Synthesis of Possible Metabolites of Chlorpromazine. V. (1) 3,7-Disubstituted Chlorpromazine Derivatives (2a,3)

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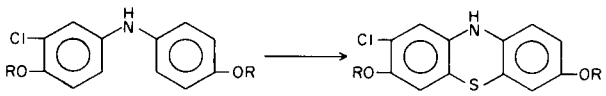
Received June 25, 1971

Various ethers of 3,7-dihydroxychlorpromazine have been prepared as outlined in Schemes 1 and 2.

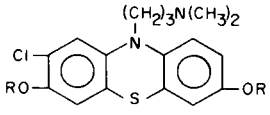
The reaction between the zinc mercaptides (I and II) and 2-chlorohydroquinone (III) (4) followed by *O*-alkylation of the resulting 7-hydroxyphenothiazines (IV and V) provided the 3,7-dialkoxy derivatives (VI and VII). The latter compound was prepared alternatively by sequent Goldberg (5) and Bernthsen (5) reactions (Scheme 2). This sequence also produced the dimethoxy analog (XIV).

Conversion of VII and XIV to the corresponding chlorpromazines (XV and XVI) was effected in the usual manner (6). Similar conversion of the dibenzyl ether (VI) failed.



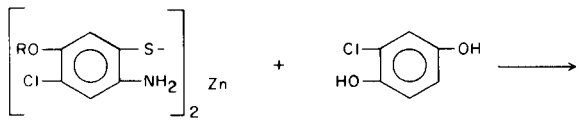
XII, R = $CH(CH_3)_2$
XIII, R = CH_3

VII, R = $CH(CH_3)_2$
XIV, R = CH_3



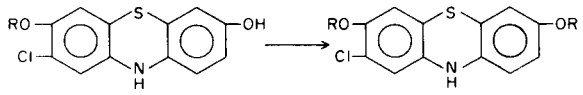
XV, R = $CH(CH_3)_2$
XVI, R = CH_3

SCHEME 1



I, R = $CH_2C_6H_5$
II, R = $CH(CH_3)_2$

III



IV, R = $CH_2C_6H_5$
V, R = $CH(CH_3)_2$

VI, R = $CH_2C_6H_5$
VII, R = $CH(CH_3)_2$

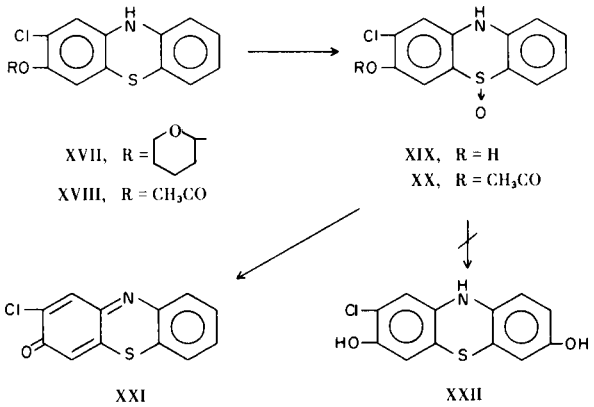
SCHEME 2

VIII, R = $CH(CH_3)_2$
IX, R = CH_3

X, R = $CH(CH_3)_2$
XI, R = CH_3

Hilditch and Smiles (7) have described the rearrangement of phenothiazine sulfoxide to 3-hydroxyphenothiazine in the presence of acetic acid. Attempts (Scheme 3) to adapt this rearrangement for the conversion of the sulfoxides, XIX and XX, to 2-chloro-3,7-dihydroxyphenothiazine (XXII) were in vain. Only 2-chloro-3*H*-phenothiazin-3-one (XXI) was isolated in each instance.

SCHEME 3



XVII, R =

XVIII, R = CH_3CO

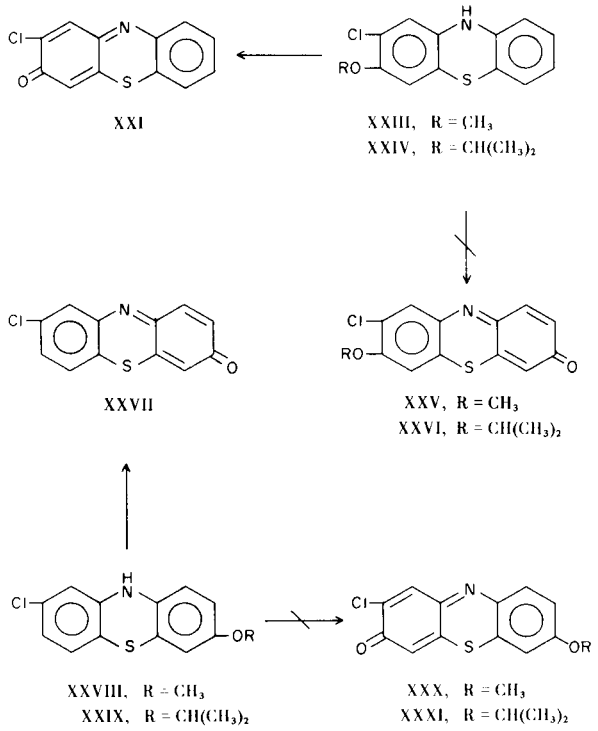
XIX, R = H
XX, R = CH_3CO

XXI

XXII

The oxidation of phenothiazine to phenothiazone with ferric chloride in dilute acetic acid was described by Bodea and Raileanu (8). Scheme 4 sketches our attempts to apply this method to the preparation of the alkoxyphenothiazones, XXV, XXVI, XXX and XXXI, from the corresponding alkoxyphenothiazines, XXIII, XXIV, XXVIII and XXIX. Instead of the desired reaction, oxidative dealkylation occurred, with formation of the phenothiazones, XXI and XXVII, in 70-80% yields. Similar conversion of 3-methoxyphenothiazine to phenothiazone-3 was encountered previously (8). The ferric chloride cleavage of 3- or 7-alkoxyphenothiazines would thus seem to constitute a simple, high-yield route to phenothiazones.

SCHEME 4



EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. All reactions were mechanically or magnetically stirred, usually under dry nitrogen and in the absence of strong, direct light. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. and Microanalysis, Inc., Wilmington, Delaware. Infrared spectra were taken as 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 always carried out under reduced pressure.

Zinc Mercaptides (I and II).

A solution of sulfur (4.8 g., 0.15 mole) and sodium sulfide nonahydrate (36 g., 0.14 mole) in 345 ml. of ethanol was slowly added to a refluxing solution of 59.6 g. (0.2 mole) of 2,5-dichloro-4-nitrophenyl benzyl ether (9) in 50 ml. of ethanol. Reflux was continued for 3 hours, the mixture was chilled and the resulting solid was washed with water to give 31 g. (53%) of bis(5-benzyloxy-4-chloro-2-nitrophenyl) disulfide as a yellow solid, m.p. 172-173.5°. Crystallization from toluene provided an analytical sample, m.p. 176-177°.

Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_6S_2$: C, 52.95; H, 3.08; N, 4.75. Found: C, 52.98; H, 2.82; N, 4.93.

To 700 ml. of boiling glacial acetic acid was added 11.8 g. (0.02 mole) of the disulfide. Zinc dust (40 g., 0.62 g.-atom) was added during 30 minutes, boiling was continued for 10 minutes and the supernatant solution was decanted. The solid residue was extracted with boiling acetic acid (2 x 100 ml.) and boiling water (200 ml.) and the extracts were added to the decantate. The mixture was further diluted with 1.6 l. of boiling water and allowed to cool, giving 11.5 g. (95%) of the mercaptide (I).

The corresponding isopropyl analog (II) was made in the same manner, starting with 2,5-dichloro-4-nitrophenyl isopropyl ether (9). The disulfide (m.p. 187-190°, used without crystallization) and zinc salt (II) were obtained in respective yields of 92% and 84%.

2-Chloro-3-alkoxy-7-hydroxyphenothiazines (IV and V).

The reaction between the zinc salt (I and II) and 2-chlorohydroquinone (III), carried out in the usual manner (4), afforded 3-benzyloxy-2-chloro-7-hydroxyphenothiazine (IV) [m.p. 193-194° (benzene); yield 53%] and 2-chloro-7-hydroxy-3-isopropoxyphenothiazine (V) [m.p. 174-177° (benzene), yield 13%].

Anal. Calcd. for $C_{19}H_{14}ClNO_2S$ (IV): C, 64.13; H, 3.93; N, 3.93. Found: C, 63.97; H, 3.99; N, 4.05.

Anal. Calcd. for $C_{15}H_{14}ClNO_2S$ (V): C, 58.53; H, 4.58; N, 4.58. Found: C, 58.67; H, 4.38; N, 4.63.

2-Chloro-3,7-dibenzyloxyphenothiazine (VI).

Benzylation of IV with benzyl bromide (sodium hydride, DMSO, sodium dithionite, 20°, 2 hours) provided 51% of VI, m.p. 154-155° (ethanol).

Anal. Calcd. for $C_{26}H_{20}ClNO_2S$: C, 70.00; H, 4.49; N, 3.14. Found: C, 69.86; H, 4.48; N, 3.14.

When this benzylation was carried out at 100-110° (5 hours) the *O,O,N*-tribenzyl derivative was obtained, m.p. 108-109° (ethanol).

Anal. Calcd. for $C_{33}H_{26}ClNO_2S$: C, 73.94; H, 4.85; N, 2.61. Found: C, 73.83; H, 4.64; N, 2.55.

The NH stretching peak, visible at 2.9 μ in the infrared spectrum of the dibenzyl derivative, was absent in the spectrum of the tribenzyl derivative.

2-Chloro-3,7-diisopropoxyphenothiazine (VII). Method A.

A mixture of 3.08 g. (0.01 mole) of V, 1.66 g. of anhydrous potassium carbonate, 0.5 g. of sodium dithionite, 2.55 g. (0.015 mole) of 2-iodopropane and 40 ml. of acetone was heated under reflux for 48 hours. The red reaction mixture was allowed to cool, poured into 500 ml. of water and extracted with ether. The extract was dried, concentrated and distilled to give 2.7 g. (77%) of VII, b.p. 213-216°/0.008 mm. Hg (used without analysis).

3-Chloro-4-isopropoxyacetanilide (VIII).

A mixture of 52.1 g. (0.3 mole) of commercial 2-chloro-4-nitrophenol, 41.4 g. (0.3 mole) of anhydrous potassium carbonate,

85 g. (0.5 mole) of 2-iodopropane and 200 ml. of *N,N*-dimethylformamide was heated under reflux for 3 hours. The mixture was worked up as described for VII to give 51.8 g. (80%) of 2-chloro-4-nitrophenyl isopropyl ether, b.p. 111-113°/0.1 mm. Hg, m.p. 34-37° (spontaneous crystallization of distillate).

Anal. Calcd. for $C_9H_{10}ClNO_3$: C, 50.14; H, 4.67; N, 6.50. Found: C, 49.82; H, 4.57; N, 6.75.

Reduction of the nitro derivative to 4-amino-2-chlorophenyl isopropyl ether was effected in 76% yield with ethanolic stannous chloride-hydrochloric acid (9); b.p. 72-72°/0.1 mm. Hg, n_D^{25} 1.5532.

Anal. Calcd. for $C_9H_{12}ClNO$: C, 58.21; H, 6.52; N, 7.54. Found: C, 58.11; H, 6.17; N, 7.33.

Hydrochloride, m.p. 210-211° (ethanol-ether).

Anal. Calcd. for $C_9H_{13}Cl_2NO$: C, 48.67; H, 5.90; N, 6.30. Found: C, 48.96; H, 5.83; N, 6.59.

The above aniline was converted to VIII (93%) with acetic anhydride, at room temperature, overnight; m.p. 147° (benzene).

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.19; N, 6.15. Found: C, 58.86; H, 6.36; N, 6.04.

4-Bromophenyl Isopropyl Ether (X).

Commercial 4-bromophenol was isopropylated in 52% yield as described in the synthesis of VIII; b.p. 110-112°/12 mm. Hg, n_D^{25} 1.5361 [lit. (10) b.p. 119-120°/20 mm. Hg, n_D^{20} 1.5368].

3-Chloro-4,4′-diisopropoxydiphenylamine (XII).

A mixture of 45.4 g. (0.2 mole) of VIII, 38.7 g. (0.18 mole) of X, 16.6 g. (0.12 mole) of anhydrous potassium carbonate and 0.9 g. of copper-bronze catalyst was heated at 200-210° for 70 hours and worked up as usual (5) to give a 55% yield of XII; b.p. 180°/0.06 mm. Hg, n_D^{25} 1.5846.

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; N, 4.38. Found: C, 68.02; H, 6.69; N, 4.54.

3-Chloro-4,4′-dimethoxydiphenylamine (XIII).

A mixture of 162 g. (0.81 mole) of 3-chloro-4-methoxyacetanilide (IX) (11), 131.6 g. (0.7 mole) of commercial 4-bromoanisole (XI), 70 g. (0.50 mole) of anhydrous potassium carbonate and 2.8 g. of copper-bronze catalyst was heated at 200° for 30 hours and worked up in the usual manner (5) to give 86 g. (47%) of XIII, b.p. 164-167°/0.1 mm. Hg, m.p. 66-68° (ethanol-petroleum ether).

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.32. Found: C, 63.66; H, 5.51; N, 5.33.

2-Chloro-3,7-diisopropoxyphenothiazine (VII). Method B.

A mixture of 31 g. (0.097 mole) of XII, 4.8 g. (0.15 mole) of sulfur and 0.3 g. of iodine was heated at 200-220° for 2 hours, allowed to cool and extracted with ether. The extract was treated with hydrogen chloride (to remove unreacted XII), filtered, washed with water, 10% potassium carbonate and again with water and dried. Removal of the ether left 22 g. (65%) of VII as an oil whose infrared spectrum was identical with that for the material obtained in Method A. This oil was used without further purification.

2-Chloro-3,7-dimethoxyphenothiazine (XIV).

A mixture of 2.64 g. (0.01 mole) of XIII, 0.64 g. (0.02 mole) of sulfur, 0.07 g. of iodine and 3 ml. of *o*-dichlorobenzene was heated at 200° for 1 hour and allowed to stand at room temperature overnight. Crystallization (ethanol) of the resulting solid gave 1.4 g. (48%) of XIV, m.p. 166-170°. Repeated crystallization from ethanol afforded an off-white analytical sample, m.p. 168.5-170°.

Anal. Calcd. for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12. Found: C, 57.27; H, 3.49.

3,7-Diisopropoxychlorpromazine (XV).

Alkylation of VII with 3-dimethylaminopropyl chloride, in dimethyl sulfoxide-sodium hydride (6), gave 69% of XV; b.p. 225-226°/0.004 mm. Hg, n_D^{25} 1.5920.

Anal. Calcd. for $C_{23}H_{31}ClN_2O_2S$: C, 63.50; H, 7.18; N, 6.44. Found: C, 63.14; H, 7.21; N, 6.42.

3,7-Dimethoxychlorpromazine Hydrochloride (XVI).

Alkylation of XIV with 3-dimethylaminopropyl chloride in sodium hydride-xylene (6), followed by treatment with ethereal hydrogen chloride gas, afforded 56% of XVI as white crystals, m.p. 198.5-200° (2-propanol-ethanol).

Anal. Calcd. for $C_{19}H_{24}Cl_2N_2O_2S$: C, 54.94; H, 5.82; N, 6.74; Cl, 17.07. Found: C, 55.27; H, 6.01; N, 6.27; Cl, 16.84.

3-Acetoxy-2-chlorophenothiazine (XVIII).

A mixture of 4.65 g. of 2-chloro-3-hydroxyphenothiazine (9), 75 ml. of pyridine, 4 g. of sodium dithionite and 1.86 ml. of acetic anhydride was stirred for 2.5 hours at room temperature, concentrated to 50 ml. and poured into 1 l. of water. The resulting solid was washed with water, dried and crystallized from benzene to give 88% of XVIII as white needles, m.p. 212-213°.

Anal. Calcd. for $C_{14}H_{10}ClNO_2S$: C, 57.63; H, 3.45; N, 4.80; Cl, 12.15. Found: C, 58.00; H, 3.24; N, 5.14; Cl, 12.20.

Acetylation of 2-chloro-3-hydroxyphenothiazine (9) with a mixture of acetic anhydride, acetic acid and sodium dithionite (reflux, 3.5 hours) gave a quantitative yield of the *O,N*-diacetyl derivative, m.p. 153-155° (benzene).

Anal. Calcd. for $C_{16}H_{12}ClNO_3S$: C, 57.57; H, 3.62; N, 4.20; Cl, 10.62. Found: C, 58.16; H, 4.03; N, 4.23; Cl, 11.06.

The infrared spectrum of the *O*-acetyl derivative (XVIII) displayed an NH peak at 2.9 μ and an ester carbonyl peak at 5.7 μ. In the diacetyl derivative the NH peak was replaced by an amide carbonyl at 5.9 μ.

2-Chloro-3-hydroxyphenothiazine 5-Oxide (XIX).

To a cooled solution of 1.66 g. (0.005 mole) of 2-chloro-3(tetrahydropyran-2-yloxy)phenothiazine (XVII) (9) in 100 ml. of ethanol was added 0.83 g. (0.0075 mole) of 30% hydrogen peroxide. The mixture was then heated under reflux for 8 hours and the resulting solid was washed with petroleum ether. Crystallization from *N,N*-dimethylformamide-xylene provided 0.5 g. (30%) of the depyranylated compound (XIX) as white crystals, m.p. 237-238°; ir 3.05 μ (w) (bonded NH), 3.15 and 3.25 μ (w) (CH), 10.1 μ (m) (S → O) (14).

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.23; H, 3.01; N, 5.28. Found: C, 54.50; H, 3.05; N, 5.33.

3-Acetoxy-2-chlorophenothiazine 5-Oxide (XX).

A solution of 4.75 g. (0.016 mole) of XVIII, 11.6 ml. of 30% hydrogen peroxide, 50 ml. of ethanol and 100 ml. of acetone was heated under reflux for 3 hours and concentrated to give 4.9 g. (98%) of XX, m.p. 225° (chloroform-ethanol); ir 3.05 (w) (bonded NH), 3.15 and 3.25 (w) (CH), 10.1 (vs) (S → O) (14).

Anal. Calcd. for $C_{14}H_{10}ClNO_3S$: C, 54.64; H, 3.28; N, 4.55. Found: C, 54.73; H, 3.13; N, 4.91.

Attempted Rearrangement of XIX and XX.

A mixture of 2 g. of XIX or XX and 40 ml. of acetic acid or trifluoroacetic acid was heated under reflux for 5 hours,

concentrated, poured into water and neutralized with solid sodium carbonate to give, in each instance, an almost quantitative yield of 2-chloro-3*H*-phenothiaz-3-one (XXI).

Oxidative De-alkylation of XXIII (9), XXIV (9), XXVIII (12) and XXIX (6).

To a solution of 1 l. of water and 120 ml. of glacial acetic acid, at 90-95°, was added 2.0 g. of the alkoxyphenothiazine and then, slowly, 9.0 g. of ferric chloride hexahydrate. The mixture was maintained at 90-95° for 0.5 hour and allowed to cool. The resulting solid was dried and extracted with boiling benzene (insoluble material discarded). The extract was treated with carbon and concentrated to give 2-chloro-3*H*-phenothiaz-3-one (from XXIII and XXIV) or 2-chloro-7*H*-phenothiaz-7-one (from XXVIII and XXIX) in yields of 70-80%. These phenothiazones (XXI and XXVII) were identical with those obtained *via* Mine's method (9,13).

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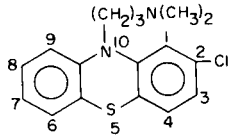
(2a) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract SA-43-ph-3758; (b) Pharmacology Section, Psychopharmacology Research Branch, National Institute of Mental Health, Rockville, Maryland 20852.

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



(4) Adaptation of the method of E. A. Nodiff and M. Hausman, *J. Org. Chem.*, **31**, 625 (1966).

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(14) We have also observed the same pattern (trio of weak peaks at 3.05, 3.15 and 3.25 μ and a peak, usually very strong, between 10.0 and 10.3 μ) in the following 10-unsubstituted phenothiazine 5-oxides: 3,7-dichloro; 2-chloro, 8-methoxy; 2-chloro and unsubstituted.