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Short Communication

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A Synthesis of (±)-Discadenine

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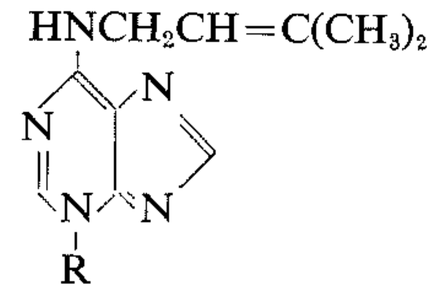
In the preceeding paper,[1] we have reported that discadenine, the potent self-germination inhibitor isolated from spores of the cellular slime mold (*Dictyostelium discoideum*), has the structure 3-(3-amino-3-carboxypropyl)-6-(3-methyl-2-butenylamino)purine (**1a**) though its configuration on the α-amino acid moiety has still remained unsolved due to scarcity of material.

The unique structure of discadenine prompted the synthesis of this and related compounds to evaluate more extensive biological activities. We wish to report a convenient synthetic rout to (±)-discadenine. Two routes yielding (±)-discadenine starting with 6-(3-methyl-2-butenylamino)purine (**3**) *via* its N-3 substituted intermediates **1b** and **1c** were examined.

In first attempt, the intermediate **1b** was separated by a preparative thin-layer chromatography from the condensation product of diethyl formylaminomalonate with the bromide (**1e**) which was prepared by the direct alkylation[2] of **3** with ethylene dibromide in 40% yield. Hydrolysis of the formyl and ester group with sodium hydroxide, then decarboxylation under mild acidic condition according to the procedure of D. K. Black *et al.*[3] gave (±)-discadenine which was isolated as the crystalline hydrochloride. The ultraviolet spectra determined in water at pH 2, 7 and 12 and the mobility on paper chromatography of this material were identical with those of natural discadenine. However, low yield of **1b** due to predominant formation of the dehydrobrominated product (**1f**) and other unidentified by-products thwarted further search of this approach for preparative work.

An alternative rout via the intermediate

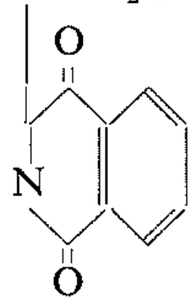


1

1a R = $CH_2CH_2CH(NH_2)CO_2H$ (discadenine)

1b $-CH_2CH_2C(CO_2Et)_2NHCH(=O)$

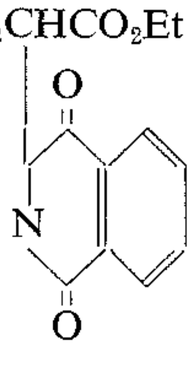
1c $-CH_2CH_2CHCO_2Et$



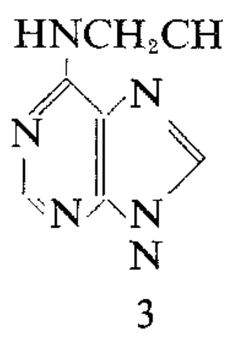
1d R = $CH_2CH_2CH(NH_2)CO_2Et$

1e $-CH_2CH_2Br$ 1f $-CH=CH_2$

$BrCH_2CH_2CHCO_2Et$



2



3

3-(3-phthalimido-3-carbethoxypropyl)-6-(3-methyl-2-butenylamino)purine (**1c**) provided a convenient synthetic method of (±)-discadenine from **3** in two stages.

The condensation of compound (**3**) (2.0 g) with ethyl α-phthalimido-γ-bromobutyrate (**2**) (5.2 g) was effected in anhydrous dimethylacetamide (20 ml) for 9～10 hr at 120～125°C. The crude hydrobromide of (**1c**) which was obtained by evaporation of the reaction solution followed by trituration of the resulting syrup with ether was converted to the free base (**1c**) by addition of aqueous ammonium hydroxide to pH 7～8 with ethyl acetate extraction. After evaporation of the solvent, the residue was dissolved in warm ethyl acetate. On standing, a crystalline precipitate was separated. Chromatography of this product in chloroform-methanol (9: 1) on silica gel followed by recrystallization from ethyl acetate-hexane afforded (**1c**) as colorless needles

(1.6 g, 35%), mp 143~4°C. $[\alpha]_D^{28}$ 0° (c=2.5, $CHCl_3$). The UV and IR data for (**1c**) are: λ_{max}^{MeOH} 292.2 nm (ε 1.58×10^4), λ_{max}^{PH2} 287.6 (2.10×10^4), λ_{max}^{PH7} 288.5 (1.93×10^4), λ_{min}^{PH2} 253.6 nm, λ_{min}^{PH7} 255.2 nm; ν_{max}^{Nujol} 1770, 1730 and 1720 (COOEt and phthalimid CO), 1630, 1570, 1535, 710 cm^{-1}. The mass spectrum showed a parent peak at m/e 462 and base peak at m/e 217. Other major peaks were m/e 260, 202, 186, 149 and four peaks m/e 188, 160, 148, 135 of characteristic for 6-(3-methyl-2-butenylamino)purine residue. The UV spectral data, especially the hyperchromic shift in acidic solution on long wave side of the maxima and the negative value (−1.6) for $\lambda_{min}^{PH2}-\lambda_{min}^{PH7}$ indicated that the substituent group is on N–3 of the purine ring.[4] This assignment was also supported by the large chemical shift ($\Delta\delta$= 42 c/s) between C_2 and C_8 protons observed in the NMR spectrum taken in dimethyl sulfoxide.[4]

Ethyl α-phthalimido-γ-bromobutyrate (**2**) was prepared by the methods of earlier workers[5] from α-phthalimido-γ-butyrolactone[6] and dry hydrogen bromide in absolute ethanol. The pale yellow oily product (86% yield) was used without further purification.

Removal of the phthaloyl and the ester residue was achieved stepwise by the method of Grassmann and Schulte-Uebbing:[7] The above-mentioned (**1c**) (0.92 g) in methanol (10 ml) was heated with 50% aqueous hydrazine hydrate (1 equiv.) under refrux for 2 hr. After filtration from phthalhydrazide, the crude amino-acid ester (**1d**) was obtained by evaporation of the filtrate. Saponification of this crude ester with N-potassium hydroxide solution, then partial neutralization of the reaction solution with 10% perchloric acid followed by adjustment of pH to 7~7.4 with acetic acid gave a crystalline precipitate. Further purification of this product containing inorganic salt was effected via the following treatments in sequence: Crystallization from 80% ethanol, dissolution of the resulting crystals in aqueous hydrochloric acid solution (pH 3~4), then reprecipitation from the solution adjusted to pH 6~6.5 with saturated aqueous sodium acetate afforded microcrystalline solids. Recrystallization from aqueous ethanol gave (±)-discadenine as colorless prisms (0.25 g, 41%), mp 193~5°C. The UV spectral data determined in methanol and water at pH 2, 7 and 12 agreed very closely with those of natural discadenine (Table I). The infrared spectrum obtained in a Nujol mull was very similar to that of the natural material.

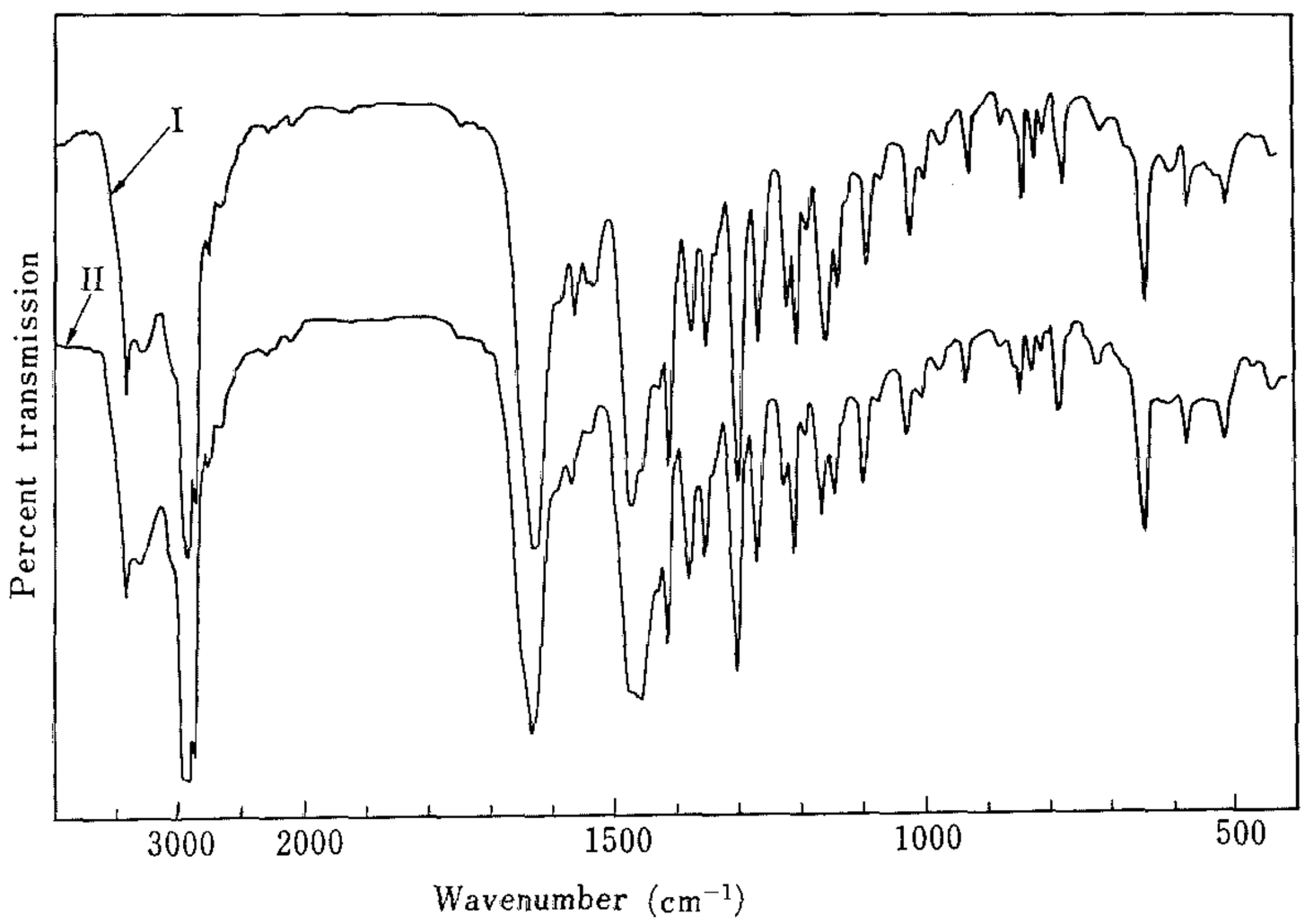


FIG. 1. Infrared Spectrum of Natural Discadenine (I) and Synthetic Discadenine (II).

Table I. Ultraviolet Absorption Spectra of Natural Discadenine (I) and Synthetic Discadenine (II)

pH	max (nm)	$\times 10^{-3}$	min (nm)	$\times 10^{-3}$
I.... 2	287.0	22.5	241.5	3.3
7	288.9	17.5	248.3	3.5
12	290.0	17.4	248.7	3.5
MeOH	292.7	15.7	248.9	3.1
II.... 2	286.2	22.2	241.5	3.1
7	289.2	17.2	248.3	4.0
12	289.3	16.1	248.5	3.6
MeOH	292.8	15.4		

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