JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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VOLUME 74 JULY 10, 1952 NUMBER 13

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

Chloromycetin.[1] The Synthesis of *p*-Phenoxy and *p*-Methoxy Compounds

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RECEIVED DECEMBER 11, 1951

The DL-*threo* and *erythro* stereoisomers of 1-*p*-methoxyphenyl and 1-*p*-phenoxyphenyl-2-dichloroacetamido-1,3-propanediol have been prepared as well as DL-1-*p*-methoxyphenyl-2-dichloroacetamido-2-hydroxymethyl-1,3-propanediol and the α-dichloroacetamido-β-hydroxy-*p*-methoxy and *p*-phenoxypropiophenones.

The synthesis of compounds in which various groups have been substituted for nitro in the aromatic nucleus of Chloromycetin (D-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol) has been described by Long, Bambas and Troutman[2,3] and Buu-Hoi, *et al.*[4,5] As a continuation of these studies the DL-*threo*- and DL-*erythro*- *p*-phenoxy and *p*-methoxy derivatives of 1-phenyl-2-dichloroacetamido-1,3-propanediol were prepared. The observation of Hillegas that α-dichloroacetamido-β-hydroxy-*p*-nitropropiophenone synthesized by Long and Troutman[6] was an effective fungicide similarly prompted the preparation of the corresponding *p*-methoxy- and *p*-methoxy-substituted propiophenones.

Recently Buu-Hoi, *et al.*, described the preparation of one of the two possible diastereoisomeric racemates of 1-*p*-methoxyphenyl-2-dichloroacetamido-1,3-propanediol and assigned the DL-*threo*-configuration to this compound.[5] In addition to this compound the other isomer has been prepared in our laboratory as well as the above α-dichloroacetamido-β-methoxypropiophenone and 1-*p*-methoxyphenyl-2-dichloroacetamido-2-hydroxymethyl-1,3-propanediol.

The isolation of both diastereoisomers of DL-1-*p*-methoxyphenyl-2-dichloroacetamido-1,3-propanediol and demonstration that the racemate melting at 132° was practically devoid of antibacterial properties while the other melting at 107° showed significant activity is biological confirmation of the assignment of configuration made by Buu-Hoi, *et al.* The DL-*erythro* isomer was obtained by condensing anisaldehyde with nitroethanol to form 1-*p*-methoxyphenyl-2-nitro-1,3-propanediol, reducing the nitro group to an amine and converting to the dichloroacetamide. The conditions of reaction were essentially those used earlier in this Laboratory in the preparation of 1-phenyl-2-dichloroacetamido-1,3-propanediol[7] in which benzaldehyde and nitroethanol are condensed. Difficulty in isolating the active isomer from the complex mixture of by-products led us to consider the synthetic approach developed by Long and Troutman for preparing Chloromycetin[8] and used by these workers for synthesizing other ring substituted compounds[2,3,9] as an easier route to this isomer. Buu-Hoi, *et al.*,[5] also adopted this approach but the conditions used differed from ours in certain respects and perhaps explain some apparent discrepancies between the results of the two laboratories.

The condensation of α-acetamido-*p*-methoxyacetophenone (I) with formaldehyde in our laboratory gave a well-defined mono- or dimethylolated product or mixture of the two (II and III) depending on the quantity of formaldehyde used and the time and temperature at which the reaction was conducted. Buu-Hoi, *et al.*, using the same general reaction obtained a product with a melting point of 158° for which structure II is claimed. The product corresponding to structure II in our work melted at 120° after repeated recrystallization, while compound III, the dimethylolated intermediate, melted at 168°.

(1) Parke, Davis & Co. registered trademark for chloramphenicol.

(2) L. L. Bambas, H. D. Troutman and L. M. Long, THIS JOURNAL, **72**, 4445 (1950).

(3) L. M. Long and H. D. Troutman, *ibid.*, **73**, 542 (1951).

(4) Buu-Hoi, N. Hoan, P. Jacquignon and H. Khoi, *Compt. rend.*, **230**, 662 (1950); *J. Chem. Soc.*, 2766 (1950).

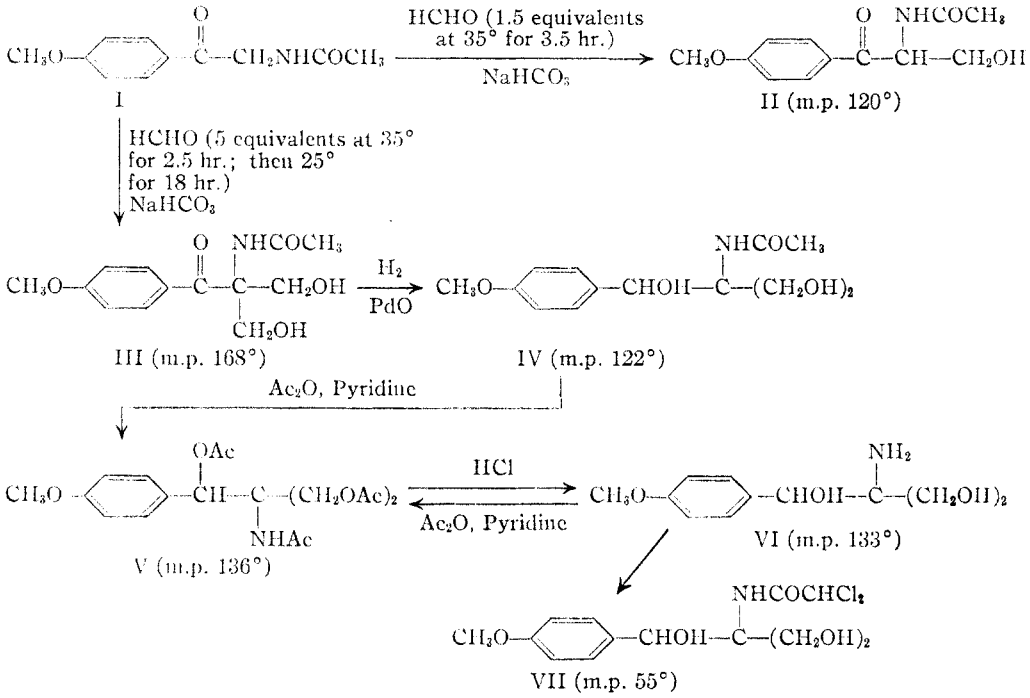
(5) Buu-Hoi, D. Xuong and H. Khoi, *ibid.*, 255 (1951).

(6) L. M. Long and H. T. Troutman, THIS JOURNAL, **73**, 481 (1951).

(7) J. Controulis, M. C. Rebstock and H. M. Crooks, Jr., *ibid.*, **71**, 2463 (1949).

(8) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2473 (1949).

(9) L. M. Long and N. Jenesel, *ibid.*, **72**, 4299 (1950).

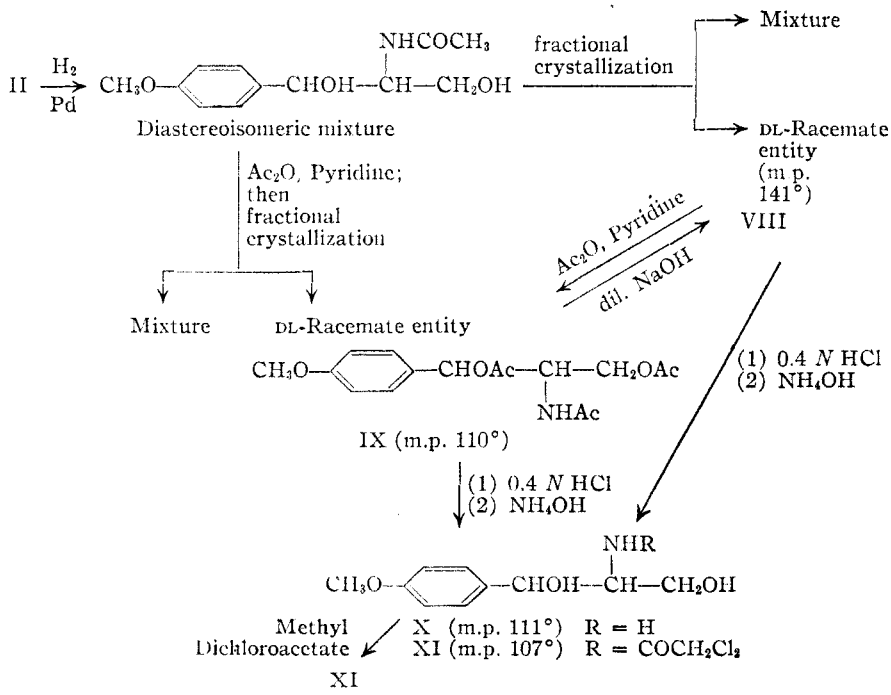


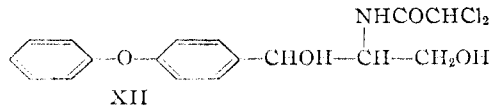
The series of reactions used in the preparation of the dichloroacetamide VII provides additional evidence for the structure of the high melting product III. Acetylation of VI, the hydrolysis product of the tetraacetate V, gave the starting material showing that no rearrangement occurred during hydrolysis.

Hydrogenation of II in the presence of palladium gave a mixture of diastereoisomeric acetamides from which one of the racemate pairs could be separated by fractional crystallization. The separation was most efficient if the amide mixture was first completely acetylated before attempting fractionation. Both the acetamide (VIII) and N,O,O-triacetate (IX) entities obtained in this manner were interconvertible and yielded the same base on hydrolysis. These reactions indicate that both compounds probably belong to the same steric family. Instead of palladium, Buu-Hoi, *et al.*, used aluminum isopropylate to reduce II and obtained an amide melting at 123° while our product VIII melted at 141° after purification by fractional crystallization. Hydrolysis of the 141° product or its triacetyl derivative under mild conditions gave base X melting at 111°[10] which was then converted to the 107° dichloroacetamide XI.[10]

(10) Buu-Hoi, *et al.*, reported melting points of 102° for X and 91° for XI.

The synthetic approach of Long and Troutman[8] also provided the means for preparing DL-*threo*- and DL-*erythro*-1-*p*-phenoxyphenyl-2-dichloroacetamide-1,3-propanediol. ω-Acetamido-*p*-phenoxyacetophenone was condensed with formaldehyde in the usual manner and the product reduced in the presence of aluminum isopropylate. A crystalline product (*p*-phenoxyphenyl-2-acetamido-1,3-propanediol) was isolated by fractional crystallization.





The acetyl group was removed by dilute hydrochloric acid hydrolysis but under somewhat more vigorous conditions than were required for hydrolysis of the corresponding *p*-methoxy amide. The free base was converted to a crystalline dichloroacetamide which showed slight activity when tested against *Shigella sonnei*. The corresponding inactive dichloroacetamide was obtained by hydrolyzing the residue from which the crystalline acetamide had been isolated after reduction and treating the basic residue with methyl dichloroacetate.

We wish to acknowledge our indebtedness to Dr. Loren M. Long for advice in carrying out certain of the reactions described; and to Mr. C. H. Childs, Mrs. Geraldine Koch and Miss Virginia Pawlik for the many microanalytical determinations.

Experimental

DL-*erythro*-1-*p*-Methoxyphenyl-2-dichloroacetamido-1,3-propanediol.—The crude sodium salt of 1-*p*-methoxyphenyl-2-nitro-1,3-propanediol (79 g.) obtained from the reaction of anisaldehyde (96 g.) and nitroethanol (64.5 g.) in methanol in the presence of sodium methylate (16.2 g. sodium) was dissolved in glacial acetic acid and hydrogenated for 24 hr. over palladium oxide catalyst. The conditions of the reaction were essentially those described previously for condensing benzaldehyde and nitroethanol.[7] The catalyst was filtered off, the solvent removed at reduced pressure and the residue taken into 300 ml. of water. The solution was extracted twice with ether to remove neutral or acidic products. The base was liberated with ammonium hydroxide and extracted with ethyl acetate several times. The acetate extracts were dried and evaporated and the gummy residue converted directly to the dichloroacetamide by heating with methyl dichloroacetate in the usual manner. The product crystallized from ethylene dichloride. After four recrystallizations 2.4 g. of pure amide melting at 149.5–150° was obtained.

Anal. Calcd. for $C_{12}H_{15}NO_4Cl_2$: C, 46.76; H, 4.91; N, 4.55. Found: C, 47.01; H, 4.95; N, 4.57.

Because of the low yield of product and difficulty in separating the *threo* isomer the method of Long and Troutman was employed to obtain the latter compound and other related derivatives.

***p*-Methoxy and *p*-Phenoxyphenacyl Bromide.**—The substituted phenacyl halides were obtained in nearly quantitative yields by brominating the corresponding acetophenones in methanol. The use of methanol as recommended in a recent patent describing the bromination of similar methoxy substituted acetophenones[11] resulted in a substantially better yield than was obtained by Kindler and Blaas[12] who carried out the reaction in chloroform.

Hexamethylenetetramine Salts of *p*-Methoxy and *p*-Phenoxyphenacyl Bromides.—The salts were prepared from the phenacyl halides by condensation with hexamethylenetetramine as described by Jacobs and Heidelberger.[13] The methoxy adduct melted at 172° as reported by the above workers and analyzed correctly. Buu-Hoi, *et al.*,[5] have reported a melting point of 222° for this product.

Anal. Calcd. for $C_{15}H_{21}N_4O_2Br$: C, 48.79; H, 5.73; N, 15.17. Found: C, 48.55; H, 5.79; N, 15.23.

The phenoxy adduct prepared in the same manner melted at 139–140° and was used without purification.

α-Acetamido-*p*-methoxyacetophenone (I) and α-Acetamido-*p*-phenoxyacetophenone.—The hexamethylenetetramine adduct of the *p*-methoxyphenacyl bromide was hydrolyzed and converted to the acetamide without isolation of the intermediate amino ketone. A 100-g. sample of the adduct was treated with a mixture of 100 ml. of concd. hydrochloric acid and 200 ml. of water for 1.2 hr. The hydrolysate was chilled to 0–10° and 55.6 ml. of acetic anhydride added, followed by 107.6 g. of sodium acetate and a second portion of 55.6 ml. of acetic anhydride. A final portion of 15 ml. of anhydride was added after 1 hr. The reaction mixture was kept at 0–10° during the acetylation by adding Dry Ice as needed and stirred throughout and for 1.5 hr. after the last addition of anhydride. After standing overnight at room temperature the acidic mixture was neutralized with solid sodium bicarbonate and extracted three times with ethyl acetate. The combined extracts were washed with 0.2 *N* sulfuric acid and water, then dried over anhydrous magnesium sulfate and evaporated at reduced pressure. The residue was crystallized from 100 ml. of ethyl acetate, a yield of 26.2 g. of product melting at 105–109° being obtained. A sample recrystallized twice for analysis melted at 111–112°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 64.06; H, 6.49; N, 6.80.

The *p*-phenoxy hexamethylenetetramine adduct was hydrolyzed in aqueous ethanolic hydrochloric acid, the α-amino-*p*-phenoxyacetophenone hydrochloride which crystallized from the hydrolysate was removed by filtration. A sample was recrystallized for analysis, the remainder being converted to the amide by treatment with acetic anhydride in the presence of sodium acetate in the usual manner. An over-all 42% yield of crude amide was obtained.

Anal. Calcd. for $C_{14}H_{14}NO_2Cl$: C, 63.76; H, 5.35; N, 5.35. Found (m.p. 206–206.5°): C, 64.02; H, 5.51; N, 5.31. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found (m.p. 98–100°): C, 71.24; H, 5.70; N, 5.16.

α-Acetamido-β-hydroxy-*p*-methoxypropiophenone (II) and α-Acetamido-β-hydroxymethyl-β-hydroxy-*p*-methoxypropiophenone (III).—The methylolation of α-acetamido-*p*-methoxyacetophenone (I) proceeded readily, two methylol groups entering the molecule if care was not taken. To obtain the desired monomethylolation product, 50 g. of I in 174 ml. of 95% ethanol containing 2.49 g. of sodium bicarbonate was mixed with mechanical stirring with 29.1 ml. of 36–38% formaldehyde (50% excess). The reaction was kept at 36.5–38° for 3.3 hr. The solvents were then evaporated and the residue extracted from water solution several times with ethyl acetate. The combined extracts were evaporated. The product obtained in 67% yield was recrystallized from ethyl acetate to a melting point of 120–122°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.71; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.33; N, 5.81.

The dimethylolated product resulted when 30 g. of I dissolved in 105 ml. of 95% ethanol was treated with 60 ml. of 36–38% formalin (5 equivalents) in the presence of 1.5 g. of sodium bicarbonate. The reaction mixture was kept at 35° for 2.5 hours, then allowed to stand at room temperature overnight. If the reaction mixture was worked up immediately a mixture of mono- and dimethylolated products was obtained; if kept overnight, only the latter could be isolated. The residue when triturated with ethyl acetate and allowed to stand at 10° for 20 hours yielded 11.5 g. of product melting at 169–171° after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.15; H, 6.33; N, 5.33.

α-Acetamido-β-hydroxy-*p*-phenoxypropiophenone.—Somewhat more drastic treatment was required to methylolate the α-acetamido-*p*-phenoxyacetophenone intermediate. To 61.7 g. of this product suspended in 617 ml. of isopropyl alcohol was added 19.5 ml. of 36–38% formalin. A solution of 0.1 *N* sodium hydroxide was then added dropwise until the solution was alkaline, additional alkali being added from time to time as needed. The reaction was carried out at 35–40° for 1.5 hr., the product being isolated in the same manner as the corresponding *p*-methoxy compound. Recrystallization from ethyl acetate gave 17.45 g. of combined first and second crop material.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found (m.p. 120–121°): C, 68.13; H, 5.90; N, 4.38.

DL-*threo*- and DL-*erythro*-2-Amino-1-*p*-methoxy-1,3-propanediol.—A sample of 30 g. of α-acetamido-β-hydroxy-*p*-methoxypropiophenone dissolved in 200 ml. of absolute ethanol was hydrogenated in the presence of 4 g. of palladium oxide catalyst for 24 hr. at 50 p.s.i. The catalyst was removed and the solvent evaporated to a crystalline residue from which one of the racemates could be separated by fractional crystallization from ethanol.

(11) British Patent 607,538, Sept. 1, 1948.

(12) K. Kindler and L. Blaas, *Ber.*, **77B**, 590 (1944).

(13) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 455 (1915).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found (m.p. 141–142°): C, 60.53; H, 7.13; N, 5.84.

For a more efficient separation the total reaction mixture is completely acetylated and the triacetates are fractionated by recrystallization. The above hydrogenation product was treated with a mixture of 70 ml. of acetic anhydride and 50 ml. of pyridine at room temperature overnight. The acetylation reagents were then removed *in vacuo* and the semi-crystalline residue recrystallized first from ethanol–low boiling petroleum ether and finally ethanol to a yield of 11.2 g. (m.p. 110–111°). By reworking the mother liquors an additional 6.95 g. was obtained. The same product results when the 141° N-acetyl derivative described above was completely acetylated.

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.54; N, 4.33. Found: C, 59.15; H, 6.72; N, 4.33.

From the mother liquors from which the crystalline triacetate had been isolated was obtained 19.4 g. of gummy residue.

For hydrolysis 5 g. of the crystalline triacetate IX was treated with a mixture of 30 ml. of distilled water and 120 ml. of 0.5 *N* hydrochloric acid (1.3 equivalents) for 1 hr. on the steam-bath. The acid solution was extracted with ethyl acetate before liberating the base with ammonia. The free base was then extracted with four portions of ethyl acetate. The combined extracts were dried and evaporated and the residue recrystallized from 20 ml. of ethylene dichloride. The product obtained in 3.05 g. yield melted at 98–106° but was substantially pure after an additional crystallization (m.p. 110–112°).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.77; H, 7.41; N, 7.01.

Heating with stronger acid in excess or for a longer period of time gave a basic product which could not be crystallized but from which a low yield of the inactive dichloroacetamide was obtained upon treatment with methyl dichloroacetate. None of the *threo*-amide could be isolated from the mother liquors although this isomer may have been present with other by-products.

DL-1-*p*-Methoxyphenyl-2-amino-2-hydroxymethyl-1,3-propanediol (VI).—A sample of 14.7 g. of the dimethylolated product III was hydrogenated in absolute ethanol in the presence of palladium oxide catalyst. The residue obtained upon evaporation of the filtrate from which the catalyst had been removed was recrystallized from 120 ml. of ethyl acetate and finally water, 10.6 g. of product being obtained. A sample recrystallized for analysis melted at 121–122°.

Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.16; H, 7.09; N, 5.19.

Ten grams of the above product was acetylated by treatment with acetic anhydride in the presence of pyridine. The tetraacetate was recrystallized from ethanol and finally ethyl acetate to a melting point of 136–137°.

Anal. Calcd. for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.70; H, 6.63; N, 3.59.

A sample of 2.4 g. of the tetraacetate was hydrolyzed by heating with 30 ml. of 20% hydrochloric acid for one hour on the steam-bath. The free base was isolated in the usual manner and recrystallized from ethyl acetate and finally ethanol to a melting point of 134–135°. Hydrolysis with 0.2 *N* hydrochloric acid for the same period gave an identical base together with a quantity of unhydrolyzed material.

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54. Found: C, 58.19; H, 7.84.

A sample of this base treated with acetic anhydride and pyridine yielded a tetraacetate identical with the product before hydrolysis.

Dichloroacetamides of DL-*threo*-1-*p*-Methoxyphenyl-2-amino-1,3-propanediol (XI) and 1-*p*-Methoxyphenyl-2-amino-2-hydroxymethyl-1,3-propanediol (VII).—The dichloroacetamides were prepared by treatment of the free bases with methyl dichloroacetate in the presence of ethanol as previously described.[14]

(14) M. C. Rebstock, THIS JOURNAL, **72**, 4800 (1950).

p-Methoxyphenyl-2-dichloroacetamido-1,3-propanediol. *Anal.* Calcd. for $C_{12}H_{15}NO_4Cl_2$: C, 46.76; H, 4.91; N, 4.55. Found for DL *threo* (m.p. 106–108°): C, 46.40; H, 5.03; N, 4.42.

p-Methoxyphenyl-2-dichloroacetamido-2-hydroxymethyl-1,3-propanediol. *Anal.* Calcd. for $C_{13}H_{17}NO_5Cl_2$: C, 46.17; H, 5.07; N, 4.14. Found (m.p. 55–56°): C, 46.24; H, 5.35; N, 4.33.

DL-*threo*- and DL-*erythro*-1-*p*-Phenoxyphenyl-2-dichloroacetamido-1,3-propanediol.—A twenty-gram sample of α-acetamido-β-hydroxy-*p*-phenoxypropiophenone dissolved in 250 ml. of isopropyl alcohol was reduced in the presence of aluminum isopropylate (29.7 g.) and in the usual manner. When no more acetone was produced, water was added together with sodium bicarbonate and Supercel to aid filtration. The filter pad was extracted twice with 90% isopropyl alcohol and ethanol. The combined extracts and filtrate were evaporated. The residue was extracted from water solution with ethyl acetate, the extracts being washed with 0.1 *N* sulfuric acid, sodium bicarbonate solution and water, and dried and evaporated. The residue was twice recrystallized from ethylene dichloride to a yield of 8.02 g. of product melting at 103–107°. A sample recrystallized for analysis melted at 104.5–105.5° but after drying *in vacuo* at 60° the melting point was found to be 124–125°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.64. Found: C, 67.46; H, 6.60; N, 4.58.

The combined mother liquors were evaporated to a gummy residue amounting to 7.3 g. which contained the *diastereoisomeric racemate*.

A sample of 7.0 g. of the crystalline amide was hydrolyzed for 1 hr. with 89 ml. of 1.0 *N* hydrochloric acid. After extracting the acid hydrolysate with ethyl acetate, the free base was liberated with ammonia and extracted with several portions of ethyl acetate. The gummy residue obtained upon evaporation was converted to a crystalline dichloroacetamide by treatment with methyl dichloroacetate. This product was recrystallized from ethanol and finally ethylene dichloride (m.p. 134–135°).

Anal. Calcd. for $C_{17}H_{17}NO_4Cl_2$: C, 55.15; H, 4.63; N, 3.78. Found: C, 55.45; H, 4.79; N, 3.81.

The other isomer was obtained by hydrolyzing the 7.3 g. of gummy residue from which the 124° amide had been separated, with hydrochloric acid as above. The gummy base was then converted to a crystalline dichloroacetamide as before. This amide melted at 149–150.5° after recrystallization from chloroform, ethylene dichloride, water and ethyl acetate. Found: C, 55.41; H, 4.80; N, 3.61.

α-Dichloroacetamido-β-hydroxy-*p*-methoxy or *p*-phenoxypropiophenone.—Since the preparations were similar only the *p*-phenoxy compound is described. To 40.0 g. of crude α-amino-*p*-phenoxyacetophenone hydrochloride in a mixture of 250 ml. of acetone and 18.8 g. of dichloroacetyl chloride at 0° was added 43.6 g. of triethylamine and 18 g. of additional acid chloride. The reaction mixture was kept at 0° for three hours and then allowed to stand at 10° overnight. The solvents were removed at reduced pressure and the residue extracted from water solution with ethyl acetate. The extracts were washed with 0.1 *N* sodium bicarbonate and water and evaporated after drying over anhydrous magnesium sulfate. A sample of 16.6 g. of the above residue (the total yield was 17.6 g.) was methylolated by treatment with 4.89 ml. of 36–38% formaldehyde solution in the presence of 0.9 g. of sodium bicarbonate using 120 ml. of 95% ethanol for the solvent. The reaction was allowed to proceed for 24 hr. at room temperature after which the product was isolated as described above.

Anal. Calcd. for $C_{17}H_{15}NO_4Cl_2$: C, 55.45; H, 4.11; N, 3.80. Found (m.p. 126.5–127.5°): C, 55.62; H, 3.94; N, 4.10.

α-Dichloroacetamido-β-hydroxy-*p*-methoxypropiophenone.—*Anal.* Calcd. for $C_{12}H_{13}NO_4Cl_2$: C, 47.06; H, 4.28; N, 4.58. Found (m.p. 142.5–144°): C, 47.34; H, 4.25; N, 4.57.

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