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Two Analogues of Chloramphenicol

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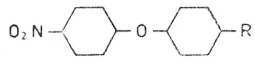
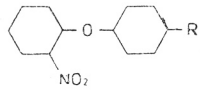
The preparation of D, L-*threo*-1-[*p*-(*p*'-nitrophenoxy)-phenyl]-2-dichloroacetamido-1,3-propanediol and D, L-*threo*-1-[*p*-(*o*'-nitrophenoxy)-phenyl]-2-dichloroacetamido-1,3-propanediol is described. Compared with chloramphenicol these compounds showed no interesting activity in antibacterial tests.

A considerable number of compounds in which various groups have been substituted for nitro group of chloramphenicol [D-(*threo*)-1-(*p*-nitrophenyl)-2-dichloroacetamido-1,3-propanediol] has been described hitherto[1—22]. Some of these compounds showed definite, although slighter antibiotic activity when compared with chloromycetin. Analogues of chloromycetin with phenoxy group instead of nitro group in para position showed no remarkable activity[9]. It was considered therefore of interest to prepare analogues of chloramphenicol in which the nitro group is replaced by nitrophenoxy radicals in para position. To prepare such compounds the procedure given by Long and Troutman[23] as a method for the preparation of chloramphenicol was followed. According to this procedure the nitrophenoxy-acetophenones I[24] and II[25] were converted to the corresponding nitrophenoxy-phenacylbromides III[26] and IV, and these reacted with hexamethylenetetramine to give their salts V resp. VI.





I, II R = —$COCH_3$

III, IV R = —$COCH_2Br$

V, VI R = —$COCH_2Br \cdot C_6H_{12}N_4$

VII, VIII R = —$COCH_2NH_2 \cdot HCl$

IX, X R = —$COCH_2NHCOCH_3$

XI, XII R = —$COCHCH_2OH$ (NHCOCH$_3$)

XIII, XIV R = —$CHCHCH_2OH$ (OH; NHCOCH$_3$)

XV, XVI R = —$CHCHCH_2OH$ (OH; $NH_2 \cdot HCl$)

XVII, XVIII R = —$CHCHCH_2OH$ (OH; $NHCOCHCl_2$)

Hydrolyzed with a mixture of ethanol and concentrated hydrochloric acid they gave nitrophenoxyphenacylamines as hydrochlorides (VII resp. VIII)

which were acetylated with acetic anhydride and sodium acetate. The acetamidoacetophenones (IX and X) thus obtained were methylolated with formaldehyde in presence of sodium hydrogen carbonate. The resulting nitrophenoxyacetamido-hydroxypropiophenones XI and XII were reduced by Meerwein-Ponndorf-Verley procedure to nitrophenoxyphenylacetamido propanediols XIII and XIV. Only a single racemate was obtained in each case in pure crystalline state from these reductions. It is considered that *threo* configuration can be assigned to the products obtained, since in all the examples reported until now, where the configuration of the isomers obtained by Meerwein-Ponndorf-Verley reduction is known, the *threo* isomer was the main product derived from analogous acetamido propanediols.

The hydrolysis of the acetamidopropanediols XIII and XIV was then effected to split off the acetyl group. The isolation of the hydrolysis products proceeded with some difficulties. In the case of the compound XIII the base XV was obtained from the crude hydrolyzate by purification of its dibenzoyltartarate. The base XVI, however, could not be obtained in the crystalline state, so it was used without purification in the next step. Heating of the bases with methyl dichloroacetate gave the expected analogues XVII and XVIII.

When compared with chloramphenicol for antimicrobial activity *in vitro*, the compound XVII showed only a slight effect on *Shigella Flexner II*, and no activity against *S. typhy abdominalis, S. paratyphy B* (Schotmüller) and *Escherichia coli*. The analogue XVIII showed no activity at all in these tests.

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EXPERIMENTAL

4-(4′-Nitrophenoxy)-acetophenone (I)

Acetyl chloride (21.4 g., 0.273 *M*) was added dropwise with stirring to a mixture of 57.9 g. (0.269 *M*) of *p*-nitrodiphenylether and 196 g. (1.47 *M*) of anhydrous aluminium trichloride in 350 ml. of carbon bisulphide heated to boiling. The stirring was continued for 1 hour under reflux. Carbon bisulphide was then distilled off and the residue dried in vacuo and quenched on 1200 g. of ice mixed with 450 ml. of concd. hydrochloric acid. The separated crystals were filtered off and dried; m. p. 76—78° C. After one crystallization from methyl alcohol 60 g. (I) (86.7% of the theoretical amount) with m. p. 81—82° C was obtained.

4-(2′-Nitrophenoxy)-acetophenone (II)

This compound was prepared in principally the same manner as the above one with the sole exception that the raction mixture was stirred for 2 hours after quenching. 45 g. (0.209 *M*) of *o*-nitrodiphenyl ether, 160 g. (1.2 *M*) of anhydrous aluminium trichloride and 15.7 g. (0.2 *M*) of acetyl chloride in 240 ml. of carbon bisulphide gave thus 48.8 g. of II (90.6% of the theoretical amount), m. p. 90—98°. After two crystallizations from methyl alcohol a product with m. p. 104—106° C was obtained in 70—80% yield.

4-(4′-Nitrophenoxy)-ω-bromoacetophenone (III)

To a stirred solution of 25.9 g. (0.1 *M*) of I in 500 ml. of methanol 19 g. (0.237 g. at.) bromine was dropwise added. The reaction mixture was left to stand 6 hours at room temperature and then concentrated by evaporation *in vacuo*. The separated crystals were filtered off, washed with water and dried on air. M. p. 94—97° C, recrystallized from methanol it melted at 99—101° C. Yield 30.2 g. (89% of the theoretical amount).

4-(2′-Nitrophenoxy)-ω-bromoacetophenone (IV)

Starting from II 4-(2'-nitrophenoxy)-ω-bromoacetophenone was prepared in 92.5% yield, by the same procedure as III; m. p. 69—75° C. For the analysis it was crystallized once from ethanol and four times from benzene, m. p. 77—77.2°C.

Anal. 18.32 mg. subst.: 33.44 mg. CO_2, 4.39 mg. H_2O
8.87 mg. subst.: 0.343 ml. N_2 (29° C, 757 mm. Hg)
38.2 mg. subst.: 5.5 ml. *N*/50 $AgNO_3$
$C_{14}H_{10}NO_4Br$ (336.14) calc'd.: C 50.02; H 3.00; N 4.17; Br 23.77%
found: C 49.81; H 2.98; N 4.35; Br 23.45%

Hexamethylenetetramine salt of 4-(4′-nitrophenoxy-ω-bromoacetophenone (V)

Hexamethylenetetramine (14.5 g., 0.103 *M*) was dissolved in 400 ml. of fresh distilled chlorobenzene and 34.2 (0.102 *M*) of III added in portions with stirring. The reaction mixture was stirred on a water bath for two hours at 50° and additional three hours at room temperature. The separated crystals were filtered off, slurried with 400 ml. of abs. ethanol and left stand for 30 min. at room temperature. After filtration the crystals were washed with 100 ml. of ethanol and dried in a desiccator. M. p. 155—157°C. After one crystallization from ethanol the m. p. rose to 158—159°C. Yield 44 g., i. e. 90.2% of the theoretical amount.

Hexamethylenetetramine salt of 4-(2′-nitrophenoxy)-ω-bromoacetophenone (VI)

A solution of 17 g. (1.21 *M*) hexamethylenetetramine in 60 ml. of chlorobenzene was added with stiring to 36 g. (0.107 *M*) IV dissolved in 120 ml. of chlorobenzene This mixture was warmed to 50°C for two hours, the stirring continued for three hours at room temperature and cooled to 5°C. The separated crystals were filtered off, mixed with 70 ml. of alcohol and left stand 30 min. After filtration and washing with 40 ml. of alcohol 46.8 g. of crystals were obtained (i. e. 91.8% of the theoretical amount) with m. p. 153—156°C. Recrystallized from alcohol it melted at 157—158° C (corr. decompn).

Hydrochloride of 4-(4′-nitrophenoxy)-ω-aminoacetophenone (VII)

89.3 g. (0.187 *M*) od the hexamethylenetetramine salt of 4-(4'nitrophenoxy)-ω-bromoacetophenone was stirred with 160 ml. of alcohol and 44 ml. of concentrated hydrochloric acid for 16 hours at room temperature, the mixture cooled to 8° C and filtered. The obtained crystals were slurried with 160 ml. of water, cooled to 10° C and filtered. 44 g. (76% of the theoretical amount) of crystals with m. p. 163—165°C (decompn.) was obtained. Recrystallization from 50% alcohol with addition of some hydrochloric acid rose the m. p. to 165—168°C.

Anal. 13.76 mg. subst.: 27.34 mg. $C0_2$, 5.53 mg. H_2O
5.353 mg. subst.: 0.392 ml. N_2 (19° C, 764 mm. Hg).
$C_{14}H_{13}N_2O_4Cl$ (308.72) calc'd.: C 54.46; H 4.24; N 9.07%
found: C 54.22; H 4.49; N 8.61%

Hydrochloride of 4-(2′-nitrophenoxy)-ω-aminoacetophenone (VIII)

This compound was prepared in essentially the same way as described for VII in 75.4% yield. M. p. 195° C (corr. decompn.) after crystallization from alcohol.

Anal. 29.9 mg. subst. 4.75 ml. 0.02 *N* $AgNO_3$
32.9 mg. subst. 5.25 ml. 0.02 *N* $AgNO_3$
$C_{14}H_{13}N_2O_4Cl$ (308.72) calc'd: Cl.11.49%
found: Cl 11.50; 11.54%

4-(4'-Nitrophenoxy)-ω-acetamidoacetophenone (IX)

To a mixture of 35.6 g. (0.115 *M*) of the hydrochloride VIII, 160 g. ice and 100 ml. water 25 g. (0.245 *M*) of acetic anhydride was dropwise added with stirring. After all the acetic anhydride was added a solution of 35 g. sodium acetate in 160 ml. of water was dropped in and the stirring continued for three hours during which time the reaction mixture attained the room temperature. It was then acidified with hydrochloric acid, the separated product filtered off, washed with 300 ml. of water and dried on air. 35 g. (96.5% of the theoretical amount) of IX was obtained with m. p. 153—158°C. Crystallized for analysis from ethyl acetate it melted at 159—160° C (corr.).

Anal. 2.422 mg. subst.: 0.186 ml. N_2 (23° C, 766 mm. Hg).
$C_{16}H_{14}O_5N_2$ (314.29) calc'd: N 8.91%
found: N 8.92%

The thiosemicarbazone was prepared in the usual manner. Its m. p. was 218—220° C (corr.) when crystallized from 60% acetic acid.

Anal. 15.7 mg. subst.: 30.68 mg. CO_2, 6.34 mg. H_2O
$C_{17}H_{17}O_4N_5S$ (387.41) calc'd: C 52.70; H 4.42%
found: C 52.43; H 4.51%

4-(2'-Nitrophenoxy)-ω-acetamidoacetophenone (X)

This compound was prepared in 80% yield by the same procedure as the preceeding substance starting from the hydrochloride of 4-(2'-nitrophenoxy)-ω-aminoacetophenone. Crystallized from ethyl acetate it melted at 143° C (corr.).

Anal. 17.48 mg. subst.: 39.02 mg. CO_2, 6.85 mg. H_2O
3.50 mg. subst.: 0.274 ml. N_2 (23° C, 755 mm. Hg)
$C_{16}H_{14}O_5N_2$ (314.29) calc'd.: C 61.14; H 4.49; N 8.91%
found: C 60.92; H 4.38; N 8.96%

4-(4'-Nitrophenoxy)-α-acetamido-β-hydroxypropiophenone (XI)

Sodium bicarbonate was added with stirring to a mixture of 48.7 g. (0.155 *M*) of 4-(4'-nitrophenoxy)-ω-acetamidoacetophenone, 210 ml. ethanol and 23.3 ml. (0.31 *M*) 37% formaldehyde until slightly alcaline. The reaction mixture was then warmed to 38—40° C and the stirring continued for two hours. After cooling to 5° C the separated crystals were filtered off, washed with 120 ml. water and dried. Yieud 43.8 g. (82.8% of the theoretical amount) m. p. 143—145.6° C. After two crystallizations from ethyl acetate it melted at 146—147.5° C (corr.).

Anal. 19.04 mg. subst.: 41.17 mg. CO_2 7.8 mg. H_2O
5.251 mg. subst.: 0.353 ml. N_2 (14° C, 764 mm. Hg)
$C_{17}H_{16}O_6N_2$ (344.31) calc'd.: C 59.30; H 4.68; N 8.14%
found: C 59.01; H 4.58; N 8.03%

The p-nitrobenzoate of XI was prepared in the usual manner and crystallized from 50% ethanol; m. p. 159—160.5° C (corr.).

Anal. 4.025 mg. subst.: 0.304 ml. N_2 (24° C, 749 mm. Hg)
$C_{24}H_{19}O_9N_3$ (493.42) calc'd.: N 8.52%
found: N 8.55%

4-(2'-Nitrophenoxy)-α-acetamido-β hydroxypropiophenone (XII)

To a mixture of 50.43 g. (0.16 *M*) of 4-(2'-nitrophenoxy)-ω-acetamidoacetophenone, 24.7 ml. (0.329 *M*) 37% formaldehyde and 325 ml. ethanol sodium bicarbonate was added until alcaline. The resulting mixture was warmed to 38—40° C for two hours, cooled, diluted with 400 ml. water and extracted with three 150 ml. portions of chloroform. The chloroform solution was dried with sodium sulphate and distilled. The residue was crystallized from ethyl acetate to yield 48.6 g. (88.3% of theoretical

amount) of white needles with m. p. 118—122° C. Recrystallized from ethyl acetate it melted at 125—127° C (corr.)

Anal. 10.80 mg subst.: 23.45 mg. CO_2 4.37 mg. H_2O
3.18 mg. subst.: 0.235 ml. N_2 (30° C, 755 mm. Hg)
$C_{17}H_{16}O_6N_2$ (344.31) calc'd.: C 59.30; H 4.68; N 8.14%
found: C 59.25; H 4.52; N 8.27%

The p-nitrobenzoate of XII was prepared in the usual manner and crystallized from 50% ethanol; m. p. 176—177° C (corr.).

Anal. 3.40 mg. subst.: 0.265 ml. N_2 (30° C, 755 mm. Hg)
$C_{24}H_{19}O_9N_3$ (493.42) calc'd.: N 8.52%
found: 6 8.72%

D, L-threo-*1-[p-(p'-nitrophenoxy)-phenyl]-2-acetamido-1,3-propanediol* (XIII)

4-(4'-nitrophenoxy) - α - acetamido - β - hydroxy propiophenone (XI) (38.6 g., 0.112 *M*) was added to a warm solution of 44 g. (0.216 *M*) of aluminium isopropoxide in 220 ml. anhydrous isopropyl alcohol. The resulting mixture was heated to the boiling point and the acetone formed distilled off through a Hahn column. 110 ml. of isopropyl alcohol was then distilled off and the remaining slurry mixed with 50 ml. water and heated for 15 min. under reflux. The aluminium hydroxide formed was filtered off, washed with 60 ml. of isopropyl alcohol, extracted with a mixture of 110 ml. isopropyl alcohol and 40 ml. of water and filtered again. The filtrates were evaporated to dryness and 80 ml. of ethyl acetate was added to the residue. After cooling 15.6 g. (40% of the theoretical amount) of XIII with m. p. 169—171° C separated. Crystallized from ethyl acetate it melted at 174—175.5°C (corr.).

Anal. 14.2 mg. subst.:30.68 mg. CO_2 6.64 mg. H_2O
6.728 mg. subst.: 0.49 ml. N_2 23°C, 757 mm. Hg)
$C_{17}H_{18}O_6N_2$ (346.33) calc'd.: C 58.95; H 5.24; N 8.09%
found: C 58.79; H 5.21; N 8.36%

D, L-threo-*1-[p-(o'-nitrophenoxy)-phenyl]-2-acetamido-1,3-propanediol* (XIV)

The reduction of 4-(2'-nitrophenoxy)-α-acetamido-β-hydroxypropiophenone with aluminium isopropoxide performed as described for XIII gave XIV in a 49.8% yield; m. p. 176—177.2° C (corr.) after crystallization from ethyl acetate.

Anal: 13.86 mg. subst.: 29.81 mg CO_2 6.80 mg. H_2O
3.49 mg. subst.: 0.245 ml. N_2 (24° C, 757 mm. Hg)
$C_{17}H_{18}O_6N_2$ (346.33) calc'd.: C 58.95; H 5.24; N 8.09%
found: C 58.69; H 5.49; N 8.03%

D, L-threo-*1-[p-(p'-nitrophenoxy)-phenyl]-2-amino-1,3-propanediol* (XV)

A suspension of 2 g. (0.0058 *M*) D,L-*threo*-1-[*p*-(*p'*-nitrophenoxy)-phenyl]-2-acetamido-1,3-propanediol (XIII) in 25 ml. 5% hydrobromic acid was heated for a few minutes on a water bath until it cleared and the heating was then continued for one hour. The resulting solution was cooled, decolorized with charcoal, neutralized with 10% ammonia solution and extracted with three 20 ml. portions of chloroform. The extracts were dried on potassium carbonate and evaporated. The residual oil (1,6 g., 94.1% of the theoretical amount) was dissolved in 14 ml. acetone and mixed with a solution of 2 g. dibenzoyl tartaric acid in 20 ml. acetone and kept warm for 15 min. After cooling 1.9 g. of dibenzoyl tartarate of D,L-*threo*-1-[*p*-(*p'*-nitrophenoxy)-phenyl] - 2 - amino-1,3-propanediol with m. p. 182—183.5° C separated. After crystallization from 50% ethanol it melted at 186.5—187.5° C (corr.). This was suspended in 30 ml. of water and neutralized with 10% ammonia. The separated oil was extracted with chloroform, the extracts were dried, concentrated and petroleum ether added. After standing 0.5 g (30%) crystals with m. p. 122—123° separated. Recrystallized from chloroform-petroleum ether

D,L - *threo* - 1 - [*p* - (*p'* - nitrophenoxy) - phenyl] - 2 - amino-1,3-propanediol melted at 123—124.5° C.

Anal. 14.33 mg. subst.: 30.94 mg. CO_2; 6.53 mg. H_2O
5.20 mg. subst.: 0.421 mg. N_2 (22° C, 756 mm. Hg)
$C_{15}H_{16}O_5N_2$ (304.29) calc'd.: C 59.20; H 5.30; N 9.21%
found: C 58.92; H 5.10; N 9.31%

The picrate was prepared by addition of sodium picrate solution to a solution of XV-hydrobromide. This was prepared by hydrolysis of the 1-[*p*-(*p'*--nitrophenoxy)-phenyl]-2-acetamido-1,3-propanediol with 5% hydrobromic acid, evaporation *in vacuo* and addition of acetone to the residue. Crystallized from aqueous ethanol the picrate melted at 195—197°C (corr.) with decomposition.

Anal. 14.77 mg. subst.: 25.43 mg. CO_2 4.63 mg. H_2O
8.70 mg. subst.: 0.99 ml. N_2 (21° C, 757 mm. Hg)
$C_{21}H_{19}N_5O_{12}$ (533.40) calc'd.: C 47.28; H 3.59; N 13.13%
found: C 46.98; H 3.50; N 13.20%

The acid oxalate was prepared in the usual manner. Crystallized from aqueous methanol it melted at 200—203° C.

Anal. 13.61 mg. subst.: 25.73 mg. CO_2 5.41 mg. H_2O
3.07 mg. subst.: 0.186 ml. N_2 (25°C, 758 mm. Hg)
$C_{17}H_{18}O_9N_2$ (394.33) calc'd.: C 51.78; H 4.61; N 7.10%
found: C 51.59; H 4.44; N 6.92%

Hydrochloride of D,L-threo-*1*-[p-(o'-*nitrophenoxy*)-*phenyl*]-*2-amino--1,3-propanediol* (XVI)

A mixture of 1 g. D,L-*threo*-1-[*p*-(o'-nitrophenoxy)-phenyl]-2-acetamido-1,3--propanediol (XIV), 10 ml. conc. hydrochloric acid and 20 ml. of water was heated on a water bath unitil it cleared, evaporated *in vacuo* to about 15 ml. and left to stand for two days. 0.73 g. (76% of the theoretical amount) of white crystals with m. p. 165—170° C was obtained, which after three crystallizations from ethanol melted at 185—186° C (corr.).

Anal. 2.18 mg. subst.: 0.157 ml. N_2 (26° C, 755 mm. Hg)
$C_{15}H_{17}O_5N_2Cl$ (340.76) calc'd.: N 8.22%
found: N 8.16%

D,L-threo-*1*-[p-(p'-*nitrophenoxy*)-*phenyl*]-*2-dichloroacetamido-1,3-propanediol* (XVII)

D,L-*threo*-1-[*p*-(o'-nitrophenoxy)-phenyl]-2-amino-1,3-propanediol (XV) (0.8 g., 0.0026 *M*) was heated two hours with 2 g. methyl dichloroacetate on a water bath. The reaction mixture was extracted with three 10 ml. portions of petroleum ether and the residual oil dissolved in chloroform. Petroleum ether was added to the chloroform solution and after two days 0.67 g. (61.4% of the theoretical amount) of white crystals were collected; m. p 141—144° C. After crystallization from chloroform-petroleum ether it melted at 148—149° C (corr.).

Anal. 13.29 mg. subst.: 23.9 mg. CO_2 4.49 mg. H_2O
6.58 mg. subst.: 0.386 ml. N_2 (22° C, 758 mm. Hg)
$C_{17}H_{16}O_6N_2Cl_2$ (415.23) calc'd.: C 49.17; H 3.88; N 6.75%
found: C 49.07; H 3.78; N 6.77%

D,L-threo-*1*-[p-(o'-*nitrophenoxy*)-*phenyl*]-*2-dichloroacetamido-1,3--propanediol* (XVIII)

A clear solution obtained by heating 1 g. D,L-*threo*-1-[*p*-(o'-nitrophenoxy)--phenyl]-2-acetamido-1,3-propanediol with 30 ml. 12% hydrochloric acid during one hour an a water bath was neutralized with ammonia and extracted with three

20 ml. portions of chloroform. The extracts were dried over potassium carbonate and evaporated to dryness. The residual oily base (0.55 g. 62.6% of the theoretical amount) was heated to 100—110° C for two hours with 2 ml. of methyl dichloroacetate. The resulting mixture was cooled and extracted with three 10 ml. portions of petroleum ether and the residual oil dissolved in benzene. This solution was passed through a column of neutral alumina and the obtained runnings evaporated to dryness. The residual oil was dissolved in warm methylene dichloride and left overnight. 0.7 g. (58% of the theoretical amount) of crystals with m.p. 146—155°C separated. After five crystallizations from methylene dichloride the melting point rose to 157—159.5° C.

Anal. 12.96 mg. subst.: 23.43 mg. CO_2 4.31 mg. H_2O
2.28 mg. subst.: 0.137 ml. N_2 (26° C, 753 mm. Hg)
$C_{17}H_{16}O_6N_2Cl_2$ (415.23) calc'd.: C 49.17; H 3.88; N 6.75%
found: C 49.33; H 3.72; N 6.79%

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Dva analoga kloramfenikola

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Polazeći od *p*- odnosno *o*-nitrofenoksiacetofenona pripremljeni su D,L-*treo*-1-[*p*-(*p'*-nitrofenoksi)-fenil]-2-dikloracetamidopropandiol-1,3- (XVII) i D,L-*treo*-1-[*p*-(*o'*-nitrofenoksi)-fenil]-2-dikloracetamidopropandiol-1,3 (XVIII), i to postupkom, što su ga za pripravu kloramfenikola dali Long i Troutman.[23] Pri usporedbi s kloramfenikolom nisu spojevi XVII i XVIII pokazali neko značajno djelovanje na mikroorganizme.

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