Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **43**, 865-872 (2000)

Synthesis of [*N*-$^{13}CH_3$] Drugs (Chlorpromazine, Triflupromazine and Promazine)

Keisuke Kitamura*, Kazuyoshi Fujitani, Keiko Takahashi, Yoshimi Tanaka, Syou Hirako, Chie Kotani, Tomoko Hashimoto and Shigehiko Takegami

Kyoto Pharmaceutical University, 5 Nakauchicho, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan.

SUMMARY

These [*N*-$^{13}CH_3$] containing drugs (chlorpromazine, trifluprornazine and promazine) have been synthesized by means of a two-step demethylation/ methylation procedure.

Keywords : chlorpromazine, trifluprornazine, promazine, ^{13}C

INTRODUCTION

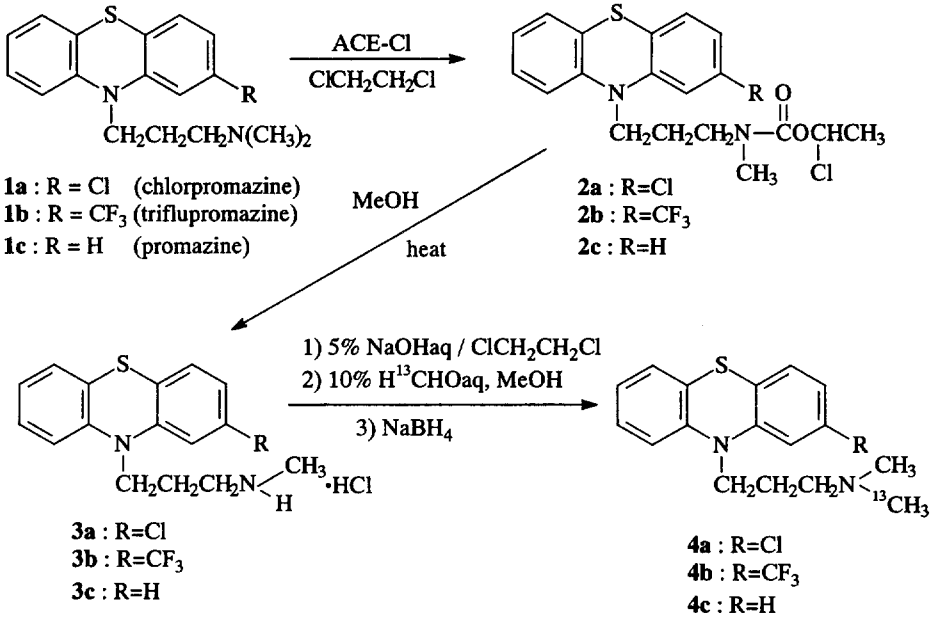
Carbon-13 labelled drugs find wide use in ^{13}C NMR studies of their interactions with biological molecules such as lipid membranes, proteins and nucleic acids. For this reason there is a need to develop simple and efficient ways of preparing the ^{13}C-compounds. Here we report on such an example, leading to the synthesis of the phenothiazine tranquilizers, [*N*-$^{13}CH_3$] chlorpromazine [2-chloro-*N*-([^{13}C]methyl)-*N*-methyl-10*H*-phenothiazine-10-propanamine] **4a**, [*N*-$^{13}CH_3$]

*Author for correspondence. E-mail : kitamura@mb.kyoto-phu.ac.jp

Received 23 February 2000
Revised 28 March 2000
Accepted 5 April 2000

triflupromazine [*N*- ([^{13}C]methyl)-*N*-methyl-2-(trifluoromethyl)- 10*H*- phenothiazine-10-propanamine] **4b**, [*N*-$^{13}CH_3$] promazine [*N*-([^{13}C] methyl)-*N*-methyl-10*H*-phenothiazine-10-propanamine] **4c**. The reactants in each case are the corresponding non-labelled phenothiazine drugs themselves, i.e., chlorpromazine (CPZ) [2-chloro-*N*, *N*-dimethyl-10*H*-phenothiazine-10-propanamine] **1a**, triflupromazine (TFZ) [*N*, *N*-dimethyl-2-(trifruoromethyl)-10*H*-phenothiazine-10-propanamine] **1b** and promazine (PZ) [*N*, *N*-dimethyl-10*H*-phenothiazine-10-propanamine] **1c**. The synthetic route proposed consists of two steps, the first being a demethylation from the *N*-dimethyl group of each drug to form an *N*-monomethyl group and the second step being the methylation of the *N*-monomethyl group to an *N*-dimethyl group using ^{13}C-enriched formalin.

RESULTS AND DISCUSSION



Demethylation of the *N*-dimethyl group of CPZ **1a** was performed by adding α -chloroethyl chloroformate (ACE-Cl) to CPZ in ethylene dichloride according to the

method reported by Olofson et al. (1). The reaction product was a mixture of the intermediate ACE-CPZ **2a** and a small amount of CPZ hydrochloride. The existence of water in the reaction mixture produced HCl from ACE-Cl to generate CPZ hydrochloride (1). The by-product CPZ hydrochloride was removed by washing an ethereal solution of the reaction product with water. From the high-resolution MS and ^{1}H NMR spectra the intermediate ACE-CPZ was confirmed to be **2a** as suggested by Olofson et al. (1).

In the ^{1}H NMR spectrum of **2a**, the methyl signal of $OCH(Cl)CH_3$ appears as two doublets (1.68 and 1.79 ppm, J = 5.8 Hz) having similar signal intensities and the methine signal of the same group appears as pair of two overlapping quartets (6.53 and 6.54 ppm, J = 5.8 Hz). The methyl signal of $-CH_2N(CH_3)C(=O)O-$ appears as two singlets (2.83 and 2.86 ppm) with similar signal intensities and the methylene signal appears as a multiplet (3.41 ppm). Similar spectral results were obtained for **2b** and **2c**. These results indicate that there are two rotational isomers of equivalent populations for each of the compounds **2** due to the restricted rotation around the N-C(=O)O bond.

The compound **2a** was refluxed in methanol (methanolysis) to obtain the monomethyl-CPZ hydrochloride, **3a**. Crude **3a** was purified by recrystallization and converted to the free base of **3a**.

To the free base of **3a** in methanol ^{13}C-enriched formalin was added, and the reaction mixture was reduced in the $NaBH_4$ (2) to obtain [*N*-$^{13}CH_3$] chlorpromazine **4a**. ^{1}H, ^{13}C NMR and high-resolution MS spectra confirmed the structure of the product as **4a**.

The [*N*-$^{13}CH_3$] triflupromazine and [*N*-$^{13}CH_3$] promazine were synthesized from TFZ and PM, respectively, in the same manner and their structures were confirmed to be **4b** and **4c**, respectively, by ^{1}H, ^{13}C NMR and high-resolution MS studies.

In summary, an efficient method for synthesizing [*N*-$^{13}CH_3$] drugs from the original [*N*-CH_3] drugs has been developed. As there are many pharmaceuticals having an *N*-methyl group, the proposed method will find wide application in the synthesis of [*N*-$^{13}CH_3$]-containing drugs.

EXPERIMENTAL

Instrumentation

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solutions using TMS as an internal reference on a Varian XL-300 spectrometer at 300 MHz and 75 MHz, respectively. Electron impact high-resolution mass spectra were recorded on a Jeol JMX-SX 102A spectrometer.

Chemicals

CPZ hydrochloride, TFZ hydrochloride and PZ hydrochloride were purchased from Sigma Chemical Company and used without further purification. ACE-Cl was purchased from Aldrich Chemical Company Inc. and distilled before use. Formalin-^{13}C (20 % aqueous solution, 99.4 atom % ^{13}C) was obtained from C/D/N ISOTOPES (Canada).

2-Chloro-*N*-(1-chloroethoxycarbonyl)-*N*-methyl-10*H*-phenothiazine-10-propanamine 2a

To a solution of **1a** (5.38 g, 16.9 mmol) in 5 ml ethylene dichloride, 3.0 g (21.0 mmol) of α-chloroethyl chloroformate (ACE-Cl) was added in small portions at 0 ℃ with stirring. The mixture was further stirred for 15 min, then refluxed for 1 hr. After cooling, the solvent was removed under reduced pressure. The residue was dissolved in 10 ml of ethylene dichloride and to the solution 100 ml of diethyl ether was added. The solution was washed three times with 20 ml of water to remove the by-product CPZ·HCl and the ethereal layer was dried over anhydrous K_2CO_3 and the ether was evaporated to give an oily product **2a** (5.61g, 13.6 mmol 81 %).

^{1}H NMR: δ 1.68 and 1.79 (d, 3 (1.5+1.5)H, J = 5.8 Hz, OCH(Cl)$\underline{CH_3}$), 2.05 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.83 and 2.86 (s, 3 (1.5+1.5)H, N-$\underline{CH_3}$), 3.41 (m, 2H, -$\underline{CH_2}$-N), 3.88 (t, 2H, J = 6.6 Hz, N-$\underline{CH_2}$-CH_2), 6.53 and 6.54 (q, 1 (0.5+0.5)H, J = 5.8 Hz, OCHCl), 6.83-7.20 (m, 7H, aromatic)

MS: m/z $[M]^+$ 410.0629, $C_{19}H_{20}N_2O_2SCl_2$ requires 410.0622

2-Chloro-*N*-methyl-10*H*-phenothiazine-10-propanamine hydrochloride 3a

Compound **2a** (5.61g, 13.6 mmol) was dissolved in 100 ml methanol and refluxed for 45 min. Then the solvent was evaporated off to give **3a** (4.28 g, 13 mmol 92 %), mp 187-190℃ (recrystallized from 2-butanone).

^{1}H NMR : δ 2.29 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.51 (s, 3H, N^+-$\underline{CH_3}$), 3.02 (broad t, 2H, CH_2-$\underline{CH_2}$-N^+), 4.03 (t, 2H, J = 6.5 Hz, N-$\underline{CH_2}$-CH_2), 6.88-7.22 (m, 7H, aromatic), 9.52 (broad s, 2H, N^+H_2) .

MS : m/z $[M-HCl]^+$ 304.0788, $C_{16}H_{17}N_2SCl$ requires 304.0801.

2-Chloro-*N*-([^{13}C]methyl)-*N*-methyl-10*H*-phenothiazine-10-propanamine 4a

To a solution of **3a** (1.81 g, 5.5 mmol) in 180 ml water, 9 g of NaOH was added and the liberated free base of **3a** was extracted with ethylene dichloride. This layer was dried over anhydrous K_2CO_3 and the solvent was evaporated to give an oily free base of **3a** (1.62 g, 5.3 mmol). The residue was dissolved in 20 ml methanol, and to the solution ^{13}C-formalin (1 g, 20 % aqueous solution, 6.5 mmol of ^{13}C-formaldehyde) was added in small portions at room temperature with stirring. After the mixture was stirred for 1 hr, $NaBH_4$ (0.8 g, 20 mmol) was added in small portions to the reaction mixture at room temperature with stirring, which was continued for an additional 1 hr before the solvent was evaporated off *in vacuo*. To the residue was added 5 % aq. NaOH and the liberated **4a** was extracted with ether. The ethereal layer was dried over anhydrous K_2CO_3, and the solvent was evaporated to give oily **4a** (1.43 g, 4.48 mmol, 85 %).

^{1}H NMR : δ 1.91 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.19 (d, 3H, $J_{^{13}C-H}$ = 132.8 Hz, N-$^{13}\underline{CH_3}$), 2.20 (d, 3H, $J_{^{13}C-N-C-H}$ = 5.6 Hz, N-$\underline{CH_3}$), 2.37 (m, 2H, -$\underline{CH_2}$-N), 3.86 (t, 2H, J = 7.0 Hz, N-$\underline{CH_2}$-CH_2), 6.88-7.17 (m, 7H, aromatic).

^{13}C NMR : δ 46.30 (qq, $J_{^{13}C-H}$ = 133 Hz, $J_{^{13}C-N-C-H}$ = 5 Hz, N-$^{13}\underline{CH_3}$).

The hydrochloride of **4a** was obtained by bubbling hydrogen chloride gas into the ethereal solution of **4a**, m.p. 193-196 [lit. 194-196] (3).

MS : m/z $[M-HCl]^+$ 319.0997, $C_{16}H_{19}{}^{13}CN_2SCl$ requires 319.0991.

_N_-(1-Chloroethoxycarbonyl)-_N_-methyl-2-(trifluoromethyl)-10_H_-phenothiazine-10-propanamine 2b

Compound **2b** was prepared in a similar manner as in **2a**. Yield 82%.

^{1}H NMR: δ 1.67 and 1.79 (d, 3 (1.5+1.5)H, J = 5.9 Hz, OCH(Cl)$\underline{CH_3}$), 2.06 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.83 and 2.86 (s, 3 (1.5+1.5)H, N-$\underline{CH_3}$), 3.42 (m, 2H, -$\underline{CH_2}$-N), 3.95 (t, 2H, J = 6.6 Hz, N-$\underline{CH_2}$-CH_2), 6.52 and 6.54 (q, 1 (0.5+0.5)H, J = 5.7 Hz, OCHCl), 6.89-7.25 (m, 7H, aromatic)

MS: m/z $[M]^+$ 444.0883, $C_{20}H_{20}N_2O_2F_3SCl$ requires 444.0886

_N_-Methyl-2-(trifluoromethyl)-10_H_-phenothiazine-10-propanamine hydrochloride 3b

Compound **3b** was prepared in a similar manner as in **3a**. Yield 94 %, mp 139-143℃ (recrystallized from 2-butanone).

^{1}H NMR : δ 2.31 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.51 (s, 3H, N^+-$\underline{CH_3}$), 3.02 (broad t, 2H, CH_2-$\underline{CH_2}$-N^+), 4.10 (t, 2H, J = 6.4 Hz, N-$\underline{CH_2}$-CH_2), 6.94-7.28 (m, 7H, aromatic), 9.58 (broad s, 2H, N^+H_2) .

MS : m/z $[M\text{-}HCl]^+$ 338.1053, $C_{17}H_{17}N_2F_3S$ requires 338.1064.

_N_-([^{13}C]Methyl)-_N_-methyl-2-(trifluoromethyl)-10_H_-phenothiazine-10-propanamine 4b

From the free base of **3b**, **4b** was prepared in a similar manner as **4a**. Yield 83 %.

^{1}H NMR : δ 1.91 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.19 (d, 3H, $J_{^{13}C-H}$ = 132.8 Hz, N-$^{13}\underline{CH_3}$), 2.20 (d, 3H, $J_{^{13}C-N-C-H}$ = 5.6 Hz, N-$\underline{CH_3}$), 2.37 (m, 2H, -$\underline{CH_2}$-N), 3.86 (t, 2H, J = 7.0 Hz, N-$\underline{CH_2}$-CH_2), 6.88-7.17 (m, 7H, aromatic).

^{13}C NMR : δ 45.610 (qq, $J_{^{13}C-H}$ = 132 Hz, $J_{^{13}C-N-C-H}$ = 5 Hz, N-$^{13}\underline{CH_3}$).

The hydrochloride of **4b** : m.p. 172-177 [lit. 170-178] (4).

MS : m/z $[M\text{-}HCl]^+$ 353.1260, $C_{17}H_{19}{}^{13}CN_2F_3S$ requires 353.1254.

N-(1-Chloroethoxycarbonyl)-N-methyl-10H-phenothiazine-10-propanamine 2c

Compound **2c** was prepared in a similar manner as in **2a**. Yield 68 %.

^{1}H NMR: δ 1.67 and 1.78 (d, 3 (1.5+1.5)H, J = 5.9 Hz, OCH(Cl)$\underline{CH_3}$), 2.05 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.81 and 2.84 (s, 3 (1.5+1.5)H, N-$\underline{CH_3}$), 3.41 (m, 2H, -$\underline{CH_2}$-N), 3.91 (t, 2H, J = 6.6 Hz, N-$\underline{CH_2}$-CH_2), 6.52 and 6.54 (q, 1 (0.5+0.5)H, J = 5.8 Hz, OCHCl), 6.86-7.19 (m, 7H, aromatic)

MS: m/z $[M]^+$ 376.1004, $C_{19}H_{21}N_2O_2SCl$ requires 376.1012

N-Methyl-10H-phenothiazine-10-propanamine hydrochloride 3c

Compound **3c** was prepared in a similar manner as in **3a**. Yield 93 %, mp 161-162℃ (recrystallized from 2-butanone).

^{1}H NMR: δ 2.29 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.48 (s, 3H, N^+-$\underline{CH_3}$), 3.01 (broad t, 2H, CH_2-$\underline{CH_2}$-N^+), 4.04 (t, 2H, J = 6.4 Hz, N-$\underline{CH_2}$-CH_2), 6.89-7.21 (m, 7H, aromatic), 9.43 (broad s, 2H, N^+H_2).

MS : m/z $[M\text{-}HCl]^+$ 270.1200, $C_{16}H_{18}N_2S$ requires 270.1191.

N-([^{13}C]Methyl)-N-methyl-10H-phenothiazine-10-propanamine 4c

From the free base of **3c**, **4c** was prepared in a similar manner as in **4a**. Yield 69 %.

^{1}H NMR : δ 1.95 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.20 (d, 3H, $J_{^{13}C-H}$ = 132.8 Hz, N-$^{13}\underline{CH_3}$), 2.20 (d, 3H, $J_{^{13}C-N-C-H}$ = 5.6 Hz, N-$\underline{CH_3}$), 2.37 (m, 2H, -$\underline{CH_2}$-N), 3.91 (t, 2H, J = 7.1 Hz, N-$\underline{CH_2}$-CH_2), 6.87-7.17 (m, 7H, aromatic).

^{13}C NMR : δ 46.28 (qq, $J_{^{13}C-H}$ = 133 Hz, $J_{^{13}C-N-C-H}$ = 5 Hz, N-$^{13}\underline{CH_3}$).

The hydrochloride **4c** : m.p. 179-181 [lit. 181](5).

MS : m/z $[M\text{-}HCl]^+$ 285.1372, $C_{16}H_{20}{}^{13}CN_2S$ requires 285.1381.

ACKNOWLEDGEMENTS

The authors thank Drs. Y.Sumida and T.Ohno for their helpful suggestions in the preparation of the manuscript and Mr. A.Hashimoto for his technical assistance.

REFERENCES

1. Olofson R.A., Martz J.T., Senet J.-P., Piteau M. and Malfroot T. *J.Org.Chem.* **49:** 2081-2082 (1984)
2. Tomita M., Masaki Y., Fujitani K. and Sakatani Y. *Chem. Pharm. Bull.* **16:** 688-694 (1968)
3. Neuhoff E.W. and Auterhoff H. *Archiv der Pharmazie* **288:** 400-407 (1955)
4. Moffat A.C. e.d. *Clarke's Isolation and Identification of Drugs* Second Ed., The Pharmaceutical Press, 1986.
5. Cadogan, J.I.G. Dictionary of Organic Compounds 6th edition. Chapman & Hall 5419, Vol.6, 1996.

