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CHEMICAL STUDIES ON TUBERACTINOMYCINS. X.[1)]
TOTAL SYNTHESIS OF TUBERACTINOMYCIN O[2)]

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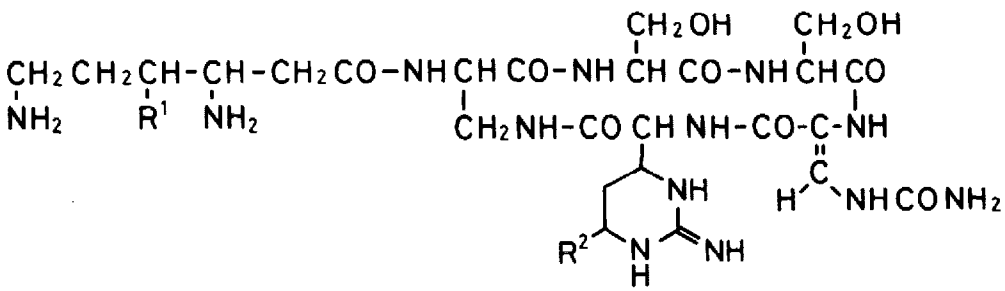
Antituberculous peptide, tuberactinomycin O, had been isolated as one of the four tuberactinomycin congeners[3)] and its chemical structure was conclusively elucidated by X-ray analysis as depicted in Fig. 1.[4,5)] A total synthesis of tuberactinomycin O seems to be worth-while to be challenged, in view of the unique structure with quite a few unusual amino acids and of an exploitation of structural study employing appropriate analogs.



		R^1	R^2
Tuberactinomycin	A	OH	OH
	B	H	OH
	N	OH	H
	O	H	H

Fig. 1 Tuberactinomycin B = Viomycin

As starting materials, L-α,β-diaminopropionic acid was synthesized from L-aspartic acid through Schmidt reaction[6)] and L-capreomycidine was prepared from

the acid hydrolyzate of natural tuberactinomycin N. Throughout the synthetic procedures, difficulties arising from especially labile character of β-ureidodehydroalanine part must be overcome by some device. In a preliminary experiment, β,β-diethoxyalanine,[7] which was prepared by acetalization of α-formylglycine, could be successfully used for peptide synthesis and converted into β-ureidodehydroalanine residue on the peptide chain at any synthetic step. Necessary fragments for total synthesis were prepared successively as mentioned in Fig. 2. Although DL-form of β,β-diethoxyalanine was used in this synthesis, diastereoisomers of the peptide intermediates have never been separated each other in any synthetic stages. A protected pentapeptide (1) was obtained by fragment condensation using dicyclohexylcarbodiimide—1-hydroxybenztriazole method at the side of carboxyl group of N^{α}-*t*-butoxycarbonyldiaminopropionic acid avoiding a possible racemization.

Ethyl ester of 1 was replaced with the active 1-succinimidyl ester (2) through saponification followed by reesterification. *o*-Nitrophenylsulfenyl (NPS) group in 2 was selectively removed under acidic conditions and the resulting pentapeptide ester was cyclized in pyridine at either 60°C or room temperature under high dilution condition to give cyclic peptide (3). [mp 250°C (decomp.), Found: C, 49.84; H, 7.47; N, 16.42 %, M.W. 811 (vapour pressure osmometry), Calcd for $C_{35}H_{62}O_{13}N_{10}\cdot H_2O$: C, 49.52; H, 7.60; N, 16.50 %, M.W., 849] The cyclization yield of about 25 % did not vary significantly depending on the reaction temperature. After removal of all protections except diethyl acetal from (3) by hydrogenolysis and then acidolysis, a solution of the peptide was refluxed in acetone—2M hydrochloric acid (1 : 1) for 10 min, and excess urea was added to afford an unprotected cyclic peptide (4) involving β-ureidodehydroalanine residue. The product thus obtained was identified with tuberactinamine N,[8] which was obtained from natural tuberactinomycin N, in all respects (Table 1). [Found: C, 36.76; H, 5.52; N, 24.79; Cl, 11.25 %, Calcd for $C_{19}H_{33}O_8N_{11}Cl_2\cdot 1/2\ H_2O$: C, 36.60; H, 5.50; N, 24.71; Cl, 11.37 %]. From the fact that the only single product was secured after addition of urea, the configuration of the double bond in β-ureidodehydroalanine part was found to be exclusively forced to Z configuration plausibly being controled by the

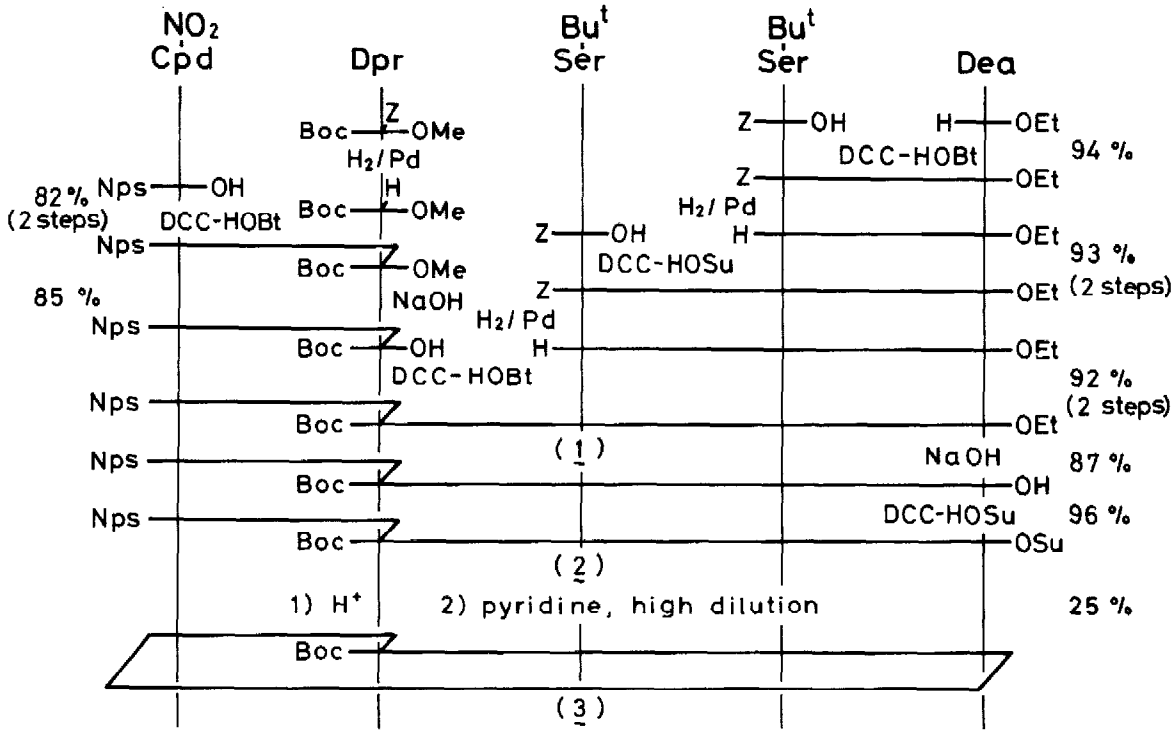


Fig. 2

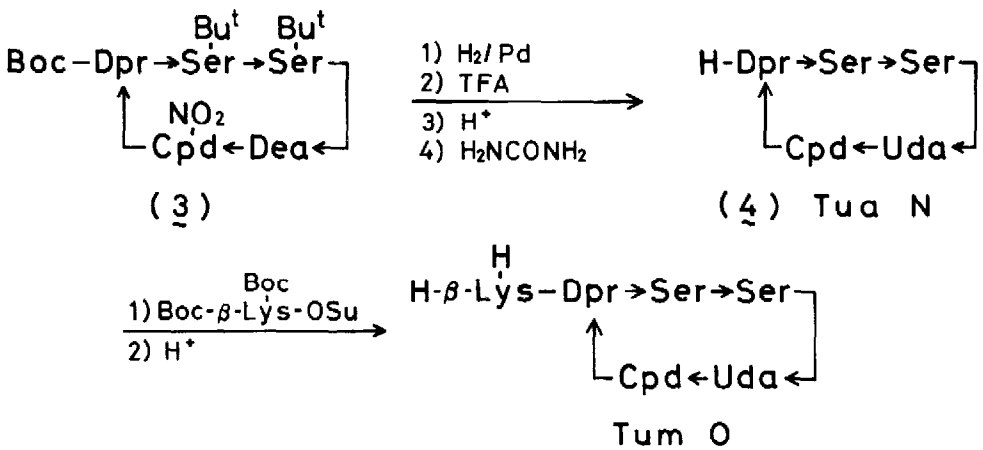


Fig. 3

Abbreviations; DCC: dicyclohexylcarbodiimide, HOSu: 1-hydroxysuccinimide, HOBt: 1-hydroxybenztriazole, Z: benzyloxycarbonyl, Boc: *t*-butoxycarbonyl, Nps: *o*-nitrophenylsulfenyl, Cpd: capreomycidine, Dea: β,β-diethoxyalanine, Uda: β-ureidodehydroalanine, Tua: tuberactinamine, Tum: tuberactinomycin

definite conformation, similar to the natural one, of the cyclic peptide moiety To the peptide 4 thus obtained, β-lysine was introduced in the branched part as shown in Fig. 3. The final synthetic product was completely identical with natural tuberactinomycin O (Table 1). [Found: C, 38.18; H, 6.05; N, 22.84; Cl, 13.55 %, Calcd for $C_{25}H_{46}O_9N_{13}Cl_3 \cdot 1/2\ H_2O$: C, 38.10; H, 6.01; N, 23.11; Cl, 13.50 %]

Table 1. Comparisons of Natural and Synthetic Compounds

		Tua N		Tum O	
		synthetic	natural	synthetic	natural
mp (decomp.)		263-264°	263-264°	240-242°	240-242°
[α] (c 0.5, H_2O)		$[\alpha]_{365}^{18}$ -54.0°	$[\alpha]_{365}^{18}$ -50.8°	$[\alpha]_D^{16}$ -16.0°	$[\alpha]_D^{16}$ -16.2°
λ_{max} nm(ε)	H_2O	268(26,600)	268(22,000)[8]	268(25,500)	268.5(23,800)[3]
	0.1M HCl	268(26,700)	268(22,000)[8]	268(26,500)	269 (24,900)[3]
	0.1M NaOH	285(17,000)	286(14,000)[8]	286(17,400)	288 (13,200)[3]

REFERENCES AND FOOTNOTES

* To whom correspondence should be addressed.

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