SYNTHESES IN THE METHYL-2-FURYLKETONE SERIES

XI. Monofunctional Derivatives of 5- and 6-(Furyl)-1,2,4-Triazine*

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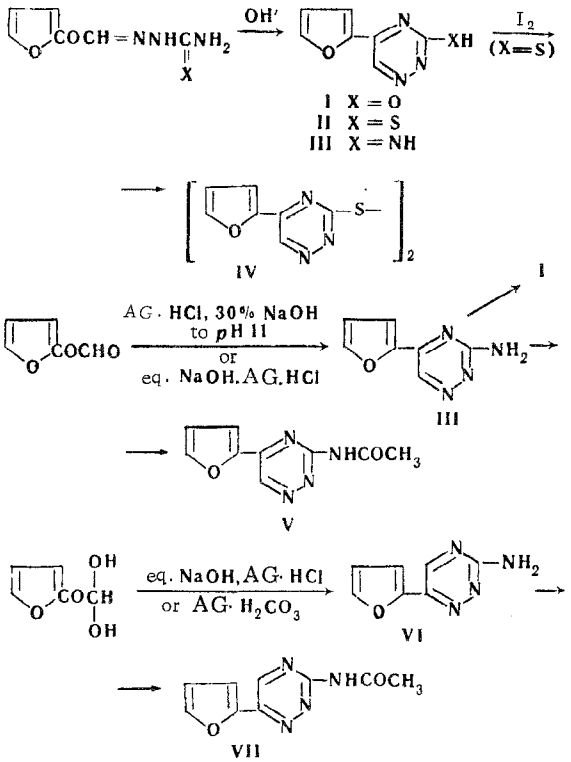
3-Hydroxy- (I), 3-mercapto- (II), and 3-amino-5-(2-furyl)-1, 2, 4-triazines (III) are prepared by cyclizing respectively the semicarbazone, thiosemicarbazone, and guanidylhydrazone of 2-furylglyoxal. Treatment of III with nitrous acid converts it to I. Iodine oxidizes II to the disulfide. Depending on the reaction conditions, 2-furylglyoxal hydrate and aminoguanidine, give 5- and also 6-(2-furyl)-substituted 3-amino-1, 2, 4-triazines. Under the same conditions the undehydrated furylglyoxal and aminoguanidine give only the 5-(2-furyl) derivative. Hydrochlorides and N-acetyl derivatives of the two amines are prepared.

Of monofunctional derivatives of 1,2,4-triazine containing furyl substituents, those mainly known are compounds whose derivation involves furyl (3-mercapto- [2], 3-amino- [3, 4], and 3-acetamino-5,6-bis(2-furyl)-1,2,4-triazines [4]).

The present paper describes synthesis of monofunctional derivatives of 5- and 6-(2-furyl)-1,2,4-triazines based on 2-furylglyoxal.



AG = aminoguanidine

Our previously prepared [5] 2-furylglyoxal semicarbazone is converted by boiling with sodium hydroxide into the sodium salt of 3-hydroxy-5-(2-furyl)-1,2,4-triazine, which by acidification with acetic or hydrochloric acid is converted into 3-hydroxy-5-(2-furyl)-1,2,4-triazine (I) itself. Similarly the action of sodium or potassium hydroxide on the furylglyoxal thiosemicarbazone [5] gives 3-mercapto-5-(2-furyl)-1,2,4-triazine (II), with a higher melting point than that given by Fatutta [6]. Ethanolic iodine oxidizes mercaptan II to disulfide IV.

While 5-nitro-2-furylglyoxal tends to form a biguanylhydrazone and not a mono- one [5], furylglyoxal gives mainly the monoguanylhydrazone. Treatment of the latter with alkali gives 3-amino-5-(2-furyl)-1,2,4-triazine (III). Its structure is shown both by its synthesis, and by its conversion, by the action of nitrous acid, to 3-hydroxy-5-(2-furyl)-1,2,4-triazine (I). The identity of the two hydroxy derivatives (obtained from the furylglyoxal semicarbazone and from III) is shown by their UV spectra and by the following qualitative reaction. Fusion with phenol, followed by addition of concentrated sulfuric acid gave (in both cases) a dark green color, changing to dark blue, converted to a cherry red on being made alkaline with sodium hydroxide.

We also investigated the possibility of preparing furyl-substituted 3-aminotriazines from furylglyoxal and aminoguanidine salts without isolating the guanylhydrazones. It was shown in [3, 7] that, depending on the reaction conditions, reaction of monosubstituted glyoxals and their hydrates with aminoguanidine can give 5- and 6-substituted aminotriazine or mixtures of these. For example, when phenylglyoxal hydrate is heated with an aqueous solution of aminoguanidine hydrochloride and then made strongly alkaline, 5-phenyl-3-aminotriazine is formed, while if an aqueous solution of phenylglyoxal hydrate is made weakly alkaline and aminoguanidine hydrochloride added, the product is 6-phenyl-3-aminotriazine, while if the two reactants are brought together in water without heating, and the solution then made strongly alkaline, a mixture of 5- and 6-phenyl derivatives is formed. Furthermore undehydrated tert-butyl glyoxal gave only 5-tert-butyl-3-amino-1,2,4-triazine [3].

In its reactions with aminoguanidine, furylglyoxal hydrate behaved similarly to phenylglyoxal hydrate. Boiling with an aqueous solution of aminoguanidine hydrochloride followed by making strongly alkaline gave III, whereas when furylglyoxal hydrate was made alkaline with about 1 equivalent of alkali, and then treated with aminoguanidine hydrochloride, the product was 3-amino-6-(2-furyl)-1,2,4-triazine (VI). The direct action of an aqueous aminoguanidine-bicarbonate

*For Part X see [1].

suspension with furylglyoxal hydrate also gave VI, whose formation could be expected by analogy with results described in the literature [8–10]. Like tert-butyl glyoxal [3], undehydrated furylglyoxal hydrate and aminoguanidine hydrochloride gives only III under the above conditions.

III and VI, as well as their hydrochlorides and acetyl derivatives, differ considerably in melting point, solubility, and UV spectrum. 5- and 6-(2-furyl)-3-amino-1,2,4-triazine give different color reactions when their melts with phenol are treated with concentrated sulfuric acid and then made alkaline with 30% sodium hydroxide solution. The melt of III with phenol gives an intense cherry red color when treated with sulfuric acid, vanishing and reappearing on adding alkali. The melt of VI with phenol was the color of strong tea when acidified and when made alkaline. The difference in color reaction is preserved when the amino group is acetylated.

EXPERIMENTAL

3-Hydroxy-5-(2-furyl)-1, 2, 4-triazine (I). 5.49 g (0.03 mole) 2-furyl-glyoxime semicarbazone [5] was boiled for 5 min in 90 ml 20% sodium hydroxide solution, the voluminous yellowish green precipitate of the sodium salt of the hydroxytriazine filtered off, washed with cold water, and dissolved in 50 ml boiling water. After treating with decolorizing charcoal, the solution was acidified with 6.6 ml glacial acetic acid (pH 5.8), and the precipitate filtered off and washed with water. Yield 2.42 g (49%), mp 258–260°, colorless needles, readily soluble in dioxane or water on heating, slightly soluble in ethanol, insoluble in cold water, mp 270–271° (decomp, ex dioxane or water). Found: C 51.85, H 3.22, N 25.80%. Calculated for $C_7H_5N_3O_2$: C 51.57, H 3.09, N 25.76%. UV spectrum (SF-4, in ethanol), λ_{max}, mμ (1g ε): 220 (3.48), 329 (4.29).

3-Mercapto-5-(2-furyl)-1, 2, 4-triazine (II). 12.0 g (0.061 mole) furylglyoxal thiosemicarbazone [5] was dissolved, with heating, in 80 ml 15% (0.085 mole) potassium carbonate or in 40 ml (0.2 mole) 20% sodium hydroxide. The solution was treated with decolorizing charcoal, and the filtrate, with cooling, acidified with 6 N hydrochloric acid to pH 2, II filtered off, washed with water, and air-dried. Yield 9.95 g (91%), mp 211–213°, orange-red glistening plates, mp 214°–215° (decomp, ex methanol). The literature gives [6] mp 200°–201°. Found: C 46.96, H 3.13, S 18.08%. Calculated for $C_7H_5N_3OS$: C 46.94, H 2.81, S 17.92%. UV spectrum (in ethanol), λ_{max}, mμ (1g ε): 235 (3.74), 250 (3.76), 310 (4.24), 325 (4.32).

Bis[5-(2-furyl)-1, 2, 4-triazinyl-3-]disulfide (IV). 0.90 g (5 mmole) II was suspended in 10 ml water and over a period of 30 min a solution of 0.64 g (2.5 mmole) iodine in 35 ml ethanol added, after which stirring was continued for 30 min longer, until the red mercaptan was completely converted to yellow disulfide. The latter was filtered off and washed with ethanol. Yield 0.83 g (93%), yellow needles, mp 205–206° (ex ethanol or dioxane). Found: C 47.07, H 2.35, S 17.83%. Calculated for $C_{14}H_8N_6O_2S_2$: C 47.18, H 2.26, S 18.00%. UV spectrum (in ethanol), λ_{max}, mμ (1g ε): 243 (4.29), 341 (4.54).

2-Furylglyoxal guanylhydrazone nitrate. A solution of 2.74 g (0.02 mole) aminoguanidine nitrate in 10 ml water was added to a solution of 2.50 g (0.02 mole) 2-furylglyoxal in 7 ml water, and after an hour the yellowish precipitate was filtered off, washed with water and dried in air. Yield 1.80 g (37%), white minute crystals, mp 183–184° (decomp, ex 1% nitric acid). Found: C 34.33, H 3.78, N 28.67%. Calculated for $C_7H_8N_4O_2 \cdot HNO_3$: C 34.56, H 3.70, N 28.80%. UV spectrum, λ_{max}, mμ (1g ε): 325 (4.08), 375 (4.16).

3-Amino-5-(2-furyl)-1, 2, 4-triazine (III). a) 1.0 g guanylhydrazone nitrate in 10 ml 30° potassium hydroxide solution was refluxed for 15 min, and then with cooling neutralized with 3.0 ml acetic acid. The precipitate was filtered off and washed with water, yield 0.30 g (45%), yellow needles, mp 231–232° (ex ethanol or dioxane). Soluble in water, ethanol, dioxane on heating, slightly soluble in the cold. Found: C 52.19, H 3.82, N 34.82%. Calculated for $C_7H_6N_4O$: C 51.85, H 3.70, N 34.55%. UV spectrum (in ethanol), λ_{max}, mμ (1g ε): 230 (4.13), 304 (4.02), 346 (3.99).

b) A solution of 9.62 g (0.077 mole) 2-furylglyoxal (or 10.90 g, 0.077 mole, of the hydrate) in 30 ml hot water was added to a solution of 9.2 g (0.08 mole) aminoguanidine hydrochloride in 92 ml water. The mixture was heated to boiling, and 50 ml 30% sodium hydroxide solution (0.375 mole) added, the solution cooled, and the precipitate filtered off, washed with ice-water, and dried at 100°. Yield 8.25 g (73%), mp 229–232°, pale yellow needles, mp 231–232° (ex ethanol, dioxane, or water). The UV spectrum was identical with that of the material prepared as described in a) above.

Hydrochloride. 1.0 g III was ground in a mortar with 4.0 ml concentrated hydrochloric acid, the white precipitate of salt filtered off, and washed with dry ethanol. Mp about 220° (decomp), not changed by recrystallizing from 6 N hydrochloric acid. Slightly soluble in cold water. Found: C 39.07, H 3.40, Cl 16.23%. Calculated for $C_7H_6N_4O \cdot HCl$: C 39.15, H 3.28, Cl 16.52%. UV spectrum (in ethanol), λ_{max}, mμ (log ε): 229 (4.20), 303 (4.09), 343 (4.06).

Picrate. Yellow needles, darkening at 214°, melting with decomposition at 218–219° (ex ethanol). Found: C 38.09, H 2.23, N 24.17%. Calculated for $C_7H_6N_4O \cdot C_6H_3N_3O_7$: C 37.95, H 2.21, N 23.85%.

3-Acetamido-5-(2-furyl)-1, 2, 4-triazine (V). 7.25 g (0.045 mole) III, 15 ml acetic anhydride, and 10 ml acetic acid were refluxed together for half an hour, cooled, diluted with water, and left overnight. The precipitate was filtered off, washed with water, and dried at 100°. Yield 8.0 g (86%). Pale yellow needles, mp 195–195.5° (ex ethanol). Found: C 53.18, H 3.97, N 27.33%. Calculated for $C_9H_8N_4O_2$: C 52.98, H 3.95, N 27.55%. UV spectrum (in ethanol) λ_{max}, mμ (1g ε): 233 (4.30), 333 (4.29).

Reaction of 3-amino-5-(2-furyl)-1, 2, 4-triazine with nitrous acid. A solution of 0.69 g (10 mmole) sodium nitrite in 7 ml water was added to a suspension of 0.58 g (3.5 mmole) III suspended in 22 ml 10% acetic acid, with shaking and ice cooling, the mixture was kept in an ice-bath for 1 hr 30 min, 3 drops concentrated sulfuric acid added, the mixture kept half an hour, heated at 50–60° for 1 hr, the temperature raised to 90°, the products left overnight at room temperature, and filtered when pale yellow prisms of I were obtained, yield 0.25 g (43%). Yellowish prisms, mp 264–266° (decomp, ex ethanol + dioxane). Found: C 51.70, H 2.76, N 25.52%. Calculated for $C_7H_5N_3O_2$: C 51.57, H 3.09, N 25.76%. The UV spectrum was identical with that of I.

3-Amino-6-(2-furyl)-1, 2, 4-triazine (VI). a) A solution of 3.8 g (25 mmole) furylglyoxal hydrate in 76 ml water was made alkaline with 3.40 ml (25 mmole) 30% sodium hydroxide, a solution of 2.75 g (25 mmole) aminoguanidine hydrochloride in 20 ml water added, and the whole left overnight, then the products were extracted with 400 ml ether. Evaporating off the ether gave 1.54 g (38%) VI, yellow glistening prisms, mp 162–163° (ex methanol). Found: C 52.03, H 4.01, N 34.80%. Calculated for $C_7H_6N_4O$: C 51.85, H 3.70, N 34.55%. UV spectrum (in ethanol), λ_{max}, mμ (1g ε): 281 (4.40), 365 (3.45).

b) 2.84 g (20 mmole) aminoguanidine-bicarbonate was stirred for 4 hr, heated on a water-bath for 30 min, and the products extracted with 350 ml ether. The ether was distilled off to give 1.68 g VI (52%) mp 161–162° (ex 10 parts of ethanol). Found: C 51.59, H 3.91, N 34.15%. Calculated for $C_7H_6N_4O$: C 51.85, H 3.70, N 34.55%. The UV spectrum resembled that described in a).

VI hydrochloride was prepared similarly to III. HCl. Yellowish crystals, mp 266–267°. Found: C 38.88, H 3.53, Cl 16.72%. Calculated for $C_7H_6N_4O \cdot HCl$: C 39.15, H 3.28, Cl 16.52%. UV spectrum (in ethanol), λ_{max}, mμ (1g ε): 281 (4.05), 351 (3.51).

3-Acetamido-6-(2-furyl)-1, 2, 4-triazine (VII). Prepared similarly to V. Yellow prisms, mp 212–213° (ex dilute ethanol). Found: C 53.01 H 4.09, N 27.70%. Calculated for $C_9H_8N_4O_2$: C 52.98, H 3.95, N 27.55%.

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