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Original Scientific Paper

Synthetic Studies in the Chloramphenicol Series. VI.* Synthesis of DL-*threo*-1-*p*-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methylsulfinyl and 3-methylsulfonyl propane

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The compounds mentioned in the title were prepared from α-phthalimido-β-methylmercaptopropiophenone (I). Reduction of I with aluminium isopropoxide gave preferentially the *threo*-carbinol II which upon acetylation and subsequent nitration gave a mixture of diastereomeric sulfoxides which were oxidized with hydrogen peroxide to the identical sulfones.

In a previous paper[1] the preparation of DL-α-phthalimido-β-methylmercapto-propiophenone (I) *via* a Friedel-Crafts condensation of the corresponding acid chloride with two moles o aluminum chloride was described. Using ketone I as starting material, the two compounds mentioned in the title of this paper were synthesized. The ketone was first reduced with aluminum isopropoxide to the corresponding alcohol II (R=H), the less soluble fraction was isolated from ethanol in 57% yield and proved to be the *threo* isomer.

The *threo* configuration was established by converting the less soluble product to *N*-phthaloyl-DL-nor-*pseudo*-ephedrine by desulfuration with Raney nickel.

The more soluble *erythro*-isomer did not crystallize from ethanol and was isolated as the 1-acetoxy derivative in a 22% yield. The predominant formation of *threo*-isomer is in accord with the rule of steric control of asymmetric induction proposed by Cram and Elhafez[2] and with the results previously obtained in our Laboratories[3].

The *threo* carbinol was acetylated with acetic anhydride in pyridine and the acetoxy derivative (II, R = $COCH_3$) nitrated with fuming nitric acid at —20°. The resulting mixture of nitrated products yielded two racemic sulfoxides melting at 193° and 213° respectively (III, R = $COCH_3$; R′ = phthaloyl).

Both sulfoxides were oxidized with hydrogen peroxide to the identical sulfones (IV, R = $COCH_3$; R′ = phthaloyl). The sulfones were proved identical by infrared spectra, the same melting point and mixed melting point and by analytical data. Thus, the sulfoxides with different melting points differed merely in the configuration of the sulfoxide group.

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* Paper IV. D. Fleš and B. Balenović, *Arhiv kem.* **27** (1955) 149; Paper V. D. Fleš and B. Balenović, *J. Am. Chem. Soc.* **78** (1956) 5903.

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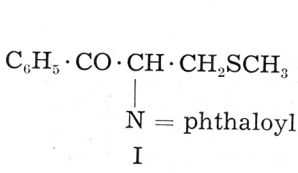
The ultraviolet spectrum of the amino sulfoxide III (R = H; R′ = H_2) with a maximum at 275 mμ, $E^{1\%}_{1\,cm}$ 256, and an inflection at 217 mμ, $E^{1\%}_{1\,cm}$ 256, is in close agreement with the spectrum published for chloramphenicol, in which the position of nitro group is known to be para.[4]

The sulfoxide III (R = $COCH_3$; R′ = phthaloyl) and the sulfone IV (R = $COCH_3$; R′ = phthaloyl) were converted to the appropriate analogues of chloramphenicol by following essentially the standard methods used in the synthesis of chloramphenicol.[3,5]

Also worthy of mention is the observation that methyl dichloroacetate gave even after prolonged heating with the amino sulfone IV (R = H; R′ = H_2) only 10% of the corresponding amide, while the amino sulfoxide III (R = H; R′ = H_2) reacted normally under the same conditions. However, dichloroacetylation of the sulfone base with dichloroacetyl chloride gave a 43% yield.



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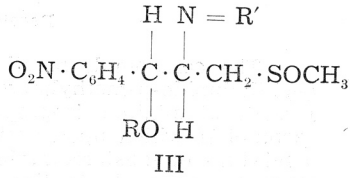

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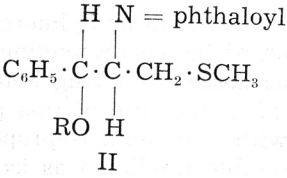
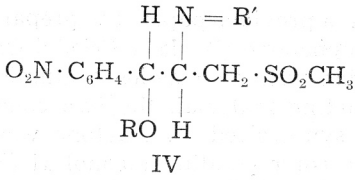


II



IV

EXPERIMENTAL

The melting points are uncorrected. All compounds described in this paper are racemic. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrophotometer using KBr pelleting technique, ultraviolet spectra were recorded on a Perkin-Elmer 202 spectrophotometer.

Threo-*1-phenyl-1-hydroxy-2-phthalimido-3-methylmercaptopropane*

In a 250 ml. round—bottomed flask were placed 5.8 g. (0.0178 mole) of α-phthalimido-β-methylmercaptopropiophenone[1], 10.87 g. (0.053 mole) of distilled aluminum isopropoxide and 100 ml. of dry isopropanol. A Hahn partial condenser was attached and the reaction mixture heated at such a rate as to maintain the slow distillation of acetone. After 8 hours 87% of the theoretical amount of acetone was distilled over. Isopropanol was removed *in vacuo* and the residue hydrolyzed with a solution of 60 g. tartaric acid in 200 ml. of water. The reaction mixture was extracted with benzene, the extract was dried, benzene removed *in vacuo* and the oily residue (6.1 g.) was dissolved in 12.5 ml. of ethanol. After cooling overnight in a refrigerator, the crystalline product was removed by suction filtration and washed with 5 ml. of cold ethanol yielding 2.91 g. of crystalline product melting at 113—114°. Evaporation of filtrate and washings gave additional 1.35 g. of the same product. Total yield was 56%. A sample was recrystallized for analysis from a mixture of benzene-petroleum ether (b.p. 40—60°) (1:1) and finally from ethanol, m.p. 115—116°.

Anal. $C_{18}H_{17}NO_3S$ (327.32) calc'd: C 66.05; H 5.24%
found: C 65.94; H 5.19%

N-*Phthaloyl-nor*-pseudo-*ephedrine* via *desulfuration of* threo-*1-phenyl-1--hydroxy-2-phthalimido-3-methylmercaptopropane*

The *threo*-carbinol II (R = H) (0.5 g., 0.0015 mole) was refluxed for 4 hours with 2.7 g. of Raney nickel in 10 ml. of absolute ethanol. Another portion of 2.7 g. of Raney nickel was added and the heating continued for additional 2 hours. The nickel was removed by filtration, washed with three 20 ml. portions of ethanol, and the combined filtrate and washings were evaporated *in vacuo*. The residue was dissolved in 1.5 ml. of ethanol yielding 0.1 g. (23%) of *N*-phthaloyl--nor-*pseudo*-ephedrine, m.p. 134—135°. The product had identical infrared spectrum, m.p. and mixed m.p. with the one obtained by Meerwein - Ponndorf reduction of DL-α-phthalimidopropiophenone.

Anal. $C_{17}H_{15}NO_3$ (281.13) calc'd: C 72.58; H 5.37; N 5.37%
found: C 72.59; H 5.36; N 5.31%

Threo-*1-phenyl-1-acetoxy-2-phthalimido-3-methylmercaptopropane*

The *threo*-carbinol II (R = H) (3.26 g., 0.01 mole) was dissolved in 13 ml. of pyridine, cooled in an ice bath and acetylated with 13 ml. of acetic anhydride. The reaction mixture was cooled with ice for 30 min., left at room temperature overnight and poured on 50 g. of ice. The oily precipitate was extracted with 50 ml. of ethyl acetate, washed with 2% sulfuric acid, neutralized with a saturated sodium bicarbonate solution, and dried over magnesium sulfate. The removal of ethyl acetate and crystallization from 8 ml. of ethanol gave 3.4 g. (93%) of needles melting at 118—119°. A sample for analysis was twice recrystallized from ethanol, m.p. 121.5—122.5°.

Anal. $C_{20}H_{19}NO_4S$ (369.36) calc'd: C 65.02; H 5.19; N 3.79%
found: C 64.91; H 4.89; N 3.89%

Erythro-*1-phenyl-1-acetoxy-2-phthalimido-3-methylmercaptopropane*

The mother liquor from which the *threo*-carbinol II (R = H) was separated, was evaporated *in vacuo* and the oily residue (2.34 g.) acetylated in 6 ml. of pyridine as previously described. After the hydrolysis of acetic anhydride the *erythro*-acetyl derivative was separated by suction filtration, washed with water and recrystallized from 100 ml. of boiling ethanol yielding 1.42 g. (22% based on ketone I) of needles melting at 194—195°.

Anal. $C_{20}H_{19}NO_4S$ (369.36) calc'd: C 65.02; H 5.19; N 3.79%
found: C 64.91; H 4.89; N 3.89%

Threo-*1-p-nitrophenyl-1-acetoxy-2-phthalimido-3-methylsulfinylpropane*

The *threo*-acetyl derivative II (R = CH_3CO) (4.20 g., 0.011 mole) was added gradually with stirring into 16 ml. of fuming nitric acid maintaining the temperature between —20° and —25°. The reaction mixture was then heated to 15° and left to stand for 30 minutes at this temperature. The nitric acid was diluted with 140 g. of ice, neutralized with solid sodium bicarbonate, and the crystalline precipitate separated by suction filtration, yielding 4.5 g. of the product melting at 165—190°. The crude nitrated product was dissolved in 35 ml. of dioxane and crystallized by the addition of 17 ml. of petroleum ether (b.p. 40—70°). After standing overnight in a refrigerator, the crystalline precipitate (2.26 g., m.p. 197—201°) was separated by filtration, and heated under reflux with 100 ml. of absolute ethanol for 15 minutes. The insoluble part was filtered from the boiling ethanol yielding 1.05 g. (21.5%) of *threo*-1-*p*-nitrophenyl-1-acetoxy-2-phthalimido-3-methylsulphinylpropane, m.p. 210—212°. A sample was recrystallized from ethanol (20 ml. of solvent *per* 100 mg. of product) and melted at 213—214°. In the infrared it showed a nitro group absorption at 1515 cm^{-1} and 1342 cm^{-1} and a sulfoxide group absorption at 1026 cm^{-1}.

Anal. $C_{20}H_{18}N_2O_7S$ (430.36) calc'd: C 55.81; H 4.22; N 6.51%
found: C 55.67; H 3.49; N 6.61%

The ethanolic mother liquor from which 1.05 g. of the nitro sulfoxide with m.p. 210—213° was separated, was cooled overnight in a refrigerator, and the crystalline product (745 mg., m.p. 190—197°) separated. The product was dissolved in 50 ml. of absolute ethanol yielding upon cooling 60 mg. (12.2%) of a product melting at 192—197°. A sample for analysis was twice recrystallized from ethanol, m.p. 193—196°. In the infrared the product showed a nitro group absorption at 1530 cm^{-1} and 1350 cm^{-1} while the sulfoxide group showed an absorption at 1040 cm^{-1}.

found: C 55.50; H 4.42; N 6.41%

Threo-*1-p-nitrophenyl-1-hydroxy-2-amino-3-methylsulfinylpropane hydrochloride*

1.0 g. (0.0023 mole) of nitro sulfoxide III (R = $COCH_3$; R′ = phthaloyl) (m.p. 213—214°) was refluxed for 2 hours with 3.5 ml. of absolute ethanol and 3.5 ml. of *M*-hydrazine hydrate in ethanol. The solvent was removed *in vacuo*, the residue suspended in 9 ml. of water and acidified to pH 3 with 5% hydrochloric acid. Phthaloyl hydrazide was removed by filtration under suction, the filtrate evaporated *in vacuo*, the traces of hydrochloric acid and water removed by repeated evaporation with absolute ethanol and the residue recrystallized from a mixture of 6 ml. of methanol and 10 ml. of ether. Yield 300 mg. (44%), m.p. 195—196° (decompn.). A sample was recrystallized from a mixture of methanol-ether (1:2), m.p. 198.5°.

Anal. $C_{10}H_{15}ClN_2O_4S$ (294.76) calc'd: C 40.74; H 5.13; N 9.51%
found: C 40.71; H 4.81; N 9.70%

Threo-*1-p-nitrophenyl-1-hydroxy-2-amino-3-methylsulfinylpropane*

An aqueous solution of 0.57 g. (0.002 mole) of the hydrochloride III (R = H; R′ = H_2) was adjusted to pH 9 with sodium hydroxide, the water removed *in vacuo*, the residue suspended in 6 ml. of ethanol, sodium chloride removed by suction filtration and the filtrate evaporated *in vacuo*. The crude base was dissolved in 4 ml. of ethanol and crystallized by addition of 20 ml. of ether yielding 250 mg. (50%) of the base, m.p. 138—140°. After two crystallizations from ethanol-ether the base melted at 140—142°. In the ultraviolet (methanol-water 1:9) the base had λ_{max} 275 mμ ($E^{1\%}_{1\,cm}$ 256) and an inflection at 278 mμ ($E^{1\%}_{1\,cm}$ 300).

Anal. $C_{10}H_{14}N_2O_4S$ (258.23) calc'd: C 46.50; H 5.47%
found: C 46.51; H 5.19%

Threo-*1-p-nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methylsulfinyl--propane*

A solution of 290 mg. (0.0001 mole) of the hydrochloride III (R = H; R′ = H_2) in 3 ml. of water was adjusted to pH 9 with 20% sodium hydroxide, water was evaporated *in vacuo* and the residue treated with 3 ml. of ethanol. Sodium chloride was removed by suction filtration, the filtrate evaporated *in vacuo*, and the crude base refluxed 1 hour with 2 ml. of methyl dichloroacetate and 6 ml. of methanol. Solvent was removed *in vacuo* and the residue crystallized twice from water yielding 150 mg. 42% based on the hydrochloride III (R = H; R′ = H_2). A sample was recrystallized from water and melted at 192—193°.

Anal. $C_{12}H_{14}Cl_2N_2O_5S$ (369.23) calc'd: C 39.03; H 3.82; N 7.59%
found: C 38.95; H 4.04; N 7.44%

Threo-*1-p-nitrophenyl-1-acetoxy-2-phthalimido-3-methylsulfonylpropane*

1.0 g. (0.0023 mole) of *threo* - 1 - *p* - nitrophenyl - 1 - acetoxy - 2 - phthalimido - 3--methylsulfinylpropane (m.p. 213—214°) was refluxed for hour and a half with 1.4 ml. of 30% hydrogen peroxide and 5 ml. of glacial acetic acid. On cooling the

sulfone crystallized in prismatic crystals. Yield 0.97 g. (93.5%), m.p. 223—225°. A sample was recrystallized from ethanol and melted at 231—232°.

Anal. $C_{20}H_{18}N_2O_8S$ (446.36) calc'd: C 53.81; H 4.06; N 6.28%
found: C 53.71; H 4.08; N 6.15%

The sulfoxide III (R = CH_3CO; R′ = phthaloyl) with m. p. 193—196° was oxidized in the same manner yielding the identical sulfone as indicated by identical m.p. and mixed m.p. and identical infrared spectra.

Threo-*1*-p-*nitrophenyl-1-hydroxy-2-amino-3-methylsulfinyl-propane hydrochloride*

1.0 g. (0.0023 mole) of the sulfone IV (R = $COCH_3$; R′ = phthaloyl) was converted to the hydrochloride IV (R = H; R′ = H_2) by hydrazinolysis with 4 ml. of *M*-hydrazine hidrate in the same manner as described for the preparation of the sulfoxide derivative. The hydrochloride was obtained in 63.5% yield (455 mg), m.p. 207—208°.

Anal. $C_{10}H_{15}ClN_2O_5S$ (310.76) calc'd: C 38.65; H 4.86; N 9.02%
found: C 38.62; H 4.81; N 9.01%

Threo-*1*-p-*nitrophenyl-1-hydroxy-2-amino-3-methylsulfonylpropane*

A solution of 0.49 g. (0.0015 mole) of the hydrochloride IV (R = H; R′ = H_2) in 6 ml. of water was made alkaline with 20% sodium hydroxide and the crystalline precipitate was removed by suction filtration. After two crystallizations from methanol, 360 mg. (86%) of long needles was obtained, m. p. 171—172°.

Anal. $C_{10}H_{14}N_2O_5S$ (274.23) calc'd: C 43.80; H 5.15; N 10.23%
found: C 43.85; H 5.22; N 10.25%

Threo-*1*-p-*nitrophenyl-1-hydroxy-2-dichloroacetamido-3-methylsulfonyl -propane*

A. *By condensation with dichloroacetyl chloride*

Into a mixture of 0.20 g. (0.00073 mole) of the base IV (R = H; R′ = H_2) and 0.23 g. (0.0027 mole) of sodium bicarbonate in 0.5 ml. of water and 1.5 g. of ice was added dropwise during 20 minutes a solution of 0.16 g. (0.0011 mole) of dichloroacetyl chloride in 2 ml. of methylene dichloride. The reaction mixture was stirred for additional 30 minutes, the precipitate removed, washed with 20% acetic acid, and the crude dichloroacetamide recrystallized from ethanol followed by water. Yield 0.12 g. (43%), m.p. 150—151°. Further crystallization from water did not change the melting point.

Anal. $C_{12}H_{14}Cl_2N_2O_6S$ (385.23) calc'd: C 37.41; H 3.66; N 7.27%
found: C 37.35; H 3.70; N 7.19%

B. *By condensation with methyl dichloroacetate*

The sulfone base IV (R = H; R′ = H_2) (0.280 g., 0.001 mole) was refluxed for 5 hours with 0.5 ml. of methyl dichloroacetate in 25 ml. of methanol. The reaction mixture was cooled and 0.125 g. of the unreacted sulfone base was recovered by suction filtration. The filtrate was evaporated and the residue crystallized from 3 ml. of water yielding 0.1 g. of a product melting between 130—160°. Washing with 20% acetic acid afforded 37 mg. (10%) of dichloroacetamide IV (R = H; R′ = = $HCOCHCl_2$), m.p. 146—147°. After recrystallization from absolute ethanol, followed by crystallization from water the product had a constant melting point at 150—151°. In admixture with the product prepared under A, the m.p. was 150—151°.

C. *By oxidation of 1-p-nitrophenyl-1-hydroxy-2-dichloroacetamido- -3-methylsulfinylpropane*

The sulfoxide analogue of chloramphenicol (65 mg.) was refluxed for 2 hours with 0.2 ml. of 30% hydrogen peroxide in 2 ml. of glacial acetic acid, the solvent

evaporated *in vacuo*, and the residue crystallized from 2 ml. of water yielding 50 mg. (74%) of sulfone IV (R = H; R′ = $HCOCHCl_2$), m.p. and mixed m.p. with the product prepared under A and B was 150—151°. The infrared spectra of the products prepared under A, B, and C were identical.

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IZVOD

Sintetske studije u redu kloramfenikola. VI. Sinteza DL-*threo*-1-*p*-nitrofenil-1-hidroksi-2-dikloracetamido-3-metilsulfinil i 3-metilsulfonil propana

M. Fleš

Redukcijom α-ftalimido-β-metilmerkaptopropiofenona (I) s aluminijskim izopropilatom dobiven je preferentno *treo*-karbinol II koji je nakon toga uobičajenim nizom reakcija preveden u sulfoksidni i sulfonski analog kloramfenikola.

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