was heated at 150° for twenty hours. The solution was cooled and filtered to remove insoluble material. The filtrate was evaporated to dryness *in vacuo* to remove excess hydrochloric acid. The residue was dissolved in 12 ml. of water containing 0.3 ml. of 1 *N* hydrochloric acid and the solution was extracted continuously with chloroform for twelve hours. The aqueous solution was then brought to *p*H 10 by the addition of 0.5 ml. of 2 *N* sodium hydroxide and extracted with fresh chloroform for twelve hours.

The chloroform solution from the extraction of the alkaline aqueous solution was concentrated to dryness and the dry residue was extracted with several portions of ether. Removal of the ether from the combined extracts yielded a basic residue which weighed about 7 mg. This residue was sublimed at 140° and a pressure of 3 mm. Traces of oily material were removed from the substantially crystalline sublimate by washing with a mixture of ether and petroleum ether (2:1). The crystalline sublimate, 6 mg., was recrystallized from ether to give 3.5 mg. of pure 5,6-dimethylbenzimidazole, m. p. 205–206° (micro block).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.17; C-methyl, 20.6 (2 moles); mol. wt., 146. Found: C, 74.34; H, 6.47; N, 19.21; C-methyl, 11.1 (1.1 moles); equiv. wt., 144 ±5 (potentiometric titration); mol. wt., 159 (ebullioscopic in acetonitrile).

5,6-Dimethylbenzimidazole Picrate.—Addition of saturated aqueous picric acid solution to an aqueous solution of the 5,6-dimethylbenzimidazole obtained from vitamin B_{12} gave immediately a yellow crystalline precipitate. The picrate was separated, washed with water, and recrystallized from aqueous ethanol, It melted at 272–273° (dec.).

Anal. Calcd. for $C_{15}H_{13}N_5O_7$: N, 18.66. Found: N, 18.76.

4,5-Dibenzamido-1,2-dimethylbenzene.—Synthetic 4,5-diamino-1,2-dimethylbenzene was benzoylated with benzoyl chloride and alkali. The product was recrystallized from ethanol, m. p. 262–262.5°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.14. Found: C, 76.70; H, 6.01; N, 8.25.

4,5-Dibenzamido-1,2-dimethylbenzene from 5,6-Dimethylbenzimidazole.—A solution of 5.1 mg. of 5,6-dimethylbenzimidazole obtained from vitamin B_{12} was cooled to 0° and 90 mg. of benzoyl chloride added. The mixture was stirred in an ice-bath for five hours, and then stored at 2° overnight. The precipitate was collected and dissolved in 2 ml. of boiling ethanol. This solution was filtered and stored at 2° for four hours. The crystals which had separated were then washed with ethanol and water and dried. The yield of 4,5-dibenzamido-1,2-dimethylbenzene, m. p. and mixed m. p. 262–263°, was 5.5 mg.

Synthetic 5,6-Dimethylbenzimidazole.—A solution of 60 mg. of 4,5-diamino-1,2-dimethylbenzene and 60 mg. of 98% formic acid in 3.5 ml. of 4 *N* hydrochloric acid was heated at the reflux temperature for two hours.[7] The reaction mixture was cooled, filtered and neutralized with concentrated ammonium hydroxide solution. A crystalline precipitate of crude 5,6-dimethylbenzimidazole formed in excellent yield. The crystals were separated by centrifugation and dried. A portion was treated with chloroform and filtered to remove insoluble material, and the filtrate was evaporated to dryness. The residue was sublimed at 140° and at a pressure of 3 mm. of mercury. The sublimate was recrystallized from ether to give 5,6-dimethylbenzimidazole, m. p. 204–205°. No depression of melting point was observed when this compound was mixed with the product from vitamin B_{12}. In solution in 95% ethanol which was 0.01 *N* with respect to hydrochloric acid, the synthetic material exhibited maxima at 2745 Å. (E_M 7500) and 2840 Å. (E_M 8100).

Acknowledgment.—The authors wish to thank Miss Janice Mayfield for technical assistance. They are indebted to Dr. N. R. Trenner and Mr. R. P. Buhs for the potentiometric titration, to Dr. J. B. Conn for the molecular weight determination, and to Mr. R. Boos and his associates for the microanalyses.

Summary

5,6-Dimethylbenzimidazole has been isolated from an acid hydrolysate of vitamin B_{12}. Its structure has been established by degradation and by synthesis.

(7) *Cf.* Phillips, *J. Chem. Soc.*, 2393 (1928).

RAHWAY, NEW JERSEY RECEIVED MARCH 29, 1950

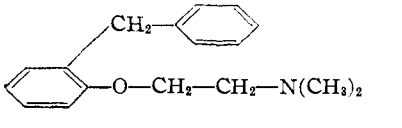
[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

2-Benzylphenol Derivatives. V.[1] Imidazolines

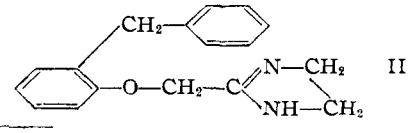
BY WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, LEE C. CHENEY AND S. B. BINKLEY

Numerous compounds containing the imidazoline (4,5-dihydroimidazole) nucleus exhibit interesting physiological properties. Furthermore, it has been observed that replacement of the dialkylaminoethyl by the 2-methylimidazoline group often results in a compound with approximately the same order of physiological activity. For example, both N-phenyl-N-benzyl-N′,N′-dimethylethylenediamine (Antergan) and its imidazoline analog 2-(N-phenyl-N-benzylaminomethyl) imidazoline (Antistin) have been shown to be effective clinically as antihistaminic drugs.[2,3]

The discovery that 2-benzylphenyl β-dimethylaminoethyl ether (I) prevents histamine-induced asthma in guinea pigs[4] made it desirable to prepare and evaluate the imidazoline analog (II). In this



I



II

(1) For the preceding paper in this series, see Wheatley, Fitzgibbon, Cheney and Binkley, THIS JOURNAL, **72**, 1655 (1950).

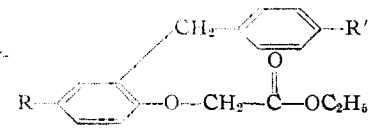
(2) Halpern, *Arch. Internat. Pharmacodynamie*, **68**, 339 (1942).

(3) Bourquin, *Schweiz. med. Wochschr.*, **76**, 296 (1946); Schindler, *ibid.*, **76**, 300 (1946); Brack, *ibid.*, **76**, 316 (1946).

(4) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949).

TABLE I

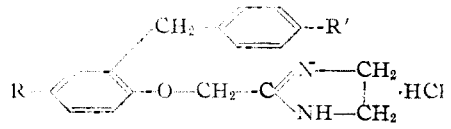
ETHYL 2-BENZYLPHENOXYACETATES: Recrystallization solvents: (*a*) Skellysolve A; (*b*) 95% ethanol; (*c*) Skellysolve B.



R	R'	Yield, %	B. p., °C.	Mm.	M. p., °C. or $n^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	90	168	1.2	41–44[a]	$C_{17}H_{18}O_3$	75.5	75.7	6.7	6.9
CH_3	H	83	159–162	2	1.5492	$C_{18}H_{20}O_3$	76.0	76.5	7.1	6.9
Cl	H	87	168–174	1	67–68[b]	$C_{17}H_{17}O_3Cl$	67.0	67.0	5.6	5.6
H	Cl	85	162–163	1	54–58[c]	$C_{17}H_{17}O_3Cl$	67.0	67.2	5.6	5.7
H	F	87	168–169	1.5	1.5362	$C_{17}H_{17}O_3F$	70.8	71.0	5.9	6.0

TABLE II

IMIDAZOLINE HYDROCHLORIDES: Recrystallized from (*a*) isopropyl alcohol; (*b*) from isopropyl alcohol–ether.



R	R'	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	183.0–195.0[a]	$C_{17}H_{19}ON_2Cl$	67.4	67.4	6.3	6.4
CH_3	H	201.0–204.0[a]	$C_{18}H_{21}ON_2Cl$	68.2	68.0	6.7	6.8
Cl	H	223.0–228.0[b]	$C_{17}H_{18}ON_2Cl_2$	60.5	60.6	5.4	5.6
H	Cl	239.5–243.5[a]	$C_{17}H_{18}ON_2Cl_2$	60.5	60.2	5.4	5.5
H	F	203.0–206.0[a]	$C_{17}H_{18}ON_2ClF$	63.7	63.6	5.7	5.8

paper the synthesis of II and several of its substitution analogs is reported.[5]

Examination of the literature reveals a variety of methods of synthesis of 2-substituted imidazolines. The synthesis from an ester and ethylenediamine[6] appeared to be the most suitable because of the high yields, simplicity of experimental procedure, and the ease of preparation of the required intermediates. Ethyl chloroacetate and the sodium *o*-benzylphenoxide reacted readily to give the desired ethyl 2-benzylphenoxyacetate. Heating the ester with an excess of anhydrous ethylenediamine on the steam-bath yielded the 2-(2-benzylphenoxymethyl)-imidazoline. Although Hill and Aspinall[6a] showed that considerably higher yields were obtained from ethyl benzoate and ethylenediamine by increasing the reaction temperature from 100 to 150°, the effect of higher reaction temperatures was not investigated in the present work, since at 100° the imidazolines were consistently obtained in yields of 70% or better.

None of the compounds is more active as an antihistaminic than 2-benzylphenyl β-dimethylaminoethyl ether.[4] The "benadryl index" as measured by the asthma chamber method is less than 0.5 for all of the compounds reported.[7]

(5) Since this work was undertaken, a number of imidazoline analogs of antihistamines has been reported; see Djerassi and Scholz, *ibid.*, **69**, 1688 (1947); Djerassi and Scholz, *J. Org. Chem.*, **13**, 830 (1948); Kyrides, *et al.*, THIS JOURNAL, **69**, 2239 (1947); Miescher and Marxer, U. S. Patent 2,485,212 (Oct. 18, 1949).

(6) (a) Hill and Aspinall, THIS JOURNAL, **61**, 822 (1939); (b) Kyrides, *et al.*, *J. Org. Chem.*, **12**, 577 (1947).

(7) Mills, Rohrmann, Dinwiddie and Lee [*Arch. internat. pharmacodyn.*, **80**, 119 (1949)] report the benadryl index of II to be 0.2 by the intestinal strip assay.

Experimental[8]

Ethyl 2-Benzylphenoxyacetate.—A solution of 184 g. (1.0 mole) of 2-benzylphenol[4] in 400 ml. of toluene was added dropwise to a stirred suspension of 24 g. (1.0 mole) of sodium hydride in 200 ml. of toluene, under a nitrogen atmosphere. After the addition had been completed, the reaction mixture was refluxed for thirty minutes. To the clear hot solution was added dropwise 129 g. (1.05 moles) of ethyl chloroacetate, whereupon sodium chloride began to precipitate. The mixture was refluxed for twenty-one hours, then cooled and hydrolyzed with ice and hydrochloric acid. The toluene layer was separated, washed with dilute sodium hydroxide, saturated sodium chloride solution, filtered through anhydrous sodium sulfate and stripped. Distillation of the residual oil gave 244 g. (90% yield) of ethyl 2-benzylphenoxyacetate, b. p. 168° at 1.2 mm.

In a similar manner were prepared esters from 2-benzyl-4-cresol,[9] 2-benzyl-4-chlorophenol,[10] 2-(4′-chlorobenzyl)-phenol,[10] and 2-(4′-fluorobenzyl)-phenol.[11] The data concerning these esters are in Table I.

2-(2-Benzylphenoxymethyl)-imidazoline (II).—A mixture of 54 g. (0.2 mole) of ethyl 2-benzylphenoxyacetate and 50 g. (0.84 mole) of anhydrous ethylenediamine was heated for thirty-four hours on a steam-bath in a sealed pressure bottle. Distillation of the resulting oil gave 39.9 g. (75% yield) of II, b. p. 203–207° at 1 mm., m. p. 90.0–91.0° (recrystallized from benzene–Skellysolve B).

Anal. Calcd. for $C_{17}H_{18}ON_2$: C, 76.7; H, 6.8; N, 10.5. Found: C, 76.7; H, 6.8; N, 10.6.

For the preparation of the imidazolines listed below, a 3:1 molar ratio of ethylenediamine to ester was used; reaction times were thirty-six to forty-eight hours.

2-(2-Benzyl-4-cresoxymethyl)-imidazoline.—In 74% yield; b. p. 206–209° at 2.5 mm.

2-(2-Benzyl-4-chlorophenoxymethyl)-imidazoline.—70% yield; b. p. 207–213° at 2 mm.

2-[2-(4′-Chlorobenzyl)-phenoxymethyl]-imidazoline.

(8) All melting points are uncorrected.

(9) Claisen, *et al.*, *Ann.*, **442**, 210 (1925).

(10) Huston, *et al.*, THIS JOURNAL, **55**, 4639 (1933).

(11) Wheatley, Cheney and Binkley, *ibid.*, **71**, 3755 (1949).

79% yield; b. p. 218–219° at 2 mm., m. p. 116.0–117.5° (recrystallized from cyclohexane).

Anal. Calcd. for $C_{17}H_{17}ON_2Cl$: C, 67.9; H, 5.7. Found: C, 67.8; H, 5.7.

2-[2-(4′-Fluorobenzyl)-phenoxymethyl]-imidazoline.—71% yield; b. p. 209–212° at 3 mm., m. p. 104.5–106.5° (recrystallized from cyclohexane).

Anal. Calcd. for $C_{17}H_{17}ON_2F$: C, 71.8; H, 6.0. Found: C, 71.9; H, 6.0.

Two other experiments were carried out on the preparation of II, and gave approximately the same results. In one experiment, the same amounts of ester and ethylenediamine as indicated above were heated for 112 hours on the steam-bath; the imidazoline was obtained in 74% yield. In the second experiment a mixture of 36 g. (0.6 mole) of ethylenediamine and 54 g. (0.2 mole) of ethyl 2-benzylphenoxyacetate was boiled under a short column topped with a total reflux-partial takeoff condenser. After 4.5 hours, the theoretical amount of ethanol had been collected. Distillation of the reaction mixture gave 36.9 g. (69% yield) of II.

Imidazoline Hydrochlorides.—Saturation of cold ethereal solutions of the imidazolines with dry hydrogen chloride caused precipitation of the hydrochlorides, which were collected by filtration and purified by recrystallization from suitable solvents. These hydrochlorides are summarized in Table II.

Acknowledgment.—The authors wish to express their appreciation to Mr. Richard M. Downing and Mrs. Neva Knight, who performed the microanalyses reported herein.

Summary

The synthesis of 2-(2-benzylphenoxymethyl)-imidazoline and certain of its substituted analogs is reported. These imidazolines were prepared by heating the ethyl 2-benzylphenoxyacetates with an excess of anhydrous ethylenediamine.

RECEIVED MARCH 17, 1950

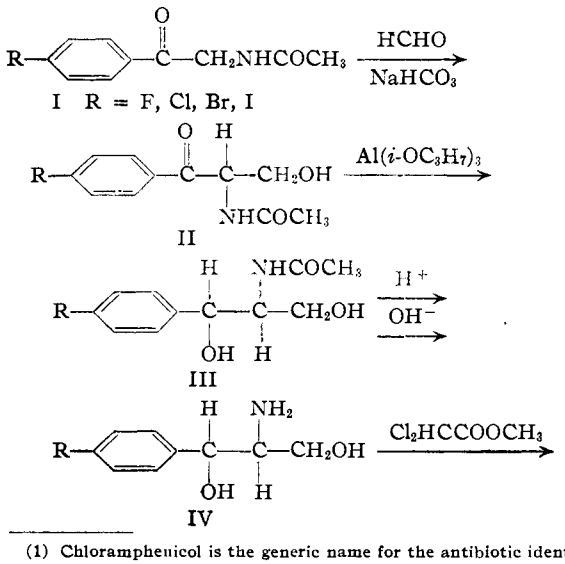
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Chloramphenicol[1] (Chloromycetin). VIII. The Synthesis of Ring Halogenated Compounds

BY L. L. BAMBAS, H. D. TROUTMAN AND LOREN M. LONG

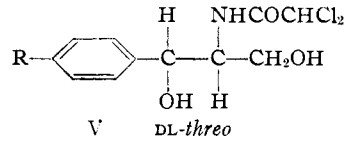
The success of the method described in paper VII[2] of this series for the preparation of essential intermediates in the synthesis of D-(levo)-*threo*-2 - dichloroacetamido - 1 - *p* - nitrophenyl - 1,3 - propanediol (chloramphenicol) has encouraged the authors to extend the procedure to a number of compounds related to the antibiotic. Application of the synthesis to compounds containing a halogen atom rather than a nitro group in the para position has proved entirely feasible. Results of the investigation are reported in this paper.

The principal reactions involved in the preparation are those outlined in the series of reactions.



(1) Chloramphenicol is the generic name for the antibiotic identified as Chloromycetin, a Parke Davis & Co. trademark.

(2) Long and Troutman, THIS JOURNAL, **71**, 2473 (1949).



V DL-*threo*

Intermediate I in the series was obtained in each case by condensing the α-bromoacetophenone derivative with hexamethylenetetramine, hydrolyzing the salt and subsequently acetylating the product with acetic anhydride. Each indicated reaction leads to the desired product in relatively high yields.

The chief product (III) obtained by the aluminum isopropoxide reduction of II is apparently the DL-*threo* derivative. Evidence for this opinion lies in the method of synthesis, which has been shown to yield the *threo* racemate, as well as similarity of the crystalline form of III to the corresponding intermediates obtained in the synthesis of chloramphenicol.[2] Also the final product (V) exhibits a higher degree of activity than the corresponding product prepared from the other racemate which is present in the reduction mixture in minor amounts.

Table I summarizes pertinent data concerning various compounds prepared in the investigation. In each case product V is reported as the *threo* racemate. Results of pharmacological testing will be made available at a later date.

Experimental

α-Bromo-*p*-fluoro, chloro, bromo and iodoacetophenone.—These intermediates were prepared by methods described in the literature. *p*,α-Dibromoacetophenone may be obtained from the Eastman Kodak Co.

Hexamethylenetetramine Salts of α-Bromo-*p*-fluoro, chloro, bromo and iodoacetophenone.—The α-bromoaceto-