## Studies on Antibiotics and Related Substances. VI. Configurations of Isomeric O-Methylphenylserines and a New Route for the Synthesis of Chloramphenicol\*

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In connection with synthetic studies on chloramphenicol in this Laboratory, the two diastereomers of O-methylphenylserine which were synthesized by Carter and Van Loon<sup>1)</sup> became attractive as possible intermediates. The synthesis involved the methoxymercuration of cinnamic acid. In another paper West, Krummel and Carter<sup>2)</sup> obtained one racemic form of  $\alpha$ -bromo- $\beta$ -methoxy- $\beta$ -phenylpropionic acid by the reaction of methyl hypobromite with cinnamic acid in the presence of silver nitrate.

The present paper describes the studies on the configuration of diastereomeric Omethylphenylserines and the synthesis of DL-threo-2-amino-1-p-nitrophenyl-1, 3-propanediol from one of the diastereomers.

Synthetic studies concerning the configuration of the O-methylphenylserine (II), which was synthesized through methoxymercuration, is described first and followed by the synthesis of DL-chloramphenicol from II via DL-threo-2-amino-1-p-nitrophenyl-1,3-propanediol. Finally, studies on the other diastereomer (XI) of O-methylphenylserines is described.

**Configuration of O-Methylphenylserine** (II) Synthesized through Methoxymercuration.-The mixture of O-methylphenylserines melting at 215-219°C (dec.) was prepared by amination of the mixture  $\alpha$ -bromo- $\beta$ -methoxy- $\beta$ -phenylpropionic of acids which was obtained by the synthetic route of Van Loon and Carter<sup>3)</sup>.



<sup>\*</sup> Presented before the Division of Organic Chemistry at the Annual Meeting of the Chemical Society of Japan, at Kyoto University, April 3, 1956.

<sup>1)</sup> H. E. Carter and E. J. Van Loon, J. Am. Chem. Soc., 60, 1077 (1938).

<sup>2)</sup> H. D. West, G. S. Krummel and H. E. Carter, J. Biol. Chem., 122, 605 (1938).
3) E. J. Van Loon and H. E. Carter, J. Am. Chem.

Soc., 59, 2555 (1937).

The mixture of O-methylphenylserines was formylated with concentrated formic acid to give a mixture of N-formyl derivatives, from which DL-threo-N-formyl-Omethylphenylserine (I) melting at 161–162°C was isolated as a single diastereomer by repeated recrystallization.

I was hydrolyzed with 1 N hydrochloric acid to yield DL-threo-O-methylphenylserine (II) melting at 218-220°C (dec.) in 89.3%yield. The N-benzoyl derivative of II which was obtained by benzoylation of II with benzoyl chloride in alkaline solution melted at 168-169°C.

II was treated with dry hydrogen chloride in absolute ethanol to give the ethyl ester hydrochloride (III) melting at 158–160°C. The free ethyl ester (IV) was obtained by bubbling ammonia through the ethereal suspension of III.

The ethyl DL-threo-O-methylphenylserinate (IV) was led to DL-threo-2-amino-1-*p*nitrophenyl-1, 3-propanediol and DL-chloramphenicol by the following procedure.

IV was reduced with hydrogen over Raney nickel catalyst to give DL-threo-Omethylphenylserinol (V) melting at 28–32°C in 41.9% yield. Acetylation of V with acetic anhydride at room temperature yielded N-acetyl derivative (VI) melting at 184–185°C. V was further acetylated by heating with acetic anhydride to yield N,O-diacetyl derivative (VII) melting at 120–121.5°C in 85.5% yield.

Nitration of VII with mixed acid under ice cooling yielded N, O-diacetyl-DL-threo-2-amino-1-methoxy-1-*p*-nitrophenyl-3-propanol (VIII) melting at 80-82°C, which, on hydrolysis with 10% hydrochloric acid, yielded DL-threo-2-amino-1-methoxy-1-*p*-nitrophenyl-3-propanol hydrochloride (IX) melting at 235-237°C (dec.).

Drastic hydrolysis of IX with 25% hydrochloric acid at  $125-130^{\circ}$ C in a sealed tube gave in a good yield a demethylated product (X), which did not depress the melting point of an authentic sample of DL-threo-2-amino-1-*p*-nitrophenyl-1, 3-propanediol.

X was converted into N-dichloroacetyl derivative, viz. DL-chloramphenicol, which showed half the potency of the natural chloramphenicol against *Escherichia coli*. One can conclude, therefore, that a diastereomer of O-methylphenylserine which is obtained through methoxymercuration is of the three configuration.

In the course of the above-mentioned investigation, we tried to demethylate the formyl derivative of O-methylphenylserine (I) by the action of concentrated hydrochloric acid. However, there was obtained 2-phenylnaphthalene, as would be expected from the report by Cater and Van Loon<sup>1)</sup>.

Derivatives of the Other Diastereomer (XI) of O-Methylphenylserine.—O-Methylphenylserine of m. p.  $251-253^{\circ}$ C (dec.) was prepared by the amination of  $\alpha$ -bromo- $\beta$ -methoxy- $\beta$ -phenylpropionic acid by the method of Cater and co-workers<sup>2</sup>).

The O-methylphenylserine afforded the corresponding N-formyl derivative (XII) melting at  $149-150^{\circ}$ C in a high yield by treatment with concentrated formic acid.

The O-methylphenylserine (XI) was treated with dry hydrogen chloride in absolute ethanol to yield the ethyl ester hydrochloride (XIII) melting at 179–181°C (dec.). The free ethyl ester was obtained by bubbling ammonia through an ethereal suspension of XIII.

Upon reduction of the ethyl ester (XIV)

with hydrogen over Raney nickel catalyst, the other diastereomer of O-methylphenylserinol (XV) was obtained as a syrup in 32.4% yield. When an ethereal solution of XV was saturated with dry hydrogen chloride, the crystalline hydrochoride of XV was obtained. This melted at 181– 182°C. By benzoylation of XV with benzoyl chloride, N, O-dibenzoyl derivative melting at 160–161°C was obtained.

Acetylation of XV with acetic anhydride at room temperature yielded N-acetyl derivative (XVI) melting at 116–118°C. XVI was further acetylated by heating with acetic anhydride to yield N,O-diacetyl derivative (XVII) melting at 77–80°C.

Nitration of XVII with mixed acid under ice cooling yielded N,O-diacetyl-DL-erythro-2-amino-1-methoxy-1-*p*-nitrophenyl-3-propanol (XVIII) melting at 150–151°C, which, on hydrolysis with 10% hydrochloric acid, yielded DL-erythro-2-amino-1-methoxy-1-*p*nitrophenyl-3-propanol hydrochloride(XIX) melting at 233–234°C (dec.).

Drastic hydrolysis of XIX with 25% hydrochloric acid at 125–130°C in a sealed tube gave DL-erythro-2-amino-1-*p*-nitrophenyl-1, 3-propanediol hydrochloride (XX) melting at 209–210°C.

Thus, there is no contradiction in the assignment of the erythro configuration to the other O-methylphenylserine (XI).

## Experimental

**Amination of**  $\alpha$ -bromo- $\beta$ -methoxy- $\beta$ -phenylpropionic acid synthesized through methoxymercuration. — The diastereomeric mixture of  $\alpha$ -bromo- $\beta$ -methoxy- $\beta$ -phenylpropionic acids was prepared through methoxymercuration by the route of Van Loon and Carter<sup>3)</sup>. Thirtyseven grams of the bromo compounds were heated with 500 cc. of concentrated ammonia water at 90-100°C for 6 hr. in an autoclave. After being kept overnight at room temperature, the content was filtered and evaporated to dryness under reduced pressure. The residue was redissolved in a small portion of water, filtered and again evaporated under reduced pressure. The residue was triturated with acetone and allowed to stand with frequent shaking. The precipitate was collected and washed with acetone. The crude product of  $\alpha$ -amino- $\beta$ -methoxy- $\beta$ -phenylpropionic acid melted at 215-219°C (dec.); yield 27 g. (97.0%).

**N-Formyl-DL-threo-O-methylphenylserine** (I).—A solution of 26 g. of the crude product of  $\alpha$ -amino- $\beta$ -methoxy- $\beta$ -phenylpropionic acid in 150 cc. of 83% of formic acid was warmed to 45°C and 80 cc. of acetic anhydride was added with stirring. The temperature of the reaction mixture rose to, and was maintained at, 70-80°C for about 15 min.. Then, the solution was settled at room temperature for 3 hr. and evaporated to dryness under reduced pressure to yield a crystalline residue. Recrystallization from dilute acetic acid and then twice from hot water, gave colorless plates, m. p. 158-160°C; yield 5.5 g. (18.5%). A final recrystallization from hot water yielded colorless plates having a constant m. p. of 161- $162^{\circ}$ C; yield 4.9 g. (16.5%).

Anal. Found: N, 6.21. Calcd. for  $C_{11}H_{13}O_4N$ : N, 6.28%. Completion of the remaining steps in the synthesis to DL-chloramphenicol proved this N-formyl derivative to be of the threo configuration.

DL-threo-O-Methylphenylserine(II). - Three and one-half grams of the above N-formyl derivative (I) was hydrolyzed with 40 cc. of 1 Nhydrochloric acid on a boiling water bath for one hr.. The solution was neutralized with 10%sodium hydroxide solution to pH 6.5 and concentrated under reduced pressure until crystalline precipitate appeared. To the concentrate was added five volumes of absolute ethanol and the mixture was allowed to stand in a refrigerator overnight. The crystals were collected and washed with absolute ethanol; m.p. 218-220°C (dec.); yield 2.5 g. (89.3%). Recrystallization from water-ethanol gave colorless plates of Omethyl-dl-threo-phenylserine, m. p. 218-220°C (dec.).

Anal. Found: N, 7.19. Calcd. for  $C_{10}H_{13}O_3N$ : N, 7.18%.

N-Benzoyl-O-methyl-DI-threo-phenylserine. —To a solution of 0.5 g. of II in 5 cc. of 10% sodium hydroxide was added 0.5 cc. of benzoyl chloride under ice cooling with vigorous shaking. The mixture was kept at room temperature for 30 min. with occasional shaking. The solution was filtered to remove insoluble matter and then acidified with concentrated hydrochloric acid under ice cooling to yield colorless crystals, which were collected and washed with toluene, m. p. 166-167°C; yield 0.6 g. (78.1%). Two recrystallizations from methanol yielded colorless crystals of N-benzoyl-O-methyl-DL-threo-phenylserine, m. p. 168-169°C.

Anal. Found: N, 4.36. Calcd. for C<sub>17</sub>H<sub>17</sub>O<sub>4</sub>N: N, 4.68%.

Ethyl O-Methyl-DL-threo-phenylserinate Hydrochloride (III).—A stream of dry hydrogen chloride was bubbled through a suspension of 4.0 g. of II in 40 cc. of absolute ethanol. After saturation, the mixture was settled at room temperature overnight, and then evaporated under reduced pressure to yield a crude ester hydrochloride; yield 5.2 g. (97.7%). Recrystallization from absolute ethanol-ether yielded colorless crystals of ethyl O-methyl-DL-threo-phenylserinate hydrochloride, m. p. 158–160°C.

Anal. Found: N, 5.22. Calcd. for  $C_{12}H_{19}O_{3}NC1$ : N, 5.39%.

Ethyl O-Methyl-DI-threo-phenylserinate (IV).—A vigorous stream of dry ammonia was passed through a suspension of 9.5 g. of III in 100 cc. of absolute ether for 20 min.. The ammonium chloride precipitated was removed and washed with absolute ether. The filtrate and washings were evaporated under reduced pressure to yield a crude, pale-yellow oil of ethyl O-methyl-DL-threo-phenylserinate; yield 5.0 g. (61.2%).

DL - three - 2 - Amino - 1 - methoxy-1-phenyl-3propanol (V).-A solution of 5.0 g. of IV in 50 cc. of absolute ethanol was hydrogenated over 10 g. of Raney nickel catalyst<sup>4)</sup> at  $50-55^{\circ}C$  for 5 hr. under an initial pressure of 120 atm.. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure to yield a pale-yellow, oily residue; yield 3.0 g.. The residue was heated with 125 cc. of 0.1 N sodium hydroxide solution for 2 hr. in order to hydrolyze any unchanged ester. The alkaline solution was extracted five times with ethyl acetate under ice cooling. The combined ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield crude crystals of DL-threo-2-amino-1methoxy-1-phenyl-3-propanol (V), m. p. 28-32°C; yield 1.7 g. (41.9%).

On bubbling dry hydrogen chloride into the ethereal solution of V, colorless crystals of crude hydrochloride was obtained; m. p. 164-166°C. Two recrystallizations from ethanol-ether gave pure crystals of the hydrochloride of V, m. p. 168-169°C.

Anal. Found: N, 6.21. Calcd. for  $C_{10}H_{16}O_2NC1$ : N, 6.43%.

N. O-Dibenzoyl-DI-threo-2-amino-1-methoxy-1-phenyl-3-propanol.—To a solution of 0.2 g. of V in 2.0 cc. of dry pyridine was added 0.3 cc. of benzoyl chloride and the mixture was allowed to stand in an ice bath for 1 hr. with occasional shaking. Cold water was added to the solution and the crystals formed were collected and washed with 2% sodium carbonate solution, 1% hydrochloric acid and finally with cold water. Recrystallization from methanol gave colorless needles, m. p. 138-139°C; yield 0.4 g. (92.9%). Further recrystallization from methanol gave an analytical pure sample of the N,O-dibenzoyl derivative of V, m. p. 139-140°C.

Anal. Found: N, 3.68. Calcd. for  $C_{24}H_{23}O_4N\colon$  N, 3.60%.

N-Acetyl-DI-threo-2-amino-1-methoxy-1phenyl-3-propanol (VI).—To a solution of 0.2 g. of V in 2.0 cc. of ether was added 0.8 cc. of acetic anhydride with stirring at room temperature. Crystals formed were collected and washed with ether to yield colorless crystals, m. p. 178- $180^{\circ}$ C; yield 0.2 g. (81.0%). Recrystallization from hot water gave colorless needles of N-acetyl derivative of V, m. p. 184-185°C.

Anal. Found: N, 6.12. Calcd. for  $C_{12}H_{17}O_3N$ : N, 6.27%.

N, O-Diacetyl-DI-threo-2-amino-1-methoxy-1-phenyl-3-propanol (VII).—V (0.8 g.) was heated with 6.0 g. of acetic anhydride on a boiling water bath for one hr.. The solution was concentrated under reduce pressure to yield crystals, which were washed with ether, m. p. 119-121°C; yield 1.0 g. (85.5%). Two recrystallizations from acetone gave colorless plates of

4) Organic Syntheses, 21, 15 (1940).

the N,O-diacetyl derivative of V, m. p. 120-121.5°C.

Anal. Found: N, 5.25. Calcd. for  $C_{14}H_{19}O_4N$ : N, 5.28%.

N, O-Diacetyl-DI-threo-2-amino-1-methoxy-I-p-nitrophenyl-3-propanol (VIII).—To 1.3 g. of VII was added 5.0 cc. of a mixture (1:1) of concentrated nitric acid (sp. gr. 1.38) and sulfuric acid (sp. gr. 1.84) under ice cooling and shaking. After 15 min. the mixture was kept at room temperature for 20 min. quenched on ice and then immediately neutralized with sodium bicarbonate. The mixture was extracted five times with ethyl acetate and the combined extract was washed with cold water, and dried over anhydrous sodium sulfate. Evaporation under reduced pressure yielded pale-yellow crystals of the nitro derivative of VII, m. p. 80-82°C; yield 1.4 g. (92.2%).

Anal. Found: N, 9.22. Calcd. for  $C_{14}H_{18}O_6N_2$ : N, 9.03%.

DI-threo-2-Amino-1 methoxy-1-p-nitrophenyl-3-propanol Hydrochloride (IX).—A portion of 1.4 g. of VIII was hydrolyzed with 10 cc. of 10% hydrochloric acid on a boiling water bath for one hr. The hydrolysate was washed twice with ether and and evaporated to dryness under reduced pressure. The crystalline residue was recrystallized from dilute hydrochloric acid to yield colorless crystals of pL-threo-2-amino-1methoxy-1-p-nitrophenyl-3-propanol hydrochloride, m. p. 235-237°C (dec.); yield 1.1 g. (92.5%). When dried in a "pistol" the compound was unstable and colored.

Anal. Found: N, 9.92. Calcd. for  $C_{10}H_{15}O_4N_2Cl$ : N, 10.67%.

DL-threo-2-Amino-1-p-nitrophenyl-1, 3-propanediol (X).-A mixture of 1.1 g. of IX and 12 cc. of 25% hydrochloric acid was placed in a sealed tube and heated at 125-130°C for 4 hr.. The contents were diluted with water, decolorized with active carbon, and then concentrated under reduced pressure to give a crystalline residue; yield 1.0 g. The residue was dissolved in 3.0 cc. of water, cooled with ice, and rendered alkaline with 10% sodium hydroxide solution to pH 10. The free base in the mixture was extracted with ethyl acetate repeatedly and the combined extract was concentrated under reduced pressure to yield 0.7 g. (82.4%) of a crystalline residue, which was recrystallized several times from hot water to give colorless crystals of m. p. 139-140°C; yield 0.3 g. (35.5%). Admixture with pL-threo-2-amino-1-p-nitrophenyl-1,3-propanediol synthesized by the route of Controulis et al.<sup>5)</sup> caused no depression in the melting point.

X was converted into the N-dichloroacetamide of m. p.  $149-150^{\circ}$ C by heating with methyl dichloroacetate. The antibacterial activity of the product, viz. pL-chloramphenicol, was 49.7% that of natural chloramphenicol by a cylinder plate assay (test organism E. coli).

**2-PhenyInaphthalene.**—A mixture of 1.0 g. of I and 10 cc. of 20% hydrochloric acid was

<sup>5)</sup> J. Controulis, M. C. Rebstock and H. M. Crooks, Jr., J. Am. Chem. Soc., 71, 2463 (1949).

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placed in a sealed tube and heated at  $115-120^{\circ}$ C for 4hr.. The contents were extracted with ether. The ether solution was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to yield a yellow crystalline residue; yield 0.4 g. (87.5%). The product was recrystallized from methanol to give pale yellow crystals of m. p.  $101-102^{\circ}$ C. Admixture with an authentic sample of 2-phenylnaphthalene caused no depression in the melting point.

N-Formyl-DL-erythro-O-methylphenylserine (XII).—The other diastereomer (XI) of Omethylphenylserine which melts at  $251-253^{\circ}C$ (dec.) was prepared by the method of Carter et  $al^{1,2}$ ).

One gram of XI was dissolved in 6 cc. of 83%formic acid, warmed to  $45^{\circ}$ C and then 3.0 cc. of acetic anhydride was added under shaking. The temperature of the reaction mixture was maintained at 70-80°C for 15 min.. Evaporation under reduced pressure gave a crystalline residue, which was recrystallized from 2 cc. of hot water to give crystals of m. p. 143-146°C; yield 0.8 g. (70.0%). Repeated recrystallization from hot water gave the N-formyl derivative of single diastereomer of O-methylphenylserine, m. p. 149-150°C.

Anal. Found: N, 6.32. Calcd. for  $C_{11}H_{13}O_4N$ : N, 6.28%.

Ethyl DL-erythro-O-Methylphenylserinate Hydrochloride (XIII).—A stream of dry hydrogen chloride was bubbled into a suspension of 10 g. of O-methylphenylserine (XI) in 150 cc. of absolute for ethanol for 1.5 hr.. After saturation, the solution was allowed to stand overnight at room temperature and evaporated under reduced pressure to yield a crystalline residue; 13.0 g.(97.7%). Recrystallization from absolute ethanol-ether gave colorless needles of the ester hydrochloride of XI, m. p. 179–181°C (dec.).

Anal. Found: N, 5.44. Calcd. for  $C_{12}H_{18}O_{3}NCI$ : N, 5.39%.

Ethyl DI-erythro-O-Methylphenylserinate (XIV).—A vigorous stream of dry ammonia was passed through a suspension of 13 g. of the hydrochloride (XIII) in 150 cc. of absolute ether for 20 min.. After-treatment was carried out just as described above in the preparation of IV. The yield of crude, pale-yellow oil was 10.0 g. (89.3%).

**DI-erythro-2-Amino-1-methoxy-1-phenyl-3propanol** (**XV**).—A solution of 9.5 g. of XIV in 100 cc. of absolute ethanol was hydrogenated with 10 g. of Raney nickel catalyst<sup>4</sup>) at  $45-52^{\circ}$ C and 120 atm. for 4 hr.. After-treatment was carried out just as described above in the preparation of V to yield a crude product of XV, a pale-yellow oil; yield 2.5 g. (32.4%).

Dry hydrogen chloride was bubbled through the ethereal solution of the crude syrup of XV to yield colorless crystals, which were collected and washed with dry ether and acetone; m. p. 175-177°C. Three recrystallizations from methanolether gave an analytical sample of the hydrochloride of XV, m. p. 181-182°C.

Anal. Found: C, 54.83; H, 7.13; N, 6.29. Calcdfor  $C_{10}H_{16}O_2NC1$ : C, 55.15; H, 7.40; N, 6.43%.

M. p. reported by Tatsuoka et al<sup>6</sup>). is  $182-183^{\circ}C$ .

N, O-Dibenzoyl-DI-erythro-2-amino-1-phenyl-3-propanol.—To a solution of 0.2 g. of the crude syrup of XV in 2.5 cc. of pyridine, was added 0.3 cc. of benzoyl chloride under ice cooling and shaking. The solution was cooled in an ice bath for 1 hr. and then allowed to stand at room temperature for 30 min.. Cold water was added to the solution to yield a crystalline precipitate, which was collected and washed with 2% sodium bicarbonate solution, 1% hydrochloric acid and finally with cold water. Three recrystallizations from methanol gave colorless needles of N, Odibenzoyl derivative of XV, m. p. 160-161°C; yield 0.3 g. (69.8%).

Anal. Found: N, 3.71. Calcd. for  $C_{24}H_{23}O_4N$ : N, 3.60%.

M. p. reported by Tatsuoka et al<sup>6</sup>). is 157–158.5°C.

N-Acetyl-DI-erythro-2-amino-1-methoxy-1phenyl-3-propanol (XVI).—To a solution of 2.2 g. of XV in 10 cc. of ether was added 4.0 cc. of acetic anhydride at room temperature. Aftertreatment was carried out just as described above in the preparation of VI to yield a crude product of XVI, m. p. 115-117°C; yield 2.1 g. (77.5%). Recrystallization from ethyl acetate gave colorless crystals of XVI, m. p. 116-118°C. Anal. Found: N, 6.05. Calcd. for  $C_{12}H_{17}O_8N$ :

Anal. Found: N, 6.05. Calcd. for  $C_{12}H_{17}O_3N$ : N, 6.27%.

N, O-Diacetyl-DL-erythro-2-amino-1-methoxy-1-phenyl-3-propanol (XVII).—A 1.0 g. sample of XVI was heated with 6.0 cc. of acetic anhydride on a boiling water bath for one hr. The solution was concentrated under reduced pressure to yield crude crystals, m. p. 77-80°C; yield 1.2 g. (100.9%).

N, O-Diacetyl-DL-erythro-2-amino-1-methoxy-1-p-nitrophenyl-3-propanol (XVIII). — To 1.0 g. of XVII was added 5.0 cc. of a mixture (1:1) of concentrated nitric acid (sp. gr. 1.38) and sulfuric acid (sp. gr. 1.84) under ice cooling and shaking. After-treatment was carried out just as described above in the preparation of VIII to yield a crude product of XVIII, m. p. 122-140°C; yield 1.2 g. (102.6%). Two recrystallizations from ethanol gave colorless crystals of XVIII, m. p. 150-151°C.

DI-erythro-2-Amino -1-Nethoxy - 1-p-nitrophenyl-3-propanol Hydrochloride (XIX).—A portion of 1.1 g. of XVIII was hydrolyzed with 10 cc. of 10% hydrochloric acid on a boiling water bath for one hr.. The hydrolysate was evaporated to dryness under reduced pressure. The crystalline residue was recrystallized from water to yield colorless crystals of DL-erythro-2amino-1-methoxy-1-*p*-nitrophenyl-3-propanol hydrochloride, m. p. 233-234°C. (dec.); yield 0.7 g. (75.2%).

<sup>6)</sup> S. Tatsuoka, M. Miyamoto, T. Kinoshita, R. Nakamori and S. Kimata, J. Pharm. Soc. Japan, 71, 608 (1951).

Anal. Found: N, 10.37. Calcd. for  $C_{10}H_{15}O_4N_2Cl$ : N, 10.67%.

M. p. reported by Tatsuoka et al<sup>6</sup>). was 232°C. Admixture with pl-threo-2-amino-1-methoxy-1-

*p*-nitrophenyl-3-propanol hydrochloride(IX) caused a depression in the melting point.

**DI-erythro-2- Amino-1-***p***-nitrophenyl-1, 3propanediol Hydrochloride** (**XX**).—A mixture of 0.7 g. of XIX and 12 cc. of 25% hydrochloric acid was placed in a sealed tube and heated at 125-130°C for 4 hr.. The contents were diluted with water and filtered. Then the filtrate was concentrated under reduced pressure to give a crystalline residue. The residue was recrystallized from methanol to yield colorless crystals, m. p. 207-209°C; yield 0.2 g. (30.3%).

Recrystallization from methanol yielded colorless crystals of DL-erythro-2-amino-1-*p*-nitrophenyl-1,3propanediol hydrochloride, m. p. 209-210°C..

Anal. Found: C, 43.41; H, 5.04; N, 11.09. Calcd. for C<sub>9</sub>H<sub>13</sub>O<sub>4</sub>N<sub>2</sub>Cl: C, 43.42; H, 5.23; N, 11.26%.

Controulis et al<sup>5</sup>). reported pL-erythro-2-amino-1-*p*-nitrophenyl-1,3-propanediol hydrochloride of m. p. 212-214°C.

## Summary

(1) DL-threo-O-Methylphenylserine has

been isolated through its N-formyl derivative from the diastereomeric mixture of O-methylphenylserines which was prepared by the route of Van Loon and Carter<sup>3</sup>.

(2) DL-threo-O-Methylphenylserine has been led to DL-threo-2-amino-1-*p*-nitrophenyl-1,3-propanediol and further to DLchloramphenicol.

(3) The other diastereomer of Omethylphenylserine (m. p. 251–253°C) has been led to DL-erythro-2-amino-1-*p*-nitrophenyl-1,3-propanediol hydrochloride.

(4) Several derivatives of the diastereomers of O-methylphenylserine and Omethylphenylserinol have been described.

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