AMINOLYSIS OF 3-ACYLTHIAZOLIDINE-2-THIONE : A SYNTHESIS OF MACROLACTAM CONTAINING AROMATIC RING(S)†

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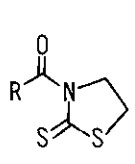
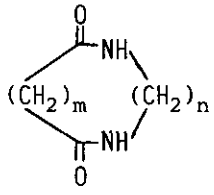
Abstract — An efficient method for synthesis of macrolactams 9~12 containing aromatic ring(s) is described. It is based upon aminolysis of thiazolidine-2-thione derivatives 4a~d with diamines, 5 and 7, spermine 6, and spermidine 8.

Development of new method for the synthesis of macrolactam especially containing aromatic ring(s) is an interesting subject for organic chemist, because such macrolactams have often been found in nature[1] and sometimes they have structures which seem fascinating as synthetic target. They are also interesting because of possibility for availability as NAD model,[2] chiral recognition compound of racemates,[3] and effective metal ion binding ligand.[4]

Recently, aminolysis of 3-acylthiazolidine-2-thione (1) was proved to be useful for the synthesis of aliphatic macrolactams 2 and 3.[5,6] We now report herein an application of this aminolysis in the preparation of macrolactams containing aromatic ring(s).



(1)



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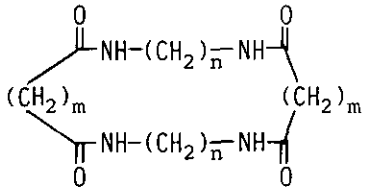
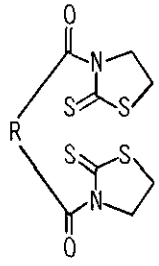


(3)

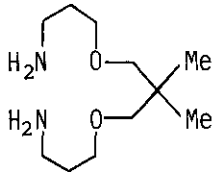
Thiazolidine-2-thione derivatives 4a~d were prepared by two methods described in the previous paper.[6] [4a : yellow and amorphous, 90% yield; 4b : not isolated; 4c : yellow prisms, mp 174~175.5° (decomp.) (from $CHCl_3$), 84% yield; 4d : yellow

† Dedicated to Professor Tetsuji Kametani on the occasion of his retirement.

prisms, mp 203.5~206.5°(decomp.) (from $CHCl_3$), 89% yield]. Subsequent macrolactam ring formation was carried out by the following procedure; typical two examples are shown. Preparation of 9a : A yellow solution of 4a (0.8 mmol) in CH_2Cl_2 (20 ml) and a solution of diamine 5 (0.96 mmol) in CH_2Cl_2 (20 ml) were added dropwise using two mechanically driven syringes ("microfeeder") over 2 hr into CH_2Cl_2 (130 ml) under nitrogen with stirring at room temperature and the mixture was stirred for further 30 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a Sephadex LH-20 column by MeOH to afford tetramide and diamide 9a : colorless needles from MeOH, mp 265~266°, *Anal*. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found : C, 65.12; H, 8.29; N, 7.99%, M^+ *m/e* = 348, IR(KBr) 3400(sh), 3280, 3100, 1662, 1638, and 1598 cm^{-1}; NMR($CDCl_3$) δ 0.88(s,6H), 1.60~2.04(m,4H), 3.08~3.80(m,12H), 7.08(m,2H), 7.42~8.10 ppm (m,4H). Preparation of 9b : Dicyclohexylcarbodiimide (2.2 mmol) and 4-dimethylamino-pyridine (0.2 mmol) were added to a suspension of dinicotinic acid (1 mmol) and thiazolidine-2-thione (2 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at room temperature over night and a precipitation (urea) was filtered off. This yellow filtrate and a solution of diamine 5 (0.96 mmol) in CH_2Cl_2 (20 ml) were subjected to the high dilution procedure using microfeeder mentioned above. Usual work up gave tetramide and diamide 9b : colorless needles, mp 259.5~261° (from MeOH), *Anal*. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87; H, 7.79; N, 12.03. Found : C, 61.74; H, 8.03; N, 11.85%, M^+ *m/e* = 349, IR(KBr) 3400(sh), 3280, 3100, 1662, 1638,1598, and 1564 cm^{-1}, NMR($CDCl_3$) δ 0.88(s,6H), 1.60~2.04(m,4H), 3.08~3.80(m,12H), 7.08(m,2H), 7.42~8.16 ppm (m,3H). The results for all macrolactams are shown in Table.



(4a~d)



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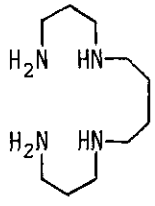

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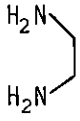

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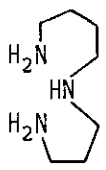

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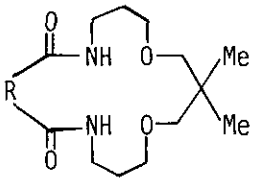
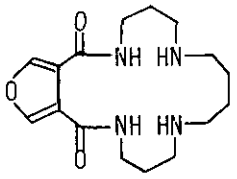


(9a~d)



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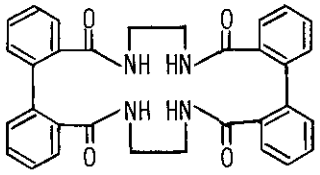

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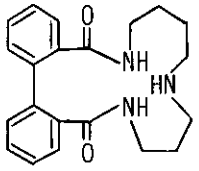


(12)

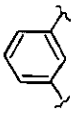
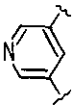
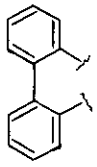
a : R =  , b: R =  , c :  , d : 

Table Preparation of Macrolactam

Reactants	Time[a]	Product (isolated yield)	
		diamide	tetramide
4a + 5	30 min	9a (91%)	(6%)
4b + 5	30 min	9b (50%)[b]	(12%)
4c + 5	c	9c (93%)	(trace)
4d + 5	7 days	9d (76%)	(17%)
4c + 6	c	10 (66%)	(21%)
4d + 7	2 days		11 (93%)
4d + 8	2 days	12 (79%)	(12%)

[a] The reaction time after complete addition of reactants.

[b] Calculated from dinicotinic acid.

[c] Work-up immediately after complete addition of reactants.

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