ACTA CHEMICA SCANDINAVICA 19 (1965) 1135–1141

Alkyl Derivatives of 3-Amino-5-(2-furyl)-1,2,4-triazole

Part I. Synthesis of Alkylated 3-Amino-5-(2-furyl)-1,2,4-triazoles by Ring Closure of 1-Furoylaminoguanidines

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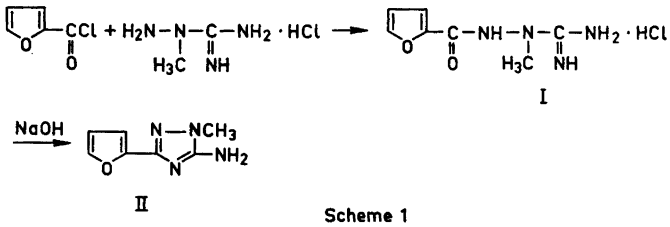
Alkylated 3-amino-5-(2-furyl)-1,2,4-triazoles and 3-imino-5-(2-furyl)-1,2,4-triazolines were obtained by cyclizing mono-, di-, and trialkylated 1-furoylaminoguanidines thermally or in alkaline solution. In this way, 3-amino-2-methyl- (II), 3-alkylamino-4-alkyl- (VIII), 3-dialkylamino- (XIII), and 3-dimethylamino-4-methyl-5-(2-furyl)-1,2,4-triazole (XV) were synthesized by alkaline ring closure. Thermal ring closure of 1-furoylamino-2-methylguanidine gave a mixture of 3-methylamino- and 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole (V and IV), whereas the alkaline ring closure gave only the 3-methylamino-derivative (V). Alkaline ring closure of 1,2-dimethyl-1-furoylaminoguanidine afforded a mixture of 5-(2-furyl)-2-methyl-3-methylamino-1,2,4-triazole (X) and 2,4-dimethyl-3-imino-5-(2-furyl)-1,2,4-triazoline (XI). 2,4-Dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (XVII) and 2,4-dimethyl-5-(2-furyl)-1,2,4-triazoline-3-one (XVIII) were obtained by alkaline ring closure of 1-furoylamino-1,2,3-trimethylguanidine. The 1-furoylaminoguanidines were prepared either by heating furoyl chloride with alkylated aminoguanidines without solvent or by treating furoylhydrazine with alkylated S-methylisothiourea. 2,2-Dialkyl-1-furoylaminoguanidine was synthesized from furoylhydrazine and dialkylcyanamide.

To study the alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole and the tautomerism of alkylated aminotriazole compounds, a number of mono-, di-, and trialkylated 3-amino-5-(2-furyl)-1,2,4-triazole and 3-imino-5-(2-furyl)-1,2,4-triazoline compounds were synthesized. Some of these derivatives were incapable of tautomerism, in others the tautomerism was limited.

Alkylated 3-amino-5-(2-furyl)-1,2,4-triazole compounds were obtained by cyclizing alkylated furoylaminoguanidines thermally or in alkaline solution. In certain reactions, the ring closure was unambiguous and could give only one alkyl derivative, while in other cases there were two possibilities thus giving two different alkyltriazole derivatives.

3-Amino-5-(2-furyl)-2-methyl-1,2,4-triazole was obtained by a method developed by Grinsteins and Cipens.[1,2] 1-Amino-1-methylguanidine hydrochloride and furoyl chloride were heated together without solvent. The furoylaminoguanidine (I) obtained was cyclized by boiling in alkaline solution. The ring closure of substance I is unambiguous and gives only the 2-alkyl derivative (II) (Scheme 1).

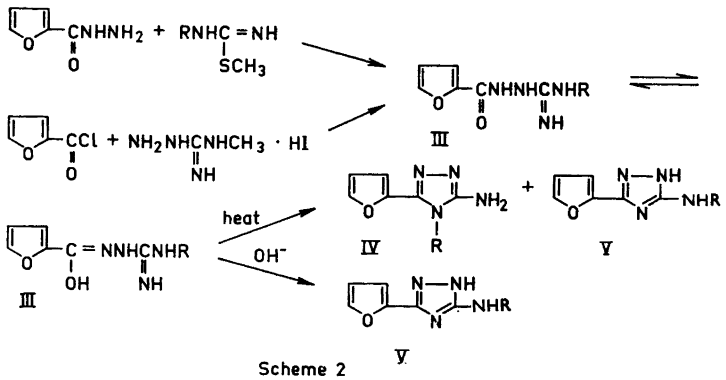


Scheme 1

2-Alkyl-1-furoylaminoguanidine (III) can cyclize to a triazole in two ways (Scheme 2). Both the imino- and the alkylamino group can react with the hydroxy group of the enol form of acylaminoguanidine (III) giving the 3-alkylamino and 4-alkyl derivative (V and IV). Gehlen *et al.*[3] have shown that cyclization of 1-acylamino-2-arylguanidine in alkaline solution gives the 3-arylamino derivative; in boiling water the 4-aryl derivatives is produced. However, when an aromatic acyl group was present, treatment with boiling water failed to effect any closure.

In accordance with the results reported by Gehlen *et al.*[3] no ring closure of 1-furoylamino-2-methylguanidine (III) was obtained in boiling water. However, cyclization of III could be achieved in boiling dimethylformamide, and 5-(2-furyl)-3-methylamino-1,2,4-triazole (V) and 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole (IV) were obtained in the proportion 1:1.8.

When the ring closure of 2-alkyl-1-furoylaminoguanidine (III) was performed in alkaline solution, the 3-alkylamino derivative V was the sole product.



Scheme 2

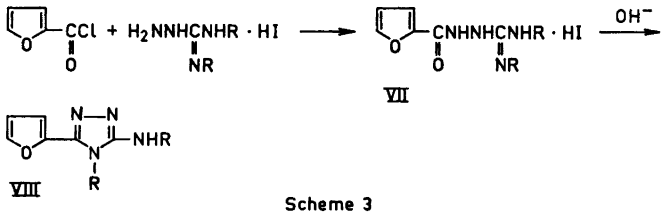
The cyclization reaction was studied by thin layer chromatography. The substances III—V have different R_F-values when developed in a sec. butanol-formic acid-water system. By thin layer chromatography the purity

of the products could also be established, and it was valuable in investigating methods for the separation of the two reaction products IV and V. The 3-alkylamino derivative (V), being a weak acid, could be extracted with dilute sodium hydroxide, leaving the insoluble 4-alkyl derivative (IV).

The structure of the two substances IV and V was verified by their chemical and spectroscopic properties. The 4-alkyl derivative (IV) had absorption bands in the IR-spectrum * characteristic of a primary amino group, and gave a benzylidene derivative.

1-Furoylamino-2-alkylguanidine (III) was synthesized by two different routes. In one method,[4] furoylhydrazide was treated with S-methyl-N-alkylthiourea for several days by room temperature, giving yields of III varying from 45 to 60 %. In the other method,[1,2] furoyl chloride was heated with 1-amino-2-alkylguanidine hydroiodide. However, the yield of the methyl derivative of III was very low with this latter method.

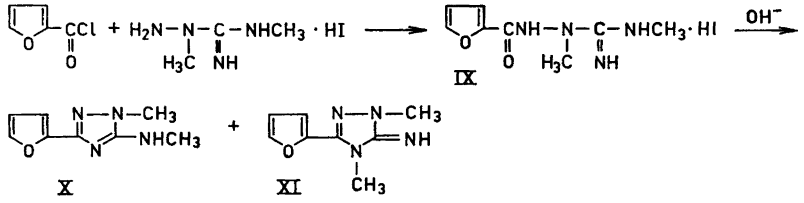
4-Alkyl-3-alkylamino-5-(2-furyl)-1,2,4-triazole (VIII) was obtained by melting together furoyl chloride and 1-amino-2,3-dialkylguanidine hydroiodide and then cyclizing the arylaminoguanidine (VII) obtained by boiling in alkaline solution. Identical alkyl substituents were chosen in order to obtain an unambigous ring closure reaction (Scheme 3).



Scheme 3

The ring closure of 1,2-dimethyl-1-furoylaminoguanidine (IX) may give two triazole derivatives but by analogy with the cyclization of 2-alkyl-1-furoylaminoguanidine (III) (Scheme 2) it was expected that cyclization of IX in alkaline solution would give 5-(2-furyl)-2-methyl-3-methylamino-1,2,4-triazole (X). It was found, however, that both X and 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (XI) were obtained (Scheme 4).

The structures of the two products X and XI were verified by their chemical behaviour and spectroscopic properties. It is known that imino heterocycles

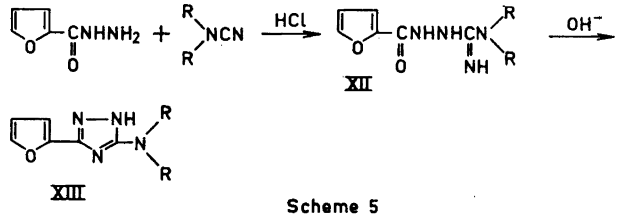


Scheme 4

* Part III. *Acta Chem. Scand.* **19** (1965) 1191.

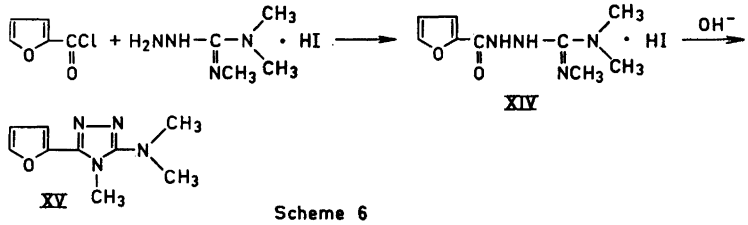
are stronger bases than amino heterocycles.[5,6] 2,4-Dimethyl-3-imino-5-(2-furyl)-1,2,4-triazole (XI) was found to be a very strong base with a pK_b-value of 4, while substance X was a weak base with a pK_b-value so high that it could not be determined in aqueous solution. Further, the UV-spectrum * of substance X had an absorption maximum in the same region as the other triazole derivatives described in this paper, while the imino compound XI had the absorption peak at longer wavelengths, in agreement with the UV-spectra of other imino heterocycles.[7]

3-Dialkylamino-5-(2-furyl)-1,2,4-triazole (XIII) was synthesized by a method developed by Cipens and Grinsteins.[8] Furoylhydrazine and dialkylcyanamide were heated in concentrated hydrochloric acid yielding 2-dialkyl-1-furoylaminoguanidine (XII), which was cyclized to XIII *in situ* with alkali. The structure of XIII was adduced from the unambiguous ring closure. (Scheme 5).



Scheme 5

3-Dimethyl-5-(2-furyl)-4-methyl-1,2,4-triazole (XV) was synthesized by melting together furoyl chloride and 1-amino-2-methyl-3-dimethylguanidine and then cyclizing the resulting acylaminoguanidine (XIV) in alkaline solution. The ring closure can only give one alkyltriazole compound (Scheme 6).



Scheme 6

2,4-Dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (XVII) was obtained similarly by fusion of furoyl chloride and 1-amino-1,2,3-trimethylguanidine hydroiodide followed by cyclization of the derivative obtained in alkaline solution (Scheme 7). The yield of XVII was very low. This may be due both to the impurity of 1-amino-1,2,3-trimethylguanidine hydroiodide and to the concomitant formation of 2,4-dimethyl-5-(2-furyl)-1,2,4-triazoline-3-one (XVIII). 1-Amino-1,2,3-trimethylguanidine hydroiodide was obtained [9] from

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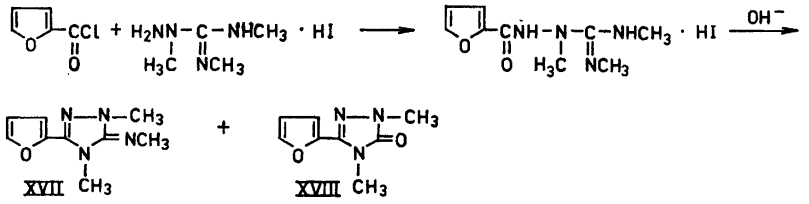
methylhydrazine and N,N¹,S-trimethylurea hydroiodide as an oil, which was characterized as its benzylidene derivative. The methylimino compound XVII was a very strong base and could only be isolated as a salt (Scheme 7).



Scheme 7

EXPERIMENTAL

3-Amino-5-(2-furyl)-2-methyl-1,2,4-triazole (II). A mixture of 54 g (0.44 mole) of 1-amino-1-methylguanidine hydrochloride and 57.5 g (0.44 mole) of furoyl chloride was heated at 130° for 30 min. Hydrogen chloride was evolved and the melt solidified. The reaction product was cooled and dissolved in 176 ml of 5 M sodium hydroxide and 75 ml of water. The solution was boiled for 2 h and then extracted with 10 × 50 ml of chloroform. After evaporation of the chloroform and recrystallization of the residue in benzene-acetone, 38 g (53 %) of (II) were obtained. M.p. 153–155°C. (Found: C 51.1; H 4.9; N 33.9. Calc. for $C_7H_8N_4O$ (164.1): C 51.2; H 4.9; N 34.1).

2-Alkyl-1-furoylaminoguanidine (III). 1 mole of furoylhydrazine and 1 mole of N-alkyl-S-methyl-isothiourea hydroiodide were dissolved in 50 ml of water and 500 ml of 2 M sodium hydroxide. Reaction occurred at room temperature with formation of a precipitate. A reaction time of about 64 h was necessary to get a satisfactory yield. The following derivatives were prepared:

1-Furoylamino-2-methylguanidine. Yield 62 %; m.p. 150–153°C (decomp.). (Found: C 45.9; H 5.9; N 30.4. Calc. for $C_7H_{10}N_4O_2$ (182.1): C 46.2; H 5.5; N 30.8).

2-Ethyl-1-furoylaminoguanidine. Yield 59 %; m.p. 162–165°C (decomp.). (Found: C 48.8; H 6.6; N 28.4. Calc. for $C_8H_{12}N_4O_2$ (196.1): C 49.0; H 6.2; N 28.6).

1-Furoylamino-2-propylguanidine. Yield 46 %; m.p. 163–165°C (decomp.). (Found: C 51.6; H 6.7; N 26.7. Calc. for $C_9H_{14}N_4O_2$ (210.1): C 51.4; H 6.7; N 26.7).

2-Allyl-1-furoylaminoguanidine. Yield 45 %; m.p. 158–160.5°C (decomp.). (Found: C 51.7; H 6.0; N 27.1. Calc. for $C_9H_{12}N_4O_2$ (208.1): C 51.9; H 5.8; N 26.9).

Ring closure of 2-alkyl-1-furoylaminoguanidine in alkaline solution. 1 mole of 2-alkyl-1-furoylaminoguanidine was dissolved in 1200 ml of 1 M sodium hydroxide. The alkaline solution was refluxed for 2 h and then cooled. By neutralization 3-alkylamino-5-(2-furyl)-1,2,4-triazole (V) precipitated. The product was recrystallized from acetone, acetonitrile or ethanol. The following derivatives were synthesized:

5-(2-Furyl)-3-methylamino-1,2,4-triazole (V). Yield 61 %; m.p. 238–240°C. (Found: C 51.0; H 5.2; N 34.3. Calc. for $C_7H_8N_4O$ (164.1): C 51.2; H 4.9; N 34.1).

3-Ethylamino-5-(2-furyl)-1,2,4-triazole (V). Yield 78 %; m.p. 210.5–214°C. (Found: C 53.8; H 5.8; N 31.5. Calc. for $C_8H_{10}N_4O$ (178.1): C 53.9; H 5.7; N 31.4).

5-(2-Furyl)-3-propylamino-1,2,4-triazole (V). Yield 73 %; m.p. 230–233°C. (Found: C 56.4; H 6.6; N 29.1. Calc. for $C_9H_{12}N_4O$ (192.1): C 56.2; H 6.3; N 29.2).

3-Allylamino-5-(2-furyl)-1,2,4-triazole (V). Yield 61 %; m.p. 209–212°C. (Found: C 56.9; H 5.4; N 29.3. Calc. for $C_9H_{10}N_4O$ (190.1): C 56.8; H 5.3; N 29.5).

3-Alkylamino-5-(2-furyl)-1,2,4-triazole (V) from furoyl chloride and 2-alkyl-1-aminoguanidine hydroiodide. 1 mole of 2-alkyl-1-aminoguanidine hydroiodide and 1 mole of furoyl chloride were melted together at 120° for 45 min. The resulting dark melt was cooled and dissolved in 1200 ml 2 M sodium hydroxide. The alkaline solution was refluxed

for 3 h. After cooling and neutralizing, 3-alkylamino-5-(2-furyl)-1,2,4-triazole (V) precipitated. The product was recrystallized from acetonitrile. The following derivatives were prepared:

5-(2-Furyl)-3-methylamino-1,2,4-triazole. Yield 12 %; m.p. 238–240°C.

3-Ethylamino-5-(2-furyl)-1,2,4-triazole. Yield 80 %; m.p. 209–212°C.

Thermal ring closure of 1-furoylamino-2-methylguanidine (III). 24.6 g (0.135 mole) of 1-furoylamino-2-methylguanidine (III) were heated in boiling dimethylformamide for 1 h. The solution was cooled and 10.7 g of 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole (IV) precipitated. M.p. 240.5–243.5°C. The mother liquor was evaporated. The residue was treated with 30 ml of 2 M sodium hydroxide leaving a further 1.5 g of substance IV as an insoluble residue. Total yield 58 %. (Found: C 51.3; H 5.1; N 34.0. Calc. for $C_7H_6N_4O$ (164.1): C 51.2; H 4.9; N 34.1).

By neutralization of the alkaline solution, 6 g of 5-(2-furyl)-3-methylamino-1,2,4-triazole (V) precipitated. Yield 27 %; m.p. 238–240°C.

3-Benzylideneamino-5-(2-furyl)-4-methyl-1,2,4-triazole. 0.2 g of 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole was boiled with 2 ml of benzaldehyde, until all had dissolved. The solution was cooled, and by addition of ether 0.15 g of a yellow substance precipitated. After recrystallization from carbon tetrachloride the substance melted at 171–172.5°C. (Found: C 66.1; H 4.5; N 22.4. Calc. for $C_{14}H_{12}N_4O$ (252.1): C 66.7; H 4.8; N 22.2).

5-(2-Furyl)-4-methyl-3-methylamino-1,2,4-triazole (VIII). 69 g (0.3 mole) of 1-amino-2,3-dimethylguanidine hydroiodide and 39 g (0.3 mole) of furoyl chloride were melted together at 150°C for 30 min. The resulting brown melt was chilled and dissolved in 300 ml of 2 M sodium hydroxide. The alkaline solution was refluxed for 2 h and then evaporated to dryness. The residue was extracted with boiling chloroform. The chloroform solution was evaporated and 26.4 g of 5-(2-furyl)-4-methyl-3-methylamino-1,2,4-triazole were obtained. The product was recrystallized from acetone. Yield 21.4 g (40 %); m.p. 186–188°C. (Found: C 53.0; H 5.9; N 31.7. Calc. for $C_8H_{10}N_4O$ (178.1): C 53.9; H 5.7; N 31.7).

4-Ethyl-3-ethylamino-5-(2-furyl)-1,2,4-triazole (VIII). 25.5 g (0.1 mole) of 1-amino-2,3-diethylguanidine hydroiodide and 13 g (0.1 mole) of furoyl chloride were melted together at 100°C for 35 min. The melt was cooled and recrystallized from acetonitrile. 19.8 g of 2,3-diethyl-1-furoylaminoguanidine hydroiodide were obtained. M.p. 176–178°C. This substance was cyclized by boiling in 60 ml of 2 M sodium hydroxide for 1 h. An oil precipitated, which crystallized by cooling. The product was recrystallized from acetone. Yield 11.1 g (54 %); m.p. 135.5–137.5°C. (Found: C 58.1; H 7.1; N 27.5. Calc. for $C_{10}H_{14}N_4O$ (206.1): C 58.2; H 6.9; N 27.2).

Ring closure of 1,2-dimethyl-1-furoylaminoguanidine (IX). 18.4 g (0.08 mole) of 1-amino-1,2-dimethylguanidine hydroiodide and 10.4 g (0.08 mole) of furoyl chloride were melted together at 115–120°C for 30 min. The brown melt obtained was dissolved in 110 ml of 2 M sodium hydroxide. The alkaline solution was refluxed for 2 h and then cooled and extracted with chloroform. The chloroform solution was dried with sodium sulphate and evaporated. The residue was an oil which did not crystallize. The oil was treated with ethanolic hydrochloric acid and 6.4 g of a mixture of the hydrochloride salts of 5-(2-furyl)-2-methyl-3-methylamino-1,2,4-triazole (X) and 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (XI) precipitated. This mixed product was extracted with acetone in a Soxhlet extraction apparatus for three days. Both substance X and XI dissolved in the acetone but 0.6 g of 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline hydrochloride (XI) remained undissolved in the thimble. M.p. 275–276°C (decomp.). (Found: C 45.1; H. 5.5; Cl 16.3; N 25.5. Calc. for $C_8H_{11}ClN_4O$ (214.7): C 44.8; H 5.2; Cl 16.5; N 26.1). The free base was obtained by dissolving the HCl-salt in 2 M sodium hydroxide and extracting the alkaline solution with chloroform. The chloroform solution was dried with sodium sulphate and evaporated. The residue was an oil which crystallized on washing with ether-petroleum ether. M.p. 61.5–65.5°C.

The ethanolic hydrochloric acid solution was evaporated. On heating the residue with acetone, 1 g of 5-(2-furyl)-2-methyl-3-methylamino-1,2,4-triazole hydrochloride (X) remained undissolved. M.p. 226–230°C. (Found: C 44.6; H 5.3; Cl 16.5; N 26.4. Calc. for $C_8H_{11}ClN_4O$ (214.7): C 44.8; H 5.2; Cl 16.5; N 26.1). The free base was obtained by dissolving the HCl-salt in 2 M sodium hydroxide and extraction of the alkaline solution with chloroform. The chloroform solution was dried with sodium sulphate and evaporated. The residue was an oil which was dissolved in ether. Addition of petroleum ether yielded

a crystalline precipite of the free base. M.p. 111—113.5°C. (Found: C 53.6; H 5.6, N 31.5. Calc. for $C_8H_{10}N_4O$ (178.1): C 53.9; H 5.7; N 31.4).

The two substances X and XI had different R_F-values on thin layer chromatography in sec. butanol-formic acid-water system. This fact was used to determine the purity of the two substances and was also very useful in the isolating operations.

3-Dialkylamino-5-(2-furyl)-1,2,4-triazole (XIII). 1 mole of furoylhydrazine and 1.1 mole of dialkylcyanamide were dissolved in 81 ml of conc. hydrochloric acid. The solution became warm and was placed on a water bath for 1.5 h. 510 ml of 2 M sodium hydroxide were added to the solution and it was then refluxed for another 40 min. The solution was chilled and the precipitate collected and recrystallized from ethanol-water. The following derivatives were prepared:

3-Dimethylamino-5-(2-furyl)-1,2,4-triazole. Yield 76 %; m.p. 190—192.5°C. (Found: C 53.7; H 5.6; N 31.3. Calc. for $C_8H_{10}N_4O$ (178.1): C 53.9; H 5.7; N 31.5).

3-Diethylamino-5-(2-furyl)-1,2,4-triazole. Yield 78 %; m.p. 145—146°C. (Found: C 58.2; H 7.0; N 27.2. Calc. for $C_{10}H_{14}N_4O$ (206.1): C 58.3; H 6.8; N 27.2).

3-Dimethylamino-5-(2-furyl)-4-methyl-1,2,4-triazole (XV). 4.9 g (0.02 mole) of 2-amino-1,3,3-trimethylguanidine hydroiodide and 2.6 g (0.02 mole) of furoyl chloride were heated together at 100°C for half an hour. Hydrogen chloride was evolved. After cooling, the melt was dissolved in 25 ml of 2 M sodium hydroxide and the alkaline solution was boiled for 2 h. The solution was chilled and extracted with chloroform. The chloroform phase was dried with sodium sulphate and evaporated giving 1.9 g of crystalline product. After recrystallization from ether-petroleum ether 1.5 g of XV were obtained (39 %). M.p. 84—86°C. (Found: C 56.4; H 6.2; N 29.1. Calc. for $C_9H_{12}N_4O$ (192.2): C 56.2; H 6.3; N 29.2).

2,4-Dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (XVII). 4 ml of furoyl chloride and 9.8 g of a crude oil of 1-amino-1,2,3-trimethylguanidine hydroiodide obtained from methylhydrazine and N,N^1,S-trimethyl-urea [9] were heated together at 110°C for 1.5 h. The resulting melt was cooled and dissolved in 50 ml of 2 M sodium hydroxide. The alkaline solution was boiled for 1.5 h and after cooling, extracted with ether. The 2,4-dimethyl-5-(2-furyl)-1,2,4-triazoline-3-one (XVIII) dissolved in the ether layer, while the imino compound (XVII) was insoluble. After evaporation of the ether and recrystallization of the residue from ether-ligroin, 0.9 g of XVIII, containing one mole of crystal water, was obtained. M.p. 50—55°C. (Found: C 48.4; H 5.9; N 22.0. Calc. for $C_8H_{11}N_3O_3$ (197.2): C 48.7; H 5.6; N 21.3). The mother liquor was evaporated to dryness. The residue was first boiled with ether to remove the remaining traces of substance XVIII and then boiled with chloroform. The chloroform solution was evaporated giving an oil. This was repeatedly washed with ether and then dissolved in etnanol. By addition of ether to the ethanol solution 0.3 g of 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline hydroiodide (XVII) precipitated. M.p. 206—210°C. (Found: C 33.8; H 4.2; I 38.9; N 17.8. Calc. for $C_9H_{13}IN_4O$ (320.1): C 33.8; H 4.1; I 39.6; N 17.8).

Acknowledgements. I am indebted to Prof. Arne Fredga for his kind interest in this investigation and to Dr. Kurt Skagius under whose guidance this work was carried out. Thanks are also due to Mr. S. O. Hall and Miss U. Löfroth for valuable assistance with parts of the experimental work.

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Received March 19, 1965.