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THE ABSOLUTE CONFIGURATION OF (−)-DIHYDROZEATIN

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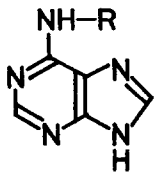
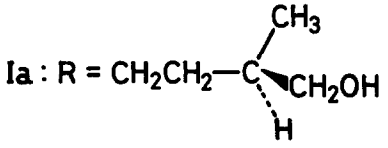
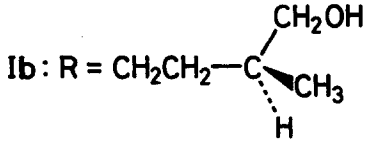
(−)-Dihydrozeatin [(−)-I], a cytokinin found in 1967 by Koshimizu et al. (1) in extracts of immature seeds of Lupinus luteus, is unique among the naturally-occurring N^6-"isoprenylated" adenines (2) in that it carries a saturated side chain on the exocyclic nitrogen atom. The absolute configuration of the $C_{(3)}$ atom of the N^6-substituent, however, has remained undetermined. In this communication we wish to present evidence that this asymmetric carbon atom has the S configuration (Ib) (3).

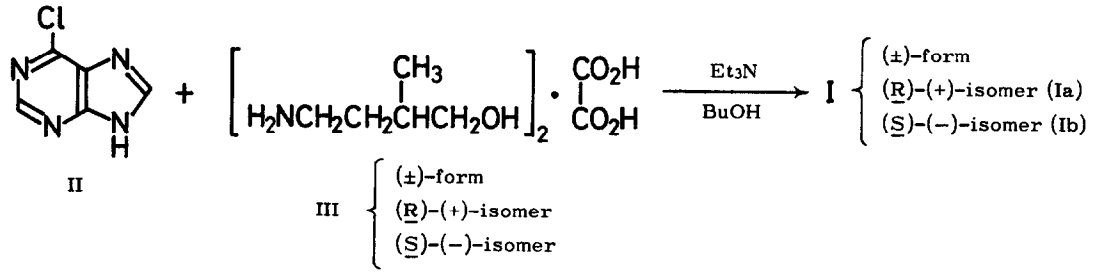


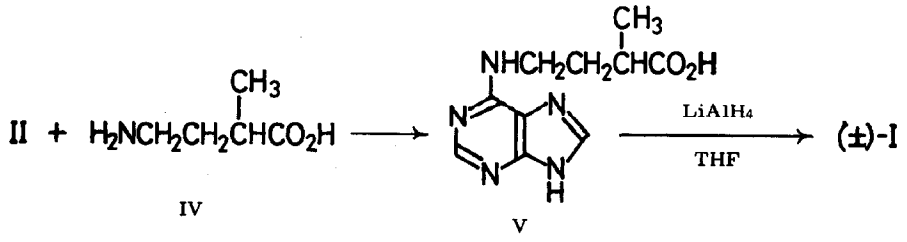
I : R = $CH_2CH_2\overset{CH_3}{\underset{|}{C}}HCH_2OH$





Condensation of 6-chloropurine (II) (4) with (±)-2-methyl-4-amino-1-butanol oxalate [(±)-III] (5) in boiling 1-butanol solution containing triethylamine provided, after treatment of the reaction mixture with Amberlite IRA-402 (HCO_3^-), racemic dihydrozeatin [(±)-I] in 72% yield. Colorless platelets, m. p. 165–167° [lit. (1) m.p. 167–168°], obtained on recrystallization from ethanol–acetonitrile (1 : 2)





or ethanol–ethyl acetate (1 : 10), were characterized by means of mass spectrum [m/e 221 (M^+)], correct analysis for $C_{10}H_{15}ON_5$, and UV, IR, and NMR spectra which, respectively, were virtually identical with those of (±)-I or (−)-I reported by Koshimizu et al. (1). Treatment of the racemic free base with picric acid in ethanol gave the picrate, m.p. 199–201° (sintered at 194°) (6), whose IR and NMR spectra were also identical to those reported (1).

Replacement of the racemic amine oxalate [(±)-III] by the dextrorotatory isomer [(R)-(+)-III], m.p. 179–180°; $[\alpha]_D^{23}$ + 15.4° (50% aq. ethanol), prepared according to the direction of Adams and Fleš (5), in the synthesis described above furnished (R)-(+)-dihydrozeatin (Ia), m.p. 153–154°; $[\alpha]_D^{21}$ + 11.7° (methanol); picrate, m.p. 187–189°. The ORD curve of Ia in methanol at 27.5° exhibited a positive plain curve within the spectral range under experimental observation: $[\alpha]_{450}$ + 13.1°, $[\alpha]_{400}$ + 20.7°, $[\alpha]_{350}$ + 33.2°, $[\alpha]_{320}$ + 46.7°.

Likewise, the reaction of II with the levorotatory amine salt [(S)-(−)-III] (5), m.p. 180–181°; $[\alpha]_D^{22}$ −15.4° (50% aq. ethanol), afforded (S)-(−)-dihydrozeatin (Ib) (75% yield), m.p. 154–155°; $[\alpha]_D^{21}$ −12.1° (methanol); ORD in methanol, 25°: $[\alpha]_{450}$ −14.2°, $[\alpha]_{400}$ −19.9°, $[\alpha]_{350}$ −33.7°, $[\alpha]_{320}$ −48°; picrate, m.p. 187–189°. The UV, IR (KBr disc), and NMR (in pyridine-d_5) spectra of both enantiomers were respectively identical, and the spectra in solution were superimposable with those of the (±)-form. Although it has been reported (1) that in the solid state the IR spectrum of naturally-occurring (−)-dihydrozeatin [(−)-I], m.p. 165–166°, is identical with that of the racemic sample [(±)-I],

m.p. 167–168°, obtained by the catalytic hydrogenation of zeatin, our synthetic (S)-(−)-dihydrozeatin (Ib) has the melting point lower than that of (±)-I by ca. 10° and the IR spectra of samples in KBr discs are not identical. A similar relationship is also observed between our optically active and racemic picrates. These facts suggest that our racemic samples of the free base and its picrate crystallized as racemates and that the synthetic samples of (−)-dihydrozeatin and its picrate were obtained in crystal forms different from those of the natural sample and its picrate. Since efforts to convert the crystals of synthetic Ia or Ib or their picrates into another crystal modification were in vain, racemization experiments were carried out. Thus, recrystallization of a mixture of equal amounts of Ia and Ib or of their picrates gave the racemic free base [(±)-I] or its picrate identical to the sample derived from the reaction of II with (±)-III.

Since the reaction, II + III ⟶ I, used in this study does not involve the asymmetric carbon center and since (−)-2-methyl-4-amino-1-butanol oxalate [(−)-III] has been correlated with (S)-(−)-methylsuccinic acid (5), the absolute configuration of the asymmetric carbon atom of (−)-dihydrozeatin may be accepted unequivocally as S.

In alternative synthesis of the racemic cytokinin [(±)-I], II was condensed with (±)-2-methyl-4-aminobutyric acid (IV) (5) in boiling aq. sodium carbonate to give 2-methyl-4-(purin-6-ylamino)butyric acid (V) (81% yield), m.p. 203–207° (dec.). Reduction of acid V to (±)-I was effected with lithium aluminum hydride in boiling tetrahydrofuran, but with less satisfactory results.

Cytokinin activity of both enantiomers of I will be investigated at Kyoto University in order to clarify the stereostructure —activity relationships (7).

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6. Sometimes the picrate was obtained as another crystal modification, needles of m.p. 194–195° (sintered at 192°), whose IR spectrum in KBr disc was slightly different from that of the picrate of m.p. 199–201°.

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