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SYNTHESIS OF CHLORAMPHENICOL *VIA* A NEW INTERMEDIATE 4-*PARA*-NITROPHENYL-5-FORMAMIDO-1,3-DIOXANE

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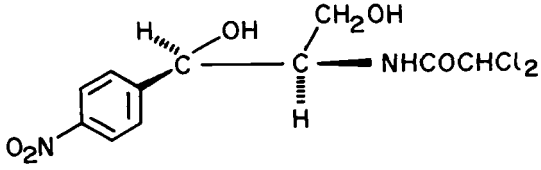
Abstract: *4-Phenyl-5-amino-1,3-dioxane 4, obtained from β-bromo styrene 2 was protected as formamido derivative 5. Nitration of 5 followed by regioselective acylative cleavage of the nitro product 12 gave N-formyl-N-acetyl hemiacetal diacetate 16, which on sequential base and acid hydrolysis followed by dichloroacetylation gave chloramphenicol 1.*

Chloramphenicol **1**, a broad spectrum antibiotic[1] was isolated from aerobic broth culture of an actinomycete *Steptomyces Venezuelae*, in 1947. It is widely used for treatment of typhoid, dysentery and bacterial infections of eye. This antibiotic is made commercially by chemical syntheses[2].



CHLORAMPHENICOL

1

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In one of the routes for the synthesis of chloramphenicol **1**, Prins reaction is carried out[3,4] on β-bromo styrene **2** to offord 4-phenyl-5-bromo-1,3-dioxane **3** (**Scheme 1**). 4-Phenyl-5-amino-1,3-dioxane **4**, obtained from **3** was protected as dichloroacetamido derivative **6**, which on nitration gave the nitro compound **15**. The compound **15** on further elaboration furnished chloramphenicol **1**[5].

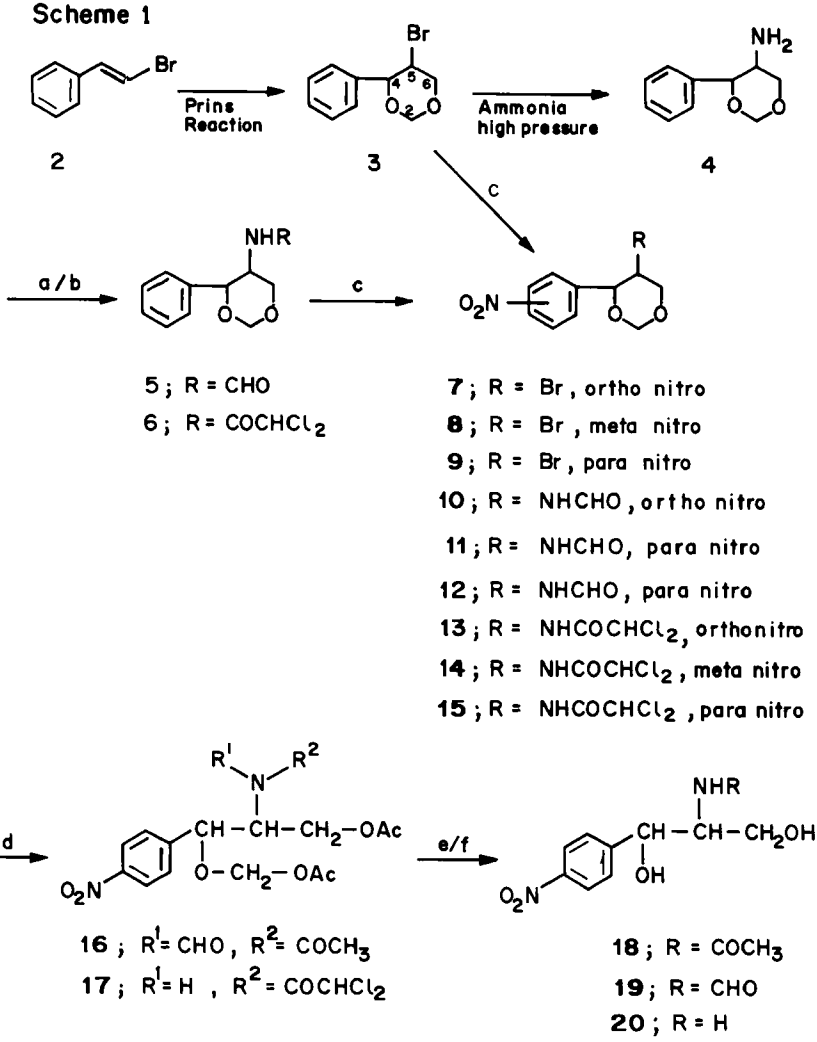
We have carried out a detailed study of nitration[6] of compounds **3**, **5** and **6** which are intermediates in the synthesis of chloramphenicol **1**. All the three compounds studied gave mixture of *ortho*, *meta* and *para* nitro products in varying proportions. The composition of the nitro products are: Compound **3** gave *ortho* **7** (31%), *meta* **8** (30%) and *para* **9** (38%); Compound **5** gave *ortho* **10** (24%), *meta* **11** (17%) and *para* **12** (58%); Compound **6** gave *ortho* **13** (35%), *meta* **14** (19%) and *para* **15** (46%). Among these three compounds formamido derivative **5** gave the highest amount of the required *para* isomer **12**(58%).

We wish to report here a new strategy for the synthesis of chloramphenicol **1**, following the reaction sequence i) formylation of amino dioxane **4** to get the formamido derivative **5**; ii) nitration of compound **5** to afford 4-*para*-nitrophenyl-5-formamido-1, 3-dioxane **12**; iii) cleavage of dioxane ring of cyclic formal **12** to obtained **16** and iv) conversion of **16** to chloramphenicol **1**.

4-Phenyl-5-formamido-1, 3-dioxane **5**, was prepared in almost quantitative yield from amino dioxane **4** using ethyl formate. Nitration of **5** with fuming nitric acid at 10°C furnished a mixture of all the three nitro products *ortho*, *meta* and *para* in 95% yield. The pure *para* nitro product **12**, was obtained in 56% yield by crystallization from this mixture.

Regioselective acylative cleavage of cyclic formal **15**, under acid catalyst, is known[5] to give only one regioisomer **17** in 97% yield which on hydrolysis with methanol-aqueous ammonia furnished chloramphenicol **1** (90%).

Scheme 1

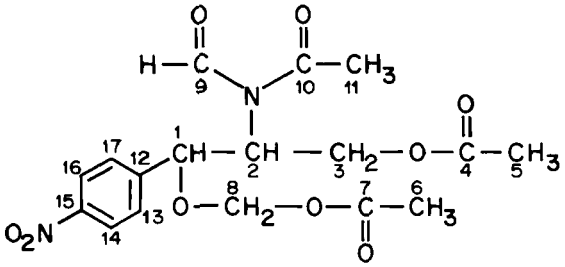


a) Ethyl formate / Reflux / 13h ; b) Dichloroketene[6] / $CHCl_3$ / 0°C / 0·5 h;

c) Fuming HNO_3 / $CHCl_3$ / 0°C – 10°C / 1·5 h ; d) PTSA / Ac_2O

e) CH_3OH / NH_4OH ; f) Methanolic HCl

Compound **12** on similar treatment with acetic anhydride in the presence of *p*-toluene sulphonic acid furnished compound **16** having N-acyl and N-formyl hemiacetal as crystalline solid, mp 134°C in 88% yield. Structure **16** for this compound was confirmed by ^{1}H, ^{13}C NMR spectroscopy, elemental analysis and mass spectroscopy.



16

Characteristic ^{1}H-NMR signals for compound **16** are; δH 1.82 ($CO\underline{CH_3}$, C-4), 1.96 ($CO\underline{CH_3}$, C-6), 2.5 ($CO\underline{CH3}$, C-11) and 9.16 ($\underline{CH}O$, C-9). ^{13}C-NMR Accounts for seventeen carbons and it shows four separate signals for carbonyl groups; δC 170.94 ($NCOCH_3$, C-10) 169.4 and 169.1 ($OCOCH_3$ of C-4 and C-7) and 162.36 (NCHO, C-9).

Compound **16** on reaction with methanol-aqueous ammonia afforded a mixture of two products **18** and **19** in 95% yield. These two products were separated by crystallization in 59 and 26% respectively. Compound **18** and **19** as a mixture or separately, on treatment with methanolic hydrogen chloride gave 1-*para*-nitrophenyl-2-amino propane 1, 3-diol **20**; mp 140-141°C (lit.[2a]141-142°C) in good yield. The conversion of **20** to chloramphenicol **1** has been carried out[2a] using methyl dichloroacetate.

EXPERIMENTAL

All the mp and bps are uncorrected. IR spectra were recorded on a Perkin Elmer 599B spectrophotometer using NaCl optics. ^{1}H NMR were recorded either at 80 MHz on Varian FT-80A or at 90 MHz on a Bruker WH-90 NMR specrophotometer. Chemical shifts are recorded in ppm (δ) using TMS as internal standard and coupling constants were expressed in Hz. Mass spectra were recorded on Finnigan Mat 1020C mass spectrometer at 70 ev. GLC was recorded on Carlo-Erba: Fracto-vap No 2450, Column: Apizone L 5% on 80-100 mesh Chromosorb WHP at 235°C, Integrater: 3390A Hewlett-Peckard, Carrier gas: Nitrogen, Flow rate: 35 ml/ min, detector: FID. The reactions were monitored by TLC using TLC aluminium sheets, silica gel 60 F_{254} precoated, Merck, Germany and locating the spots spraying with ethanolic solution of phosphomolybdic acid followed by heating and also by UV light.

cis (±)-4-Phenyl-5-formamido-1, 3-dioxane 5

A mixture of *cis* (±) 4-Phenyl-5-amino-1, 3-dioxane **4** (1.01g, 5.7 mmol) bp 95°C/ 0.4mm (lit[2e] bp 100°C/ 0.4mm) and ethyl formate (4ml) was refluxed for 13 h. Ethyl formate was removed under vacuum and the crude product was distilled at 180-185°C/ 0.7mm to furnish a pure material 1.2g, 96% which was solidified; mp 101-102°C (ethyl acetate-hexane); νmax (nujol)/ cm^{-1} 3310 (NH), 1675 (NHCO); δH ($CDCl_3$) 4.05 (d, 2H, CH_2-6, J=2HZ), 4.4 (m, 1H, CH-5), 4.95 (d, 1H, CH-4, J=3Hz), 4.9 and 5.2 (AB pattern, 2H, CH-2, J=6Hz), 6.45 (bd, 1H, NH), 7.28 (s, 5H, Ar), 7.92 (s, 1H, CHO); m/z 207 (m^+), 177, 162, 132, 118, 105, 91, 77.

cis (±) 4-*para*-Nitrophenyl-5-formamido-1, 3-dioxane 12

A 50 ml two necked flask equipped with magnetic stirring bar, pressure equalized addition funnel and a thermometer was charged with fuming nitric acid (8 ml, 193 mmol, d=1.52). It was cooled to -20°C and a solution of (±)-**5** (4g, 19.3 mmol) in dry chloroform (15 ml) was added during 20 minutes maintaining the temperature at -20 to -15°C. The temperature was allowed to raise to 10°C and it was stirred at this temperature for 1.5 h. Reaction mixture was then poured over ice and extracted with chloroform. Chloroform solution was washed successively with water (2x50 ml), saturated sodium bicarbonate solution (2x50 ml), water (2x50 ml), and

brine. It was dried over anhydrous sodium sulphate and solvent was removed under vacuum to furnish a mixture of isomeric nitro products (4.62g, 95%). GLC analysis of this product shows that it is a mixture of *ortho* **10** (24.7%), *meta* **11** (16.9%) and *para* **12** (58.3%). This mixture on crystallization with chloroform-hexane furnished pure *para* isomer **12** (2.4g, 56%); mp 159°C; vmax (nujol)/ cm^{-1} 3220 (NH), 1680 (NHCO), 1650, 1160; δH ($CDCl_3$) 4.06 (d, 2H, CH_2-6, J=2Hz), 4.5 (m, 1H, CH-5), 5.04 (bs, 1H, CH-4), 4.96 and 5.26 (AB pattern, 2H, CH_2-2, J=7Hz), 6.24 (bd, 1H, NH), 7.92 (s, 1H, CHO) 7.44 and 8.15 (AB pattern, 4H, Ar, J=8Hz); m/z 222 (M^+-CH_2O), 101, 71 (100%); Found: C, 52.45; H, 4.91; N, 10.78%. $C_{11}H_{12}N_2O_5$ require C, 52.38; H, 4.8; N, 11.11%.

***threo* (±)-1-Acetoxymethoxy-3-acetoxy-2-(N-formyl-N-acetyl)amino-1-*para*-nitrophenyl propane 16**

A mixture of (±) **12**-(1.01g, 4 mmol), acetic anhydride (8 ml) and *p*-toluene sulphonic acid (0.06g) was heated at 100-110°C for 10 h with stirring. The reaction mixture was then poured on ice and extracted with ethyl acetate. The ethyl acetate extract was washed successively with water (2x50 ml), saturated sodium bicarbonate solution (2x50 ml), water (2x50 ml), and brine(2x50 ml). It was dried over anhydrous sodium sulphate and solvent was removed under vacuum to furnish (±) hemiacetal diacetate as a solid(1.7g). This was crystallised from chloroform-methanol to afford pure (±) **16**(1.4g, 88%); mp 134°C ; vmax (nujol)/ cm^{-1} 1750 ($OCOCH_3$), 1680 (NHCO), 1525, 1225, 755; δH ($CDCl_3$) 1.82 (s, 3H, $OCOCH_3$), 1.96 (s, 3H, CH_2OCOCH_3), 2.5 (s, 3H, $NCOCH_3$), 3.82- 4.49 (m, 3H), 4.77 and 5.18 (AB pattern, 2H, J=6Hz), 4.31 (d, 1H, J=10Hz), 7.62 and 8.27 (AB pattern, 4H, Ar, J=8Hz), 9.16 (s, 1H, CHO); m/z 307 (M^+-OCH_2OCOCH_3), 279, 265, 237, 153, 88, 84 (100%), 71; δC ($CDCl_3$) 170.94 (C-10, $NCOCH_3$), 169.4 and 169.18 (C-4 and C-7 CO), 162.36 (C-9, N-CHO), 147.84 (C-15, *ipso*-NO_2), 144.32 (C-12, *ipso*), 128.48 (C-14 and C-16 *ortho* to NO_2), 123.2 (C-13 and C-17 *meta* to NO_2), 84.92 (C-6, OCH_2), 75.24 (C-1, benzylic), 59.85 (C-3, CH_2), 55.44 (C-2, CH-N), 22.44 (C-11, $NCO\underline{CH_3}$), 19.8 (C-8, OCH_2-$OCO\underline{CH_3}$), 19.38 (C-5, $OCO\underline{CH_3}$); Found: C, 51.23; H, 5.22; N, 6.74%. $C_{17}H_{20}N_2O_9$ require C, 51.52; H, 5.05; N, 7.07%.

***threo* (±)-N-(2-Hydroxy)-1-(hydroxymethyl)-2-[(*para*-nitrophenyl)ethyl]acetamide 18 and *threo* (±)-N-(2-hydroxy)-1-(hydroxymethyl)-2-[(*para*-nitrophenyl) ethyl] formamide 19**

A mixture of compound (±) **16** (0.4g, 0.096 mmol) in chloroform (3 ml), methanol (15 ml) and ammonium hydroxide (15 ml, 25%) was stirred at room temperature for 3 h. Solvents were removed under vacuum and the residue was extracted with ethyl acetate. The ethyl acetate extract was washed with water and brine, dried over anhydrous sodium sulphate and solvent was removed to get a mixture of compound **18** and **19**, 0.280g,95%. It was crystallised from ethylacetate-acetone. Compound **18** was obtained as crystalline solid(0.172g, 59%); mp 159-160°C (lit.[2a] mp 159-164°C); νmax (nujol)/ cm^{-1} 3360 (OH), 3220, 1670 (NHCO), 1530, 1465, 1380; δH (d_6 acetone) 1.76 (s, 3H), 2.82 (s, 2H, OH), 3.64 (m, 2H), 4.09 (m, 1H), 5.18 (d, 1H), 7.0 (bd, 1H, NH), 7.67 and 8.16 (AB pattern, 4H, Ar, J=8Hz); Found: C, 52.24; H, 5.70; N, 11.58%. $C_{11}H_{14}N_2O_5$ require C, 51.92; H, 5.55; N, 11.02%. The mother liquor on column chromatography purification afforded compound **19** as viscus oil (0.078g,26 %); νmax (nujol)/ cm^{-1} 3520 (OH), 3220, 1650 (NHCO), 1510, 1460, 1375; δH (d_6 acetone) 3.91 (s, 2H, OH), 3.73 (m, 2H), 4.24 (m, 1H), 5.24 (d, 1H, J=2Hz), 7.27 (bd, 1H, NH), 7.71 and 8.24 (AB pattern, 4H, Ar, J=8Hz), 8.07 (s, 1H, CHO).

***threo* (±)-1-*para*-Nitrophenyl-2-amino-1, 3-propanediol 20**

A mixture of **18** and **19** (0.4g) and 5% methanolic HCl (10 ml) was refluxed for 3 h. Methanol was removed completely and the residue was extracted with ethyl acetate. Ethyl acetate extract was washed successively with water (2x25 ml), cold sodium bicarbonate solution (2x25 ml), water (2x25 ml) and brine and was dride over anhydrous sodium sulphate. Solvent was removed to get crude product which was crystallised from methanol to get pure diol **20** (0.295g). The tlc, IR, ^1H NMR of this compound was identical with the authentic[5] sample prepared earlier.

(±) Chloramphenicol 1

A mixture of Compound **20** (0.260g, 1.2 mmol) and methyl dichloroacetate (2 ml,20 mmol) was heated at 100 to 110°C for 2h. Solvent was removed to get crude

product which was crystallised from ethyl acetate-hexane to get pure (±) chloramphenicol **1** (0.376g, 95%); mp 148-149°C (lit.[2a,5] 150-151°C and 144°C). It was identical in all respects with the authentic[5]sample.

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6. Hazra, B.G., Pore, V.S. and Maybhate, S.P., (Unpublished work, Nitration of compounds **3**, **5** and **6** were carried out with fuming nitric acid in chloroform, and the percentage of ortho, meta, para products were evaluated by GC analysis. All these products were fully characerised by 1H NMR, mass spectral and by C, H, N microanalysis).

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