

New Compounds: 5-Chloro-2-(3-chloro-2-hydroxypropoxy)-benzhydrylamine and Related Compounds

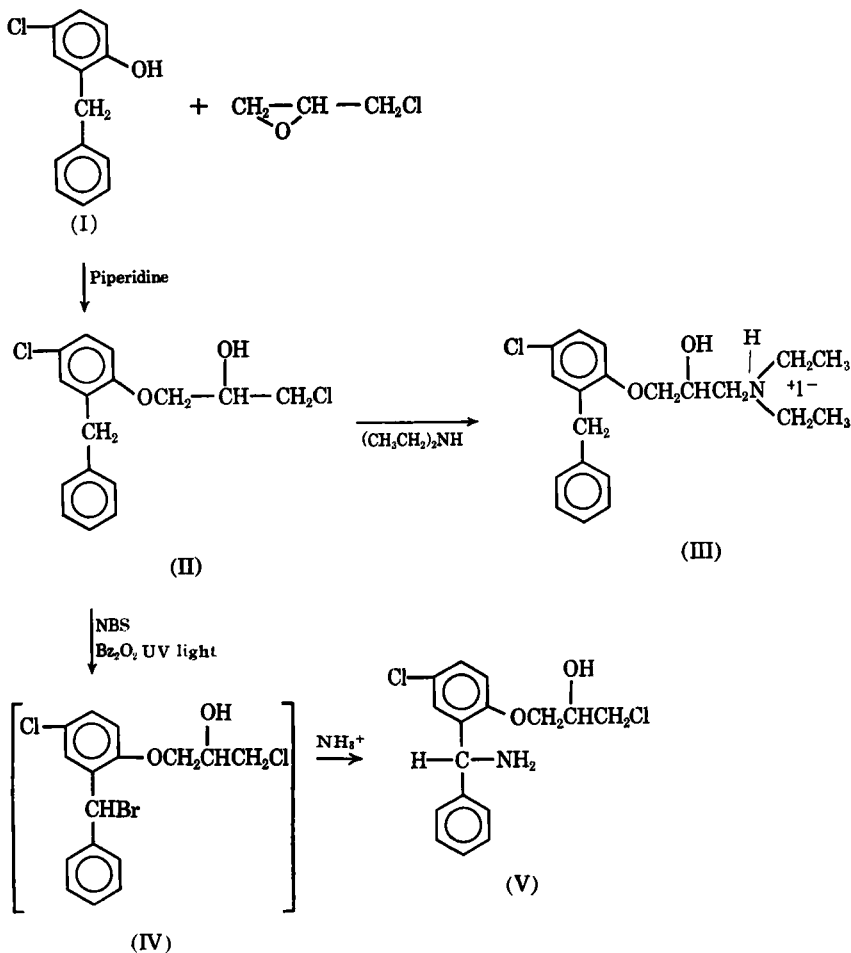
By HEINO A. LUTS*, and D. YAMASHIRO†

In connection with the chemical-medicinal work 5-chloro-2-(3-chloro-2-hydroxypropoxy)-benzhydrylamine was prepared by a three-step synthesis. Compound I was reacted with epichlorohydrin and the formed 3-(2-benzyl 4-chlorophenoxy)-2-hydroxypropylchloride (II) was then converted to III by free-radical bromination, which was not isolated, but converted to compound V by amination.

EXPERIMENTAL—SCHEME I

3-(2-Benzyl-4-chlorophenoxy)-2-hydroxypropyl chloride (II)—A solution of 21.65 g. (0.100 mole) of 2-benzyl-4-chlorophenol (I) (Dow Santophen), 24.8 g. (0.269 mole) of epichlorohydrin, and 2.0 ml. of piperidine was heated at 90–95° for 4.5 hr. with

The excess epichlorohydrin was removed by distillation of all material boiling to 40°/0.7 mm. The residual oil was dissolved in an equal volume of chloroform, then shaken for 10 min. with 35 ml. of concentrated hydrochloric acid. The lower chloroform phase was separated and washed with four 30-ml. portions of water. The chloroform solution was



Scheme I

stirring. Occasional cooling of the exothermic reaction was required during the initial stages.

steam distilled. The oily, nondistillable residue was extracted with 50 ml. of benzene. The benzene solution was washed with two 30-ml. portions of water, dried over anhydrous calcium sulfate, and evaporated *in vacuo* to remove the solvent. The crude oil was distilled under vacuum twice to yield 8.5 g. (27% yield) of pure 3-(2-benzyl-4-chlorophenoxy)-2-hydroxypropylchloride, b.p. 188–190°/0.6 mm.

Received February 28, 1968, from Horizons Inc., Cleveland, Ohio, and Bristol Laboratories Inc., Syracuse, NY 13201
Accepted for publication April 10, 1968.

* Eastern Kentucky University, Richmond, KY 40475

† Stanford Research Institute, Menlo Park, Calif.

¹ All melting points are uncorrected. Microanalyses were performed by G. Robertson, Jr., Florham Park, N. J.

Anal.—Calcd. for $C_{16}H_{16}Cl_2O_2$: C, 61.75; H, 5.18; Cl, 22.79. Found: C, 61.49; H, 5.13; Cl, 22.71.

5-Chloro-2-(3-chloro-2-hydroxypropoxy)benzhydrylamine Hydrochloride (V)—A solution of 44 g. (0.142 mole) of 3-(2-benzyl-4-chlorophenoxy)-2-hydroxypropyl chloride in 150 ml. of carbon tetrachloride was brought to reflux. The solution was exposed to 275-w., 110–125 v., 60-cycle AC General Electric sunlamp held at a distance of 8 in. While stirring the refluxing solution there was added 5.7 g. (0.032 mole) of *N*-bromosuccinimide and 0.31 g. (0.00128 mole) of benzoyl peroxide. The initial dark red solution disappeared in 10 min. The process was repeated three more times until a total of 22.8 g. (0.128 mole) of *N*-bromosuccinimide and 1.24 g. (0.0051 mole) of benzoyl peroxide had been reacted. An additional 1.5 hr. of refluxing under irradiation was permitted. The mixture was filtered to remove the succinimide, and the filtrate was evaporated *in vacuo* to an oil. The crude oil (IV) was dissolved in a mixture of 300 ml. of dimethylformamide and 175 ml. of concentrated ammonium hydroxide with vigorous stirring at room temperature. The solution was allowed to stand overnight and then diluted with 1,600 ml. of water. The crude mixture was extracted with two 300-ml. portions of chloroform. The combined chloroform solutions were washed with two 200-ml. portions of water, dried over anhydrous calcium sulfate, and evaporated *in vacuo* to an oil. The oil was shaken with 800 ml. of ether and 500 ml. of water. The aqueous phase was separated, made basic with 80 ml. of 10% sodium hydroxide, and extracted with two 200-ml. portions of ether. The three ether solutions were combined, washed with two 100-ml. portions of water, dried over anhydrous calcium sulfate, and saturated with dry hydrogen chloride. A total of 7.5 g. (15% yield) of crude salt was obtained. Trituration with chloroform–petroleum ether (75:100 ml.) did not improve the purity of the product, which is somewhat hygroscopic. It was dissolved in 50 ml. of chloroform, treated with char-

coal, and the solution evaporated *in vacuo* to an oil. Trituration with anhydrous ether gave 4.87 g. of 5-chloro-2-(3-chloro-2-hydroxypropoxy)benzhydrylamine hydrochloride, m.p. 97–100°.

Anal.—Calcd. for $C_{16}H_{18}Cl_2NO_2$: C, 52.98; H, 5.00; Cl, 29.33; N, 3.86. Found: C, 53.21; H, 5.24; Cl, 29.21; N, 3.71.

***N,N*-Diethyl-3-(2-benzyl-4-chlorophenoxy)-2-hydroxypropylamine Hydrochloride (III)**—A solution of 31.1 g. (0.100 mole) of 3-(2-benzyl-4-chlorophenoxy)-2-hydroxypropyl chloride in 14.6 g. (0.200 mole) of diethylamine was refluxed for 5.5 hr. with stirring. The excess of amine was removed by distillation. The oily residue was dissolved in 250 ml. of ether and extracted with two 100-ml. portions of 10% hydrochloric acid. The combined aqueous acid solutions were washed with 100 ml. of ether and then made basic with 200 ml. of 10% sodium hydroxide. The mixture was extracted with three 100-ml. portions of ether. The combined ether solutions were washed with two 50-ml. portions of water, dried over anhydrous calcium sulfate, and saturated with dry hydrogen chloride. The crude salt was collected and triturated with absolute ethanol–absolute ether (50:250 ml.) to give 16.3 g. (42% yield) of product, m.p. 128–131°. Recrystallization from methanol–ether (75:300 ml.) gave 14.4 g. of pure *N,N*-diethyl-3-(2-benzyl-4-chlorophenoxy)-2-hydroxypropylamine hydrochloride, m.p. 131–133°.

Anal.—Calcd. for $C_{20}H_{27}Cl_2NO_2$: C, 62.50; H, 7.08; Cl, 18.45; N, 3.65. Found: C, 62.53; H, 7.08; Cl, 18.48; N, 3.84.



Keyphrases

5-Chloro-2-(3-chloro-2-hydroxypropoxy)-benzhydrylamine, related compounds—syntheses

UV light—reaction irradiation