

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

Part. II. Alkylation of 3-Amino-5-(2-furyl)-1,2,4-triazole

EVA ÅKERBLOM

Research Division, AB Pharmacia, Uppsala, Sweden

Alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole with methyl iodide in alkaline and neutral solution has been studied. It was found that methylation in alkaline solution gave a mixture of 1- and 2-methyl-3-amino-5-(2-furyl)-1,2,4-triazole. Methylation in neutral solution gave 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole, 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline, and 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline, and a substance the structure of which was not determined but which is probably derived from a quaternary furyl-triazole compound. The di- and trialkylated derivatives were presumably produced by further alkylation of the 4-methyl derivative. This was shown by studying the alkylation reaction of 1-, 2-, and 4-methyl-3-amino-5-(2-furyl)-1,2,4-triazole.

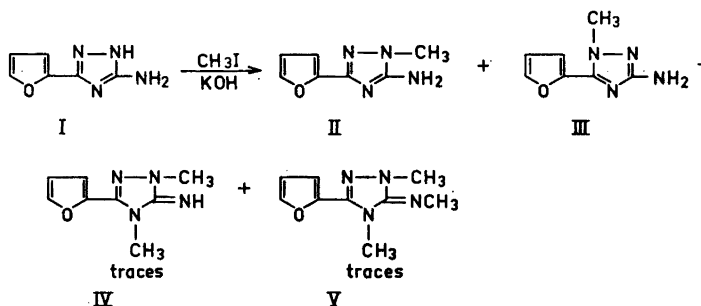
There is very little information in the literature about the alkylation reaction of 1,2,4-triazoles. Atkinson and Polya¹ have studied the alkylation of 5-phenyl- and 3-methyl-5-phenyl-1,2,4-triazole with methyl iodide in alkaline solution and with diazomethane in neutral solution. In this case, three isomeric N-methyl derivatives could theoretically be obtained but only the nitrogen atoms in 1- and 2-position were alkylated. The observed pattern of the N-methylation is in agreement with the calculated values of the π -electron densities at the nitrogen centres of the neutral molecule and of the anionic form of 1,2,4-triazole. By calculation, the nitrogen atom in the 4-position of the neutral molecule had the highest electron density while in the anionic form the values for the nitrogen atoms in the 1- and 2-position were higher.¹

In the alkylation of 3-amino-1,2,4-triazole, fourteen alkyl derivatives may theoretically be obtained, since di- and trialkylated derivatives may also be formed. Some results on the alkylation of amino-triazoles have been published but there seems to be no paper reporting a detailed study of all reaction products obtained. Most of the papers report only the predominating alkyl derivatives. Thus, Van Den Bos² has reported that alkylation of 3-amino-5-phenyl-1,2,4-triazole with ethyl iodide in alkaline solution gave the 1- and 2-ethyl derivatives. Cipens *et al.*³ found that when the same compound was

alkylated with dimethyl sulphate in neutral solution, 2,4-dimethyl-3-imino-5-phenyl-1,2,4-triazoline was obtained.

In this paper the results from the alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole with methyl iodide in neutral and alkaline solution are presented. The products obtained from the alkylation reaction were examined by thin layer chromatography and then isolated. The products were identified by comparing their chemical and spectroscopic properties with alkylated 3-amino-5-(2-furyl)-1,2,4-triazoles of known structure. The structures of the latter were established either by their mode of synthesis or by other methods.*

The alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole with methyl iodide in alkaline ethanolic solution gave a mixture of two alkyl derivatives (Scheme 1). One was 2-methyl-3-amino-5-(2-furyl)-1,2,4-triazole (II) and the other was, according to its elementary analysis, a monoalkyl derivative not identical with 2- or 4-methyl-3-amino-5-(2-furyl)-1,2,4-triazole or 5-(2-furyl)-3-methylamino-1,2,4-triazole. The only possible structure for the substance is therefore 1-methyl-3-amino-5-(2-furyl)-1,2,4-triazole (III). The IR-spectrum of this substance was also consistent with the structure III and showed bands characteristic of a primary amino group.** Substances II and III were obtained in approximately equal quantities. No other product could be isolated. However, thin layer chromatography of the reaction products suggested the presence of smaller quantities of 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (IV) and 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (V).



Scheme 1

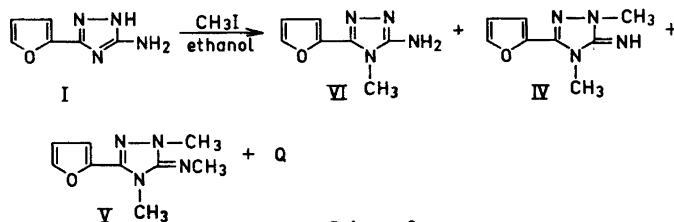
Alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole (I) with an equivalent quantity of methyl iodide in ethanol gave an oil from which 3-amino-4-methyl-5-(2-furyl)-1,2,4-triazole (VI), 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (IV) and the starting substance I were isolated (Scheme 2). These compounds were identified by their mobilities on thin layer chromatography, their IR-spectra and their melting points.

A product (Q) was also isolated from the oil but its structure has not been determined. The elementary analysis gave the composition $\text{C}_{12}\text{H}_{17}\text{N}_4\text{O}_2$,

* Part I. *Acta Chem. Scand.* **19** (1965) 1135.

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

and the product is not therefore an alkylated furyl triazole compound since the carbon content is too high. Quaternary products are probably produced during the alkylation reaction. Substance Q may have been produced by alkaline degradation of the triazole ring of the quaternary compounds during the isolation of the reaction products.



Thin layer chromatography of the reaction products also indicated the presence of a small quantity of 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (V) but it has not been possible to isolate this product. On the other hand, the presence of the 1- and 2-methyl derivatives (III and II) in the reaction mixture could not be established. Consequently, if the 1- and 2-methyl derivatives were formed they had presumably reacted further giving the di- and trialkylated derivatives. To verify this the alkylation of 1-, 2-, and 4-methyl-3-amino-5-(2-furyl)-1,2,4-triazole (III, II, and VI) was studied.

It was found that the 1-methyl derivative (III) was alkylated very slowly. Thin layer chromatography showed that a reaction time of 4 h at 60°C gave only traces of a reaction product. The 2-methyl derivative (II) gave on alkylation, 2,4-dimethyl-3-imino-5-(2-furyl)-1,2,4-triazoline (IV). A reaction time of 4 h at 60°C gave only a small quantity of IV. After 30 h about 25 % of substance II had been alkylated. The 4-methyl derivative (VI) was more readily alkylated than the two monoalkyl derivatives II and III. After 4 h at 60°C about 35 % of substance VI had been alkylated giving 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (IV) and a smaller quantity of 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (V).

These results show that during the alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole (I) in neutral solution, preferential alkylation of the 4-alkyl derivative (VI) affords the di- and trialkylated derivatives (Scheme 2). Thus, it may be deduced that for the alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole (I) in neutral solution, the nitrogen in 4-position is the most reactive centre. Further, the 4-methyl substituent in the triazole (VI) enhances the reactivity of the 2-position towards alkylation. However, in the anionic form of 3-amino-5-(2-furyl)-1,2,4-triazole (I), the nitrogen atoms at the 1- and 2-positions are the more nucleophilic centres and are alkylated in preference to the nitrogen atom in 4-position.

EXPERIMENTAL

Alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole (I) in alkaline solution. 7.5 g (0.05 mole) of 3-amino-5-(2-furyl)-1,2,4-triazole (I) were dissolved in 25 ml of an alkaline ethanolic solution containing 4.2 g (0.075 mole) of potassium hydroxide. To this solution

6.2 ml (0.1 mole) of methyl iodide dissolved in 10 ml of ethanol were slowly added during 30 min. Potassium iodide precipitated and the reaction mixture became warm. The mixture was stirred for 14 h at room temperature and finally filtered. 8.5 g (0.05 mole) of potassium iodide were collected. The ethanolic solution was evaporated to dryness and the residue, an oil, was dissolved in water. The pH of the water solution was adjusted to 8 and the alkaline solution extracted with chloroform. The chloroform solution was dried with sodium sulphate and evaporated. 7.6 g of an oil remained which crystallized on scratching. A thin layer chromatogram showed that the reaction product was a mixture of 3-amino-5-(2-furyl)-1-methyl-1,2,4-triazole (III) and 3-amino-5-(2-furyl)-2-methyl-1,2,4-triazole (II) and further indicated the presence of smaller quantities of 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (IV) and 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (V). The reaction product was recrystallized from benzene and 6.4 g of a mixture of II and III were obtained. M.p. 100–103°C. (Found: C 51.3; H 5.0; N 34.2. Calc. for $C_7H_8N_4O$ (164.1): C 51.2; H 4.9; N 34.1). This product gave no melting point depression with 3-amino-5-(2-furyl)-2-methyl-1,2,4-triazole (II); mixed m.p. 100–138°C. This indicated that the 2-methyl derivative was one component of the reaction mixture. This was also confirmed by the UV- and IR-spectra. From a quantitative IR-spectroscopic examination it could be established that the mixture contained 48 % of II and 52 % of III.

By treating the reaction product with 50 ml of absolute ethanol, 1.7 g of 3-amino-5-(2-furyl)-1-methyl-1,2,4-triazole (III) was left undissolved. M.p. 134–137°C. (Found: C 51.0; H 5.0; N 34.1. Calc. for $C_7H_8N_4O$ (164.1): C 51.2; H 4.9; N 34.1).

Thin layer chromatography of the aqueous solution, after extraction with chloroform, showed only spots corresponding to the 1- and 2-methyl derivatives (III and II). The 4-methyl derivative was not detected.

Alkylation of 3-amino-5-(2-furyl)-1,2,4-triazole in neutral solution. 7.5 g (0.05 mole) of 3-amino-5-(2-furyl)-1,2,4-triazole (I), 3.1 ml (0.05 mole) of methyl iodide and 100 ml of ethanol were placed in a sealed bottle. The bottle was placed in an oven at 80°C for 3 h. The solution obtained was cooled and the ethanol was evaporated. The residue was an oil which did not crystallize. By treating this oil with acetone 0.85 g of 2,4-dimethyl-3-imino-5-(2-furyl)-1,2,4-triazoline hydroiodide (IV) was left undissolved. M.p. 260–262°C. (Found: C 31.9; H 3.8; I 41.4; N 18.4. Calc. for $C_9H_{11}IN_3O$ (306.1): C 31.4; H 3.6; I 41.5; N 18.3). The IR-spectrum of the free base was identical with the IR-spectrum of substance IV synthesized by another route.*

The acetone solution was evaporated to dryness and the residue was dissolved in water. A dark-coloured oil remained. The pH of the solution was adjusted to 7 with sodium hydroxide. Upon cooling, 0.55 g of 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole (VI) precipitated. This substance gave no melting point depression with substance (VI), synthesized independently* and the IR-spectra of the two substances were identical.

The aqueous solution was extracted with chloroform. The chloroform solution was dried with sodium sulphate and evaporated giving 2 g of an oil. Thin layer chromatography showed that the oil consisted mainly of one product. By washing the oil with acetone-benzene, 0.7 of a crystalline product precipitated. The product was recrystallized from ethyl acetate. M.p. 200–203°C. (Found: C 58.0; H 6.8; N 22.4). Equivalent weight 245 determined by titration with acid. This substance may not be an alkylated furan triazole derivative since the percentage of carbon is too high. A structure has not been assigned to this compound.

The aqueous solution was finally evaporated. The residue was treated with acetone and an inorganic salt was filtered off. By evaporation of the acetone, 0.7 g of the starting material 3-amino-5-(2-furyl)-1,2,4-triazole (I) was recovered. Thin layer chromatography of the acetone solution indicated the presence of 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (V) in addition to the substances I, III, and IV. It has not been possible to isolate substance V.

Alkylation of 3-amino-5-(2-furyl)-1-methyl-1,2,4-triazole (III). 0.5 g (0.0031 mole) of 3-amino-5-(2-furyl)-1-methyl-1,2,4-triazole (III), 0.44 g (0.0031 mole) of methyl iodide and 10 ml of ethanol were mixed in a sealed bottle. The bottle was warmed for 4 h at 60°C. Thin layer chromatography of the reaction mixture showed that negligible reaction had occurred.

* Part I. *Acta Chem. Scand.* **19** (1965) 1135.

Alkylation of 3-amino-5-(2-furyl)-2-methyl-1,2,4-triazole (II). 2 g (0.0122 mole) of 3-amino-5-(2-furyl)-2-methyl-1,2,4-triazole (II), 1.73 g (0.0122 mole) of methyl iodide and 40 ml of ethanol were mixed in a sealed bottle. The bottle was warmed for 4 h at 60°C. Thin layer chromatography of the reaction product showed that only traces of II had reacted giving 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline (IV).

In a second experiment, the reaction time was prolonged to 20 h and 0.92 g (25 %) of 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline hydroiodide (IV) was obtained by cooling the reaction solution.

Alkylation of 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole (VI). 2 g (0.0122 mole) of 3-amino-5-(2-furyl)-4-methyl-1,2,4-triazole (VI), 1.73 g (0.0122 mole) of methyl iodide and 40 ml of ethanol were mixed in a sealed bottle. The bottle was warmed for 4 h at 60°C. By cooling 1.7 g of a mixture of the starting material VI and 2,4-dimethyl-5-(2-furyl)-3-imino-1,2,4-triazoline hydroiodide precipitated. This mixture had an iodide analysis of 27 % indicating that 30 % of VI had been alkylated. Thin layer chromatography showed that in addition to substance VI, a small quantity of 2,4-dimethyl-5-(2-furyl)-3-methylimino-1,2,4-triazoline (V) had been produced.

Acknowledgements. I am deeply indebted to Professor Arne Fredga for his kind interest in this investigation and to Dr. Kurt Skagius under whose guidance this work was carried out.

REFERENCES

1. Atkinson, M. R. and Polya, J. B. *J. Chem. Soc.* **1954** 3319.
2. Van den Bos, B. G. *Rec. Trav. Chim.* **79** (1960) 1129.
3. Cipens, G. and Grinsteins, V. *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* **1962** 263; *Chem. Abstr.* **59** (1963) 12790.

Received March 19, 1965.