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Chloromycetin (Chloramphenicol[1]). Related Compounds Having Alkyl Side Chain Variations

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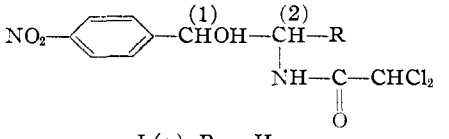
During the preparation of compounds related to Chloromycetin, D-(levo)-*threo*-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol, a number were synthesized with variations in the alkyl side chain. In the present series changes were made in carbon atoms (1) and/or (3) which involved either the replacement of hydroxyl with hydrogen or alkyl or the complete omission of these carbon atoms from the structure. Nitration of the acetyl derivatives of phenylalkylamino alcohols or the dichloroacetamides of phenylalkylamines led to the corresponding *para* nitro substituted compounds. The acetyl groups of the former were removed by hydrolysis and the bases converted to dichloroacetamides.

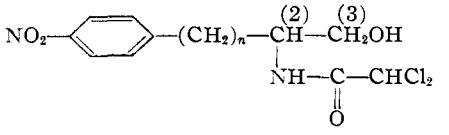
The chemical characterization of Chloromycetin and the confirmation of the proposed structure, D-(levo)-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol, by synthesis have been described recently.[2,3,4] It was noted that the diastereoisomers of the DL-*erythro* configuration as well as the L-(dextro)-*threo* isomer had considerably lowered biological Chloromycetin activity.[3] To extend these observations a number of related compounds representing other variations of the alkyl side chain have been synthesized.

First to be considered are those compounds which preserve the substituents on carbon atoms (1) and (2) of the Chloromycetin side chain, variation in the molecule being effected by changing the groups attached to carbon atom (3) or by replacing this carbon atom with hydrogen. An interpretation of the effect of these alterations in the light of the steric configurations found in this group of compounds should prove interesting. In this connection the asymmetry of carbon atom (2) may be eliminated by replacement of the primary hydroxymethyl group with hydrogen I(a); or, the effect of double asymmetry of carbon atoms (1) and (2) may be preserved by replacement of the primary hydroxymethyl group with methyl I(b) or ethyl I(c).



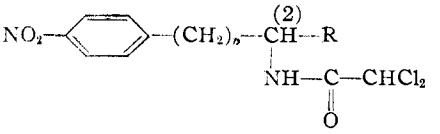
I (a), R = H
(b), R = CH_3
(c), R = C_2H_5

In the second group are compounds preserving those groups attached to carbon atoms (2) and (3) of the Chloromycetin side chain.



II(a), n = 0, (b) n = 1

The third type of compound to be considered includes products in which only the groups attached to carbon atom (2) are preserved.



III(a), n = 0, R = H (e), n = 1, R = CH_3
(b), n = 0, R = CH_3 (f), n = 2, R = H
(c), n = 0, R = C_2H_5
(d), n = 1, R = H (g), n = 2 $\left(-\underset{|}{C}H-CH_3\right)$, R = H

The approach to these compounds involved the preparation of unsubstituted phenylalkylamino alcohols and the phenylalkylamines which were not commercially available. In preparation for nitration these compounds were acylated, a step which involved preparing acetoxyacetamides or acetoxydichloroacetamides of the phenylalkylaminoalcohols. The phenylalkylamines were converted to dichloroacetamides. Nitration of these derivatives using fuming nitric acid or a mixture of concentrated nitric and sulfuric acids yielded a mixture of the ortho and para substituted isomers in which the para isomer was predominant.

The crude nitration products of the acetoxyacetamides of phenylalkylamino alcohols were hydrolyzed with dilute hydrochloric acid. The hydrochlorides were usually separated from the ortho isomer by recrystallization. The corresponding bases were converted to the dichloroacetamides I(a), (b) and (c) by reaction with methyl dichloroacetate.

The crude products from the nitration of the acetoxydichloroacetamides of phenylalkylamino alcohols were recrystallized to remove ortho isomer and selectively hydrolyzed with acid or base to free the hydroxyl group. Compounds II(a) and (b) were obtained by this procedure.

Similarly by recrystallization of the crude nitrophenyldichloroacetamidoalkanes the para nitrophenyl compounds of Group III(a) to (g), inclusive, were obtained.

Proof that the products isolated in the above series of reactions were the para nitrophenyl isomers rests primarily upon the ultraviolet absorption of these compounds. The extensive studies by Doub and Vandenbelt[5,6] of the ultraviolet absorption of various ortho, meta and para isomers of the disubstituted benzene ring including the nitrophenylalkanes served as a basis. The absorption maximum in the ultraviolet (the first primary band) of the *o*-nitrophenylalkanes occurs at a lower wave length and with a lower molecular extinction than when the nitro group is *para* (see Table I). The ultra-

(1) Chloramphenicol is the antibiotic drug for which Parke, Davis & Company has adopted the trademark Chloromycetin.

(2) Rebstock, Crooks, Controulis and Bartz, THIS JOURNAL, **71**, 2458 (1949).

(3) Controulis, Rebstock and Crooks, *ibid.*, **71**, 3463 (1949).

(4) Long and Troutman, *ibid.*, **71**, 2469 (1949).

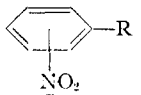
(5) Doub and Vandenbelt, *ibid.*, **69**, 2714 (1947).

(6) Doub and Vandenbelt, *ibid.*, **71**, 2414 (1949).

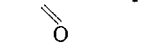
violet absorption curves for the above compounds were compared with the absorption curves for *o*- and *p*-nitrotoluene, *o*- and *p*-nitrobenzyl alcohol, and fermentation-produced Chloromycetin. These data are offered in evidence that the compounds isolated were the *p*-nitrophenyl isomers.

TABLE I

THE ULTRAVIOLET ABSORPTION CHARACTERISTICS OF DICHLOROACETAMIDES RELATED TO CHLOROMYCETIN I, II AND III



R	First primary band 0.1 *N* HCl λ	$\epsilon_{max.}$	0.1 *N* NaOH λ	$\epsilon_{max.}$
$-CH_3$(ortho)	266(H_2O)	5,300		
$-CH_3$ (para)	285(H_2O)	9,250		
$-CH_2OH$ (ortho)	267.5	5,600		
$-CH_2OH$ (para)	276	9,200		
-CHOH-CHNHR'*-CH_2OH (D-*threo*) (para)	277	9,700	279	9,560
-CHOH-CHNHR'-CH_2OH (DL-*erythro*)	275.5	9,760	278.5	9,120
-CHOH-CHNHR'-CH_3 (D-*threo*)	278	9,680	279	9,420
-CHOH-CHNHR'-CH_3 (DL-*threo*)	278	9,950	279.5	9,680
-CHOH-CHNHR'-CH_3 (DL-*erythro*)	277	10,400	278.5	9,760
-CHOH-CHNHR'-C_2H_5 (DL-*threo*)	279	9,550	280	9,090
-CHOH-CHNHR'-C_2H_5 (DL-*erythro*)	277	9,790	278.5	9,220
-CHOH-CH_2NHR'	276	9,790	278.5	9,360
-CHNHR'-CH_2OH	274.5	10,200	280	9,670
-CHNHR'-CH_3	276	9,560	279	9,320
-CHNHR'-CH_2-CH_3	276	9,140	278	8,920
-CH_2NHR'	276	10,200	280.5	9,960
-CH_2CH_2NHR'	280.5	9,240	282	9,260
-$CH(CH_3)$-CH_2NHR'	284.5	9,480	285	9,370
-CH_2-CHNHR'-CH_3	281.5	9,070	282	8,590
-CH_2-CHNHR'-CH_2OH	281	9,430	282	9,370
-CH_2-CH_2-CH_2NHR'	282	10,100	282.5	10,000

* R' = 

DL-1-Phenyl-1-hydroxy-2-aminoethane was obtained in good yield by the low pressure hydrogenation of ω-aminoacetophenone hydrobromide in the presence of a palladium catalyst, the conditions being similar to those used by Mannich and Thiele[7] for preparing this compound. ω-Aminoacetophenone hydrobromide was obtained by hydrolyzing the hexamethylenetetramine complex of phenacyl bromide as described by Mannich and Hahn.[8]

The *erythro* and *threo* isomers of DL-1-phenyl-1-hydroxy-2-aminopropane were obtained by either of two procedures. 1-Phenyl-1-hydroxy-2-nitropropane, prepared by condensing benzaldehyde with nitroethane by a modification of the procedure reported by Kanao and Nagai,[9] and later studied by Kamlet,[10] and Hoover and Hass,[11] was hydrogenated in glacial acetic acid over palladium oxide catalyst to yield nearly equal amounts of the two diastereoisomeric amines. Although the isomers could be separated by fractional crystallization of the hydrochlorides as reported by Jarowski and Hartung,[12] the separations were not quantitative. A search for other derivatives which could be more easily separated or other techniques of separation was not made. Instead, a second method of synthesis in which only the DL-*erythro* isomer is obtained was used. This method consisted in the hydrogenation of isonitrosopropiophenone, a synthesis first reported by Hunnius and Rabe[13] and developed by Hartung and Munch.[14]

Several methods have been described for the inversion of this type of compound, consequently the occurrence of only one pair of isomers was not critical. It was found that when the N-acetyl derivative of DL-*erythro*-1-phenyl-1-hydroxy-2-aminopropane was treated with thionyl chloride inversion occurred smoothly to give the DL-*threo* isomer in 81% yield. In this case it is likely that the inversion occurred in the usual manner with the intermediate formation of an oxazoline although such a compound was not isolated. A detailed discussion of inversions of this type by Johnson and Schubert[15] has recently appeared.

Since the D-*threo* configuration is the most active arrangement against microörganisms in the case of the 1-*p*-nitrophenyl-2-amino-1,3-propanediol molecule, and since the same configurational relationship exists in the 1-phenyl-1-hydroxy-2-aminopropane structure, it was of interest to resolve the DL-*threo* isomer of the latter compound and prepare the dichloroacetamide of the D-(levo) base.[16] The resolution was accomplished by fractional recrystallization of the *l,d*-bitartrate salt as described by Kanao and Nagai.[9]

DL-1-Phenyl-1-hydroxy-2-aminobutane was obtained in both diastereoisomeric forms by the type reactions used for preparing the 1-phenyl-1-hydroxy-2-aminopropane stereoisomers. A mixture of the DL-diastereoisomeric bases obtained by low pressure hydrogenation of DL-1-phenyl-1-hydroxy-2-nitrobutane was converted to the acetamides. The *erythro* isomer was readily separated from this mixture by fractional crystallization. The assignment to this isomer of the DL-*erythro* configuration is based on the fact that the same amide was obtained from the base prepared by hydrogenating isonitrosobutyrophenone, a procedure which was used as an alternate method for obtaining this compound. The hydrogenation was similar to that described by Hartung, *et al.*,[17] who have reported the preparation of this aminoalcohol. Some liberty is taken in assuming by analogy that the product isolated from the hydrogenation of isonitrosobutyrophenone is the same configuration as that obtained when isonitrosopropiophenone is hydrogenated.

The *threo* isomer of the series was obtained by inversion of the *erythro* amide by treatment with thionyl chloride. When the first preparatory proce-

(7) Mannich and Thiele, *Arch. Pharm.*, **253**, 181 (1915).
(8) Mannich and Hahn, *Ber.*, **44**, 1542 (1911).
(9) Kanao and Nagai, *Ann.*, **470**, 157 (1929).
(10) Kamlet, U. S. Patent 2,151,517.
(11) Hoover and Hass, *J. Org. Chem.*, **12**, 506 (1947).
(12) Jarowski and Hartung, *ibid.*, **8**, 564 (1943).
(13) Hunnius and Rabe, *Ber.*, **45**, 2166 (1912).
(14) Hartung and Munch, THIS JOURNAL, **51**, 2262 (1929).
(15) Johnson and Schubert, *ibid.*, **72**, 2187 (1950).
(16) Using the conventions for establishing configurational relationships in carbohydrate derivatives, DL-*threo*-1-phenyl-1-hydroxy-2-aminopropane is equivalent to *dl*-norisoephedrine and the DL-*erythro* isomer to *dl*-norephedrine. The D-*threo* isomer is similarly equivalent in configuration to *levo*-norisoephedrine.
(17) Hartung, Munch, Deckert and Crossley, THIS JOURNAL, **52**, 3317 (1930).

dure was used which gives a mixture of diastereoisomers (*vide supra*), the *threo* racemate was separated in crystalline form by completely acetylating the residue remaining in the mother liquor from which the acetamide of the *erythro* compound had been isolated.

DL-1-Phenyl-1-amino-2-hydroxyethane and DL-1-phenyl-2-amino-3-hydroxypropane were prepared by the reduction of the ethyl esters of DL-phenylglycine and DL-phenylalanine with lithium aluminum hydride. The preparation of the latter compound by this procedure was recently described by Karrer, *et al.*[18]

DL-1-Phenyl-1-aminoethane, DL-1-phenyl-1-aminopropane and DL-1-phenyl-2-aminopropane were obtained by reducing the oximes of acetophenone, propiophenone and phenylacetone at three atmospheres over Raney nickel W-5.

The remaining phenylalkylamines in the series were commercially available.

The Chloromycetin related compounds of Groups I, II and III above have been tested for antibacterial, antifungal and antiviral activity. The results of these studies will be published subsequently.

We wish to acknowledge our indebtedness to Drs. Leon A. Sweet and George Rieveschl for continued interest and encouragement in this work; to Dr. Harry M. Crooks, Jr., for numerous suggestions and advice; to the Misses Denise Lundquest and Patricia Welch for the ultraviolet determinations; and to Mr. C. E. Childs, Mrs. Geraldine Koch and Miss Virginia Pawlik for the many microanalytical determinations.

Experimental

DL-1-Phenyl-1-hydroxy-2-aminoethane.—ω-Aminoacetophenone hydrobromide was prepared by the method of Mannich and Hahn.[8] The crude product melting at 196–198° was obtained in 83% yield.

The phenylacylamine salt (53 g.) was hydrogenated in 600 ml. of 80% ethanol over palladium oxide catalyst (4 g.) until one molecular equivalent of hydrogen had been absorbed. At 50 p.s.i. and room temperature the reaction required seven hours. The catalyst was then removed, the solvent evaporated, and the base liberated by adjusting the *p*H of an aqueous solution of the amine salt to 11–12 with concd. NaOH. The oily base was extracted with three portions of ether. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated. A 91% yield of base was obtained.

DL-1-*p*-Nitrophenyl-1-hydroxy-2-aminoethane.—A thirty-gram portion of the above base was acetylated with 65 ml. of acetic anhydride. When the initial reaction had subsided, 50 ml. of dry pyridine was added and the reaction mixture kept overnight at room temperature. The product was obtained as an oil. The crude oil was nitrated by adding in portions during 20 minutes to 120 ml. of fuming nitric acid (sp. gr. 1.5) at 10 to 20°, the temperature being controlled by adding Dry Ice directly to the reactants. The reaction was allowed to proceed at room temperature for 30 minutes longer. The nitration mixture was then quenched on ice, neutralized with $NaHCO_3$, and extracted into ethyl acetate. The combined extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated.

The gummy product was at once hydrolyzed with 300 ml. of 10% HCl for three hours on the steam-bath. The cooled hydrolysate was extracted with ether to remove a yellow impurity and the aqueous solution evaporated at reduced pressure. The crystalline hydrochloride was twice recrystallized from absolute ethanol to a 49% yield of product melting at 225–230° dec. A sample recrystallized twice more from methanol melted at 238–240° dec.

Anal. Calcd. for $C_8H_{11}N_2O_3Cl$: C, 43.9; H, 5.08; N, 12.80. Found: C, 44.19; H, 5.13; N, 12.76.

The hydrochloride was converted to the free base by dissolving 10 g. of the product melting at 225–230° in 50 ml. of distilled water and adjusting the *p*H of the ice-cold solution to 11 with concd. NaOH or NH_4OH. The crystalline base separated in 91% yield; m.p. 134–136°. A sample recrystallized twice from hot water and finally from ethylene dichloride melted at 137–138°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.37. Found: C, 52.72; H, 5.70; N, 15.16.

DL-1-*p*-Nitrophenyl-1-hydroxy-2-dichloroacetamidoethane.—The amide was prepared by heating 3.8 g. of the above base with 14 ml. of methyl dichloroacetate for 1.5 hours on the steam-bath. The cooled mixture was slurried with low-boiling petroleum ether to dissolve excess ester. The petroleum ether solution was decanted and the crystalline residue recrystallized from hot ethylene dichloride to a yield of 4.32 g. of product which melted at 110–112°. Recrystallization from 50% aqueous methanol and ethylene dichloride raised the melting point to 115.5–116°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4Cl_2$: C, 40.98; H, 3.44; N, 9.56. Found: C, 41.03; H, 3.70; N, 9.82.

DL-*threo*-, DL-*erythro*- and D-*threo*-1-Phenyl-1-hydroxy-2-aminopropane. Method A.—The DL-*threo* and DL-*erythro* diastereoisomers were first obtained by a modification of the procedure of Kanao and Nagai[9] in which benzaldehyde and nitroethane are condensed. In our work the sodium salts of the nitroalcohols were dissolved in glacial acetic acid and hydrogenated in the presence of palladium oxide catalyst. The bases were isolated in the usual manner and the isomers separated by fractional crystallization of the hydrochloride salts.

Since the yield of pure isomers obtained by this route is 30% or less, Method B is the recommended preparative procedure. In the latter approach only the DL-*erythro* isomer is obtained thus averting the problem of separating diastereoisomers. The DL-*erythro* isomer can then be converted in good yield to the *threo* isomer. Two forty-gram portions of isonitrosopropiophenone[19] were hydrogenated in 400 ml. of 1.25 *N* ethanolic HCl over 1.5 g. of palladium oxide catalyst. After four hours the catalyst was removed and solvents evaporated. The combined crystalline residues were recrystallized from 400 ml. of absolute ethanol to a yield of 29.5 g. of the *erythro* base hydrochloride melting at 185–190°. By reworking the mother liquors 10.2 g. of additional material was obtained. Finally the combined mother liquors were evaporated and the residue taken into excess dil. HCl. Extraction with ether removed all but 4 g. of material which was isolated by evaporation of the aqueous residue and identified as the above base hydrochloride. Since the *threo* isomer is not extracted from dilute hydrochloric acid with ether, it was assumed not to be present. The ether extractable material was not identified.

The DL-*threo* isomer was obtained by inversion of the DL-N-acetyl *erythro* isomer with $SOCl_2$. A portion of 21.5 g. of the latter compound, m.p. 135–137°, prepared by treatment of the base with excess acetic anhydride (3 ml./g.) at 65° for ten minutes was added in portions during 25 minutes to 125 ml. of $SOCl_2$ at 30–35°. After standing for 20 minutes longer at room temperature, the excess $SOCl_2$ was decomposed by adding 220 ml. of distilled water. The reaction mixture was then hydrolyzed by heating on the steam-bath for two hours. Removal of solvents at reduced pressure left a crystalline residue which was recrystallized by dissolving in 100 ml. of ethanol and adding four volumes of ether gradually. An 81% yield of DL-*threo* base hydrochloride melting at 169–170° was obtained.

Kanao and Nagai[9] resolved DL-*threo*-1-phenyl-1-hydroxy-2-aminopropane by recrystallizing the *d*-bitartrate salt. Since it was of interest to obtain the D-*threo* isomer which has the same configuration as the most active chloramphenicol intermediate, a portion of the DL-*threo* isomer was resolved by this method. After three recrystallizations from water the salt melted at 202°. The D-base was isolated in the usual manner. A sample converted to the hydrochloride melted at 183–185° as reported.

DL-*threo* and DL-*erythro*-1-Phenyl-1-hydroxy-2-amino-*n*-butane. Method A.—The DL-diastereoisomers were prepared by hydrogenating DL-1-hydroxy-2-nitrobutane which was obtained by condensing benzaldehyde with nitropropane. The condensation and hydrogenation techniques

(18) Karrer, Portmann and Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

(19) Gilman and Blatt, "Organic Synthesis," Coll. Vol. II, p. 363.

were essentially those used to prepare 1-phenyl-1-hydroxy-2-aminopropane by Method A described above. From 75 g. of benzaldehyde and 62 g. of 1-nitropropane was obtained a semicrystalline residue of 58 g. of the crude base diastereoisomers.

Method B.—Hartung, *et al.*,[17] have reported the reduction of isonitrosobutyrophenone and isolation of one of the two possible racemates. Isonitrosobutyrophenone was prepared by condensing butyrophenone with butyl nitrite in the usual manner. The product of this reaction was hydrogenated in excess 1.25 *N* ethanolic hydrochloric acid over palladium oxide catalyst. The base hydrochloride isolated from this reaction melted at 242° as reported. A portion of the free base was converted to the acetamide by treatment with acetic anhydride (3 ml./g.) for ten minutes at 65°. The product (m.p. 121–122°) was then treated with thionyl chloride to effect inversion as above. The hydrochloride obtained from hydrolysis of the inversion melted at 78–79°. A portion was converted to the free base which melted at 204–205°.

Anal. Calcd. for $C_{10}H_{16}NOCl$: C, 59.55; H, 7.99. Found: C, 59.75; H, 7.95.

Anal. Calcd. for $C_{10}H_{15}N$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.61; H, 8.94; N, 8.41.

DL-*threo*- and DL-*erythro*-1-Phenyl-1-acetoxy-2-acetamidobutane.—The crude mixture of diastereoisomeric bases obtained by Method A was N-acetylated by treatment with excess acetic anhydride (3 ml./g.) at 70° for 20 minutes. The acetylating reagents were removed *in vacuo* and the residue crystallized first by trituration with ligroin, then from ether, and finally ethylene dichloride. A yield of 8.0 g. of product melting at 121–122° was obtained. Since this derivative was identical with the amide obtained in the above experiment, it was assumed to have the DL-*erythro* configuration.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.37; H, 8.45; N, 6.86.

The mother liquors from the isolation of this amide were combined and evaporated to a gum which was completely acetylated by treatment with excess 1:1 pyridine–acetic anhydride at room temperature overnight. After evaporation of the acetylating agents, the residue was crystallized from ether. A yield of 11 g. of the DL-*threo* isomer was obtained. A sample recrystallized twice from ether melted at 88–89°.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.63. Found: C, 67.37; H, 7.54; N, 5.69.

The acetamide of the DL-*erythro* base was completely acetylated in the same manner. The product melted at 105–106° after recrystallization from ether. Found: C, 67.65; H, 7.38; N, 5.75.

DL-*erythro*-, DL-*threo*- and D-*threo*-1-*p*-Nitrophenyl-1-hydroxy-2-aminopropane and DL-*threo*- and DL-*erythro*-1-*p*-Nitrophenyl-1-hydroxy-2-amino-*n*-butane.—The isomeric bases were completely acetylated by treatment with excess 1:1 pyridine–acetic anhydride. The diacetylated derivatives were nitrated with fuming nitric acid. The nitration procedure was essentially the same as that described above. The nitration products were hydrolyzed with excess 5% HCl (20 ml./g.) for three hours on the steam-bath. The cooled hydrolysates were extracted with ether and evaporated under reduced pressure. The hydrochlorides were purified by recrystallization from ethanol or isopropyl alcohol. The free bases were precipitated from solutions of their hydrochlorides by addition of NH_4OH or NaOH. The products were recrystallized from water and methanol or ethylene dichloride.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.16; N, 14.27. Found for 1-*p*-nitrophenyl-1-hydroxy-2-aminopropane: DL-*erythro* base (m.p. 133–134°): C, 54.88; H, 6.30; N, 14.15. DL-*threo* base (m.p. 122–123°): C, 54.78; H, 6.17; N, 14.56. DL-*threo* base (m.p. 150–151°): C, 55.06; H, 6.11; N, 14.33. $[\alpha]^{26}D$ 41.9° (*c* 2.0% in 1.0 *N* HCl).

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found for 1-*p*-nitrophenyl-1-hydroxy-2-amino-*n*-butane, DL-*erythro* base (m.p. 118–119°): C, 56.92; H, 6.77; N, 13.32. DL-*threo* base (m.p. 120–121°): C, 57.14; H, 6.70; N, 13.04.

Dichloroacetamides of DL-*erythro*-, DL-*threo*- and D-*threo*-1-*p*-Nitrophenyl-1-hydroxy-2-aminopropane and DL-*erythro*- and DL-*threo*-1-*p*-Nitrophenyl-1-hydroxy-2-amino-*n*-butane.—The amides were prepared in 80–90% yields by refluxing the corresponding bases with three equivalents of methyl dichloroacetate in absolute ethanol (10 ml./g.) for 45 minutes on the steam-bath. This procedure is preferable to the one described above. The ethanol was then evaporated and the residue after triturating with low boiling petroleum ether to remove excess ester was dissolved in ethyl acetate. The ethyl acetate solution was then washed with 0.1 *N* H_2SO_4, 5% $NaHCO_3$ and water; then dried over anhydrous $MgSO_4$ and evaporated. The dichloroacetamide of the DL-*erythro* base (propane) was recrystallized from chloroform–low boiling petroleum ether, 50% aqueous methanol and ethylene dichloride. The dichloroacetamide of the DL-*threo* isomer (propane) was recrystallized from chloroform and ethylene dichloride; and the D-*threo* isomer from ethylene dichloride–low boiling petroleum ether, 50% aqueous methanol, and finally ethylene dichloride–low boiling petroleum ether. The DL-*erythro* isomer of the butane series was recrystallized from ethanol–low boiling petroleum ether and 50% aqueous methanol. The DL-*threo* isomer of this series was recrystallized from ethylene dichloride.

Anal. Calcd. for $C_{11}H_{12}N_2O_4Cl_2$: C, 43.02; H, 3.94; N, 9.12. Found for the dichloroacetamide of 1-*p*-nitrophenyl-1-hydroxy-2-aminopropane: DL-*erythro* isomer (m.p. 116–1171): C, 42.93; H, 3.89; N, 9.26. DL-*threo* isomer (m.p. 142–143°): C, 43.11; H, 4.01; N, 9.30. D-*threo* isomer (m.p. 104–105°): C, 43.22; H, 4.04. $[\alpha]^{28}D$ +50.6 (*c* 1.5% in absol. ethanol).

Anal. Calcd. for $C_{12}H_{14}N_2O_4Cl_2$: C, 44.88; H, 4.39; N, 8.72. Found for 1-*p*-nitrophenyl-1-hydroxy-2-dichloroacetamido-*n*-butane: DL-*erythro* isomer (m.p. 141–142°): C, 44.90; H, 4.62; N, 8.88. DL-*threo* isomer (m.p. 120–121°): C, 45.06; H, 4.61; N, 8.95.

DL-1-Phenyl-1-amino-2-hydroxyethane.—A sample of 50 g. of the ethyl ester hydrochloride of phenylglycine dissolved in 250 ml. of $CHCl_3$ was converted to the free base by treatment with anhydrous ammonia. The precipitated NH_4Cl was removed by filtration and the filtrate evaporated to 35 g. of a yellow oil. The oil was dissolved in 100 ml. of dry ether and added to a solution of 7 g. of $LiAlH_4$ in 600 ml. of ether during 3.5 hours. After standing overnight, the excess $LiAlH_4$ was decomposed with 50 ml. of distilled water. The mixture was filtered and the solid washed with several portions of absolute alcohol. The yellow filtrate and washes were combined and evaporated. The product was a yellow oil which was used without purification.

DL-1-*p*-Nitrophenyl-1-dichloroacetamido-2-hydroxyethane.—The oily base obtained in the preceding experiment was converted to the dichloroacetamide by heating on the steam-bath for two hours with excess methyl dichloroacetate. An oily solid obtained upon evaporation was recrystallized from absolute ethanol to give 10.3 g. of product melting at 120°.

The acetoxy derivative was prepared by acetylation of the dichloroacetamide with pyridine–acetic anhydride as usual. Without purification the product which melted at 113° was added to 50 ml. of fuming HNO_3 during one-half hour. The temperature was kept at 0 to 10° by immersion in an ice-bath. The nitration product separated when the reaction mixture was poured on ice. After recrystallization from ether, 5.5 g. of DL-1-*p*-nitrophenyl-1-dichloroacetamido-2-acetoxyethane which melted at 124–125° was obtained.

Anal. Calcd. for $C_{12}H_{12}N_2O_5Cl_2$: C, 43.01; H, 3.61. Found: C, 43.34; H, 3.80.

The acetoxy group was hydrolyzed by warming for a few minutes with (1) a little alcohol and concd. HCl or (2) 10% $NaHCO_3$. The products which separated melted at 129–132° in each case. Recrystallization from aqueous methanol, ethylene dichloride, and finally ethyl acetate raised the melting point to 146–147°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4Cl_2$: C, 40.98; H, 3.44. Found: C, 41.06; H, 3.54.

DL-1-Phenyl-2-amino-3-hydroxypropane.—Recently Karrer, Portmann and Suter[18] have reported the preparation of this base by the reduction of the ethyl ester of phenylalanine with $LiAlH_4$. This being the method of choice, the procedure used was the same as that described for the reduction of the ethyl ester of phenylglycine. The product of the reduction was an oily base which was used without purification.

TABLE II

DICHLOROACETAMIDES OF DL-PHENYLALKYLAMINES

Dichloroacetamide of	M.p., °C.	Calcd. for	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_6H_5–CH_2–CH_2NH_2	78–79	$C_{10}H_{11}NOCl_2$	51.74	52.00	4.78	4.91	6.04	5.74
C_6H_5–$CHNH_2$–CH_3	141		51.74	51.92	4.78	4.88	6.04	
C_6H_5—CH(CH$_3$)—CH_2NH_2	87–88	$C_{11}H_{13}NOCl_2$	53.68	54.02	5.32	5.50	5.69	5.62
C_6H_5–CH_2–CH_2–CH_2NH_2	75–76		53.68	53.91	5.32	5.53	5.69	5.45
C_6H_5–$CHNH_2$–CH_2–CH_3	Used without purification							
C_6H_5–CH_2–$CHNH_2$–CH_3	120 Used without purification							

TABLE III

DICHLOROACETAMIDES OF DL-*p*-NITROPHENYLALKYLAMINES

Dichloroacetamide of	M.p., °C.	Calcd. for	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-$NO_2C_6H_4$–CH_2–CH_2NH_2	89–90	$C_{10}H_{10}N_2O_3Cl_2$	43.34	43.41	3.64	3.73	10.11	10.10
p-$NO_2C_6H_4$–$CHNH_2$–CH_3	153	$C_{10}H_{10}N_2O_3C_2$	43.34	43.31	3.64	3.68	10.11	
p-$NO_2C_6H_4$—CH(CH$_3$)—CH_2NH_2	95–96	$C_{11}H_{12}N_2O_3Cl_2$	45.38	45.59	4.16	4.39	9.62	9.47
p-$NO_2C_6H_4$–CH_2–CH_2–CH_2NH_2	91	$C_{11}H_{12}N_2O_3Cl_2$	45.38	45.71	4.16	4.17	9.62	9.42
p-$NO_2C_6H_4$–$CHNH_2$–CH_2–CH_3	110	$C_{11}H_{12}N_2O_3Cl_2$	45.38	45.23	4.16	4.18	9.62	
p-$NO_2C_6H_4$–CH_2–$CHNH_2$–CH_3	146	$C_{11}H_{12}N_2O_3Cl_2$	45.38	45.30	4.16	4.28	9.62	

DL-1-*p*-**Nitrophenyl-2-dichloroacetamide-3-hydroxypropane.**—The oily base obtained in the preceding experiment was converted to the dichloroacetamide as usual. The product melted at 104–105° when recrystallized from ethyl acetate.

Anal. Calcd. for $C_{11}H_{13}NO_2Cl_2$: C, 50.40; H, 5.00. Found: C, 50.11; H, 5.51.

Acetylation of 5 g. of the dichloroacetamide with pyridine–acetic anhydride gave 3.9 g. of crystalline acetoxy product melting at 88–89° which was nitrated without purification by adding to 25 ml. of fuming HNO_3 in the usual manner. The product which precipitated upon quenching melted at 110°.

Anal. Calcd. for $C_{13}H_{14}N_2O_5Cl_2$: C, 44.70; H, 4.04. Found: C, 44.55; H, 4.00.

The acetoxy linkage was hydrolyzed by treatment with a mixture of ethanol and concd. HCl at room temperature. The product was recrystallized from aqueous alcohol to a melting point of 154°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4Cl_2$: C, 43.02; H, 3.94. Found: C, 43.16; H, 4.03.

DL-**1-Phenyl-2-aminopropane.**—The oxime of phenylacetone was prepared by mixing 13.4 g. of the ketone with 7.0 g. of hydroxylamine hydrochloride and 8.2 g. of anhydrous sodium acetate in 70 ml. of absolute alcohol as described by Neber and von Friedolsheim.[20] After standing for a week the reaction mixture was diluted with two volumes of water and the oil which separated extracted into ether. The ether extract was evaporated and the oily product hydrogenated in absolute ethanol over 2 ml. of W-5 Raney nickel at three atmospheres. In 16 hours the hydrogen uptake was 81% of the theoretical. The catalyst was then removed and the filtrate evaporated. The product was an oil.

DL-**1-Phenyl-1-aminopropane and** DL-**1-Phenyl-1-aminoethane.**—The oximes of propiophenone and acetophenone prepared as above were hydrogenated over Raney nickel W-5. The products were oils.

1-Phenyl-2-aminoethane, 1-Phenyl-3-aminopropane, DL-**2-Phenyl-1-aminopropane.**—The samples of the bases used in this work were obtained from Eastman Kodak Co., Sharples Chemical Co. and Chemical Specialties, Inc. (Zeeland, Mich).

(20) Neber and von Friedolsheim, *Ann.*, **449**, 121 (1926).

Dichloroacetamides of DL-**Phenylalkylamines.**—The following procedure for preparing 1-phenyl-2-dichloroacetamidoethane was typical. A mixture of 20 g. (0.17 mole) of β-phenylethylamine and 40 ml. of methyl dichloroacetate was warmed on the steam-bath for one hour, then let stand at room temperature until crystallization occurred. The solid, amounting to 29 g., was collected on a Buchner funnel. Evaporation of the filtrate gave a second crop of 9 g. of somewhat gummy material. Recrystallization of the first crop from aqueous ethanol gave needles of the dichloroacetamide which melted at 78–79°.

Nitration of Dichloroacetamides of Phenylalkylamines.—An example of the nitration procedure used for this series follows. Ten grams (0.043 mole) of 1-phenyl-2-dichloroacetamidoethane; m.p. 78–79°, was added in portions to 40 ml. of fuming nitric acid maintained at −5° to −10° by adding Dry Ice to the reaction mixture. After the addition was completed, the mixture was let stand five minutes, then poured with stirring onto 100 g. of cracked ice. A layer of ethyl acetate was added and the mixture made alkaline with anhydrous sodium carbonate. The aqueous solution was extracted (three times) with ethyl acetate. Evaporation of the extracts which had been dried with anhydrous $MgSO_4$ gave an oil which was crystallized from diluted ethanol. Eight grams of solid melting at 70–73° was collected on a Buchner funnel. After two recrystallizations from 70% ethanol the product melted at 89–90°.

DL-**1-*p*-Nitrophenyl-1-dichloroacetamidomethane.**—A sample of 107 g. of benzylamine dissolved in 200 ml. of pyridine was treated with one equivalent of acetyl chloride. The acetylated base was isolated by pouring the reaction mixture into water and adding NH_4OH to precipitate the product. After washing the oily acetylated amine several times with water the 118 g. thus obtained was added to 300 ml. of fuming HNO_3 in the usual manner. Sixty-five grams of product melting at 124–125° was obtained. Without recrystallization the amide was hydrolyzed by refluxing in 50 ml. of 5 *N* HCl for several hours. The cooled solution was made basic with NH_4OH and extracted with ether. The extract was dried and evaporated to give a brown oil which was converted to the dichloroacetamide by treatment with methyl dichloroacetate as usual. The product was recrystallized from methanol to a melting point of 139–140°.

Anal. Calcd. for $C_9H_8N_2O_3Cl_2$: C, 38.59; H, 2.42. Found: C, 38.26; H, 2.49.

DETROIT, MICH. RECEIVED JANUARY 29, 1951