Synthesis and Anticonvulsant Activity of 3-[3-[(Dimethylamino)-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine

Vinod K. Arora and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta,
Edmonton, Alberta, Canada T6G 2N8

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Wolff-Kishner reduction of 3-amino-4-(*o*-chlorobenzoyl)pyridine (**3**) afforded 3-amino-4-(*o*-chlorobenzyl)pyridine (**5**), which on subsequent reaction with triethyl orthoformate and then acetyl hydrazide yielded 1-acetyl-2-[*N*-[4-(*o*-chlorobenzyl)pyridin-3-yl]formimidoyl]hydrazone (**7**). Cyclization of hydrazone **7** gave 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine (**8**), which on Jones oxidation yielded 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine (**9**). The Mannick reaction of 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine (**9**) with aqueous formalin and dimethylamine hydrochloride afforded 3-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)-pyridine (**10**). 3-[3-[(Dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (**10**) exhibited good anticonvulsant activity in the subcutaneous pentylenetetrazole anticonvulsant screen indicating that an appropriately substituted-pyridine ring moiety can serve as a bioisostere of a chlorobenzene ring with respect to anticonvulsant activity.

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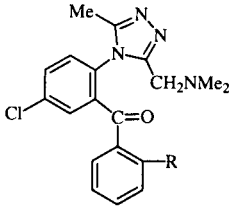
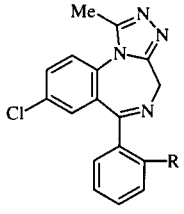
Introduction.

A novel type of 5-chloro-2-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenones (**1**) exhibit potent sedative, muscle relaxant and anticonvulsant activities [1]. It was subsequently proposed that 5-chloro-2-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenones (**1**) may act as prodrugs due to their *in vivo* conversion by enzymatic *N*-demethylation and then chemical cyclization to the pharmacological active benzodiazepine analogs **2** [2].

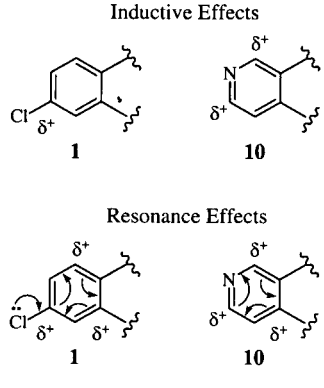


1a, R = H
1b, R = Cl



2a, R = H (alprazolam)
2b, R = Cl (triazolam)

It is well documented that introduction of an electron-withdrawing substituent (Cl, Br, NO_2, CF_3) at the C-7 position of 1,4-benzodiazepin-2-ones results in a significant enhancement of anxiolytic activity. In contrast, introduction of an electron-donating substituent at the C-7 position, or any substituent at the C-6, C-8 or C-9 positions, causes a decrease in potency [3]. Accordingly, this study was undertaken to investigate the hypothesis that a suitably substituted-pyridine ring system as in 3-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (**10**) is bioisosteric with the chlorobenzene ring in 5-chloro-2-[3-[(dimethylamino)-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (**1**) due to their similar size and shape, and the fact that both ring systems possess similar electron-density profiles at equivalent positions. For example, comparison of the inductive and resonance effects for the chloro substituent and ring nitrogen in 5-chloro-2-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenones (**1**) and 3-[3-[(dimethylamino)-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (**10**) (see Figure 1) show the resulting electron-densities are qualitatively similar for both compounds at the same position. Conditions are therefore suitable for 5-chloro-2-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenones (**1**) and 3-[3-[(dimethylamino)-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (**10**) to interact with the same receptor site(s), and for **10** also to exhibit anticonvulsant activity.



1 **10**

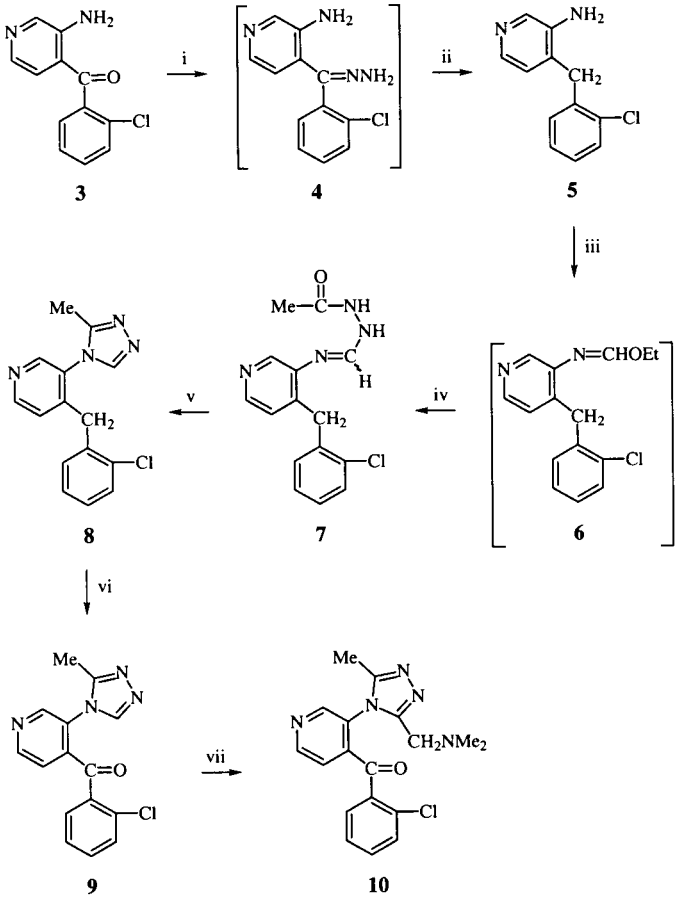
Figure 1. A comparison of the inductive and resonance effects exhibited by the chloro subtituent in a chlorobenzene (**1**) and the ring nitrogen atom in a pyridine ring (**10**).

Chemistry.

Reduction of 3-amino-4-(*o*-chlorobenzoyl)pyridine (**3**) using hydrazine monohydrate and potassium hydroxide under Wolff-Kishner conditions afforded 3-amino-

4-(*o*-chlorobenzyl)pyridine (**5**) in 62% yield (see Scheme 1). Reaction of 3-amino-4-(*o*-chlorobenzyl)pyridine (**5**) with triethyl orthoformate gave the intermediate forminino ether **6** which on further reaction with acetyl hydrazide yielded 1-acetyl-2-[*N*-[4-(*o*-chlorobenzyl)pyridin-3-yl]formimidoyl]hydrazone (**7**) in 55% yield. The subsequent cyclization of 1-acetyl-2-[*N*-[4-(*o*-chlorobenzyl)pyridin-3-yl]formimidoyl]hydrazone (**7**) at 80° during six hours using pyridine as solvent afforded 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine (**8**) in 53% yield. Oxidation of 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)-pyridine (**8**) using Jones reagent (chromium trioxide, sulfuric acid, water) in hot glacial acetic acid yielded 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (**9**) in 76% yield. 3-(3-Methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (**9**) was elaborated using a Mannick reaction to the target product 3-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (**10**) upon treatment with 37% aqueous formalin in the presence of dimethylamine hydrochloride at 70° for twenty-four hours in 22% yield.

Scheme 1 [a]



[a] Reagents and conditions: i, $H_2NNH_2 \cdot H_2O$, diethylene glycol, 160°, 16 hours; ii, KOH, 140°, 8 hours; iii, $HC(OEt)_3$, 3-amino-4-(*o*-chlorobenzyl)pyridine•HCl catalyst, 120°, 8 hours; iv, $MeCONHNH_2$, EtOH, 50°, 9 hours; v, pyridine, 80°, 6 hours; vi CrO_3, H_2SO_4, HOAc, 80°, 24 hours; vii, 37% formalin, Me_2NH•HCl, diglyme, 70°, 24 hours.

Biological Results.

The anticonvulsant activities of 3-[3-[(dimethylamino)-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)-pyridine (**10**) against subcutaneous pentylenetetrazole and maximal electroshock induced seizures, which are models for absence (petit mal) and generalized tonic clonic (grand mal) epilepsy, respectively were determined [4]. The title compound 3-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (**10**) was active in the subcutaneous pentylenetetrazole test (ED_{50} = 7.84 mg/kg intraparietoneal (ip dose), but inactive in the maximal electroshock test (ED_{50} > 150 mg/kg ip dose) at thirty minutes, respectively. The ED_{50} value for the standard reference drugs in these screens were clonazepam (subcutaneous pentylenetetrazole, ED_{50} = 0.02 mg/kg; maximal electroshock, ED_{50} = 86.6 mg/kg) and valproic acid (subcutaneous pentylenetetrazole, ED_{50} = 148.6 mg/kg; maximal electroshock, ED_{50} = 271.7 mg/kg). These results suggest that the pyridine ring in 3-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (**10**) is bioisoteric with the central chlorobenzene ring of 2',5-dichloro-2-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (**1b**) due to their mutual ability to bind to the same receptor site.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capilliary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H nmr) were recorded on a Bruker AM-300 spectrometer. The assignment of exchangeable protons (N*H*) was confirmed by the addition of deuterium oxide. The progress of reactions was monitored using Machery-Nagel Polygram SilG/UV_{254} precoated thin layer chromatography (tlc) plates, 0.25 mm in thickness. Silica gel column chromatography was carried out using Merck 7734 (70-230 mesh) silica gel. 3-Amino-4-(*o*-chlorobenzoyl)pyridine (**3**) was prepared according to the literature procedure [4].

3-Amino-4-(*o*-chlorobenzyl)pyridine (**5**).

A mixture of 3-amino-4-(*o*-chlorobenzoyl)pyridine (7.75 g, 33 mmoles) and hydrazine monohydrate (6.8 ml, 140 mmoles) in diethylene glycol (50 ml) was heated at 160° for sixteen hours with stirring. Monitoring reaction progress by silica gel thin layer chromatography using benzene-methanol (85:15, v/v) as development solvent indicated that conversion of 3-amino-4-(*o*-chlorobenzoyl)pyridine (R_f = 0.51) to the corresponding hydrazone intermediate (**4**, R_f = 0.41) was complete. The reaction mixture was cooled to 60°, pulverized potassium hydroxide (11.22 g, 200 mmoles) was added in small aliquots and the reaction was allowed to proceed at 140° for eight hours with stirring at which time evolution of nitrogen gas had ceased. After cooling to 25°, the reaction mixture was poured onto ice-cold sodium hydroxide solution (25 ml of 5% w/v), and this mixture was extracted with benzene (4 x 50 ml). The organic extracts were dried (magnesium sulfate) and the solvent was removed *in vacuo* to afford an oil, which was purified by silica

gel column chromatography using chloroform-methanol (95:5, v/v) as eluant. Recrystallization of the product from ether-hexane afforded 3-amino-4-(*o*-chlorobenzyl)pyridine (4.5 g, 62%), mp 71-73°; ^{1}H nmr (deuteriochloroform): δ 3.63 (br s, 2H, NH_2), 3.90 (s, 2H, CH_2), 6.74-7.42 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-5), 7.00-7.42 (m, 4H, phenyl hydrogens), 7.95 (d, 1H, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-6), 8.04 (s, 1H, pyridine H-2).

Anal. Calcd. for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81. Found: C, 66.24; H, 4.91; N, 12.89.

1-Acetyl-2-[*N*-[4-(*o*-chlorobenzyl)pyridin-3-yl]formimidoyl]-hydrazone (**7**).

A mixture of 3-amino-4-(*o*-chlorobenzyl)pyridine (10.61 g, 49 mmoles), triethyl orthoformate (13.6 g, 117 mmoles) and a catalytic quantity of 3-amino-4-(*o*-chlorobenzyl)pyridine hydrochloride [0.9 g, 3 mmoles; prepared by passage of dry hydrogen chloride gas through an ice-cold solution of the amine (1.0 g) in dry ether (50 ml) until the solution was saturated, filtration of the white solid formed, washing the solid with dry ether and drying the solid provided the amine hydrochloride salt (1.1 g)] was heated at 120° for eight hours. Ethanol produced in the reaction evaporated from the reaction mixture. Removal of excess triethyl orthoformate *in vacuo* at 60° afforded a near quantitative yield of the imino intermediate product **6**; ^{1}H nmr (deuteriochloroform): δ 1.02 (t, J = 7.0 Hz, 3H, CH_2CH_3), 4.12 (s, 2H, benzyl CH_2), 4.35 (q, J = 7.0 Hz, 2H, OCH_2), 6.90 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-5), 7.07-7.45 (m, 4H, phenyl hydrogens), 7.66 (s, 1H, N=CH), 8.07 (s, 1H, pyridine H-2), 8.26 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-6). A solution of the imino compound **6** in absolute ethanol (75 ml) and acetyl hydrazide (23.7 g, 320 mmoles) was heated at 50° for nine hours with stirring. The reaction mixture was cooled to 25°, the insoluble product was removed by filtration, washed with ice-cold dry ethanol and dried *in vacuo*. Recrystallization from *n*-propanol-hexane afforded 1-acetyl-2-[*N*-[4-(*o*-chlorobenzyl)pyridin-3-yl]formimidoyl]hydrazone as a white solid (8.0 g, 55%), mp 162-163°; ^{1}H nmr (deuteriodimethyl sulfoxide) (mixture of *syn* and *anti* imines and nitrogen-to-carbonyl rotameric amide species): δ 1.89, 1.93, 2.06 and 2.11 (four s, 3H total, $COCH_3$), 4.09 and 4.15 (two s, 2H total, CH_2), 6.63-9.00 (complex m, 8H total, pyridine and benzene hydrogens, =C*H*), 10.1-10.55 (m, 2H, N*H*-N*H*).

Anal. Calcd. for $C_{15}H_{15}ClN_4O$: C, 59.50; H, 4.99; N, 18.51. Found: C, 59.28; H, 4.99; N, 18.41.

3-(3-Methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine (**8**).

A suspension of 1-acetyl-2-*N*-[4-(*o*-chlorobenzyl)pyridin-3-yl]-formimidoyl]hydrazone (5.75 g, 19 mmoles) in diglyme (50 ml) was heated at 80° to give a clear solution at which time pyridine (5 ml) was added, and then the reaction was allowed to proceed for an additional six hours at 80° with stirring. Removal of the solvent under high vacuum gave an oil which was purified by silica gel column chromatography using ethyl acetate-methanol (75:25, v/v) as eluant. Recrystallization of the elution product from ethyl acetate-hexane afforded 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine as colorless needles (2.88 g, 53%), mp 113-115°; ^{1}H nmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 6.90-7.40 (m, 5H, pyridine H-5, benzene hydrogens), 8.12 (s, 1H, triazole H-5), 8.42 (s, 1H, pyridine H-2), 8.64 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-6),

Anal. Calcd. for $C_{15}H_{13}ClN_4$: C, 63.27; H, 4.60; N, 19.68. Found: C, 63.11; H, 4.48; N, 19.74.

3-(3-Methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (**9**).

Chromium trioxide (2.88 g, 28.8 mmoles), distilled water (7.8 ml) and then concentrated sulfuric acid (2.88 ml) were added consecutively to a solution of 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzyl)pyridine (2.88 g, 10 mmoles) in glacial acetic acid (10 ml) and the reaction was allowed to proceed with stirring at 80° for 24 hours. After cooling to 25°, the reaction mixture was poured onto chilled aqueous sodium hydroxide (50 ml of 5% w/v). Extraction with ethyl acetate (2 x 25 ml), washing the extracts with brine (50 ml), drying the ethyl acetate extract (magnesium sulfate) and removal of the solvent *in vacuo* yielded a yellow solid. Recrystallization from ethyl acetate-hexane yielded 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (2.3 g, 76%), mp 135-137°; ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 3H, CH_3), 7.32-7.52 (m, 4H, benzene hydrogens), 7.62 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-5), 8.06 (s, 1H, triazole =C*H*), 8.64 (s, 1H, pyridine H-2), 8.94 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-6).

Anal. Calcd. for $C_{15}H_{11}ClN_4O \cdot 1/10H_2O$: C, 59.95; H, 3.76; N, 18.64. Found: C, 59.57; H, 3.71; N, 18.67.

3-[3-[(Dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (**10**).

A mixture of 3-(3-methyl-4*H*-1,2,4-triazol-4-yl)-4-(*o*-chlorobenzoyl)pyridine (0.30 g, 1.0 mmole), 37% w/v aqueous formalin (0.25 ml, 3 mmoles) and dimethylamine hydrochloride (0.20 g, 3 mmoles) in diglyme (5 ml) was heated at 70° for twenty-four hours with stirring. After cooling to 25°, the reaction mixture was neutralized with ice-cold 10% w/v aqueous sodium bicarbonate solution. Extraction with chloroform (3 x 10 ml), drying the chloroform extract (magnesium sulfate) and removal of the solvent at 50° *in vacuo* gave a residue that was purified by silica gel column chromatography. Elution with ethyl acetate-methanol (75:25, v/v) gave a semi-solid which was recrystallized from ethyl acetate-hexane to afford 3-[3-[(dimethylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-4-(*o*-chlorobenzoyl)pyridine (80 mg, 22%) as colorless crystals, mp 107-108°; ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 6H, $N(CH_3)_2$, 2.24 (s, 3H, triazole C-5 CH_3), 3.38 (s, 2H, CH_2), 7.31-7.50 (m, 4H, benzene hydrogens), 7.53 (d, $J_{5,6}$= 5.0 Hz, 1H, pyridine H-5), 8.64 (s, 1H, pyridine H-2), 8.92 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridine H-6).

Anal. Calcd. for $C_{18}H_{18}ClN_5O \cdot 1/10H_2O$: C, 60.45; H, 4.91; N, 19.41. Found: C, 60.12; H, 5.13; N, 19.59.

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