Research Institute of Temple University

Synthesis of Possible Metabolites of Chlorpromazine. I. 7-Hydroxy Derivatives of Chlorpromazine, nor_1-Chlorpromazine and nor_2-Chlorpromazine (1a,2)

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The title compounds and various derivatives have been prepared as analytical standards for the identification of chlorpromazine metabolites in biological materials. Additional evidence is presented for the existence of a halogen-induced Smiles rearrangement in the phenothiazine series.

Despite the widespread use of psychopharmacological agents for the treatment of mental illness, their mode of action is still equivocal.

In order to elucidate the therapeutic mechanism of these drugs it is important to know their metabolic fate. The National Institute of Mental Health is therefore trying to develop analytical techniques for the identification of psychoactive drug metabolites in biological materials.

Because of its intensive use in modern psychiatric practise, chlorpromazine (2) has been chosen for initial investigation. The synthesis of several possible metabolites of chlorpromazine, for use as reference standards in the analytical studies, has been effected as outlined in Schemes 1, 2 and 3 of this paper (3).

The preparation of 7-hydroxychlorpromazine (Scheme 1) was begun with the conversion of 2-chloro-7-hydroxyphenothiazine (I) (4) to its isopropyl ether (II).

Alkylation of II with 3-dimethylaminopropyl chloride, in the systems shown in Table I, provided 7-isopropoxychlorpromazine (III).

7-Hydroxychlorpromazine (IV) was obtained on hydrolysis of III with refluxing, concentrated hydrochloric acid. A single attempt to prepare IV by cleavage of its methyl ether with pyridine hydrochloride was unsuccessful. Demethylation was accompanied by removal of the *N*-side chain and the only isolated product was 2-chloro-7-hydroxyphenothiazine (I).

TABLE I

Method	Solvent	Base	Temp. °C	Time hr.	Yield %
A	DMF	$NaNH_2$	100	5	32
B	Toluene	$NaNH_2$	reflux	8	40
C	Xylene	NaH	reflux	3	96
D	DMSO	NaH	115	5	62

The sequent reactions used to convert IV to its sulfoxide (VIII), and those outlined for the Nor_1-derivatives in Scheme 2, (5) were routine and are detailed in the Experimental Section.

The reaction between 2-chloro-7-hydroxyphenothiazine (I) (4) and dihydropyran (Scheme 3), in the presence of a catalytic quantity of concentrated hydrochloric acid or alcoholic hydrogen chloride gave 45% of 2-chloro-7-tetrahydropyranyloxyphenothiazine (XVII). When the reaction between I and dihydropyran was carried out in benzene, in the presence of *p*-toluenesulfonic acid, the yields of XVII were erratic and its quality was poor.

Cyanoethylation of XVII provided the *N*-cyanoethyl derivative (XVIII), m.p. 133-135°. A lower-melting (m.p. 115-117°) polymorph of XVIII was also isolated.

Catalytic (Raney nickel) hydrogenation of XVIII in acetic anhydride, at 30°, afforded 59% of 10-(3-acetamidopropyl)-2-chloro-7-tetrahydropyranyloxyphenothiazine (XIX). At 50°, the same reaction gave 55% of the diacetyl derivative (XX). The latter compound was also prepared by treating XIX with acetic anhydride in glacial acetic acid (yield, 61%).

Conversion of XX to its sulfoxide (XXI) was effected by oxidation with ethanolic 30% hydrogen peroxide. The *O*-deacetylated sulfoxide (XXV) was isolated as a by-product of this reaction.

7-Hydroxy-nor_2-chlorpromazine (XXIII) and its hydrochloride (XXIV) were prepared using the four methods outlined in Scheme 3.

In Method A, XXIII was obtained in 42% yield by hydrolysis of XIX. Reduction of XVIII with lithium aluminum hydride (Method B) or with hydrogen (Method C) provided XXIII in respective yields of 37 and 52% (as the hydrochloride). Method D involved initial hydrolysis of XVIII with ethereal hydrogen chloride (90% yield) or ethanolic hydrochloric acid (95% yield) and subsequent catalytic reduction of XXII (49%).

An attempt to prepare XXII more directly by

cyanoethylation of 2-chloro-7-hydroxyphenothiazine (I) was unsuccessful. An impure product was obtained whose infrared spectrum and lack of solubility in dilute base indicated that it was most probably the *O*-cyanoethyl derivative of I. (I and XXII are both soluble in dilute base.)

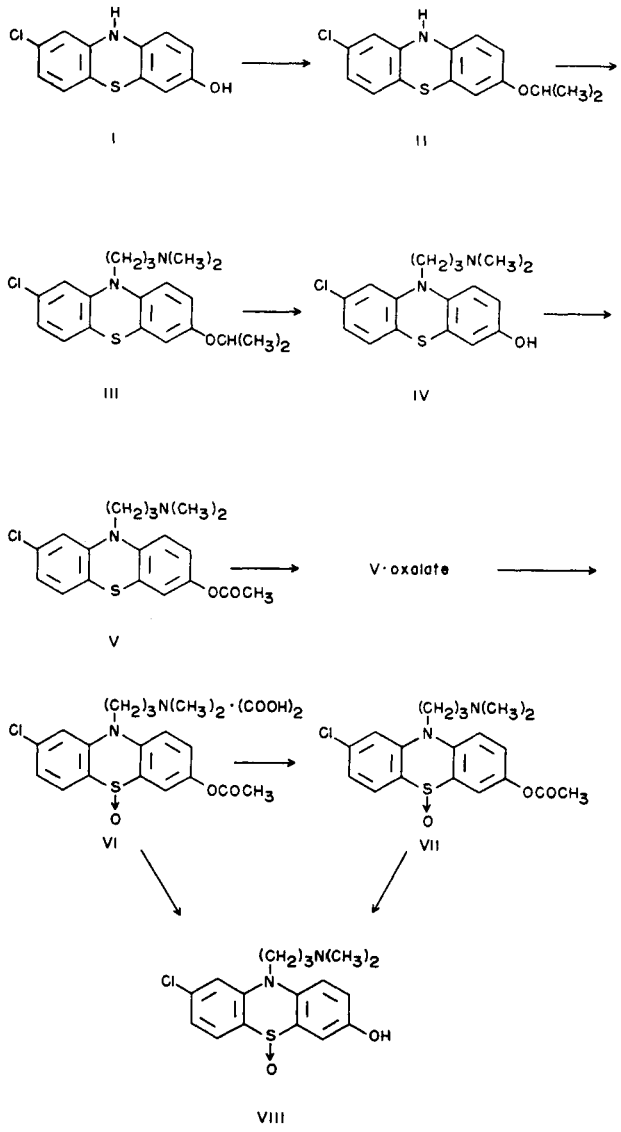
An early attempt to prepare 2-chloro-7-benzyloxyphenothiazine (XXXI), as a possible intermediate in the synthesis of 7-hydroxychlorpromazine (IV), is outlined in Scheme 4.

This preparation of XXXI was initiated with the reaction between 3-chloro-4-nitrophenol (XXVI) (6) and 2-bromo-4-chlorothiophenol (XXVII) (7). The resulting diphenylsulfide (XXVIII) was routinely reduced, formylated and benzylated to provide 2-bromo-4-chloro-2'-formamido-5'-benzyloxydiphenylsulfide (XXIX).

On cyclodehydrohalogenation of XXIX in refluxing DMF (potassium carbonate, copper-bronze) a benzyloxychlorophenothiazine (consistent elemental and infrared analyses) was isolated. This compound (XXX) was not identical with authentic 7-benzyloxy-2-chlorophenothiazine (XXXI) obtained by benzylation of 2-chloro-7-hydroxyphenothiazine (I).

Subsequent discovery of a halogen-induced Smiles rearrangement in the phenothiazine series (8) indicated that XXX was most probably 7-benzyloxy-3-chlorophenothiazine.

SCHEME I



EXPERIMENTAL

Melting points were determined in sealed, evacuated, capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected.

All reactions were mechanically stirred under dry nitrogen and in the absence of strong, direct light.

Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Infrared spectra were taken as liquid films or Nujol mulls on a Perkin-Elmer Model 137B, Infracord Spectrophotometer.

Organic solutions were dried with anhydrous magnesium sulfate and decolorized with Darco G-60. Concentration and complete solvent removal were carried out in round-bottom flasks connected through a dry-ice trap to a water aspirator or a vacuum pump.

2-Chloro-7-isopropoxyphenothiazine (II).

To a mixture of 25 g. (0.1 mole) of 2-chloro-7-hydroxyphenothiazine (I) (4,9), 5 g. of sodium hydrosulfite and 110 ml. of 10% ethanolic potassium hydroxide was added 23.8 g. (0.14 mole) of 2-iodopropane. The reaction mixture was heated under reflux for 8 hours and the resulting green suspension was poured into 2 l. of cold water. The pale green solid which separated was filtered and dried *in vacuo*. Crystallization from benzene provided 19.4 g. (67%) of II, m.p. 161.5-169°. This material was used for the next step without further purification.

Additional crystallization of an aliquot of II from methanol provided an analytical sample as pale tan crystals, m.p. 170-170.5°.

Anal. Calcd. for $C_{15}H_{14}ClNOS$: C, 61.75; H, 4.80; N, 4.80. Found: C, 61.69; H, 4.76; N, 4.92.

2-Chloro-10-(3-dimethylaminopropyl)-7-isopropoxyphenothiazine (III). Method C (Table I).

A mixture of 17 g. (0.059 mole) of II, 3.1 g. (0.064 mole) of sodium hydride (50% dispersion in mineral oil) (10) and 200 ml. of dry xylene was heated under reflux for 1 hour. The mixture was cooled to room temperature and a solution of 10.5 g. (0.087 mole) of 3-dimethylaminopropyl chloride in 90 ml. of dry xylene was added. Reflux was continued for 3 hours. After cooling, the mixture was poured into 1 l. of cold water containing 3.7 g. of ammonium chloride. The layers were separated and the aqueous layer was extracted with ether. The xylene and ether layers were combined and extracted with 3 x 200 ml. of 10% hydrochloric acid. The combined acid extracts were slowly basified with 10% sodium hydroxide solution until separation of oil was complete. The oil was extracted with 3 x 200 ml. of ether, dried and stripped of solvent. The residual yellow oil solidified on standing, yield 21 g. (96%), m.p. 45-47°. Distillation provided an analytical sample, b.p. 210-219°/0.008 mm., m.p. 53-55°.

Anal. Calcd. for $C_{20}H_{25}ClN_2OS$: C, 63.73; H, 6.68; N, 7.43. Found: C, 63.68; H, 6.76; N, 6.83.

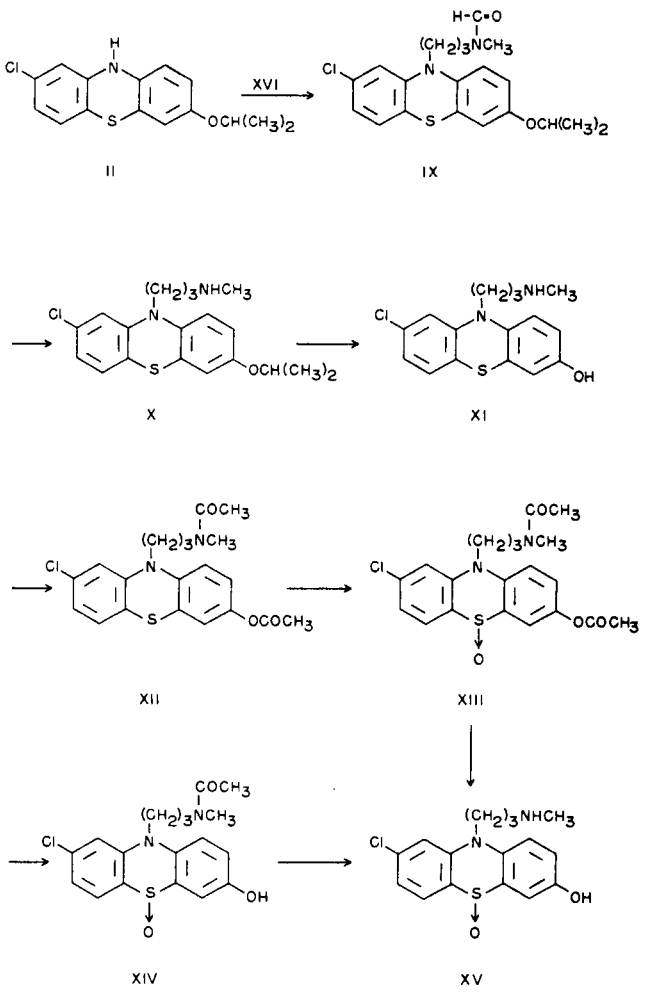
Methods A, B and D (Table I) were carried out using essentially the same ratio of II, base, solvent and dimethylaminopropyl chloride and the same workup as described above. The infrared spectra of samples of III obtained by all four methods were identical.

2-Chloro-10-(3-dimethylaminopropyl)-7-hydroxyphenothiazine (IV).

A mixture of 10 g. (0.027 mole) of III and 150 ml. of concentrated hydrochloric acid was heated under reflux for 1 hour. The solution was cooled, diluted with 1 l. of water, and adjusted to *p*H 8 with 10% sodium hydroxide solution. The resulting pink gum was taken up in ether, dried and decolorized. Concentration of the ether solution gave 4 g. of pink solid, m.p. 171-178°. Repeated crystallization from ether provided 2.7 g. (30%) of IV as white crystals, m.p. 177-178°.

Anal. Calcd. for $C_{17}H_{19}ClN_2OS$: C, 60.98; H, 5.72; N, 8.36. Found: C, 61.15; H, 5.97; N, 8.24.

SCHEME 2



2-Chloro-10-(3-dimethylaminopropyl)-7-methoxyphenothiazine.

Alkylation of 2-chloro-7-methoxyphenothiazine (8,11), with dimethylaminopropyl chloride (xylene, sodium amide, 3 hour reflux, same workup as for III) gave 39% of oil, b.p. 210-213°/0.3 mm. Redistillation provided an analytical sample, b.p. 212°/0.3 mm.

Anal. Calcd. for $C_{18}H_{21}ClN_2OS$: C, 61.94; H, 6.07; N, 8.04. Found: C, 61.82; H, 6.36; N, 8.19.

An aliquot was dissolved in absolute ether and treated with hydrogen chloride gas. The resulting precipitate was recrystallized from isopropyl alcohol to give white crystals of the hydrochloride, m.p. 207-209°.

Anal. Calcd. for $C_{18}H_{21}ClN_2OS \cdot HCl$: C, 56.08; H, 5.76; N, 7.27. Found: C, 56.03; H, 6.02; N, 7.40.

The xylene layers, which had been extracted with hydrochloric acid, were concentrated to yield 25% of the starting material, 2-chloro-7-methoxyphenothiazine.

Attempted Demethylation of 2-Chloro-10-(3-dimethylamino)-7 methoxyphenothiazine.

A mixture of 8 g. (0.023 mole) of the methoxy compound and 13.3 g. (0.12 mole) of pyridine hydrochloride was heated at 200° for 5 hours. The melt was allowed to cool and added to ice water yielding 5.2 g. of solid, m.p. 212-213°. Recrystallization gave a white solid, m.p. 224-226° which was identical with 2-chloro-7-hydroxyphenothiazine (infrared and mixture melting point comparison).

7 Acetoxy-2-chloro-10-(3-dimethylaminopropyl)phenothiazine (V).

A mixture of 3.35 g. (0.01 mole) of IV, 50 ml. of glacial acetic acid, 50 ml. of acetic anhydride and 0.4 g. of sodium hydrosulfite was heated under reflux for 4 hours. The solution was concentrated to 50 ml., poured into 500 ml. of water and adjusted to *p*H 10 with 20% sodium hydroxide solution. The resulting solid was dissolved in ether, washed with water and dried. Removal of the solvent left a tan oil which, on trituration with petroleum ether, gave 3.0 g. (80%) of V as pale yellow crystals, m.p. 72-73°. Repeated crystallization from ligroin (b.p. 60-90°) provided an analytical sample as glistening white crystals, m.p. 70-71°.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_2S$: C, 60.56; H, 5.58; N, 7.44. Found: C, 60.65; H, 5.48; N, 6.81.

Oxalate of V.

To 2.64 g. (0.007 mole) of V in 40 ml. of ether was added a solution of 0.63 g. (0.007 mole) of anhydrous oxalic acid in a mixture of 15 ml. of ether and 1 ml. of ethanol. The resulting white crystals were washed with ether and crystallized from ligroin-ethanol (1:1) to give 2.78 g. (85%) of the oxalate of V, m.p. 160.5-161.5°.

Anal. Calcd. for $C_{21}H_{23}ClN_2O_6S$: C, 54.02; H, 4.96; N, 6.00. Found: C, 54.00; H, 5.44; N, 6.58.

7-Acetoxy-2-chloro-10-(3-dimethylaminopropyl)phenothiazine-5-oxide Oxalate (VI).

To a solution of 2.34 g. (0.005 mole) of the oxalate of V in 30 ml. of ethanol and 10 ml. of water was added 0.51 g. (0.0045 mole) of 30% hydrogen peroxide. The mixture was heated under reflux for 7 hours and the solvent was removed. The pale yellow residue was washed with ethanol and then ether to give 2.0 g. (83%) of VI, m.p. 194-195° (foaming). This material was used in the next step without further purification.

7-Acetoxy-2-chloro-10-(3-dimethylaminopropyl)phenothiazine-5-oxide (VII).

To a cooled (water-ice bath) solution of 3.5 g. (0.007 mole) of VI in 1.8 l. of water was added 0.76 g. (0.007 mole) of sodium carbonate in 15 ml. of water. The resulting white suspension was stirred at room temperature for 30 minutes and then extracted with chloroform. The pale brown extract was washed with water, dried and concentrated. Trituration of the residual oil with ether gave 1.3 g. (46%) of VII, m.p. 137-139.5°. Repeated crystallization from ligroin-ethanol provided the analytical sample as white needles, m.p. 149.5-150.5°.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_3S$: C, 58.07; H, 5.39; N, 7.15. Found: C, 58.18; H, 5.51; N, 7.30.

2-Chloro-10-(3-dimethylaminopropyl)-7-hydroxyphenothiazine-5-oxide (VIII).

A mixture of 1.0 g. of VII and 30 ml. of 5% ethanolic sodium hydroxide was heated under reflux for 50 minutes. The mixture was allowed to cool, poured into 300 ml. of water, acidified with 10% hydrochloric acid (*p*H 2) and extracted with chloroform (extract discarded). The acid layer was adjusted to *p*H 8 with solid sodium carbonate and extracted with chloroform. The dried extract was concentrated and the residual oil was triturated with ether. The resulting tan solid was washed with ether (0.35 g., m.p. 155-157°) and crystallized from ether-ethanol (5:1) to give 0.15 g. of VIII as white crystals, m.p. 163.5-164.5°.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.99. Found: C, 58.29; H, 5.67; N, 7.58.

Identical hydrolysis of VI provided 39% of VIII as white needles, m.p. 166-167° (chloroform-ether, 1:1).

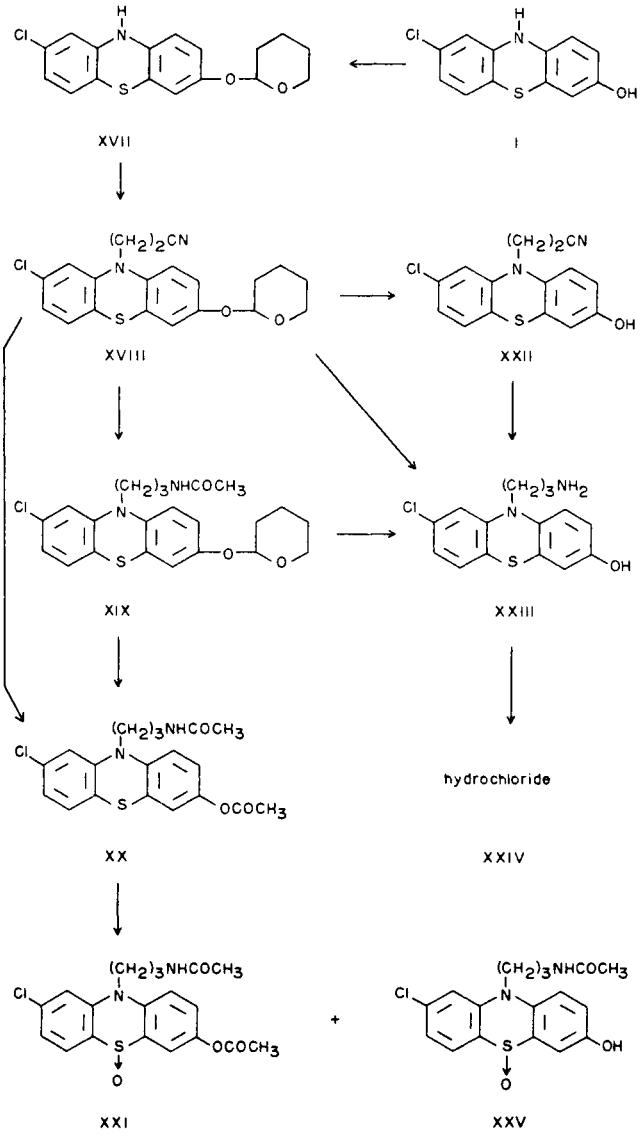
N-(3-Chloropropyl)-*N*-methylformamide (XVI).

To a suspension of 14.4 g. (0.3 mole) of sodium hydride (50% dispersion in mineral oil) in 250 ml. of dry toluene was added, at 0-5°, during 1 hour, a solution of 14.8 g. (0.25 mole) of *N*-methylformamide in 50 ml. of dry toluene. The mixture was stirred for 2 hours at room temperature and 55.1 g. (0.35 mole) of trimethylene chlorobromide was then added over a period of 1 hour. The mixture was heated under reflux for 8 hours, filtered and concentrated. The residue was distilled to give 13.6 g. (40%) of XVI, b.p. 125-133°/10 mm., n_D^{24} 1.4793 (lit., (5) b.p. 148-150°/30 mm.; n_D^{25} 1.4722).

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

To a suspension of 8.16 g. (0.17 mole) of a 50% dispersion of sodium hydride (mineral oil) in 50 ml. of dimethyl sulfoxide (DMSO) was added a solution of 40.9 g. (0.14 mole) of 2-chloro-7-isopropoxyphenothiazine (II) in 150 ml. of DMSO. The mixture was stirred at room temperature for 2 hours and there was then added 28.5 g. (0.21 mole) of *N*-(3-chloropropyl)-*N*-methylformamide (XVI) in 30 ml. of DMSO. The mixture was heated at 115-120° for 5 hours, allowed to cool, and poured into 2.5 l. of cold water containing 25 g. of ammonium chloride. The resulting tan gum was taken up in ether, washed with water, dried and decolorized. Evaporation of the ether

SCHEME 3



gave 49.5 g. of IX as pale brown oil which was used without further purification.

2-Chloro-7-isopropoxy-10-(3-methylaminopropyl)phenothiazine (X).

A mixture of 5.45 g. of IX, 180 ml. of ethanol and 25 ml. of 20% sodium hydroxide was heated under reflux for 3 hours, concentrated to half its volume and poured into 500 ml. of cold water. The resulting oil was extracted with ether, the ether was extracted with 5% phosphoric acid and the acid extracts were basified with solid potassium carbonate. The basic mixture was extracted with ether and the ether was washed with water and dried. Evaporation of the ether gave a tan oil which on distillation provided 3.25 g. (64%) of X, b.p. 196-200°/0.005 mm., n_D^{25} 1.6246.

Anal. Calcd. for $C_{19}H_{23}ClN_2OS$: C, 62.88; H, 6.39; N, 7.73. Found: C, 62.55; H, 6.55; N, 7.11.

2-Chloro-7-hydroxy-10-(3-methylaminopropyl)phenothiazine (XI).

A mixture of 1.13 g. (0.003 mole) of the isopropyl ether (X) 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 adjusted to *p*H 7 with 20% sodium hydroxide and to *p*H 8 with solid sodium carbonate. The resulting mixture was extracted with ether and the extract was dried, decolorized and concentrated. The tan residual oil was solidified by trituration with petroleum ether and the solid was crystallized from ether-petroleum ether (1:2) to give 0.52 g. of XI as off-white crystals, m.p. 160-161°.

Anal. Calcd. for $C_{16}H_{17}ClN_2OS$: C, 59.89; H, 5.34; N, 8.73. Found: C, 60.03; H, 5.49; N, 8.52.

Concentration of the mother liquor gave an additional 0.20 g. of XI (m.p. 158-160°) for a total yield of 0.72 g. (77%).

Compound XI was insoluble in 10% sodium hydroxide. It was soluble in 5% phosphoric acid and 3% hydrochloric acid. In 10% hydrochloric acid a hydrochloride precipitated whose IR spectrum was identical with that obtained by passing hydrogen chloride into an ethereal solution of XI, m.p. 204-206°.

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2OS$: C, 53.90; H, 5.08; N, 7.84. Found: C, 53.72; H, 5.12; N, 7.96.

7-Acetoxy-2-chloro-10-[3-(*N*-methylacetamido)propyl]phenothiazine (XII).

Acetylation of XI, using the procedure described for the preparation of V, gave 96% of XII as a tan oil.

Efforts to crystallize this material were unsuccessful. Attempted distillation of an aliquot at 0.005 mm. resulted in tar formation.

The infrared spectrum of the tan oil was consistent with the structure XII (12) and it was used in the next step without further purification.

7-Acetoxy-2-chloro-10-[3-(*N*-methylacetamido)propyl]phenothiazine-5-oxide (XIII).

A solution of 1.6 g. (0.004 mole) of XII, 20 ml. of ethanol and 0.49 g. (0.004 mole) of 30% hydrogen peroxide was heated under reflux for 7 hours. The solvent was removed and the residue was washed with ether. Crystallization from ligroin-ethanol (10:1) gave 0.5 g. (31%) of XIII, m.p. 197-198°.

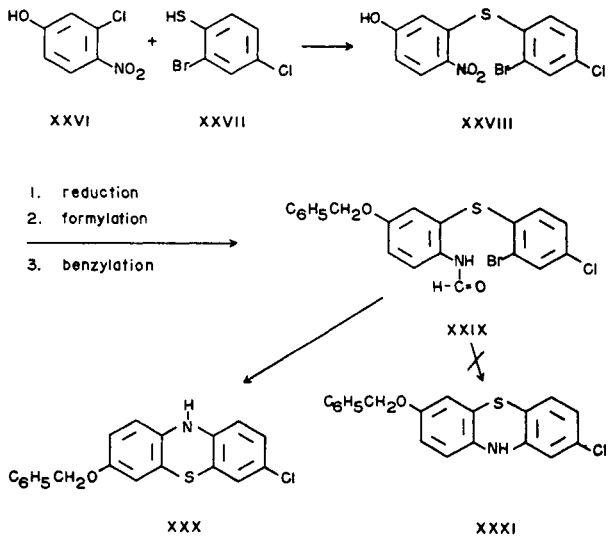
Anal. Calcd. for $C_{20}H_{21}ClN_2O_4S$: C, 57.07; H, 5.03; N, 6.66. Found: C, 57.18; H, 5.28; N, 6.40.

2-Chloro-7-hydroxy-10-[3-(*N*-methylacetamido)propyl]phenothiazine-5-oxide (XIV).

A mixture of 2.1 g. (0.005 mole) of XIII, 50 ml. of ethanol and 2 ml. of 10% ethanolic sodium hydroxide (0.005 mole) was heated under reflux for 50 minutes. The mixture was poured into 500 ml. of water and acidified with 10% hydrochloric acid. The resulting pink solid was extracted with chloroform, washed with water, dried and decolorized. Removal of the solvent left a pink solid which was crystallized from ligroin-ethanol (1:1) to give 1.24 g. (65%) of XIV as white crystals, m.p. 245-245.5° (dec.).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_3S$: C, 57.06; H, 5.05; N, 7.40. Found: C, 56.77; H, 5.28; N, 7.10.

SCHEME 4



2-Chloro-7-hydroxy-10-(3-methylaminopropyl)phenothiazine-5-oxide (XV). Method A.

A mixture of 2.1 g. (0.005 mole) of XIII and 30 ml. of 20% ethanolic potassium hydroxide was heated under reflux for 5 hours, allowed to cool, poured into 300 ml. of water, adjusted to *p*H 2 with 10% hydrochloric acid and extracted with chloroform. The aqueous phase was adjusted to *p*H 8 with solid sodium carbonate and extracted with chloroform. The dried extract was concentrated and the resulting pale yellow solid was washed with ether and crystallized from ether-ethanol (4:1). A 46% yield (0.77 g.) of XV was obtained as white crystals, m.p. 189-190° (dec.). Repeated crystallization from ether-ethanol raised the melting point to 201.5-202.5°.

Anal. Calcd. for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32. Found: C, 56.91; H, 5.22; N, 8.24.

2-Chloro-7-hydroxy-10-(3-methylaminopropyl)phenothiazine-5-oxide (XV). Method B.

A mixture of 0.38 g. (0.001 mole) of XIV and 10 ml. of 10% ethanolic potassium hydroxide was treated as described in Method A. Crude XV was obtained as off-white crystals, m.p. 180-181°. The infrared spectrum of this material indicated that it was the same as that isolated in Method A.

2-Chloro-7-tetrahydropyranyloxyphenothiazine (XVII).

A mixture of 25 g. (0.1 mole) of 2-chloro-7-hydroxyphenothiazine (I) (4), 300 ml. of dihydropyran and 1 ml. of concentrated hydrochloric acid was stirred at room temperature for 3 hours and at 60° for an additional hour. The mixture was allowed to cool, diluted with 300 ml. of ether and washed successively with 10% sodium hydroxide and water. The dried, decolorized ether solution was evaporated and the residue was pumped at 100° for 4 hours. Crystallization from ethanol gave a 45% yield (15 g.) of XVII, m.p. 159-161°.

The infrared spectrum of this material was identical with that of the analytical sample (m.p. 157-158°).

Anal. Calcd. for $C_{17}H_{16}ClNO_2S$: C, 61.17; H, 4.80; N, 4.20. Found: C, 61.40; H, 4.90; N, 3.85.

2-Chloro-10-(2-cyanoethyl)-7-tetrahydropyranyloxyphenothiazine (XVIII).

To a solution of 50 g. (0.15 mole) of XVII, 220 ml. of benzene and 2.2 ml. of Triton B (40% benzyltrimethylammonium hydroxide in methanol) was added, dropwise, 23.8 g. (0.45 mole) of acrylonitrile. The addition rate was adjusted to maintain the reaction temperature at 60°. The mixture was stirred at 70° for an additional hour, diluted with 200 ml. of hot methanol, decolorized and allowed to stand at room temperature overnight. The resulting solid was crystallized from ethanol-benzene to give 44.2 g. (76%) of XVIII as white needles, m.p. 126-130°. Recrystallization from methanol gave an analytical sample, m.p. 133-135°.

Anal. Calcd. for $C_{20}H_{19}ClN_2O_2S$: C, 62.10; H, 4.92; N, 7.24. Found: C, 61.96; H, 4.84; N, 7.39.

In an earlier synthesis, repeated crystallization from methanol gave a polymorph of XVIII, m.p. 115-117°.

Anal. Calcd. for $C_{20}H_{19}ClN_2O_2S$: C, 62.10; H, 4.92; N, 7.24. Found: C, 62.22; H, 5.20; N, 7.04.

The infrared spectra of the polymorphs of XVIII displayed only minor differences.

10-(3-Acetamidopropyl)-2-chloro-7-tetrahydropyranyloxyphenothiazine (XIX).

A mixture of 7.7 g. (0.02 mole) of XVIII, 14 g. of Raney nickel (13) and 130 ml. of acetic anhydride was shaken at 30° with hydrogen at 60 psig. for 3 hours. The mixture was filtered and the excess anhydride was then removed. The residual oil was dissolved in ethyl acetate, washed with water, 10% sodium carbonate, dried and concentrated. Addition of ligroin (b.p. 60-90°) precipitated XIX as a white solid (5 g., 59%), m.p. 134-135°. The infrared spectrum of this material was identical with that of the analytical sample (white needles) which melted at 127-128.5° after two crystallizations from ethanol-ligroin (b.p. 60-90°).

Anal. Calcd. for $C_{22}H_{25}ClN_2O_3S$: C, 61.02; H, 5.82; N, 6.47. Found: C, 60.96; H, 5.88; N, 6.78.

10-(3-Acetamidopropyl)-7-acetoxy-2-chlorophenothiazine (XX). Method A.

A mixture of 7.7 g. (0.02 mole) of XVIII, 130 ml. of acetic anhydride and 14 g. of Raney nickel was shaken at 50°, for 5 hours in a hydrogen atmosphere at 60 psig. After filtration and concentration, the residual oil was dissolved in ethyl acetate, washed with 10% sodium carbonate and water and dried. The pale yellow solution was concentrated to 10 ml. and refrigerated. The resulting white solid was washed with ether to give XX (4.3 g., 55%), m.p. 146-148°, which was used without further purification. Repeated crystallization from ethanol-ligroin (b.p. 60-90°) provided an analytical sample as white needles, m.p. 165.5-166.5°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_3S$: C, 58.34; H, 4.91; N, 7.16. Found: C, 58.35; H, 4.98; N, 7.28.

10-(3-Acetamidopropyl)-7-acetoxy-2-chlorophenothiazine (XX). Method B.

A solution of 2 g. (0.0046 mole) of XIX in 40 ml. of glacial acetic acid and 40 ml. of acetic anhydride was heated under reflux for 3 hours. The pale yellow solution was concentrated to one third its volume and poured into 100 ml. of water. The resulting mixture of water and yellow-brown oil was cooled in water-ice, adjusted to *p*H 10 with 10% sodium hydroxide and extracted with ethyl acetate. The extract was washed with water, dried, concentrated and diluted with petroleum ether to give 1.1 g. (61%) of XX, m.p. 141-145°. This material was the same as that described in Method A. It was used without further purification.

10-(3-Acetamidopropyl)-7-acetoxy-2-chlorophenothiazine-5-oxide (XXI).

A mixture of 4.5 g. (0.012 mole) of XX, 100 ml. of ethanol and 2.57 g. (0.023 mole) of 30% hydrogen peroxide was heated under reflux for 5 hours. Concentration provided a white solid which on washing with acetone gave 2.85 g. (61%) of XXI, m.p. 194-195°. The infrared spectrum of this material was identical with that of an analytical sample obtained by crystallization from acetone containing a small amount of ethanol, m.p. 199-200.5°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_4S$: C, 56.08; H, 4.71; N, 6.89. Found: C, 56.07; H, 4.66; N, 6.91.

Further concentration of the filtrate of the 2.85 g. of solid (above) left a deep red oil which solidified on trituration with acetone. Crystallization from ligroin-ether (2:1) gave a white solid, m.p. 242-244°, whose elemental analysis and infrared spectrum indicated that it was 10-(3-acetamidopropyl)-2-chloro-7-hydroxyphenothiazine-5-oxide (XXV).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_3S$: C, 55.96; H, 4.68. Found: C, 56.06; H, 4.86.

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine (XXIII). Method A.

A mixture of 3.4 g. (0.0078 mole) of 10-(3-acetamidopropyl)-2-chloro-7-tetrahydropyranyloxyphenothiazine (XIX) and 130 ml. of 30% ethanolic potassium hydroxide was heated under reflux for 5 hours. After cooling, the mixture was poured into 600 ml. of water and the resulting emulsion was adjusted to *p*H 2 with 10% hydrochloric acid. The insoluble hydrochloride was collected and washed with ether, m.p. 255-257.5° (1.3 g., 48%). This material was identical with that isolated in Methods B and C.

Solution of the hydrochloride in 300 ml. of water and adjustment to *p*H 8 with solid sodium carbonate gave a precipitate which was dissolved in ether, washed with water and dried. Removal of the solvent provided 1 g. (42%) of XXIII, m.p. 192-195°. Repeated crystallization from benzene-ethanol gave an analytical sample, m.p. 196.5-197°.

Anal. Calcd. for $C_{15}H_{15}ClN_2OS$: C, 58.74; H, 4.92; N, 9.13. Found: C, 58.47; H, 4.66; N, 9.51.

In another experiment a polymorph of XXIII was obtained which after repeated crystallization from the same solvent mixture melted 184-185°.

Anal. Calcd. for $C_{15}H_{15}ClN_2OS$: C, 58.74; H, 4.92; N, 9.13; Cl, 11.56. Found: C, 58.74; H, 4.80; N, 8.84; Cl, 11.44.

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine Hydrochloride (XXIV). Method B.

2-Chloro-10-(2-cyanoethyl)-7-tetrahydropyranyloxyphenothiazine (XVIII) (7.7 g., 0.02 mole) was extracted, in a soxhlet apparatus, during 20 hours, with 1 l. of ether containing 2 g. (0.053 mole) of lithium aluminum hydride. To the cooled, stirred mixture was cautiously added, in succession, 20 ml. of ice-water, 30 ml. of 20% sodium hydroxide solution and 50 ml. of ice-water. The ether layer was washed with water, dried, decolorized and saturated with hydrogen chloride gas to give 2.5 g. (37%) of XXIV, m.p. 255-260° (foaming). Crystallization from ethanol-ether (1:5) provided an analytical sample as white needles, m.p. 260-264°.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2OS$: C, 52.48; H, 4.70; N, 8.16; Cl, 20.66. Found: C, 52.66; H, 4.75; N, 8.08; Cl, 20.72.

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine Hydrochloride (XXIV). Method C.

A mixture of 4.3 g. (0.011 mole) of XVIII, 150 ml. of ethanol, 6.5 ml. of ethanol saturated with hydrogen chloride and 2 g. of platinum oxide was shaken with hydrogen (60 psig.) at 50° for 3 hours and at 30° for an additional 3 hours. The mixture was filtered and concentrated to dryness. The resulting solid was dissolved in water, extracted with ether (discarded) and adjusted to *p*H 8 with solid sodium carbonate. The white solid which separated was dissolved in ethyl acetate and the solution was washed with water and dried. Concentration gave 1.8 g. of the free amine (XXIII) as a white solid, m.p. 181-183.5°. Solution in 50 ml. of warm 0.6 *N* hydrochloric acid and cooling to room temperature provided 2.0 g. (52%) of the hydrochloride (XXIV) as white needles, m.p. 263.5-265°.

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine (XXIII). Method D.

A mixture of 6.1 g. (0.02 mole) of 2-chloro-10-(2-cyanoethyl)-7-hydroxyphenothiazine (XXII), 300 ml. of ethanol, 4.4 g. of platinum oxide and 5 ml. of ethanol saturated with hydrogen chloride gas was shaken under hydrogen (60 psig.) at 50° for 3 hours and at room temperature for an additional 3 hours. The filtered mixture was concentrated to dryness and the off-white solid was dissolved in 800 ml. of water and extracted with ether. (Concentration of the ether gave a trace of 2-chloro-7-hydroxyphenothiazine.) The aqueous layer was adjusted to *p*H 8 with 20% sodium carbonate and the resulting pale pink solid was dissolved in ethyl acetate. After washing (water), drying and decolorization, the solution was concentrated to give an off-white solid. Washing with ether-petroleum ether (2:1) provided 3.0 g. (49%) of XXIII as white crystals, m.p. 181.5-183°.

2-Chloro-10-(2-cyanoethyl)-7-hydroxyphenothiazine (XXII).

Hydrogen chloride gas was introduced, at room temperature, into a stirred solution of 10 g. (0.025 mole) of XVIII in 1 l. of ether. The resulting white solid was washed with ether and crystallized from methanol to give 7 g. (90%) of XXII as white needles, m.p. 220-222°. The infrared spectrum of this material was identical with that of the analytical sample, m.p. 223-225° (methanol).

Anal. Calcd. for $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.64; N, 9.26. Found: C, 59.61; H, 3.64; N, 9.47.

2-Bromo-4-chloro-2'-nitro-5'-hydroxydiphenylsulfide (XXVIII).

A solution of 24.6 g. (0.11 mole) of 2-bromo-4-chlorothiophenol (XXVII) (7), 30 ml. of ethanol, 4.4 g. (0.11 mole) of sodium hydroxide and 6 ml. of water was evaporated to dryness to give the anhydrous sodium salt of XXVII. To this salt, in 70 ml. of absolute ethanol, was added a solution of 3-chloro-4-nitrophenol (6) (19.1 g., 0.11 mole) in 70 ml. of absolute ethanol. The mixture was heated under reflux for 5 hours and the alcohol was then removed. After extraction of the residue with benzene, the benzene-insoluble material was dissolved in dilute sodium hydroxide, filtered, and the filtrate was acidified with hydrochloric acid. The precipitate was dissolved in ethanol and diluted with water to give 16.3 g. (41%) of XXVIII as yellow crystals, m.p. 185.5-186.5°. The analytical sample was obtained by recrystallization from benzene-ligroin, m.p. 186.5-187.5°.

Anal. Calcd. for $C_{12}H_7BrClNO_3S$: C, 39.96; H, 1.96; N, 3.89. Found: C, 39.91; H, 2.06; N, 4.08.

Also isolated in this synthesis was a small quantity of bis(2-bromo-4-chlorophenyl)disulfide; white crystals, m.p. 111-112°.

Anal. Calcd. for $C_{12}H_6Br_2Cl_2S_2$: C, 32.37; H, 1.36. Found: C, 31.82; H, 1.11.

2-Bromo-4-chloro-2'-amino-5'-hydroxydiphenylsulfide.

A mixture of 15.7 g. (0.043 mole) of XXVIII, 41 g. of stannous chloride dihydrate and 36.4 ml. of concentrated hydrochloric acid was heated under reflux for 2 hours. Recrystallization of the resulting solid from benzene-ligroin gave 12.5 g. (87%) of white solid; m.p. 123.5-124.5°.

Anal. Calcd. for $C_{12}H_9BrClNOS$: C, 43.57; H, 2.74; N, 4.24. Found: C, 43.62; H, 2.74; N, 4.21.

2-Bromo-4-chloro-2'-formamido-5'-hydroxydiphenyl Sulfide.

A mixture of 8.6 g. of 2-bromo-4-chloro-2'-amino-5'-hydroxydiphenylsulfide, and 86 g. of 90% formic acid was heated under reflux for 6 hours to yield 7.45 g. (80%) of the formamido derivative, m.p. 168.5-170.5°. Crystallization from benzene-ligroin raised the melting point to 171-172° and this material was used without further purification.

2-Bromo-4-chloro-2'-formamido-5'-benzyloxydiphenyl Sulfide (XXIX).

A mixture of 6.89 g. (0.02 mole) of 2-bromo-4-chloro-2'-formamido-5'-hydroxydiphenylsulfide, 2.48 ml. of benzyl bromide, 10 ml. of acetone and 2.8 g. of anhydrous potassium carbonate was heated under reflux for 4 hours. Crystallization of the resulting solid from ethanol-water gave 6.1 g. (71%) of XXIX, m.p. 82.5-83.5°.

Anal. Calcd. for $C_{20}H_{15}BrClNO_2S$: C, 53.50; H, 3.37; N, 3.12. Found: C, 53.52; H, 3.53; N, 3.39.

7-Benzyloxy-3-chlorophenothiazine (XXX).

A mixture of 21.3 g. (0.047 mole) of XXIX, 8 g. (0.057 mole) of anhydrous potassium carbonate, 0.95 g. of copper-bronze catalyst and 125 ml. of DMF was stirred under reflux until carbon dioxide evolution had ceased (8.5 hours). The reaction mixture was filtered and the solid material was washed with 25 ml. of DMF. The combined filtrates and washings were poured into 2 l. of ice water and the resulting precipitate was collected and dried. Recrystallization from benzene provided 6.44 g. (40%) of white glistening plates of XXX, m.p. 180-182°. An additional crystallization from benzene gave the analytical sample, m.p. 184-185°.

Anal. Calcd. for $C_{19}H_{14}ClNOS$: C, 67.13; H, 4.15; N, 4.12. Found: C, 67.08; H, 4.46; N, 4.38.

7-Benzyloxy-2-chlorophenothiazine (XXXI).

A mixture of 12 g. (0.048 mole) of 2-chloro-7-hydroxyphenothiazine, 7.6 ml. (0.063 mole) of benzyl bromide, 35 g. (0.25 mole) of anhydrous potassium carbonate and 175 ml. of dry acetone was refluxed for 20 hours. The hot reaction mixture was poured into ice water and the resulting precipitate was filtered. Several crystallizations from benzene gave 4.7 g. of XXXI as glistening white plates, m.p. 195.5-197°. An additional crystallization from toluene raised the melting point to 200-201°.

Anal. Calcd. for $C_{19}H_{14}ClNOS$: C, 67.13; H, 4.15; N, 4.12. Found: C, 67.29; H, 4.24; N, 4.09.

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REFERENCES

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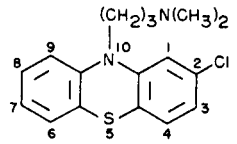
(2) Chlorpromazine is the generic name for 2-chloro-10-(3-dimethylaminopropyl)phenothiazine.



Nor$_1$- and nor$_2$-chlorpromazine are derivatives of chlorpromazine in which the 10- side chain has lost, respectively, one or both methyl groups.

(3) Although the phenothiazine literature has grown quite massive (reviewed by E. Schenker and H. Herbst in "Drug Research", Vol. 5, E. Jucker, Ed., Birkhäuser Verlag, Basel, 1963, p. 269) it reports the chemical synthesis of only two 10-aminoalkylhydroxyphenothiazines. Both of these are derivatives of 2-hydroxyphenothiazine and contain no ring substituent other than the hydroxyl group [J. P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Galdimann, V. Thens, E. Schenher and J. Renz, *Helv. Chim. Acta*, 42, 259 (1959); P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavlov and C. L. Zirkle, *J. Org. Chem.*, 25, 944 (1960)].

(4) A simple preparation for I was described earlier by E. A. Nodiff and M. Hausman, *ibid.*, 31, 625 (1966).

(5) H. L. Yale and F. Sowinski [*J. Med. Chem.*, 7, 609 (1964)] reported a 15% yield in the preparation of *N*-(3-chloropropyl)-*N*-methylformamide (XVI) from *N*-methylformamide and trimethylene chlorobromide in toluene in the presence of sodium amide. By substituting sodium hydride for sodium amide we have raised the yield of reasonably pure XVI to 40%.

(6) H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 127, 1599 (1925).

(7) A. J. Saggiomo, P. N. Craig and M. Gordon, *J. Org. Chem.*,

23, 1906 (1958).

(8) E. A. Nodiff and M. Hausman, *ibid.*, 29, 2453 (1964).

(9) 2-Chloro-7-hydroxyphenothiazine varies in color from tan to white, depending on its purity. On brief exposure to light and air it turns deep red. If not handled with care this material scatters an almost invisible dust which subsequently colors skin, clothes, walls and anything else on which it has settled. Removal of the deep red color is quite troublesome.

(10) Metal Hydrides, Inc., Beverly, Mass.

(11) J. Cymerman-Craig, W. P. Rogers and M. E. Tate, *Australian J. Chem.*, 9, 397 (1956); P. K. Kadaba and S. P. Massie, *J. Org. Chem.*, 24, 986 (1959).

(12) Strong peaks at 5.7 μ (ester carbonyl) and 6.1 μ (amide carbonyl).

(13) Raney Catalyst Co., Chattanooga, Tenn.

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