1,2,4-Triazoles. V (1). Nuclear Magnetic Resonance Study of *N*-Methyl Derivatives of 1,2,4-Triazoles

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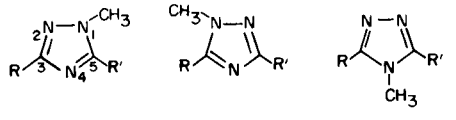
The chemical shifts of the *N*-methyl protons of a number of *N*-methylated-1,2,4-triazoles were studied. Substitution of methyl and methylthio groups in position 3 causes upfield shifts of the *N*-methyl signals, while substitution of α-pyridyl, γ-pyridyl, and phenyl groups causes downfield shifts. In 3,5-disubstituted 1,2,4-triazoles, substituents in positions 3 and 5 have additive effects on the chemical shifts of *N*-methyl groups, so that the chemical shifts of the *N*-methyl groups of such compounds can be calculated. In this way, it was possible to assign the peaks of mixtures of *N*-monomethylated derivatives obtained by methylation of 1,2,4-triazoles.

The 1,2,4-triazole ring has three nitrogen atoms, so there are three possible isomeric *N*-methyl derivatives as shown in Chart I. Nmr spectroscopy is an effective method for distinguishing between these isomers, and we have used this method to deduce the structures of the *N*-methyl derivatives of 3-α-pyridyl-5-methylthio-1,2,4-triazole (2). Much nmr spectral data for the *N*-methyl groups of 1,2,4-triazoles have been reported (3-10), but no systematic analyses have yet been made which can be used in structural assignment. In this investigation, various factors which affect the chemical shifts of the *N*-methyl groups in 1,2,4-triazoles were studied, and the positions of the *N*-methyl groups were deduced from their chemical shifts.

Chart I



1-Methyl Isomer 2-Methyl Isomer 4-Methyl Isomer

Analysis of the chemical shifts of *N*-methyl groups on the three nitrogen atoms of the triazole ring is difficult, since they are influenced by substituents in positions 3 and 5. Therefore, the nmr spectra of the simple *N*-methyl derivatives of 1,2,4-triazole were first examined. As Table I shows, 1-methyl-1,2,4-triazole (**1**) and 4-methyl-1,2,4-triazole (**2**) have *N*-methyl peaks at 3.93 and 3.76 ppm, respectively. Thus the *N*-methyl signal of **1** is shifted 0.17 ppm downfield from that of **2**.

The chemical shifts of the *N*-methyl groups in the *N*-methyl derivatives of the five 3-substituted 1,2,4-triazoles are shown as δ values in Table I. To assess the influence of the substituents in position 3 on the chemical shifts of the *N*-methyl protons of 1,2,4-triazoles, the differences between the chemical shifts of the *N*-methyl signals of each compound and those of the unsubstituted parent compounds (**1** and **2**) are shown as Δδ values in the second column in Table I. Positive and negative signs indicate downfield and upfield shifts, respectively. For example, 1,3-dimethyl-1,2,4-triazole (**3**) and 2,3-dimethyl-1,2,4-triazole (**4**) have *N*-methyl peaks at 3.86 and 3.81 ppm, respectively. The differences between these values and that (3.93) of the parent compound **1** are -0.07 and -0.12, respectively. This means that substitution of a methyl group in position 3 causes diamagnetic shifts of the signals of *N*-methyl groups in positions 1 and 2 by 0.07 and 0.12 ppm, respectively. The Δδ value (-0.14) of the 4-methyl derivative (**5**) was obtained by subtracting the chemical shift (3.76) of the *N*-methyl group in the unsubstituted parent compound **2** from that (3.62) of the *N*-methyl group of **5**. The Δδ values of compounds **6-17** in Table I were obtained in a similar way.

The Δδ values in Table I show that 3-methyl and 3-methylthio groups cause diamagnetic shifts of *N*-methyl signals, while 3-phenyl, 3-α-pyridyl, and 3-γ-pyridyl groups cause paramagnetic shifts. In both the series of 3-methyl derivatives (**3-5**) and the series of 3-methylthio derivatives (**6-8**), the 1-methyl group appears at lowest field, the 2-methyl at an intermediate position and the 4-methyl at highest field. Freiberg *et al.* (11) reported that the signal of the C_5-H proton in 1,2,4-triazole is shifted to a lower field (0.04 ppm) by substitution of a methylthio group in

position 3. Our results, however, indicate that methylthio group causes an upfield shift (0.06-0.18 ppm) of the *N*-methyl peaks of 1,2,4-triazoles. This seems to be due to the shielding of *N*-methyl protons by electrons supplied by conjugation of the lone pair of the sulfur atom in the methylthio group with the triazole ring. We reported in the preceding paper (1) that a methylthio group conjugates with the triazole ring, and the above data support this result.

On the other hand, in the case of 3-phenyl derivatives (**9-11**), the *N*-methyl peaks of the 2-methyl (**10**) and 4-methyl (**11**) derivatives are shifted downfield. The paramagnetic shifts of these *N*-methyl peaks are unexpectedly small. Among the 3-γ-pyridyl derivatives (**15-17**), the *N*-methyl peaks of the 2-methyl (**16**) and 4-methyl (**17**) derivatives are shifted further downfield than those of the 3-phenyl derivatives. These results are attributed to the electron-attracting effect of the 3-γ-pyridyl group on the neighboring *N*-methyl groups.

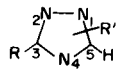
On the other hand, substitution of an α-pyridyl group in position 3 in the *N*-methylated 1,2,4-triazoles produces very large downfield shifts of the signals of the *N*-methyl groups in positions 2 and 4. As a result, the order of resonance position of *N*-methyl groups in the 1-methyl (**12**) and 4-methyl (**14**) derivatives is the reverse of those of the 3-phenyl and 3-γ-pyridyl derivatives. These results can be interpreted by supposing that these *N*-methyl groups are affected by not only the electron-attracting effect but also the anisotropic effect of the α-pyridyl group in position 3. Namely, the α-pyridyl group in position 3 has an appreciable anisotropic effect on the neighboring *N*-methyl groups due to the lone pair of an sp^2 hybridized nitrogen atom. It has been reported that the anisotropic effect of the nitrogen atom of the pyridine ring causes a downfield shift of the signal of the α-proton (12).

To examine the effects of substitution at both positions 3 and 5 in 1,2,4-triazoles on the chemical shifts of the *N*-methyl groups, the *N*-methyl derivatives of 3-substituted 5-methylthio-1,2,4-triazoles were synthesized. The chemical shifts of the *N*-methyl groups are listed in Table II as δ values (obsd.).

To investigate whether the substituent chemical shifts reported in Table I were additive for 3,5-disubstitution, the expected chemical shifts were calculated. For instance, the expected value for the *N*-methyl group of compound **18** (3.68) was obtained by adding the sum of the Δδ values of compound **3** (-0.07) and compound **7** (-0.18) to the δ value for the *N*-methyl peak of the unsubstituted compound **1** (3.93 ppm). The calculated value for the *N*-methyl group of **18** (3.68) is in excellent agreement with the observed value (3.68 ppm). The expected values for the *N*-methyl groups of the 2-methyl (**19**) and the 4-methyl (**20**) derivatives calculated in a similar way were 3.75 and 3.44, respectively, and these are also in close agreement with the observed values (3.73 and 3.43). The expected values for the other 3,5-disubstituted derivatives (**21-29**) in Table II

(TABLE I)

Nmr Data for *N*-Methyl Derivatives of 3-Substituted 1,2,4-Triazoles

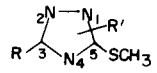


Compound No.	R	Substituents R′ 1	2	4	Chemical Shift of *N*-CH_3 (δ)	Δδ
1	H	CH_3	--	--	3.93 (a)	--
2	H	--	--	CH_3	3.76 (b)	--
3	CH_3	CH_3	--	--	3.86 (c)	-0.07
4	CH_3	--	CH_3	--	3.81 (d)	-0.12
5	CH_3	--	--	CH_3	3.62 (e)	-0.14
6	S-CH_3	CH_3	--	--	3.87	-0.06
7	S-CH_3	--	CH_3	--	3.75	-0.18
8	S-CH_3	--	--	CH_3	3.58	-0.18
9	Ph	CH_3	--	--	3.93	0
10	Ph	--	CH_3	--	3.96	+0.03
11	Ph	--	--	CH_3	3.77	+0.01
12	α-Py	CH_3	--	--	4.00	+0.07
13	α-Py	--	CH_3	--	4.36	+0.43
14	α-Py	--	--	CH_3	4.12	+0.36
15	γ-Py	CH_3	--	--	3.97	+0.04
16	γ-Py	--	CH_3	--	4.04	+0.11
17	γ-Py	--	--	CH_3	3.87	+0.11

(a) Ref. 4, 3.93. (b) Ref. 4, 3.63. (c) Ref. 4, 3.84. (d) Ref. 4, 3.82. (e) Ref. 4, 3.64.

(TABLE II)

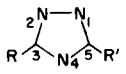
Nmr Data for *N*-Methyl Derivatives of 3-Substituted 5-Methylthio-1,2,4-triazoles



Compound No.	R	Substituents R′ 1	2	4	Chemical Shift of *N*-CH_3 (δ) Obsd.	Calcd.
18	CH_3	CH_3	--	--	3.68	3.68
19	CH_3	--	CH_3	--	3.73	3.75
20	CH_3	--	--	CH_3	3.43	3.44
21	Ph	CH_3	--	--	3.77	3.75
22	Ph	--	CH_3	--	3.90	3.90
23	Ph	--	--	CH_3	3.57	3.59
24	α-Py	CH_3	--	--	3.81	3.82
25	α-Py	--	CH_3	--	4.31	4.30
26	α-Py	--	--	CH_3	3.97	3.94
27	γ-Py	CH_3	--	--	3.81	3.79
28	γ-Py	--	CH_3	--	3.97	3.98
29	γ-Py	--	--	CH_3	3.65	3.69

(TABLE III)

Nmr Data for Methylated 3,5-Disubstituted 1,2,4-Triazoles



Substrates			*N*-Methyl Derivatives		
				Chemical Shift	
Compound	Substituents		Position	of *N*-CH_3 (δ)	
No.	R	R′	of *N*-CH_3	Calcd.	Obsd.
30	CH_3	CH_3	1	3.74	3.72
			4	3.48	3.45
31	CH_3	Ph	1	3.89	3.84
			2	3.81	3.75
			4	3.63	(a)
32	CH_3	α-Py	1	4.29	4.27
			2	3.88	3.86
			4	3.98	3.95
33	CH_3	γ-Py	1	3.97	3.96
			2	3.85	3.86
			4	3.73	(a)
34	Ph	Ph	1	3.96	3.98
			4	3.78	(a)
35	Ph	α-Py	1	4.36	4.35
			2	4.03	4.02
			4	4.13	4.11 (b)
36	Ph	γ-Py	1	4.04	4.04
			2	4.00	4.01
			4	3.88	(a)
37	α-Py	α-Py	1	4.43	4.44
			4	4.48	4.48
38	α-Py	γ-Py	1	4.11	4.12
			2	4.40	4.41
			4	4.23	(a)
39	γ-Py	γ-Py	1	4.08	4.10
			4	3.98	(a)

(a) No appreciable peak. (b) Very small peak.

were calculated in a similar way, and all were found to be in good agreement with the observed values.

This method is useful when it is difficult to assign a peak to the *N*-methyl group of a 1,2,4-triazole derivative because of the opposite effects of substituents in positions 3 and 5. Excellent agreement is found between calculated and observed values in chemical shifts, even in the 3-α-pyridyl-5-methylthio derivatives (**24-26**) which have a deshielding group in position 3 and a shielding group in position 5.

Next, attempts were made to assign the peaks of mixtures of *N*-methyl derivatives obtained by methylation of ten 3,5-disubstituted 1,2,4-triazoles (**30-39**) by use of the chemical shifts expected from additivity. Table III lists these compounds with the calculated δ values for the possible *N*-monomethyl derivatives and the observed values obtained for methylated mixtures of the parent compounds (**30-39**). These data show that the nmr spectra of all these *N*-methylated mixtures, except that of compound **31**, gave *N*-methyl peaks corresponding to the expected δ values. No appreciable amounts of the 4-methyl derivatives were observed in methylation of compounds **31, 33, 34, 36, 38,** and **39**. Methylation of **37** gave two *N*-methyl peaks of 4.44 and 4.48 ppm, and the latter was assigned to 4-methyl-3,5-di-α-pyridyl-1,2,4-triazole. It is noteworthy that the *N*-methyl peak of the 4-methyl derivative appeared at a lower field than that of the 1-methyl derivative. This must be due to the intense deshielding effects of the two α-pyridyl groups, because these are both immediately adjacent to the *N*-methyl group in position 4.

Using this method, the chemical shifts of the *N*-methyl groups of *N*-methyl-3,5-disubstituted 1,2,4-triazoles can be predicted from the shifts for substituents in positions 3 and 5. Conversely, the positions of *N*-methyl substituents in a 1,2,4-triazole derivative can be deduced from the chemical shifts of the *N*-methyl groups.

EXPERIMENTAL

Nmr spectra were taken on a JOEL PS-100 spectrometer (100 MHz) using tetramethylsilane as an internal standard. The solvent used was spectroscopy grade deuteriochloroform, and concentrations are 0.1 mole/l.

The compounds used in the present study were prepared as follows. All melting points are uncorrected.

Compounds **9**, **10**, **11**, **13**, **14**, **15**, **16**, and **17** were obtained by reductive desulfurization of 1-methyl-3-phenyl-1,2,4-triazoline-5-thione (**40a**) (13), 2-methyl-3-phenyl-1,2,4-triazoline-5-thione (**40b**) (9), 4-methyl-3-phenyl-1,2,4-triazoline-5-thione (**40c**) (14), 2-methyl-3-α-pyridyl-1,2,4-triazoline-5-thione (**40d**) (2), 4-methyl-3-α-pyridyl-1,2,4-triazoline-5-thione (**40e**) (2), 1-methyl-3-γ-pyridyl-1,2,4-triazoline-5-thione (**40f**) (1), 2-methyl-3-γ-pyridyl-1,2,4-triazoline-5-thione (**40g**) (1), and 4-methyl-3-γ-pyridyl-1,2,4-triazoline-5-thione (**40h**) (1), respectively, with Raney nickel.

General Procedure for *N*-Methylated 3-Substituted 1,2,4-Triazoles (**9-11** and **13-17**).

To a solution of the corresponding *N*-methylated 3-substituted 1,2,4-triazoline-5-thiones (**40a-h**) (1.0 g., 0.005 mole) in 1*N* ammonium hydroxide (10 ml.) was added a slurry of Raney nickel (W-4) (15) (1.5 g.) in water (5 ml.), and the mixture was refluxed on a water bath for 4-10 hours. After the reaction mixture had been cooled, excess Raney nickel was removed by filtration. The filtrate was evaporated to dryness *in vacuo*. Recrystallization from the solvent listed in Table IV gave purified product. Detailed data are summarized in Table IV.

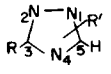
Compound **12** was obtained by condensation of *N*-methyl picolinic acid amidrazone (**41**) with formic acid.

N-Methyl Picolinic Acid Amidrazone (**41**).

A mixture of 2-cyanopyridine (3.0 g.), methylhydrazine (7.0 g.), and absolute ethanol (20 ml.) was allowed to stand at room temperature for 24 hours under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from benzene to give yellow prisms (4.3 g.), m.p. 109-110°.

(TABLE IV)

N-Methyl Derivatives of 3-Substituted 1,2,4-Triazoles

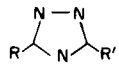


Compound No.	R	Substituents R' 1	2	4	Reaction time (hours)	Yield (%)	Appearance (Recrystallization solvent)	M.p. °C	Formula	Analysis (%) Found (Calcd.) C	H	N
9	Ph	CH_3	--	--	5	60	colorless prisms (a)	23-24	$C_9H_9N_3$	67.72 (67.90)	5.90 (5.70)	26.41 (26.40)
10	Ph	--	CH_3	--	5	56	colorless prisms (ligroin)	56-57	$C_9H_9N_3$	67.75 (67.90)	5.55 (5.70)	26.61 (26.40)
11	Ph	--	--	CH_3	5	78	colorless needles (benzene)	112-113	$C_9H_9N_3$	67.61 (67.90)	5.67 (5.70)	26.66 (26.40)
13	α-Py	--	CH_3	--	10	75	colorless needles (isopropylether)	47-48	$C_8H_8N_4$	59.87 (59.99)	5.01 (5.03)	35.12 (34.98)
14	α-Py	--	--	CH_3	4	80	colorless needles (isopropylether)	104-105	$C_8H_8N_4$	59.95 (59.99)	5.08 (5.03)	35.17 (34.98)
15	γ-Py	CH_3	--	--	4	72	colorless needles (isopropylether)	92-93	$C_8H_8N_4$	59.81 (59.99)	5.05 (5.03)	35.10 (34.98)
16	γ-Py	--	CH_3	--	5	65	colorless needles (ethanol)	65-67	$C_8H_8N_4$	59.72 (59.99)	5.06 (5.03)	35.21 (34.98)
17	γ-Py	--	--	CH_3	8	75	colorless prisms (isopropylether)	170-172	$C_8H_8N_4$	59.85 (59.99)	5.01 (5.03)	35.15 (34.98)

(a) Purified by distillation (b.p. 120-122°/2 mm.).

(TABLE V)

3,5-Disubstituted 1,2,4-Triazoles



Compound No.	R (mole hydrazide)	R′ (mole nitrile)	Reaction time (hours)	Yield (%)	Appearance (Recrystallization solvent)	M.p. °C	Formula	Analysis (%) Found (Calcd.) C	H	N
32	CH_3 (0.02)	α-Py (0.14)	3	58	colorless needles (chloroform)	165-166	$C_8H_8N_4$	60.08 (59.99)	4.94 (5.03)	34.78 (34.98)
33	CH_3 (0.02)	γ-Py (0.14)	6	74	colorless plates (water)	201-203	$C_8H_8N_4$	59.91 (59.99)	4.87 (5.03)	34.96 (34.98)
35	Ph (0.01)	α-Py (0.1)	8	85	colorless fine needles (ethanol)	210-212	$C_{13}H_{10}N_4$	70.04 (70.26)	4.41 (4.54)	25.42 (25.21)
37	α-Py (0.01)	α-Py (0.1)	10	57	colorless needles (ethanol)	209-211	$C_{12}H_9N_5$	64.79 (64.56)	4.01 (4.06)	31.25 (31.37)
38	γ-Py (0.01)	α-Py (0.1)	6	90	colorless fine needles (methanol)	269-271	$C_{12}H_9N_5$	64.84 (64.56)	4.01 (4.06)	31.21 (31.37)
39	γ-Py (0.01)	γ-Py (0.07)	5	78	colorless needles (ethanol)	282-284	$C_{12}H_9N_5$	64.46 (64.56)	4.10 (4.06)	31.45 (31.37)

Anal. Calcd. for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 55.73; H, 6.87; N, 37.49.

1-Methyl-3-α-pyridyl-1,2,4-triazole (**12**).

Compound **41** (1.0 g.) was added portionwise to 99% formic acid under cooling. The mixture was allowed to stand at room temperature for 30 minutes, and then refluxed on a water bath for 1.5 hours. The reaction mixture was evaporated *in vacuo*, neutralized with 10% sodium carbonate, and extracted with chloroform (10 ml. x 3). Removal of the solvent from the chloroform extract gave a light yellowish oil. The oily residue was purified by distillation (b.p. 135°/2.5 mm.) to give colorless crystals (0.9 g.), m.p. 22-23°; nmr (deuteriochloroform): δ 8.14 (s, 1H, 5-C*H*).

Anal. Calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.70; H, 5.18; N, 35.13.

Compounds **32**, **33**, **35**, **37**, **38**, and **39** were synthesized by reaction of the acid hydrazides with the aryl nitriles, using a procedure similar to that described in the literature (16).

General Procedure for 3,5-Disubstituted 1,2,4-Triazoles (**32**, **33**, **35**, and **37-39**).

A mixture of the acid hydrazide and an excess of the nitrile was heated on an oil bath at 220-225° for 3-10 hours. After cooling, a precipitate which formed was collected by filtration, and then recrystallized from the solvent listed in Table V. When 4-cyanopyridine was used, the unreacted nitrile which sublimated on a neck of a flask and equipped cooler was removed. Detailed data are summarized in Table V.

Compounds **1** (17), **2-5** (4), **6** (1), **7-8** (18), **18** (18), **19** (1), **20** (18), **21-22** (9), **23** (19), **24-26** (2), **27-29** (1), **30** (20), **31** (16), **34** (16), and **36** (16) were prepared by the method described in the literature.

General Procedure for Methylation of 3,5-Disubstituted 1,2,4-Triazoles (**30-39**).

A mixture of methyl iodide (0.002 mole) and ethanol (0.1 ml.) was added to a solution of the appropriate 3,5-disubstituted 1,2,4-triazoles (**30-39**) (0.001 mole) in 1*N* sodium hydroxide (2 ml.). The mixture was shaken at room temperature for 24 hours, and then extracted with chloroform (3 ml. x 5). The chloroform layer was dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave an oily product which is a mixture of *N*-methylated 3,5-disubstituted 1,2,4-triazoles. The nmr data summarized in Table III.

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