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1,2,4-Triazoles. IV.[1] Tautomerism of 3,5-Disubstituted 1,2,4-Triazoles

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Tautomerism of ten 3,5-disubstituted 1,2,4-triazoles, which can exist in three tautomeric forms, has been studied. The nuclear magnetic resonance (NMR) and ultraviolet (UV) spectra of these 1,2,4-triazoles were compared with those of the N-methyl derivatives, which are the model compounds of the three kinds of tautomeric forms. Results indicate that a tautomeric hydrogen atom of the predominant tautomer of 3,5-disubstituted 1,2,4-triazoles is attached to the nitrogen atom at position 1 or 2 which is closer to the more electron-releasing substituents in the 3 or 5 position. For instance, 3-*p*-nitrophenyl-, 3-*p*-chlorophenyl-, and 3-*γ*-pyridyl-5-methylthio-1,2,4-triazole exist predominantly in the 1H form, while 3-*p*-aminophenyl- and 3-*p*-methoxyphenyl-5-methylthio-1,2,4-triazole exist predominantly in the 2H form.

These results are explained in terms of the formation of cyclic dimer-type hydrogen bonds involving the N-1 and N-2 atoms of triazole rings with an exchange of a proton between the molecules. However, 5-methylthio-3-*α*-pyridyl-1,2,4-triazole is exceptional in existing in the 2H form, since this compound can form hydrogen bonds of another type involving the nitrogen atom of the *α*-pyridyl group.

1,2,4-Triazoles can exist in three tautomeric forms as shown in Chart 1. It has been reported that 1,2,4-triazole itself exists overwhelmingly in the 1H form,[3-9] and 3-alkylamino-5-(2-furyl)-1,2,4-triazoles[10] and 5-methylthio-3-*α*-pyridyl-1,2,4-triazole[11] exist predominantly in the 2H form. Previous reports were only concerned with determination of the predominant tautomers of individual compounds and no general rule was established to deduce the predominant tautomer of 1,2,4-triazoles from the properties of their substituents in positions 3 and 5. To clarify this point, we examined the influence of the substituents on tautomeric equilibria, using several 1,2,4-triazoles with different substituents in positions 3 and 5. The reason why compounds exist in such forms is discussed.

In this investigation, nuclear magnetic resonance (NMR) and ultraviolet (UV) spectroscopy were used to study tautomerism. The 1,2,4-triazoles used all had an S-methyl or O-methyl group in position 5 and various groups in position 3. Several different 3-*p*-substituted phenyl-1,2,4-triazoles were used to examine the electronic influence of the substituents in position 3 on the tautomeric equilibria of the 1,2,4-triazoles. The NMR and UV spectra of the tautomeric compounds (**1**—**10**) were compared with those of the N-methyl derivatives (1-methyl, 2-methyl, and 4-methyl derivatives) which were synthesized as model compounds of the three kinds of tautomers.

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6) P. Goldstein, J. Ladell, and G. Abowitz, *Acta Crystallogr.*, Sect. B, **25**, 135 (1969).
7) K. Bolton, R.D. Brown, F.R. Burden, and A. Mishra, *J. Chem. Soc.* (*D*), **1971**, 873.
8) M. Witanowski, L. Stefaniak, H. Januszewski, and Z. Grabowski, *Tetrahedron*, **28**, 637 (1972).
9) H. Saito, Y. Tanaka, and S. Nagata, *J. Am. Chem. Soc.*, **95**, 324 (1973).
10) E. Akerblom and M. Sandberg, *Acta Chem. Scand.*, **19**, 1191 (1965).
11) S. Kubota and M. Uda, *Chem. Pharm. Bull.* (Tokyo), **20**, 2096 (1972).

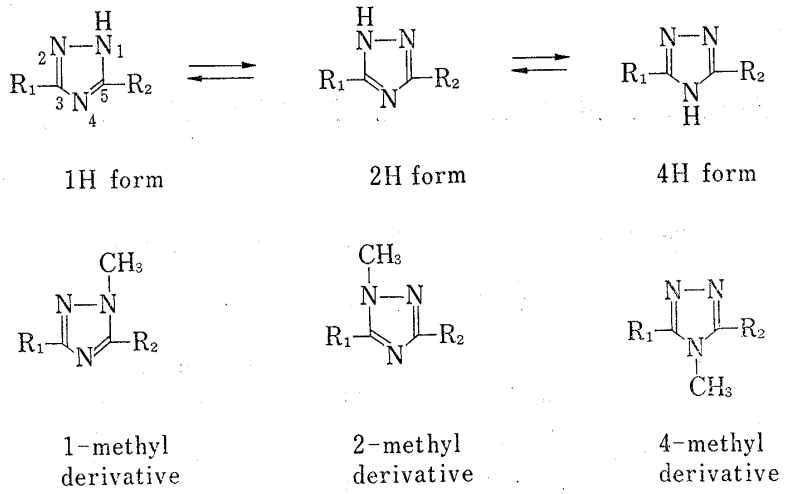


Chart 1

Preparation of Compounds

The tautomeric compounds (**1**—**10**) and their N-methyl derivatives (**11**—**40**) used in the present study were synthesized as follows.

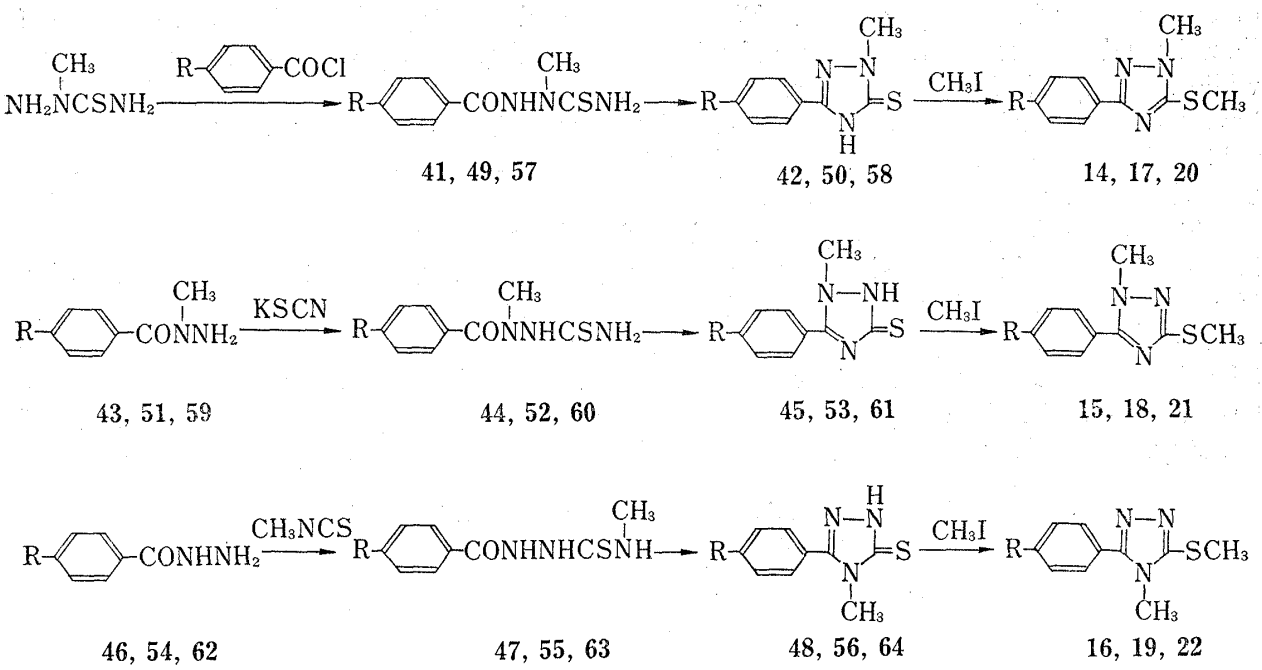
Tautomeric compound **2** was obtained by S-methylation of 3-*p*-nitrophenyl-1,2,4-triazoline-5-thione, which was prepared by cyclization of 1-*p*-nitrobenzoylthiosemicarbazide in alkaline solution.

Ring N-methyl derivatives, model compounds, were synthesized by S-methylation of the corresponding 1,2,4-triazoline-5-thiones, which were obtained by cyclization of the corresponding N-methyl-1-aroylthiosemicarbazides previously methylated at the desired position (Chart 2). 1-Methyl derivatives (**14**, **17**, and **20**) were obtained as follows. 3-*p*-Substituted phenyl-1,2,4-triazoline-5-thiones (**42**, **50**, and **58**) were prepared by cyclization of the corresponding 1-aroyl-2-methylthiosemicarbazides (**41**, **49**, and **57**) obtained from 2-methylthiosemicarbazide.[12] These compounds (**42**, **50**, and **58**) were S-methylated with methyl iodide in alkaline solution. 2-Methyl derivatives (**15**, **18**, and **21**) were synthesized similarly *via* the corresponding 1-aroyl-1-methylthiosemicarbazides (**44**, **52**, and **60**). Compounds **44**, **52**, and **60** were obtained by reaction of the 1-aroyl-1-methylhydrazines (**43**, **51**, and **59**) with potassium thiocyanate. 4-Methyl derivatives (**16**, **19**, and **22**) were prepared by S-methylation of the corresponding 4-methyl-1,2,4-triazoline-5-thiones (**48**, **56**,[13] and **64**[14]). The latter were easily obtained by cyclization of the corresponding 1-aroyl-4-methylthiosemicarbazides (**47**, **55**,[13] and **63**[14]).

3-*p*-Aminophenyl derivatives (**5**, **23**, **24**, and **25**) were synthesized by reduction of the corresponding 3-*p*-nitrophenyl derivatives (**2**, **14**, **15**, and **16**), which were prepared by the methods described above.

3-γ-Pyridyl derivatives (**8**,[15] **32**, **33**, and **34**[16]) were synthesized by similar methods to those of the corresponding 3-α-pyridyl derivatives (**7**, **29**, **30**, and **31**).[17]

12) A.H. Greer and G.B.L. Smith, *J. Am. Chem. Soc.*, **72**, 874 (1950).
13) M.Y. Mhasalkar, M.H. Shah, S.T. Nikam, K.G. Anantanarayanan, and C.V. Deliwala, *J. Med. Chem.*, **13**, 672 (1970).
14) E. Hoggarth, *J. Chem. Soc.*, **1949**, 1163.
15) S. Yoshida and M. Asai, *Yakugaku Zasshi*, **74**, 948 (1954).
16) D.H. Jones, R. Slack, S. Squires, and K.R.H. Wooldridge, *J. Med. Chem.*, **8**, 676 (1965).
17) S. Kubota, M. Uda, and M. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **19**, 2331 (1971).



14−16, 41−48 : R=NO_2−
17−19, 49−56 : R=Cl−
20−22, 57−64 : R=CH_3O−

Chart 2

The other authentic compounds **1**,[18] **3**,[19] **4**,[18] **6**,[20] **9**—**10**,[21] **11**—**12**,[1] **13**,[22] **26**—**28**,[1] **35**—**40**[21] were synthesized as described in the literature.

Results

NMR Spectra

The chemical shifts (δ values) of the S-methyl or O-methyl group in the 5 position of the ten tautomeric compounds (**1**—**10**) and those of their N-methyl derivatives (**11**—**40**) in $CDCl_3$ are shown in Tables I and II.

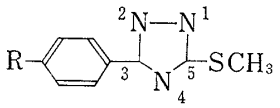
These data show a slight difference between the S-methyl or O-methyl groups in the three kinds of N-methyl derivatives in each group. A similar relationship was observed in the orders of these chemical shifts. That is, the signals of the S-methyl or O-methyl groups of the 4-methyl, 1-methyl, and 2-methyl derivatives appeared in that order from the lower field. The 2-methyl derivatives showed peaks of the S-methyl group at an especially high field compared with the other two derivatives. These results may be caused by various factors, and the difference between the types of conjugation in the S-methyl group and triazole ring is considered to be the most important factor in this case. The conjugation of the lone pair on the sulfur atom in the S-methyl group to the triazole ring must be greatly influenced by the arrangement of double bonds in the triazole ring. The linear conjugation of the S-methyl group with the conjugated system of the triazole ring is considered to lower the electron density of the S-methyl group more than their cross conjugation and should cause a downfield shift

18) E. Hoggarth, *J. Chem. Soc.*, **1949**, 1160.
19) E. Hoggarth, *J. Chem. Soc.*, **1950**, 612.
20) H. Gehlen and G. Blankenstein, *Liebigs Ann. Chem.*, **651**, 137 (1962).
21) C.F. Kröger and W. Sattler, and H. Beyer, *Liebigs Ann. Chem.*, **643**, 128 (1961).
22) J. Sandstrom and I. Wennerbeck, *Acta Chem. Scand.*, **20**, 57 (1966).

of the signals of S-methyl groups. The 4-methyl and 1-methyl derivatives are conjugated linearly and the former have a more effective conjugated system, –C=N–N=C–, than the latter, while 2-methyl derivatives have cross conjugation. As a result, the 4-methyl derivatives have S-methyl peaks at the lowest field and 2-methyl derivatives have them at the highest field. The effects of linear and cross conjugation on the UV spectra of the 1,2,4-triazoles have been discussed in previous papers.[11,23]

Two other factors, the inductive and steric effects of the ring N-methyl groups, must be taken into consideration, since the local diamagnetic shielding effect of the electron-donating N-methyl group should cause an upfield shift of the adjacent S-methyl signals and the steric effect of the N-methyl groups to force the adjacent S-methyl group out of the plane of the triazole ring is also expected to cause an upfield shift. However, these factors probably have less effect in this case, because the signals of the S-methyl groups of the 1-methyl and 4-methyl derivatives were at a lower field than those of the 2-methyl derivatives.

Table I. Chemical Shifts of 3-*p*-Substituted Phenyl-5-methylthio-1,2,4-triazoles (in $CDCl_3$)



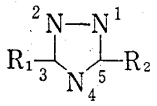
No.	R	Substituents 1	2	4	Chemical shift S–CH_3 (δ)
1	H	—	—	—	2.68
11	H	CH_3	—	—	2.72
12	H	—	CH_3	—	2.60
13	H	—	—	CH_3	2.77
2	NO_2	—	—	—	2.72
14	NO_2	CH_3	—	—	2.74
15	NO_2	—	CH_3	—	2.60
16	NO_2	—	—	CH_3	2.78
3	Cl	—	—	—	2.69
17	Cl	CH_3	—	—	2.72
18	Cl	—	CH_3	—	2.60
19	Cl	—	—	CH_3	2.76
4	CH_3O	—	—	—	2.65
20	CH_3O	CH_3	—	—	2.72
21	CH_3O	—	CH_3	—	2.60
22	CH_3O	—	—	CH_3	2.74
5	NH_2	—	—	—	2.63
23	NH_2	CH_3	—	—	2.71
24	NH_2	—	CH_3	—	2.59
25	NH_2	—	—	CH_3	*a*)

a) insoluble in $CDCl_3$

Therefore, the predominant tautomer of a tautomeric compound can be deduced by comparing the chemical shift of its S-methyl group with those of N-methyl derivatives, which are model compounds of the three tautomeric forms. For instance, the peak of the S-methyl group of the 3-*p*-nitrophenyl derivative (**2**) is at 2.72 ppm, while the model compounds, the 1-methyl (**14**), 2-methyl (**15**), and 4-methyl (**16**) derivatives, show resonance signals at 2.74, 2.60, and 2.78 ppm, respectively. The fact that the chemical shift of **2** is most similar to that of the 1-methyl derivative (**14**) indicates that **2** exists predominantly as the 1H form, which has the same arrangement of double bonds as that of the 1-methyl derivative (**14**).

23) M.R. Atkinson, E.A. Parkes, and J.B. Polya, *J. Chem. Soc.*, **1954**, 4256.

TABLE II. Chemical Shifts of 3,5-Disubstituted 1,2,4-Triazoles (in $CDCl_3$)



No.	R_1	Substituents 1	2	4	R_2	Chemical shift SCH_3 (δ)
6	Ph	—	—	—	OCH_3	4.08[a]
26	Ph	CH_3	—	—	OCH_3	4.12[a]
27	Ph	—	CH_3	—	OCH_3	3.98[a]
28	Ph	—	—	CH_3	OCH_3	4.17[a]
7	α-Py	—	—	—	SCH_3	2.65
29	α-Py	CH_3	—	—	SCH_3	2.76
30	α-Py	—	CH_3	—	SCH_3	2.62
31	α-Py	—	—	CH_3	SCH_3	2.77
8	γ-Py	—	—	—	SCH_3	2.72
32	γ-Py	CH_3	—	—	SCH_3	2.75
33	γ-Py	—	CH_3	—	SCH_3	2.61
34	γ-Py	—	—	CH_3	SCH_3	2.79
9	SCH_3	—	—	—	H	2.66
35	SCH_3	CH_3	—	—	H	2.58
36	SCH_3	—	CH_3	—	H	2.68
37	SCH_3	—	—	CH_3	H	2.73
10	CH_3	—	—	—	SCH_3	2.59
38	CH_3	CH_3	—	—	SCH_3	2.64
39	CH_3	—	CH_3	—	SCH_3	2.53
40	CH_3	—	—	CH_3	SCH_3	2.66

a) OCH_3 Ph=phenyl Py=pyridine

The predominant forms of the other compounds can be deduced in the same way. However, when none of the tautomers is predominant, the peak of the S-methyl group appears in an intermediate position between the S-methyl peaks of the model compounds, and hence it is difficult to determine the composition of the equilibrium mixture. In this investigation, only the 1H and 2H tautomers were considered as possible tautomeric forms, because it is known that 1,2,4-triazole itself[3-9] and 3,5-disubstituted 1,2,4-triazoles,[10,11] exist in the 1H and 2H forms, respectively. The reason for this will be discussed in later.

On the basis of these facts, the S-methyl signals of the tautomeric compounds were compared with those of the N-methyl derivatives. It was found that **2** and **3**, which have electron-attracting groups in the 3 position, exist predominantly in the 1H form, while **4** and **5**, which have electron-releasing groups in the 3 position, exist predominantly in the 2H form. Compound **1** seems to exist as a mixture of tautomeric forms, with a slight predominance of the 1H form, in which a ring hydrogen atom is closer to the relatively electron-releasing S-methyl group. This relationship is applicable to all the compounds in Table II except **7** and the ring hydrogen atom of the predominant tautomer is attached to the nitrogen atom which is closer to the more electron-releasing S-methyl or O-methyl group in the 3 or 5 position. Compound **10** seems to exist as a mixture of almost equal amounts of the 1H and 2H forms, since **10** has an electron-donating methyl group in the 3 position in addition to an S-methyl group in the 5 position.

Compound **7** is exceptional in existing in the 2H form, in spite of the strong electron-attracting effect of the α-pyridyl group in the 3 position. This is in contrast with the fact that **8** which has a γ-pyridyl group with a similar electronic effect, exist predominantly in the 1H form.

UV Spectra

Comparison of individual UV spectra of the tautomeric compounds (**1**—**8**) with those of the model derivatives (1-methyl, 2-methyl, and 4-methyl derivatives) in each group gave results in good agreement with those obtained by NMR method. Compounds **1**, **2**, **3**, **6**, and **8** exist predominantly in the 1H form, while **4**, **5**, and **7** exist predominantly in the 2H form. In particular, **2**, **5**, **7**, and **8** show marked predominance of one tautomer, probably due to the

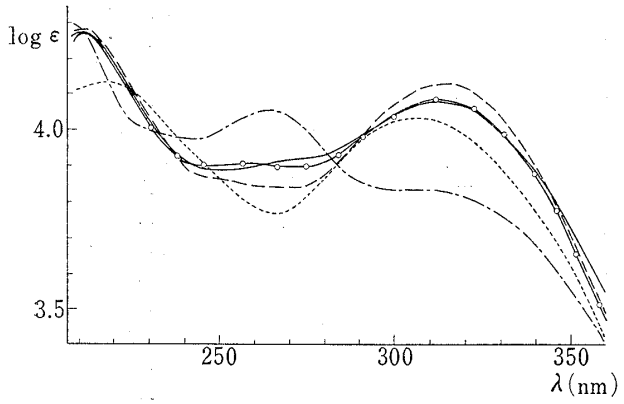


Fig. 1. Ultraviolet Spectra of —— : **2**, ----- : **14**, ——— :**15**, and ------ :**16** in EtOH

—○— : the UV curve calculated for a ratio of the 1-methyl (**14**) and 2-methyl (**15**) derivatives of 75 : 25

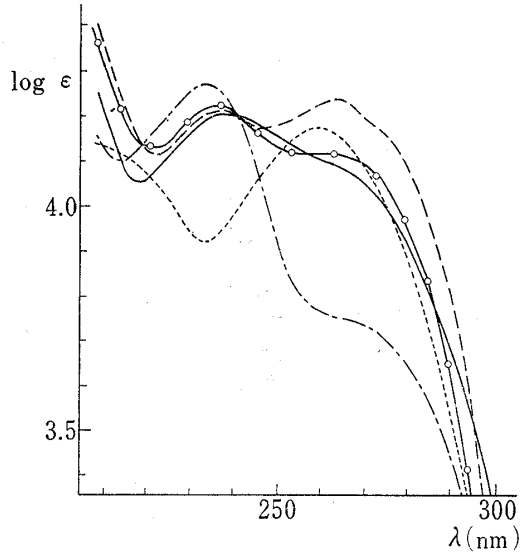


Fig. 2. Ultraviolet Spectra of —— : **3**, ——— : **17**,——— : **18**, and ------ :**19** in EtOH

—○— : the UV curve calculated for a ratio of the 1-methyl (**17**) and 2-methyl (**18**) derivatives of 65 : 35

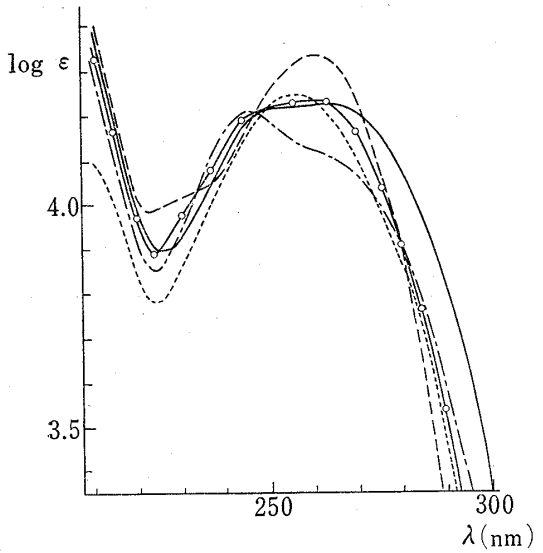


Fig. 3. Ultraviolet Spectra of —— : **4**, ——— : **20**, ——— : **21**, and ------ : **22**, in EtOH.

—○— : the UV curve calculated for a ratio of the 1-methyl (**20**) and 2-methyl (**21**) derivatives of 35: 65

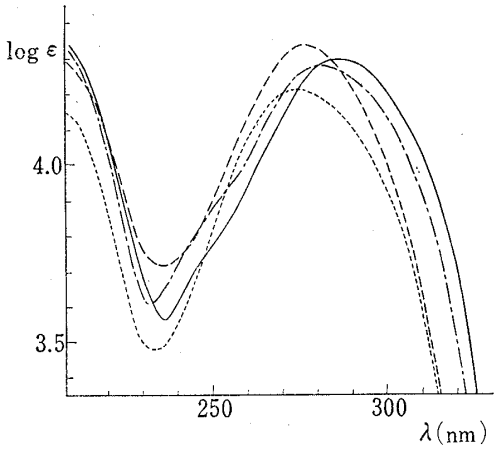


Fig. 4. Ultraviolet Spectra of ——:**5**, ----- : **23**, ——— : **24**, and ------ : **26** in EtOH

influence of the more effective substituents in position 3. As representative examples, the UV spectra of the five tautomeric compounds (**2**—**5** and **8**) and their model compounds (**14**—**25** and **32**—**34**) in ethanol are shown in Fig. 1—5.

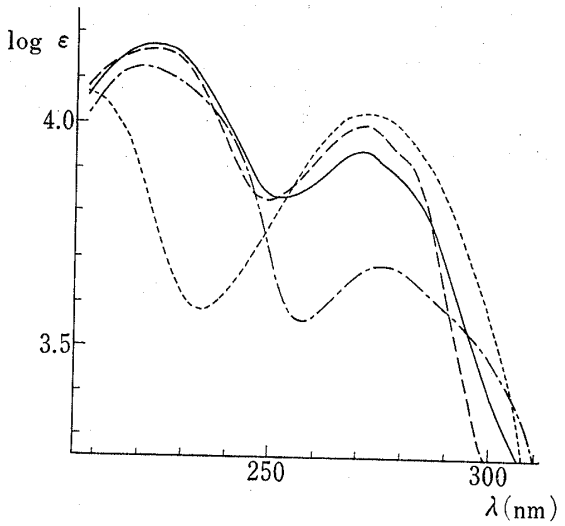


Fig. 5. Ultraviolet Spectra of —— : **8**, ——— : **32**, ——— : **33**, and ---------: **34** in EtOH

As Fig. 1 shows, the UV spectrum of the 3-*p*-nitrophenyl derivative (**2**) resembles that of the 1-methyl derivative (**14**) more closely than those of the other two model compounds. This indicates that **2** exists predominantly in the 1H form, with the same conjugated system as that of the 1-methyl derivative (**14**). However, the slight difference of the UV absorption intensities of **2** and **14** near 264 and 312 nm suggests the coexistence of a minor amount of the 2H form tautomer. The UV spectra of various proportions of the 1-methyl (**14**) and 2-methyl (**15**) derivatives were calculated. It was found that the UV spectrum of **2** was most similar to the curve calculated for a ratio of the 1-methyl and 2-methyl derivatives of 75: 25.

In the same way, it was found that the 4-*p*-chlorophenyl derivative (**3**) exists predominantly in the 1H form, since the UV spectrum of the compound was very similar to the curve calculated for a ratio of the 1-methyl (**17**) and 2-methyl (**18**) derivatives of 65: 35.

On the other hand, the UV spectra of the 3-*p*-methoxyphenyl (**4**) and 3-*p*-aminophenyl (**5**) derivatives, which have electron-releasing groups in the 3 position are similar to those of the 2-methyl derivatives (**21** and **24**), the model compounds of the 2H form, respectively, as shown in Fig. 3 and 4.

As Fig. 5 shows, the UV spectrum of the 3-γ-pyridyl derivative (**8**) is similar to that of the 1-methyl derivative (**32**) indicating that **8** exists predominantly in the 1H form. This result is expected. However, the 3-α-pyridyl derivative (**7**) was concluded to exist in the 2H form from the UV data given in our previous paper.[11] The reason for this is explained in the discussion.

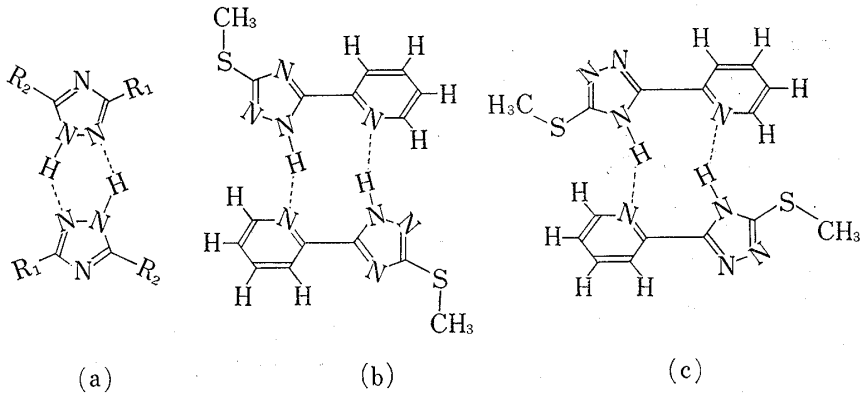
Discussion

On the basis of the results described above, it is concluded that a tautomeric hydrogen atom of the predominant tautomer of 3,5-disubstituted 1,2,4-triazoles is attached to the nitrogen atom at position 1 or 2 which is closer to the more electron-releasing substituent in the 3 or 5 position.

The question arises of why 1,2,4-triazoles exist predominantly in the 1H or 2H form. This can be explained in terms of the contribution of hydrogen bonding as follows. As shown in Chart 3a, 1,2,4-triazoles are considered to form dimer-type hydrogen bonds with an exchange of a proton between the molecules. When they become monomers, the molecules separate, and the proton is attracted to the nitrogen atom which has higher electron density. Although 1,2,4-triazoles are known to be strongly intermolecular hydrogen bonded,[6,9,11,24–27] it is unknown what type of hydrogen bond they form in solution. The type shown in Chart 3a

24) K.T. Potts, *Chem. Rev.*, **61**, 87 (1961).
25) N. Joop and H. Zimmerman, *Z. Physik. Chem.* (Frankfurt), **42**, 61 (1964).
26) E.J. Browne and J.B. Polya, *J. Chem. Soc.* (*C*), **1969**, 1056.
27) W. Sessler and G. Zundel, *Z. Physik. Chem.* (Frankfurt), **79**, 180 (1972).

seems to be stable in view of the stability of the hydrogen bonding type and steric factors. Accordingly, if interconversion between tautomers occurrs by this mechanism, it is understandable that there is no appreciable amount of the tautomer of the 4H form and that at equilibrium the predominance of the 1H or 2H form is affected by the electronic effects of the substituents in the 3 and 5 positions.



(a) (b) (c)

Chart 3

However, the NMR and UV spectral data indicate that **7** is exceptional. This can be explained by the specific character of the α-pyridyl group of **7** which can form stable intermolecular hydrogen bonds of another type. Since this compound has the ability to chelate with metal ions, as reported in the previous papers,[11,28] hydrogen bonds involving the α-pyridyl group pictured in Chart 3b are considered to be formed. The intermolecular proton exchange by this mechanism suggests that **7** exists entirely in the 2H form, and in fact, the UV spectrum of **7** was almost the same as that of the 2-methyl derivative (**29**).[11] Probably **7** can not form a hydrogen bond involving the 4H form as shown in Chart 3c due to the very great steric hindrance of the substituents in the 3 and 5 positions. This deduction was confirmed by comparison with the 3-γ-pyridyl derivative (**8**), which unlike **7** has no ability to form hydrogen bonds involving 3-γ-pyridyl group. Compound 8 exists predominantly in the 1H form due entirely to the electron-attracting effect of its 3-γ-pyridyl group.

Experimental

All melting points were uncorrected. NMR spectra were taken with a JOEL PS-100 spectrometer at 100 MHz using tetramethylsilane (TMS) as an internal standard. UV spectra were recorded on a Hitachi Model 124 spectrophotometer.

5-Methylthio-3-*p*-nitrophenyl-1,2,4-triazole (**2**)——To a solution of 3-*p*-nitrophenyl-1,2,4-triazoline-5-thione[29] (1.0 g) in 1 N NaOH (10 ml) was added a solution of methyl iodide (0.6 g) in EtOH (2 ml). The mixture was stirred at room temperature for 10 hr. A small amount of precipitate which formed was removed by filtration, and the filtrate was shaken with $CHCl_3$ (5 ml). The H_2O layer was neutralized with 10% HCl. The precipitate which separated was collected by filtration and recrystallized from EtOH giving yellow fine needles (0.6 g), mp 200—202. *Anal.* Calcd. for $C_9H_8O_2N_4S$: C, 45.75; H, 3.41; N, 23.72. Found: C, 45.73; H, 3.48; N, 23.41. NMR ($CDCl_3$) δ: 2.72 (3H, singlet, S-CH_3).

1-Methyl-3-*p*-nitrophenyl-1,2,4-triazoline-5-thione (**42**)——*p*-Nitrobenzoyl chloride (2.85 g) was added dropwise to a solution of 2-methylthiosemicarbazide[12] (1.5 g) in pyridine (40 ml) with stirring. The mixture was stirred at room temperature over night, and then neutralized with 10% HCl. A yellow precipitate (2.2 g) containing 1-*p*-nitrobenzoyl-2-methylthiosemicarbazide (**41**) and a small amount of **42** was formed. The precipitate was dissolved in 1 N NaOH (50 ml), and the solution was refluxed for 5 hr, and cooled, then neutralized with 10% HCl. A yellow solid which separated was collected by filtration, dissolved in 1 N NaOH, and then reprecipitated by neutralization with 10% HCl. A precipitate which separated was collected

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29) H.L. Yale and J.J. Piala, *J. Med. Chem.*, **9**, 42 (1966).

by filtration and washed with EtOH giving a yellow powder (1.7 g), mp 268—270°. *Anal.* Calcd. for $C_9H_8O_2N_4S$: C, 45.75; H, 3.41; N, 23.72. Found: C, 45.62; H, 3.59; N, 23.32.

1-Methyl-5-methylthio-3-*p*-nitrophenyl-1,2,4-triazole (14)——To a solution of **42** (0.4 g) in 1 N NaOH (10 ml) was added a solution of methyl iodide (0.6 g) in EtOH (3 ml). The mixture was stirred at room temperature for 3 hr. A solid which precipitated was collected by filtration and recrystallized from CH_3OH to give light yellow fine needles (0.32 g), mp 177—179°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.87; H, 3.98; N, 22.14. NMR ($CDCl_3$) δ: 2.74 (3H, singlet, S-CH_3), 3.80 (3H, singlet, $N_{(1)}$-CH_3).

1-Methyl-1-*p*-nitrobenzoylthiosemicarbazide (44)——A mixture of methylhydrazine sulfate (5 g), CH_3OH (4 ml) and acetone (30 ml) was refluxed for 2 hr. After removal of the solvent *in vacuo*, the residual oil was dissolved in dry pyridine (50 ml). To this solution was added dropwise *p*-nitrobenzoyl chloride (7.8 g) with stirring at room temperature. The mixture was warmed at 70° for 1 hr. After evaporation of the pyridine *in vacuo*, 28% ammonia was added to the residue until the pH value of the solution became to 8—9. The alkaline solution was evaporated to dryness *in vacuo* and the residue was extracted with $CHCl_3$ (100 ml × 2). Removal of the solvent gave an oily 1-methyl-1-*p*-nitrobenzoylhydrazine (**43**, 2.0 g). A mixture of **43** (2.0 g), 38% HCl (2 ml), H_2O (20 ml) and potassium thiocyanate (2.0 g) was refluxed for 3 hr. After being cooled, a yellowish precipitate which formed was recrystallized from H_2O to give a light yellow powder (0.8 g), mp 188—190°. *Anal.* Calcd. for $C_9H_{10}O_3N_4S$: C, 42.51; H, 3.96; N, 22.04. Found: C, 42.50; H, 3.94; N, 22.11.

2-Methyl-3-*p*-nitrophenyl-1,2,4-triazoline-5-thione (45)——A solution of **44** (0.6 g) in 1 N NaOH (10 ml) was refluxed for 2 hr. After being cooled, the reaction mixture was acidified with 10% HCl. A yellow solid which separated was collected by filtration, and dissolved in 1 N NaOH. The solution was acidified with 10% HCl. Repetition of this procedure gave a yellow powder (0.46 g), mp 175—178°. *Anal.* Calcd. for $C_9H_8O_2N_4S$: C, 45.75; H, 3.41; N, 23.72. Found: C, 45.82; H, 3.36; N, 23.45.

2-Methyl-5-methylthio-3-*p*-nitrophenyl-1,2,4-triazole (15)——A mixture of methyl iodide (0.5 g) and EtOH (0.3 ml) was added to a solution of **45** (0.4 g) in 1 N NaOH (4 ml). The mixture was stirred at room temperature for 3 hr. A precipitate which formed was collected by filtration, and recrystallized from EtOH to give light yellow needles (0.2 g), mp 116—118°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.99; H, 3.97; N, 21.97. NMR ($CDCl_3$) δ: 2.60 (3H, singlet, S-CH_3), 3.96 (3H, singlet, $N_{(2)}$-CH_3).

4-Methyl-1-*p*-nitrobenzoylthiosemicarbazide (47)——*p*-Nitrobenzoylhydrazine[13] (**46**, 4 g) was suspended in EtOH (50 ml), and a solution of methylisothiocyanate (1.6 g) in EtOH (10 ml) was added dropwise with stirring. The mixture was refluxed with stirring for 1 hr. After being cooled, a precipitate which formed was collected and recrystallized from EtOH to give a light yellow powder (4.5 g), mp 200—202°. *Anal.* Calcd. for $C_9H_{10}O_3N_4S$: C, 42.51; H, 3.96; N, 22.04. Found: C, 42.38; H, 3.94; N, 21.88.

4-Methyl-3-*p*-nitrophenyl-1,2,4-triazoline-5-thione (48)——A solution of **47** (3.0 g) in 1 N NaOH (50 ml) was refluxed for 5 hr. After the reaction mixture had been allowed to come to room temperature, a small amount of precipitate which formed was removed by filtration. Neutralization of the filtrate with 10% HCl gave a precipitate, which was dissolved in 1 N NaOH. The alkaline solution was neutralized with 10% HCl to give a precipitate. After two repetition of this procedure, the precipitate was washed with EtOH to give a light yellow powder (2.0 g), mp 258—260°. *Anal.* Calcd. for $C_9H_8O_2N_4S$: C, 45.75; H, 3.41; N, 23.72. Found: C, 45.63; H, 3.40; N, 23.80.

4-Methyl-5-methylthio-3-*p*-nitrophenyl-1,2,4-triazole (16)——To a solution of **48** (1.0 g) in 1 N NaOH (8 ml) was added a solution of methyl iodide (1.3 g) in EtOH (1.5 ml). The mixture was stirred at room temperature for 3 hr. A precipitate which formed was crystallized from EtOH to give yellow plates (0.75 g), mp 205—207°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 48.10; H, 3.92; N, 22.28. NMR ($CDCl_3$) δ: 2.78 (3H, singlet, S-CH_3), 3.63 (3H, singlet, $N_{(4)}$-CH_3).

1-*p*-Chlorobenzoyl-2-methylthiosemicarbazide (49)——A solution of *p*-chlorobenzoyl chloride (2.6 g) in pyridine (10 ml) was added dropwise to a solution of 2-methylthiosemicarbazide[12] (1.5 g) in pyridine (50 ml) with stirring. The mixture was stirred at room temperature over night. Removal of the solvent by evaporation *in vacuo* gave an oily residue, which slowly crystallized on cooling as colorless needles (2.6 g), mp 172—174°. *Anal.* Calcd. for $C_9H_{10}ON_3SCl$: C, 44.35; H, 4.14; N, 17.24. Found: C, 44.56; H, 4.26; N, 17.49.

3-*p*-Chlorophenyl-1-methyl-1,2,4-triazoline-5-thione (50)——A solution of **49** (2.0 g) in 1 N NaOH (20 ml) was refluxed for 5 hr. After being cooled, a small amount of insoluble material was removed by filtration. The filtrate was neutralized with 10% HCl to give a colorless precipitate, which crystallized from EtOH as colorless fine needles (1.2 g), mp 263—265. *Anal.* Calcd. for $C_9H_8N_3SCl$: C, 47.89; H, 3.57; N, 18.62. Found: C, 47.76; H, 3.52; N, 18.48.

3-*p*-Chlorophenyl-1-methyl-5-methylthio-1,2,4-triazole (17)——To a solution of **50** (1.0 g) in 1 N NaOH (10 ml) was added a solution of methyl iodide (1.0 g) in EtOH (2 ml), and the mixture was stirred at room temperature for 1 hr. A precipitate which separated was collected, and then shaken with a mixture of $CHCl_3$ (10 ml) and H_2O (10 ml). The $CHCl_3$ layer was dried over anhyd. Na_2SO_4. Evaporation of the $CHCl_3$ *in vacuo* gave a solid, which crystallized from isopropylether to give colorless needles (0.89 g), mp 84—85°.

Anal. Calcd. for $C_{10}H_{10}N_3SCl$: C, 50.10; H, 4.21; N, 17.53. Found: C, 50.03; H, 4.11; N, 17.56. NMR ($CDCl_3$) δ: 2.72 (3H, singlet, S-CH_3), 3.78 (3H, singlet, $N_{(1)}$-CH_3).

1-*p*-Chlorobenzoyl-1-methylthiosemicarbazide (52)——To a solution of methylhydrazine (1.0 g) in dry pyridine (14 ml) was added by portions *p*-chlorobenzoic anhydride (3.2 g) with stirring at room temperature. After stirring was continued for 3.5 hr, the solvent was removed by evaporation *in vacuo*. The residual yellowish oil was dissolved in EtOH (5 ml) and an insoluble material (*p*-chlorobenzoic acid) was removed by filtration. After evaporation of the EtOH *in vacuo*, the residue was dissolved in $CHCl_3$ (5 ml) with warming, and a precipitate which formed on cooling was removed by filtration. After evaporation of the solvent, the residual oil was purified by column chromatography on alumina (Woelm activity I, neutral) using $CHCl_3$–benzene (2: 1) as eluent to give 0.85 g of colorless oil of 1-*p*-chlorobenzoyl-1-methylhydrazine (**51**). A mixture of **51** (0.8 g), 38% HCl (0.8 ml), H_2O (5 ml) and potassium thiocyanate (0.8 g) was refluxed for 4 hr. After the reaction mixture had been allowed to come to room temperature, a precipitate which separated was collected by filtration. Repeated recrystallization from EtOH gave colorless needles (0.67 g), mp 207—209°. *Anal.* Calcd. for $C_9H_{10}ON_3SCl$: C, 44.35; H, 4.14; N, 17.24. Found: C, 44.50; H, 4.04; N, 17.34.

3-*p*-Chlorophenyl-2-methyl-1,2,4-triazoline-5-thione (53)——A solution of **52** (0.2 g) in 1 N NaOH (4 ml) was refluxed for 3 hr. After being cooled, the reaction mixture was neutralized with 10% HCl. A precipitate which formed was recrystallized from EtOH as a colorless powder (0.15 g), mp 182—184. *Anal.* Calcd. for $C_9H_8N_3SCl$: C, 47.89; H, 3.57; N, 18.62. Found: C, 47.76; H, 3.49; N, 18.77.

3-*p*-Chlorophenyl-2-methyl-5-methylthio-1,2,4-triazole (18)——To a solution of **53** (0.12 g) in 1 N NaOH (1 ml) was added a solution of methyl iodide (0.14 g) in EtOH (0.03 ml). The mixture was stirred at room temperature over night. Neutralization of the reaction mixture with 10% HCl gave a colorless precipitate. The precipitate was collected, and shaken with a mixture of $CHCl_3$ (10 ml) and H_2O (2 ml). The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and then evaporated *in vacuo*. A residual oil solidified slowly on cooling. The solid was recrystallized from isopropylether to give colorless needles (0.08 g), mp 70—71°. *Anal.* Calcd. for $C_{10}H_{10}N_3SCl$: C, 50.10; H, 4.21; N, 17.53. Found: C, 49.87; H, 4.19; N, 17.58. NMR ($CDCl_3$) δ: 2.60 (3H, singlet, S-CH_3), 3.90 (3H, singlet, $N_{(2)}$-CH_3).

3-*p*-Chlorophenyl-4-methyl-5-methylthio-1,2,4-triazole (19)——To a solution of 3-*p*-chlorophenyl-4-methyl-1,2,4-triazoline -5-thione[13] (**56**, 1.0 g) in 1 N NaOH (10 ml) was added a mixture of methyl iodide (1.0 g) and EtOH (2 ml). The mixture was stirred at room temperature for 3 hr. A precipitate which formed was collected by filtration, washed with H_2O, and recrystallized from EtOH to give colorless needles (0.95 g), mp 210—211°. *Anal.* Calcd. for $C_{10}H_{10}N_3SCl$: C, 50.10; H, 4.21; N, 17.53. Found: C, 50.05; H, 4.05; N, 17.37. NMR ($CDCl_3$) δ: 2.76 (3H, singlet, S-CH_3), 3.56 (3H, singlet, $N_{(4)}$-CH_3).

1-*p*-Methoxybenzoyl-2-methylthiosemicarbazide (57)——To a solution of 2-methylthiosemicarbazide[12] (1.0 g) in dry pyridine (20 ml) was added dropwise a solution of *p*-methoxybenzoyl chloride (1.7 g) in dry pyridine (5 ml) with stirring. The mixture was stirred at room temperature over night. Removal of the solvent by evaporation *in vacuo* gave an oil, which solidified slowly on cooling. The solid was recrystallized from EtOH to give colorless needles (1.78 g), mp 207—208°. *Anal.* Calcd. for $C_{10}H_{13}O_2N_3S$: C, 50.19; H, 5.48; N, 17.56. Found: C, 50.23; H, 5.43; N, 17.38.

3-*p*-Methoxyphenyl-1-methyl-1,2,4-triazoline-5-thione (58)——A solution of **57** (1.5 g) in 1 N NaOH (15 ml) was refluxed for 4 hr. After being cooled, the reaction mixture was neutralized with 10% HCl to give a precipitate. Recrystallization from EtOH gave colorless plates (1.25 g), mp 239—240°. *Anal.* Calcd. for $C_{10}H_{11}ON_3S$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.10; H, 4.97; N, 18.81.

3-*p*-Methoxyphenyl-1-methyl-5-methylthio-1,2,4-triazole (20)——To a solution of **58** (1.0 g) in 1 N NaOH (10 ml) was added methyl iodide (1.0 g) in EtOH (2 ml), and the mixture was stirred at room temperature for 3 hr. A precipitate formed was collected by filtration and crystallized from EtOH as colorless needles (0.7 g), mp 70—71°. *Anal.* Calcd. for $C_{11}H_{13}ON_3S$: C, 56.62; H, 5.57; N, 17.86. Found: C, 56.35; H, 5.51; N, 17.85. NMR ($CDCl_3$) δ: 2.72 (3H, singlet, S-CH_3), 3.77 (3H, singlet, $N_{(1)}$-CH_3), 3.82 (3H, singlet, O-CH_3).

1-*p*-Methoxybenzoyl-1-methylthiosemicarbazide (60)——Methylhydrazine (0.8 g) was dissolved in dry pyridine (10 ml), and *p*-methoxybenzoic anhydride (2.5 g) was added by portions with stirring at room temperature (30 min). After stirring was continued for 2.5 hr, the solvent was removed by evaporation *in vacuo*. The residual oil solidified slowly on cooling. EtOH was added to the solid, and a small amount of insoluble material (*p*-methoxybenzoic acid) was removed by filtration. The filtrate was evaporated *in vacuo*, and dissolved in $CHCl_3$. After insoluble material was removed by filtration, the solvent was removed by evaporation. The resulting oil was purified by column chromatography on alumina using $CHCl_3$–benzene (2: 1) as eluent to give 1-*p*-methoxybenzoyl-1-methylhydrazine (**59**, 0.53 g). A mixture of **59** (0.5 g), 38% HCl (0.5 ml), and potassium thiocyanate (0.5 g) was refluxed for 3 hr. After being cooled, a precipitate which formed was collected, washed with H_2O, and recrystallized from EtOH to give colorless needles (0.25 g), mp 188—189°. *Anal.* Calcd. for $C_{10}H_{13}O_2N_3S$: C, 50.19; H, 5.48; N, 17.56. Found: C, 50.41; H, 5.40; N, 17.55.

3-*p*-Methoxyphenyl-2-methyl-1,2,4-triazoline-5-thione (61)——A solution of **60** (0.2 g) in 1 N NaOH (4 ml) was refluxed for 3 hr. After being cooled, the reaction mixture was acidified with 10% HCl. A

precipitate which formed was recrystallized from EtOH to give colorless needles (0.15 g), mp 201—203°. *Anal.* Calcd. for $C_{10}H_{11}ON_3S$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.23; H, 4.96; N, 18.69.

3-*p*-Methoxyphenyl-2-methyl-5-methylthio-1,2,4-triazole (21)——To a solution of **61** (0.1 g) in 1 N NaOH (3 ml) was added a solution of methyl iodide (0.12 g) in EtOH (0.02 ml). The mixture was stirred at room temperature over night. The reaction mixture was extracted with $CHCl_3$ (5 ml×3). The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and then evaporated to dryness. The residue was recrystallized from isopropylether giving colorless rods (0.66 g), mp 98—100°. *Anal.* Calcd. for $C_{11}H_{13}ON_3S$: C, 56.62; H, 5.57; N, 17.86. Found: C, 56.55; H, 5.52; N, 17.65. NMR ($CDCl_3$) δ: 2.60 (3H, singlet, S-CH_3), 3.85 (3H, singlet, O-CH_3, 3.88 (3H, singlet, $N_{(2)}$-CH_3).

3-*p*-Methoxyphenyl-4-methyl-5-methylthio-1,2,4-triazole (22)——To a solution 3-*p*-methoxyphenyl-4-methyl-1,2,4-triazoline-5-thione[14] (**64**, 1.2 g) in 1 N NaOH (10 ml) was added a solution of methyl iodide (1.2 g) in EtOH (0.1 ml), and the mixture was stirred at room temperature for 3 hr. A precipitate which formed was filtered, washed with hot water, and recrystallized from EtOH to give colorless fine needles (1.1 g), mp 153—155°. *Anal.* Calcd. for $C_{11}H_{13}ON_3S$: C, 56.62; H, 5.57; N, 17.86. Found: C, 56.23; H, 5.55; N, 17.83. NMR ($CDCl_3$) δ: 2.74 (3H, singlet, S-CH_3), 3.54 (3H, singlet, $N_{(4)}$-CH_3), 3.84 (3H, singlet, O-CH_3).

3-*p*-Aminophenyl-5-methylthio-1,2,4-triazole (5)——Zinc dust (0.5 g) was added by portions to a suspension of **2** (0.3 g) in 38% HCl (5 ml) and H_2O (5 ml) with stirring at 70°. (1 hr). Stirring was continued for 6 hr at 70°. A precipitate which formed was collected by filtration, dissolved in H_2O (5 ml), and the solution was neutralized with 1 N NaOH. A precipitate which separated was collected and dissolved in EtOH (3 ml). A small amount of insoluble material was removed by filtration. After the filtrate was evaporated *in vacuo*, a yellowish oily residue was dissolved in hot water. An insoluble material was removed by filtration, and the filtrate was cooled. A precipitate which separated was collected by filtration and crystallized from H_2O to give colorless fine needles (0.15 g), mp 174—175°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.64; H, 4.81; N, 27.35. NMR ($CDCl_3$) δ: 2.63 (3H, singlet, S-CH_3).

3-*p*-Aminophenyl-1-methyl-5-methylthio-1,2,4-triazole (23)——Compound **14** (0.3 g) was treated in a manner similar to that for **5**, and recrystallization from H_2O gave slightly yellowish needles (0.71 g), mp 127—129°. *Anal.* Calcd. for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43. Found: C, 54.37; H, 5.28; N, 25.19. NMR ($CDCl_3$) δ: 2.71 (3H, singlet, S-CH_3), 3.76 (3H, singlet, $N_{(1)}$-CH_3).

3-*p*-Aminophenyl-2-methyl-5-methylthio-1,2,4-triazole (24)——Compound **15** (0.1 g) was treated in a manner similar to that for **5**, and recrystallization from H_2O gave colorless needles (0.05 g), mp 123—124°. *Anal.* Calcd. for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43. Found: C, 54.61; H, 5.42; N, 25.59. NMR ($CDCl_3$) δ: 2.59 (3H, singlet, S-CH_3), 3.86 (3H, singlet, $N_{(1)}$-CH_3).

3-*p*-Aminophenyl-4-methyl-5-methylthio-1,2,4-triazole (25)——Compound **16** (0.3 g) was treated in a manner similar to that for **5**, and recrystallization from EtOH gave colorless needles (0.2 g), mp 185—186°. *Anal.* Calcd. for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43. Found: C, 54.67; H, 5.41; N, 25.54. NMR (MeOH-d_4) δ: 2.66 (3H, singlet, S-CH_3), 3.59 (3H, singlet, $N_{(4)}$-CH_3).

1-Methyl-3-γ-pyridyl-1,2,4-triazoline-5-thione (65)——A mixture of 1-isonicotinoyl-2-methylhydrazine[30] (4.0 g), potassium thiocyanate (5.4 g), and 10% HCl (15 ml) was heated at 110° on an oil bath for 1 hr. After being cooled, a precipitate which formed was collected by filtration and washed with H_2O. Two recrystallizations from EtOH gave colorless needles (1.5 g), mp 273—274°. *Anal.* Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.18; N, 29.14. Found: C, 50.20; H, 4.19; N, 29.14.

1-Methyl-5-methylthio-3-γ-pyridyl-1,2,4-triazole (32)——To a solution of **65** (1.0 g) in 1 N NaOH (15 ml) was added a solution of methyl iodide (0.74 g) in EtOH (1.5 ml). The mixture was stirred at room temperature for 1 hr, and then acidified with 10% HCl (pH 4—5). A precipitate which formed was collected and recrystallized from isopropylether to give colorless fine needles (0.66 g), mp 95.5—96.5°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.54; H, 4.98; N, 26.90. NMR ($CDCl_3$) δ: 2.75 (3H, singlet, S-CH_3), 3.81 (3H, singlet, $N_{(1)}$-CH_3).

2-Methyl-5-methylthio-3-γ-pyridyl-1,2,4-triazole (33)——To a solution of 5-methylthio-3-γ-pyridyl-1,2,4-triazole[15] (**8**, 1.0 g) in 1 N NaOH (5 ml) was added methyl iodide (1.1 g) and EtOH (0.5 ml). The mixture was stirred at room temperature for 5 hr, and then extracted with $CHCl_3$ (5 ml×3). The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and then evaporated. The oily residue containing the 1-methyl (**32**), 2-methyl (**33**), and 4-methyl (**34**) derivatives was chromatographed on silicagel using a solvent system benzene-$CHCl_3$ (1: 1) as eluent. Removal of the solvent of the second fraction gave a solid (**33**), which was recrystallized from isopropylether to give colorless needles (0.2 g), mp 87—88°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.11; H, 4.82; N, 26.76. NMR ($CDCl_3$) δ: 2.61 (3H, singlet, S-CH_3), 3.97 (3H, singlet, $N_{(2)}$-CH_3).

4-Methyl-5-methylthio-3-γ-pyridyl-1,2,4-triazole (34)——To a solution of 4-methyl-3-γ-pyridyl-1,2,4-triazoline-5-thione[16] (3.0 g) in 1 N NaOH (25 ml) was added methyl iodide (4.5 g) in EtOH (6 ml), and the mixture was stirred at room temperature over night. The reaction mixture was extracted with $CHCl_3$

30) M. Shimizu, T. Naito, G. Ohta, K. Suzuki, S. Kasai, K. Murai, and K. Asano, *Yakugaku Zasshi*, **72**, 1639 (1952).

(10 ml × 5). The $CHCl_3$ layer was washed with H_2O and then dried over anhyd. Na_2SO_4. Evaporation of the $CHCl_3$ gave a solid, which was crystallized from isopropylether as colorless needles (1.2 g), mp 160—161°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.13; H, 4.85; N, 26.81. NMR ($CDCl_3$) δ: 2.79 (3H, singlet, S-CH_3), 3.64 (3H, singlet, $N_{(4)}$-CH_3).

2-Methyl-3-methylthio-1,2,4-triazole (36)——To a solution of 3-methylthio-1,2,4-triazole[21] (**9**, 1.5 g) in 1 N NaOH (15 ml) was added methyl iodide (3.7 g) in EtOH (5 ml). The mixture was stirred at room temperature for 10 hr, and then extracted with $CHCl_3$ (20 ml × 5). Removal of the $CHCl_3$ gave an oily residue containing the 1-methyl (**36**), 2-methyl (**36**), and 4-methyl (**37**) derivatives. The residue was column chromatographed on silicagel using $CHCl_3$ as eluent to give three fractions. Removal of the solvent of the second fraction gave an oily product (**35**), which was crystallized from ether as colorless crystals, mp 48—49°. *Anal.* Calcd. for $C_4H_7N_3S$: C, 37.19; H, 5.46; N, 32.11. Found: C, 37.46; H, 5.45; N, 32.42. Mass Spectrum *m/e*: 129 (M^+). NMR ($CDCl_3$) δ: 2.58 (3H, singlet, S-CH_3), 3.88 (3H, singlet, $N_{(1)}$-CH_3), 8.01 (1H, singlet, $C_{(5)}$-H).

2,3-Dimethyl-5-methylthio-1,2,4-triazole (36)——This compound (**39**) was prepared in the same way as in **36**. 3-Methyl-5-methylthio-1,2,4-triazole[21] (**10**, 1.2 g) gave 0.23 g of colorless crystals of **39** (recrystallized from H_2O), mp 35.5—36.5°. *Anal.* Calcd. for $C_5H_9N_3S$: C, 41.93; H, 6.33; N, 29.34. Found: C, 41.83; H, 6.30; N, 29.28. Mass Spectrum *m/e*: 143 (M^+). NMR ($CDCl_3$) δ: 2.39 (3H, singlet, $C_{(3)}$-CH_3), 2.53 (3H, singlet, S-CH_3), 3.72 (3H, singlet, $N_{(2)}$-CH_3).

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