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A FACILE SYNTHESIS OF 7-PHENYLPYRIDO[3,4-d]PYRIDAZINE-1,4(2H,3H)-DIONE

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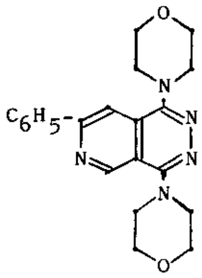
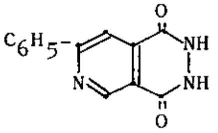
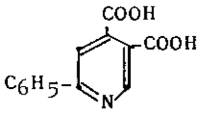
1,4-Cycloaddition reactions of 4-phenyloxazole (IV) with a variety of maleic acid derivatives were undertaken. Maleimide derivatives were proved to be the most efficient dienophiles, affording 1,4-cycloadduct, 3-phenyl-7-oxa-2-azabicyclo[2.2.1]hept-2-ene-5,6-dicarboximide derivatives (XII) in good yields.

Acid-catalyzed **dehydration** of XII, followed by the reaction of the resulting XIII with hydrazine, gave 7-phenylpyrido[3,4-d]pyridazine-1,4(2H,3H)-dione (II), which is the key compound for the synthesis of a potent diuretic, DS-511 (I). Structures of by-products formed in those reactions were elucidated.

7-Phenylpyrido[3,4-d]pyridazine-1,4(2H,3H)-dione (II) which is the key intermediate in the synthesis of 1,4-dimorpholino-7-phenylpyrido[3,4-d]pyridazine (I: DS-511), a potent diuretic[1], has been synthesized by the reaction of anhydride, ester or imide of 6-phenylpyridine-3,4-dicarboxylic acid (III) with hydrazine[2,3]. Although III has been available by employing Hantzch's method[4] or its modified procedures[5], those methods appeared to be rather disadvantageous for a large scale synthesis of I.


I: DS-511


II


III

As an alternative approach to III, we attempted a 1,4-cycloaddition reaction of maleic acid derivatives to 4-phenyloxazole (IV).

The 1,4-cycloaddition of maleic acid derivatives to alkyl-substituted oxazoles has been reported by Kondrat'eva[6], Miki[7], Bergen[8] and some others. As for the reaction with aryl-substituted oxazoles, however, only a few examples with poor yields have hitherto been reported[6].

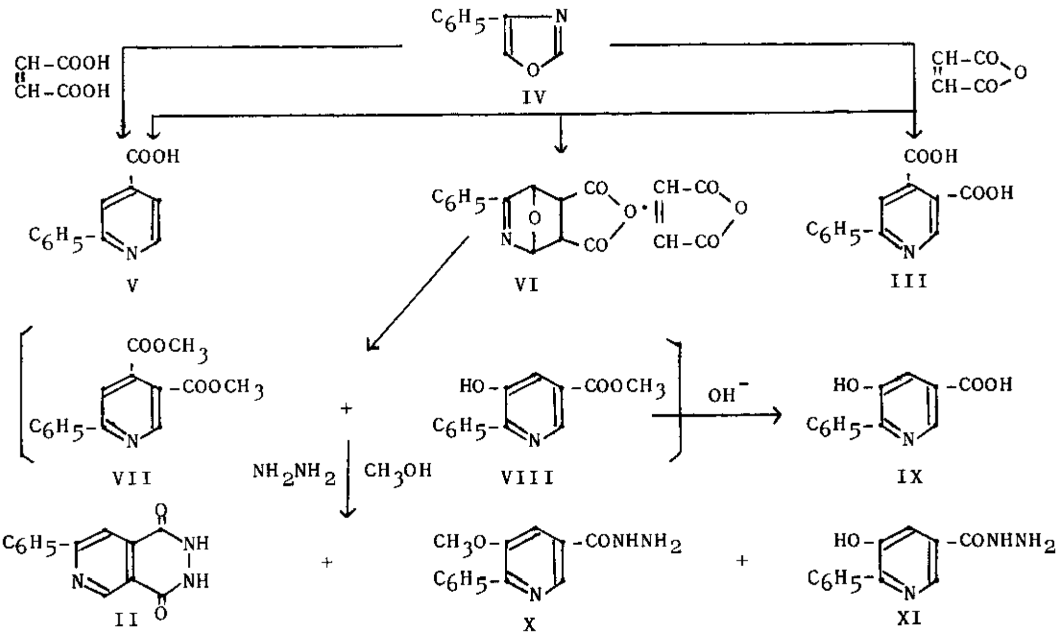


Figure 1

Although attempted reactions of IV with ethyl maleate under a variety of conditions were unsuccessful, it was found that the reaction with maleic acid occurred only when the mixture was fused at 110°, affording 2-phenylisonicotinic acid (V)^{9*}, mp 268-269°, in 65% yield. This result indicates that dehydration and mono-decarboxylation of the addition product occurred besides the expected 1,4-cycloaddition. However, the reaction of IV with 3 equivalent maleic anhydride at 85-90° for 3 h afforded the desired addition product, 3-phenyl-7-oxa-2-azabicyclo-[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride, as a maleic anhydride adduct (VI), mp 92-94°, in 75% yield, along with III^{10} and V as minor products. Refluxing a methanol solution of VI in the presence of sulfuric acid gave a mixture of dimethyl 6-phenylpyridine-3,4-dicarboxylate (VII) and methyl 5-hydroxy-6-phenylnicotinate (VIII), mp 212-213°. The structure of the latter was confirmed by elemental analysis and nmr, especially chemical shift and coupling constant of proton at the 2-position (Table 1) and by those of the corresponding carboxylic acid (IX), mp 296-298°, obtained by alkaline hydrolysis of VIII. Treatment of the resulting mixture of VII and VIII with 80% hydrazine hydrate under reflux in methanol for 3 h gave hydrazinium salt of II in 24% yield and 5-methoxy-6-phenylnicotinic

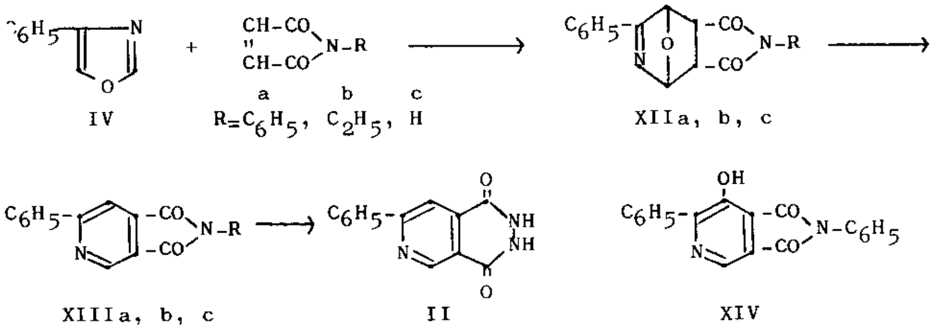


Figure 2

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* All compounds in this paper gave satisfactory elemental analyses.

acid hydrazide (X), mp 212-213°, in 25% yield in addition to 5-hydroxy-6-phenylnicotinic acid hydrazide (XI), mp 275-277°, as a minor product. (Figure 1)

The cycloaddition reaction was found to proceed more cleanly by employing N-phenylmaleimide as the dienophile. Thus, the reaction of IV with N-phenylmaleimide under reflux in benzene gave N,3-diphenyl-7-oxa-2-azabicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (XIIa), mp 183-185°, in 95.6% yield. Refluxing an ethanol solution of XIIa in the presence of an acid effected dehydration to give N,6-diphenylpyridine-3,4-dicarboximide (XIIIa), mp 238.5-241°, in 60-80% yield, accompanied by a dehydrogenated minor product, N,6-diphenyl-5-hydroxypyridine-3,4-dicarboximide (XIV), mp 227-229°. The ratio of XIII and XIV varied with the kind of acids and solvents used. Imide XIII could be directly led to II, mp 337-338°, in 96% yield by heating with 80% hydrazine hydrate in ethylene glycol at 108-110° for 50 min. The cycloaddition with N-ethylmaleimide and maleimide similarly proceeded to give XIIb, mp 163-164°, and XIIc, mp 209-210°, affording XIIIb, mp 163-164°, and XIIIc, mp 245-246°, by dehydration, respectively. XIIIb and XIIIc were also led to II in good yields. (Figure 2)

The steric configuration of VI and XII obtained in the above reaction was confirmed to be exo configuration by nmr, respectively. It showed that the spin-spin coupling between the protons at the 1- and 6-position or the 4- and 5-position is absent, while the protons of the 5- and 6-position form AB quartet with a coupling constant 6 Hz. These correponded to exo configuration which has nearly a right angle in dihedral angle containing $H-C_1-C_6-H$ or $H-C_4-C_5-H$ bonds and cis-form in $H-C_5-C_6-H$ bonds.

Table 1 NMR Spectral Data of 2-Phenylpyridine Derivatives and Related Compound (60 Mc)

Compound	Solvent	Chemical shifts (ppm)
III	NaOD+D$_2$O	7.36-7.88(5H, m, Ar$\underline{H}$) 7.67(1H, s, 5-H) 8.70(1H, s, 2-H)
V	d$_6$-DMSO	7.4-8.35(5H, m, Ar$\underline{H}$) 7.72(1H, dt, J 4 Hz, 5-H) 8.21(1H, s, 3-H) 8.76(1H, dt, J 4 Hz, 6-H)
VI	CDCl$_3$	3.2(2H, q, J 6 Hz, 5-H,6-H) 5.9(1H, s, 1-H or 4-H) 6.4(1H, s, 1-H or 4-H) 7.08(2H, s, C$\underline{H}$=C$\underline{H}$) 7.3-7.9(5H, m, Ar$\underline{H}$)
VIII	d$_6$-DMSO	3.90(3H, s, C$\underline{H}_3$) 7.75(1H, dt, J 2 Hz, 5-H) 8.7 (1H, dt, J 2 Hz 2-H) 10.6(1H, s, O$\underline{H}$) 7.3-8.0(5H, Ar$\underline{H}$)
IX	d$_6$-DMSO	7.3-8.0(5H, m, Ar$\underline{H}$) 7.73(1H, dt, J 2 Hz 4-H) 8.65(1H, dt, J 2 Hz, 2-H) 10.4(1H, br, O$\underline{H}$)
X	d$_6$-DMSO	3.88(3H, s, C$\underline{H}_3$) 4.5(2H, s, N$\underline{H}_2$) 7.8(1H, dt, J 2 Hz, 4-H) 8.65(1H, dt, J 2 Hz, 2-H) 9.95(1H, s, N$\underline{H}$) 7.2-8.0(5H, m, Ar$\underline{H}$)
XI	d$_6$-DMSO	4.35(2H, br, N$\underline{H}_2$) 7.20-7.95(5H, m, Ar$\underline{H}$) 7.58(1H, dt, J 2 Hz, 4-H) 8.42(1H, dt, J 2 Hz, 2-H)9.7(1H, br, N$\underline{H}$) 10.03(1H, br, O$\underline{H}$)
XIIa	d$_6$-DMSO	3.12(2H, q, J 6 Hz, 5-H,6-H) 6.16(1H, s, 1-H or 4-H) 6.30(1H, s, 1-H or 4-H) 7.05-8.0(10H, m, Ar$\underline{H}$)
XIIb	d$_6$-DMSO	1.0(3H, t, C$\underline{H}_3$) 2.85(2H, q, J 6 Hz, 5-H,6-H) 3.4 (2H, q, C$\underline{H}_2$) 6.10(1H, s, 1-H or 4-H) 6.25(1H, s, 1-H or 4-H) 7.2-7.9(5H, m, Ar$\underline{H}$)
XIIc	d$_6$-DMSO	3.0(2H, q, J 6 Hz, 5-H,6-H) 6.13(1H, s, 1-H or 4-H) 6.22(1H, s, 1-H or 4-H) 7.5-8.02(5H, m, Ar$\underline{H}$) 11.5(1H, s, N$\underline{H}$)

XIIIa	d_6-DMSO	7.2-8.4(10H, m, Ar$\underline{H}$) 8.48(1H, s, 5-H) 9.32(1H, s, 2-H)
XIIIb	$CDCl_3$	1.3(3H, t, C$\underline{H}_3$) 3.77(2H, q, C$\underline{H}_2$) 8.1(1H, s, 5-H) 9.1(1H, s, 2-H) 7.4-8.18(5H, m, Ar$\underline{H}$)
XIIIc	d_6-DMSO	7.4-8.2(5H, m, Ar$\underline{H}$) 8.2(1H, s, 5-H) 9.0(1H, s, 2-H) 11.5(1H, s, N$\underline{H}$)
XIV	d_6-DMSO	7.25-8.15(10H, m, Ar$\underline{H}$) 8.68(1H, s, 2-H)

The above results indicate that maleimide derivatives are the most appropriate dienophiles for the 1,4-cycloaddition to IV, providing a simple and profitable method for the synthesis of II. The nmr spectral data of the compounds obtained in the above reactions are listed in Table 1.

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