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# 8-Chloro-11-[4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazino]-5*H*-dibenzo[*b,e*][1,4]diazepine

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**Abstract:** A method to synthesize desmethylclozapine, **3**, is reported. The procedure afforded the target compound in 69% yield. A by-product, isolated from the reaction mixture in 11% yield, proved to be the title compound, **4**.

**Keywords:** desmethylclozapine, amidine formation, titanium tetrachloride.

## Introduction

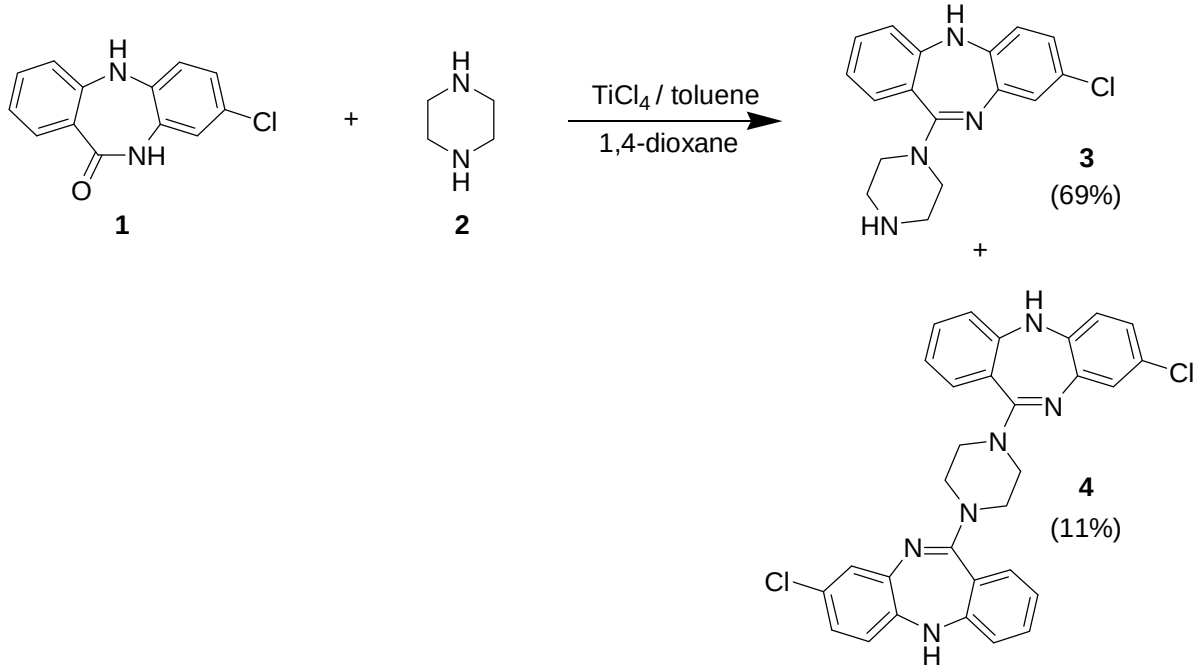
Clozapine is an atypical antipsychotic drug used clinically to treat schizophrenia. Unlike other drugs used to treat this condition, clozapine is virtually devoid of movement disorders. Clozapine, however, has been found to induce the blood disorder agranulocytosis that can, in some cases, be fatal. The major metabolite of clozapine, desmethylclozapine (**3**), has been implicated in this serious blood dyscrasia [1].

A modified synthetic procedure [2] was employed to synthesize 8-chloro-11-piperazino-5*H*-dibenzo[*b,e*][1,4]diazepine (desmethylclozapine, **3**) [3] as a versatile intermediate towards clozapine-like analogues potentially devoid of any blood disorders, and for use in haematological studies to investigate clozapine-induced agranulocytosis. The procedure, entailed reaction of a titanium tetrakisamine complex, formed from piperazine and titanium tetrachloride, with the tricyclic lactam, **1**.

Upon work-up and column chromatography, a by-product, **4**, was isolated and characterized (Scheme 1).

## Results and Discussion

A high $R_f$ component initially thought to be unreacted lactam **1** was discovered by TLC when UV light was used as a visualizing aid. Removal of the lactam from the target compound **3** was achieved with an ethyl acetate wash of the acidic aqueous phase. Subsequent basification of the aqueous phase followed by extraction with ethyl acetate isolated the target compound **3** and the high $R_f$ component. The original lactam and the organic layer were analysed by TLC. Visualization with iodine vapor revealed an orange coloration for the reaction extract as opposed to green for the lactam. This component was separated from desmethylclozapine chromatographically. The $^1$H NMR spectrum showed aromatic hydrogen resonances consistent with the tricyclic nucleus of desmethylclozapine. A broad singlet at *d* 3.54 ppm displayed a relative integral of four protons. This resonance, in addition to the overall integration pattern, suggested a symmetrical structure. The presence of a solitary methylene carbon resonance at *d* 48.20 ppm in the $^{13}$C NMR spectrum also supported this. ESI mass spectral analysis confirmed the presence of two chlorine atoms in the molecule with the major protonated molecular ion peak at *m/z* 539, and was evidence for the structural integrity of **4**. Microanalysis, in conjunction with low and high resolution ESI-MS, confirmed a molecular formula of $C_{30}H_{24}Cl_2N_6$.




**Scheme 1.**

## Conclusion

We have presented the isolation and structural determination of a by-product **4** from an alternative route for the synthesis of desmethylclozapine. The title compound **4** is easily separated from the desired compound **3** using column chromatography. The target compound **3** was obtained in moderate yield.

## Experimental

### *General*

The melting point was determined on a Reichert Micro-melting point apparatus and is uncorrected. Thin-layer chromatography (TLC) was carried out on silica gel 60 $F_{254}$ pre-coated plates (0.25 mm, Merck, ART. 5554). Elemental analysis was carried out on a sample dried under vacuum over phosphorus pentoxide at 30 $^{o}$C for 24 h. The UV-VIS spectrum was recorded on a Pharmacia Biotech Ultraspec 2000 UV-VIS spectrophotometer. The IR spectrum was recorded on a Hitachi 270-30 Infra-Red spectrophotometer. $^{1}$H and $^{13}$C NMR spectra were obtained using a Bruker Avance DPX 300 spectrometer and were recorded at 300.13 and 75.4 MHz respectively. The low resolution electrospray ionization (ESI) mass spectrum was determined in positive ion mode using a Micromass Platform II Mass Spectrometer at the specified cone voltage. The high resolution electrospray ionization (ESI) mass spectrum was determined using a Bruker BioApex II FTICR Mass Spectrometer.

### *Method*

To a solution of piperazine (**2**, 5.28 g, 61.3 mmol) in anhydrous 1,4-dioxane (30 mL) under nitrogen was added a solution of titanium tetrachloride in dry toluene (1.0 M, 13.5 mL, 13.5 mmol) and an immediate yellow/brown coloration was observed (titanium tetrakisamine complex). The mixture was warmed to 50-55 $^{o}$C and a solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (**1**, 3.00 g, 12.3 mmol) in anhydrous 1,4-dioxane (50 mL) was added. The mixture was heated to reflux for 24 h after which time it was evaporated to dryness *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and aqueous hydrochloric acid (2 M, 100 mL) and the mixture filtered under vacuum. The aqueous phase was washed with ethyl acetate (2 × 50 mL), basified with solid sodium hydroxide to a pH of 14 then extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (2 × 30 mL), brine (30 mL), dried over anhydrous sodium sulfate then evaporated to dryness. The residue was dissolved in dichloromethane (5 mL) and purified by flash column chromatography (silica gel; ethyl acetate:hexane, 1:2) to yield, upon evaporation, 8-chloro-11-[4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazino]-5*H*-dibenzo-[*b,e*][1,4]diazepine (**4**), as a yellow solid. The crude product was recrystallized from acetone-hexane as yellow microplatelets (0.350 g, 11%). Desmethylclozapine (**3**) was eluted from the column with ethyl acetate:methanol (1:1) and the major frac-

tion evaporated to dryness. The purified product was taken up in dichloromethane (10 mL), filtered, then evaporated to dryness affording a bright yellow foam (**3**, 2.65 g, 69%).

*Spectral Data for Compound* **4**

M.p. 333-335 $^{o}$C.

$R_f$ (silica; ethyl acetate:hexane, 1:1) 0.63.

Anal. calc. for $C_{30}H_{24}Cl_2N_6$ (539.46): C 66.8, H 4.5, N 15.6; found: C 66.9, H 4.5, N 15.5.

UV (ethanol) $\lambda$ ($\log_{10}\varepsilon$) 215 (4.67), 229 (4.65), 262 (4.54), 301 (4.35) nm.

IR (KBr disc) $\nu_{max}$ 3296 (m, N-H), 3004 (w, Ar-H), 2896 (w, aliphatic C-H), 1598 (s, C=N), 1556 (s, C=N), 1006 (s, C-N) cm$^{-1}$.

$^{1}$H-NMR (300 MHz, $d_6$-acetone) $d$ 3.54 (br s, 8H, H2', H3', H5', H6'), 6.53 (s, 2H, 2 × NH), 6.82 (dd, $J$ = 8, 2 Hz, 2H, H7, H7''), 6.89 (d, $J$ = 8 Hz, 2H, H6, H6''), 6.96 (d, $J$ = 2 Hz, 2H, H9, H9''), 7.0-7.1 (m, 4H, H2, H4, H2'', H4''), 7.3-7.4 (m, 4H, H1, H3, H1'', H3'').

$^{13}$C-NMR (75 MHz, $d_6$-acetone) $d$ 48.20 ($CH_2$), 121.3 (CH), 121.5 (CH), 123.6 (CH), 123.8 (CH), 124.6 ($C_q$), 127.2 (CH), 128.7 ($C_q$), 131.2 (CH), 133.1 (CH), 143.1 ($C_q$), 143.4 ($C_q$), 155.2 ($C_q$), 164.3 ($C_q$).

MS-ESI (70 V) 543 (M[$^{37}$Cl$^{37}$Cl]H$^{+}$, 5%), 541 (M[$^{35}$Cl$^{37}$Cl]H$^{+}$, 29%), 539 (MH$^{+}$, 43%), 298 (10%), 296 (30%), 272 (33%), 271 (18%), 270 (100%), 192 (70%).

HRMS-ESI 539.152266. MH$^{+}$ ($C_{30}H_{25}{}^{35}Cl_2N_6$) requires 539.151775.

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*Samples Availability*: available from MDPI.