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SYNTHESIS OF 2-CYANOMETHYL-1-METHYLPIPERIDINE

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Abstract: An improved method for the synthesis of 2-cyanomethyl-1-methylpiperidine is reported.

Recently, two reports have been published on the synthesis of the phenothiazine drug, thioridazine (**I**).[1,2] These reports describe the synthesis of both the racemic and the enantiomerically pure form of **I** as well as its deuterated analog. Thioridazine is used as an anti-psychotic agent while its deuterated analog can be used in metabolic and pharmacokinetic studies and as an internal standard for GC-MS assays (see reference 1). In both the published reports, 2-cyanomethyl-1-methylpiperidine (**II**, or its deuterated form) has been used as the precursor leading to the formation of **I**. Synthesis of **II** has been achieved via two different routes, as shown in Scheme I (reference 1 and 2). In both these routes, 2-chloromethyl-1-methyl-piperidine (**III**), which is formed *in situ* in the

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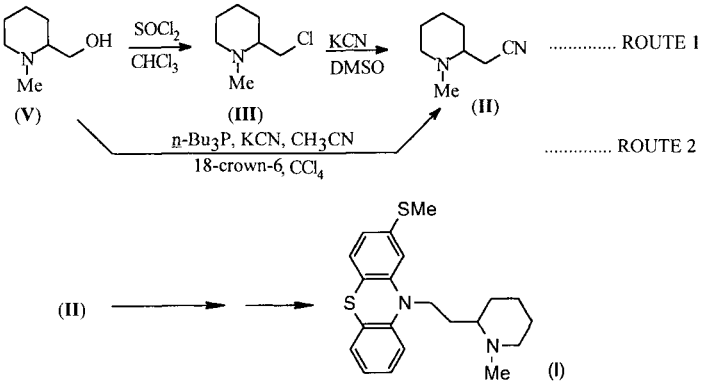
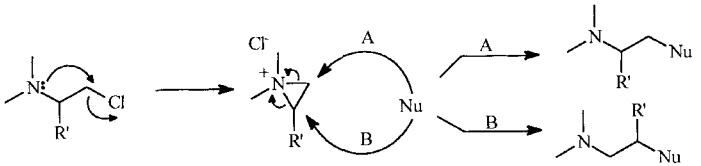
case of Route 2, was treated with KCN or NaCN, which resulted in the formation of **II**.



Scheme I

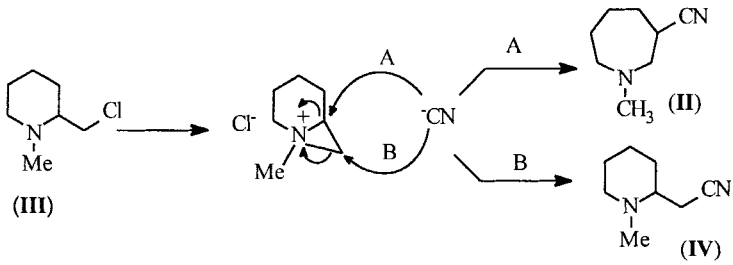
β-Chloroamines have previously been reported to undergo substitution reactions with various nucleophiles via a reaction pathway involving an aziridinium intermediate (Scheme II).[3] Ring opening of this aziridinium intermediate by a nucleophile can give rise to the formation of two regioisomers (see pathways A and B, Scheme II).



Nu = Nucleophile

Scheme II

The formation of isomeric products in the substitution reactions of 2-chloromethyl-1-methylpyrrolidine and other similar aliphatic β–chloroamines has been reported.[3,4] Based on these studies it might be expected that substitution reactions of **III** utilized in the preparation of **II** could give rise to the formation of two isomeric products, as shown in Scheme III. Pathway 'B' would give rise to the piperidine derivative **II**, whereas pathway 'A' would afford the 1-azacycloheptane derivative **IV**. It was, therefore, surprising to us that the reported syntheses of **II** that utilize the chloro derivative **III**, did not produce any of the isomeric product **IV**.



Scheme III

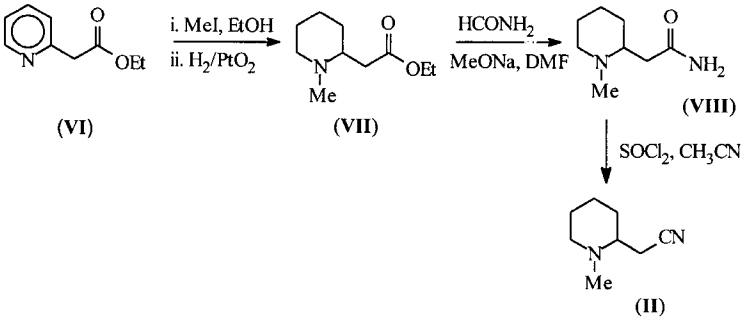
We have carefully examined the reported procedures for the synthesis of **II** and have found that, contrary to the published data,[1,2] two isomeric products are indeed formed in these syntheses. When **III** was reacted with KCN (or NaCN) in DMSO the product obtained appeared to be homogeneous by TLC and GC-MS analysis. However, ^{1}H- and ^{13}C- NMR analysis indicated the presence of two isomeric species in the mixture.[5] A detailed analysis of the NMR data indicated

that the major isomer (78%) in the mixture was **II**; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22-1.84 (m, 6H, 3,4,5-CH_2), 2.06-2.16 (m, 1H, 2-CH), 2.17-2.24 (m, 1H, 6-CH_a), 2.50 (s, 3H, N-CH_3), 2.44-2.60 (m, 2H, -CH_2CN), 2.84 (dtd, J_1 = 1.5 Hz, J_2 = 3.6 Hz, J_3 = 11.7 Hz, 1H, 6-CH_b); ^{13}C NMR: δ 22.1, 23.4, 25.3 (3,4,5-CH_2), 31.8 (-$\underline{C}H_2$CN), 43.2 (-NCH_3), 56.2 (-NCH_2), 59.7 (-NCH), 118.4 (-CN) ppm. The minor isomer (22%) was assigned structure **IV** based on the following NMR data: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22-1.90 (m, 6H, 4,5,6- CH_2), 2.08-2.22 (m, 1H, CHCN), 2.42 (s, 3H, NCH_3), 2.59-2.69 (m, 2H, 7-CH_2), 2.80-2.85 (m, 2H, 2-CH_2) ppm; ^{13}C-NMR: δ 23.6, 28.2 (4,5-CH_2), 30.8 (-$\underline{C}$HCN), 31.0 (6-CH_2), 46.9 (N-CH_3), 58.2 (7-CH_2), 58.4 (2-CH_2), 122.3 (-CN) ppm. Several attempts to purify the isomeric mixture using chromatography and distillation were unsuccessful.

In other attempts to synthesize **II**, we treated amino alcohol **V** with methanesulfonyl chloride in $CHCl_3$. After completion of the reaction, $CHCl_3$ was removed on a rotary evaporator and the residue was dissolved in water and treated with KCN.[6] The work-up yielded an isomeric mixture of **II** and **IV** in a 73:27 ratio, respectively. Similarly, when **V** was treated with KCN in CH_3CN in the presence of $\underline{n}$-Bu_3P, CCl_4 and 18-crown-6, **II** and **IV** were obtained in an 81:19 ratio, respectively.

Our observations indicate that a synthetic route to **II**, which excludes the use of piperidine derivatives having a good leaving group β to the ring nitrogen is required in order to avoid the formation of a mixture of **II** and **IV**, which are

formed from the common aziridinium intermediate. Such a route was developed as shown in Scheme IV. Ethyl-2-pyridyl acetate (**VI**) was converted to ethyl-[2-(1-methylpiperidyl)] acetate[7] (**VII**). The corresponding amide **VIII**[8,9] was synthesized by treating **VII** with formamide in the presence of methanolic sodium methoxide. Treating **VIII** with thionyl chloride resulted in dehydration to afford **II**. The product obtained in this manner had ^{1}H and ^{13}C NMR spectra identical to the spectra of the major component in the mixture of products obtained by reaction of **III** with NaCN or KCN.



Scheme IV

Our observations clearly demonstrate that contrary to the earlier reports, when **III** is reacted with NaCN (or KCN) in DMSO or when **V** is reacted with a mixture of KCN, n-Bu_3P, and CCl_4 in CH_3CN in the presence of 18-crown-6, the product formed is not only **II** but also its isomeric analog 3-cyano-1-methyl-1-azacycloheptane, **IV**.[10] To the best of our knowledge, this is the first time that piperidine compounds, such as **III**, have been shown to undergo ring expansion yielding azacycloheptanes. Thus, syntheses of **II** that utilize **III** or

its equivalent are not recommended, due to generation of an aziridinium ion intermediate and formation of **IV** as a significant side product which is difficult to separate from **II**. The alternative synthetic approach to **II** that we have developed, overcomes this problem.

Experimental:

Ethyl-[2-(1-methylpiperidyl] acetate (**VII**): Ethyl-2-pyridylacetate (**VI**, 4.13g, 25 mmol) was refluxed with MeI (7.1g, 50 mmol) in absolute ethanol (25 mL) for eight hours. Ethanol and excess MeI were removed on a rotary evaporator and the residue obtained was washed with diethyl ether. After dissolving the resulting yellow solid in 95% ethanol (50 mL) and adding PtO_2 (150 mg), the reaction mixture was subjected to hydrogenation in a Parr apparatus at 50 psi for forty eight hours. The reaction mixture was then filtered through celite and concentrated on a rotary evaporator. The oil obtained was dissolved in 10% HCl (25 mL) and then neutralized with solid K_2CO_3. Extraction with $CHCl_3$ (3 x 25 mL) yielded 4.16g of **VII** as a pale yellow oil, which was purified by distillation under reduced pressure (b.p. 70 - 73°C at 0.25 mm Hg, lit.[7] 119-121°C at 29 mm) to obtain **VII** (3.97g, 85% yield) as a colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 1.20-1.74 (m, 6H, 3,4,5-CH_2), 2.11 - 2.18 (m, 1H, 6-H_a), 2.19-2.29 (m, 1H, $\underline{CH_a}$-CO_2Et), 2.27 (s, 3H, N-CH_3), 2.40-2.49 (m, 1H, 2-CH), 2.63-2.70 (m, 1H, $\underline{CH_b}$-CO_2Et), 2.78 (td, J_1 = 11.5 Hz, J_2 = 2.4 Hz, 1H, 6-H_b), 4.14 (q, J = 6.9 Hz, 2H, $CO_2CH_2\underline{CH_3}$) ppm; ^{13}C-NMR: δ 12.0 (-$OCH_2\underline{C}H_3$), 23.7, 24.8, 32.0 (3,4,5-CH_2), 38.1 (-$\underline{C}H_2CO$), 42.7 (N-CH_3),

56.0 (CH_2-N), 60.0 (CH-N), 60.1 (-OCH_2), 172.0 (-CO-OEt) ppm; IR (neat): 2934 (m), 2782 (w), 1735 (s), 1374 (m), 1032 (m) cm^{-1}; CI mass spectrum (m/z) 186 ($M^+ + 1$), 98 (100%).

2-(1-Methylpiperidyl) acetamide (**VIII**): Freshly distilled $HCONH_2$ (3.4g, 75 mmol) was added to the solution of **VII** (3.70g, 20 mmol) in anhydrous DMF (10mL) under N_2. The reaction mixture was heated to 100^0C in an oil bath and methanolic sodium methoxide (25% w/v, 3.0 mL) was added dropwise. The temperature of the reaction mixture was maintained at 100^0C until TLC monitoring indicated absence of starting material (usually 3-8 hours). After all of **VII** was consumed, heating was stopped and the reaction mixture was poured into water (20 mL). The resulting aqueous mixture was saturated with potassium carbonate and extracted with $CHCl_3$ (3 x 20 mL). The combined organic extracts were dried over K_2CO_3, concentrated on a rotary evaporator followed by distillation under reduced pressure (to remove DMF) to afford **VIII** (2.85g, 91%) as a pale yellow solid, which can be used in the next step without further purification or it can be crystallized from acetonitrile (m.p. 113-115°C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.19-1.78 (m, 6H, 3,4,5-CH_2), 2.01-2.24 (m, 3H, 2-CH, 6-CH_a and CH_aCONH_2), 2.29 (s, 3H, N-CH_3), 2.67-2.75 (m, 1H, CH_bCONH_2), 2.85-2.93 (m, 1H, 6-CH_b), 5.75 (br, 1H, NH_2), 8.30 (br, 1H, NH_2) ppm; ^{13}C-NMR: δ 20.4, 20.6, 30.0 (3,4,5-CH_2), 39.1 (N-CH_3), 42.4 (6-CH_2), 56.5 (2-CH), 60.9 (CH_2-$CONH_2$), 174.1 (-$CONH_2$) ppm; IR (KBr): 3332 (m), 3166 (m), 2973 (m), 2777 (m), 1672 (s), 1627 (s), 1422 (m), 1150 (m), 733 (m) cm^{-1}; CI

mass spectrum (m/z) 157 (M^++1), 98 (100%).

Anal calcd. for $C_8H_{16}N_2O$ C, 61.53; H, 10.25; N, 17.94: Found: C, 61.25; H, 10.33; N, 17.96.

Synthesis of 2-cyanomethyl-1-methylpiperidine (**II**) and 3-cyano-1-methyl-1-aza-cycloheptane (**IV**):

Method A: 2-Chloromethyl-1-methylpiperidine[1] (**III**, 0.5 g, 3.4 mmol) was added to a solution of KCN (0.44 g, 6.8 mmol) in anhydrous DMSO (3.0 mL) and the reaction mixture was heated to 65^{0}C for 16 hours. After cooling to room temperature, the reaction mixture was poured in water (10 mL). Extraction with $CHCl_3$ (3 x 15 mL) followed by concentration of the combined, dried (K_2CO_3) organic extracts, yielded a pale yellow oil (425 mg) which consisted of an isomeric mixture of **II** and **IV** (78:22 ratio, respectively). Column chromatography using silica gel followed by distillation under reduced pressure failed to resolve the isomeric mixture.

Method B: To a solution of $MeSO_2Cl$ (0.09 mL, 1.1 mmol) in dry $CHCl_3$ (2.0 mL) was added a solution of **III** (115 mg, 1.0 mmol) in dry $CHCl_3$ (2.0 mL). After stirring the solution for 2 hours, $CHCl_3$ was removed on a rotary evaporator and the resulting pale yellow viscous oil was dissolved in water (5 mL) containing KCN (130.2 mg, 2.0 mmol). The reaction mixture was stirred overnight and solid K_2CO_3 was then added to adjust the pH to 8. Extraction with $CHCl_3$ (3 x 10 mL), followed by concentration of the combined, dried (K_2CO_3) organic extracts yielded a pale brown oil (98 mg, 71%). The ^{1}H-NMR spectrum of this crude

reaction product indicated formation of **II** and **IV** in a 73:27 ratio, respectively.

Method C: KCN (130 mg, 2 mmol) and 18-crown-6 (26.2 mg, 0.1 mmol) were stirred in CH_3CN (2.0 mL) for 15-20 minutes under a nitrogen atmosphere. A mixture of **V** (115 mg, 1.0 mmol) and n-Bu_3P (222 mg, 1.1 mmol) in CH_3CN (1.0 mL) was then added, and the reaction mixture was cooled in an ice/methanol bath. Carbon tetrachloride (169 mg, 1.1 mmol) was then added, and the ice/methanol bath removed. The reaction mixture was then refluxed for forty eight hours and concentrated to low volume on a rotary evaporator. Distillation of the oily residue under reduced pressure (73-79^{0}C, 0.25 mm Hg) yielded 108 mg of crude product (76% yield). ^{1}H NMR analysis indicated a 81:19 ratio of **II** and **IV**, respectively.

Method D: Amide **VIII** (468 mg, 3 mmol) was treated with thionyl chloride (0.65 mL, 9 mmol) in refluxing CH_3CN (10 mL) for 16 hours. CH_3CN was removed on a rotary evaporator, followed by treatment of the resulting residue with aqueous KOH (40%, w/v) to a pH of 11. Extraction with $CHCl_3$ (3 x 10 mL) yielded a brown oil, which was purified by column chromatography ($CHCl_3$:MeOH, 90:10) using silica gel, followed by distillation (b.p.,77-80^{0}C at 2mm Hg) to yield 220 mg (53% from **VIII**) of **II** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22-1.84 (m, 6H, 3,4,5-CH_2), 2.06-2.16 (m, 1H, 2-CH), 2.17-2.24 (m, 1H, 6-CH_a), 2.50 (s, 3H, N-CH_3), 2.44-2.60 (m, 2H, -CH_2CN), 2.84 (dtd, J_1 =1.5 Hz, J_2 = 3.6 Hz, J_3 = 11.7 Hz, 1H, 6-CH_b); ^{13}C NMR: δ 22.1, 23.4, 25.3 (3,4,5-CH_2), 31.8 (-$\underline{C}H_2CN$), 43.2 (-NCH_3), 56.2 (-NCH_2), 59.7 (-NCH),

118.4 (-CN) ppm; IR (neat): 2940 (s), 2225 (m), 1665 (w), 1450 (s), 1040 (m) cm^{-1}; CI mass spectrum (m/z) 139 (M^+ + 1), 98 (100%).

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References and notes:

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5. A ^{1}H-NMR spectrum of 2-cyano-[$^2H_2$]-methyl-1-methylpiperidine kindly supplied by Dr. E. M. Hawes' laboratory (see reference 1) exhibited the presence of deuterated analogs of **II** and **IV** in a 85:15 ratio.

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9. 'Conventional' methods to convert ester **VII** to the corresponding amide by treating it with either liquid ammonia in ethanol, or aqueous ammonia under varying conditions of temperature and pressure, failed in our hands.

10. Similar results were observed when **III** was treated with imidazole in DMSO.

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