HETEROCYCLES, Vol. 6, No. 5, 1977

CONVENIENT SYNTHESIS OF NICOTINAMIDE DERIVATIVES

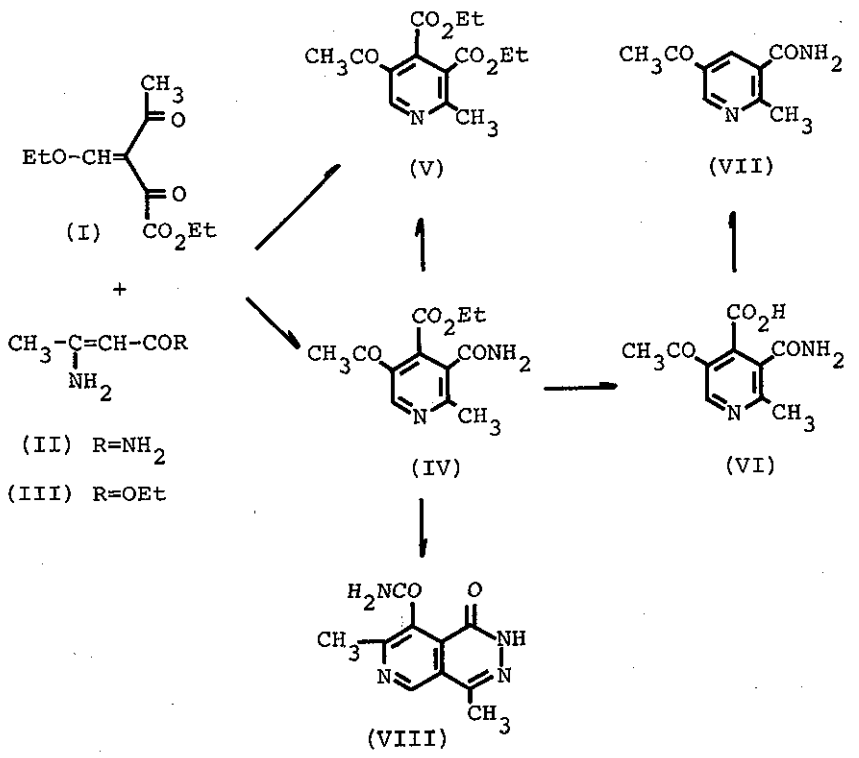
Takushi Kurihara* and Toshiko Uno

Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka, Japan

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

In 1951, Jones[1] has reported that the reaction of ethyl hydroxymethyleneoxaloacetate with ethyl β-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[2]. The present communication describes the reaction of I with β-aminocrotonamide[3](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 ν max(KBr) cm^{-1} : 3400, 3200, 1725, 1690, and 1620. Nuclear magnetic resonance(nmr) spectrum(DMSO-d_6) δ : 1.30(3H, t, J=6.5 Hz, $-CH_2\underline{CH_3}$), 2.60 and 2.61(each 3H, each s, 2 × $\underline{CH_3}$), 4.35 (2H, q, J=6.5 Hz, $-\underline{CH_2}CH_3$), 7.85 and 8.15(each 1H, each bs, $-\underline{NH_2}$),

8.40(1H, s, C_6-H). Ultraviolet(uv) spectrum λ max(EtOH)(log ε) nm: 213(4.28), 240(3.93), and 275(3.58). Mass spectrum m/e : 250(M^+).

Similarly reaction of I with ethyl β-aminocrotonate(III) gave a 58% yield of diethyl 5-acetyl-2-methyl-3,4-pyridinecarboxylate (V)(mp 68°). ir ν max(KBr) cm^{-1} : 1730, 1720, and 1710. nmr(DMSO-d_6) δ : 1.31(6H, m, 2 × $-CH_2CH_3$), 2.60 and 2.76(each 3H, each s, 2 × CH_3), 4.40(4H, m, 2 × $-CH_2CH_3$), and 8.60(1H, s, C_6-H). This was alternatively obtained by treatment of IV with dry hydrogen chloride in refluxing ethanol[4].

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 ν max(KBr) cm^{-1} : 3450, 3250, 1710, and 1690. nmr(DMSO-d_6) δ : 2.62(3H, s, $-COCH_3$), 7.70 and 8.05(each 1H, each bs, $-NH_2$), 8.25(1H, d, J=3 Hz, C_6-H), and 9.05(1H, d, J=3 Hz, C_4-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[5]. 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.

Acknowledgement

We thank Drs. S. Matsunaga and A. Numata for the measurements of mass and nmr spectra, and also Miss Y. Okano for the microanalyses.

REFERENCES

1. R.G. Jones, J. Am. Chem. Soc., 73, 5244(1951)
2. R.G. Jones, ibid., 73, 3684(1951)
3. T. Kato, H. Yamanaka and T. Schibata, Tetrahedron, 23, 2965(1967).
4. J.M. Bobbitt and D.A. Scola, J. Org. Chem., 25, 560(1960).
5. K. Omura, N. Tada, M. Tomimoto, Y. Usui, Y. Oka, and S. Yurugi, Chem. Pharm. Bull.(Tokyo), 24, 2699(1976).

Received, 28th February, 1977