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Total Synthesis of PDE-I

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PDE-I (I), a new inhibitor of cyclic adenosine-3′,5′-monophosphate phosphodiesterase, was synthesized in seven steps of reactions from 1-acetyl-2,3-dihydro-7-hydroxy-6-methoxy-5-nitro indole (III) via the key intermediate, 5-amino-1-carbamoyl-2,3-dihydro-7-hydroxy-6-methoxy indole (VII), which has the hydroindole skelton and the sites for the introduction of the pyrrole moiety necessary for the preparation of I.

Enomoto *et al.*[1] isolated PDE-I and PDE-II, inhibitors of cyclic adenosine-3′,5′-monophosphate phosphodiesterase, from culture filtrate of streptomyces. They also determined the structure of PDE-I and PDE-II as I and II respectively.[2] In the preceding paper,[3] we reported the total synthesis of PDE-II (II) and a method to prepare 1,2-dihydro-3H-pyrrolo [3,2-e]indole skelton. As shown in Fig. 1, the only difference between PDE-I and PDE-II concerns the substituent at N-3 position, therefore we tried the synthesis of PDE-I based on essentially the same method as that applied to the synthesis of PDE-II. This paper describes

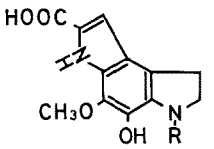

FIG. 1. I: R=$CONH_2$ PDE-I
II: R=$COCH_3$ PDE-II

the first total synthesis of PDE-I. The synthetic route is outlined in Fig. 2.

The similarity of the structure between PDE-I and II prompted us to utilize III[3] as a starting material for the synthesis of I. Treatment of III with benzyl chloride in the presence of

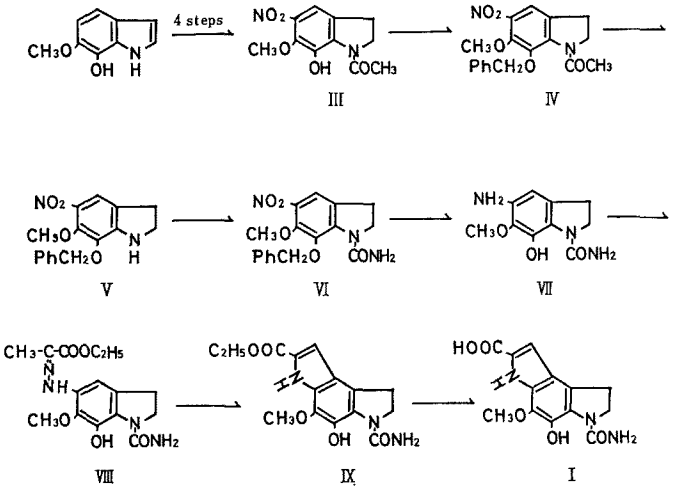

FIG. 2. Synthetic Route of PDE-I.

anhydrous potassium carbonate gave IV. Alkaline deacetylation of IV afforded V, which was carbamoylated with sodium cyanate in acetic acid to afford VI in quantitative yield. Catalytic hydrogenation of VI in the presence of 10% palladium charcoal in ethanol resulted in reduction of nitro group and concurrent cleavage of the benzyl ether, giving VII. The amine (VII) was converted into the corresponding diazonium salt, which was treated with ethyl 2-acetylpropionate under neutral condition giving VIII (Japp-Klingemann reaction[4]). The hydrazone (VIII) was converted into the ethyl ester of PDE-I (IX) by the general method of Fisher's cyclization under acidic condition.

Finally, the conversion of IX into I was successfully carried out by treating IX with 0.01~0.05 N potassium hydroxide solution. This prevented unexpected reactions otherwise occurred.

The synthetic compound showed the IR and NMR data identical with those of the authentic sample. Further, the melting point of the natural PDE-I showed no depression on admixture with the synthetic sample.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded on a JASCO IRA-I grating infrared spectrophotometer. Proton magnetic resonance spectra were determined on JEOL 3H-60 (60 MHz) nuclear magnetic resonance spectrometer using TMS as an internal standared.

1-Acetyl-7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro indole (IV)

A mixture of III (2.2 g), benzyl chloride (2.3 g), anhydrous potassium carbonate (5.5 g) and dimethylformamide (10 ml) was stirred at 110~120°C. After 30 min the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, decolorized with charcoal, dried over anhydrous sodium sulfate and freed from the solvent. The resulted crude product was recrystallized from *n*-hexane-methylene chloride. Yield: 2.8 g (94%). mp 159°C. IR ν_{max}^{KBr} cm^{-1}: 1660, 1605, 1580, 1510, 1360. NMR $\delta_{Me_4Si}^{CDCl_3}$: 2.25 (3H, s, $COCH_3$), 2.92 (2H, t, J=7.5 Hz, $-CH_2-$), 4.05 (2H, t, 7.5 Hz, $-CH_2-$), 4.10 (3H, s, OCH_3), 5.03 (2H, s, $ArCH_2-$), 7.38 (5H, s, Ar-H), 7.55 (1H, s, Ar-H). *Anal.* Found: C, 63.44; H, 5.33; N, 8.08. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18%.

7-Benzyloxy-2,3-dihydro-6-methoxy-5-nitro indole (V)

To a suspension of IV (13.0 g) in ethanol (250 ml) was added 1 N sodium hydroxide solution (145 ml). The resulting mixture was heated at 79°C for 20 min and poured into water. The product was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and freed from the solvent. Yield: 10.8 g (95%). mp 93~94°C. IR ν_{max}^{KBr} cm^{-1}: 3340, 1615, 1490, 1300, 1250, 1230. NMR $\delta_{Me_4Si}^{CDCl_3}$: 3.02 (2H, t, J=6.8 Hz, $-CH_2-$), 3.59 (2H, t, J=6.8 Hz, $-CH_2-$), 3.98 (3H, s, OCH_3), 4.30 (1H, broad s, NH), 5.40 (2H, s, $ArCH_2-$), 7.44 (5H, s, Ar-H), 7.63 (1H, s, Ar-H). *Anal.* Found: C, 64.11; H, 5.37; N, 9.44. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.38; N, 9.33%.

7-Benzyloxy-1-carbamoyl-2,3-dihydro-6-methoxy-5-nitro indole (VI)

To a warm (50~60°C) solution of V (6.0 g) in acetic acid (90 ml) and water (9 ml) was added dropwise sodium cyanate (9.0 g) in water (90 ml). The reaction mixture was stirred at 80~90°C for 1 hr and poured into water. The separated crystals were collected. Yield: 6.7 g (98%). mp 184~186°C. IR ν_{max}^{KBr} cm^{-1}: 3460, 1680, 1605. NMR $\delta_{Me_4Si}^{DMSO\text{-}d_6}$: 3.02 (2H, t, J=7.5 Hz, $-CH_2-$), 3.93 (3H, s, OCH_3), 4.08 (2H, t, J=7.5 Hz, $-CH_2-$), 5.04 (2H, s, $ArCH_2-$), 6.78 (2H, s, $CONH_2$), 7.45 (5H, s, Ar-H). *Anal.* Found: C, 60.19; H, 4.98; N, 12.19. Calcd. for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24%.

5-Amino-1-carbamoyl-2,3-dihydro-7-hydroxy-6-methoxy indole (VII)

In a 500 ml volume of autoclave, a solution of VI (6.1 g) in ethanol (300 ml) containing 10% Pd/C (2.0 g) was stirred at room temperature under the hydrogen pressure at 15 kg/cm^2. When the hydrogen uptake ceased, the catalyst was filtered off and the filtrate was evaporated. The residue was recrystallized from methanol. Yield: 3.5 g (88%). mp 196~197°C. IR ν_{max}^{KBr} cm^{-1}: 3480, 3350, 2320~2390 (broad), 1615. NMR $\delta_{Me_4Si}^{DMSO\text{-}d_6}$: 2.90 (2H, t, J=8.3 Hz, $-CH_2-$), 3.65 (3H, s, OCH_3), 3.81 (2H, t, J=8.3 Hz, $-CH_2-$), 4.50 (2H, broad s, NH_2), 6.05 (1H, s, Ar-H), 6.67 (2H, s, $CONH_2$), 12.93 (1H, s, OH). *Anal.* Found: C, 53.72; H, 5.78; N, 18.85. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83%.

1-Carbamoyl-2,3-dihydro-5-[N-(1-ethoxycarbonylethylidene)hydrazino]-7-hydroxy-6-methoxy indole (VIII)

A cold (−10~5°C) solution of VII (2.5 g) dissolved in a mixture of concentrated hydrochloric acid (9.6 ml) and water (20 ml) was diazotized by addition of a saturated solution of sodium nitrite (0.78 g). This

solution was stored at $-5\sim-6$°C, while ethyl 2-acethyl propionate (2.1 g) in ethanol (25 ml) was mixed at -10°C with a solution of sodium hydroxide (4.5 g) in water (6.7 ml). Then the preserved diazonium solution was added dropwise with stirring below 2°C and stirred for additional 1 hr at the same temperature. The precipitated crystals were collected, dissolved in ethyl acetate, decolorized with charcoal, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from ethanol. Yield: 3.3 g (88%). mp 194~195°C.

Ethyl 3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo [3,2-e]indole-7-carboxylate (IX)

Through a suspension of VIII (1.0 g) in dry ethanol (15 ml) was passed dry hydrogen chloride gas at 30°C for 70 min. The reaction mixture was poured into ice-water and the precipitated crystals were collected. Further quantities of the product were recovered from the aqueous mother liquor by extraction with chloroform. The combined crude product was purified through silica gel column eluted with chloroform–methanol (50: 1) followed by recrystallization from chloroform-methanol. Yield: 0.11 g (12%). mp 213~214°C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3420, 3310, 1220 (sh), 2520~2570 (broad), 1680, 1625. NMR $\delta_{Me_4Si}^{DMSO\text{-}d_6}$: 1.35 (3H, t, J=7.5 Hz, CH_3), 3.20 (2H, t, J=8.5 Hz, $-CH_2-$), 3.83 (3H, s, OCH_3), 4.03 (2H, t, J=8.5 Hz, $-CH_2-$), 4.27 (2H, q, J=7.5 Hz, OCH_2Me), 6.90 (2H, s, $CONH_2$), 7.00 (1H, d, J=2.0 Hz, indolic H), 11.47 (1H, s, NH), 13.00 (1H, s, OH). *Anal.* Found: C, 56.26; H, 5.40; N, 13.01. Calcd. for $C_{15}H_{13}N_3O_5$: C, 56.72; H, 5.37; N, 13.16%.

3-Carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e]indole-7-carboxylic acid (I)

To 0.05 N potassium hydroxide solution (300 ml) was added IX (0.2 g) and the reaction mixture was allowed to stand overnight at room temperature. The content was acidified with diluted hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate and evaporated. The residue was applied to preparative thin-layer chromatography using silicic acid (Merck GF_{254}). Development with chloroform–methanol (3: 1) afforded crystals. The product was dissolved in a small amount of 0.05 N potassium hydroxide solution, acidified with diluted hydrochloric acid and extracted with ethyl acetate. The dried extract was condensed to a small portion to afford crystals upon cooling. The crystals were collected and dried. Yield: 0.11 g (60%). mp 235°C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3500, 3350, 3220, 2950, 2550, 1670, 1635. NMR $\delta_{Me_4Si}^{DMSO\text{-}d_6}$: 3.19 (2H, t, J=8.5 Hz, $-CH_2-$), 3.78 (3H, s, OCH_3), 4.01 (2H, t, J=8.5 Hz, $-CH_2-$), 6.84 (1H, s, $CONH_2$), 6.90 (1H, d, J=2.0 Hz, indolic H), 11.23 (1H, broad s, NH), 12.81 (1H, s, OH). *Anal.* Found: C, 53.43; H, 4.65; N, 13.67. Calcd. for $C_{13}H_{13}N_3O_5$: C, 53.48; H, 4.50; N, 14.43%.

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