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CHLOROMYCETIN[1] METHYL ETHERS

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Received November 9, 1953

The preparation of DL-*threo*- and DL-*erythro*-1-phenyl-1-methoxy-2-amino-3-hydroxypropane as intermediates in the synthesis of Chloromycetin has been described by Tatsuoka, *et al.* (1), Miyamoto (2, 3), and Kollonitsch (4). Miyamoto (3) resolved DL-*threo*-1-*p*-nitrophenyl-1-methoxy-2-amino-3-hydroxypropane with *d*-tartaric acid, then hydrolyzed the ether linkage of the resolved compound with 48% hydrobromic acid, and converted the product to Chloromycetin in the usual manner (5). This worker also succeeded in relating DL-*erythro*-1-phenyl-1-methoxy-2-benzamido-3-hydroxypropane to norephedrine through appropriate transformations (6).

A different synthetic approach in our laboratory led to the preparation of the corresponding "3-methyl" ethers of the 1-*p*-nitrophenyl-2-amino-1,3-propanediol diastereoisomers. The intermediates, DL-*threo*- and DL-*erythro*-1-*p*-nitrophenyl-1-acetoxy-2-phthalimido-3-methoxypropane (V) were utilized in the preparation of DL-*threo*- and DL-*erythro*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol (IX). In addition, the dichloroacetamides of DL-*threo*- and DL-*erythro*-1-*p*-nitrophenyl-1-hydroxy-2-amino-3-methoxypropane (VIII) were prepared for biological studies. Both compounds proved to be inactive in *in vitro* antibacterial tests.[2]

In Figure I the synthetic approach by which these compounds were obtained is outlined. α-Bromo-β-methoxypropiophenone (I) was prepared by condensing benzene and α-bromo-β-methoxypropionyl chloride under the usual Friedel Crafts conditions. The oily product containing the desired compound along with other by-products was condensed with potassium phthalimide. Crystalline α-phthalimido-β-methoxypropiophenone (II) was isolated from the products of the reaction by suitable fractionation techniques. Reduction of this ketone with hydrogen in the presence of palladium oxide catalyst led to a 50–50 mixture of diastereoisomers (III) which were readily separated by fractional crystallization and carried independently through the remaining series of reactions. From isomer series A, DL-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol was obtained, while series B gave the corresponding *erythro* diastereoisomer.

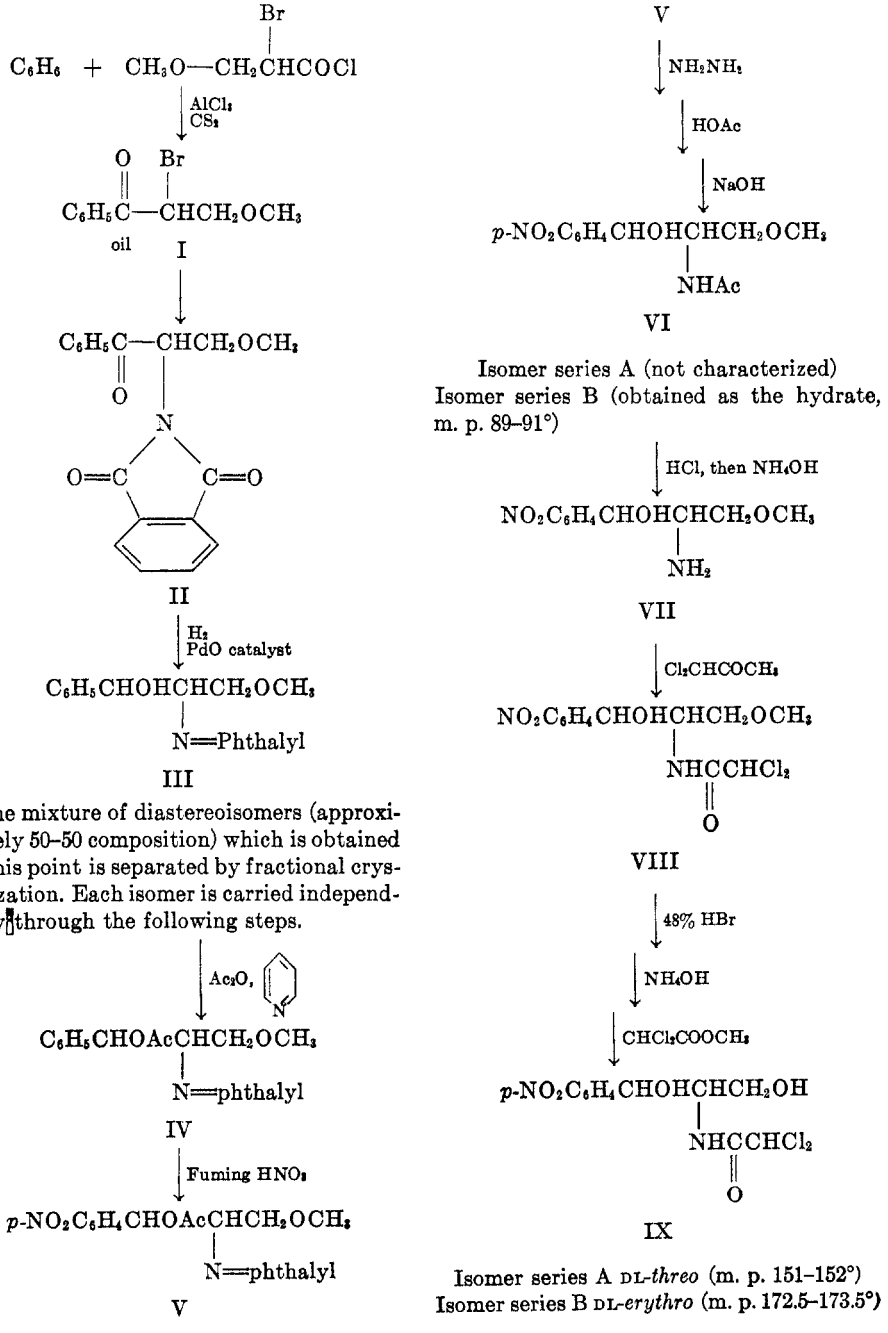
Possible inversions in this synthetic approach are not excluded but seem unlikely. Closely analogous to the nitration described here, Fodor and co-workers (7) showed that nitration of DL-*threo*-1-phenyl-2-amino-1,3-propanediol triacetyl derivatives did not cause inversion since subsequent removal of the nitro group by diazotization techniques gave the *threo* base.

Since the adjacent hydroxyl groups in compounds of type V are protected by

[1] Parke, Davis and Co., registered trademark for chloramphenicol.

[2] We are indebted to Drs. J. Ehrlich and A. S. Schlingman and Mrs. Della Fox and Mrs. M. Galbraith for the antibacterial tests.

FIGURE I



The mixture of diastereoisomers (approximately 50–50 composition) which is obtained at this point is separated by fractional crystallization. Each isomer is carried independently through the following steps.

acetyl and methyl groups, removal of the phthalyl group is probably also uncomplicated. The fact that the acetamides (VI) are isolated following cleavage of the imide would indicate that a simple O→N shift of the acetyl group occurs due to the basic environment after the loss of the phthalyl group. Such shifts have also not been reported to involve inversions.

Finally, there is evidence that the hydrolysis of the methoxy ethers (VIII) to give DL-*threo* and DL-*erythro*-1-*p*-nitrophenyl-2-amino-1,3-propanediol is also straightforward since treatment of DL-*threo*- and DL-*erythro*-1-*p*-nitrophenyl-2-dichloroacetamido-1-3-propanediol with 48% hydrobromic acid under the same conditions gave the corresponding DL-*threo* and DL-*erythro* bases.[3]

EXPERIMENTAL

Preparation of α-phthalimido-β-methoxypropiophenone (II). To a stirred suspension of 105.3 g. of aluminum chloride in 400 ml. of benzene was added dropwise 145 g. of α-bromo-β-methoxypropionyl chloride (8)[4] at such rate as to maintain gentle refluxing. The addition required 35 min. The mixture was refluxed for 1½ hrs. longer then poured into a mixture of ice and 50 ml. of conc'd hydrochloric acid. The layers were separated and the aqueous phase was extracted twice more with ethyl acetate. The combined extracts were washed with saturated sodium bicarbonate and water and finally dried over magnesium sulphate and evaporated. The product, a brown oil obtained in 163 g. yield was not further purified. The presence of the phenone structure was indicated by substantial absorption at λ 255 in the ultraviolet (E_1^1 446).

The 163 g. of crude α-bromo-β-methoxypropiophenone (I) was dissolved in 350 ml. of dimethylformamide and 116 g. of potassium phthalimide was added. The reaction mixture warmed spontaneously to 70°. When the mixture had cooled to 25°, it was heated on the steam-bath for two hours longer. After standing overnight at room temperature the dark brown solution was diluted with 500 ml. of ethyl acetate. The ethyl acetate solution was washed first with saturated sodium bicarbonate solution then twice with water. The dried ethyl acetate layer was evaporated at reduced pressure to give a semi-crystalline product which was taken into 500 ml. of benzene. After standing for 4 hrs. at room temperature 26.5 g. of crystals which melted at 202–205° were collected. A sample was recrystallized for analysis from benzene and finally from ethyl acetate. From these results together with the U.V. absorption of the compound it seems likely that the product is α,β-diphthalimidopropiophenone. The mechanism by which this product arises is unknown, but since α,β-dibromopropionic acid is a recognized contaminant of α-bromo-β-methoxypropionic acid prepared by the above method (8) the product might arise from this impurity.

Anal.[5] Calc'd for $C_{25}H_{16}N_2O_5$: C, 70.51; H, 3.80; N, 6.60.
Found: C, 70.67; H, 4.19; N, 6.44.

The benzene mother liquor from which the above product was isolated was evaporated under reduced pressure and the residue was taken into 200 ml. of ethyl acetate. After standing overnight in the refrigerator a crop of 68 g. of crystalline product was isolated. Recrystallization from absolute ethanol yielded 63 g. (m.p. 130–132°). A sample was recrystallized for analysis from ethanol and finally from ethyl acetate (m.p. 137–138°).

Anal. Calc'd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53.
Found: C, 69.68; H, 4.69; N, 4.66.

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[3] Unpublished work in this laboratory.

[4] α-Bromo-β-methoxypropionyl chloride is prepared from the acid (8) by refluxing with thionyl chloride in the usual manner.

[5] We are indebted to Mr. C. Childs, Miss Virginia Pawlick, and Mrs. Claire Johnston for the microanalyses reported in this paper.

Preparation of DL-*threo- and* DL-*erythro-1-phenyl-1-hydroxy-2-phthalimido-3-methoxypropane* (III). A 21.5-g. batch of α-phthalimido-β-methoxypropiophenone (m.p. 130–132°) was dissolved in 500 ml. of absolute ethanol and hydrogenated over 3 g. of PdO catalyst at 50 lbs. p.s.i. for 20 hrs. Two other batches totaling 36 g. of material were similarly reduced. The combined filtrates were evaporated at reduced pressure and the semicrystalline residue was recrystallized from 150 ml. of absolute ethanol to yield 15.5 g. of product (m.p. 131–133°). This isomer when taken through the remaining steps of the synthesis outlined in Figure I gave DL-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol. A sample recrystallized for analysis from benzene and finally from ethanol melted at 137–138°.

Anal. Calc'd for $C_{18}H_{17}NO_4$: C, 69.40; H, 5.50; N, 4.50.

Found: C, 69.27; H, 5.51; N, 4.55.

The mother liquor from which the *threo* isomer had been isolated was evaporated under reduced pressure to a gummy residue (36 g.) which subsequently proved to be rich in the other isomer, presumably the *erythro*.

Preparation of DL-*threo- and* DL-*erythro-1-phenyl-1-acetoxy-2-phthalimido-3-methoxypropane* (IV). The 36 g. of gummy residue obtained in the preceding experiment was dissolved in 65 ml. of dry pyridine and 75 ml. of acetic anhydride was added. After standing overnight at room temperature the reaction mixture was poured on ice. The partially crystallized product was extracted into ethyl acetate. The extract was washed with 5 *N* sulfuric acid, water, saturated sodium bicarbonate solution until neutral, and finally with water. The dried extract was evaporated at reduced pressure and the product was crystallized from 70 ml. of ethyl acetate to give 13.3 g. of crystals which melted at 159–160°. A portion was prepared for analysis by recrystallization from ethyl acetate and finally from ethanol to a melting point of 165–166°.

A 13.8-g. sample of the crystalline series A isomer (III) was similarily acetylated. An analytical sample recrystallized twice from absolute ethanol melted at 132–133°.

Anal. Calc'd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96.

Found for isomer series A, m.p. 132–133°: C, 67.94; H, 5.51; N, 4.07.

Found for isomer series B, m.p. 165–166°: C, 67.92 H, 5.44; N, 3.82.

Preparation of DL-*threo- and* DL-*erythro-1-p-nitrophenyl-1-acetoxy-2-phthalimido-3-methoxypropane* (V). Nitration was carried out by adding 13.0 g. of DL-(isomer series B)-1-phenyl-1-acetoxy-2-phthalimido-3-methoxypropane (m.p. 159–160°) to 45 ml. of fuming nitric acid at −20° over a period of 15 min. The temperature of the reaction mixture was controlled by adding chunks of Dry Ice as needed. After the final addition of the phenyl compound the reaction mixture was allowed to come to room temperature for the next 30 min. and then was quenched on ice. The quench mixture was neutralized with solid sodium bicarbonate and the product was extracted into ethyl acetate. The extract was washed with water, dried over magnesium sulphate, and evaporated at reduced pressure to a gummy product which was immediately used in the next conversion.

Similar nitration of the series A isomer (m.p. 132°) gave a solid product. An analytical sample was prepared by recrystallization of a portion from ethyl acetate, an ethanol-ethyl acetate mixture, and again from ethyl acetate to a melting point of 195–197°.

Anal. Calc'd for $C_{20}H_{18}N_2O_7$: C, 60.30; H, 4.55; N, 7.03.

Found: C, 60.13; H, 4.57; N, 7.24.

Preparation of DL-*threo- and* DL-*erythro-1-p-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methoxypropane* (VIII). The gummy product obtained from the nitration of the series B isomer was dissolved in 150 ml. of absolute ethanol and 5 ml. of 85% hydrazine hydrate solution was added. The mixture was refluxed for 2 hrs. on the steam-bath after which the solvent was removed at reduced pressure and the residue was taken into 150 ml. of water. The solution was adjusted to *p*H 5 with glacial acetic acid, the phthalylhydrazide was filtered off, and the residue was made strongly alkaline with ammonium hydroxide. The alkaline solution was extracted four times with ethyl acetate. The combined extracts were dried and evaporated at reduced pressure to give a gummy residue which was taken into

50 ml. of water. A crop of 3.3 g. of white crystals separated which melted at 78–82°. A small portion was recrystallized for analysis from ethylene dichloride and finally twice from ethyl acetate to a melting point of 89–91°. The product proved to be the acetamide of 1-phenyl-2-hydroxy-2-amino-3-methoxypropane, obtained as a monohydrate (VI).

Anal. Calc'd for $C_{12}H_{16}N_2O_5 \cdot H_2O$: C, 50.31; H, 6.33; N, 9.78.
Found: C, 50.42; H, 6.51; N, 10.05.

This product was converted to the free base by heating with 10% hydrochloric acid on the steam-bath. The mother liquor from which the 3.3 g. above was isolated was evaporated and the residue similarly was hydrolyzed to give an additional quantity of base. The analytical sample VII was recrystallized from water to a melting point of 115–117°.

Anal. Calc'd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38.
Found: C, 53.06; H, 6.20; N, 12.42.

The solid nitration product from the series A isomer (V) was treated in similar fashion. A mixture of free base and acetyl derivative was again obtained although fractional crystallization in this case gave the free base as the crystalline product. Hydrolysis of the residue from the mother liquors as before gave more of the same. An analytical sample (VII) was prepared by recrystallizing from ethylene dichloride, ethanol, and finally from ethylene dichloride (m.p. 132–133°).

Anal. Found: C, 53.17; H, 6.06; N, 12.59.

Both bases were converted to the dichloroacetamides by refluxing with excess methyl dichloroacetate in absolute ethanol solution for 2½ hrs. on the steam-bath. The ethanol was evaporated, the residues were triturated with low-boiling petroleum ether to remove excess ester, and the products finally were taken into 200-ml. portions of ethyl acetate. The acetate solutions were washed with 0.1 *N* sulfuric acid, saturated sodium bicarbonate solution, and water, and dried and evaporated at reduced pressure.

DL-Isomer series B-1-*p*-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methoxypropane was recrystallized from benzene and finally twice from water to a melting point of 91–92°. The corresponding series A isomer was recrystallized from benzene and ethanol to a melting point of 105–106°.

Anal. Calc'd for $C_{12}H_{14}Cl_2N_2O_5$: C, 42.75; H, 4.18; N, 8.31.
Found for series B isomer: C, 42.65; H, 4.22; N, 8.47.
Found for series A isomer: C, 42.99; H, 4.27; N, 8.36.

Preparation of DL-*threo- and* DL-*erythro-1-p-nitrophenyl-2-dichloroacetamido-1,3-propanediol* (IX). A one-gram portion of DL-(series A)-1-*p*-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methoxypropane was treated with 9 ml. of 48% hydrobromic acid in a sealed tube at 130° for 30 min. then at 120° for 1 hr. The furnace was turned off at this point and the bomb allowed to cool to room temperature overnight. Most of the acid was removed by repeated evaporation with water at 60° under reduced pressure. The residue was then taken into 20 ml. of water which was made alkaline with ammonium hydroxide and the free base was extracted into ethyl acetate. Five ethyl acetate extracts were combined and evaporated. The crystalline base was recrystallized from 8 ml. of water to give 340 mg. of product melting at 130–135° and representing a 49% yield of crude base. No melting point depression was observed on mixing with an authenic sample of DL-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol. The base was converted to DL-*threo*-Chloromycetin by reaction with methyl dichloroacetate in the manner previously described. The product melted at 148–150°, gave no depression of melting point on admixture with an authentic sample, and had the same I.R. and U.V. absorption as DL-*threo*-Chloromycetin. *S. sonnei* assay showed 480γ of Chloromycetin per mg. (theory, 500) (5).

DL-*erythro*-1-*p*-Nitrophenyl-2-dichloroacetamido-1,3-propanediol was prepared in comparable yield by hydrolysis of DL-(series B)-1-*p*-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methoxypropane with 48% hydrobromic acid followed by conversion of the free base to the corresponding dichloroacetamide which melted at 173–174° and gave no melting point depression with an authenic sample.

SUMMARY

As part of a series of studies designed to determine the effect of a variety of structural variations in the Chloromycetin molecule on biological activity DL-*threo*- and DL-*erythro*-1-*p*-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methoxypropane were prepared. Since these compounds and intermediates can be converted to Chloromycetin by appropriate reactions a new synthesis of the antibiotic has also been achieved.

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