Communications to the Editor

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ISOLATION AND CHARACTERIZATION OF A NEW 5-AMINOFURYLTHIAZOLE FROM THE CATALYTIC REDUCTION OF 4-(5-NITRO-2-FURYL)THIAZOLE

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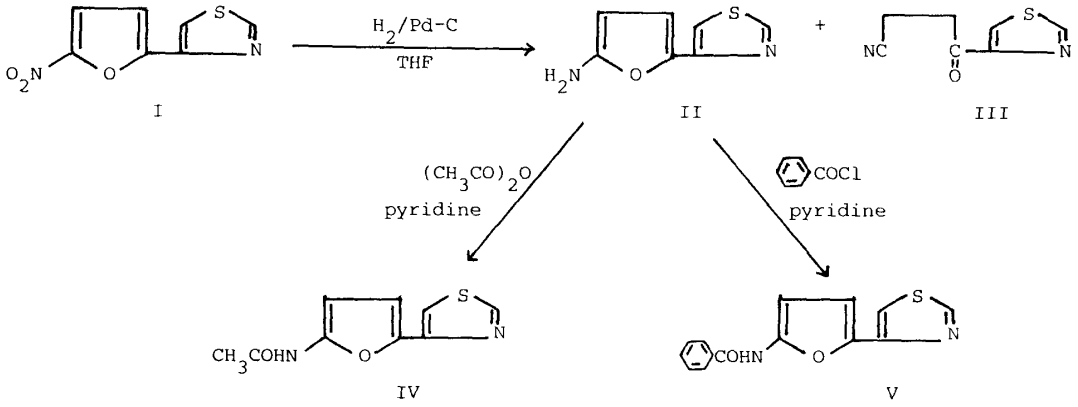
As a new extension of catalytic hydrogenation of 4-(5-nitro-2-furyl)thiazole, a convenient procedure for the synthesis of 4-(5-amino-2-furyl)thiazole has been developed using tetrahydrofuran and n-heptane to isolate enough 5-amino compound to determine the empirical formula. The 5-aminofurylthiazole was converted to 4-(5-acetylamino-2-furyl)thiazole and 4-(5-benzoylamino-2-furyl)thiazole. The stability of the 5-aminofuran ring in the pH 4.0 to 9.0 region was measured kinetically.

KEYWORDS ——— 4-(5-nitro-2-furyl)thiazole; 4-(5-amino-2-furyl)thiazole; 4-(5-benzoylamino-2-furyl)thiazole; 1-(4-thiazolyl)-3-cyano-1-propanone; catalytic reduction; half life

The 5-nitrofurans have been widely used as human and veterinary medicines, and as food preservatives and feed additives.[1a)] A large number of these compounds were shown to be carcinogenic[1b)] and mutagenic.[1c)] Certain typical members of this class, whose carcinogenic activity has been well-documented, include numerous 2-acylamino-4-(5-nitro-2-furyl)thiazole analogs such as 2-NH_2,[2,3)] 2-NHCHO,[4,5)] 2-$NHCOCH_3$,[5,6)] 2-$NHNH_2$,[2,7)] and 2-NHNHCHO.[8)] All biological effects seem to require the reduction of the 5-nitro group to a metabolically reactive intermediate.[1b,c,d)] Prior in vitro metabolic studies of several 5-nitrofurans demonstrated that the 5-nitro group was reduced easily by rat and mouse liver homogenates or cytosols.[9-12)] The postulated reduction products have not been identified conclusively as they are unstable and authentic samples have not yet been synthesized. Utilizing carcinogenic 4-(5-nitro-2-furyl)thiazole (I),[13)] structurally the least complex of these analogs, catalytic hydrogenation with palladium and activated carbon in tetrahydrofuran (THF) was examined. This report presents evidence that the reduction of I affords a new 4-(5-amino-2-furyl)thiazole (II) when n-heptane is used to minimize chemical instability during isolation procedures.

In recent studies,[11-15)] the component corresponding with the metabolite derived from enzymatic reduction has been isolated from chemically reduced 4-(5-nitro-2-furyl)thiazole and identified as 1-(4-thiazolyl)-3-cyano-1-propanone,[11,12)] which could have occurred through involvement of either 5-amino- or 5-hydroxylaminofuran as precursors. We are attempting to determine whether a 5-aminofuran is a precursor for 3-cyano-1-propanone structure.

The catalytic hydrogenation of I was successfully carried out in nonhydroxylic solvent systems (e. g., THF, ethyl acetate): I (2 g) was dissolved in THF (100 ml), and commercially available 5% Pd-C (2.5 g) was added. The mixture was stirred over hydrogen at 20 to 25°C for 18h under an atmospheric pressure. After removal of the catalyst by filtration, the solution was evaporated in vacuo below 35°C. The residue was extracted with a mixture of n-heptane (30 ml) and ethyl acetate (20 ml) at room temperature for 10 min with agitation. The extract was concentrated to 15 ml in vacuo below 35°C, during which period gummy materials, then crystals separated. The crystals were collected by suction and dissolved in a mixture of n-heptane (40 ml) and ethyl acetate (5 ml) below 50°C. The solution was concentrated to 10 ml in vacuo below 35°C to separate crystals which were purified by repetition of the above procedure to give 4-(5-amino-2-furyl)thiazole (II) as pale yellow needles, mp 105-106°C (300 mg). Anal. Calcd for $C_7H_6N_2OS$: C, 50.58; H, 3.63; N, 16.85. Found : C, 50.72; H, 3.67; N, 16.70. MS m/e : 166 (M^+). A solution of II in THF gives a reddish-orange color upon addition of the Ehrlich reagent (2% p-dimethylaminobenzaldehyde in 5% HCl methanolic solution). The insoluble materials left after the purification of II were extracted with THF (40 ml), and the extract was separated by silica gel column chromatography to give 30 mg of III, mp 116-118°C, which was confirmed by direct comparison with the authentic 1-(4-thiazolyl)-3-cyano-1-propanone (mp 116-118°C).[11] The authenticity of II was established by spectroscopic analysis. The IR spectrum (KBr) had bands at 3200 and 3360 cm^{-1} corresponding with the 5-amino group. The ^{1}H-NMR in $(CD_3)_2CO$ revealed chemical shifts at 8.78 ppm and 7.12 ppm as a doublet (J=2 Hz) corresponding with the thiazole ring protons, and at 6.55 and 5.12 ppm as a doublet (J=4 Hz) corresponding with the furan ring protons. The 5-amino proton was broad and weak but definite at 3.92 ppm. It disappeared upon addition of D_2O.



Acetic anhydride (5 ml) and pyridine (0.5 ml) were added to II (100 mg), and the mixture was stirred at 30°C for 5 h. At the end of the reaction, 10 ml of water was added and the solution was evaporated to dryness in vacuo below 30°C. The residue was redispersed in 10 ml of ice-cold water and the crystalline precipitate was filtered. The crystalline mass (60 mg) was dissolved in a small amount of ethyl acetate and then chromatographed on a column of silica gel using a mixture of ethyl acetate and n-heptane (3 : 1) as the eluting solvent. The eluate was concentrated to give IV as colorless needles, mp 168-170°C. This substance was identical with the authentic 4-(5-acetylamino-2-furyl)-thiazole (mp 168-170°C) reported previously.[12] It was isolated as a stable derivative, unlike earlier unsuccessful to isolate the amino analog.

Additionally, benzoylchloride (85 mg) and pyridine (0.2 mg) were added to a solution of II (100 mg) in THF (5 ml) at 0°C and the mixture was stirred at 5 to 10°C for 20 h. The reaction mixture was evaporated in vacuo below 30°C, and the residue was chromatographed on a column of silica gel using 5% ethyl acetate in benzene as the eluting solvent. The eluate was concentrated in vacuo and the residue was recrystallized from ethyl acetate and benzene to give 4-(5-benzoylamino-2-furyl)thiazole (V) as pale yellow needles, mp 139-141°C (90 mg). Its structural assignment was based on satisfactory elemental analysis [$C_{14}H_{10}N_2O_2S$], the mass spectrum [m/e : 270 (M^+)], the IR spectrum [ν_{max}^{KBr} cm^{-1}: 1650 (C=O)], and the ^{1}H-NMR spectrum [δ (d_6-DMSO) : 6.47 and 6.83 (1H, d, J=4 Hz, furan ring), 7.42-8.00 (5H, m, phenyl), 8.05 and 9.07 (1H, d, J=2 Hz, thiazole ring), 11.18 (1H, br s, amido disappeared with D_2O)]. The 5-acylaminofuran derivatives obtained are fairly stable, but their deacylation by hydrolysis resulted in the failure to isolate II as crystals during the entire course of the reaction.

In our preliminary experiments, the λ_{max} of II in methanol was observed at 296 nm, and the $t_{\frac{1}{2}}$ in a mixture of methanol and water was found to be within 50 min. Therefore, the change in concentration of II at different pH values was determined in situ by spectrophotometry. Figure 1 shows in a typical run a significant decrease in absorbance of II at 292 nm in the buffer solution of pH 7.0 with respect to time, while an increase in absorbance occurs at 236 nm corresponding with III. Half-lives of II in the pH 4.0 to 9.0 region were determined by measuring the rate constant (k_1) using the decrease in absorbance of II at 292 nm as shown in Table I. The 5-aminofuran is readily hydrolyzed in acidic buffers, but has distinctive stability with increase in basic buffers. The mechanism of nitroreduction to metabolically reactive intermediates may be further clarified at the stage of the aminofuran-thiazole structure.

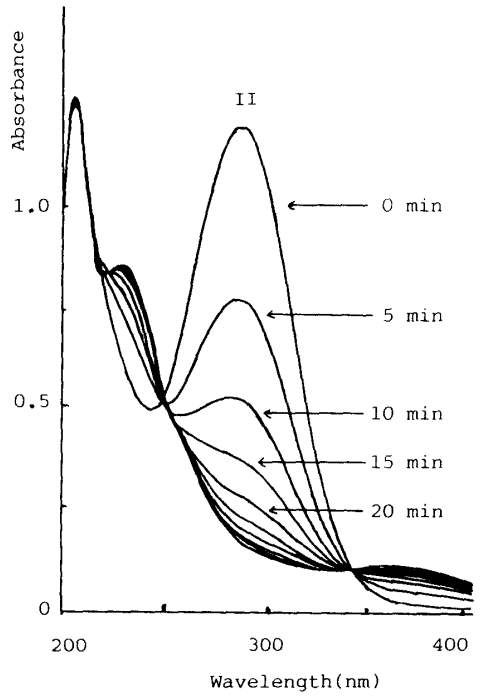


Fig. 1. Absorption Spectra of II with the Elapse of Time (min) at pH 7.0 [II] 2.71 x 10^{-4}; 25°C.

Table I. Rate Constant (k_1) and Half-Lives of II at 25°C ± 1

pH[a)]	k_1(min^{-1})	$t_{\frac{1}{2}}$(min)
4.0	6.07 x 10^{-2}	11.4
6.0	5.50 x 10^{-2}	12.6
8.0	4.44 x 10^{-2}	15.6
9.0	1.28 x 10^{-2}	54.2

a) As buffer solutions, a mixture of 0.1 M citric acid and 0.1 M trisodium citrate was used in the range of 4 to 5, a mixture of 0.2 M Na_2HPO_4 and 0.2 M NaH_2PO_4 in the range of 6 to 8, and a mixture of 0.25 M $Na_2B_4O_7$ and 0.1 M HCl for 9.

The results presented here demonstrate that the 5-aminofuryl-thiazole (II) is formed during the reductive metabolism of 4-(5-nitro-2-furyl)thiazole (I) and could act as a transient precursor for the formation of 1-(4-thiazolyl)-3-cyano-1-propanone (III).

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