$ (190.21)	50.51 50.41	5.30 5.42	44.19 44.10	116-117 (2-PrOH)
3a-b/32	H	Pyridine-3-yl-methyl	H	C	92	207-208 (H_2O)	$C_8H_{10}N_6$ (190.21)	50.51 50.55	5.30 5.28	44.19 44.21	153-154 (2-PrOH)
3a-b/33	H	Pyridine-4-yl-methyl	H	C	89	226-228 (H_2O)	$C_8H_{10}N_6$ (190.21)	50.51 50.63	5.30 5.48	44.19 44.28	171-173 (2-PrOH)
3a-b/34	H	Furane-2-yl-methyl	H	C	78	133-134 (H_2O)	$C_7H_9N_5O$ (179.18)	46.92 46.83	5.06 5.21	39.09 38.96	137-138 (CH_3CN)
3a-b/35	H	Phenyl	H	C	93	161-162 (CH_3CN)	Lit [10] 163-165				see **3a/14**
3a-b/36	H	2-Methyl-phenyl	H	C	91	165-167 (2-PrOH)	$C_9H_{11}N_5$ (189.22)	57.12 57.22	5.86 5.98	37.02 37.13	see **3a/15**
3a-b/37	H	4-Methyl-phenyl	H	C	91	181-183 (BuOH)	Lit [10] 183				see **3a/16**
3a-b/38	H	Pyridine-3-yl	H	C	70	252-254 (DMF)	$C_7H_8N_6$ (176.18)	47.72 47.70	4.58 4.68	47.71 47.64	168-170 (H_2O)
3/39	Methyl	H	H	A	62	154-155 (2-PrOH)	Lit [5] 157-159				175-176 (2-PrOH) Lit [17] 175-176
3/40	Benzyl	H	H	B	63	228-230 (H_2O)	$C_9H_{11}N_5$ (189.22)	57.12 57.30	5.86 6.01	37.02 36.95	see **3/39**

[a] Mp not given.

chemical shifts of the NH_2 groups can vary with different recording conditions (thus, for example, Kristinson and Winkler [5] obtained for an isomeric pair of 1-methyl-3-dimethylamino-5-amino-1*H*-1,2,4-triazole (**3a**, $R^1 = R^2 = R^3 = CH_3$) and 2-methyl-3-dimethylamino-5-amino-2*H*-1,2,4-triazole (**3b**, $R^1 = R^2 = R^3 = CH_3$) in deuteriochloroform the δ values of 5.3 and 4.4 ppm, respectively) this prediction could not give an unequivocal proof of the above structures.

On the other hand the above prediction was in good agreement with the shift of the highest uv maxima of the Schiff bases **4a/3** and **4b/3** (λ max = 361 nm, and 308 nm, respectively) prepared from the isomeric **3a/3** and **3b/3**, respectively (Scheme 3). Namely, as a consequence of the prolonged linear conjugation the higher uv maxima is expected in case of **4a/3**.

Table II

Compound No.	ir (cm^{-1}) ν C=N and some other characteristic bands				pmr (ppm) δ NH_2(5)	pmr (ppm) δ NH	cmr (ppm) δ C(3)	cmr (ppm) δ C(5)	uv λ max (ϵ 10^{-3}) EtOH	10 % EtOH + 90 % 0.1 N NaOH	10 % EtOH + 90 % 0.1 N HCl
3b/1	1643	1570	1518	1493	5.0 bs		158.4	162.0	203 (18.8) 229 (12.2)	227 (16.0)	236 (11.5)
3a/2	1653	1593	1537	1489	5.95 s		163.8	156.6	202 (11.1) 216 sh (8.6)	≪220	
3a/3	1660	1585	1535	1485	6.2 bs		164.0	156.5	215 sh (11.1) 225 sh (7.3)	216 (17.2) 225 sh (11.8)	207 (18.5) 223 sh (11.8)
3b/3	1635 1450	1560 1430	1525 1410	1490	5.1 bs		159.0	162.7	230 (5.8)	228 (6.2)	239 (7.9)
3a-b/4	1650	1620	1545		5.65 bs	11.0 b	162.2	158.1	216 (12.2)	220 (18.9)	
3a-b/6	1650 1485	1630 1465	1600 1450	1550 1395	5.0 bs	9.0 b			215 sh (7.4)	≪220	217 (11.1)
3a-b/7	1665 1485	1645 1450	1600	1550	5.7 bs	9.6 b	164.5	159.2	214 sh (6.7)	≪220	217 (9.6)
3a-b/8	1653	1595	1560	1495	5.8 bs	11.0 b	163.9	159.2	217 sh (7.8) 241 sh (2.6)	240 sh (4.2)	210 (9.4) 235 sh (5.5)
3a-b/9	1665 1455	1610 1430	1555	1495	5.5 bs	11.0 b			206 sh (7.9) 216 sh (7.4)	≪220	218 sh (8.9)
3b/10	1625 1420	1600	1530	1510	4.7 bs	6.05 t	157.0	161.5	216 sh (9.5)	221 (12.9)	212 (13.8) 216 sh (11.1)
3b/11	1607	1545	1512	1435	4.85 bs	6.05 t	157.0	161.8			
3b/12	1590	1535	1415	1350	4.8 bs	6.4 d	156.8	161.4	218 (10.2)	221 (14.2)	227 sh (13.9)
3b/13	1622	1551	1528		4.9 bs	6.75 t	156.7	161.8	203 (13.3) 226 sh (6.0)	219 (8.0) 225 sh (5.5)	225 sh (7.9)
3a/14	1653 1502	1612	1558	1531	6.1 bs	8.6 bs	158.5	155.8	202 (21.7) 259 (16.2)	257 (15.6)	
3b/14	1601 1474	1578 1420	1541 1400	1499	3.8 bs	8.6 b	151.7	161.9	259 (18.8)	256 (15.9)	252 (13.7)
3b/15	1593	1574	1535	1464	5.0 bs	7.65 bs	153.1	162.2	203 (23.2) 253 (11.8)	218 (19.8) 249 (20.8)	
3b/16	1622	1570	1531	1520	5.0 bs	8.5 bs	152.4	162.1	202 (19.5) 261 (19.6)	257 (17.5)	
3a-b/17	1655 1435	1615 1380	1560	1465	5.4 bs	5.6 qa 10.5 b			216 sh (5.3)	≪220	216 sh (7.6)
3a-b/18	1650 1355	1615	1570	1450	5.4 bs	5.7 bt 10.8 b			216 sh (6.1)	≪220	216 sh (8.0)
3a-b/19	1620 1420	1565	1515	1460	5.4 bs	5.6 bd 10.5 b	160.9	159.9	216 sh (5.9)	≪220	216 sh (8.9)
3a-b/20	1647	1601	1556	1516	5.3 bs	5.95 s 11.1 b				≪220	
3a-b/21	1620	1575	1460	1390	5.3 bs	5.5 bt 9.0 b			210 sh (12.8)	≪220	220 (9.6)
3a-b/22	1640 1390	1630	1615	1570	5.4 bs	5.7 bt ≈ 11 b			215 sh (5.3)	≪220	216 sh (8.6)
3a-b/23	1640 1460	1620 1440	1565	1520	5.3 bs	6.0 t 8.2 s	158.1	159.8	214 sh (6.2)	≪220	214 sh (8.7)
3a-b/24	1645 1375	1565	1540	1395	5.4 bs	6.15 t 9.0 b					
3a-b/25	1670 1490	1595	1565	1530	4.7 bs	5.3 d [a] ≈ 9 b			218 (14.8)	≪220	219 (17.3)
3a-b/26	1665 1480	1575 1430	1560 1410	1520 1365	5.25 b	5.5 bt ≈ 11 b					
3a-b/27	1645 1480	1625 1440	1575	1520	5.6 bs	5.9 bt 10.8 b			212 sh (16.0)	≪220	211 sh (18.4)
3a-b/28	1645 1480	1625 1450	1575 1440	1525 1360	5.5 bs	5.6 bt ≈ 11 b			217 sh (9.8) 270 (10.0)	266 (15.0)	216 sh (13.5) 270 (1.9)
3a-b/29	1625 1450	1590 1380	1565	1470	5.4 bs	5.6 bt 9.0 b	161.7	159.8	203 (24.0) 217 sh (6.9)		
3a-b/30	1635 1520	1590 1475	1565	1550	5.3 bs	5.6 bt 10.7 b			212 sh (15.9)	≪220	211 sh (18.6)
3a-b/31	1660 1435	1595	1540	1475	5.4 bs	6.2 bt 10.8 b			256 (7.0) 260 (8.2)	255 (7.4) 259 (8.8)	260 (7.0)

[a] Taken in deuteriochloroform solution.

Table II continued

Compound No.	ir (cm^{-1}) ν C=N and some other characteristic bands				pmr (ppm) δ NH_2(5)	pmr (ppm) δ NH	cmr (ppm) δ C(3)	cmr (ppm) δ C(5)	uv λ max (ε 10^{-3}) EtOH	uv λ max (ε 10^{-3}) 10 % EtOH + 90 % 0.1 N NaOH	uv λ max (ε 10^{-3}) 10 % EtOH + 90 % 0.1 N HCl
3a-b/32	1660	1565	1545	1470	5.5 bs	6.2 t			258 (2.8)	257 (3.0)	258 (4.9)
	1425	1400	1360			10.8 b					
3a-b/33	1675	1605	1580	1550	5.5 bs	6.3 t			249 (5.6)	248 (6.9)	252 (10.5)
	1420	1395							254 (5.4)	254 (6.9)	
3a-b/34	1650	1625	1590	1565	5.5 bs	6.1 bt			213 (12.6)	≪220	214 (15.3)
	1520	1505				10.9 b					
3a-b/35	1635	1590	1530	1505	5.8 bs	8.5 bs	158.0	159.8	257 (9.1)	260 (12.4)	250 (8.3)
	1470					11.0 b					
3a-b/36	1663	1616	1597	1570	5.8 bs	7.25 bs	158.2	159.2	203 (24.0)		
	1539	1489				11.05 b			255 (14.0)		
3a-b/37	1620	1570	1559	1545	5.85 bs	8.5 bs	156.7	159.5	203 (23.0)	261 (21.0)	
	1512					11.1 bs			259 (19.2)		
3a-b/38	1660	1590	1560	1540	5.9 bs	9.0 bs			260 (15.3)	264 (11.7)	213 sh (9.8)
	1480	1415				11.3 b			302 (3.7)	308 sh (3.4)	245 (12.9)
											260 (11.6)
											312 (3.4)
3/39	1641	1595	1547	1499	6.15 bs	4.4 bs [a]	161.8	156.1	211 (6.9)	220 (11.1)	
	1431	1410									
3/40	1628	1580	1549	1487	6.05 bs	4.75 bs	162.2	156.2			
	1454	1439	1418								

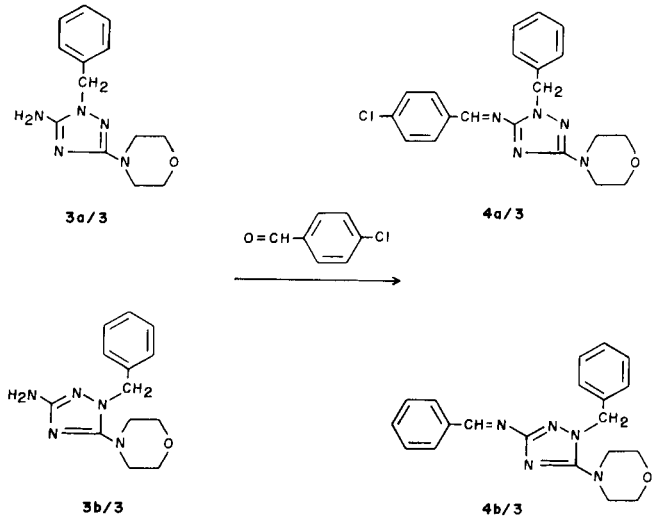
The final and unequivocal ordering of these derivatives to structures **3a** and **3b** made possible the cmr spectra taken in DMSO-d_6 solution by comparing the chemical shifts of the triazole carbon atoms 5 with those of model compounds **3/39** and **3/40**, respectively (**3/39**: δ C (3) = 161.8 ppm, δ C (5) = 156.1 ppm; **3/40**: δ C (3) = 162.2 ppm, δ C (5) = 156.2 ppm) having fully analogous chemical surroundings. Thus derivative **3/3** melting at 180-181° (δ C (5) = 156.5 ppm) have to correspond to structure **3a/3** and that of melting at 148-149.5° (δ C (5) = 162.7 ppm) have to correspond to structure **3b/3**.

This decision is in agreement with that made on the basis of the pmr and uv spectra and conforms also with the multiplicity of the triazole carbon atoms arising from β-couplings observed in the proton coupled cmr. Namely the carbon atom 5 of derivative **3b/3** appears as a sharp singlet, the corresponding carbon atom 3 as a multiplet, while in case of **3a/3** both carbon atoms appear as multiplets.

To summarise the above results it can be stated that in DMSO-d_6 solution the triazole carbon atom 5 of derivatives **3a** is expected with the chemical shift of about 156 ppm, while the corresponding carbon atom 5 of derivatives **3b** is expected with the chemical shift of about 162 ppm, respectively (see Table II).

Our results are again in agreement with those of Kristinson and Winkler's [5] obtained for the isomeric 1-methyl-3-dimethylamino-5-amino-1*H*-1,2,4-triazole (**3a**, $R^1 = R^2 = R^3 = CH_3$) and 2-methyl-3-dimethylamino-5-amino-2*H*-1,2,4-triazole (**3b**, $R^1 = R^2 = R^3 = CH_3$) in deuteriochloroform solution. Namely they measured for **3a**, ($R^1 = R^2 = R^3 = CH_3$) δ C (5) = 154.0 ppm and for **3b**$R^1 = R^2 = R^3 = CH_3$) δ C (5) = 160.1 ppm, respectively.

Scheme 3



2. Structural Study of Derivatives **3** (R^1 = H, R^2, $R^3 \neq$ H). (Derivatives **3/4-3/9**, Table I).

After proving the structure of derivatives **3** where all three substituents R^1, R^2 and R^3 were different from a hydrogen atom we turned to the study of the structure of those derivatives **3** where R^1 = H and R^2, $R^3 \neq$ H. In this case, as it was just mentioned, besides structures **3a** and **3b** (R^1 = H) structures **3c** must also be taken in account.

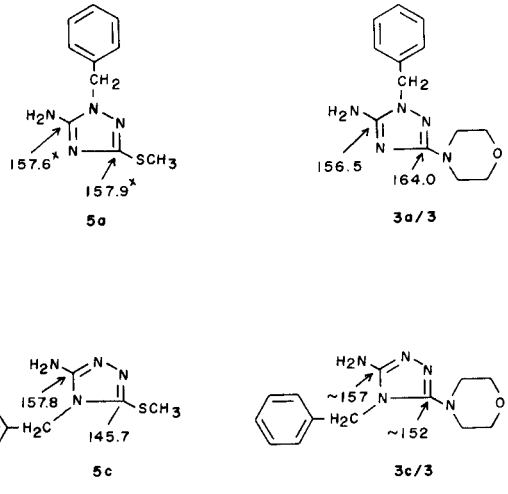
The ir ν C=N bands of these derivatives appearing between 1665-1630 cm^{-1}, as well as the shoulder at about 215 nm in the uv (Table II) were again not characteristic for any of the structures **3a-3c** making the ir and uv spectra unsuitable for structure determination.

The situation was the same with the chemical shifts of the NH_2 groups appearing between 5.5 and 5.7 ppm, *i.e.* at

values which were just between the ones characteristic for structures **3a** and **3b**. Moreover on this basis structure **3c** could not be excluded as well, as our previous results made in the 3-methylthio-5-amino-1,2,4-triazole series [1] showed that the chemical shift of the NH_2 group of derivatives **3c** was expected with practically the same value as that of in **3a**.

The final decision among structures **3a-c** again was made possible by the cmr spectra. Thus, as it was shown previously [1] those triazole carbon atoms to which two pyridine-like (sp^2) nitrogen atoms were attached appeared shifted paramagnetically (downfield) by about 12 ppm as compared with those to which a pyridine-like (sp^2) and a pyrrole-like (sp^3) nitrogen atom was attached. (Compare for example the chemical shifts of the triazole carbon atoms 3 in **5a** and **5c**, respectively, Scheme 4.) On the basis of this consideration the triazole carbon atom 3 in **3c/3** (and of course in all other **3c** type derivatives) is expected to possess a chemical shift of about 152 ppm. The

Scheme 4



triazole carbon atoms 3 of our **3** (R^1 = H, R^2, $R^3 \neq$ H) type derivatives appeared with chemical shifts of 162-164.5 ppm (Table II), thus structure **3c** could be excluded. On the other hand the triazole carbon atoms 5 of these derivatives appeared with the chemical shifts of 158.1-159.2 ppm (Table II), *i.e.* just between the values of 156 and 162 ppm characteristic for structures **3a** and **3b**, respectively, indicating that derivatives **3** (R^1 = H, R^2, $R^3 \neq$ H) existed, at least in DMSO-d_6 solution, as a mixture of the tautomeric forms **3a** and **3b**, respectively. This result is again in agreement with that obtained by Winkler and Kristinson [6] who reported for the carbon atom 5 of the 3-dimethylamino-5-amino-1*H*-1,2,4-triazole **3a-b** (R^1 = H, R^2 = R^3 = CH_3) in deuteriochloroform solution the value of 158.0 ppm. Nevertheless the above authors reported this derivative to be in tautomeric form **3a**.

3. Structural Study of Derivatives **3** (R^1, $R^2 \neq$ H, R^3 = H). (Derivatives **3/10-3/17**, Table I).

In the case of derivatives **3** (R^1, $R^2 \neq$ H, R^3 = H) besides structures **3a** and **3b** structures **3d-3f** arising from the possible 3-imino tautomerism have to be taken in account.

The ir spectra of these derivatives (ν C=N = 1660-1620 cm^{-1}, Table II) gave again no information about their structure.

The uv spectra of those derivatives where R^2 was alkyl or aralkyl were analogous to those obtained for derivatives **3** (R^1 = H, R^2, $R^3 \neq$ H) discussed in paragraph 1 again giving no information about their structure. In those cases when R^2 was phenyl or substituted phenyl the uv spectrum of the corresponding aniline part of the molecule overwhelmed the uv spectrum of the triazole ring possessing one peak at about 260 nm being again completely useless for structure determination.

The pmr spectra of those derivatives **3** (R^1, $R^2 \neq$ H, R^3 = H) where the meaning of R^2 was alkyl or aralkyl showed two NH peaks. One of them corresponding to one proton appeared at about 6-7 ppm with the multiplicity corresponding to the coupling with the R^2 group (see for example δ NH of **3b/12** = 6.4 d ppm; **3b/10** = 6.05 t ppm, or **3b/13** = 6.75 t ppm, respectively). This observation is again in agreement with that of Kristinson and Winkler [5] made for the 2-methyl-3-methylamino-5-amino-2*H*-1,2,4-triazole (**3b**, R^1 = R^2 = CH_3, R^3 = H). Namely the NH group of this derivative appears in DMSO-d_6 solution as a doublet at 6.0 ppm.

The fact that the NH group is coupled with R^2 means that it has to be attached to it excluding all the possible tautomeric structures **3d-3f**. Thus there remains only the possibility of isomeric structures **3a** and **3b**. On the basis of the chemical shift of the NH_2 groups (δ NH_2 = 4.8 ppm, Table II) these derivatives have to correspond to structure **3b** (see paragraph 1).

The above statement is in full agreement with the chemical shift of the carbon atoms 5 in the cmr spectra appearing in all cases between 161.5-162 ppm (see Table II, and paragraph 1) as well as with the observation of Kristinson and Winkler [5] made for 2-methyl-3-methylamino-5-amino-2*H*-1,2,4-triazole (**3b**, R^1 = R^2 = CH_3, R^3 = H) in deuteriochloroform solution where the carbon atom 5 appeared with the chemical shift of 159.9 ppm.

In the case of those derivatives **3** (R^1, $R^2 \neq$ H, R^3 = H) where R^2 was phenyl or substituted phenyl the NH group appeared with the chemical shift of 7.5-8.6 ppm indicating that it has again to be in the neighbourhood of the phenyl group excluding all those tautomeric structures **3d-3f**.

On the basis of the chemical shift of the NH_2 protons structure **3a/14** was assigned to the derivative possessing the NH_2 singlet at 6.1 ppm and structure **3b/14** to its

isomer possessing the NH_2 singlet at 3.8 ppm. Analogously derivatives **3/15** and **3/16** (δ NH_2 = 5.0 ppm and 5.0 ppm, respectively) have to correspond to structure **3b/15** and **3b/16**, respectively (Table II).

These results are again in full agreement with the cmr data as the triazole carbon atoms 5 of the isomeric pair **3a/14** and **3b/14** appeared with the chemical shifts of 155.8 and 161.9 ppm, respectively, as well as with the data recorded for derivatives **3b/15** and **3b/16** (162.2 and 162.1 ppm, respectively (Table II).

4. Structural Study of Derivatives **3** ($R^1 = R^3 = H$, $R^2 \neq H$). (Derivatives **3/18-3/38**, Table I).

In this case all possible tautomeric forms **3a-3f** have to be taken in account. The ν C=N bands appearing between 1670-1620 cm^{-1} in the ir spectra as well as the uv spectra of these derivatives (Table II) were again not characteristic for any of these tautomeric structures. On the other hand the exocyclic NH groups in the pmr appeared again with the multiplicity corresponding to the splitting with the R_2 groups indicating that the tautomeric forms **3d-3f** could be neglected. The tautomeric structure **3c** could be rejected on the same basis as in paragraph 2. Thus remained for derivatives **3** ($R^1 = R^3 = H$, $R^2 \neq H$) the tautomeric structures **3a** and **3b** only. On the basis of the chemical shifts of the NH_2 protons in the pmr (δ NH_2 = 5.25-5.85 ppm, Table II) as well as the chemical shifts of the carbon atoms 5 in the cmr (δ C_5 = 158.1-159.9 ppm, Table II) it can be stated that these derivatives exist, at least in DMSO-d_6 solution, as a mixture of the tautomeric forms **3a** and **3b**.

Our results are in accordance with the X-ray measurements [7,8] made with the 3,5-diamino-1,2,4-triazole pointing to its **3a** ≡ **3b** tautomeric structure in the crystalline form. On the other hand they made it possible to correct the error in the literature describing these derivatives in 3,5-diimino- [9], or (4*H*)- [10,11] tautomeric forms.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 577 spectrophotometer. The ultraviolet spectra were obtained by a Varian Cary 118 and a Pye Unicam SP 8-150 instrument. The ^{1}H-nmr and the ^{13}C-nmr measurements were performed using a Varian XL-100, Brucker WM-250 and Brucker WP-80 SY instruments.

General Methods for the Preparation of Derivatives **3**. Method A.

A mixture of 0.01 mole of the appropriate isothiourea derivative, 0.02 mole of the corresponding alkyl- or aralkylhydrazine and 10 ml of butanol was refluxed for 2-10 hours. During the reaction methylthiol was liberated. After the reaction was completed (t*l*c) the solution obtained was allowed to crystallise. If the product crystallised it was filtered off and recrystallised from an appropriate solvent (Table I). If the product did not crystallise the solution was evaporated to dryness, partitioned between benzene and water, the benzene layer was washed with water, dried and evaporated to dryness. The residue thus obtained was recrystallised from an appropriate solvent (Table I).

Method B.

A mixture of 0.02 mole of the appropriate isothiourea derivative, 0.022 mole of benzylhydrazine oxalate, 2.6 g (3.57 ml = 0.026 mole) of triethylamine and 20 ml of butanol was refluxed while stirring for 6-12 hours. During the reaction methylthiol was liberated. After the reaction was completed (t*l*c) the mixture was evaporated to dryness, the residue obtained was partitioned between water and benzene, the benzene layer was washed with water, dried and evaporated *in vacuo* to dryness. The residue thus obtained was recrystallised from an appropriate solvent (Table I).

Method C.

To a mixture of 0.02 mole of the appropriate isothiourea derivative and 10 ml of ethanol 2.76 ml (0.04 mole) of 72% hydrazine hydrate was added and the mixture refluxed for 1-5 hours. During the reaction methylthiol was liberated. After the reaction was completed (t*l*c) the reaction mixture was left to crystallise. If it crystallised the crystals were filtered off and recrystallised from an appropriate solvent (Table I). If it did not crystallise the solution was evaporated to dryness and the residue crystallised from an appropriate solvent (Table I).

Method D.

To a mixture of 0.96 g (0.04 mole) of sodium hydride and 10 ml of dry dimethylformamide 5.25 g (0.03 mole) of 3-phenylamino-5-amino-1*H*-1,2,4-triazole dissolved in 15 ml of dry dimethylformamide was added while stirring at room temperature. The reation mixture was then heated to 100° and kept at this temperature for 1 hour. After cooling to room temperature 2.2 ml (5.0 g = 0.035 mole) of methyl iodide dissolved in 5 ml of dry dimethylformamide was added through a dropping funnel during a period of 10 minutes. The reaction mixture was then stirred for a further hour at room temperature, then 80 ml of water was added and the solution extracted three times with 50 ml portions of chloroform. The combined chloroform layers were dried over sodium sulfate, evaporated to dryness and the residue crystallised from 2-propanol to give 1.4 g (25%) of 1-methyl-3-phenylamino-5-amino-1*H*-1,2,4-triazole, mp 215-217°.

1-Benzyl-3-morpholino-5-(4-chlorobenzalimino)-1*H*-1,2,4-triazole.

A mixture of 2.74 g (0.01 mole) of 1-benzyl-3-morpholino-5-amino-1*H*-1,2,4-triazole (**3a/3**), 2.10 g (0.015 mole) of 4-chlorobenzaldehyde, 10 ml of 2-propanol and 1 drop of piperidine was refluxed while stirring for 3 hours. After cooling the product crystallised to yield (after being washed with ether) 3.2 g (84%) of the title product, mp 181-182°; uv: λ max = 285 nm (ϵ = 18,600), 361 nm (ϵ = 9600); cmr: δ C_3 = 165.4 bs ppm, δ C_5 = 156.7 m ppm.

2-Benzyl-3-morpholino-5-(4-chlorobenzalimino)-2*H*-1,2,4-triazole (**4b/3**).

A mixture of 1.0 g (0.00385 mole) of 2-benzyl-3-morpholino-5-amino-2*H*-1,2,4-triazole (**3b/3**), 0.56 g (0.004 mole) of 4-chlorobenzaldehyde, 20 ml toluene and 10 g of Klinosorb^R 4 Å was refluxed while stirring for 4 hours. The molecular sieve was filtered off and the filtrate was evaporated to dryness. The residue crystallised upon adding a small amound ot ether to give 1.22 g (83%) of the title product, mp 135-137°; uv: λ max = 222 sh nm (ϵ = 14.500), 272 nm (ϵ = 14,550) and 308 nm (ϵ = 13,500); cmr: δ C_3 = 159.8 t ppm, δ C_5 = 164.1 d ppm.

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