The Acyl-Exchange Reactions of N-Acyl Lactams with Amines. A Novel Synthesis of N-Substituted Amides

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The *N*-acylated lactam has two carbonyl groups in each molecule, so two types of nucleophilic reaction are possible. If an amine attacks the ring carbonyl, a ring-opening reaction may be expected to occur, while if it attacks the acyl carbonyl, an acyl-exchange reaction will occur.

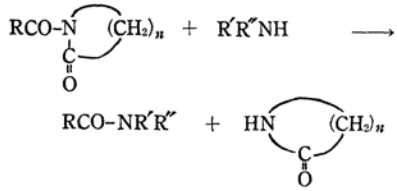
The hydrolysis of the acyl lactam has been investigated,[1] but its aminolysis has not yet been reported. Of various amides, on the other hand, acylimidazole has been successfully used as an acylating reagent in the synthesis of peptides, and it is thought to be an active amide.[2,3]

The present paper is concerned with the aminolysis of some acyl lactams, i.e., the *N*-acetyl or *N*-benzoyl derivatives of 2-pyrrolidone, 2-piperidone and ε-caprolactam. The reactions were studied by means of product isolation techniques; it was found that *N*-acyl lactams generally exchange their *N*-acyl groups readily with a hydrogen atom of the amines, thus producing corresponding amides in good yields. The results obtained indicate that *N*-acyl lactams can be considered as a kind of active amides.

Results and Discussion

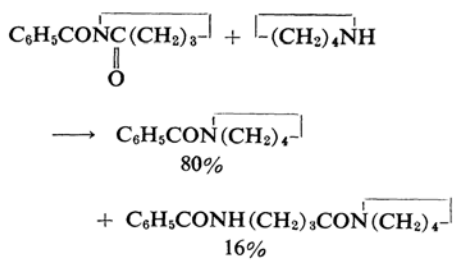
The general procedure for the aminolysis of *N*-acyl lactams was as follows: a tetrahydrofuran solution of an *N*-acyl lactam and an amine (aniline, benzylamine, *n*-butylamine, diethylamine, pyrrolidine or piperidine) was sealed in a glass tube and kept standing for a predetermined length of time in a bath. The temperature of the bath was about 50°C in the case of *N*-benzoyl lactams and about 90°C in the case of *N*-acetyl lactams, varying with the reactivity of the series of lactams.

All of the acetyl lactams used readily reacted with amines and gave corresponding amides in good yields. *N*-Benzoyl lactam also reacted with amines and gave satisfactory results. These results are summarized in Tables II and III.



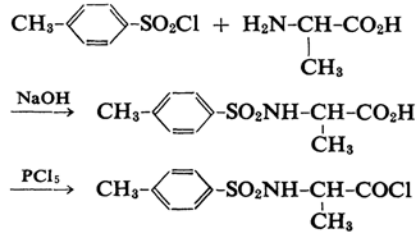
The chemical behavior of the acyl lactams described above indicates that these compounds are good acylating reagents and may be regarded as active amides.

It is noteworthy that small amounts (ca. 20%) of ring opened products were obtained by the reaction of *N*-benzoyl-2-pyrrolidine with such secondary amines as diethylamine, pyrrolidine and piperidine. In the other cases studied, however, no ring-opened product was obtained.

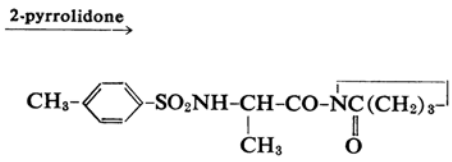


On the other hand, the results of alkaline hydrolysis by potassium hydroxide (Table IV) indicate that the ring-opened products were always obtained, along with lactams, regardless of the number of carbon atoms in the lactam rings. The reason why secondary amines attack the carbon atom of the ring carbonyl of *N*-benzoyl-2-pyrrolidone in an exceptional manner is an interesting but as yet unclarified problem.

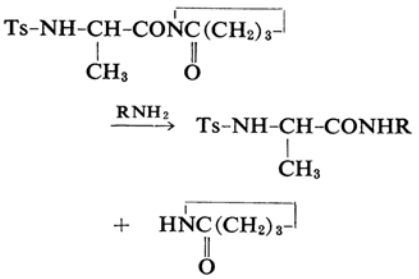
Applications: The novel acyl-exchange reaction presented above was applied to peptide synthesis. *N*-Tosyl-DL-alanyl-2-pyrrolidone was synthesized by the following route.



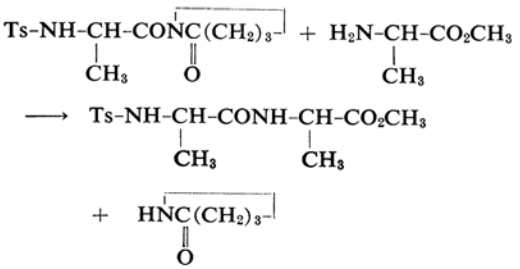
1) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 1956, 2076.
2) G. W. Anderson and R. Paul, *J. Am. Chem. Soc.*, **80**, 4423 (1958).
3) R. Paul and G. W. Anderson, ibid., **82**, 4596 (1960).



Tosyl-DL-alanyl-2-pyrrolidone was converted almost quantitatively to tosyl-DL-alanine *N*-benzylamide by reaction with benzylamine, or to tosyl-DL-alanine *N*-(*n*-butyl)amide by reaction with *n*-butylamine. The results are listed in Table V.



The extension of this reaction to dipeptide synthesis seemed to be interesting. In fact, when the alanine methyl ester was allowed to react with *N*-(tosyl-DL-alanyl)-2-pyrrolidone, the normal acyl-exchange reaction occurred and gave a dipeptide in a good yield:



Experimental

Materials.—*N*-Acetyl lactams were prepared by the acylation of corresponding lactams with acetyl or benzoyl chloride in benzene containing triethylamine. Crude *N*-acyl lactams were purified by fractional distillation or repeated recrystallization. The *N*-acyl lactams used are listed in Table I.

Solvent.—Tetrahydrofuran (THF) was purified by the usual method.

The Reaction of *N*-Acyl Lactams with Amines.—*General Procedure.—i) Reaction*: An *N*-acyl lactam 0.01～0.04 mol. (1 part) and 0.02～0.08 mol. of an amine were dissolved in THF (10～70 ml.). The mixture was then heated in a sealed tube for 16～48 hr. at temperatures ranging from 50 to 90°C.

ii) Methods of Fractionation: The solvent and the unreacted amine were removed under reduced pressure. When the residue solidified, it was purified by recrystallization from suitable solvents (procedure A). When the residue was oily, it was purified by distillation under reduced pressure (procedure B). When the oily residue could not be distilled, two methods were used. One was to dissolve the residue in ethyl acetate and to wash the solution first with 0.5 N hydrochloric acid and second with water, and then to dry it with anhydrous sodium sulfate (procedure C); the other was column chromatography on activated alumina (procedure D). The results are tabulated in Tables II and III, together with the experimental conditions and the methods of purification.

The Hydrolysis of *N*-Benzoyl Lactams.—*General Procedure.*—An *N*-benzoyl lactam (1.9 g.) was dissolved in 20 ml. of dioxane containing 20 ml. of 0.5 N potassium hydroxide and an excess of water (10 ml.). After the mixture had been allowed to stand for half an hour at 14°C, the solution was concentrated in vacuo to one-third of its volume. After the concentrate had been extracted twice with 10 ml. of ethyl acetate, the water layer was acidified (pH 3) with 3 N hydrochloric acid and extracted five times with petroleum benzine (150 ml.). By evaporating the petroleum extract, benzoic acid (m. p. 120～121°C) was obtained. The water layer of the extraction was re-extracted with ethyl acetate. After the ethyl acetate had been removed, the corresponding *N*-benzoyl-*ω*-amino acid was obtained; this was then recrystallized from ethyl acetate. The corresponding *N*-benzoyl-*ω*-amino acids were thus obtained. The results are listed in Table IV.

Tosyl-DL-alanine.—Into a solution of DL-alanine (0.7 mol.) dissolved in 330 ml. of 2 N sodium hydroxide and 400 ml. of water, tosyl chloride

TABLE I. *N*-ACYL LACTAMS PREPARED

Lactam	M. p. °C	B. p. °C/mmHg	n_D	Analysis % C	H	N
	N-Acetyl lactams					
N-Acetyl-2-pyrrolidone	—	90～91/4	1.4843[a]	57.01	7.22	10.86
N-Acetyl-2-piperidone	—	109/9	1.4890[b]	59.56	7.85	9.81
N-Acetyl-ε-caprolactam	—	97～99/5		62.12	8.52	8.79
	N-Benzoyl lactams					
N-Benzoyl-2-pyrrolidone	92～93	—	—	68.53	5.91	7.47
N-Benzoyl-2-piperidone	110～111	—	—	70.64	6.45	6.78
N-Benzoyl-ε-caprolactam	74～75	—	—	71.91	6.93	6.29

a) At 8.3°C b) At 25°C

Table II. Reactions of *N*-acetyl lactams with amines

Amine	Methods of fractionation[a]	Product	Uncorrected M. p. °C	Uncorrected B. p. °C/mmHg	Yield %	Analysis % C	Analysis % H	Analysis % N	Identification[e]	Presence of the ring-opened product	Reaction temp. °C
		N-Acetyl-2-pyrrolidone[b]									
Aniline[c]	A	Acetanilide[d]	112~114	—	69	70.59	6.62	10.30	IR, Mixing	None	90
Benzylamine[f]	A	*N*-Benzylacetamide[g]	60~ 61	—	87	72.56	7.36	9.35	IR, Mixing	None	70
		N-Acetyl-2-piperidone[h]									
Aniline	A	Acetanilide[d]	113~115	—	65	71.15	6.65	10.18	IR, Mixing	None	90
Benzylamine	B	*N*-Benzylacetamide[g]	60~ 61	139~140/5	76	72.38	7.47	9.30	IR, Mixing	None	90
n-Butylamine	D[i]	*N*-(*n*-Butyl)acetamide	—	116/7	91	61.06	11.40	11.98	IR	None	90
Diethylamine	B	*N*, *N*-Diethylacetamide	—	58~60/5.5	72	61.99	11.31	10.93	IR	None	90
Pyrrolidine	B	*N*-Acetylpyrrolidine	—	85~88/6.5	92	62.39	9.69	12.27	IR	None	90
Piperidine	D[i]	*N*-Acetylpiperidine	—	89/5	91	65.52	10.30	10.90	IR	None	90
		N-Acetyl-ε-caprolactam[j]									
Aniline	A	Acetanilide[k]	113	—	74	70.86	6.43	10.38	IR, Mixing	None	90
Benzylamine	A	*N*-Benzylacetamide[k]	59.8	—	66	72.17	7.56	9.39	IR, Mixing	None	90
n-Butylamine	D[i]	*N*-(*n*-Butyl)acetamide	—	116~117/7	75	62.27	11.29	12.01	IR	None	90
Diethylamine	B	*N*, *N*-Diethylacetamide	—	56.5~61.5/5	97	63.24	11.46	12.15	IR	None	90
Pyrrolidine	B	*N*-Acetylpyrrolidine	—	82~86/9	93	64.47	9.73	12.39	IR	None	90
Piperidine	B	*N*-Acetylpiperidine	—	65~70/2	78	66.09	10.23	10.28	IR	None	90

a) See text. b) 0.01 mol. of lactam and 0.02 mol. of amine were used. Reaction was continued for overnight. c) Solvent 10 ml. was used. d) Recrystallized from hot water. e) "IR" denotes that infrared spectrum of sample was identical with that of authentic one which was prepared through other route. "Mixing" denotes that the melting point did not show any of depression by mixing with the authentic sample. f) Solvent 20 ml. was used. g) Recrystallized from ether. h) 0.04 mol. of lactam and 0.08 mol. of amine were used. Solvent 70 ml. Reaction was continued for 36~40 hr. i) Elute of ethyl acetate was collected. Chromatographic column had a dimension of 22.5 mm.×102 mm. j) 0.04 mol. of lactam and 0.08 mol. of amine were used. Solvent 70 ml. Reaction time was 20 hr. k) Recrystallized from the mixture of ethyl acetate and *n*-hexane (1 : 1 v/v).

TABLE III. REACTIONS OF *N*-BENZOYL LACTAMS WITH AMINES

Amine	Methods of fraction-ation[a]	Product	M. p. °C	B. p. °C/mmHg	Yield %	Analysis % C	H	N	Identification[b]	Presence of the ring-opened products	Reaction temp. °C
		N-Benzoyl-2-pyrrolidone[c]									
Aniline	A	*N*-Phenylbenzamide[d]	160～161	—	86	78.70	5.63	6.94	IR, Mixing	None	50
Benzylamine	A	*N*-Benzylbenzamide[e]	105～105.5	—	96	79.89	6.28	6.68	IR, Mixing	None	28
n-Butylamine	A	*N*-(*n*-Butyl)benzamide[d]	40～41	—	89	74.86	8.56	7.73	IR, Mixing	None	50
Pyrrolidine	B	*N*-Benzoylpyrrolidine	—	153～154/7	80	74.90	7.60	7.72	IR	$C_6H_5CONH(CH_2)_3CON(CH_2)_4$ is ring-opened one	50
	A	$C_6H_5CONH(CH_2)_3CON(CH_2)_4$[f]	170～171	—	16	69.09	7.71	10.86	IR[g]		
Piperidine	B	*N*-Benzoylpiperidine	—	145～147/4	63	76.48	8.04	7.66	IR	$C_6H_5CONH(CH_2)_3CON(CH_2)_5$ is ring-opened one	50
	A	$C_6H_5CONH(CH_2)_3CON(CH_2)_5$[e]	86～87	—	22	69.77	7.96	10.26	IR[g]		
Diethylamine	B	*N*, *N*-Diethylbenzamide	—	115～118/4	63	74.40	8.53	7.57	IR	Some but unidentified[h]	50
		N-Benzoyl-2-piperidone[c]									
Aniline	A	*N*-Phenylbenzamide[e]	162	—	Quant.	78.91	6.27	7.04	IR, Mixing	None	50
Benzylamine	A	*N*-Benzylbenzamide[i]	106	—	Quant.	79.69	6.19	6.47	IR, Mixing	None	50
n-Butylamine	C	*N*-(*n*-Butyl)benzamide[d]	40～41	—	91	72.96	8.54	7.33	IR, Mixing	None	50
Pyrrolidine	B	*N*-Benzoylpyrrolidine	—	135/2	91	74.24	7.55	8.03	IR	None	50
Piperidine	B	*N*-Benzoylpiperidine	—	134～134.5/2	Quant.	73.14	8.17	7.52	IR	None	50
Diethylamine	B+C	*N*, *N*-Diethylbenzamide	—	115～120/4	62	74.40	8.53	7.57	IR	None	50
N-Methylaniline	No reaction occured										50
		N-Benzoyl-ε-caprolactam[c]									
Aniline	A	*N*-Phenylbenzamide[f]	160.5～162	—	90	78.79	5.54	6.92	IR, Mixing	None	50
Benzylamine	A	*N*-Benzylbenzamide[j]	102～103	—	95	79.73	6.21	6.55	IR, Mixing	None	50
n-Butylamine	C	*N*-(*n*-Butyl)benzamide[d]	40～41	—	90	73.77	8.48	7.59	IR, Mixing	None	50
Diethylamine	B+C	*N*, *N*-Diethylbenzamide	—	104/2	76	74.56	8.47	7.80	IR	Trace, if present[k]	50
Piperidine	B	*N*-Benzoylpiperidine	—	121～123/1	95	75.97	8.23	7.61	IR	None	50
N-Methylaniline	No reaction occured										50

a) See text. b) See foot-note e) of Table II. c) 0.01 mol. of lactam and 0.02 mol. of amine were used. Solvent 20 ml. Reaction was continued for overnight. d) Recrystallized from ethanol. e) Recrystallized from ethyl acetate. f) Recrystallized from methanol. g) Infrared-absorption bands were seen at 1623 cm^{-1} and 1546 cm^{-1}. h) Infrared spectrum seemed to contain some ring-opened products. i) Recrystallized from petroleum benzine. j) Recrystallized from 60% methanol. k) Very small amounts of amorphus precipitate was obtained.

TABLE IV. ALKALINE HYDROLYSIS OF *N*-BENZOYL LACTAMS

Lactam	Benzoic acid %	Ring-opened product	M. p. °C	%
N-Benzoyl-2-pyrrolidone	82	$C_6H_5CONH(CH_2)_3CO_2H$[a]	81～82	13.5
N-Benzoyl-2-piperidone	33	$C_6H_5CONH(CH_2)_4CO_2H$[b]	106～107	50
N-Benzoyl-ε-caprolactam	67	$C_6H_5CONH(CH_2)_5CO_2H$[a]	76～77	30

a) Recrystallized from ethyl acetate. b) Recrystallized from chloroform.

TABLE V. REACTIONS OF *N*-(TOSYL-DL-ALANYL)-2-PYRROLIDONE WITH AMINES

	Methods of fractionation[a]	Product	M. p. °C	Yield %	Analysis % C H N	Identification
Benzylamine[b]	A	*N*-(Tosyl-DL-alanyl)-benzylamide[c]	133～134	98	Found 61.53 6.12 8.24 Calcd. 61.42 6.06 8.43	IR (Presence of amide I, II and absence of ring carbonyl)
n-Butylamine[d]	A	*N*-(Tosyl-DL-alanyl)-*n*-butylamide[e]	104～105	92	Found 56.14 7.44 9.47 Calcd. 56.37 7.38 9.40	IR
DL-Alanine methyl ester[f]	A	Tosyl-DL-alanyl-DL-alanine methyl ester[g]	95～97	89	Found 51.72 6.19 8.55 Calcd. 51.29 6.10 8.53	IR

a) See text of the reactions of *N*-acyl lactam with amines. b) *N*-(Tosyl-DL-alanyl)-2-pyrrolidone 0.003 mol. and amine 0.01 mol. were used with 20 ml. of THF. Reaction was continued for overnight at 60°C c) Recrystallized from ethyl acetate. d) *N*-(Tosyl-DL-alanyl)-2-pyrrolidone 0.005 mol. and amine 0.03 mol. were used with 20 ml. of THF, at 60°C for overnight. e) Recrystallized from ether. f) *N*-(Tosyl-DL-alanyl)-2-pyrrolidone 0.003 mol. and DL-alanine methyl ester 0.006 mol. in 10 ml. of THF were used, at 60°C for overnight. g) Recrystallized from the mixture of acetone and petroleum ether.

(1 mol.) was stirred; the stirring was then continued for 5 hr. at room temperature. After the reaction had been completed, the reaction mixture was extracted with benzene in an adjusted basic media (pH 9). The residue was acidified to pH 3 by adding 3 N hydrochloric acid. A crystalline material precipitated. It was recrystallized from ethyl acetate, m. p. 136～137°C. Yield, 72.5%.

Tosyl-DL-ananyl-2-pyrrolidone. — Eighteen grams of phosphorus(V) chloride were added to the solution of 19.2 g. of tosyl-DL-alanine in 280 ml. of ether, and the mixture stirred for half an hour. After the removal of the ether, colorless needles were obtained. They were then dissolved in 240 ml. of THF, and the solution was cooled to 0°C. Fifty milliliters of THF solution containing 2-pyrrolidone (16 ml.) and triethylamine (8.8 g.) was then added drop by drop to the tosylalanyl chloride solution. The precipitate was separated off, and the THF was removed. The residue was dissolved in 100 ml. of ethyl acetate. The solution was washed with a 5% solution of potassium bicarbonate, a 5% solution of hydrochloric acid, and then with water, and dried with sodium sulfate. After the ethyl acetate had been removed, a crystalline material was obtained. It was recrystallized from ethyl acetate, m. p. 133～134°C. Yield, 76%.

Found: C, 54.05; H, 5.78; N, 8.95. Calcd. for $C_{14}H_{18}O_4N_2S$: C, 54.18; H, 5.58; N, 9.03%.

The Reaction of *N*-(Tosyl-DL-alanyl)-2-pyrrolidone with Amines.—The procedure was the same as that in the reaction of *N*-acyl lactams with amines. The results are listed in Table V.

Summary

N-Acetyl and *N*-benzoyl lactams consisting of a five-to-seven-membered ring were found to be good acylation reagents. Several amines were acylated with these reagents to give the corresponding amides in good yields.

When *N*-benzoyl-2-pyrrolidone was used, ring-opened by-products were obtained by the reaction with a secondary amine, such as pyrrolidine and piperidine.

Tosylalanyl-2-pyrrolidone reacted with primary amines to produce the corresponding tosylalanine amides. The alanine methyl ester reacted as a primary amine with tosylalanyl-2-pyrrolidone to afford a dipeptide.

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