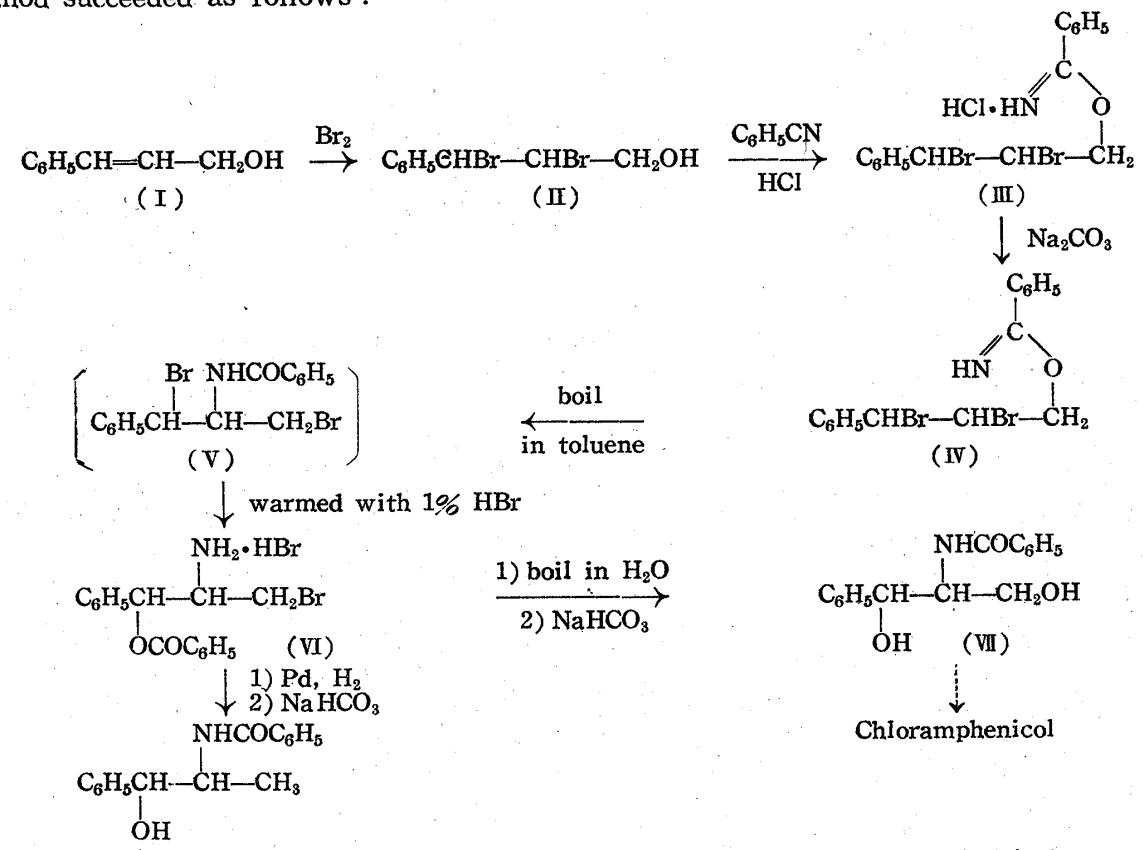
Communications to the Editor

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 :

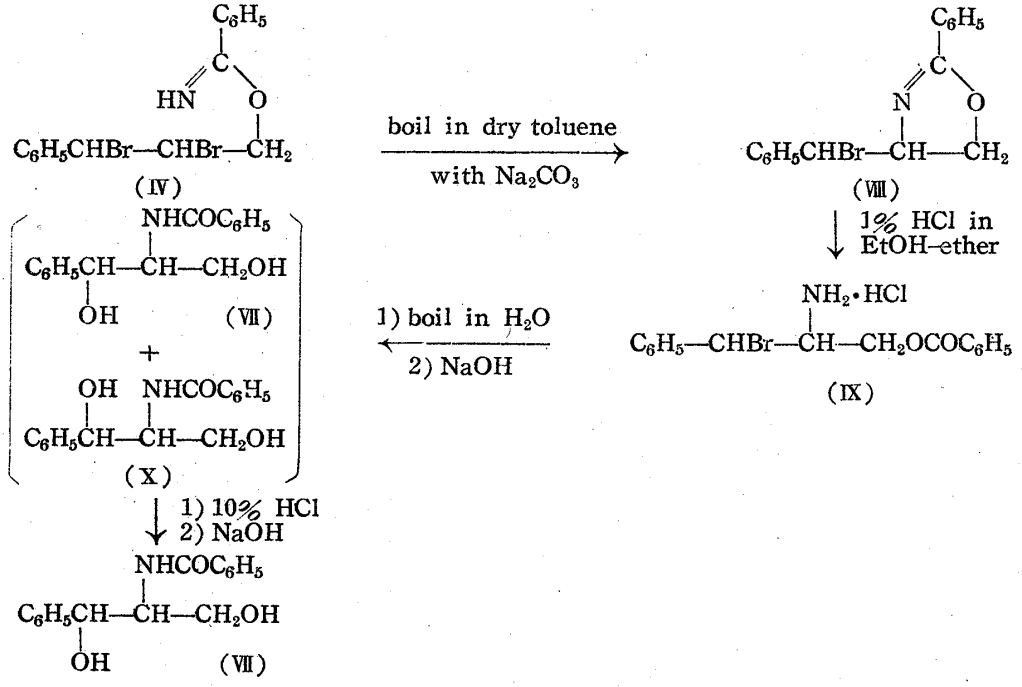


By bromination of the one stereoisomer (m.p. 33°) of cinnamic alcohol (I), racemic dibromocinnamic alcohol (II), m.p. 73~74°,[1] was obtained whose configuration has not yet been clarified. A dry ether solution containing (II) and benzonitrile was saturated with dry hydrogen chloride, yielding *dl*-dibromocinnamyl benzimino ether hydrochloride (III), m.p. 148~150°, (yield, 79%. *Anal.* Calcd. for $C_{16}H_{16}ONBr_2Cl$: 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 $C_{16}H_{15}ONBr_2$: 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-benzoylamino-1,3-dibromopropane (V), which was then converted to *dl-threo*-1-phenyl-1-benzoyloxy-2-amino-3-bromopropane hydrobromide (VI) (m.p. 206~208°; yield, 53%. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$: 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*-ψ-norephedrine by catalytic reduction with palladium-charcoal and also to *dl-threo*-1-phenyl-2-benzoylamino-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

1) Brimaux : Bull. soc. chim. France, [2] **20**, 120(1873).

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-Δ^2-oxazoline (Ⅷ), m.p. 103~105°(yield, 87%. *Anal.* Calcd. for $C_{16}H_{14}ONBr$: C, 60.77; H, 4.46; N, 4.43. Found : C, 60.97; H, 4.20; N, 4.62).



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 $C_{16}H_{17}O_2NBrCl$: 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_1, following inversion of the *erythro*-form to the *threo*-form whilst retaining the *threo*-form, *per se*, and the later NaOH treatment causes the reverse acyl migration with retention of both forms.[2,3] 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*-nitrocinnamic alcohol is used as the starting material instead of cinnamic alcohol.

Pharmaceutical Institute,
Medical Faculty,
University of Kyushu.
Katakasu, Fukuoka.
September 27, 1954

Tanezo Taguchi
Munemitsu Tomoeda
(田口胤三
友枝宗光)

2) Brit. Pat. 671,531.
3) M. Miyamoto : J. Pharm. Soc. Japan, **72**, 677(1952).