# Syntheses of Some Hydroxylated Metabolites of Psychotropic Trifluoromethyl Analogs of Chlorpromazine

*E. A. Nodiff (1), H. L. Sharma (2), P. C. Taunk, A. P. Shukla, M. D. Sadhnani, (Miss) S. B. Tambi and R. L. Mital* (3)*

Department of Chemistry, University of Rajasthan,
Jaipur-302004, India

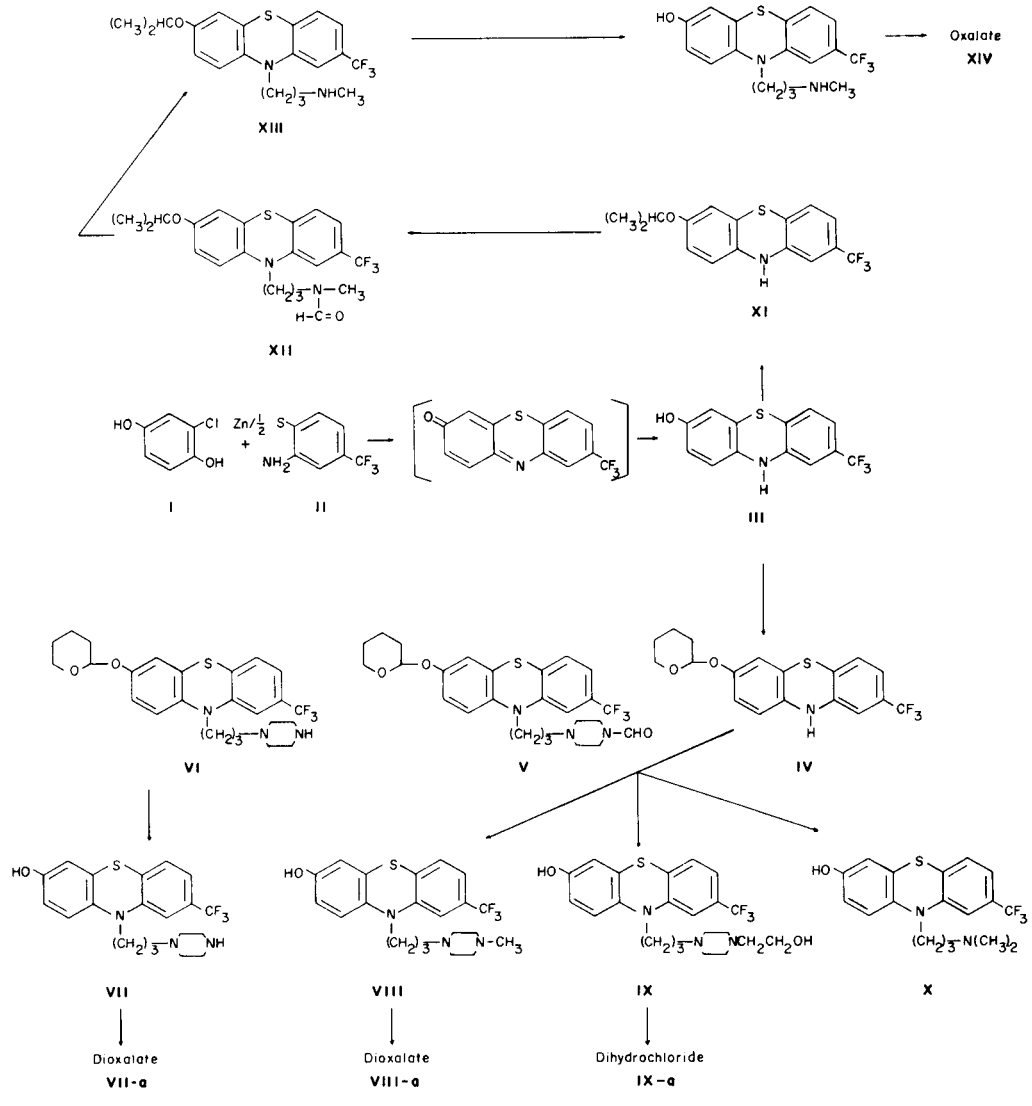
Received April 24, 1981

The syntheses of 7-hydroxy derivatives of trifluoperazine, nor$_1$-trifluoperazine, fluphenazine, triflupromazine and nor$_1$-triflupromazine are described. These were prepared as analytical standards for the identification of these metabolites in biological materials.

*J. Heterocyclic Chem.*, 18, 1529 (1981).

In order to design more effective psychotropic agents it is important to fully understand their mode of action. Essential to this understanding, is the knowledge of their metabolites whose identification depends upon the availability of appropriate reference standards. To date a fair number of reference standards of this sort are available for the earliest of phenothiazine tranquillisers, chlorpromazine (4-8). The objective of this program was to synthesise

Scheme I



reference analytical standards for the metabolites of the newer potent trifluoromethyl analogs of chlorpromazine *viz* trifluoperazine, fluphenazine and triflupromazine. The major metabolic pathway of chlorpromazine in schizophrenic humans is *via* ring hydroxylation particularly at the 7-position of the drug molecule (9). Another metabolic modification includes *N*-demethylation leading to $nor_1$ and $nor_2$ derivatives (10). Hence 7-hydroxy derivatives of trifluoperazine, $nor_1$-trifluoperazine, fluphenazine, triflupromazine and $nor_1$-triflupromazine (11) were synthesised and made available to the Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Maryland, USA as our contribution in their expanded program to elucidate the therapeutic mechanism of these important phenothiazine tranquillisers.

The preparation of 7-hydroxytriflupromazine (X), 7-hydroxyfluphenazine (IX), 7-hydroxytrifluoperazine (VIII), 7-hydroxy-$nor_1$-trifluoperazine (VII) and 7-hydroxy-$nor_1$-triflupromazine (XIV) is outlined in Scheme I. The prepartion of this family of compounds was begun with the synthesis of 2-trifluoromethyl-7-hydroxyphenothiazine (III) by adaptation of the procedure reported by Nodiff and Hausman (12) for the preparation of III to IV and its *N*-alkylation (xylene-sodium hydride) with 3-dimethylaminopropyl chloride, 3-[4-$\beta$-hydroxyethyl-1-piperazinyl]-propyl chloride (13) and 3-(4-methyl-1-piperazinyl)propyl chloride (14) furnished X, IX, and VIII, respectively. Similarly *N*-alkylation of IV with 1-formyl-4-(3-chloropropyl)piperazine (15) gave V. Its alkaline hydrolysis to VI followed by acidic depyranylation provided VII. Similar conversion of III to its 7-isopropyl ether (XI) and its alkylation with *N*-(3-chloropropyl)-*N*-methylformamide (16) yielded XII. Subsequent alkaline hydrolysis of XII to XIII followed by acidic cleavage of its ether linkage furnished XIV.

## EXPERIMENTAL

Melting points were determined in sealed evacuated capillary tubes and are uncorrected. All reactions were mechanically stirred under dry nitrogen and in the absence of strong direct light. Infrared spectra were taken as Nujol mulls on a Perkin-Elmer (Model 137B) Infracord spectrophotometer. All compounds had their ir spectra compatible with their assigned structures. Organic solutions were dried with anhydrous magnesium sulphate and decolorised with Darco G-60. Concentration and complete solvent removal were carried out under reduced pressure. Elemental analyses were performed by Micro Analysis Inc., Wilmington, Delaware.

2-Trifluoromethyl-7-hydroxyphenothiazine (III).

The reaction between 25.35 g (0.0564 mole) of the zinc salt II (17) and 15 g (0.1038 mole) of 2-chlorohydroquinone (I) (Aldrich Chemical Co.) carried out in the usual manner (12) afforded III as tan plates, mp 211-214° (benzene) in 70% yield. Vacuum sublimation at 160-180° at 0.01 mm pressure provided an analytical sample, mp 211-213° [lit mp (18) 211-214°].

*Anal.* Calcd. for $C_{13}H_8F_3NOS$: C, 55.12; H, 2.82; N, 4.94. Found: C, 55.02; H, 2.78; N, 4.54.

2-Trifluoromethyl-7-tetrahydropyranyloxyphenothiazine (IV).

A mixture of 28.3 g (0.1 mole) of III, 300 ml of dihydropyran, 0.5 g sodium hydrosulphite and 1 ml of concentrated hydrochloric acid was stirred at room temperature for 3 hours at 80° for an additional 2 hours. After standing overnight, the solution was washed with 10% sodium hydroxide and water, dried, decolorised and concentrated. The residual dark red oil was pumped for 4 hours at 110°, dissolved in 300 ml of ethanol, decolorised and allowed to evaporate slowly at room temperature. The residual pink solid was washed with chilled methanol to give 12.2 g (34%) of IV as a white solid which melted initially at 171° then solidified and remelted at 211°. Recrystallisation from methanol provided an analytical sample, mp 172°.

*Anal.* Calcd. for $C_{18}H_{16}F_3NO_2S$: C, 58.85; H, 4.35; N, 3.81. Found: C, 58.39; H, 4.35; N, 3.51.

2-Trifluoromethyl-7-tetrahydropyranyloxy-10-[3-(4-formamido-1-piperazinyl)propyl]phenothiazine (V).

To a solution of 5.13 g (0.014 mole) of IV in 30 ml of dry zylene was added 0.81 g (0.017 mole) of sodium hydride (50% dispersion in mineral oil). The mixture was stirred at room temperature for 2 hours. A solution of 3.99 g (0.021 mole) of 1-formyl-4-(3-chloropropyl)piperazine (15) in 15 ml of dry xylene was then added and refluxed for 5 hours. After cooling the mixture was poured into 250 ml of water containing 2.5 g of ammonium chloride. The separated organic layer was washed with water and dried. Removal of solvent under reduced pressure gave 4.92 g (66%) of V as yellow viscous oil which decomposes on attempted distillation. It was used as such for the next step without further purification.

2-Trifluoromethyl-7-tetrahydropyranyloxy-10-(3-piperazinopropyl)phenothiazine (VI).

A mixture of V, 180 ml of ethanol, 25 ml of 20% sodium hydroxide was heated under reflux for 3 hours. Concentration to half of its volume with subsequent pouring into 500 ml of ice cold water provided an oil which was then taken up in benzene. The benzene layer was washed with water and dried. Evaporation of the solvent gave a yellow viscous oil (70%). Attempted purification by distillation under reduced pressure resulted in decomposition. Hence, it was used as such for the next step of the reaction.

2-Trifluoromethyl-7-hydroxy-10-(3-piperazinopropyl)phenothiazine (VII).

The above oil (VI) was taken up in 10% hydrochloric acid and the acid extracts were then basified with 30% ammonia to give a semi solid mass. The product was extracted with benzene, washed with water, dried, decolorised and concentrated. The residual tan oil on trituration with petroleum ether (60-80°) afforded VII (69%) as a light yellow solid, mp 110° (benzene-petroleum ether). Sublimation at 260° at 0.05 mm pressure provided an analytical sample, mp 111°.

*Anal.* Calcd. for $C_{20}H_{22}F_3N_3OS$: C, 58.67; H, 5.37; N, 10.26. Found: C, 58.54; H, 5.29; N, 9.86.

2-Trifluoromethyl-7-hydroxy-10-(3-propylpiperazine)phenothiazine Dioxalate (VIIa).

To 2.863 g (0.007 mole) of VII in 40 ml of dry ether was added, dropwise with stirring, a solution of 1.36 g (0.0151 mole) of anhydrous oxalic acid in 15 ml of dry ether. The resulting white crystalline solid was washed with petroleum ether and crystallised from ligroin-ethanol to give 2.92 g (71%) of VIIa, mp 208-209°.

*Anal.* Calcd. for $C_{24}H_{26}F_3N_3O_9S$: C, 48.89; H, 4.41; N, 7.13. Found: C, 48.84; H, 4.32; N, 7.00.

2-Trifluoromethyl-7-hydroxy-10-3-(4-methyl-1-piperazinyl)propyl]phenothiazine (VIII).

To a suspension of 0.77 g (0.016 mole) of sodium hydride (50% disper-

sion in mineral oil) in 50 ml of dry xylene was added a solution of 5.13 g (0.014 mole) of IV in dry xylene. The mixture was stirred for 1 hour at room temperature. A solution of 3.872 g (0.022 mole) of 1-(3-chloropropyl)-4-methylpiperazine (14) in 25 ml of dry xylene was then added dropwise and refluxed for 3 hours. After cooling the mixture was poured into 250 ml of chilled water containing 1 g of ammonium chloride. Extraction with ether, followed by extraction of ethereal layer with 10% hydrochloric acid and basification of combined acid extracts with 30% ammonium hydroxide produced a white solid. The resulting solid was again extracted with ether, dried, decolorised and concentrated to furnish 2.82 g (49%) of VIII, mp 195°, as white neeles (ethanol-ligroin).

*Anal.* Calcd. for $C_{21}H_{24}F_3N_3OS$: C, 59.57; H, 5.67; N, 9.92. Found: C, 59.54; H, 5.61; N, 10.10.

2-Trifluoromethyl-7-hydroxy-10-[3-(4-methyl-1-piperazinyl)propyl]phenothiazine Dioxalate (VIIIa).

Compound VIII was converted to its dioxalate salt VIIIa in 80% yield as described in the synthesis of VIIa, mp 205-206°, white crystalline solid (ethanol-ligroin).

*Anal.* Calcd. for $C_{25}H_{28}F_3N_3O_9S$: C, 49.75; H, 4.64; N, 6.96. Found: C, 49.69; H, 4.41; N, 6.79.

2-Trifluoromethyl-7-hydroxy-10-[3-(4-β-hydroxyethyl-1-piperazinyl)propyl]phenothiazine (IX).

Alkylation of IV with 3-(4-β-hydroxyethyl-1-piperazinyl)propyl chloride (13) (xylene, sodium hydride, 2 hours stirring at room temperature, 3 hours stirring at 80° after addition of side chain material and 8 hours reflux thereafter and with the same work up as for VIII) gave yellow oil. This was taken up in ethyl acetate, the organic layer was washed with water, dried and concentrated. The resulting oil was purified by distillation under reduced pressure to provide pale yellow oil in 40% yield (bp 270-280° at 0.01 mm pressure).

*Anal.* Calcd. for $C_{22}H_{26}F_3N_3O_2S$: C, 58.28; H, 5.74; N, 9.27. Found: C, 57.96; H, 5.71; N, 8.89.

2-Trifluoromethyl-7-hydroxy-10-[3-(4-β-hydroxyethyl-1-piperazinyl)propyl]phenothiazine Dihydrochloride (IXa).

To an ice cold solution of IX (2.27 g, 0.005 mole) in 12 ml of dry chloroform-methanol was added dropwise an excess of ethereal hydrogen chloride solution. The crude hydrochloride salt on recrystallisation with ethanol provided IXa (60%) as a white crystalline solid (mp 216-218°).

*Anal.* Calcd. for $C_{22}H_{28}Cl_2F_3N_3O_2S$: C, 50.19; H, 5.32; N, 7.98. Found: C, 49.98; H, 5.10; N, 7.62.

2-Trifluoromethyl-7-hydroxy-10-(3-dimethylaminopropyl)phenothiazine (X).

Alkylation of IV with 3-dimethylaminopropyl chloride (DMPC, Koch Light Labs Ltd.) (xylene, sodium hydride, stirring at room temperature for 1 hour refluxing for an additional hour and further refluxing for 17 hours after adding DMPC and with the same work up as for VIII) gave 2.82 g (55%) of X as a yellow solid. Recrystallisation from ethanol-petroleum ether (60-80°) provided an analytical sample as an off-white crystalline solid, mp 174-176°.

*Anal.* Calcd. for $C_{18}H_{19}F_3N_2OS$: C, 58.69; H, 5.16; N, 7.60. Found: C, 58.54; H, 5.12; N, 7.32.

2-Trifluoromethyl-7-isopropoxyphenothiazine (XI).

A mixture of 2.83 g (0.01 mole) of III, 0.5 g of sodium dithionite, 110 ml of 10% ethanolic potassium hydroxide and 1.722 g (0.014 mole) of 2-bromopropane was refluxed for 2 hours and the resulting yellow suspension was poured into 2 l of cold water. The precipited yellow solid was filtered and dried in vacuum. Crystallisation from benzene provided 72% of XI as pale yellow crystals. An analytical sample was obtained by recrystallisation from methanol, mp 171°.

*Anal.* Calcd. for $C_{16}H_{14}F_3NOS$: C, 59.07; H, 4.30; N, 4.30. Found: C, 58.92; H, 4.21; N, 4.01.

2-Trifluoromethyl-7-isopropoxy-10-[3-(*N*-methylformamido)propyl]phenothiazine (XII).

To a suspension of 0.77 g (0.016 mole) of sodium hydride (50% dispersion in mineral oil) in 25 ml of dry xylene was added a solution of 4.65 g (0.014 mole) of XI in dry xylene. The mixture was stirred at room temperature for 2 hours. A solution of 2.85 g (0.021 mole) of *N*-(3-chloropropyl)-*N*-methylformamide (16) in 15 ml of dry xylene was added dropwise and the mixture was then refluxed for 8 hours. After cooling, the mixture was poured into 250 ml of cold water containing 2.5 g of ammonium chloride. Evaporation of xylene in vacuum provided 1.82 g (31%) of XII as pale brown oil which was used without further purification.

2-Trifluoromethyl-7-isopropoxy-10-[3-(*N*-methylaminopropyl)]phenothiazine (XIII).

A mixture of 5.93 g (0.014 mole) of XII, 25 ml of ethanol and 2.5 ml of 20% sodium hydroxide was heated under reflux for 3 hours, concentrated to half of its volume and poured into 100 ml of cold water. The resulting gum was extracted with ether, and the ethereal layer was extracted with 5% hydrochloric acid and the acid extracts were basified with 10% sodium hydroxide. The resulting gummy mass was then taken up in ether, washed with water, dried and concentrated in vacuum to furnish 58% of a tan oil which decomposes on attempted distillation. It was used as such for the next step.

2-Trifluoromethyl-7-hydroxy-10-[-3-(*N*-methylaminopropyl)] phenothiazine Oxalate (XIV).

A mixture of 1.2 g (0.003 mole) of XIII and 30 ml of concentrated hydrochloric acid was heated at 105° for 1 hour. The solution was cooled, diluted with 300 ml of water and extracted with ether (discarded). The aqueous layer was brought to *p*H-8 with 10% sodium hydroxide. The resulting pink gum was taken up in ether, dried, decolorised and concentrated to dryness to afford 1 g of yellow viscous oil. The latter was converted to its oxalate salt (XIV) using the procedure reported for VIIa, mp 195° (89%) (ethanol-ligroin).

*Anal.* Cacld. for $C_{19}H_{19}F_3N_2O_5S$: C, 51.35; H, 4.27; N, 6.30. Found: C, 51.19; H, 4.35; N, 6.42.

Acknowledgement.

The authors are grateful to Dr. Albert A. Manian of the Psychopharmacology Research Branch, National Institute of Mental Health, for his interest and helpful suggestions. These compounds were prepared under PL-480 program, Agreement Project No. 01-125-A-PL-480 with the Psychopharmacology Research Branch, National Institute of Mental Health.

## REFERENCES AND NOTES

(1) Germantown Laboratories, Inc. (Affiliated with Franklin Institute), 4150 Henry Avenue, Philadelphia, PA 19144, USA.

(2) Department of Pharmacology, S. M. S. Medical College, Jaipur-302004, India.

(3) To whom correspondence should be addressed at The Department of Chemistry, University of Rajasthan, Jaipur, India.

(4) E. A. Nodiff, S. Ina, N. Oda, T. Hayazaki, S. Nisibe, T. Khono, M. Hausman and A. A. Manian, *J. Heterocyclic Chem.*, **4**, 239 (1967).

(5) E. A. Nodiff, N. Oda, T. Hayazaki, S. Ina, T. Ito, S. Nisibe, T. Ueda, K. Suzuki, M. Hausman and A. A. Manian, *ibid.*, **5**, 165 (1968).

(6) E. A. Nodiff, K. Tanabe, F. Schnierle, S. Morosawa, T. W. Hoffman, K. Takeda and A. A. Manian, *ibid.*, **7**, 203 (1970).

(7) E. A. Nodiff, H. L. Sharma, T. Khono, F. Schnierle, M. Mori and A. A. Manian, *ibid.*, **8**, 321 (1971).

(8) E. A. Nodiff, T. Hayazaki, T. Ito, H. L. Sharma, T. Khono, T. Ueda, S. Morosawa and A. A. Manian, *ibid.*, **8**, 1075 (1971).

(9) H. Goldenberg and V. Fishman, *Biochem. Biophys. Res. Commun.*, **14**, 404 (1964).

(10) C. F. Rodriguez and D. E. Johnson, *Life Sci.*, **5**, 1283 (1966).

(11) Trifluopromazine, trifluoperazine and fluphenazine are the

generic names for 2-trifluoromethyl-10-(3-dimethylaminopropyl)phenothiazine, 2-trifluoromethyl-10-[3-(4-methyl-1-piperazinyl)propyl]phenothiazine and 2-trifluoromethyl-10-[3-(4-β-hydroxyethyl-1-piperazinyl)-propyl]phenothiazine, respectively. $Nor_1$-trifluoperazine and $nor_1$-triflupromazine are the derivatives of trifluoperazine and triflupromazine in which the 10-side chain has lost one methyl group from the piperazino or the dimethylamino moiety.

(12) E. A. Nodiff and M. Hausman, *J. Org. Chem.*, **31**, 625 (1966).

(13) Japanese Patent 11841 (1960); *Chem. Abstr.*, **55**, 11448b (1961).

(14) P. A. Barrett, A. G. Caldwell and L. P. Walls, *J. Chem. Soc., Part II*, 2404 (1961).

(15) P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff and C. L. Zirkle, *J. Org. Chem.*, **25**, 944 (1960).

(16) E. A. Nodiff, S. Ina, N. Oda, T. Hayazaki, S. Nishibe, T. Khono, M. Hausman and A. A. Manian, *J. Heterocyclic Chem.*, **4**, 239 (1967).

(17) A. I. Kiprianov and L. M. Yagupolsky, *Zh. Obshch. Khim.*, **22**, 2209 (1952); *Chem. Abstr.*, **47**, 4769f (1953).

(18) A. J. Saggiomo and B. M. Sutton, *J. Med. Chem.*, **11**, 1089 (1968).