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1,2,4-Triazoles. I. Methylation of 3-α-Pyridyl-1,2,4-triazoline-5-thione

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Methylation of 3-α-pyridyl-1,2,4-triazoline-5-thione (II) with methyl iodide in alkaline solution gave 5-methylthio-3-α-pyridyl-1,2,4-triazole (III) and its N-methyl derivatives, 1-, 2-, and 4-methyl-5-methylthio-3-α-pyridyl-1,2,4-trizaole (IV, V and VI). The structures of these compounds were established by elemental analysis, spectral data and the identification with the compounds prepared by different methods. IV, V and VI were also produced by methylation of III with methyl iodide in alkaline solution.

Methylation of III with dimethyl sulfate in alkaline solution or diazomethane in methanol also gave the same products. The ratios of the amount of IV:V:VI in the products were determined by nuclear magnetic resonance spectroscopy and it was found that IV was predominantly formed in every case.

During the course of an investigation of the synthesis of 3-α-pyridyl-1,2,4-triazoline-5-thione (II) and its S-alkyl derivatives, it was found by thin-layer chromatography (TLC) and gas chromatography (GLC) that the methylation of II with methyl iodide in alkaline solution gave four products.

The present paper deals with the characterization of these four products as 5-methylthio-3-α-pyridyl-1,2,4-triazole (III) and its N-methyl derivatives by the spectral data, and the identification of the products with the compounds synthesized by different methods.

It has been reported that alkylation of 1,2,4-triazole,[2,3] 3-substituted[4,5] or 3,5-disubstituted 1,2,4-triazoles[2,4,6] gave only one or two 1,2,4-triazole derivatives of the three expected N-methyl derivatives.

In view of the literature described above, it was expected that the reaction of II with methyl iodide afforded III and its N-methyl derivatives. The reaction of II with equimolar methyl iodide in 1N sodium hydroxide gave crystals, mp 140—141°. The mass spectrum of this compound showed *m/e* 192 parent peak. The infrared (IR) absorption bands in 3200—2500 cm^{-1} region suggestad the presence of associated NH group. The nuclear magnetic resonance (NMR) spectrum showed a singlet peak due to S-methyl protons at 7.32 τ which is similar to the chemical shift of methylthio group of 1,2,4-triazole derivative.[7]

These spectral data indicated that the compound should be III. This was confirmed by comparison of melting point and spectroscopic properties with the compound synthesized by the cyclization of 1-picolinoyl-S-methylisothiosemicarbazide (VIII) which was obtained from 1-picolinoylthiosemicarbazide[8] (VII).

When an excess of methyl iodide was used in this reaction, formation of three products with III obserbed by TLC and GLC. Since the three products were also obtained from the reaction of III with methyl iodide, they were considered to be formed *via* III (Fig. 1 and 2).

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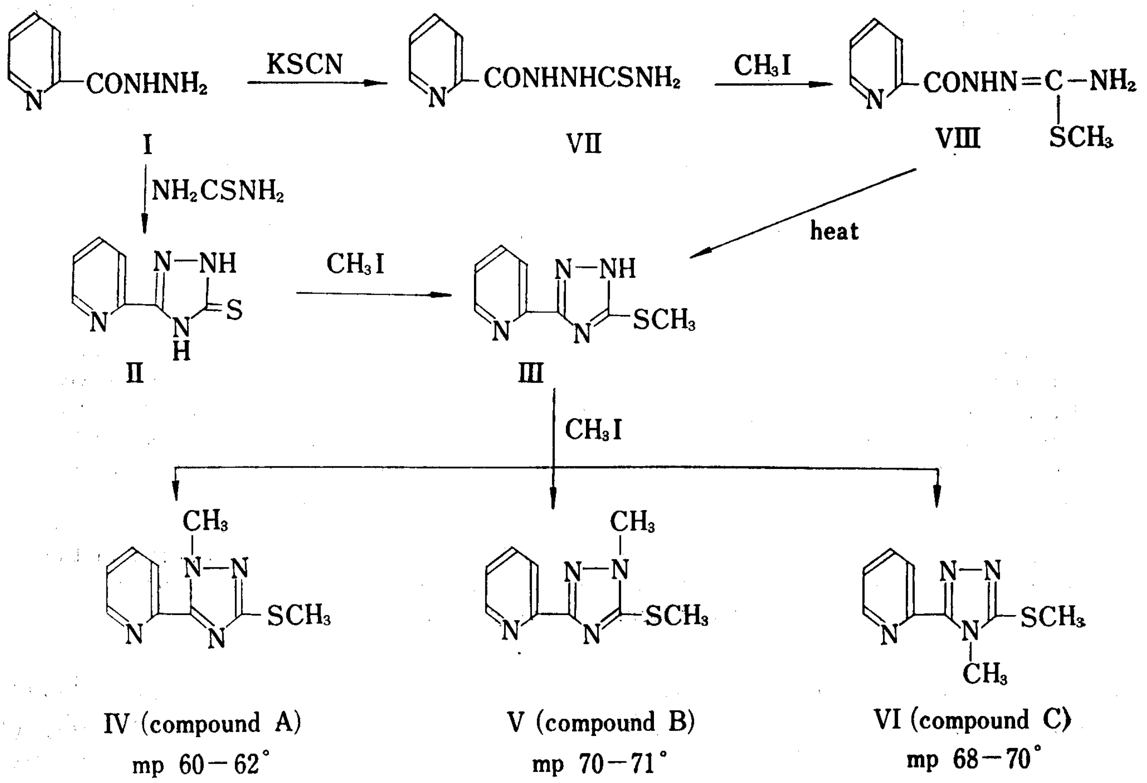


Chart 1

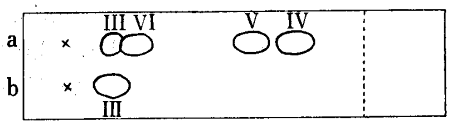


Fig. 1. Thin-Layer Chromatogram of the Reaction Products of II with an Excess of CH_3I

solvent: $CHCl_3$-MeOH (40:1 v/v)
plate: Aluminium Oxide G (Merck)
a: the reaction products of II with an excess of CH_3I
b: authentic sample (III)
All spots were visualized with 5% $FeCl_3$ solution (spot III; dark brown, spot IV; orange, spot V; yellow, spot VI; brown), and also detected with I_2 vapor or UV light.

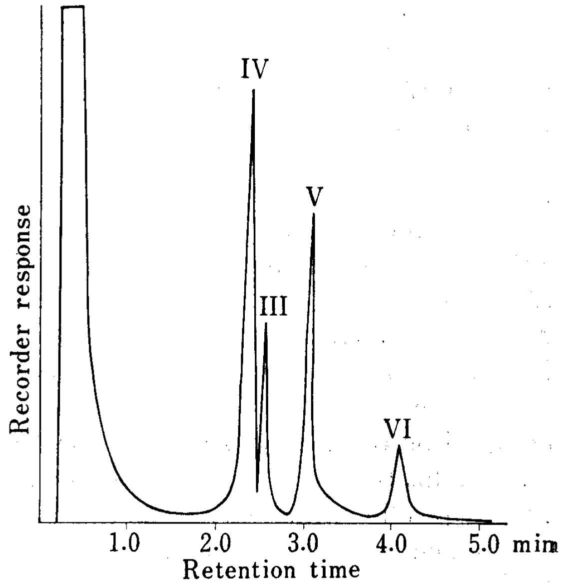
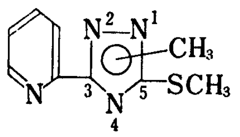


Fig. 2. Gas Chromatogram of the Reaction Products of II with an Excess of CH_3I

column: 5% SE-30 (1 m × 3 mm *i.d.*)
temperature: column 200°
carrier gas: H_2, 28 ml/min

The reaction of II with an excess of methyl iodide in alkaline solution afforded three kinds of crystals having mp 60—62° (compound A), 70—71° (compound B) and 68—70° (compound C). These compounds gave the same analytical values corresponding to $C_9H_{10}N_4S$ and showed the same mass spectral peak at *m/e* 206 (molecular ion) which is fourteen higher than that of III. The IR spectra of them showed the bands of N-methyl group at 2850 cm^{-1} and the NMR spectra showed signals of two methyl protons. On the basis of these facts, they were considered to be the isomers which have a methyl group attached to the different nitrogen of the triazole nucleus together with a methylthio-group. The NMR spectra of these four pyridyl-1,2,4-trizaole derivatives were measured in $CDCl_3$ at 60 MHz (Table I).

Table I. Nuclear Magnetic Resonance Spectral Data of III, IV, V and VI



	NCH_3	SCH_3
III	—	7.32
IV (compound A)	5.66 (N-2)	7.35
V (compound B)	6.17 (N-1)	7.23
VI (compound C)	6.00 (N-4)	7.22

The signals for the N-2 and N-4 methyl protons of the triazole should appear at lower field than that for the N-1 methyl protons, because of the electron withdrawing influence of the adjacent α-pyridyl group and anisotropic effect of the pyridine ring. Since the S-methyl group has little influence for the chemical shift of the N-methyl protons, the N-2 methyl protons should absorb at lower field than those of N-4 because of adjacent nitrogen atom.[9]

From these NMR data described above, it was concluded that the N-2 methyl protons should absorb at the lowest field and the N-1 methyl protons at the highest field. In order to confirm the above assumption, each N-methyl derivative was prepared by the following sequence.

2-methyl-5-methylthio-3-α-pyridyl-1,2,4-triazole (IV) was obtained by methylation of 2-methyl-3-α-pyridyl-1,2,4-triazoline-5-thione (X) which was prepared by treating 2-cyanopyridine (IX) with 1-methylthiosemicarbazide[10] at 130°. The melting point of the product was 60—62° and not depressed by admixture with the compound A. The behavior on the TLC and IR spectra of them were also identical.

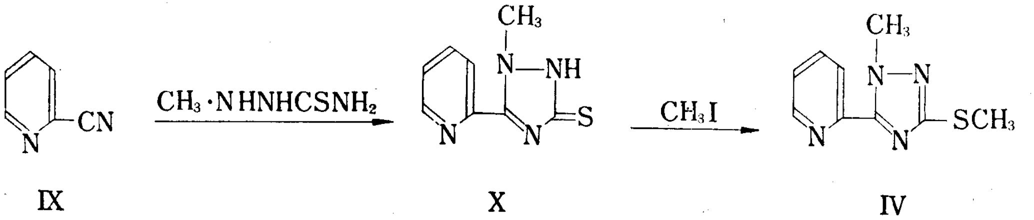


Chart 2

1-Methyl-5-methylthio-3-α-pyridyl-1,2,4-triazole (V) was synthesized by methylation of 1-methyl-3-α-pyridyl-1,2,4-triazoline-5-thione (XIII) with methyl iodide in alkaline solution. XIII was prepared by cyclization of 1-picolinoyl-2-methylthiosemicarbazide (XII) which was obtained from 1-picolinoyl-2-methylhydrazine (XI) by reaction with potassium thiocyanate. It has been reported that the reaction of ethyl picolinate with methylhydrazine gave XI.[11] However, since XI was obtained with small amount of 1-picolinoyl-1-methylhydrazine in this reaction, the mixture was separated by column chromatography on alumina. The reaction of XI with potassium thiocyanate gave the mixture of XII and XIII. XII was easily converted to XIII on heating. XIII was also obtained by direct heating of IX with 2-methylthiosemicarbazide.[12] Comparison of the IR, NMR spectra and the thin-layer chromatogram of V

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with those of the compound B obtained from the reaction of II with methyl iodide proved that they were identical.

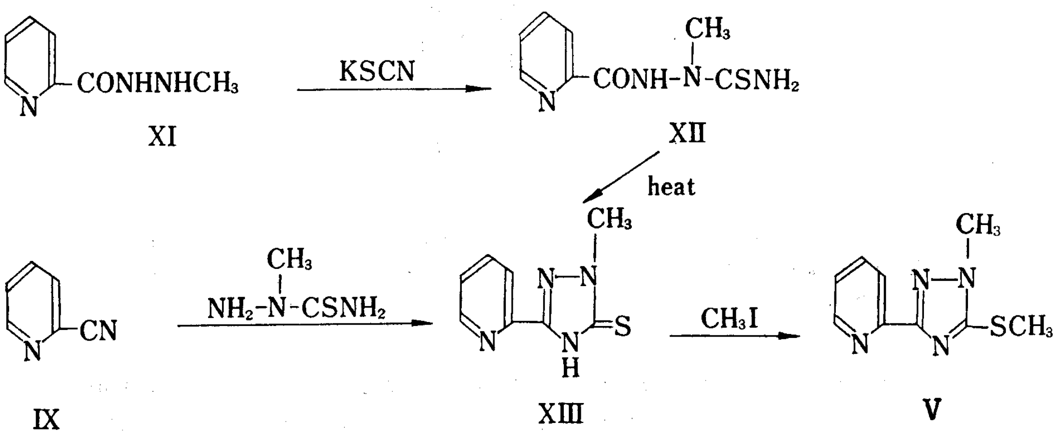

Chart 3

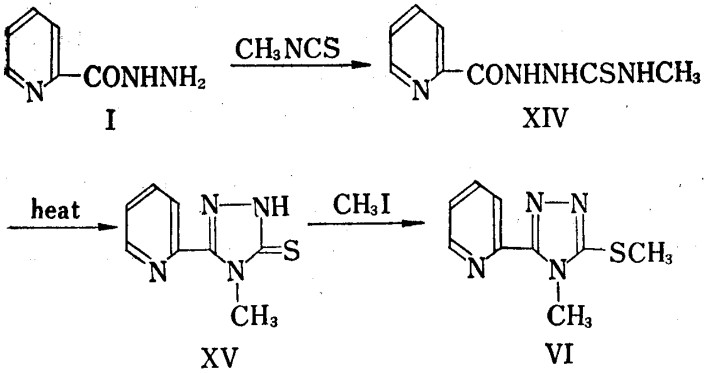

Chart 4

4-Substituted-1,2,4-triazoline-5-thiones have been prepared by heating the thiosemicarbazides in alkaline solution.[13] Application of this procedure to 1-picolinoyl-4-methylthiosemicarbazide (XIV) which was prepared from 1-picolinoylhydrazine[14] and methylisothiocyanate gave 4-methyl-3-α-pyridyl-1,2,4-triazoline-5-thione (XV). Methylation of XV with methyl iodide in alkaline solution afforded 4-methyl-5-methylthio-3-α-pyridyl-1,2,4-triazole (VI). The IR, NMR spectra and the thin-layer chromatogram of VI agreed with those of the compound C.

Methylation of III with dimethyl sulfate or diazomethane also gave the same three N-methyl derivatives. The ratios of IV: V: VI in the products obtained by methylation of III with methyl iodide, dimethyl sulfate or diazomethane were determined by NMR spectroscopy. IV was predominantly formed in every case as shown in table II.

Table II. Ratios of IV:V:VI in the Products Obtained by Methylation of III

Reagent	IV	V	VI
CH_3I in 1N NaOH	4.3	2.3	1.0
$(CH_3)_2SO_4$ in 1N NaOH	4.7	1.7	1.0
CH_2N_2 in methanol	3.4	0.87	1.0

Experimental

All melting points are uncorrected. IR and UV spectra were determined with Hitachi EPI-G_2 spectrometer and Hitachi Model 124 spectrophotometer, respectively. NMR spectra were taken with Varian A-60

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13) Y. Postovskii and N.N. Vereshchagina, *Z. Obshch. Khim.*, **26**, 2583 (1956). [*C.A.*, **51**, 50556 (1957)].
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(at 60 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Gas chromatography was performed on a Hitachi K-23 gas chromatograph. For TLC and column chromatography, Aluminium Oxide G (Merck) and Aluminium Oxide Woelm neutral were used, respectively.

3-α-Pyridyl-1,2,4-triazoline-5-thione (II)——This compound was prepared in the same way as in 3-γ-pyridyl-1,2,4-triazoline-5-thione.[15] A mixture of 5.0 g of 1-picolinoylhydrazine (I) and 3.3 g of thiourea was heated on an oil bath at 150° for 5 hr. After the reaction mixture had been allowed to come to room temperature, the solid obtained was dissolved in 10% NaOH, reprecipitated with 10% HCl. Further repetition of this procedure gave 2.74 g (63.7%) of light brown powder, mp 270—272° (decomp.). *Anal.* Calcd. for $C_7H_6N_4S$: C, 47.17; H, 3.39; N, 31.44. Found: C, 47.43; H, 3.43; N, 31.59.

Methylation of II with Equimolar Methyl Iodide——A mixture of 0.2 g II in 3 ml of NaOH and 0.16 g of CH_3I in 0.3 ml of EtOH was stirred at room temperature for 2 hr. The reaction mixture was neutralized with 10% HCl to give the precipitate which was recrystallized from EtOH to give 0.135 g of 5-methylthio-3-α-pyridyl-1,2,4-triazole (III) as white needles, mp 140—141°. *Anal.* Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14. Found: C, 50.36; H, 4.23; N, 29.38. NMR ($CDCl_3$) τ; 7.32 (3H, s, -SCH_3) UV λ_{max}^{EtOH} mμ (log ε): 235 (4.14), 286 (3.90).

Methylation of II with an Excess of CH_3I in Alkaline Solution——A mixture of 1.0 g of II, 6 ml of 1N NaOH and 0.25 g of CH_3I in 2 ml of EtOH was stirred at room temperature for 10 hr. The reaction mixture was extracted with five portions of 15 ml of $CHCl_3$, the $CHCl_3$ extract was dried over Na_2SO_4. Removal of the solvent gave yellowish brown oily substance. TLC of this substance on alumina (Solvent; $CHCl_3$–CH_3OH (40:1, V/V)) exhibited three spots which showed different fluorescence when exposed to UV light and produced different color with Fe^{+++} ion. The substance was chromatographed on alumina using benzene–$CHCl_3$ (2:1) as an eluent giving three fractions. Each fraction, after removal of the solvent, was extracted with isopropyl ether. Evaporation of the solvent and keeping the concentrated solution in refrigerater for three days gave colorless crystals. The following three kinds of pure crystals were obtained by repetition of the same procedure. Elemental analytical values of them were in good agreement with that calculated for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. The first fraction; mp 60—62°, 0.23 g, *Anal.* Found: C, 52.81; H, 5.01; N, 27.07. NMR ($CDCl_3$) τ; 5.66 (3H, s, >NCH_3), 7.35 (3H, s, -SCH_3), UV λ_{max}^{EtOH} mμ (log ε): 236 (4.10), 2.85 (3.88). The second fraction; mp 70—71°, 0.14 g, *Anal.* Found: C, 52.37; H, 5.10; N, 27.21. NMR ($CDCl_3$) τ; 6.17 (3H, s, >NCH_3), 7.23 (3H, s, -SCH_3), UV λ_{max}^{EtOH} mμ (log ε): 281 (3.91). The third fraction; mp 68—69°. 0.065 g. *Anal.* Found: C, 52.63; H, 4.90; N, 27.46. NMR ($CDCl_3$) τ: 6.00 (3H, s, >NCH_3), 7.22 (3H, s, -SCH_3), UV λ_{max}^{EtOH} mμ (log ε): 285 (4.00).

Methylation of III with Methyl Iodide——A mixture of 1.0 g of III in 6 ml of 1N NaOH and 1.5 g of CH_3I in 2 ml of EtOH was stirred at room temperature for 9 hr. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated to dryness to give 0.65 g of an oil. The preparative thin–layer chromatography of the oil on alumina was carried out using $CHCl_3$–MeOH (40:1) as developing solvent. The three fractions which showed different fluorescence when exposed to ultraviolet light were collected. Each fraction was extracted with $CHCl_3$, then the extract was recrystallized from isopropyl ether to give three kinds of products IV (mp 60—62°), 0.185 g; V (mp 70—71°), 0.115 g; VI (mp 68—69°), 0.042 g.

1-Picolinoyl-S-methylisothiosemicarbazide (VIII)——To a solution of 0.3 g of 1-picolinoylthiosemicarbazide (VII) in 4 ml of 1N NaOH was added 0.8 ml of CH_3I in 1 ml of EtOH and the mixture was stirred at room temperature for 1 hr. Recrystallization of the resulting precipitate from EtOH gave 0.15 g of colorless needles, mp 164—165°. *Anal.* Calcd. for $C_7H_{10}ON_4S$: C, 45.70; H, 4.79; N, 26.65. Found: C, 45.84; H, 5.03; N, 26.21.

Thermal Cylization of VIII——When 1.3 g of VIII was heated on an oil-bath, it began to decompose at 160°. After being kept at 200° for 5 min, the resulting liquid was allowed to come to room temperature yielding the solid. Recrystallization from EtOH gave 0.85 g of light yellow crystals, mp 140—141°, which were shown to be identical with III by mixed melting point determination and comparison of IR spectra.

2-Methyl-3-α-pyridyl-1,2,4-triazoline-5-thione (X)——A mixture of 0.4 g of 2-cyanopyridine (IX) and 0.4 g of 1-methylthiosemicarbazide was heated at 130° for 8 hr. The resulting brown solid was washed with 10 ml of water and dissolved in $CHCl_3$. The $CHCl_3$ layer was shaken with 1N NaOH. The alkaline solution was neutralized with diluted HCl and extracted with $CHCl_3$. Removal of the solvent by evaporation gave 0.1 g of the residue, which recrystallized from EtOH to colorless crystals, mp 163—164°. *Anal.* Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14. Found: C, 50.40; H, 4.42; N, 29.02.

2-Methyl-5-methylthio-3-α-pyridyl-1,2,4-triazole (IV)——A mixture of 0.1 g of X in 2 ml of 1N NaOH and 0.15 g of CH_3I in 0.5 ml of EtOH was stirred at room temperature for 2 hr. The resulting precipitate was collected by filtration, recrystallized from isopropyl ether to give 0.024 g of colorless needles, mp 60—62°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 51.96; H, 4.87; N, 27.25. This was proved to be identical with compound A by mixed melting point determination and comparison of IR spectra.

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[15] H.C. Beyerman, J.S. Bontakoe, W.J. Van der Burg and W.L.C. Veer, *Rec. Trav. Chim.*, 73, 109 (1954).

1-Picolinoyl-2-methylhydrazine (XI)——A mixture of 3.0 g of ethyl picolinate and 3.0 g of methylhydrazine was refluxed for 4 hr. Removal of excess methylhydrazine by evaporation *in vacuo* gave the light yellowish brown oil which was chromatographed on alumina with benzene–$CHCl_3$. The crystals obtained from the first fraction were recrystallized from EtOH to give 0.4 g of colorless prisms, mp 58—60°. *Anal.* Calcd. for $C_7H_9O_3N$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.15; H, 6.28; N, 27.30. The second fraction gave a small amount of 1-picolinoyl-1-methylhydrazine which was identical with the authentic sample by TLC and IR spectra.

1-Methyl-3-*α*-pyridyl-1,2,4-triazoline-5-thione (XIII)——a) A mixture of 0.5 g of XI, 0.8 g of KSCN, 0.55 ml of concentrated HCl and 2.2 ml of water was heated on a water bath for 2 hr. After the mixture had been allowed to come to room temperature, the resulting precipitate was collected by filtration and washed with EtOH giving 0.5 g of the mixture of 1-picolinoyl-2-methylthiosemicarbazide (XII) and XIII. A solution of 0.1 g of the mixture in 1 ml of 2N NaOH was refluxed at 150° for 2 hr. The solution had been allowed to come to room temperature, neutralized with 10% HCl. The precipitate appeared was collected by filtration and recrystallized from EtOH to give colorless powder, 0.08 g, mp 255—260° (decomp.). *Anal.* Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14. Found: C, 50.16; H, 4.23; N, 29.49. UV λ_{max}^{EtOH} mμ (log ε): 221 (3.98), 251 (4.14), 307 (3.83).

b) A mixture of 1.5 g of IX and 1.5 g of 2-methylthiosemicarbazide was heated at 150° for 1 hr. Ammonia was evolved during the reaction. Water was added to the reaction mixture and resulting precipitate was collected by filtration and recrystallized from EtOH to give 0.19 g of XIII as light brown crystals. The $CHCl_3$ extract of the mother liquor was shaken with 1N NaOH, and the alkaline solution was neutralized with 10% HCl, then extracted with $CHCl_3$. After removal of the solvent by evaporation, the residue was recrystallized from EtOH to give 0.07 g of XIII, mp 254—258° as colorless powder. The IR spectrum of this compound was identical with that of the compound prepared by method a.

1-Methyl-5-methylthio-3-*α*-pyridyl-1,2,4-triazole (V)——A mixture of 0.1 g of XIII in 5 ml of 2N NaOH and 0.15 g of CH_3I in 2 ml of EtOH was stirred at room temperature for 1 hr. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent by evaporation, the residue was recrystallized from isopropyl ether giving 0.075 g of colorless needles, mp 70—71°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.65; H, 4.99; N, 27.57. This was proved to be identical with compound B by mixed melting point determination and comparison of IR spectra.

1-Picolinoyl-4-methylthiosemicarbazide (XIV)——A mixture of 1.37 g of I, 0.37 g of methylisothiocyanate and 4 ml of EtOH was refluxed for 15 min. The solid formed was collected by filtration, washed with EtOH to give 1.73 g of colorless powder, mp 203—204° (decomp.). *Anal.* Calcd. for $C_8H_{10}ON_4S$: C, 45.70; H, 4.79; N, 26.65. Found: C, 45.77; H, 5.01; N, 26.57.

4-Methyl-3-*α*-pyridyl-1,2,4-triazoline-5-thione (XV)——A solution of 0.5 g of XIV in 3 ml of 1N NaOH was heated for 30 min at 130°. The solution had been cooled, neutralized with 10% HCl. The resulting precipitate was recrystallized from EtOH to give 0.388 g of colorless needles, mp 210—213°. *Anal.* Calcd. for $C_8H_8N_4S$: C, 49.88; H, 4.19; N, 29.14. Found: C, 50.27; H, 4.10; N, 29.06. UV λ_{max}^{EtOH} mμ (log ε): 218 (4.05), 252 (4.28), 303 (3.98).

4-Methyl-5-methylthio-3-*α*-pyridyl-1,2,4-triazole (VI)——A mixture of 1.0 g of XV in 6 ml of 5% NaOH and 1.5 g of CH_3I in 2 ml of EtOH was stirred at room temperature for 2 hr. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4. After the solvent had been removed, the residue was recrystallized from isopropyl ether giving 0.315 g of colorless needles, mp 68—70°. *Anal.* Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.30; H, 5.07; N, 26.97.

Determination of Ratios of IV:V:VI in the Products obtained by Methylation of III——The ratios of IV:V:VI in the products were determined by the intensity of each peak of the N-methyl groups of the compound in the products obtained by the following procedures.

a) Methylation of III with CH_3I: To a solution of 2.2 g of III in 2.5 ml of 1N NaOH, was added 0.21 g of CH_3I in 0.5 ml of EtOH and stirred for 10 hr at room temperature. The reaction mixture was extracted with 5 portions of 5 ml of $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4. Evaporation of the solvent under reduced pressure gave an oily product.

b) Methylation of III with Dimethyl Sulfate: A mixture of 0.2 g of III in 2.5 ml of 1N NaOH and 0.2 g of dimethyl sulfate was stirred for 10 hr at room temperature. The reaction mixture was extracted with five portions of 5 ml of $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4. Evaporation of the solvent under reduced pressure gave an oily product.

c) Methylation of III with Diazomethane: A mixture of 0.2 g of III in 2 ml of MeOH and 3 molar equivalent diazomethane in ether was allowed to stand over night at room temperature. Evaporation of the solvents and excess diazomethane gave an oily product.

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