Chem. Pharm. Bull. 17(11)2273—2278(1969)

UDC 547.855.3.07

Synthesis of 2-Substituted-6-amino-4,5-dihydropyrimidine[1]

Yoshihisa Okamoto,[2a] Tadakazu Tsuji[2b] and Takeo Ueda[2c]

Pharmaceutical Institute, Keio Gijuku University,[2a] Department of Chemistry, Japan Women's University[2b] and College of Pharmaceutical Sciences, Kitasato University[2c]

(Received April 21, 1969)

The convenient synthesis of 2-substituted-6-amino-4,5-dihydropyrimidine from the reaction of imidic ester with 3-aminopropionitrile was reported. Next, 2-phenyl- (V) and 2-(2-acylaminoethyl)-6-amino-4,5-dihydropyrimidines were investigated to clarify their predominant form in the possible tautomerism from the aspects of infrared spectra. Thus, it was found that V exists as the imino-form and 2-(2-acylaminoethyl)-6-amino-4,5-dihydropyrimidines as the amino-form in the solid state.

Further, it was described the synthesis of 3-acylaminopropionamidine possessing the heterocyclic ring for the purpose of potenciating the activity of benzamidopropionamidine which was studied previously.

The syntheses of 2-amino-4,5-dihydropyrimidine derivatives were, hitherto, intensively investigated.[3-5] On the other hand, 6-amino-4,5-dihydropyrimidines were scarcely investigated, and 6-amino-4,5-dihydro-2-phenylpyrimidine (V) seemed to be the only known compound among 6-amino-4,5-dihydropyrimidines. Compound V was prepared by Pietra from the reaction of benzamidine with acrylonitrile.[6] However, the re-examination of this method yielded only a trace amount of V.

Now the authors found that V and 2-(2-acylaminoethyl)-6-amino-4,5-dihydropyrimidine were obtained by the reaction of imidic esters with 3-aminopropionitrile. This cyclization is of interest for the new synthetic route to yield 6-amino-4,5-dihydropyrimidines. The present paper concerns the synthesis of 2-substituted-6-amino-4,5-dihydropyrimidine.

At first, the synthesis of N-(2-amidinoethyl) benzamidine (IV), which possessed imino group in lieu of carbonyl group on benzamidopropionamidine, was conceived for finding a biological active agent, since benzamidopropionamidine was found to exert the antiviral activity.[7] For this purpose, N-(2-cyanoethyl)benzamidine hydrochloride (II), which was prepared from ethyl benzimidate hydrochloride (I) and 3-aminopropionitrile, was converted to the imidic ester (III) with hydrogen chloride in ethanol, and thence III was treated with ammonia to yield the objective compound IV. It was, however, found that III did not give any anticipated compound IV, but 6-amino-4,5-dihydro-2-phenylpyrimidine (V), which was identical with the sample prepared from the reaction of benzamidine with acrylonitrile according to the method of Pietra.[6] Meanwhile, the imidate III was found to be cyclized to the dihydropyrimidine dihydrochloride (VII), when allowed to stand in a desicator in vacuum for one month, or heated for 3 hr at 120°. These findings suggested that the dihydropyrimidine hydrochloride might

1) Papers read at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, Apl. 1968.
2) Location: *a*) *Shinanomachi, Shinjuku-ku, Tokyo*; *b*) *Mejirodai, Bunkyo-ku, Tokyo*; *c*) *Shirogane, Minato-ku, Tokyo.*
3) G.H. Hitchings, P.B. Russell and N. Whittaker, *J. Chem. Soc.*, **1956**, 1019.
4) W. Traube and R. Schwarz, *Chem. Ber.*, **32**, 3163 (1899).
5) V.M. Rodionov and O.S. Urbanskaya, *J. Gen. Chem. USSR* (Eng. Transl.), **18**, 2023 (1948) [*C.A.*, **43**, 3793 (1948)].
6) S. Pietra, *Bull. Sci. Fac. Chim. Ind. Bologna*, **11**, 78 (1953) [*C.A.*, **49**, 13976b (1955)].
7) T. Ueda, Y. Okamoto, T. Tsuji and M. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **16**, 2355 (1968).

be directly produced through the reaction of the imidic ester I with 3-aminopropionitrile. In fact, it was clarified that the dihydropyrimidine monohydrochloride (VI) was obtained directly by the reflux of the imidic ester I with 3-aminopropionitrile in ethanol. These synthetic courses are summarized in Chart 1.

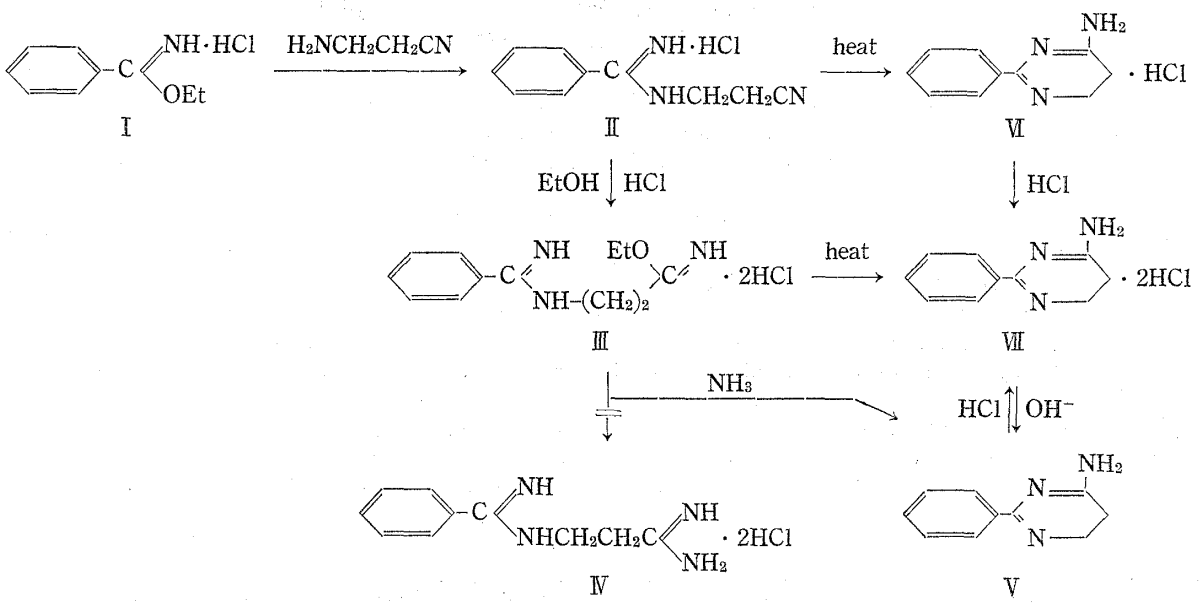


Chart 1

This synthetic method of VI from II appeared to be applicable to the other types of 6-amino-4,5-dihydropyrimidines. By the application of this method, several compounds of 2-(2-acylaminoethyl)-6-amino-4,5-dihydropyrimidine were successfully synthesized from the reaction between ethyl 3-acylaminopropionimidate and 3-aminopropionitrile, as shown in Chart 2. The compounds thus obtained are listed in Table I.

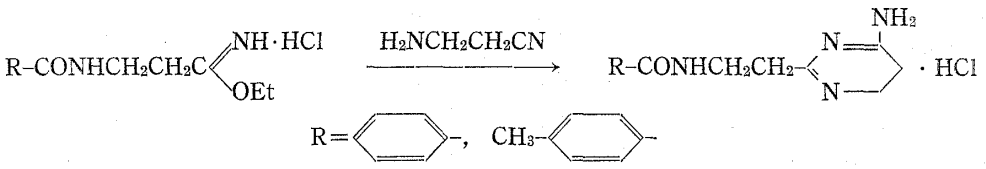
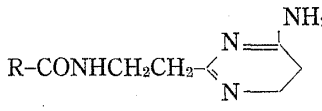
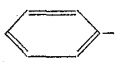
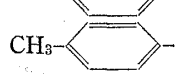


Chart 2

Table I. 2-Acylaminoethyl-6-amino-4,5-dihydropyrimidine

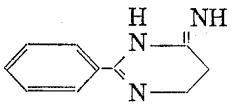
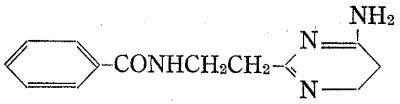
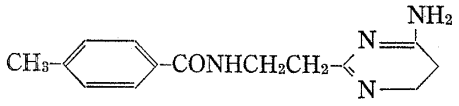


R	mp (°C)	Appearance (recryst. solvt.)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
	161—164	needles (H_2O)	$C_{13}H_{16}ON_4$	63.91	6.60	63.71	6.47
	188—190	needles (H_2O)	$C_{14}H_{18}ON_4$	65.09	7.02	64.37	6.87

In this step, V and 2-(2-acylaminoethyl)-6-amino-4,5-dihydropyrimidine were studied to reveal their predominant form in the equilibrium with possible two forms, *i.e.* 6-amino-4,5-

dihydropyrimidine and 1,4,5,6-tetrahydro-6-imino-pyrimidine, from the aspects of infrared spectra. These data are shown in Table II. It is of interest that V exists as the imino-form and 2-(2-acylaminoethyl)-6-amino-4,5-dihydropyrimidine as the amino-form in the solid state.

Table II. Infrared Spectra of 2-Substituted-6-amino-4,5-dihydropyrimidine (KBr cm^{-1})

Compound	ν_{NH}			δ_{NH}	
	$-NH_2$	=NH	–NH–	$-NH_2$	–NH–
 (V)	—	3256	3027	—	1537
	3435 3355	—	3235[a]	1653	1542[a]
	3430 3350	—	3235[a]	1654	1543[a]

a) Absorption originated from acylamino group.

Next, pyridine- and quinolinecarboxamidopropionamidine were synthesized for comparison of their biological activities with those of benzamidopropionamidine derivatives studied previously.[7] The synthetic processes of these compounds are shown in Chart 3. Pyridine-

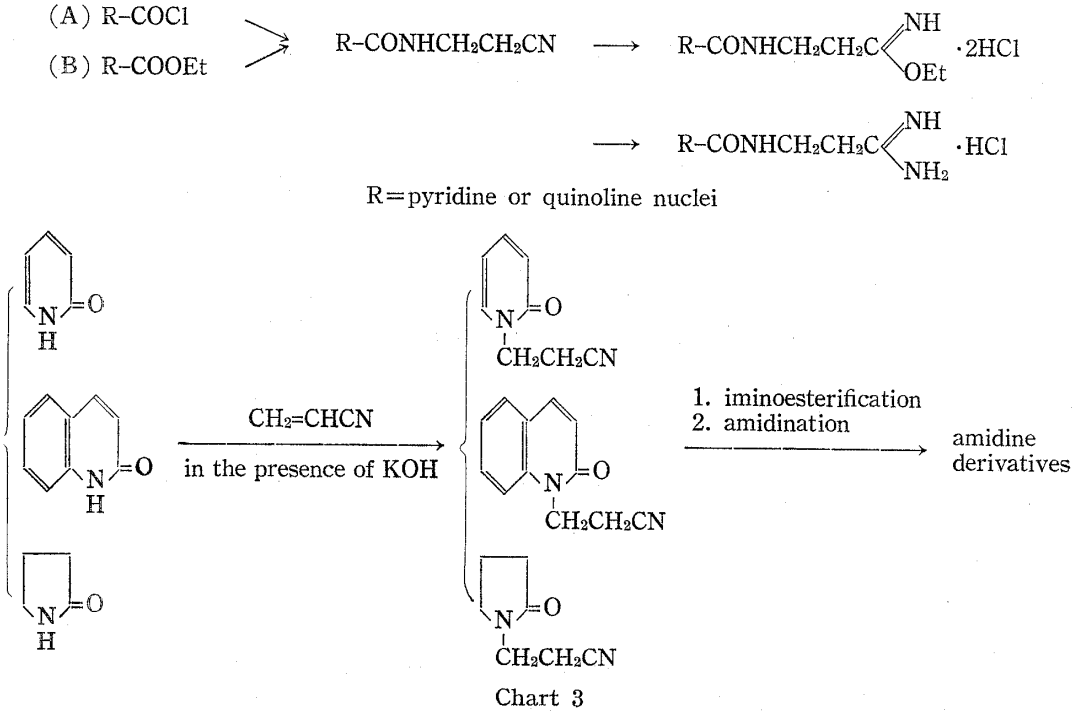
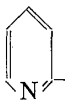
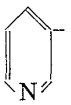
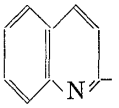
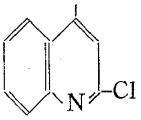
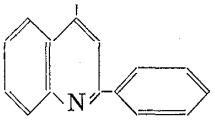
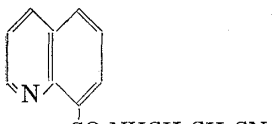
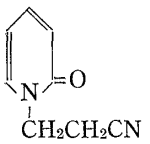
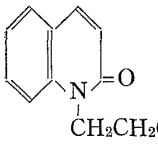


Chart 3

and quinolinecarboxamidopropionitrile were prepared from the corresponding acid chlorides and esters with 3-aminopropionitrile. 2-Pyridone-, 2-quinolinone- and 2-pyrrolidone-1-propionitrile were synthesized by the reflux of 2-pyridone, 2-qinolinone or 2-pyrrolidone with acrylonitrile in the presence of base as a catalyst, respectively. The nitriles thus obtained are listed in Table III. The conversion of the nitriles into the amidines was carried out by

Pinner's method.[8] Amidines thus obtained are listed in Table IV. All of the amidines shown in Table IV are new compounds as far as we can determine.

Table III. N-(2-Cyanoethyl)carboxamide R–CONHCH$_2$CH$_2$CN

Method	R	Yield (%)	Appearance (recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
B		24	needles (EtOH)	116—117	$C_9H_9ON_3$	61.70	5.18	23.99	62.16	5.08	23.92
A		—	plates (EtOH)	164—166	$C_9H_{10}ON_3Cl$[a]	51.07	4.76	19.86	—	—	19.42
B		33	plates (EtOH)	137—139	$C_9H_9ON_3$	61.70	5.18	23.99	61.50	5.12	23.71
B		50	needles (EtOH)	138.5—140	$C_{13}H_{11}ON_3$	69.32	4.92	18.66	69.15	4.97	18.79
A		—	needles (dil. EtOH)	153—154	$C_{13}H_{10}ON_3Cl$	60.12	3.88	16.18	60.15	4.12	—
A		78	needles (EtOH)	144.5—145.5	$C_{19}H_{15}ON_3$	75.73	5.02	13.95	—	—	13.97
		89	needles (EtOH+MeOH)	123—124	$C_{12}H_{11}O_2N_3S$	55.15	4.24	16.08	55.39	4.27	15.96
		70	needles (EtOH)	94—95	$C_8H_8ON_2$	64.85	5.44	18.91	64.85	5.13	18.75
		68	needles (EtOH)	121—123	$C_{12}H_{10}ON_2$	72.71	5.09	14.13	73.65	5.09	—

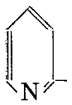
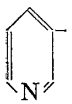
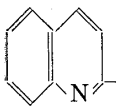
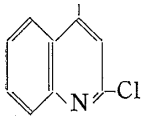
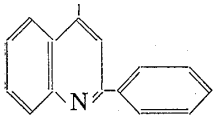
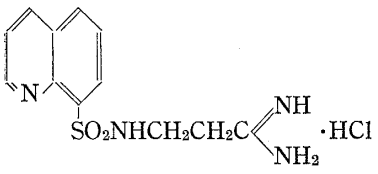
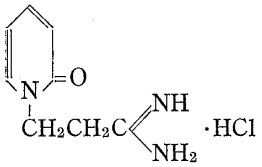
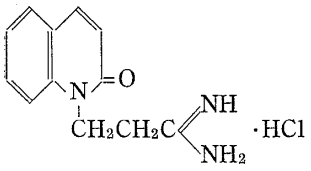
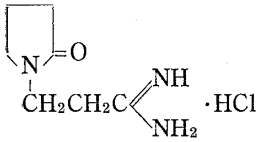
a) hydrochloride salt

Attempts were made to survey the reaction of these imidic esters with 3-aminopropionitrile. It was, however, found that no pyrimidine derivative could be isolated from the reaction mixture.

All of the compounds synthesized in the present paper were screened as to their activity on influenza A-2 type virus in mice. Among them, hydrochlorides of quinoline-2-carboxamido-

8) A.W. Dox, "Organic Syntheses," Coll. Vol. I, ed. A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1932, p. 5.

Table IV. Amidopropionamidine R–CONHCH$_2$CH$_2$C(=NH)NH$_2$·HCl

R	Yield(%)[a]	Appearance (recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	54	powders (EtOH ether)	137—139	$C_9H_{13}ON_4Cl$	47.27	5.73	24.50	47.24	5.78	24.32
	11	powders (EtOH EtOAc)	191—191.5	$C_9H_{13}ON_4Cl$	47.27	5.73	24.50	47.29	5.97	—
	58	needles (dil. EtOH ether)	238—240	$C_9H_{13}ON_4Cl$	47.27	5.73	24.50	46.85	5.83	—
	62	powders (EtOH ether)	202—204	$C_{13}H_{15}ON_4Cl$	56.01	5.42	20.10	56.23	5.93	19.88
	56	needles (EtOH ether)	241—242	$C_{13}H_{14}ON_4Cl_2$	49.85	4.51	17.89	49.55	4.65	—
	65	plates (EtOH)	208—210	$C_{19}H_{19}ON_4Cl$	64.31	5.40	15.79	64.31	5.55	15.47
	12	prisms (dil. EtOH)	185—186	$C_{12}H_{15}O_2N_4SCl$	45.78	4.80	17.80	45.96	5.27	—
	61	needles (EtOH ether)	189—191	$C_8H_{12}ON_3Cl$	47.65	6.00	20.84	47.19	6.03	—
	64	plates (EtOH ether)	186—187	$C_{12}H_{14}ON_3Cl \cdot \frac{1}{2}H_2O$	55.28	5.80	16.12	55.31 55.41	5.85 5.73	—
	48	needles (EtOH ether)	176—177.5	$C_7H_{14}ON_3Cl$	43.86	7.36	21.93	43.86	6.99	—

a) from the corresponding nitriles

propionamidine, 2-chloroquinoline-4-carboxamidopropionamidine, quinoline-8-sulfonamidopropionamidine, 2-quinolinone-1-propionamidine and 2-pyridone-1-propionamidine exerted inhibitory effect on the viral growth in mice lung. The first member was selected as the promising from the balancing between the mice experiment and toxity test. Those data will be reported in a medical journal in the near future.

Experimental

N-(2-Cyanoethyl)benzamidine Hydrochloride (II)——Excess amounts (0.085 mole) of 3-aminopropionitrile were added to a solution of 0.027 mole of ethyl benzimidate hydrochloride in 3 ml of EtOH at 0 to 5°. Resulted precipitates were collected and recrystallized from EtOH to give colorless needles, decomp. 174°. Yield, 89.2%. *Anal.* Calcd. for $C_{10}H_{12}N_3Cl$: C, 57.29; H, 5.77; N, 20.04. Found: C, 56.93; H, 5.65; N, 20.14.

Ethyl 3-(Benzamidino)propionimidate Hydrochloride (III)——Dry HCl gas was passed through into a suspension of 0.019 mole of N-(2-cyanoethyl)benzamidine hydrochloride II in 40 ml of $CHCl_3$ and 0.9 g of anhyd. EtOH at 0 to 5°, until 0.019 mole of HCl was absorbed. After allowed to stand for one day, crystals suspended were changed to oily substances and C≡N absorption band (2260 cm^{-1}) was disappeared in the infrared spectrum. Treatment of the oily substances with excess amounts of anhyd. ether gave colorless powders, decomp. 105°. Yield, 96.4%. This compound was used as a crude state in the followed experiments.

6-Amino-4,5-dihydro-2-phenylpyrimidine (V)——Method A: Imidate III (0.018 mole) was added into an excess amount of anhyd. ethanolic ammonia solution. Then anhyd. ether was added to the solution until any more amount of NH_4Cl was not deposited. After removal of NH_4Cl, the filtrate was concentrated and the remained yellow crystalswere recrystallized from EtOH to give colorless powders, mp 176°. Yield, 36.4%. *Anal.* Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 68.88; H, 6.25; N, 23.99.

Method B: Imidate III (0.018 mole) was heated at 120° *in vacuo* for 3 hr. After treatment of the resulted yellow crystals with 10% NaOH solution, NaOH insoluble substances were recrystallized from EtOH–ether to afford colorless powders which were the same product to that of the method A on comparison of infrared spectrum and melting point (lit.[6] 177°). Yield, 49.8%.

General Procedure for Synthesis of 2-(2-Acylaminoethyl)-6-amino-4,5-dihydropyrimidine——A solution of 0.02 mole of ethyl 3-acylaminopropionimidate hydrochloride and 1.4 g of 3-aminopropionitrile in 20 ml of EtOH was refluxed on a water bath for 6 hr. After removal of the solvent, the residue was dissolved in a small amount of water and the solution was made basic with Na_2CO_3. The precipitates were recrystallized from water.

General Procedure for Syntheses of N-(2-Cyanoethyl)pyridinecarboxamides and -Quinolinecarboxamides—— Method A: At the temperature between 5 to 13°, 0.04 mole of pyridine- (or quinoline-) carboxylic acid chloride was slowly added to a solution of excess amounts of 3-aminopropionitrile in 30 ml of acetone. The mixture was then refluxed on a water bath for 1 hr, and poured into an ice–water. The precipitates were collected and purified by recrystallization.

Method B: To a solution of 0.066 mole of ethyl pyridinecarboxylate (or ethyl quinolinecarboxylate) in 60 ml of EtOH was added excess amounts of 3-aminopropionitrile. After refluxed for 5 hr, the mixture was concentrated and the precipitates were purified by recrystallization.

General Procedure for Syntheses of 2-Pyridone-, 2-Quinolinone- and 2-Pyrrolidone-1-propionitrile——The reflux of 2-pyridone, 2-quinolinone and 2-pyrrolidone with equimolecular amount of acrylonitrile (0.01 mole) in the presence of 0.05 g of KOH for 3 hr in anhyd. EtOH gave crude 2-pyridone-, 2-quinolinone- and 2-pyrrolidone-1-propionitrile, respectively.

Of the three compounds, 2-pyridone- and 2-quinolinone-1-propionitrile were obtained as the crystals, but 2-pyrrolidone-1-propionitrile was obtained as the oil. Therefore, 2-pyrrolidone-1-propionitrile was used to the following iminoesterification without purification.

General Procedure for Syntheses of Ethyl Propionimidate Hydrochloride Derivatives——To a solution (or suspension) of 0.029 mole of propionitrile derivative in 40 ml of $CHCl_3$–dioxane (1:1), 0.03 mole of anhyd. EtOH was added, and then dry HCl gas was passed into the solution below 5° until 0.06 mole of HCl was absorbed. The whole was allowed to stand for at least a week until the absorption of nitrile group (2260 cm^{-1}) in the infrared spectrum was disappeared. The crude product thus obtained was used for the following amidination without further purification.

General Procedure for Syntheses of Propionamidine Hydrochloride Derivatives——The crude imidate hydrochloride (0.025 mole) was dissolved in 50 ml of 9% anhyd. ethanolic NH_3. After then, the solution was filtered and anhyd. ether was added to yield the corresponding derivative of propionamidine hydrochloride.

Acknowledgement The authors thank Miss H. Yoda, this Institute, for elementary analysis.