Chloramphenicol: A New Synthesis and Its Stereochemical Findings

From the stereochemical point of view, it is interesting that dibromocinnamic alcohol may be introduced step by step to chloramphenicol by substitutions. A new synthetic method succeeded as follows:

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\begin{align*}
\text{C}_6\text{H}_5\text{CH} &= \text{CH} = \text{CH}_2\text{OH} \quad \xrightarrow{\text{Br}_2} \quad \text{C}_6\text{H}_5\text{CHBr} = \text{CH} = \text{CH}_2\text{OH} \\
\text{C}_6\text{H}_5\text{CHBr} &= \text{CH} = \text{CH}_2\text{OH} \quad \xrightarrow{\text{C}_6\text{H}_5\text{CN}} \quad \text{C}_6\text{H}_5\text{CHBr} = \text{CH} = \text{CH}_2 \\
\text{Br} \quad \text{NHCOC}_6\text{H}_5 \\
\text{C}_6\text{H}_5\text{CH} &= \text{CH} = \text{CH}_2\text{Br} \quad \xrightarrow{\text{boil}} \quad \text{C}_6\text{H}_5\text{CHBr} = \text{CH} = \text{CH}_2 \\
\xrightarrow{\text{NH}_2\cdot\text{HBr}} & \quad \text{C}_6\text{H}_5\text{CH} = \text{CH} = \text{CH}_2\text{Br} \\
\xrightarrow{\text{COCO}_6\text{H}_5} & \quad \text{C}_6\text{H}_5\text{CH} = \text{CH} = \text{CH}_2 \\
\xrightarrow{\text{1) Pd, H}_2} & \quad \text{C}_6\text{H}_5\text{CH} = \text{CH} = \text{CH}_2\text{OH} \\
\xrightarrow{\text{2) NaHCO}_3} & \quad \text{C}_6\text{H}_5\text{CH} = \text{CH} = \text{CH}_2 \\
\text{NHCOC}_6\text{H}_5 & \quad \xrightarrow{\text{OH}} \quad \text{H}_2\text{O} \\
\text{C}_6\text{H}_5\text{CH} &= \text{CH} = \text{CH}_2\text{OH} \\
\end{align*}
\]

By bromination of the one stereoisomer (m.p. 33°) of cinnamic alcohol (I), racemic dibromocinnamic alcohol (II), m.p. 73~74°,1) was obtained whose configuration has not yet been clarified. A dry ether solution containing (II) and benzonitrile was saturated with dry hydrogen chloride, yielding dl-dibromocinnamamyl benzimino ether hydrochloride (III), m.p. 148~150°, (yield, 79%). *Anal.* Calcd. for C_{10}H_{18}ONBr_2Cl : N, 3.23. Found : N, 3.18), which was then converted to the free base (IV), m.p. 133.5~135° (yield, 92%). *Anal.* Calcd. for C_{10}H_{18}ONBr_2 : C, 48.39; H, 3.81; N, 3.53. Found : C, 48.54; H, 3.77; N, 3.48) on treatment with sodium carbonate. (IV) was boiled in dry toluene and converted to an oily product assumed to be dl-erythro-1-phenyl-2-benzoylemimo-1,3-dibromopropane (V), which was then converted to dl-threo-1-phenyl-1-benzyloxy-2-amino-3-bromopropane hydrobromide (VI) (m.p. 206~208°; yield, 55%). *Anal.* Calcd. for C_{16}H_{20}O_2NBr_2 : C, 46.29; H, 4.13; N, 3.37. Found : C, 46.55; H, 3.89; N, 3.24) by hydrolysis with 1% hydrobromic acid with warming for an hour. Because (VI) is converted to dl-ephedrine by catalytic reduction with palladium-charcoal and also to dl-threo-1-phenyl-2-benzoylemimo-1,3-propanediol (VII) by the method described below, its configuration was finally confirmed as the threo-form. (VI) was boiled in water for three hours and then

made alkaline, resulting in \(dl\)-threo-1-phenyl-2-benzoylamino-1,3-propanediol (VII), m.p. 163–165° (yield, 73%). \(Anal.\) Calcd. for \(C_{16}H_{17}O_3N\): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.77; H, 5.98; N, 4.80) which was identified by a mixed m.p. determination with an authentic sample. (VII) was converted to chloramphenicol by the known method.

The intermediates mentioned above may be converted to chloramphenicol through other ways. For example, a dry toluene solution containing (IV) and anhydrous sodium carbonate was heated, resulting in one stereoisomer of \(dl\)-2-phenyl-4-phenylbromomethyl-\(\alpha\)-oxazoline (VIII), m.p. 103–105° (yield, 87%). \(Anal.\) Calcd. for \(C_{19}H_{14}ON\): C, 60.77; H, 4.46; N, 4.43. Found : C, 60.97; H, 4.20; N, 4.62.

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\begin{align*}
\text{C}_6\text{H}_5\text{CHBr} & \text{CHBr} \text{CH}_2 \quad \text{(IV)} \\
\text{NHCOC}_6\text{H}_5 & \\
\text{C}_6\text{H}_5\text{CH} & \text{CHCH}_2 \text{OH} \\
\text{OH} & \text{OH} \\
\text{C}_6\text{H}_5\text{CH} & \text{CHCH}_2 \text{OH} \\
\text{OH} & \text{OH} \\
\text{C}_6\text{H}_5\text{CH} & \text{CHCH}_2 \text{OH} \\
\text{OH} & \text{OH} \\
\end{align*}
\]

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\begin{align*}
\text{C}_6\text{H}_5\text{CH} & \text{CHCH}_2 \text{OH} \\
\text{OH} & \text{OH} \\
\text{C}_6\text{H}_5\text{CH} & \text{CHCH}_2 \text{OH} \\
\text{OH} & \text{OH} \\
\end{align*}
\]

To an ether solution containing (VIII) was added aq. EtOH–HCl and the mixture was allowed to stand for 3 days, resulting in one stereoisomer of \(dl\)-1-phenyl-1-bromo-2-amino-3-benzoyloxypropane hydrochloride (IX), m.p. 174–176° (yield, 96%). \(Anal.\) Calcd. for \(C_{19}H_{17}O_2N\): C, 51.84; H, 4.62; N, 3.78. Found : C, 51.61; H, 4.29; N, 3.86. Aqueous solution containing (IX) was boiled for several hours and made alkaline, affording impure solids (m.p. 110–128°), which appeared as a mixture consisting of \(dl\)-threo- and \(dl\)-erythro-1-phenyl-2-benzoylamino-1,3-propanediol (VII and X). On treatment with HCl and subsequently with NaOH, the mixture of (VII) and (X) changed to (VII) in the pure state (yield, 30%). It is already known that the former HCl treatment causes acyl migration from N to O attached to C, following inversion of the erythro-form to the threo-form whilst retaining the threo-form, \textit{per se}, and the later NaOH treatment causes the reverse acyl migration with retention of both forms.\(^{3,3}\) These facts explain the phenomenon of elimination of the erythro-form in the course of treatment with HCl.

The details of these experiments will be presented elsewhere, including another case, in which \(p\)-nitrocinnamyl alcohol is used as the starting material instead of cinnamic alcohol.

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2) Brit. Pat. 671,531.