

## CONVENIENT SYNTHESIS OF NICOTINAMIDE DERIVATIVES

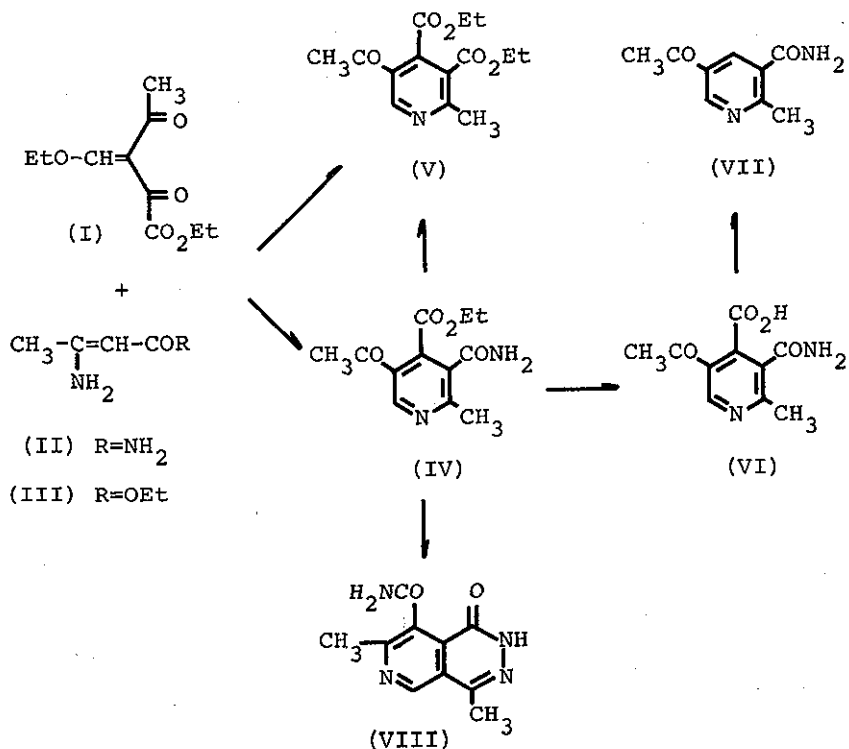
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A one-step synthesis of 5-acetyl-4-ethoxycarbonyl-2-methylnicotinamide(IV) by the reaction of ethyl 3-ethoxymethylene-2,4-dioxovalerate(I) with  $\beta$ -aminocrotonamide(II) was described, and this was easily converted to nicotinamide derivatives(VI, VII, and VIII).

In 1951, Jones<sup>1</sup> has reported that the reaction of ethyl hydroxymethyleneoxaloacetate with ethyl  $\beta$ -aminocrotonate gave diethyl 2-carboethoxy-1-methylvinylaminomethyleneoxaloacetate, which was then cyclized to triethyl 2-methyl-3,4,5-pyridinecarboxylate by treatment with concentrated sulfuric acid.

While Jones has also described the synthesis of ethyl 3-ethoxymethylene-2,4-dioxovalerate(I) which was assumed to be a good material for the synthesis of heterocyclic compounds, the reactivity of this compound has little attention<sup>2</sup>. The present communication describes the reaction of I with  $\beta$ -aminocrotonamide<sup>3</sup>(II).



Refluxing a mixture of I and II in ethanol for 5 hours afforded a 36% yield of 5-acetyl-4-ethoxycarbonyl-2-methylnicotinamide (IV) (mp 188-189°). Anal. Calcd. for  $C_{12}H_{14}N_2O_4$ : C, 57.59; H, 5.64; N, 11.20. Found: C, 57.58; H, 5.49; N, 10.94. Infrared (ir) spectrum  $\nu_{\max}(\text{KBr}) \text{ cm}^{-1}$ : 3400, 3200, 1725, 1690, and 1620. Nuclear magnetic resonance (nmr) spectrum (DMSO- $d_6$ )  $\delta$ : 1.30 (3H, t,  $J=6.5$  Hz,  $-\text{CH}_2\text{CH}_3$ ), 2.60 and 2.61 (each 3H, each s,  $2 \times \text{CH}_3$ ), 4.35 (2H, q,  $J=6.5$  Hz,  $-\text{CH}_2\text{CH}_3$ ), 7.85 and 8.15 (each 1H, each bs,  $-\text{NH}_2$ ),

8.40(1H, s, C<sub>6</sub>-H). Ultraviolet (uv) spectrum  $\lambda$  max (EtOH) (log  $\epsilon$ ) nm: 213(4.28), 240(3.93), and 275(3.58). Mass spectrum m/e : 250(M<sup>+</sup>).

Similarly reaction of I with ethyl  $\beta$ -aminocrotonate(III) gave a 58% yield of diethyl 5-acetyl-2-methyl-3,4-pyridinecarboxylate (V) (mp 68°). ir  $\nu$  max (KBr) cm<sup>-1</sup> : 1730, 1720, and 1710. nmr (DMSO-d<sub>6</sub>)  $\delta$  : 1.31(6H, m, 2  $\times$  -CH<sub>2</sub>CH<sub>3</sub>), 2.60 and 2.76 (each 3H, each s, 2  $\times$  CH<sub>3</sub>), 4.40(4H, m, 2  $\times$  -CH<sub>2</sub>CH<sub>3</sub>), and 8.60(1H, s, C<sub>6</sub>-H). This was alternatively obtained by treatment of IV with dry hydrogen chloride in refluxing ethanol<sup>4</sup>.

Compound IV which allowed to react with potassium hydroxide in ethanol gave the corresponding carboxylic acid(VI) (mp 187-188°), which was easily decarboxylated at this temperature to 5-acetyl-2-methylnicotinamide(VII) (mp 224-225°) in 92% yield. ir  $\nu$  max (KBr) cm<sup>-1</sup> : 3450, 3250, 1710, and 1690. nmr (DMSO-d<sub>6</sub>)  $\delta$  : 2.62(3H, s, -COCH<sub>3</sub>), 7.70 and 8.05 (each 1H, each bs, -NH<sub>2</sub>), 8.25(1H, d, J=3 Hz, C<sub>6</sub>-H), and 9.05(1H, d, J=3 Hz, C<sub>4</sub>-H).

Finally a number of derivatives of pyrido[3,4-d]pyridazine have been synthesized in connection with the relationship between the structure and diuretic activity<sup>5</sup>. Treatment of IV with hydrazine dihydrochloride gave 8-aminocarbonyl-4,7-dimethylpyrido[3,4-d]pyridazine-1(2H)-one(VIII) (mp over 300°) in good yield.

From these results, ethyl 3-ethoxymethylene-2,4-dioxovalerate (I) is useful for the synthesis of substituted nicotinamide derivatives, and the reaction of I with various kinds of amine, such as methyl- or phenylhydrazines, phenylhydroxylamine and so on, is in progress.

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