# Synthetic Studies in the Chloramphenicol Series. III.* Synthesis of threo-DL-Chloramphenicol from DL-Serine Ethyl Ether**

*D. Fleš, B. Balenović, R. Marušić and N. Manger*

*Research Department, »Pliva« Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia*

Received January 21, 1955

A synthesis of *threo*-DL-chloramphenicol (I) from α-phthalimido-β-ethoxy-DL-propiophenone (II) is described. The crude ketone II obtained from α-phthalimido-β-ethoxy-DL-propionyl chloride via Friedel-Crafts reaction was reduced with aluminium isopropoxide to give a yield of 17.2% of the corresponding carbinol III. This carbinol gave in a series of reactions *threo*-DL-chloramphenicol in an over-all yield of 2.4%.

In a previous paper[1] we described the synthesis of α-phthalimido-β-ethoxy-DL-propiophenone (II), the key intermediate in our model synthesis for the preparation of *threo*-D-(-)-chloramphenicol, starting with optically active serine. In this paper we record the full experimental details of the synthesis of *threo*-DL-chloramphenicol (I), starting with α-phthalimido-β-ethoxy-DL-propiophenone. In the above mentioned work, ketone II was prepared by condensation of α-phthalimido-β-ethoxy-DL-propionyl chloride with diphenylcadmium and with benzene in the presence of anhydrous aluminium chloride. In the first reaction, II was isolated in the form of 2,4-dinitrophenylhydrazone, in a yield of 3.5%. When α-phthalimido-β-ethoxy-DL-propionyl chloride was condensed with benzene using the Friedel-Crafts reaction, the pure ketone was isolated with Girard T reagent in a yield of 2.3%. But when the crude condensation product of the Friedel-Crafts reaction was reduced with aluminium isopropoxide under the conditions of the Meerwein-Ponndorf-Verley reaction, a 17.2% yield of *threo*-1-phenyl-1-hydroxy-2-phthalimido-3-ethoxypropane (III) was obtained. Apparently the isolation of II with Girard T reagent was not very effective. When the pure ketone, prepared in the manner described in the above mentioned paper, was reduced with aluminium isopropoxide, carbinol III was obtained in a yield of 65.5%. No attempt has been made to isolate the *erythro*-1-phenyl-1-hydroxy-2-phthalimido-3-ethoxypropane.

At this stage of our work, a synthesis of chloramphenicol methyl ether was published by Mildred C. Rebstock.[2] In her synthesis α-bromo-β-methoxy-DL-propionyl chloride was condensed with benzene under the Friedel-Crafts reaction, and the crude oily product was then condensed with potassium phthalimide to give the crystalline α-phthalimido-β-methoxy-DL-propiophenone.

* Paper II, D. Fleš, M. Brajdić and N. Štimac, *Arhiv kem.* **26** (1954) 183.
** Yugoslav Patent Application, P-911/54, Dec. 20, 1954.

Reduction of this ketone with hydrogen in the presence of palladium oxide led to a mixture of *threo*-and *erythro*-isomers of the corresponding carbinols, which gave, after a series of reactions, DL-*threo* and DL-*erythro*-chloramphenicol.

Our work on the synthesis of chloramphenicol was continued using reactions similar to those described by Rebstock. Carbinol III was acetylated with acetic anhydride in pyridine to give a good yield of *threo*-1-phenyl-1-acetoxy-2-phthalimido-3-ethoxypropane (IV). This acetylated product IV was then nitrated with fuming nitric acid, and the mixture of the nitrated isomers was once crystallized from ethanol. Many difficulties were encountered in the isolation of the pure p-nitro-derivative, and in the subsequent steps we therefore used the once crystallized product. The phthaloyl group was hydrazinolyzed, the acetyl group was hydrolyzed with dilute hydrochloric acid, and the resulting hydrochloride treated with hydrobromic acid, the ethyl ether of chloramphenicol base being thus isolated in the form of its hydrobromide (IX).

The same hydrobromide was also prepared in another series of reactions: first, the acetylated product IV was hydrazinolyzed and then acetylated with acetic anhydride in pyridine, and *threo*-1-phenyl-1-acetoxy-2-acetamido-3-ethoxy-propane (VII) was thus obtained. VII was then nitrated, and the acetyl groups were hydrolyzed in the usual manner. The crude hydrochloride was then treated with hydrobromic acid yielding hydrobromide IX. The free bases, *threo*-1-phenyl-1-hydroxy-2-amino-3-ethoxypropane (V) and *threo*-1-p-nitrophenyl-1-hydroxy-2-amino-3-ethoxypropane (X), were also prepared.

The cleavage of the ethyl ether bond of the compound IX, was effectively performed by heating the hydrobromide with 48% hydrobromic acid under the conditions described by Rebstock[2]. After neutralization with ammonia, the free base XI was obtained in a yield of 72.7%. The base XI, was converted to *threo*-DL-chloramphenicol by a method previously published.[3]

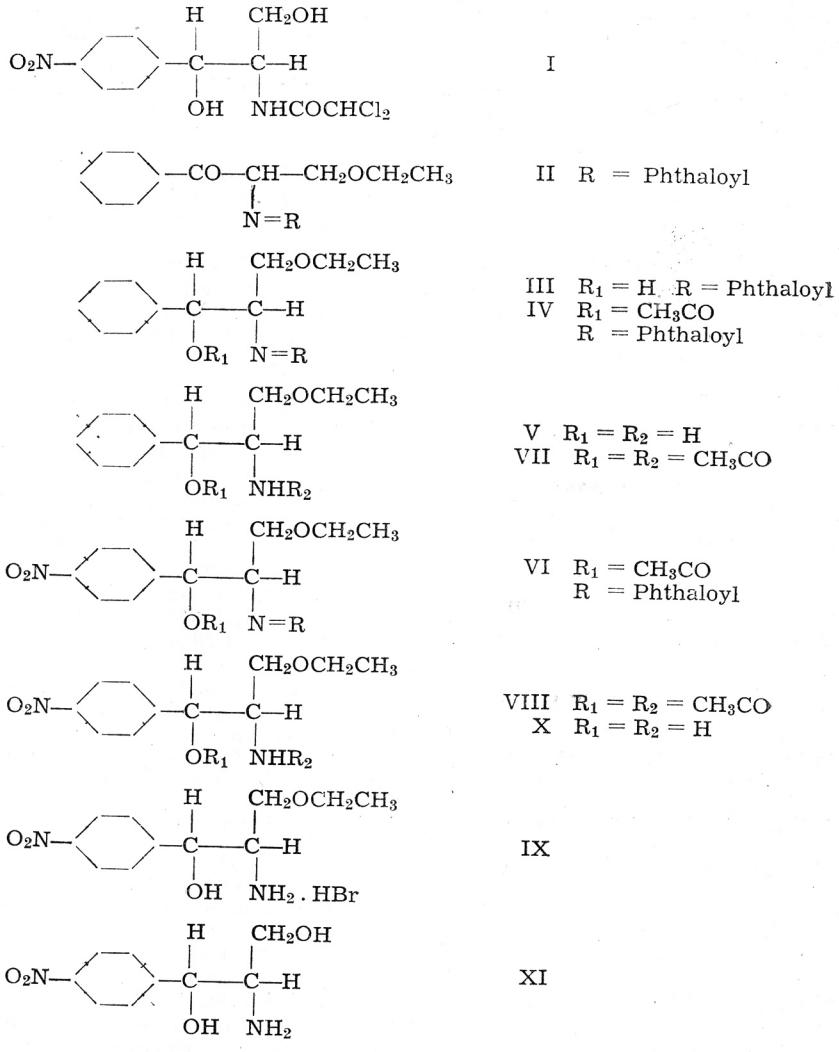
The synthetic approach which led to the preparation of the chloramphenicol (I) via 1-phenyl-1-acetoxy-2-acetamido-3-ethoxypropane (VII), gave I in an over-all yield of 2.4% (based on the α-phthalimido-β-ethoxy-DL-propionyl chloride).

We can not exclude the possible inversion in the course of this synthesis, but there is evidence from the literature, that the reactions used in our model synthesis are straightforward.

Mc Kenzie et al.[4] reported the preparation of optically active β-phenyl-β-phthalimido-propiophenone using the usual Friedel-Crafts reaction. Meerwein-Ponndorf-Verley reaction was also used for reduction of optically active ketone.[5] The acetylation, performed under the same conditions as described in the experimental part, was used in the preparation of diacetyl-D-*threo*-chloramphenicol.[6] There is also evidence that the cleavage of an ether bond is a straightforward reaction, if performed under the conditions described in the experimental part of this communication.[2, 7]

We therefore feel justified in claiming that this synthesis is capable of producing D- (-) -*threo*-chloramphenicol, if performed with the optically active intermediates.

Figure I




## EXPERIMENTAL*

### DL-threo-*1-Phenyl-1-hydroxy-2-phthalimido-3-ethoxypropane* (III)

A. From the pure α-phthalimido-β-ethoxy-DL-propiophenone: In a 500-ml. round bottomed flask are placed 2.2 g. (0.007 mole) of the ketone II and 4.15 g. (0.02 mole) of distilled aluminium isopropoxide and 40 ml. of dry isopropanol. A Hahn partial condenser was attached and the solution was heated with an oil bath at such a rate that slow distillation of acetone occurred. Seven hours were required to distil over the theoretical amount of acetone.** After that time the isopropanol was removed

* The melting points are uncorrected.

** The acetone was determined according to a titration method with hydroxylamine hydrochloride.

under reduced pressure, and the residue was hydrolyzed with a solution of 30 g. of tartaric acid in 50 ml. of water. Benzene (20 ml.) was added to facilitate the hydrolysis by dissolving the hydrolyzed product. The water layer was removed and extracted with three 10 ml. portions of benzene. The combined benzene solutions were dried over anhydrous sodium sulphate and the solvent removed in vacuo. 2.2 g. of a crystalline product was obtained. The crude carbinol was recrystallized from 8 ml. of ethanol to give 1.45 g. (65.5%) of a product melting at 153—155°. The analytical sample, recrystallized twice from ethanol, melted at 156—157°.

*Anal.* 24.81 mg. subst.: 63.63 mg. $CO_2$, 12.94 mg. $H_2O$
$C_{19}H_{19}O_4N$ (325.35) calc'd.: C 70.13 H 5.89%
found: C 69.99 H 5.83%

B. Reduction of crude α-phthalimido-β-ethoxy-DL-propiophenone.*** Fifty grams of α-phthalimido-β-ethoxy-DL-propionyl chloride was condensed with benzene in the presence of 46 g. of anhydrous aluminium chloride in the manner described in a previous publication[1]. After the reaction mixture was hydrolyzed, the benzene solution of the crude ketone was neutralized with a saturated sodium bicarbonate solution, and the benzene layer was dried over anhydrous sodium sulphate. The benzene was evaporated under reduced pressure, and 41 g. of a dark brown oil was obtained. Without further purification, this oil was used in the next step.

The crude α-phthalimido-β-ethoxy-DL-propiophenone (41 g.) was reduced with 24 g. of aluminium isopropoxide in 200 ml. of dry isopropanol by heating the reaction mixture with an oil bath for a period of 12 hours. 2.1 g. of acetone was detected in the distillate. Isopropanol was then removed under reduced pressure and the residue hydrolyzed with a solution of 120 g. of tartaric acid in 200 ml. of water in the presence of 150 ml. of benzene. The water layer was extracted with three 50 ml. portions of benzene, the benzene solution was dried over anhydrous sodium sulphate, and the solvent removed in vacuo. 41.4 g. of a dark semi-crystalline oil resulted. The product was dissolved in a mixture of 20 ml. of benzene and 20 ml. of ether and crystallized in a refrigarator overnight. A crop of 12.8 g. of a crystalline product melting at 141—148° was obtained. The carbinol was recrystallized from 50 ml. of ethanol to give 10 g. of a white crystalline product melting at 151—155°. The yield based on the acid chloride was 17.2%. An analytical sample was recrystallized from ethanol, m. p. 156—157°. No melting point depression was observed on mixing with a sample of product obtained under A.

DL-threo-*1-Phenyl-1-acetoxy-2-phthalimido-3-ethoxypropane* (IV)

Ten grams of the carbinol III (m. p. 151—155°) was dissolved in 19 ml. of dry pyridine, and acetylated with 30 ml. of acetic anhydride. After standing overnight at room temperature, the reaction mixture was poured on 240 g. of ice and the crystalline product was taken into 80 ml. of ethyl acetate. The water layer was extracted with three 10 ml. portions of ethyl acetate. The organic layer was washed with three 10 ml. portions of 25% sulphuric acid, and then neutralised with a saturated solution of sodium bicarbonate. The dried extract was evaporated in vacuo and 12.2 g. of an oily product was obtained. The crude product was dissolved in 30 ml. of ethanol and after standing overnight in a refrigerator, 10 g. of crystals melting at 90—91° separated. The melting point did not change on further crystallisation. The analytical sample was distilled at 200—210°, at a pressure of 0.07 mm. The yield, based on carbinol III was 89%.

*Anal.* 21.06 mg, subst.: 52.90 mg. $CO_2$, 10.52 mg. $H_2O$
$C_{21}H_{21}O_5N$ (367.38) calc'd.: C 68.65 H 5.76%
found: C 68.54 H 5.59%

DL-threo-*1-Phenyl-1-hydroxy-2-amino-3-ethoxypropane* (V)

The acetylated product IV (2.5 g.) was dissolved in 35 ml. of absolute ethanol and 0.85 ml. of 80% hydrazine hydrate was added. The reaction mixture was refluxed on a water bath for an hour. The solvent was removed under reduced

*** In collaboration with Mr. M. Brajdić.

pressure, and the residue heated for 10 minutes with 25 ml. of *N*-hydrochloric acid at 50°. After standing for 30 minutes at room temperature, the phthalylhydrazide was filtered off. The theoretical amount of phthalylhydrazide was obtained. The filtrate was heated under reflux for one and a half hour, was then cooled with ice and made strongly alkaline with a 20% sodium hydroxide solution. The alkaline solution was extracted with eight 20 ml. portions of ethyl acetate. The extract was dried over anhydrous sodium sulphate, and the solvent evaporated under reduced pressure. 1.32 g. of a colourless oil was obtained. An analytical sample was twice distilled at 110—120° and 0.06 mm. The yield of the crude oil was quantitative.

*Anal.* 23.38 mg subst.: 57.83 mg. $CO_2$, 17.80 mg. $H_2O$
3.825 mg. subst.: 0.2352 ml. $N_2$ (22°, 757 mm.)
$C_{11}H_{17}O_2N$ (195.25) calc'd.: C 67.66 H 8.78 N 7.17%
found: C 67.50 H 8.52 N 7.08%

DL-threo-*1-p-Nitrophenyl-1-acetoxy-2-phthalimido-3-ethoxypropane* (VI)

The acetylated product IV (4.6 g.) was added in the course of 15 minutes to 18 ml. of fuming nitric acid at a temperature of -20°. The nitration was performed in a test tube, immersed in an acetone dry-ice bath, and the reaction mixture was stirred with a termometer. After the addition of IV was completed, the test tube was kept for further 35 minutes at room temperature. After that time the temperature in the reaction mixture was 25°. The nitrated product was then quenched on 150 g. of ice, and neutralised with solid sodium bicarbonate. The crystalline product which separated was taken into ethyl acetate, the extract washed with water and dried over anhydrous sodium sulphate. 5.12 g. of a semi-crystalline product was obtained after the ethyl acetate was evaporated in vacuo. The crude product, was recrystallized from 50 ml. of ethanol. to give 3.9 g. of a crystalline product, m. p. 110—120°. The product was used without further purification in the next step. The analytical sample was purified by crystallization from ethanol, and finally from a mixture of acetone-petroleum ether (b. p. 40—60°). Melting point 129—131° (with previous softening at 110°).

*Anal.* 15.50 mg. subst.: 34.63 mg. $CO_2$, 6.39 mg. $H_2O$
$C_{21}H_{20}O_7N_2$ (412.38) calc'd.: C 61.16 H 4,89%
found: C 60.97 H 4.61%

DL-threo-*1-Phenyl-1-acetoxy-2-acetamido-3-ethoxypropane* (VII)

Five grams (0.014 mole) of the acetylated product IV was refluxed for 2 hours with 14.5 ml (0.0145 mole) of a N-hydrazine hydrate in absolute ethanol. The reaction mixture was cooled, phthalylhydrazide was filtered off and washed with 10 ml. of dichloromethane. The filtrate and washings were evaporated under reduced pressure, the residue was redissolved in 20 ml. of dichloromethane, and the solution kept for 2 hours in ice. An additional quantity of phthalylhydrazide was obtained. The total yield of phthalylhydrazide was 92%. The dichloromethane solution was evaporated to dryness and the remaining oil (3.56 g.) was acetylated as follows: 3.56 g. of the crude product was dissolved in 2.4 ml. of dry pyridine and 2.4 ml. of acetic anhydride was added. After standing overnight at room temperature, the reaction mixture was poured on 30 g. of ice. The oily product was extracted with five 5 ml. portions of ethyl acetate, washed twice with 3 ml. of 10% sulphuric acid and neutralised with a saturated sodium bicarbonate solution. The ethyl acetate solution was dried and the solvent evaporated in vacuo. The oily product (4.3 g.) was crystallized from 15 ml. of ether. Three grams of needlelike crystals, representing a yield of 78.9% was obtained. The analytical sample was sublimed at a temperature of 100—110° at a pressure of 0.04 mm. Melting point 87—89°.

*Anal.* 13.00 mg. subst.: 30.82 mg. $CO_2$, 8.46 mg. $H_2O$
$C_{15}H_{21}O_4N$ (279.32) calc'd.: C 64.50 H 7.58%
found: C 64.69 H 7.28%

DL-threo-*1-p-Nitrophenyl-1-acetoxy-2-acetamido-3-ethoxypropane* (VIII)

The crystalline diacetyl product VII (1.2 g.) was added to 4.5 ml. of fuming acid at a temperature of —20° to —15° over a period of 20 minutes. After the final addition of diacetyl compound, the reaction mixture was allowed to rise to room temperature, during half an hour, and was then poured on ice. The nitric acid was neutralized with solid sodium bicarbonate, and the oily product was taken in ethyl acetate, dried over sodium sulphate and the solvent evaporated in vacuo. 1.4 g. of a yellow viscous oil was obtained. This product was used directly in the next step.

DL-threo-*1-p-Nitrophenyl - 1 - hydroxy - 2 - amino - 3 - ethoxypropane hydrobromide* (IX)

The crude nitrated product VIII (1.4 g.) was heated for two and a half hours on the water bath with 12 ml. of a 5% hydrochloric acid. The hydrochloric acid was evaporated in vacuo, and the crude hydrochloride (1.24 g.) was dissolved in 4 ml. of 48% hydrobromic acid. After a few minutes, a yellow crystalline product separated. The excess of hydrobromic acid was evaporated in vacuo and the residue was recrystallized from a mixture of ethanol-ether. 0.42 g. of crystals melting at 191—192° was obtained. The analytical sample melted at 193—194.5°. The yield calculated on the diacetyl product VII, was 30.4%.

*Anal,* 19.98 mg. subst.: 30.10 mg $CO_2$, 9.31 mg. $H_2O$
4.528 mg. subst.: 0.343 ml. $N_2$ (22°, 747 mm)
$C_{11}H_{17}O_4N_2Br$ (321.18) calcid.: C 41.13 H 5.34 N 8.72%
found: C 41.11 H 5.21 N 8.61%

The same hydrobromide (IX) was also prepared from DL-*threo*-1-phenyl-1-acetoxy-2-phthalimido-3-ethoxypropane (IV): Two grams of the nitrated product VI (m. p. 110—129°) was refluxed for one and a half hour with 5.2 ml. of a *N*-hydrazine hydrate solution in absolute ethanol. The reaction mixture was diluted with 6 ml. of absolute ethanol, and cooled to room temperature. Phthalylhydrazide was filtered off and the filtrate was evaporated to dryness. The residue was then treated with 20 ml. of dichloromethane and a total of 640 mg (82% of the theoretical amount) og phthalylhydrazide was obtained. Dichloromethane was evaporated and the residue was hydrolyzed by refluxing with 30 ml. of a 5% hydrochloric acid for two and a half hours. The reaction mixture was cooled, extracted with ether from the unreacted portion (170 mg.) and the hydrochloric acid was removed under reduced pressure. The residue was treated with 4 ml. of 48% hydrobromic acid. 400 mg. of a crystalline product separated after two days at room temperature. The crystalline product was filtered off and recrystallized from a mixture of ethanol-ether to a melting point of 192—193°. This product gave no melting point depression with the hydrobromide previously described.

DL-threo-*1-p-Nitrophenyl-1-hydroxy-2-amino-3-ethoxypropane* (X)

The crude nitrated product VIII (1.4 g.) was treated in the same way as described for the preparation of the hydrobromide IX. The crude hydrochloride (1.2 g.) was dissolved in 5 ml. of water and made strongly alkaline with a 10% sodium hydroxide solution. The solution was extracted with ethyl acetate, and the dried ethyl acetate solution was evaporated in vacuo to an oily residue which crystallised after few days. The analytical sample was purified by distillation at 140—150° at a pressure of 0.05 mm.

*Anal.* 13.30 mg. subst.: 26.68 mg. $CO_2$, 7.77 mg. $H_2O$
6.295 mg. subst.: 0.628 ml. $N_2$ (22°, 767 mm)
$C_{11}H_{16}O_4N_2$ (240.25) calc'd.: C 54.99 H 6.71 N 11.66%
found: C 54.75 H 6.54 N 11.65%

DL-threo-*1-p-Nitrophenyl-2-amino-1,3-propanediol* (XI)

One and a half gram of the hydrobromide IX was heated with 13.5 ml. of 48% hydrobromic acid in a sealed tube at 130° for half an hour and at 120° for

one hour. The heating was discontinued and the tube cooled overnight. The acid was removed under reduced pressure, and the residue dissolved in 8 ml. of water and made strongly alkaline (pH 11) with a concentrated ammonium hydroxide solution. The crystalline product which separated was extracted with 100 ml. of ethyl acetate, dried over anhydrous sodium sulphate, the solvent was removed in vacuo and the crystalline residue (924 mg.) was recrystallized from 10 ml. of water. 720 mg. (72.7% of the theoretical yield) of the base melting at 140—141° was obtained. The base XI gave no depresion of melting point when mixed with the original DL-*threo*-chloramphenicol base.

DL-threo-*1-p-Nitrophenyl-2-dichloroacetamido-1,3-propanediol* (I)

The base XI (m. p. 140—141°) was converted to the DL-threo-chloramphenicol by refluxing with an excess of methyl dichloroacetate in absolute methanol, according to the method described by Long and Jenesel[3]. The DL-*threo*-chloramphenicol I melted at 150—151° and gave no depression of melting point when mixed with an authentic sample of DL-*threo*-chloramphenicol.

*Anal.* 17.01 mg. subst.: 25.42 mg. $CO_2$, 5.34 mg. $H_2O$
8.710 mg. subst.: 0.637 ml. $N_2$ (20°, 766 mm)
$C_{11}H_{12}O_5N_2Cl_2$ (323.14) calc'd.: C 40.88 H 3.74 N 8.68%
found: C 40.78 H 3.51 N 8.59%

*Acknowledgment.* The authors are grateful to Professor K. Balenović for suggesting this investigation and for his continued encouragement and interest. We also wish to thank to Mr. M. Brajdić for the generous supply of dibromo propionic acid used for the preparation of β-ethoxy-serine.

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## IZVOD

### Sintetske studije u redu kloramfenikola. III. Sinteza DL-treo-kloramfenikola iz etilnog etera DL-serina

*D. Fleš, B. Balenović, R. Marušić i N. Manger*

U prije objavljenoj publikaciji[1] opisana je priprava α-ftalimido-β-etoksi-DL-propiofenona (II). Keton II priređen je kondenzacijom α-ftalimido-β-etoksi-DL-propionil klorida s difenilkadmijem i kondenzacijom s benzenom u prisutnosti bezvodnog aluminijskog triklorida. U prvoj reakciji dobiven je keton II u obliku 2,4-dinitrofenilhidrazona s 3,5%-tnim iskorištenjem, a Friedel-Craftsovom reakcijom dobiven je, s pomoću reagensa Girard T, keton II s 2,5%-tnim iskorištenjem. Međutim, kad se sirovi keton, dobiven Friedel-Craftsovom reakcijom, reducira aluminijskim isopropilatom, uz uvjete Meerwein-Ponndorf-Verleyeve reakcije, dobije se pripadni karbinol III s iskorištenjem od 17,2% i s talištem kod 156—157°. Relativno veliko iskorištenje u pogledu karbinola III pokazuje, da je izolacija ketona II reagensom Girard T bila nepotpuna. Karbinol III dao je u nastavku sinteze *treo*-DL-kloramfenikol, pa je zbog toga zaključeno, da i karbinol III ide u red treo spojeva.

U nastavku sinteze acetiliran je karbinol III anhidridom octene kiseline u piridinu, pri čemu je dobiven *treo*-DL-1-fenil-1-acetoksi-2-ftalimido-3-etoksipropan IV.

Iskorištenje 89%, talište 90—91°. Iz acetiliranog spoja IV priređen je DL-*treo*-kloramfenikol na dva načina. Najprije je IV nitriran s dimljivom dušičnom kiselinom, a zatim je kuhanjem nitro spoja VI s N-hidrazin hidratom u apsolutnom alkoholu odcijepljena ftaloilna grupa. Monoacetilni derivat nije izoliran, nego je sirovi produkt hidroliziran 5%-tnom solnom kiselinom; otapanjem hidroklorida u bromovodičnoj kiselini dobiven je zatim DL-*treo*-1-p-nitrofenil-1-hidroksi-2-amino-3-etoksipropan hidrobromid (IX). Isti hidrobromid priređen je iz spoja IV tako da je najprije hidrazinolizom odcjepljena ftaloilna grupa, a zatim je dobiveni spoj acetiliran. Diacetilni derivat VII (talište 87—89°) je zatim nitriran, a sirovi nitro spoj VIII preveden je hidrolizom sa solnom kiselinom i obrađivanjem s bromovodičnom kiselinom — u hidrobromid IX. Priređene su i slobodne baze DL-*treo*-1-fenil-1-hidroksi-2-amino-3-etoksipropan (V) i DL-*treo* - 1 - p - nitrofenil - 1-hidroksi-2-amino-3-etoksipropan (X). DL-*treo*-kloramfenikolska baza XI priređena je cijepanjem eterskog veza u spoju IX, kuhanjem sa 48%-tnom bromovodičnom kiselinom. XI je dobiven s iskorištenjem od 72,7% i s talištem kod 140—141°. Baza XI prevedna je — kuhanjem s metil-dikloracetatom u metanolu — u DL-*treo*-kloramfenikol (I). I je dobiven s iskorištenjem od 2,4% prema α-ftalimido-β-etoksi-DL-propionil kloridu.

Ne može se isključiti mogućnost steričke inverzije u procesu opisane sinteze kloramfenikola, no prema analogiji sa sintezama iz reda kloramfenikola i sličnih spojeva možemo pretpostaviti, da su sve upotrebljene reakcije sterički jednoznačne.

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 21. januara 1955.