Synthesis of Nevirapine and its Major Metabolite

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Received June 23, 1994

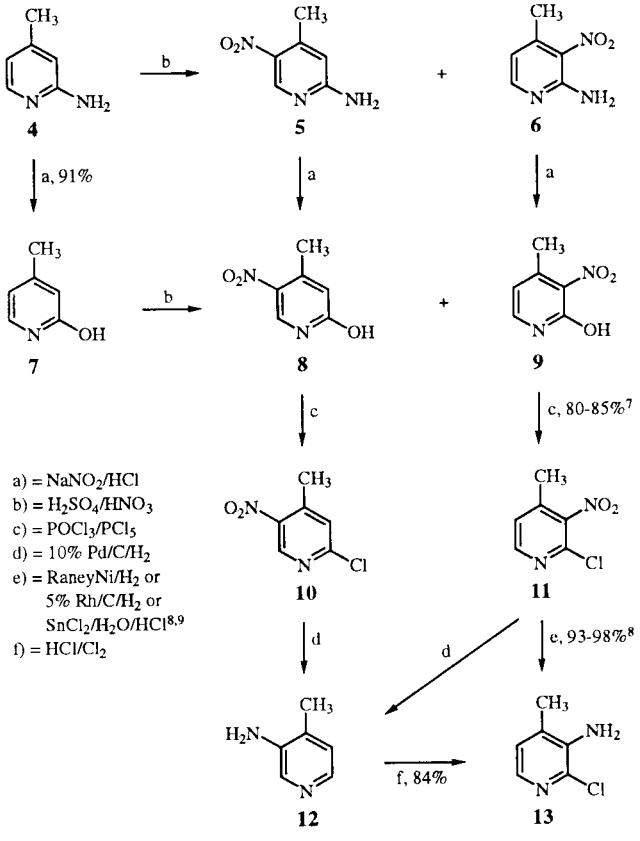
Several synthetic methods were developed during the process optimization for the large scale synthesis of nevirapine (**1**), a non-nucleoside inhibitor of HIV-1 Reverse Transcriptase. The synthesis of its putative major metabolite 11-cyclopropyl-5,11-dihydro-4-hydroxymethyl-6*H*-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**2**) and the oxidation of **2** to the corresponding aldehyde **3**, are described.

J. Heterocyclic Chem., **32**, 259 (1995).

Introduction.

Nevirapine (**1**) is a highly selective non-competitive inhibitor of HIV-1 reverse transcriptase and is currently undergoing phase II clinical evaluation for the treatment of HIV-infected individuals. An earlier published synthetic route to nevirapine [1] is environmentally burdensome when produced in multi-kilogram quantities due to a low yielding nitration step to produce the pivotal intermediate 3-amino-2-chloro-4-methylpyridine (**13**). We report different pathways to **13** and an additional synthesis of nevirapine (**1**) by dehalogenation of 2-chloro-11-cyclopropyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1-4]-diazpine-6-one (**25**). During ADME studies, **2** was isolated as the major metabolite. The synthesis of **2** and its oxidation to **3**, are described. Both compounds served as intermediates for the preparation of 4-substituted derivatives of **1**.

Scheme 1



Results and Discussion.

The original large-scale procedure to prepare **1** started from the commercially available 2-chloro-3-nitro-4-methylpyridine (**11**), which can be obtained from **4** either *via* nitration of 2-amino-4-methylpyridine to give a mixture of **5** and **6** or by nitration of **7** to give a mixture of **8** and **9**.

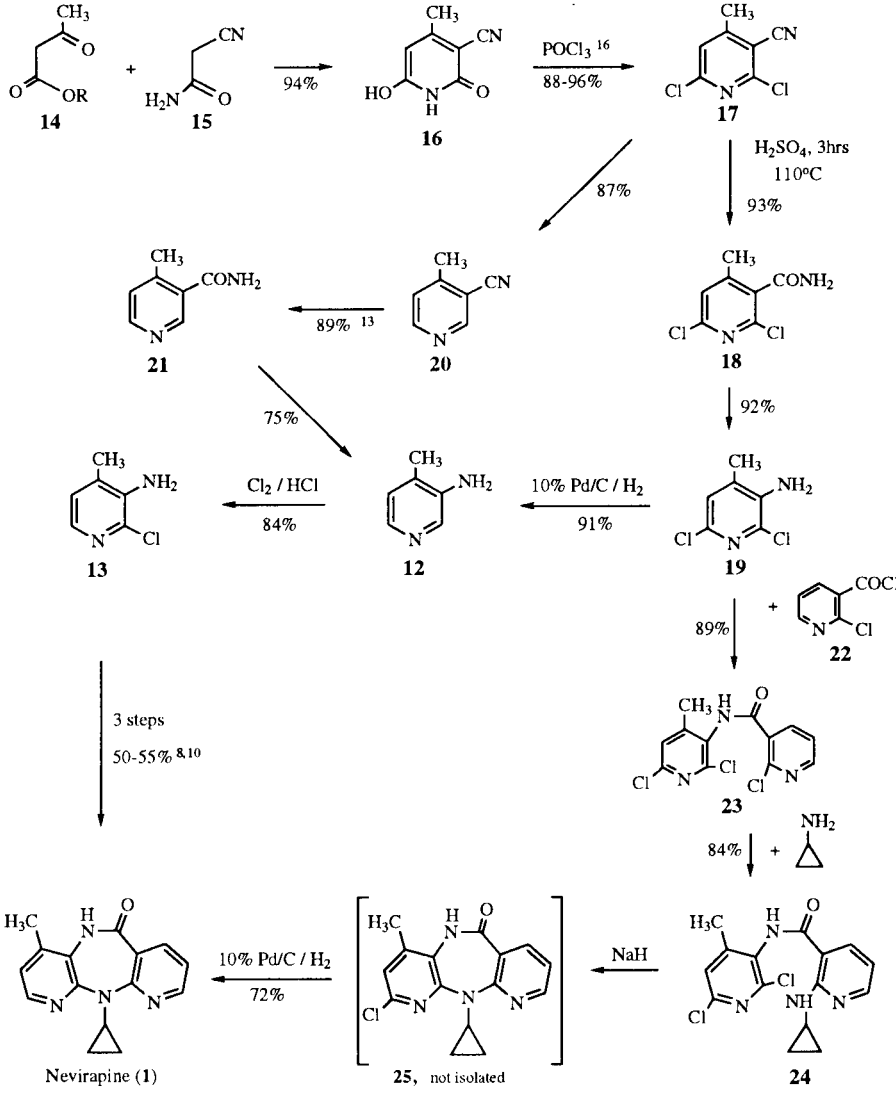
The nitration of **4** was extensively studied [2-5]. The required 3-nitro-isomer **6** could be separated from the mixture of **5** and **6** by steam distillation in 20-25% yield [2,3] or by sublimation [5] in 22% yield. Diazotization of **4** gave 2-hydroxy-4-methylpyridine (**7**) [2] in 91% yield. Nitration of **7** is reported to give 82% of **9** [6]. However, optimization experiments and multi-kilogram synthesis gave **9** in yields of 28-32% only, with the 5-nitro-isomer **8** as the major reaction side product together with extensive oxidation decomposition of the starting pyridine. Conversion to the chloride with phosphorus oxychloride [7] **9** followed by reduction of the nitro group, using stannous chloride in hydrochloric acid [8,9] or either rhodium [1] or Raney nickel [10] as catalyst, gave the pivotal intermediate **13** in 90-98% yield. Using catalytic reduction traces of dehalogenated by-product **12** was isolated. The overall yield based on 2-amino-4-methylpyridine (**4**) was 20-26%, which is unacceptable for the multi-kilogram production of **1**.

In order to utilize the 5-nitro-isomers **5** or **8**, the isomeric mixture obtained by nitration of **4** was diazotized to a mixture of **8** and **9**, chlorinated [11-13] to a mixture of **10** and **11** and then dehalogenated with Pd/H_2 to **12** in 48-50% overall yield [12,14]. 3-Amino-4-methylpyridine (**12**) was monochlorinated using either the conditions of Schick and Binz [15] or a slightly modified procedure giving **13** in 84% yield and resulting in an overall yield of approximately 40% from **4**. This procedure favors the use of the nitration mixture over the single isomer. However, to circumvent the nitration procedure entirely on a com-

mercial scale, we developed two alternative procedures to **13**. Condensation of ethylacetoacetate (**14**), R = CH_2CH_3 with cyanoacetamide (**15**) gave 3-cyano-2,6-dihydroxy-4-methylpyridine (**16**). Chlorination was effected with phosphorus oxychloride at 130° in an autoclave under pressure, or with phenyl phosphonic dichloride at atmospheres pressure to give the dichloropyridine **17** [16]. Hydrolysis of the nitrile group in concentrated sulfuric acid at 100° for 3 hours gave the amide **18** in 93% yield, and subsequent Hofmann reaction gave the amine **19**. Catalytic dehalogenation as noted above to 3-amino-4-methylpyridine (**12**) and selective 2-chlorination [15] gave **13** in 59% overall yield based on the inexpensive starting materials **14** and **15** [18]. Alternatively, **12** could be obtained by first dehalogenating **17** to **20**, with subsequent hydrolysis to **21** [16,17] and Hofmann reaction to **12**. Using this procedure [19], 3-amino-2-chloro-4-methylpyridine (**13**) was produced in 44% overall yield from **14** and **15**. A lower yield using this alternate pathway resulted during dechlorination from **17** to **20**, where appreciable amount of 3-aminomethyl-4-methylpyridine is formed [20,21]. In addition, the Hofmann reaction of 2,6-dichloro-4-methyl-3-pyridine carboxamide (**18**) gave higher yields (92%) in comparison with the Hofmann reaction of the carboxamide **21**, from which **12** was obtained in 75% yield. The pivotal intermediate, 3-amino-2-chloro-4-methylpyridine (**13**) was converted to nevirapine (**1**) in three steps by a previous published procedure [1].

Nevirapine (**1**) can also be prepared by condensation of 3-amino-2,6-dichloro-4-methylpyridine (**19**) with 2-chloronicotinic acid chloride (**22**) to provide the corresponding trichloroamide **23**, which was converted to **24** by treatment with cyclopropylamine. The ring closure was effected with sodium hydride to give **25**, which was cat-

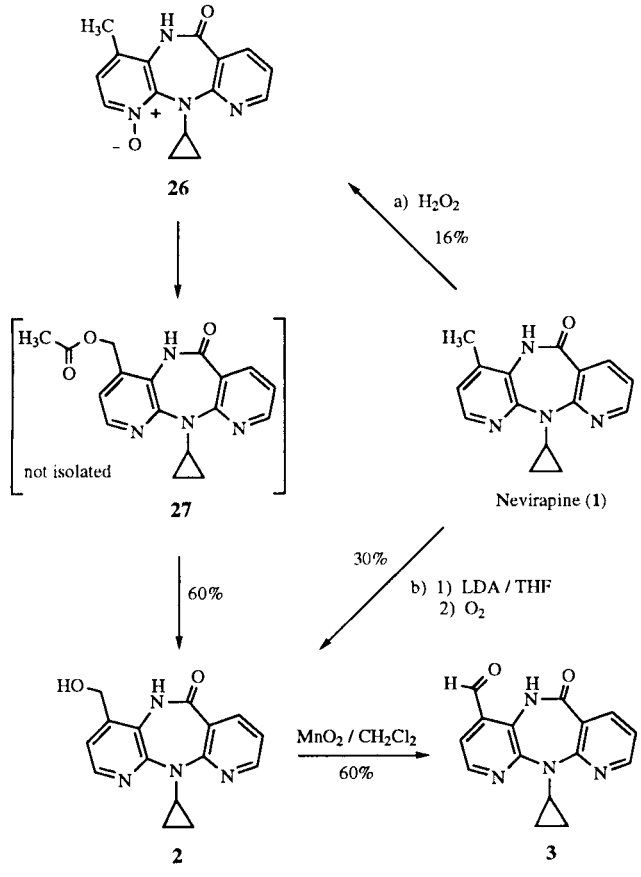
Scheme 2



alytically dehalogenated without isolation using 10% Pd/C and hydrogen to provide **1** in 54% overall yield starting from **19** [22]. This route, although slightly shorter, was not deemed to be suitable for large scale operations because of the poor solubility of **25**.

In vitro experiments with **1** in liver microsomes from humans, rats, monkeys and dogs show the primary metabolic fate to be hydroxylation of the 4-methyl substituent to give the alcohol **2** [23]. We were interested in using readily available **1** as the starting material in the synthesis of **2** in sufficient quantities for toxicological studies and for further SAR investigations of substituents at the 4-position of **1**. Recently, it was found that the 4-methyl moiety is susceptible to direct metalation [24]. This procedure, however, suffers from the use of the unstable reagent [25] oxodiperoxymolybdenum (pyridine)-hexamethylphosphoramide (MoOPH). We evaluated two routes to synthesize **2**. Reacting nevirapine (**1**) with hydrogen peroxide in acetic acid yielded a mixture of three *N*-oxides. After chromatographic separation, the 1-*N*-oxide **26** was reacted with acetic anhydride to 4-acetoxymethyl **27** [26]. After hydrolysis, **2** was obtained in approximately 10% overall yield based on **1**. This low yield synthesis was unsuitable for multi-gram scale.

Scheme 3



Consequently, it was found [27] that direct oxidation of **1** could be achieved by the reaction of **1** with LDA to form the dianion, and subsequent addition of oxygen at <-30° using a five fold excess base gave the desired alcohol **2** in 30% isolated yield. This simple, one pot reaction provided sufficient quantities of **2** required for biological evaluation and further allowed us to oxidize **2** in the presence of manganese(IV) oxide in dioxane to the corresponding 4-carboxaldehyde **3** which is presently used as a synthetic intermediate to study 4-substituted tricyclic dipyridodiazepinones as inhibitors of Reverse Transcriptase.

Conclusion.

Several syntheses of Nevirapine were evaluated. The route starting from ethyl acetoacetate and 2-cyanoacetamide *via* **19** to the pivotal intermediate **13**, was selected for bulk production and possible commercialization.

EXPERIMENTAL

Melting points were determined on a Büchi S10 MP apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Brucker WM-250 spectrometer. Elemental analyses were determined by Midwest Laboratories, Indianapolis, IN.

3-Amino-4-methylpyridine (**12**) from **21**.

To a cold solution of 7.8 g (0.196 mole) of sodium hydroxide in 75 ml water was added 3.0 ml (0.587 mole) of bromine with stirring at a rate to maintain the temperature at 0-5°. To the cold mixture was added 7.0 g (0.0514 mole) of 4-methyl-3-pyridinecarboxamide (**21**) [16] at once. The ice-bath was removed and the reaction mixture was warmed to 70-75° for 1 hour. After cooling, the product was extracted with 3 x 100 ml of ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated. The product was stirred with petroleum ether and filtered to yield 4.2 g (76%), mp 99-101°, identical by nmr, ir and tlc to an authentic sample [14].

3-Amino-2,6-dichloro-4-methylpyridine (**19**).

To a solution of 204 g (5.1 moles) of sodium hydroxide in 1.9 l of water previously cooled to 0-5°, was added 79 ml (1.53 moles) of bromine over 30 minutes maintaining the temperature at 0-5°. To the cold mixture was added 275 g (1.34 moles) of 2,6-dichloro-4-methyl-3-pyridinecarboxamide (**18**) [17,28] over 10 minutes at 0-5°. The solution was heated to 70-75° for 1 hour, cooled to 60° and diluted with 2.3 l of water. The resulting solid was filtered and washed with 2 l of water. The product was dried at 60° *in vacuo* to yield 218 g (92%) of a beige solid, mp 83-85°. ^{1}H-nmr (DMSO-d_6): δ 2.16 (s, 3H), 5.47 (bs, NH_2), 7.09 (s, 1H); ms: (M^++H) 177. Mol. wt. 177.03;

Anal. Calcd. for $C_6H_6N_2Cl_2$: C, 40.71; H, 3.42, N, 15.82; Cl, 40.05. Found: C, 40.59; H, 3.40; N, 15.58; Cl, 39.95.

3-Amino-4-methylpyridine (**12**) from **19**.

A mixture of 108 g (0.61 mole) of **19**, 100 g of anhydrous sodium acetate and 10 g of 10% Pd/C in 550 ml of methanol was hydrogenated at 80-90° at 50 psig for 16 hours. The catalyst and insoluble inorganic materials were removed by filtering

through celite, washed with 1.2 l of methanol, and concentrated to dryness. The residue was suspended in 400 ml of water and basified with a 6*N* potassium hydroxide solution. The product was extracted with 3 x 500 ml, dried over anhydrous sodium sulfate, and concentrated. Addition of petroleum ether gave 60 g (91%) of **12**, mp 101-102°. Identical by nmr, ir and tlc with an authentic sample [14].

3-Amino-2-chloro-4-methylpyridine (**13**) from **12**.

3-Amino-4-methylpyridine (21.6 g, 0.2 mole) was suspended in 75 ml of water. The mixture was dissolved by the addition of 25 ml concentrated hydrochloric acid. Chlorine gas, 15.6 g (0.22 mole) was introduced with stirring through an inlet tube reaching below the surface of the reaction mixture at 20° over 25 minutes. Then the mixture was purged with nitrogen for 30 minutes, and cooled to 10°, and basified by the addition of 70 ml of a 12*N* sodium hydroxide solution. Additional water (100 ml) was added to maintain efficient agitation of the mixture. The precipitate was collected, washed with water, and dried *in vacuo* to give 14.5 g of **13**. The aqueous phase was extracted 3 times with 100 ml of dichloromethane. The organic phases were combined and washed with water, dried over anhydrous magnesium sulfate, and concentrated to give an additional 9.4 g of **13**, mp 62-64°. Total yield, 23.9 g (84%), identical by ir, nmr and tlc with an authentic sample [1].

N-(2,6-Dichloro-4-methyl-3-pyridyl)-2-chloronicotinamide (**23**).

A solution of **19** (100 g, 0.565 mole) in 650 ml of toluene was heated to reflux and 75 ml of toluene was distilled out. The resulting solution was cooled to rt and 48 ml (0.593 mole) of anhydrous pyridine was added. To the stirred solution was added 104 g, 0.593 mole of 2-chloronicotinic acid chloride **22** [1] in 575 ml of dry toluene over 1 hour maintaining the temperature at 20°. To the resulting slurry was added 0.5 l of water. The mixture was filtered, and the product was washed with 250 ml of toluene followed by 250 ml of water. The solid was dried in vacuo at 60° to constant weight. A total of 159 g (89%) was obtained, mp 170-172°; ^{1}H-nmr (DMSO-d_6): δ 2.38 (s, 3H), 7.65 (s, 1H), 8.11 (dd, J = 1.9, 7.6), 8.59 (dd, J = 1.9, 4.8), 10.64 (s, NHCO); ms: (M^++H) 316, Mol. wt. 316.57.

Anal. Calcd. for $C_{12}H_8Cl_3N_3O$: C, 45.53; H, 2.55; Cl, 33.60; N, 13.27. Found: C, 45.57; H, 2.38; Cl, 32.90; N, 13.08.

2,6-Dichloro-3-(2'-cyclopylamino-3'-pyridyl)carboxamido-4-methylpyridine (**24**).

A mixture of 90 g (0.284 mole) of **23** and 79 ml (1.14 moles, 4 equivalents) of cyclopropylamine in 900 ml of xylene was heated to 120° in a 2 l stainless steel autoclave for 48 hours. After cooling, the xylene was concentrated and to the suspension was added 1 l of water. The resulting solid was filtered and washed with 1 l of water. The product was dried *in vacuo* at 80° to give 80.5 g (84%), mp 172-174°. ^{1}H-nmr (DMSO-d_6): δ 0.42-0.72 (m, 4H), 2.25 (s, 3H), 2.83 (m, 1H), 6.73 (dd, 1H), 7.60 (s, 1H), 8.20 (dd, 1H), 8.31 (dd, 1H), 8.3 (m, NH), 10.38 (bs, 1H); ms: (M^++H) 337, Mol. wt. 337.2.

Anal. Calcd. for $C_{15}H_{14}N_4Cl_2O$: C, 53.43; H, 4.18; Cl, 21.03; N, 16.61. Found: C, 53.41; H, 4.18, Cl, 20.90; N, 16.43.

Nevirapine (**1**) from **24**.

To a solution of 33 g (0.825 mole) of a 60% sodium hydride suspension in mineral oil, 100 ml of 2-methoxyethyl ether, heated to 120° under nitrogen, was added a solution of 80 g (0.238 mole) of **24** in 400 ml of 2-methoxyethyl ether. The mixture was stirred at 130-135° for an additional 1 hour, cooled to rt, and quenched by the careful addition of ethanol. This solution was then hydrogenated with 8 g of 10% Pd/C catalyst for 12 hours at 100° at 50 psig. The catalyst was filtered through celite filter aid and the ethanol removed under reduced pressure. The mixture was added to 3 l of water and neutralized to *p*H 7 with glacial acetic acid. The crystalline product was stirred overnight and collected by filtration. The filter cake was dissolved in 500 ml of hot pyridine, slow addition of 3 l of water gave a crystalline product. The product was collected and suspended in 500 ml of 2-propanol, heated to reflux, cooled, and filtered. Final recrystallization from pyridine and water gave, after drying in vacuo at 100°, 45.8 g (73%), of nevirapine (**1**), mp 253-254°, identical by nmr, ir and tlc with an authentic sample [1].

Nevirapine *N*-oxides.

A mixture of **1** (52.6 g, 0.2 mole) and 0.4 l of acetic acid was warmed to 45°. To the solution was added 120 ml of a 30% hydrogen peroxide solution, then heated to 95° and maintained for 18 hours. The dark mixture was concentrated to 300 ml and diluted with 1 l of water. The product was extracted with 3 x 200 ml of dichloromethane, dried over anhydrous magnesium sulfate, concentrated and purified on a column containing 2 kg of silica gel (200-400 mesh). The first product eluted with dichloromethane/ethanol (95:5) was unreacted **1**, followed by the 11-cyclopropyl-5,11-dihydro-4-methyl-8-hydroxy-1,10-dioxy-6*H*-dipyrido[3,2-*b*:2',3'-*e*] [1,4] diazepin-6-one, mp 264-266°, 4 g (9%); ^{1}H-nmr, (DMSO-d_6): δ 0.31-0.83 (m, 4H), 2.32 (s, 3H), 3.57 (m, 1H), 7.03 (d, 1H), 7.39 (d, 1H), 8.07 (d, 1H), 9.83 (bs, NHCO), 9.94 (s, OH). Mol. wt. 314.30.

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.35; H, 4.56; N, 17.47.

The second major product was identified as the *N*-10-oxide, yield 0.5 g (0.9%). ^{1}H-nmr, (DMSO-d_6): δ 0.26-0.67 (m, 4H), 2.31 (s, 3H), 4.25 (m, 1H), 7.10 (d, 1H), 7.27 (dd, 1H), 7.50 (dd, 1H), 8.10 (d, 1H), 8.37 (dd, 1H), 10.08 (bs, NH); ms: (M^++H) 283, Mol. wt. 282.30.

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.39; H, 5.01; N, 19.55.

The last fraction eluted gave 6.9 g (17%) of white crystalline, *N*-1-oxide **26**, mp 268-269°. ^{1}H-nmr, (DMSO-d_6): δ 0.23-0.75 (m, 4H), 2.31 (s, 3H), 4.26 (m, 1H), 7.14 (d, 1H), 7.24 (dd, 1H), 8.04 (dd, 1H), 8.04 (d, 1H), 8.55 (dd, 1H), 10.03 (bs, NH); Mol. wt. 282.30.

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82, H, 5.00; N, 19.85. Found: C, 63.84; H, 4.99; N, 19.56.

11-Cylopropyl-5,11-dihydro-4-(hydroxymethyl)-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**2**) from 26, Method A [26].

A mixture of **26** (1.4 g, 5 mmoles), acidic anhydride (2 g, 20 mmoles) in 50 ml of acetic acid was heated to 90° for 6 hours. The mixture was concentrated and diluted with 50 ml of water. The precipitate was filtered and dried *in vacuo* at 60° and the solid dissolved in 50 ml of methanol. To the stirred solution was added a trace of sodium metal and the *p*H adjusted to about 10. After 3 hours the solution was neutralized by the dropwise addition of acetic acid. The mixture was concentrated and purified on a silica gel column eluted with dichloromethane/ethanol (97:3) to give 0.85 g (60%) of **26**, mp 242° and identical by nmr, ir and tlc to an authentic sample [24].

11-Cyclopropyl-5,11-dihydro-4-(hydroxymethyl)-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**2**) from 1, Method B.

To a stirred suspension of nevirapine (**1**) (53.2 g, 0.2 mole) in 1 l of THF was added 100 ml (0.2 mole) of a 2*M* LDA solution in THF at -30° to -40°. The resulting dark solution was cooled to -70° and an additional 500 ml (1 mole) of a 2*M* LDA in THF solution was added. At -70°, oxygen was bubbled through the reaction mixture, using a fritted glass tube reaching to the bottom of the reaction flask, at such a rate to maintain the exothermic reaction between -40° and -20°. The mixture was stirred at rt overnight, poured into 2 l of water, and neutralized with 2*N* hydrochloric acid. The product was extracted with 3 x 200 ml of dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated to 50 ml. The unreacted **1** was removed by filtration. The filtrate was concentrated, and addition of methanol and ethyl acetate gave 17.3 g (31%) of **2**, identical by nmr, ir and tlc to an authentic sample [24].

11-Cyclopropyl-5,11-dihydro-4-formyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**3**).

To a mixture of **2** (10 g, 0.035 mole) in 500 ml dichloromethane and 250 ml of dioxane at 40° was added in portions with stirring 40 g of manganese dioxide. The suspension started to reflux (exothermic), and after the initial reaction subsided, the mixture was heated and refluxed for 3 hours. The solid was removed by filtration and the filtrate treated with 0.5 l water containing 50 g of sodium bisulfate. The organic phase was separated and the aqueous phase basified with a 6*N* sodium hydroxide solution to *p*H 11, the aldehyde was extracted with 2 x 100 ml dichloromethane, dried over anhydrous magnesium sulfate, and concentrated. Addition of ether gave 6.0 g (60%) of yellow crystals, mp 221-223°. ^{1}H-nmr, (DMSO-d_6): δ 0.40-0.92 (m, 4H), 3.66 (m, 1H), 7.26 (dd, 1H), 7.49 (d, 1H), 8.08 (dd, 1H), 8.42 (d, 1H), 8.58 (dd, 1H), 10.19 (s, 1H), 10.64 (bs, NH); ms: (M^++H) 281, Mol. wt. 280.28.

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.27, H, 4.32, N, 19.99. Found: C, 63.98; H, 4.33; N, 19.85.

REFERENCES AND NOTES

† Analytical Chemistry.

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