Synthesis of 2- and 6-Chloro-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridines

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A convenient synthesis of 2- and 6-chloro-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridines, **3** and **10**, utilizing the readily available amide **7** is described. Incorporation of the 3-*t*-butylamino-2-hydroxypropoxy side chain onto **3** provided **2**, a potential bioisostere of **1**. The antihypertensive activities of **2** and **12** were evaluated in the spontaneously hypertensive rat model.

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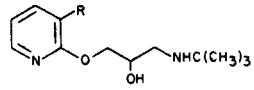
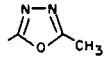
The antihypertensive activity of (*S*)-2-(3-*t*-butylamino-2-hydroxypropoxy)-3-cyanopyridine (**1**) has generated considerable interest into the synthesis and evaluation of other similarly substituted pyridines (1,2). In particular, a recent report by Adelstein and co-workers (3) has described a potency advantage in a series of antidiarrheal agents which occurs upon substitution of a cyano group by a 5-methyl-1,3,4-oxadiazolyl moiety. Therefore, it was of considerable interest to evaluate a similar modification of **1**, as illustrated by the 3-(5-methyl-1,3,4-oxadiazolyl)- derivative **2**. A survey of the literature revealed that neither 2-chloro-3-(5-methyl-1,3,4-oxadiazol-2-yl)-pyridine (3) the necessary intermediate for the synthesis of **2**, nor any positional isomer has been reported. In this communication, we wish to describe the synthesis of **3** and its conversion to **2**.



(S)-isomer

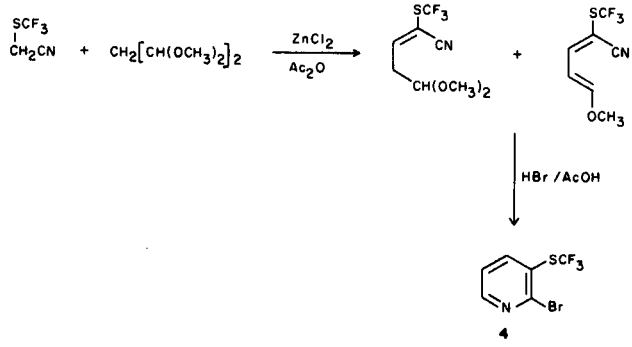
1 R = —CN

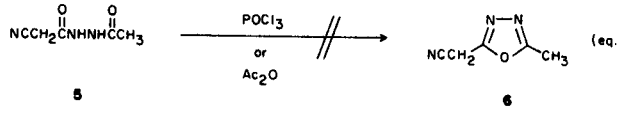
2 R = 

In a previous communication (4), we have described the synthesis of 2-bromo-3-trifluoromethylthiopyridine (**4**) *via* the condensation of trifluoromethylthioacetonitrile with 1,1,3,3-tetramethoxypropane followed by cyclization of the condensation product with hydrogen bromide/acetic acid, as outlined in Scheme I. Utilizing this synthetic strategy, we attempted to convert the hydrazide **5** (5) to (5-methyl-1,3,4-oxadiazol-2-yl)acetonitrile (**6**) (eq. 1). However, dehydration of **5** using either phosphorus oxychloride or acetic anhydride failed to yield oxadiazole **6** as determined by careful spectrographic examination of the reaction products. Thus, an alternate route directed toward the preparation of **3** was sought.

The high regioselectivity in the conversion of nicotinamide *N*-oxide (**7**) to yield 2-chloronicotinonitrile (6) raised the question as to whether that selectivity could

Scheme I





(eq. 1)

be extended to the reaction of the acyl hydrazide **9** with phosphorus oxychloride-phosphorus pentachloride. In essence, an oxadiazole ring closure could be accomplished in one step along with the introduction of the required leaving group into the 2-position, as illustrated in Scheme II. The required acyl hydrazide **9** was prepared in quantitative yield from nicotinoyl hydrazine (**8**) (7) on reaction with one equivalent of acetic anhydride in boiling acetic acid. Like amide **7**, dehydration and rearrangement of **9** occurred to give oxadiazole ring formation and halogen introduction, however, regioselectivity was not observed and a 1:1 mixture of the 2- and 6-chloro isomers was obtained in 50% yield. These two compounds could be conveniently separated by chromatography on silica gel and were characterized by ^{1}H nmr. The aminohydroxypropoxy side chain was incorporated by reaction of **3** with the potassium salt of (*S*)-2-phenyl-3-*t*-butyl-2-hydroxymethyloxazolidine (**11**) (8) in *t*-butyl alcohol followed by deprotection *via* acid hydrolysis of the oxazolidine moiety to afford a 36% yield of **2**. Likewise, treatment of **10** with **11** provided (*S*)-6-(3-*t*-butylamino-2-hydroxypropoxy)-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine (**12**) in 24% yield.

Oral antihypertensive activity was estimated in the

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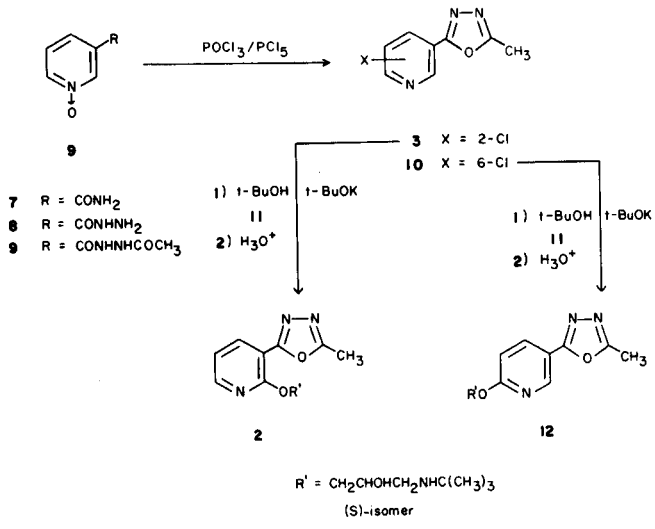
Scheme II



spontaneously hypertensive (SH) rats as described by Watson and Ludden (9). In this model, compound **2** lowered blood pressure 25 mm at 5 mg./kg. (p.o.) while **12** was essentially inactive at 20 mg./kg. (p.o.). Since the 3-cyano derivative **1** lowered blood pressure 30 mm at 0.312 mg./kg. (p.o.) (1) in the (SH) rat model, it is clear that the SAR found by Adelstein (3) is not generally applicable. In our particular example, such a substitution did not only fail to increase biological potency but actually had a severe negative input on the observed biological response.

EXPERIMENTAL

^{1}H Nmr spectra were determined in the indicated solvent on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken on an AEI MS 902 high resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The samples were processed by a DS50 data acquisition system. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Silica gel 60, 70-230 mesh, (E. Merck, Darmstadt) was used for column chromatography. Solutions were dried over sodium sulfate and concentrated to dryness using a Büchi rotary evaporator under water aspirator pressure (20 mm).

Nicotinoylhydrazine *N*-Oxide (**8**).

A mixture of **7** (10) (31 g., 0.22 mole) and hydrazine hydrate (80 ml.) was heated on a steam bath. After 0.5 hour, ethanol was added and the solid filtered to yield 26 g. of **8** (76%), m.p. 230° (lit. (7) m.p. 230°); ^{1}H nmr (deuteriohydrochloric acid/deuterium oxide): δ 5.4 (3H, exch.), 8.13 (1H, dd, J = 8 and 6), 8.67 (1H, dt, J = 8 and 2), 8.93 (1H, dt, J = 6 and 2) and 9.2 (1H, t, J = 2).

N'-Nicotinoyl-*N*^{2}-acetylhydrazine *N*-Oxide (**9**) (11).

A solution of **8** (25.4 g., 0.17 mole), acetic acid (85 ml.) and acetic anhydride (16.9 g., 0.17 mole) was heated at reflux for 1.5 hours. After cooling, the solution was diluted with ether and the solid filtered to yield 32 g. of **9** (100%) of m.p. 210-212°; ^{1}H nmr (DMSO-d_6): δ 1.97 (1H, s), 7.67 (2H, m), 8.42 (1H, dt, J = 6 and 2), 8.6 (1H, s), 10.0 (1H, s, exch.) and 10.6 (1H, bs, exch.).

Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.09; H, 4.63; N, 21.14.

2-Chloro-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine (**3**) and 6-Chloro-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine (**10**).

A mixture of **9** (30 g., 0.15 mole), phosphorus oxychloride (120 ml.) and phosphorus pentachloride (42 g., 0.2 mole) was heated at reflux. After 1.5 hours, the mixture was concentrated to dryness. The residual oil was treated with ice-water and extracted with ether and methylene chloride (2x). After concentration of the organic layers, the residue was chromatographed on silica gel to yield three main fractions: *A* containing 7.2 g. of **10**, *B* containing 1.3 g. of a mixture of **3** and **10**, and *C* containing 6.8 g. of **3** (total 15.3 g., 50%).

An analytical sample of **3** was prepared by recrystallization of fraction *C* from *n*-butyl chloride, m.p. 127-129°; ^{1}H nmr (deuteriochloroform): δ 2.6 (3H, s), 7.33 (1H, dd, J = 8 and 5), 8.22 (1H, dd, J = 8 and 2) and 8.43 (1H, dd, J = 5 and 2); ms: m/e M^+ 195, (M + 2) 197.

Anal. Calcd. for $C_8H_6ClN_3O$: C, 49.12; H, 3.09; N, 21.48. Found: C, 49.35; H, 3.06; N, 21.77.

An analytical sample of **10** was prepared by recrystallization of fraction *A* from *n*-butyl chloride, m.p. 147-149°; ^{1}H nmr (deuteriochloroform): δ 2.67 (3H, s), 7.47 (1H, d, J = 8), 8.33 (1H, dd, J = 8 and 2) and 9.0 (1H, d, J = 2); ms: m/e M^+ 195, (M + 2) 197.

Anal. Calcd. for $C_8H_6ClN_3O$: C, 49.12; H, 3.09; N, 21.48. Found: C, 48.93; H, 2.94; N, 21.86.

(*S*)-2-(3-*t*-Butylamino-2-hydroxypropoxy)-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine Maleate Salt (**2**).

Into a flamed out flask was placed *t*-butyl alcohol (50 ml.), potassium (0.4 g., 0.01 g.-atom) and **11** (2.35 g., 0.01 mole). The mixture was heated with stirring at 70° until the evolution of hydrogen ceased. Then, **3** (1.95 g., 0.01 mole) was added and the mixture heated at 70° for 15 hours. After concentration, the residue was treated with water (100 ml.) and acetic acid (6 g., 0.1 mole) and stirred 5 hours at room temperature. The solution was basified with saturated sodium carbonate solution and extracted with chloroform (3x). Concentration of the organic layer yielded a residue which was treated with maleic acid and the resulting salt crystallized from 2-propanol/ether to yield 1.5 g. (36%) of **2**, m.p. 127-128°; ^{1}H nmr (DMSO-d_6): δ 1.33 (9H, s), 2.6 (3H, s), 3.33 (2H, m), 4.33 (3H, m), 6.1 (2H, s, olefinic protons of maleic acid), 7.27 (1H, dd, J = 8 and 6) and 8.33 (2H, m).

Anal. Calcd. for $C_{15}H_{22}N_4O_3 \cdot C_4H_4O_4$: C, 54.02; H, 6.20; N, 13.26. Found: C, 53.60; H, 6.43; N, 13.05.

(*S*)-6-(3-*t*-Butylamino-2-hydroxypropoxy)-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine Maleate Salt (**12**).

Using essentially the same procedure described for the preparation of **2**, compound **12** was obtained in 24% yield as the maleate salt, m.p. 155-156°; ^{1}H nmr (deuteriochloroform) of the free base: δ 1.15 (9H, s), 2.6 (3H, s), 2.73 (2H, m), 3.93 (1H, p), 4.4 (2H, d, J = 5), 6.87 (1H, d, J = 8), 8.17 (1H, dd, J = 8 and 2) and 8.72 (1H, d, J = 2).

Anal. Calcd. for $C_{15}H_{22}N_4O_3 \cdot C_4H_4O_4$: C, 54.02; H, 6.20; N, 13.26. Found: C, 54.01; H, 6.14; N, 13.26.

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(11) Prepared as described in reference 5.