Synthesis of 3-Chloro-2-hydroxyimipramine and 3-Chloro-8-hydroxyimipramine (1), Hypothetical Metabolites of Clomipramine

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Fremy salt oxidation of 3-chloroiminodibenzyl yields a mixture of two isomeric iminequinones, which can be separated and reduced to aminophenols and the phenolic group protected with addition of dihydropyran. Introduction of the *N,N*-dimethylaminopropyl side chain and removal of the protective group provided the two chlorohydroxyimipramines, which can serve as standards for the identification of possible biotransformation products of the parent drug, clomipramine.

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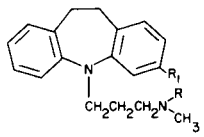
Imipramine (IMI), **1**, and desmethylimipramine (DMI), **2**, are marketed drugs of therapeutic value as major psychoanaleptic agents. Clomipramine (CMI), **3**, (Anafranil, Geigy), a 3-chloro analog of IMI is presently being employed in Europe for the treatment of severe depression and reported to be of value in the management of obsessional and phobic illness and certain other indications (3).

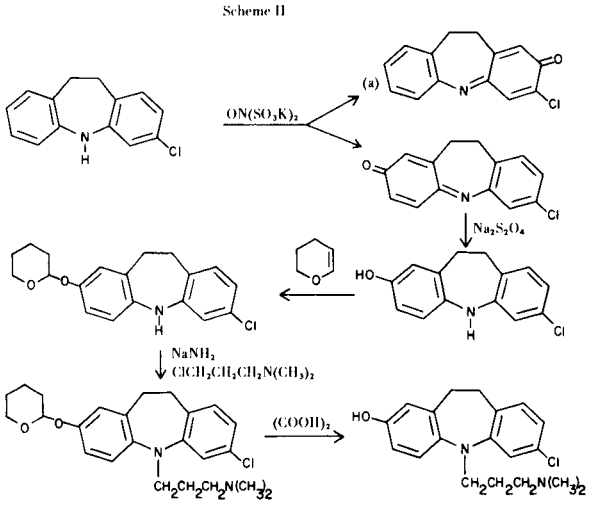
The major hydroxylation pathway of the non-chlorinated drugs in humans is initiated at the 2 (or 8) position (4,5); whereas, the hydroxylation at the 10 position of these drugs represents a minor pathway (6). Further evidence that the 2 position is the principal site of hydroxylation has been obtained from animal studies (7-9). As a projection from this pattern as well as from a knowledge of the development of the hydroxylation pathways of chlorpromazine (10), **4**, a major psycholeptic drug with a structural resemblance, it could be postulated that CMI is primarily hydroxylated at the 8 position and that a minor pathway is initiated at the 2 position on the molecule. Faigle and Dieterle have indicated the presence of hydrophilic, polar metabolites from a study on the metabolism and pharmacokinetics of CMI (11) but to our knowledge no reports have appeared in the literature on specific monohydroxylated compounds. This prompts us to report our successful synthesis of some hypothetical hydroxylated metabolites of this drug.

Scheme I



The synthesis of the title compounds is outlined in Scheme II.

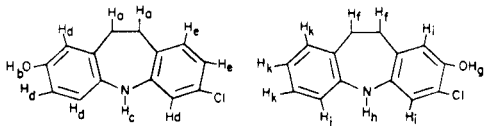
Scheme II



(a) All consecutive steps follow the route for the isomer.

Table I

Nuclear Magnetic Resonance Spectra of Iminodibenzyl Derivatives



Proton(s)	Number Protons	Chemical Shift (δ) in C^2HCl_3 from TMS
H_a	4	3.07
H_b	1	4.55
H_c	1	5.75
H_d	4	6.70
H_e	2	7.10-6.80
H_f	4	3.07
H_g	1	5.10
H_h	1	5.75
H_i	3	6.80
H_k	3	7.20-6.80

Table II

Isotopic Analysis of 3-Chloro-8-hydroxyimipramine (a) and 3-Chloro-2-hydroxyimipramine (b)

m/e	$C_{19}H_{23}ClN_2O$ Theoretical	Measured (a)	(b)
330	150	150	150
331	21.7	21.9	21.7

The oxidation step follows a method described for the synthesis of 2-hydroxyimipramine (12). Reduction of the iminequinone had to be done chemically, as catalytic hydrogenation easily removes the halogen (13). For the same reason the hydroxy function had to be protected with a group which could be removed chemically. Difficulties were encountered in introduction of the 1-*N*,*N*-dimethylaminopropyl 3-chloride side chain. Yields for this step varied from 5% to 43%. Similar problems are reported in the literature (14). The two isomers of hydroxychloroiminodibenzyl were identified with nmr spectral data, as shown in Table I. Mass spectra for 3-chloro-2-hydroxyimipramine and 3-chloro-8-hydroxyimipramine show m.w. 330 (^{35}Cl) as expected. Isotopic analysis is given in Table II. Fragmentation patterns for the two isomers are almost identical and consistent with the proposed structure.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Ultraviolet spectra were recorded on a Perkin-Elmer spectrophotometer Model 202. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

3-Chloro-2-hydroxyiminodibenzyl and 3-Chloro-8-hydroxyiminodibenzyl.

To a stirred solution of 25.0 g. (0.11 mole) of 3-chloroiminodibenzyl in 2.4 l. of acetone was added a solution of 70 g. of Fremy salt in 4.2 l. of water, to which had been added 600 ml. of 1/6 *M* dipotassium phosphate solution. The mixture was stirred at RT overnight and the volume reduced to 3.5 l. A dark brown precipitate was filtered off and the filtrate was extracted three times with chloroform. The solid was dissolved in the chloroform extracts, and the solutions washed with water twice and dried over sodium sulfate. The solvent was removed to leave 18 g. of a reddish brown semisolid. Two g. of material was removed and chromatographed twice over silica gel, eluting with 1) benzene, 2) benzene/chloroform 4:1 and 3) benzene/chloroform 1:1. Elution 2) gave a red solid, m.p. 134-136° after recrystallization from ethanol.

Anal. Calcd. for 3-chloro-2-oxo-10,11-dihydro-2*H*-dibenzo-[*b*,*f*]azepin, $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 69.28; H, 4.24; N, 5.74.

Elution 3) gave a red solid, m.p. 126-128° after recrystallization from ethanol.

Anal. Calcd. for 3-chloro-8-oxo-10,11-dihydro-2*H*-dibenzo-[*b*,*f*]azepin. $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 69.30; H, 4.17; N, 5.75.

The two isomers were obtained in a ratio of 1:4, with less of the higher melting point compound. On prolonged exposure to air and light both products are converted to brown, amorphous powders with no definite melting point.

The crude mixture of iminequinones above, 16 g. (0.066 mole), was dissolved in 300 ml. of methanol and added to a well-stirred solution of 20 g. of sodium dithionite in 800 ml. of water at 70°. After 5 minutes of stirring, when the initially dark red solution had become pale brown, the volume was reduced under vacuum to 500

ml. and the product was taken up in ether. The ether extracts were washed twice with water and dried over sodium sulfate. The solvent was removed and the remaining greenish brown semisolid was chromatographed on silica gel, eluting with 1) hexane/benzene 1:1, 2) benzene and 3) benzene/chloroform 3:1. Elution 2) gave a brownish oil, which was brought to crystallization by trituration with hexane. A light tan solid, 3.3 g. (0.013 mole), 12%, m.p. 148-150° was obtained. A sample was recrystallized twice from hexane for analysis, m.p. 150-151°, after drying in vacuum over phosphorus pentoxide at 65° for 3 hours.

Anal. Calcd. for 3-chloro-2-hydroxyiminodibenzyl, $C_{14}H_{12}ClNO$: C, 68.43; H, 4.92; N, 5.70. Found: C, 68.51; H, 4.96; N, 5.63.

Elution 3) gave 8.5 g. (0.035 mole), 32%, of a solid, m.p. 136-137°. A sample was recrystallized from toluene/petroleum ether (100-115°) 1:20 to a m.p. 139-140°, after drying in vacuum over phosphorus pentoxide at 78° for 4 hours.

Anal. Calcd. for 3-chloro-8-hydroxyiminodibenzyl, $C_{14}H_{12}ClNO$: C, 68.43; H, 4.92; N, 5.70. Found: C, 68.50; H, 5.01; N, 5.65.

3-Chloro-2-tetrahydropyranyloxyiminodibenzyl.

To a solution of 3.2 g. (0.013 mole) of 3-chloro-2-hydroxyiminodibenzyl in 40 ml. of ethyl acetate and 5 ml. of dihydropyran was added 0.5 ml. of methanolic hydrogen chloride. The mixture was kept dark at RT for 20 hours. It was washed twice with dilute carbonate solution and with water and dried over sodium sulfate. The solvent was removed and the remaining red oil chromatographed over a short silica gel column. The product was eluted with benzene. Some removal of the protective group occurred on the column and the late fractions were contaminated with the regenerated starting material. The product was obtained as a light tan solid, m.p. 103-104°, 2.1 g. (0.0064 mole), 49%, was collected. A sample was recrystallized from hexane and dried in a vacuum over phosphorus pentoxide at 65° for 3 hours, m.p. 104-105°.

Anal. Calcd. for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.24. Found: C, 69.03; H, 6.19; N, 4.12.

3-Chloro-2-tetrahydropyranyloxyimipramine Hydrogen Oxalate 1/4 Hydrate.

To a solution of 1 g. (0.003 mole) of 3-chloro-2-tetrahydropyranyloxyiminodibenzyl in 50 ml. of benzene was added 118 mg. (0.003 mole) of sodium amide. The mixture was refluxed under nitrogen for 4 hours and allowed to cool to 60°. *N,N*-Dimethyl-3-chloropropylamine, 370 mg. (0.003 mole) dissolved in 10 ml. of benzene was added and the mixture was refluxed overnight. The salts were filtered off, washed well with benzene and the solvent was removed to leave 0.9 g. of a brown oil. It was dissolved in 20 ml. of ethyl acetate and added to a warm solution of 270 mg. of oxalic acid in 20 ml. of ethyl acetate. On cooling a white solid precipitated. It was filtered and dried to yield 680 mg. (0.0013 mole), 44%, of product, m.p. 134-135°. A sample was recrystallized twice from ethanol-ether 1:1 to a m.p. 136-137° after drying in vacuum over phosphorus pentoxide at 100° for 2 hours.

Anal. Calcd. for $C_{24}H_{31}ClN_2O_2 \cdot C_2H_2O_4 \cdot \frac{1}{4} H_2O$: C, 61.29; H, 6.63; N, 5.50. Found: C, 61.03; H, 6.77; N, 5.85.

3-Chloro-2-hydroxyimipramine Hydrogen Oxalate ¼ Hydrate.

To a stirred solution of 200 mg. of oxalic acid in 100 ml. of ethanol and 70 ml. of distilled water was added 550 mg. (0.0011 mole) of 3-chloro-2-tetrahydropyranyloxyimipramine hydrogen oxalate ¼ hydrate. The solution was kept at 50° for 2 hours. The volume was reduced to 50 ml., the solution treated with Norit and filtered through Celite. The clear, colorless solution was poured into ice cold well-stirred dilute ammonia. An oil precipitated and was taken up in ethyl acetate. The extracts were washed with water, dried over sodium sulfate and the solvent was removed. The remaining oil could not be brought to crystallization. It was then dissolved in 5 ml. of ethyl acetate and added to a warm solution of 100 mg. (0.0011 mole) of oxalic acid in 30 ml. of ethyl acetate. The white solid which precipitated was recrystallized from ethanol-ether 1:2 and dried in vacuum over phosphorus pentoxide at 78° for 3 hours. The yield was 220 mg. (0.00052 mole), 50%, m.p. 108-112°; λ max (ethanol): 220 and 251 nm (ε, 17,450 and 11,060).

Anal. Calcd. for $C_{19}H_{23}ClN_2O \cdot C_2H_2O_4 \cdot \frac{1}{4} H_2O$: C, 59.29; H, 6.04; N, 6.59. Found: C, 59.12; H, 6.12; N, 6.55.

A sample of the base was converted to the hydrogen maleate salt, m.p. 145-147° dec.

Anal. Calcd. for $C_{19}H_{23}ClN_2O \cdot C_4H_4O_4$: C, 61.81; H, 6.09; N, 6.27. Found: C, 61.56; H, 6.23; N, 6.30.

3-Chloro-8-tetrahydropyranyloxyiminodibenzyl.

This compound was prepared as described above for the 3-chloro-2-tetrahydropyranyloxy isomer. From 8.3 g. (0.034 mole) of 3-chloro-8-hydroxyiminodibenzyl, 8.9 g. (0.027 mole), 79% of product, m.p. 120-122° was obtained. A sample was recrystallized from toluene to m.p. 121-122° after drying in vacuum over phosphorus pentoxide at 78° for 3 hours.

Anal. Calcd. for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.24. Found: C, 69.17; H, 6.22; N, 4.22.

3-Chloro-8-tetrahydropyranyloxyimipramine Hydrogen Oxalate ½ Hydrate.

This compound was prepared as described above for its isomer. The crude reaction product was chromatographed over alumina (activity IV) and the base eluted with chloroform, before conversion to the hydrogen oxalate salt. From 6.2 g. (0.019 mole) of 3-chloro-8-tetrahydropyranyloxyiminodibenzyl 4.3 g. (0.0083 mole), 43%, of product, m.p. 123-125° was obtained. A sample was recrystallized from ethanol-ether to m.p. 125-126° after drying in vacuum over phosphorus pentoxide at 78° for 1 hour.

Anal. Calcd. for $C_{24}H_{31}ClN_2O_2 \cdot C_2H_2O_4 \cdot \frac{1}{2} H_2O$: C, 60.17; H, 6.60; N, 5.40. Found: C, 60.10; H, 6.60; N, 5.60.

3-Chloro-8-hydroxyimipramine.

This compound was prepared analogously to its isomer. After hydrolysis and extraction the base was titurated with hexane and brought to crystallization. It was recrystallized from ether-hexane, 1:2, to give an off-white solid, m.p. 167-168° dec. From 4.1 g. (0.008 mole) of 3-chloro-8-tetrahydropyranyloxyimipramine hydrogen oxalate ½ hydrate, 1.3 g. (0.0039 mole), 49%, of product was obtained; λ max (ethanol): 222, 252 and 271 nm (ε, 17,040, 8,770 and 9,100).

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.91; H, 7.01; N, 8.47. Found: C, 69.03; H, 7.16; N, 8.48.

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