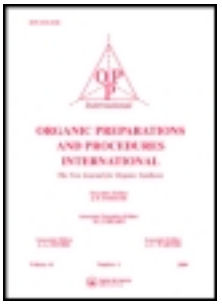

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NITRATION STUDIES ON 4-PHENYL-5-SUBSTIUTED-1,3-DIOXANES AS CHLORAMPHENICOL INTERMEDIATES

B. G. Hazra [a] , V. S. Pore [a] , S. P. Maybhate [a] , B. V. Bapat [a] , V. K. Gumaste [a] & A. S. Rao [a]

[a] Organic Chemistry Synthesis Division, National Chemical Laboratory, Pune, 411008, India

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OPPI BRIEFS

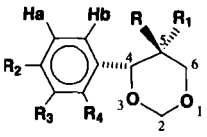
NITRATION STUDIES ON 4-PHENYL-5-SUBSTITUTED-1,3-DIOXANES AS CHLORAMPHENICOL INTERMEDIATES

Submitted by (06/30/98)

B. G. Hazra*, V. S. Pore, S. P. Maybhate, B. V. Bapat, V. K. Gumaste and A. S. Rao

Organic Chemistry Synthesis Division, National Chemical Laboratory Pune 411008, INDIA

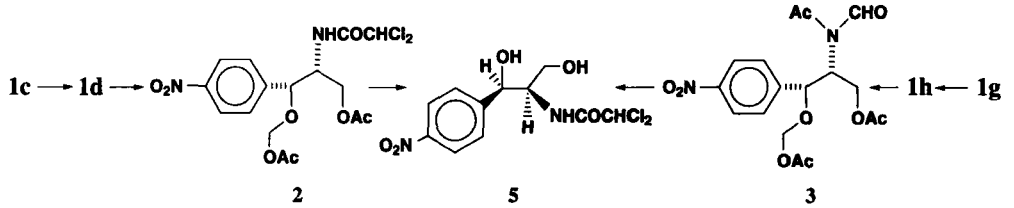
Chloramphenicol (**5**), a broad spectrum antibiotic,[1] isolated from the aerobic broth culture of an actinomycete, *Steptomyces Venezuelae*, is widely used for the treatment of typhoid, dysentry and bacterial eye infections. Among the several routes[2] for the synthesis of **5**, 4-phenyl-5-bromo-1,3-dioxane (**1a**), which may be obtained by the Prins reaction[2g,3] of β-bromostyrene with formaldehyde,



1a-h

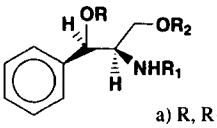
a) R = Br, R_1, R_2, R_3, R_4 = H
b) R, R_2, R_3, R_4 = H; R_1 = NH_2
c) R, R_2, R_3, R_4 = H; R_1 = NHCOCHCl$_2$
d) R, R_3, R_4 = H; R_1 = NHCOCHCl$_2$; R_2 = NO_2
e) R, R_2, R_3 = H; R_1 = NHCOCHCl$_2$; R_4 = NO_2
f) R, R_2, R_4 = H; R_1 = NHCOCHCl$_2$; R_3 = NO_2
g) R, R_2,R_3, R_4 = H; R_1 = NHCHO
h) R, R_3, R_4 = H; R_1 = NHCHO; R_2 = NO_2
i) R_1, R_3, R_4 = H; R = Br; R_2 = NO_2

appeared attractive as a starting material. A similarly attractive candidate for nitration to **1d** was 4-phenyl-5-dichloroacetamido-1,3-dioxane (**1c**, obtained[4] in 98% yield from the corresponding amino-dioxane **1b**) in which the two hydroxy and the amino groups of 1-phenyl-2-amino-1,3-propanediol are protected. We previously described[4] the regioselective acylative cleavage of 4-(*p*-nitrophenyl)-5-dichloroacetamido-1,3-dioxane (**1d**) with acetic anhydride and *p*-toluenesulfonic acid to furnish hemi-acetal **2** in excellent yield. Compound **2** on exposure to methanol-aqueous ammonia afforded **5** in 90% yield.[4] Very recently, a synthesis of chloramphenicol **5** from 4-*p*-nitrophenyl-5-formamido-1,3-dioxane



2 **5** **3**

(**1h**) *via* hemiacetal **3** was also reported from this laboratory.[5] The majority of the processes for the manufacture of chloramphenicol introduce the nitro group in the phenyl ring which already bears the required protected functional groups. Thus nitration at the *para* position is one of the most important steps in the preparation of chloramphenicol. However, the reported nitration[2a] of *threo*-triacetyl-1-phenyl-2-amino-1,3-propanediol (**4b**) with fuming nitric acid specified neither the yield of the desired *para*-nitro product nor the formation of any *ortho* and *meta* nitro isomers. This is also the case in the nitration[2g] of *threo*-1-phenyl-2-amino-1,3-propanediol (**4a**) and 4-phenyl-5-substituted-1,3-dioxane derivatives.[2e,6,7] We now describe the nitration of three 4-phenyl-5-substituted-1,3-dioxane derivatives **1a**, **1c** and **1g** to products suitable for further elaborations[4,5] to chloramphenicol.



4a,b a) R, R_1, R_2 = H
b) R, R_1, R_2 = Ac

According to a patent report,[2e] the nitration of **1c** with fuming nitric acid in chloroform at -20° furnished the *para* nitro derivative **1d** in 88% yield. When we repeated this experiment, the product obtained in 95% yield was a mixture of *ortho* **1e** (35%), *meta* **1f** (19%) and *para* **1d** (46%) according to GC analysis. The TLC of nitration product showed two distinct spots. The higher R_f spot represents the *ortho* isomer, which can be isolated easily by column chromatography followed by crystallization in 32% yield. The lower R_f spot consists of a mixture of *meta* and *para* isomers in which the *meta* isomer is slightly less polar. The *meta* isomer was separated from the *para* isomer by careful column chromatography using a very high silica to compound ratio. The *meta* isomer was obtained as a low melting solid, mp. 48°. Variation of the concentration of nitric acid, temperature (from -45° to 0°), reaction time (from 30 min to 3 h) and the use of chloroform as a solvent (or no solvent) failed to alter the percentages of **1d**, **1e** and **1f** significantly. Other nitrating agents such as *tert*-butyl nitrate, tetrabutylammonium nitrate and zeolites, sulfonate polystyrene cation exchange resins with nitric acid of different concentrations gave very poor yield or no reaction at all. Bromo dioxane **1a** gave even higher yield of the *meta* isomer (*ortho* 31%, *meta* 30% and *para* 39%) than **1c** while N-formyl dioxane **1g** gave the lowest amount of *meta* nitrated product and the highest amount of *para* product (*ortho* 26%, *meta* 17% and *para* 55%).

The present studies show that the nitration of 4-phenyl-1,3-dioxane derivatives **1a**, **1c** and **1g** furnishes mixtures of *ortho*, *meta* and *para* nitro isomers. It also suggests that although the synthesis of chloramphenicol from N-formyl derivative **1g** involves two extra steps, **1g** may be a better candidate for the synthesis of **5** than N-dichloroacetamide **1c**, since it affords the required *para* nitro isomer **1h** in higher yield.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were determined as nujol mulls on a Perkin-Elmer model 599B spectrophotometer. NMR spectra were recorded on Bruker WH-90 spectrometer. Mass spectra taken on a Finnigan Mat 1020C mass spectrometer at 70 ev. GC was recorded on Carlo-Erba: Fractovap No. 2450, Column: Apiezon L 5% on 80-100 mesh chromosorb WHP at 235°, Integrator: 3390A Hewlett Packard, Carrier gas: Nitrogen, Flow rate: 35mL/min, Detector: F.I. D. The

percentage of nitro products in the reaction mixture was determined by comparison of the observed GC peak heights and retention time with that of pure **1i**, **1d**, **1e**, **1f** and **1h**.

***cis*(-)-(4R, 5R)-4-Nitrophenyl-5-dichloroacetamido-1,3-dioxanes (1d-1f).**- A 100 mL two necked round bottom flask, equipped with magnetic stirring bar, addition funnel and a thermometer was charged with fuming nitric acid (12.6 mL, 304 mmol, sp. gr. 1.52). It was cooled to -30° and a solution of *cis*-(4R, 5R)-4-phenyl-5-dichloroacetamido-1,3-dioxane **1c**[4] (9.6 g, 33 mmol) in dry chloroform (20 mL) was added dropwise, keeping the temperature between -30 to -25°. Addition was completed in 30 min. Small portions of reaction mixture were taken at intervals of 15 min, 1h, 2h and 3h and the products formed were analysed by GC. Starting material **1c** was absent after 3h. Reaction mixture was poured on crushed ice. It was then extracted with chloroform (2x75 mL). Chloroform extract was washed with water (2x50 mL), saturated $NaHCO_3$ (2x50 mL), water (2x50 mL), dried (Na_2SO_4) and evaporated to afford pale yellow solid (10.2 g, 92%), mp. 134-136°. This crude nitration product on three crystallizations from methanol furnished pure *para* nitro isomer **1d**, 1.85 g, mp. 161-162°; $[\alpha]_D^{30}$ = -66° (c = 2.5, $CHCl_3$); IR: 3320 (NH), 1680 (NHCO), 1515, 1345, 1175 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.59 (brs, 1H, NH), 4.12 (d, 2H, CH_2-6, *J* = 2Hz), 4.33 (m, 1H, CH-5), 5.04 (brs, 1H, CH-4), 4.97 and 5.35 (AB pattern, 2H, CH_2 -2, *J* = 6Hz), 5.66 (s, 1H, $CHCl_2$), 7.48 and 8.18 (AB pattern, 4H, Ar Ha, R^1 and Hb, R^2, *J* = 8Hz); MS m/z: 304, 306, 251, 221, 191, 183, 177, 164, 154 (100%).

Anal. Calcd. for $C_{12}H_{12}Cl_2N_2O_5$: C, 43.00; H, 3.61; N, 8.36. Found: C, 42.94; H, 3.59; N, 8.15

Column chromatography of the mother liquor over silica gel and elution with hexane-ethyl acetate (75:25) gave the *ortho* isomer followed by a mixture of *meta* and *para* isomers. The pure *ortho* isomer **1e** was obtained by recrystallization from methanol as white crystals, (3.26 g, 32%), mp. 98°; $[\alpha]_D^{26}$ = -4.5° (c = 2.8, $CHCl_3$); IR: 3250 (NH), 1670 (NHCO), 1540, 1510, 1365, 1330, 1165, 1085, 1025, 990 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.61 (brs, 1H, NH), 4.12 (m, 2H, CH_2-6), 4.52 (brd, 1H, CH-5), 4.98 and 5.28 (AB pattern, 2H, CH_2-2, *J* = 6Hz), 5.60 (s, 1H, $CHCl_2$), 5.63 (brs, 1H, CH-4), 7.28-7.68 (m, 3H), 8.06 (brd, 1H); MS m/z: 339, 337, 335, 308, 306, 304, 182, 153 (100%), 135, 118.

Anal. Calcd. for $C_{12}H_{12}Cl_2N_2O_5$: C, 43.0; H, 3.61; N, 8.36. Found: C, 42.82; H, 3.74; N, 8.04

The mixture of the *meta* and *para* isomers was rechromatographed over large excess of silica gel (120 times) and on elution with hexane-ethyl acetate (75:25) afforded the *meta* isomer **1f** as low melting solid, (1.63 g, 16%), mp. 48°; $[\alpha]_D^{26}$ = -32° (c = 1, $CHCl_3$); IR: 3400 (NH), 1690 (NHCO), 1530, 1345, 1175cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.64 (s, 1H, NH), 4.13 (d, 2H, CH_2-6, *J* = 2Hz), 4.35 (brd, 1H, CH-5), 5.07 (d, 1H, CH-4, *J* = 2Hz), 5.01 and 5.34 (AB pattern, 2H, CH_2-2, *J* = 6Hz), 5.67 (s, 1H, $CHCl_2$), 7.4-7.73 (m, 2H, Ha and Hb), 8.15 (brd, 1H, RH), 8.26 (brs, 1H, R^2H); MS m/z: 304 (M^+-CH_2O), 221, 177, 153 (100%), 118.

Anal. Calcd. for $C_{12}H_{12}Cl_2N_2O_5$: C, 43.0; H, 3.61; N, 8.36. Found: C, 43.24; H, 3.88; N, 8.07

Further elution with the same solvent furnished the same *para* isomer **1d**, 2.65 g, isolated earlier by recrystallization of the nitration mixture. The total *para* isomer thus obtained was 4.5 g, 44%.

(±)-4-*para*-Nitrophenyl-5-formamido-1,3-dioxane (1h).- A 50 mL two necked round bottom flask equipped with magnetic stirring bar, addition funnel and a thermometer was charged with fuming

nitric acid (8 mL, 193 mmol, sp. gr. 1.52). A solution of (±)-**1g**,[5] mp. 101-102° (4 g, 19 mmol) in dry chloroform (15 mL) was added dropwise during 20 min maintaining the temperature between -20° to -15°. The temperature of the reaction mixture was raised to 10° and it was stirred at this temperature for 1.5h for the reaction to complete. Reaction mixture was then poured on ice and was extracted with chloroform (2x75 mL), washed with water (3x50 mL), saturated $NaHCO_3$ (2x50 mL) and with brine (2x50 mL). Chloroform extract was dried (Na_2SO_4) and evaporated to furnish crude solid (4.63 g, 95%). This on GC analysis was found to be a mixture of *ortho* (25.7%), *meta* (16.9%) and *para* (55.3%) isomers. The mixture on crystallization from chloroform-hexane furnished the pure *para* isomer (±)-**1h**, (2.45 g, 53%), mp. 159°; IR: 3220 (NH), 1680 (NHCO), 1650, 1560, 1340, 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.06 (d, 2H, CH_2-6, J=2Hz), 4.5 (m, 1H, CH-5), 5.04 (brs, 1H, CH-4), 4.96 and 5.26 (AB pattern, 2H, CH_2-2, *J* = 7Hz), 6.24 (brd, 1H, NH), 7.92 (s, 1H, CHO), 7.44 and 8.15 (AB pattern, 4H, Ar-H, *J* = 8Hz); MS m/z: 222 (M^+-CH_2O), 101, 71 (100%).

Anal. Calc. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.45; H, 4.91; N, 10.78

(±)-4-*para*-Nitrophenyl-5-bromo-1, 3-dioxane (1i).- Fuming nitric acid (4.15 mL, 100 mmol, sp.gr. 1.52) was taken in a two necked round bottom flask, equipped with magnetic stirrng bar, addition funnel and a thermometer. A solution of (±)-**1a** (2.42g, 10mmol) in dry chloroform (10 mL) was added slowly during 20 min at -10° to 0°. The reaction mixture was further stirred at -10° to 0° for 3h. It was then poured on crushed ice and was extracted with chloroform (2x75 mL). The chloroform extract was washed with water (2x50 mL), saturated $NaHCO_3$ (2x50 mL), water (2x50 mL) and finally with brine (2x50 mL). The extract was dried (Na_2SO_4) and evaporated to afford white solid (2.7g, 94%). This on GC analysis was found to be a mixture *ortho* (31.5%), *meta* (30.0%) and *para* (38.5%) isomers. The mixture on crystallization from chloroform-hexane furnished the pure *para* isomer (±)-**1i**, (0.95 g, 35%), mp. 132-133° (Lit,[8] 132-135°); IR: 1615, 1520, 1350, 1170, 1115, 1090, 1955, 1020, 1005, 940, 850, 775cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89 (m, 1H, H6a), 4.42 (m, 1H, H6e), 4.08 (m, 1H, H5a), 4.67 (m, 1H, H4a), 4.92 (m, 1H, H2a), 5.27 (m, 1H, H2e), 7.64 and 8.28 (AB pattern, 4H, Ar-H, *J* = 8Hz); ^{13}C NMR ($CDCl_3$): δ 46.7 (C-5), 72.2 (C-6), 83.7 (C-4), 94.6 (C-2), 123.8 (C *meta* to nitro), 129 (C *ortho* to nitro), 144.8 (C *para* to nitro), 148.7 (C attached to nitro).

REFERENCES

1. J. Ehrlich, Q. R. Bartz, R. M. Smith, D. A. Josylyn and P. R. Burkholder, *Science*, **106**, 417 (1947); J. Ehrlich in *Encyclopedia of Chemical Technology*, Editor Kirk-Othmer, 3rd Edition, Wiley-Interscience, **2**, pp. 920-930 (1978).

2. a) J. Controulis, M. C. Rebstock and H. M. Crooks, Jr., *J. Am. Chem. Soc.*, **71**, 2463 (1949); b) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2469 (1949); c) L. M. Long and H. D.Troutman, *ibid.*, **71**, 2473 (1949); d) M. Nagawa and Y. Murace, *Takamin Kenkyujo Nempo*, **8**, 1 (1956); *Chem. Abstr.*, **52**, 307f (1958); e) C. F. Boehringer, Soehne, GmbH., BP 741, 711 (1955); *Chem. Abstr.*, **51**, 5830h (1957); f) A. V. Rama Rao, S. P. Rao and M. N. Bhanu, *Chem. Commun.*, 859 (**1992**); g) A. Heath, *Chem. Eng.*, August 24, pp. 60 (1970).

3. L. Bernard and A. Leone, *Tetrahedron Lett.*, 499 (**1964**)

4. B. G. Hazra, V. S. Pore, S. P. Maybhate, M. V. Natekar and A. S. Rao, *Synthetic Commun.*, **19**, 1763 (1989).

5. B. G. Hazra, V. S. Pore and S. P. Maybhate, *ibid.*, **27**, 1857 (1997).

6. Chi-yi Hsing, Chien-Huan Tai and Lian-Chy Hsueh, *Hua Hsueh Pao*, **23**, 19 (1957); *Chem. Abstr.*, **52**, 12870f (1958).

7. M. Nagawa, *Takamine Kenkyujo Nempo*, **9**, 1 (1957); *Chem. Abstr.*, **55**, 1504d (1961); J. M. A. J. Batteur Jacques, Fr. Patent, 1,290,352/1962; *Chem. Abstr.*, **57**, 16489b (1962).

8. M. Karpaty, M. Hellin, M. Davidson and F. Coussemant, *Bull. Soc. Chim. France*, 1736 (**1971**).

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AN EFFICIENT SYNTHESIS OF MEQUITAZINE

Submitted by (10/26/98)

Yves Guminski, Valerie Fabre†, Patrick Lesimple† and Thierry Imbert*

Division of Medicinal Chemistry, Centre de Recherche Pierre Fabre F 81100 Castres, FRANCE

† *Development Department, Plantes et Industries, F 81603.-Gaillac, FRANCE*

Mequitazine (**1**), a phenothiazine quinuclidine derivative known for more than two decades exhibits potent antihistamine properties and is the active constituent of some pharmaceuticals. The previously described synthesis in a patent is not satisfactory, leading to poor yields.[1] The strategy involves the preparation of the 3-hydroxymethyl quinuclidine (**6**) which was condensed *via* its chloro derivative with phenothiazine. The original six-step synthesis of **6** (5% overall yield) of Grob[2] was later modified[3] to enhance the yield to 30%. Then, another strategy,[4] using a Wittig reaction, furnished the formyl precursor **5** with no mention of the yield. Our need of large amounts of mequitazine prompted us to improve the process.

We chose to improve the preparation of 3-hydroxymethylquinuclidine (**6**), as the key intermediate, and assess the best conditions to effect the coupling reaction with phenothiazine. Our synthetic approach was based on the use of dimsylsodium reagent according to the method of Corey and Chaykovsky,[5] to yield 3-methylene quinuclidine oxide (**3**) derived from 3-quinuclidinone (**2**). Interestingly, this known 3-methylene quinuclidine oxide[6] (**3**) was prepared *in situ* by analogy with a recently described similar methodology.[7] A mixture of 3-quinuclidinone (**2**), trimethylsulfoxonium