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7-데아자퓨린 유도체의 합성

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Synthesis of 7-Deazapurine Derivatives

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Abstract—A new series of 7-deazapurine derivatives[7,8] as purine antagonists was prepared. Diethyl 4-cyano-N-(diphenylmethylene)-3-arylglutamate[3] were synthesized by LDA-catalyzed Michael addition of N-(diphenylmethylene)glycine ethyl ester with (E)-2-cyano-3-arylacrylate. Deprotection yields diethyl 4-cyano-3-arylglutamate, which were easily cyclized to 4-cyano-2-ethoxycarbonyl-5-oxo-3-arylpyrrolidine[4]. The compounds[4] were treated with $NaBH_4$ and then with $(C_2H_5)_3OBF_4$ to give 4-cyano-5-ethoxy-2H-2-ethoxymethyl-3-aryl-3,4-dihydropyrrole[6], which were converted to 7-aryl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione[7] and 7-aryl-2,6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine[8] with possible activity against neoplastic disease.

Keywords □ Purine antagonist, LDA-catalyzed Michael addition, 4-Cyano-2-ethoxycarbonyl-5-oxo-3-arylpyrrolidine, 4-Cyano-5-ethoxy-2H-2-ethoxymethyl-3-aryl-3,4-dihydropyrrole, 7-Aryl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione, 7-Aryl-2, 6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine, neoplastic disease.

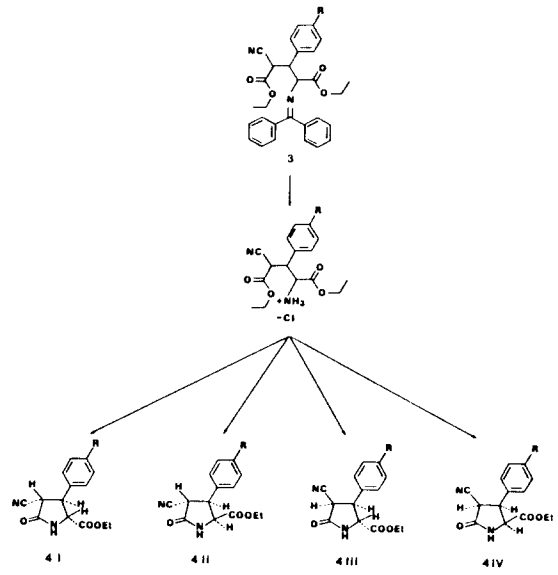
Purine 고리의 7번 질소를 탄소로 치환시킨 7-deazapurine 유도체는 purine antagonists로서 항암효과, 항바이러스효과 및 항균효과를 나타낸다고 보고[1-15]되었다.

천연물로부터 최초로 분리된 7-deazapurine 유도체는 1956년 Nishimura 등이 Streptomyces toyocaensis로부터 분리한 toyocamycin과 1957년 Anzai 등이 Streptomyces tubericidus로부터 분리한 tubercidin이며 이들 역시 항암효과, 항바이러스효과 및 항균효과를 나타낸다고 보고[1,2] 되었다.

1968년에 tyocamycin이, 1969년에 tubercidin이 Tolman 등에 의해 전합성[3,4]되어진 이후 다양한 7-deazapurine 유도체[5-10] 및 7-deazapurine-nucleoside 유도체[11-15]들이 합성되었으며 이들 유도체의 대부분은 *in vitro*에서 L1210과 P388 leukemia에 대한 세포억제효과, 항바이러스효과 또는 항균효과 등을 나타낸다고 보고되었다.

본 실험에서는 이러한 약리활성을 갖는 7-deazapurine 고리에 aryl기를 도입시키면 지용성이 증가되어 이들의 약리활성이 증가되리라 사료되어 7번 위치에 aryl기를 치환시킨 7-Aryl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7) 및 7-Aryl-2,6-di-amino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine(8)을 합성했다. 화합물(7) 및 화합물(8)은 purine antagonists로 항암효과 등 약리활성이 기대되며, 9번 위치의 질소에 β-D-ribofuranose 등을 첨가시키면 7-deazapurine-nucleoside을 합성할 수 있어

#본 논문에 관한 문의는 이 저자에게로.

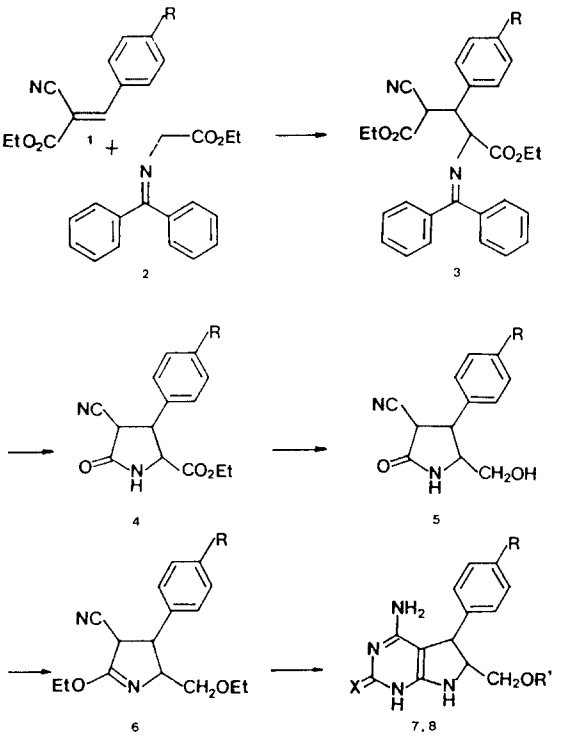


Scheme 1.

이들을 합성하는데 전구물질로 이용할 수 있다.

간단한 아미노산인 glycine으로부터 N-(diphenylmethylene)glycine ethyl ester(2)를 합성[16]하고 LDA 촉매하에서 (E)-2-cyano-3-arylacrylate(1)와 Michael addition 시켜 diethyl 4-cyano-N-(diphenylmethylene)-3-arylglutamate(3)을 합성[17]했다. 화합물(3)을 2 N-HCl로 가수분해하여 보호기(protecting group)을 제거한 후, 축합시켜 5환 헤테로화합물인 4-cyano-2-ethoxycarbonyl-5-oxo-3-arylpyrrolidine(4)을 합성했다. 화합물(4)는 2번, 3번 및 4번에 치환기를 가진 헤테로고리화합물이므로 4개(2,3-trans/trans-, 2,3-cis/trans-, 2,3-trans/cis-, 2,3-cis/cis-) 이성질체의 생성이 가능하다(Scheme 1). 본 실험에서는 축합시 상대적으로 입체장애가 적은 trans/trans-, cis/trans-이성질체만 얻었다. 화합물(4)를 $NaBH_4$로 환원한 후 $(C_2H_5)_3OBF_4$와 반응시켜 3-aryl-4-cyano-5-ethoxy-2H-2-ethoxymethyl-3,4-dihydropyrrole(6)을 합성하고, 이것을 thiourea 및 guanidine hydrochloride와 반응시켜 새로운 7-deazapurine 유도체인 7-aryl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7) 및 7-aryl-2,6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deaza-purine(8)을 합성했다(Scheme 2).

본 실험에서 합성한 7-aryl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7) 및 7-aryl-2,6-diamino-8-ethoxymethy-7,8-dihydro-7(9H)-deazapurine(8)은 항균효과 및 항암효과를 검정할 예정이다.



Scheme 2.

실험방법

기기 및 시약－융점측정은 Fisher-Johns 융점측정기를 사용했으며 이에 대한 보정은 하지 않았다. IR 스펙트럼은 Perkin elmer 783 spectrometer로, ^{1}H-NMR-스펙트럼은 TMS를 내부표준물질로 하여 Bruker AM-300와 Varian Gemini-200으로 얻었다. 반응에 사용한 시약은 주로 Aldrich사와 Sigma사의 제품을 사용했으며, 용매류는 일반적인 방법으로 정제하여 사용했다.

Diethyl 4-cyano-N-(diphenylmethylene)-3-arylglutamate(3)의 합성－잘 건조한 500 ml 삼구 플라스크

에 80 ml 무수 THF를 넣고 건조관을 장치한 후 빙냉하, 질소기류하에서 3.08 mml(22 mol) 무수 diisopropylamine과 21 mmol(1.6 M로서 13.2 ml) n-butyllithium을 넣은 다음 30분 동안 0℃를 유지하면서 교반했다. 이 용액을 methanol-dry ice bath를 써서 −78℃로 냉각한 후 5.52g(20 mmol) N-(diphenylmmethylene)glycine ethyl ester를 녹인 60 ml 무수 THF를 적가했다. 반응액을 −78℃를 유지하면서 1시간 더 저어준 다음 실온으로 온도를 높히고 계속해서 4시간 교반했다. 반응이 끝나면 2 ml pH 7-완충액(8.6% KH_2PO_4, 1.4% NaOH 수용액)을 가하고 감압하에서 증발농축했다. 잔사에 50 ml pH 7-완충액을 가하고 에테르로 추출한 다음 감압하에서 용매를 제거한 후 메타놀로 재결정했다.

Diethyl 4-cyano-N-(diphenylmethylene)-3-phenylglutamate(3a)−8.90g(95%), mp 114~115℃ (methanol), IR(KBr, cm $^{-1}$): 2260, 1745, 1730, 1620, ^{1}H-NMR($CDCl_3$, δ=ppm): 0.85(t, 3H); 1.10(t, 3H); 3.78 (q, 2H); 4.07(q, 2H); 4.26(dd, J=9.8, J=4.9, 1h, 3-H); 4.41(d, J=4.9, 1H, H-4); 4.57(d, J=9.8, 1H, 2-H); 7.02~7.74(m, 15H, aromat.)

Diethyl 4-cyano-N-(diphenylmethylene)-3-(p-chlorophenyl)glutamate(3b)−9.66g(96%), oil, IR(KBr, cm^{-1}): 2250, 1740, ^{1}H-NMR($CDCl_3$, δ=ppm): 0.86(t, 3H); 1.12(t, 3H); 3.79(q, 2H); 4.02(q, 2H); 4.19(dd, J=9.8, J=4.7, 1H, 3-H); 4.37(d, J=4.7, 1H, H-4); 4.50(d, J=9.8, 1H, 2-H); 6.90~7.92(m, 14H, aromat.)

Diethyl 4-cyano-N-(diphenylmethylene)-3-(p-methoxyphenyl)glutamete(3c)−9.27g(93%), oil, IR(KBr, cm^{-1}): 2220, 1740, ^{1}H-NMR($CDCl_3$, δ=pm): 0.86(t, 3H); 1.12(t, 3H); 3.63(s, 3H, OCH_3); 3.83(q, 2H); 4.07(q, 2H); 4.07(, 2H); 4.22(dd, J=9.4, J=5.1, 1H, 3-H); 4.35(d, J=5.1, 1H, H-4); 4.52(d, J=9.4, 1H, 2-H); 6.75~8.05(m, 14H, aromat.)

4-cyano-2-ethoxycarbonyl-5-oxo-3-phenylpyrrolidine(4)의 합성−10 mmol diethyl 4-cyano-N-(diphenylmethylene)-3-arylglutamate를 50 ml 에테르에 녹이고 빙냉하에서 6 ml 2N-HCl을 30분 동안 적하하면서 교반하고 계속해서 실온에서 12시간 교반했다 에테르층을 분리하여 무수 망초로 수분을 제거하고 감압하에서 증발농축했다. 수층을 K_2CO_3 용액으로 pH 8로 한 후 50 ml chloroform를 넣고 12시간 교반했다. chloroform층을 분리하고 무수망초로 수분을 제거한 후 감압하에서 증발농축했다. 에테르 및 chloroform층의 잔사를 silicagel(70~230 mesh, Merck Art. 7734)column chromatography[eluent; $CHCl_3$: MeOH(95 : 5)]로 이성질체를 분리하고 ethyl acetate/petroleum ether 또는 메타놀로 재결정했다.

4-trans-Cyano-2-trans-ethoxycarbonyl-5-oxo-3-phenylpyrrolidine(4aI)−1.69g(65.4%, from 3a), mp 117~118℃ (ethyl acetate/petroleum ether), IR(KBr, cm^{-1}): 3250, 2240, 1735, 1700, ^{1}H-NMR($CDCl_3$, δ=ppm): 1.22(t, 3H, 2-trans-$COOCH_2C\underline{H}_3$); 3.67(d, J=10, 1H, 4-H); 3.92(dd, J=10, J=7.4, 1H, 3-H); 4.19(m, 2H, $COOC\underline{H}_2CH_3$); 4.36(d, J=7.4, 1H, 2-H); 6.52(s, NH); 7.25~7.50(m, 5H, aromat.)

4-trans-Cyano-2-cis-ethoxycarbonyl-5-oxo-3-phenylpyrrolidine(4aII)−0.21g(8.0%, from 3a), mp 147~148℃ (methanol), IR(KBr, cm^{-1}): 3360, 2260, 1745, 1720, ^{1}H-NMR($CDCl_3$, δ=ppm): 0.80(t, 3H, 2-cis-$COOCH_2C\underline{H}_3$); 3.77(m, 2H, $COOC\underline{H}_2CH_3$); 4.08(d, J=10.4, 1H, 4-H); 4.22(dd, J=10.4, J=7.8, 1H, 3-H); 4.53(d, J=7.8, 1H, 2-H); 6.55(s, NH); 7.20~7.45(m, 5H, aromat.)

4-trans-Cyano-2-trans-ethoxycarbonyl-5-oxo-3-(p-chlrophenyl)pyrrolidine(4bI)−0.15g(5.0%, from 3b), mp 132~133℃ (ethyl acetate/petroleum ether), IR (KBr, cm^{-1}): 3335, 2250, 1720, ^{1}H-NMR($CDCl_3$, δ=ppm): 1.22(t, 3H, 2-trans-$COOCH_2C\underline{H}_3$); 3.63(d, J=10.2, 1H, 4-H); 3.90(dd, J=10.2, J=7.8, 1H, 3-H); 4.21(m, 2H, $COOC\underline{H}_2CH_3$); 4.32(d, J=7.8, 1H, 2-H); 6.58(s, NH); 7.22~7.50(m, 4H, aromat.)

4-trans-Cyano-2-cis-ethoxycarbonyl-5-oxo-3-(p-chlorophenyl)pyrrolidine(4bII)−1.93g(65.8%, from 3b), mp 147~148℃ (methanol), IR(KBr, cm^{-1}): 3240, 2250, 1735, 1710, ^{1}H-NMR($CDCl_3$, δ=ppm): 0.88(t, 3H, 2-cis-$COOCH_2C\underline{H}_3$); 3.83(m, 2H, $COOC\underline{H}CH_3$); 4.03(d, J=10.4, 1H, 4-H); 4.20(dd, J=10.4, J=7.8, 1H, 3-H); 4.53(d, J=7.8, 1H, 2-H); 6.50(s, NH); 7.12~7.40(m, 4H, arommat.)

4-trans-Cyano-2-trans-ethoxycarbonyl-5-oxo-3-(p-methoxyphenyl)pyrrolidine(4cI)−1.3g(45%, from 3c), mp 131~132℃ (ethyl acetate/petroleum ether), IR (KBr, cm^{-1}): 3220, 2260, 1720, ^{1}H-NMR($CDCl_3$, δ

=ppm): 1.21(t, 3H, 2-trans-$COOCH_2C\underline{H}_3$); 3.64(d, J=10.2, 1H, 4-H); 3.81(s, 3H, OCH_3); 3.87(dd, J=10.2, J=7.8, 1H, 3-HH); 4.20(m, 2H, $COOC\underline{H}_2CH_3$); 4.35 (d, J=7.8, 1H, 2-H); 6.78(s, NH); 6.90~7.30(m, 4H, aromat.)

4-trans-Cyano-2-cis-ethoxycarbonyl-5-oxo-3-(p-methoxyphenyl)pyrrolidine(4cII)－0.98g(34%, from 3 c), mp 173~174℃ (methanol), IR(KBr, cm^{-1}): 3440, 2250, 1735, 1690, ^{1}H-NMR($CDCl_3$, δ=ppm): 0.86(t, 3HH, 2-cis-$COOCH_2C\underline{H}_3$); 3.78(s, 3H, OCH_3); 3.80(m, 2HH, $COOC\underline{H}_2CH_3$); 4.05(d, J=10.8, 1H, 4-H); 4.17 (dd, J=10.8, J=7.6, 1H, 3-H); 4.48(d, J=76, 1H, 2-H); 6.77(s, NH); 6.82~7.18(m, 4H, aromat.)

4-Cyano-2-hydroxymethyl-5-oxo-3-arylpyrrolidie(5)의 합성－5 mmol 4-cyano-2-ethoxycarbonyl-5-oxo-3-arylpyrrolidine을 50 m*l* 무수에타놀에 용해시키고 여기에 0.38g(10 mmol) sodium borohydride를 가하고 건조관을 장치한 후 실온에서 5~8 시간 교반했다. 반응이 끝난 후 1N-HCl로 중화하고 감압하에 증발농축한 후 chloroform/H_2O로 추출했다. 물층을 2N-HCl로 pH 1~2이 되게 한 후 chloroform으로 2~3회 추출했다. Chloroform층을 합친 후 무수망초로 수분을 제거한 후 감압하에서 증발농축한 다음 methanol 또는 ethyl acetate/petroleum ether로 재결정했다.

trans-4-Cyano-2-trans-hydroxymethyl-5-oxo-3-phenylpyrrolidine(5aI)－1.71g(79%, from 4aI), mp 167~168℃ (methanol), IR(KBr, cm^{-1}): 3420, 3210, 2250, 1710, ^{1}H-NMR(DMSO-d_6, δ=ppm): 3.28 and 3.47(m, 2H, $C\underline{H}_2OH$); 3.57(dd, J=11.3, J=9.0, 1H, 3-H); 3.62 (m, 1H, 2-H); 4.33(d, J=11.3, 1H, 4-H); 4.85(t, J=5.5, 1H, OH); 7.23~7.48(m, 5H, aromat.); 8.36(s, NH)

trans-4-Cyano-2-cis-hydroxymethyl-5-oxo-3-phenylpyrrolidine(5aII)－1.75g(81%, from 4aII), mp 152~153℃ (ethyl acetate/petroleum ether), IR(KBr, cm^{-1}): 3365, 3215, 2250, 1700, ^{1}H-NMR(DMSO-d_6, δ=ppm): 2.98 and 3.10(m, 2H, $C\underline{H}_2OH$); 3.77(m, 1H, 2-H); 4.08(dd, J=12.5, J=7.5, 1H, 3-H); 4.59(d, J=12.5, 1H, 4-H); 4.78(t, J=4.5, 1H, OH); 7.20~7.45(m, 5H, aromat.); 8.36(s, NH)

trans-4-Cyano-2-cis-hydroxymethyl-5-oxo-3-(p-chlorophenyl)pyrrolidine(5bII)－2.13g(85%, from 4bII), mp 203~204℃ (methanol), IR(KBr, cm^{-1}): 3440, 3220, 2260, 1700, ^{1}H-NMR(DMSO-d_6, δ=ppm): 3.01 and 3.13(m, 2H, $C\underline{H}_2OH$); 3.79(m, 1H, 2-H); 4.10(dd, J=12.7, J=7.9, 1H, 3-H); 4.54(d, J=12.7, 1H, 4-H); 4.73(t, J=4.3, 1H, OH); 7.40~7.55(m, 4H, aromat.); 8.38(s, NH)

trans-4-Cyano-2-trans-hydroxymethyl-5-oxo-3-(p-methoxyphenyl)pyrrolidine(5cI)－1.95g(79%, from 4 cI), mp 178~179℃ (methanol), IR(KBr, cm^{-1}): 2250, 1700 ^{1}H-NMR(DMSO-d_6, δ=ppm): 3.27 and 3.43(m, 2H, $C\underline{H}_2OH$); 3.51(dd, J=11.3, J=8.5, 1H, 3-H); 3.57 (m, 1H, 2-H); 3.75(s, 3H, OCH_3); 4.33(d, J=11.3, 1H, 4-H); 4.86(t, J=5.4, 1H, OH); 6.87~7.42(m, 4H, aromat.); 8.37(s, NH)

trans-4-Cyano-2-cis-hydroxymethyl-5-oxo-3-(p-methoxyphenyl)pyrrolidine(5cII)－2.12g(86%, from 4 cII), mp 204~205℃ (methanol), IR(KBr, cm^{-1}): 3440, 3210, 2250, 1700, ^{1}H-NMR(DMSO-d_6, δ=ppm): 2.99 and 3.12(m, 2H, $C\underline{H}_2OH$); 3.76(s, 3H, OCH_3); 3.76(m, 1H, 2-H); 4.01(dd, J=12.8, J=7.6, 1H, 3-H); 4.44(d, J=12.8, 1H, 4-H); 4.72(t, J=4.9, 1H, OH); 6.86~7.40(m, 4H, armat.); 8.39(s, NH)

4-Cyano-5-ethoxy-2H-2-ethoxymethyl-3-aryl-3,4-dihydropyrrole(6)의 합성－질소 기류하에서 5 mmol 4-cyano-2-hydroxymethyl-5-oxo-3-arylpyrrolidine을 100 m*l* dichloromethane에 현탁시키고 여기에 2.85g (15 mmol) triethyloxonium tetrafluoroborate을 가한 후 실온에서 12시간 교반했다. 반응이 끝나면 $NaHCO_3$ 포화수용액을 가한 다음 유기용매층을 분리하고 감압하에서 증발농축하고 silica gel(70~230 mesh, Merck Art. 7734) column chromatography[eluent; $CHCl_3$: MeOH(99 : 1)]로 정제했다.

4-trans-Cyano-5-ethoxy-2H-2-trans-ethoxymethyl-3-phenyl-3,4-dihydropyrrole(6aI)－2.51g(92%, from 5 aI), oil, IR(Nest, cm^{-1}): 2240(－CN), 1650

4-trans-Cyano-5-ethoxy-2H-2-cis-ethoxymethyl-3-phenyl-3,4-dihydropyrrole(6aII)－2.53g(93%, from 5 aII), oil, IR(Nest, cm^{-1}): 2240, 1650

4-trans-Cyano-5-ethoxy-2H-2-cis-ethoxymethyl-3-(p-chlorophenyl)-3,4-dihydropyrrole(6bII)－2.91g(95 %, from 5bII), oil, IR(Nest, cm^{-1}): 2250, 1650

4-trans-Cyano-5-ethoxy-2H-2-trans-ethoxymethyl-3-(p-methoxyphenyl)-3,4-dihydropyrrole(6cI)－2.87g

(95%, from 5cI), oil, IR(Nest, cm^{-1}): 2240(−CN), 1660

4-trans-Cyano-5-ethoxy-2H-2-cis-ethoxymethyl-3-(p-methoxyphenyl)-3,4-dihydropyrrole(6cII)−2.84g (94%, from 5cII), oil, IR(Nest, cm^{-1}): 2250, 1655

7-Aryl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7)의 합성−10 mg 금속 나트륨을 20 ml 무수 에타놀에 녹여 C_2H_5ONa 용액을 만든 후 여기에 0.152g(2 mmol) thiourea 및 2 mmol 4-cyano-5-ethoxy-2H-2-ethoxymethyl-3-aryl-3,4-dihydropyrrole을 넣고 130℃ 유욕에서 5시간 동안 환류시켰다. 반응이 끝나면 1N-HCl로 중화하고 감압하에서 증발 농축하고 silica gel(70～230 mesh, Merck Art. 7734) column chromatography [eluent;$CHCl_3$: MeOH(95 : 5)]로 분리 정제하고 methanol로 재결정했다.

7-trans-Phenyl-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7aI)−133 mg (22%, 6aI), mp 206～207℃ (methanol), IR(KBr, cm^{-1}): 3440, 3380, 3120(NH), 1660, 1580, ^{1}H-NMR(DMSO-d_6, δ=ppm): 1.14(t, 3H, $OCH_2C\underline{H}_3$); 3.41(m, 2H, -CH_2O-); 3.50(q, 2H, $OC\underline{H}_2CH_3$); 3.62(m, 1H, 8-H); 4.11(d, J=2.9, 1H, 7-H); 5.97(s, 2H, NH_2); 7.14～7.33(m, 5H, aromat.); 7.55(s, 1H, N9-H); 10.9(s, N3-H)

7-trans-Phenyl-6-amino-8-hydroxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7aI′)−44 mg(8%, from 6aI), ^{1}H-NMR(DMSO-d_6, δ=ppm): 3.33(m, 2H, -CH_2O-); 3.48(m, 1H, 8-H); 4.13(d, J=2.1, 1H, 7-H); 6.03(s, 2H, NH_2); 7.15～7.54(m, 5H, aromat.); 7.54(s, 1H, N9-H); 10.9(s, N3-H)

7-cis-(p-Chlorophenyl)-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7bII)−236 mg(35%, 6bII), mp 219～220℃ (methanol), IR (KBr, cm^{-1}): 3440, 3380, 1655, 1560, ^{1}H-NMR (DMSO-d_6, δ=ppm): 0.96(t, 3H, $OCH_2C\underline{H}_3$); 2.88 and 3.14(m, 2H, -CH_2O-); 3.04(m, 2H, $OC\underline{H}_2CH_3$); 4.28(m, 1H, 8-H); 4.46(d, J=9.6, 1H, 7-H); 6.59(s, 2H, NH_2); 7.12～7.36(m, 4H, aromat.); 7.68(s, 1H, N9-H)

7-trans-(p-Methoxyphenyl)-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7cI)−286 mg(43%, from 6cI), mp 214～241℃ (methanol), IR(KBr, cm^{-1}): 3470, 3300, 3150, 1655, 1570, ^{1}H-NMR(DMSO-d_6, δ=ppm): 1.12(t, 3H, $OCH_2C\underline{H}_3$); 3.55(m, 2H, -CH_2O-); 3.47(q, 2H, $OC\underline{H}_2CH_3$); 3.60(m, 1H, 8-H); 3.71(s, 3H, OCH_3); 4.03(d, J=2.6, 1H, 7-H); 5.72(s, 2H, NH_2); 6.83～7.09(m, 4H, aromat.); 7.09(s, 1H, N9-H)

7-cis-(p-Methoxyphenyl)-6-amino-8-ethoxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7cII)−86 mg(13%, from 6cII), mp 235～236℃ (methanol), IR(KBr, cm^{-1}): 3440, 3380, 3180, 1655, 1560, ^{1}H-NMR(DMSO-d_6, δ=ppm): 0.97(t, 3H, $OCH_2C\underline{H}_3$); 2.88 and 3.16(m, 2H, -CH_2O-); 3.04(m, 2H, $OC\underline{H}_2CH_3$); 3.71(m, 3H, 8-H); 4.29(d, J=9.3, 1H, 7-H); 5.76(s, 2H, NH_2); 6.80～6.96(m, 4H, aromat.); 6.85(s, 1H, N9-H)

7-cis-(p-Methoxyphenyl)-6-amino-8-hydroxymethyl-7,8-dihydro-7(3H, 9H)-deazapurine-2-thione(7cII′)−91 mg(15%, from 6cII), mp 235～236℃ (methanol, dec), IR(KBr, cm^{-1}): 3470, 3300, 1655, 1570, ^{1}H-NMR(DMSO-d_6, δ=ppm): 2.99(m, 2H, -CH_2O-); 3.69(s, 3H, OCH_3); 3.93(m, 1H, 8-H); 4.26(d, J=9.4, 1H, 7-H); 4.43(t, J=4.8, OH); 5.84(s, 2H, NH_2); 6.85 (m, 1H, NH); 6.75～6.97(m, 4H, aromat.)

7-Aryl-s,6-diamino-8-ethoxymethyl-7,8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine(8)의 합성−10 mg 금속나트륨을 20 ml 무수 에타놀에 녹여 C_2H_5 ONa 용액을 만든후 여기에 0.191g(2 mmol) guannidine hydrochloride 및 2 mmol 4-cyano-5-ethoxy-2H-2-ethoxymethyl-3-aryl-3,4-dihydropyrrole을 넣고 130℃ 유욕에서 5시간 동안 환류시켰다. 반응이 끝나면 1N-HCl로 중화하고 감압하에서 증발 농축하고 silica gel(70～230 mesh, Merck Art. 7734) column chromatography[eluent; $CHCl_3$: MeOH(95 : 5)]로 분리 정제하고 methanol 또는 acetone/n-hexane으로 재결정했다.

7-cis-Phenyl-2,6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine(8aII)−86 mg(15%, from 6aII),mp170～171℃ (acetone/n-hexane),IR(KBr,cm^{-1}): 3420, 3360, 3320, 3180, 1630, 1600, ^{1}H-NMR(DMSO-d_6, δ=ppm): 0.97(t, 3H, $OCH_2C\underline{H}_3$); 2.85 and 3.17(m, 2H, -CH_2O-); 3.02(m, 2H, $OC\underline{H}_2CH_3$); 3.99(m, 1H, 8-H); 4.24(d, J=9.0, 1H, 7-H); 5.06(s, 2H, NH_2); 5.44

(s, 2H, NH_2); 6.00(s, 1H, NH); 7.04~7.26(m, 5H, aromat.)

7-cis-Phenyl-2,6-diamino-8-hydroxymethyl-7,8-dihydro-7(9H)-deazapurine(8aII′)—51 mg(10%, from 6 aII), mp 222~223℃ (methanol), IR(KBr, cm^{-1}): 3420, 3340, 1660, ^{1}H-NMR(DMSO-d_6, δ=ppm): 2.90 and 3.01(m, 2H, -CH_2O-); 3.45(t, 1H, OH); 3.93(m, 1H, 8-H); 4.24(d, J=9.0, 1H, 7-H); 5.01(s, 2H, NH_2); 5.45(s, 2H, NH_2); 5.96(s, 1H, NH); 7.05~7.30(m, 5H, aromat.)

7-cis-(p-Chlorophenyl)-2,6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine(8bII)—51 mg(8%, from 6bII), mp 146~147℃ (acetone/n-hexane), IR(KBr, cm^{-1}): 3490, 3460, 3350, 3310, 1660, ^{1}H-NMR(DMSO-d_6, δ=ppm): 0.98(t, 3H, $OCH_2C\underline{H}_3$); 2.85 and 3.17(m, 2H, -CH_2O-); 3.05(m, 2H, $OC\underline{H}_2CH_3$); 4.00(m, 1H, 8-H); 4.26(d, J=9.0, 1H, 7-H); 5.13(s, 2H, NH_2); 5.45(s, 2H, NH_2); 6.03(s, 1H, NH); 7.04~7.30(m, 4H, aromat.)

7-cis-(p-Chlorophenyl)-2,6-diamino-8-hydroxymethyl-7,8-dihydro-7(9H)-deazapurine(8bII′)—76 mg(13%, from 6bII), mp 243~244℃ (methanol), IR(KBr, cm^{-1}): 3440, 3380, 3120, 1650, 1580, ^{1}H-NMR (DMSO-d_6, δ=ppm): 3.00(m, 2H, -CH_2O-); 3.91(m, 1H, 8-H); 4.24(d, J=8.9, 1H, 7-H); 4.39(t, 1H, OH); 5.09(s, 2H, NH_2); 5.43(s, 2H, NH_2); 5.96(s, 1H, NH); 7.03~7.32(m, 4H, aromat.)

7-trans-(p-Methoxyphenyl)-2,6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine(8cI)—126 mg (20%, from 6cII), mp 220℃ (methanol, dec.), IR(KBr, cm^{-1}): 3400, 3380, 3120, 1650, 1580, ^{1}H-NMR (DMSO-d_6, δ=ppm): 1.12(t, 3H, $OCH_2C\underline{H}_3$); 3.34(m, 2H, -CH_2O-); 3.47(m, 2H, $OC\underline{H}_2CH_3$); 3.71(s, 3H, CH_3); 3.92(d, J=3.4, 1H, 7-H); 4.94(s, 2H, NH_2); 5.42(s, 2H, NH_2); 6.17(s, 1H, NH); 6.81~7.09(m, 4H, aromat.)

7-cis-(p-Methoxyphenyl)-2,6-diamino-8-ethoxymethyl-7,8-dihydro-7(9H)-deazapurine(8cII)—139 mg (22%, from 6cII), mp 215~217℃ (methanol), IR(KBr, cm^{-1}): 3500, 3380, 3170, 1650, 1590, ^{1}H-NMR (DMSO-d_6, δ=ppm): 0.97(t, 3H, $OCH_2C\underline{H}_3$); 2.85 and 3.16(m, 2H, -CH_2O-); 3.01(m, 2H, $OC\underline{H}_2CH_3$); 3.70(s, 3H, OCH_3); 3.94(m, 1H, 8-H); 4.17(d, J=9.1, 1H, 7-H); 5.10(s, 2H, NH_2); 5.48(s, 2H, NH_2); 5.98(s, 1H, NH); 6.72~6.96(m, 4H, aromat.)

결과 및 고찰

간단한 아미노산인 glycine 유도체(2)를 LDA 촉매하에서 (E)-2-cyano-3-arylacrylate(1)와 Michael addition시켜 화합물(3)을 얻었고, 이것을 가수분해하고 축합시켜 화합물(4)을 얻었다. 화합물(4)는 4개의 이성질체의 생성이 가능하며(Scheme I), 본 실험에서는 축합시 상대적으로 입체장애가 적은 2,3-trans/trans-및 2,3-cis/trans-이상질체만 얻었다. 두 이성질체에 대한 구조분석은 2번-탄소에 붙어있는 -$COOCH_2CH_3$ 기의 ^{1}H-NMR-스펙트럼으로 알 수 있다. 2번 탄소의 -$COOCH_2CH_3$기는 trans체의 경우에서는 δ=1.2 및 4.2 ppm 부근에 나타나는데 반해, cis체에서는 δ=0.9 및 3.8 ppm 부근에서 나타났으며 이는 cis체에서의 -$COOCH_2CH_3$기가 trans체에서의 -$COOCH_2CH_3$기 보다 3번 탄소의 방향족고리와 더 밀접하므로 차폐효과가 커져서 고자장으로 이동한 결과이다. 화합물(4)를 $NaBH_4$로 환원한 후 $(C_2H_5)_3OBF_3$와 반응시켜 화합물(6)을 합성하고, 이것을 thiourea 및 guanidine·HCl과 축합시켜 목적화합물인 7-deazapurine 유도체(7, 8)를 합성했다.

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