on the basis of two moles of hydrocarbon reacting upon an  $SO_2$  of the  $S_2O_6$  component of the re-

versible  $SO_3 \implies S_2O_6$  system of the anhydride. CAMBRIDGE, MASS. RECEIVED NOVEMBER 19, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

# Researches on Pyrimidines. CXLIX. The Synthesis of Aryl Substituted Dihydrouracils and their Conversion to Uracil Derivatives<sup>1</sup>

# BY TREAT B. JOHNSON AND JOHN E. LIVAK

In laying out the program of pyrimidine research to be discussed in this paper the authors had three major objectives in mind, namely:

(1) To develop a convenient and practical method for preparing aromatic  $\beta$ -amino acids of the type RCH(NH<sub>2</sub>)CH<sub>2</sub>COOH (R = an aryl group C<sub>6</sub>H<sub>5</sub>, NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, C<sub>7</sub>H<sub>7</sub>, C<sub>10</sub>H<sub>7</sub>, etc.) to be used for the synthesis of a series of substituted  $\beta$ -ureido acids.

(2) To make a study of the factors influencing and limiting the cyclization of these  $\beta$ -ureido acids to hexahydropyrimidines or 4,5-dihydrouracils.

(3) To determine the general utility of Fischer's<sup>2</sup> method for converting 4,5-dihydrouracils into their corresponding uracil derivatives.

## 1. Synthesis of $\beta$ -Amino Acids

In order to obtain the  $\beta$ -amino acids desired for our research, we utilized a method of preparation which the Russian chemist, Rodionov,<sup>3</sup> developed as a result of a critical study of the well-known Knoevenagel reaction.<sup>4</sup> He found that the reaction between an aromatic aldehyde, like benzaldehyde, for example, and malonic acid in alcoholic ammonia solution, gives not only cinnamic acid (Knoevenagel) as a reaction product, but that in addition a  $\beta$ -amino acid C<sub>6</sub>H<sub>5</sub>CH(NH<sub>2</sub>)CH<sub>2</sub>COOH is produced in practically equal amount. Rodionov demonstrated this reaction to be one of general application,<sup>5</sup> and later carried out a corresponding condensation with malonic ester, thereby obtaining a  $\beta$ -aminodicarboxylic ester which yielded after saponification and partial decarboxylation the same  $\beta$ -amino acid as was obtained directly by condensation of benzaldehyde with

(1) From a dissertation presented by John E. Livak to the Graduate Faculty of Yale University in June, 1935, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(5) (a) Rodionov and Vyazkova, J. Gen. Chem. (U. S. S. R.), 3, 628 (1933);
(b) Rodionov and Postovskaja, THIS JOURNAL, 51, 841 (1929);
(c) Rodionov, *ibid.*, 51, 851 (1929);
(d) Rodionov and Federowa, Arch. Pharm., 266, 121 (1928).

malonic acid. In our work we modified the procedure applied by Rodionov by using in place of the aldehyde and ammonia the corresponding hydrobenzamide formed by interaction of the aldehyde with ammonia. The reactions involved in this method of synthesizing  $\beta$ -phenyl- $\beta$ -aminopropionic acid IV may be explained as follows C<sub>6</sub>H<sub>5</sub>CH=N<sub>5</sub>

$$C_{6}H_{5}CH=N$$

$$C_{8}H_{5}CH=N$$

$$C_{8}H_{5}CH=N$$

$$C_{8}H_{5}CH=N$$

$$C_{6}H_{5}CH=NH$$

$$C_{6}H_{5}CH-NH$$

$$C_{6}H_{5}CH-NH$$

$$C_{6}H_{5}CH-NH$$

$$C_{1}(COOH)_{2}$$

$$II$$

$$2C_{6}H_{5}CH(NH_{2})CH(COOH)_{2} \longrightarrow$$

$$III$$

$$2C_{6}H_{5}CH(NH_{2})CH_{2}COOH + C_{6}H_{5}CHO + 2CO_{2}$$

Starting with anishydramide  $\beta$ -(p-methoxyphenyl)- $\beta$ -aminopropionic acid<sup>6</sup> is prepared according to the same technique.

IV

# 2. Cyclization of $\beta$ -Ureido Acids to 4,5-Dihydrouracils

 $\beta$ -Ureido acids are easily prepared by interaction of  $\beta$ -amino acids with cyanic acid and alkyl and aryl isocyanates. All the ureido- and thioureido-constructions prepared by the authors in their research from  $\beta$ -phenyl- $\beta$ -aminopropionic acid and  $\beta$ -(p-methoxyphenyl)- $\beta$ -aminopropionic acids are well-defined crystalline substances and were all easily purified by crystallization from hot water or alcohol. For conversion of this type of acids into 4,5-dihydrouracils various methods have been used: (1) cyclization by treatment with acetyl chloride;<sup>7</sup> (2) by the application of heat;<sup>8</sup> (3) cyclization by digestion with acetic anhy-

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(6) Posner, Ann., 389, 62 (1912).
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(7) Hoogewerf and Van Dorp, Rec. trav. chim., 9, 57 (1876); Fischer and Leuchs, Ber., 85, 3797 (1902).

(8) Posner and Rohde, ibid., 42, 2791 (1909).

<sup>(2)</sup> Fischer and Roeder, Ber., 34, 3751 (1901).

<sup>(3)</sup> Rodionov and Malewinskaja, *ibid.*, **59**, 2952 (1926).

<sup>(4)</sup> Knoevenagel, ibid., 31, 2596 (1898).

dride;<sup>8</sup> and (4) by digestion with aqueous hydrochloric acid,<sup>10</sup> and also by the action of hydrochloric acid in attempts to esterify  $\beta$ -ureido acids.<sup>11</sup>

Of these four different methods it was our experience that method 3 was the best suited for our work. With the exception of one case we were able to convert all the  $\beta$ -ureido acids prepared to their corresponding 4,5-dihydrouracils by the action of this reagent. Both Morsch<sup>12</sup> and Rodionov<sup>5</sup> failed to bring about the same condensation by means of strong hydrochloric acid in the case of the phenylureido derivative prepared from ethyl  $\beta$ -phenyl- $\beta$ -aminopropionate, and the corresponding  $\alpha$ -naphthylureido acid. Both of these combinations undergo ring closure when treated in acetic anhydride solution.

1,4-Diphenyl-4,5-dihydrouracil was formed in the highest yield of any hexahydropyrimidine prepared by cyclization of an aryl substituted  $\beta$ ureido acid. When the phenyl group on nitrogen was replaced by a substituted phenyl group we obtained ureido acids which showed less tendency to undergo cyclization. This resistance to ring closure was especially strong in the case of a nitro substituted group. That the relative positivity or negativity of the group attached to a nitrogen of the  $\beta$ -ureido acid is not the only factor involved in influencing cyclization is shown by the o-tolyl grouping. This  $\beta$ -ureido acid has defied all attempts to bring about ring closure. The question of juxtaposition in space has to be considered here in offering an explanation for the increased hindrance to cyclization. In the case of unsubstituted  $\beta$ -thioureido acids, cyclization was hard to effect and the yields of dihydrouracils were low, which is in distinct contrast to the oxygen analogs. In fact, our observations lead us to conclude that sulfur, being more negative than oxygen, inhibits ring formation in the case of unsubstituted thioureido acids. Or, it is possible that we may be dealing here with a pseudothiourea structure which in this case is not as reactive as the normal thioureido form. In the case of the N-arylthioureido acids we have two negative groups on adjacent nuclear atoms and yet ring closure is easily effected. A plausible explanation is to assume that here we are dealing with the normal form of the thioureido acid.

A third factor influencing cyclization is the character of the aryl grouping in the  $\beta$ -position of the respective ureido acid. That the nature of the group occupying this position affects markedly the ease of formation of dihydrouracils is demonstrated by the work of Morsch.<sup>12</sup> He found that the  $\beta$ -ureido acid ester formed by the action of phenyl isocyanate on ethyl  $\beta$ -aminobutyrate suffered the loss of alcohol under the influence of boiling mineral acids to give 1-phenyl-4-methyl-4,5-dihydrouracil. Replacement of the methyl group by phenyl in the  $\beta$ -amino acid ester prevented the formation of a pyrimidine.

In our work we limited ourselves to the study of the effect of two aryl groups, namely, phenyl- and *p*-methoxyphenyl-. When hydrochloric acid was used as a dehydrating agent, the  $\beta$ -ureido acids possessing a phenyl group in the  $\beta$ -position either underwent ring closure or else were recovered unchanged. The replacement of phenyl by pmethoxyphenyl conferred instability on the molecule and while in some cases the  $\beta$ -ureido acid was recovered unchanged when treated with boiling hydrochloric acid, in the majority of cases, decomposition resulted with the formation of pmethoxycinnamic acid as one of the degradation products. The use of acetic anhydride obviated the formation of p-methoxycinnamic acid, and at the same time effected ring closure, where hydrochloric acid had failed. Cyclization of  $\beta$ -ureido acids in alkaline media was out of the question, as 4,5-dihydrouracils are unstable in hot alkaline solutions and revert back to  $\beta$ -ureido acids.<sup>10</sup> From our study of the effect of aryl groups it was apparent that *p*-methoxyphenyl had a less retarding effect than did phenyl on the ease of ring closure. However, this difference is very slight and the nature of the aryl grouping attached to nitrogen exerted a far greater influence.

## 3. Synthesis of Aryl Substituted Uracils

Theoretically, 4,5-dihydrouracils may be converted into the corresponding uracils in either of two ways: (1) by oxidation, and (2) by bromination in the 5-position with subsequent expulsion of hydrobromic acid. Of these two methods, only the second method, first applied by Fischer,<sup>13</sup> is of practical use. This method was later extended by Evans and Johnson<sup>10</sup> to nitrogen substituted 4,5-dihydrouracils. In the case of aryl substituted dihydrouracils the method is limited (13) (a) Tafel, Ber., 33, 3385 (1900); (b) Fischer and Roeder, *ibid.*, 36, 3751 (1901).

<sup>(9)</sup> Formation of 1-methyl-5-benzyl-4,5-dihydrouraeil: Mannich and Ganz, Ber., 55, 3490 (1922).

<sup>(10)</sup> Evans and Johnson, THIS JOURNAL, **52**, 4993 (1930).

<sup>(11)</sup> Ref. 5a, p. 630; C. A., 28, 2716 (1934).

<sup>(12)</sup> Morsch, Monatsh., 64, 333 (1934).

in scope for the synthesis of substituted uracils. We found that the presence of substituents on nitrogen of a highly electro-negative character prevented the substitution of bromine in the 5position of the hexahydropyrimidine, while in some cases, depending on the nature of the aryl group, the bromine attacked the benzene ring in preference to the pyrimidine nucleus.

To summarize, substitution of hydrogen, phenyl and *o*-tolyl on nitrogen in position 1 favors bromination in the 5-position of the pyrimidine ring, while  $\beta$ -naphthyl and *p*-nitrophenyl retard bromination. Substitution of phenyl in position 4 favors bromination in the 5-position of the ring, while *p*-methoxyphenyl leads to bromination first in the benzene nucleus. Excess of bromine and bromination at higher temperature leads to substitution also in the 5-position of the pyrimidine ring except in cases where a substituent in position 1 retards bromination.

It appears that an increase in negativity of the substituent in position 1 tends to repel the substitution of bromine in the pyrimidine ring. In the case of 1-nitrophenyl-4-(p-methoxyphenyl)-4,5-dihydrouracil bromination of the benzene ring could not be effected below 100°, while in all other cases where p-methoxyphenyl was present, the bromine substituted easily at room temperature. Bromination in the pyrimidine nucleus could not be accomplished in the case of p-nitrophenyl substituted 4,5-dihydrouracils.

# **Experimental Part**

### Synthesis of $\beta$ -Amino Acids

Preparation of Hydrobenzamide and Anishydramide.— The aldehyde (60-70 g.) was sealed in a soda bottle with about 75 cc. of concentrated aqueous ammonia and 75 cc. of 95% alcohol. The bottle was then fastened to a rotating wheel and allowed to rotate at ordinary temperature for eight hours. The reaction was complete after the expiration of this time and the respective hydrobenzamide was obtained in a crystalline form. These were used for our syntheses without further purification.

β-Phenyl-β-aminoethane-dicarboxylic Acid, C<sub>6</sub>H<sub>3</sub>CH-(NH<sub>2</sub>)CH(COOH)<sub>2</sub>.--Eight grams of malonic acid dissolved in 25 cc. of alcohol was added to an ice-cooled solution of 12 g. of hydrobenzamide in 100 cc. of alcohol. During the operation the solution was constantly agitated with a motor stirrer. The odor of benzaldehyde was detected at once. Stirring was continued for about one hour and the mixture allowed to stand. Seven and five-tenths grams of the dibasic acid separated and melted at 147-149°. Five grams more was obtained from the filtrate. After recrystallization from alcohol the acid melted at 153°.<sup>50</sup> Anal. Calcd. for  $C_{10}H_{11}O_4N$ : N, 6.70. Found: N, 6.56.

β-Phenyl-β-aminopropionic Acid,  $C_6H_5CH(NH_2)CH_2$ -COOH. (a) Ammonium Acetate as a Source of Ammonia.— Benzaldehyde (20 g.), malonic acid (20 g.), and ammonium acetate (30 g.) were mixed with 40 cc. of 95% alcohol and the mixture digested on a steam-bath. Carbon dioxide began to be evolved at 55° and the reaction was complete at the end of five hours. We obtained 15 g. of the βamino acid which separated from the alcohol solution and after recrystallization from hot water melted at 216°. From the alcohol filtrate we obtained 7 g. of cinnamic acid<sup>10</sup> (p. 5001). Use of absolute ethanol or isopropyl alcohol as a solvent did not lead to any increase in the yield of the βamino acid.

(b) With Alcoholic Ammonia.—The above experiment was repeated with substitution of alcoholic ammonia for ammonium acetate but without any increase in the yield of  $\beta$ -amino acid.

(c) Hydrobenzamide as a Source of Benzaldehyde and Ammonia.—Eight grams of hydrobenzamide and 5 g. of malonic acid were digested in 20 cc. of 95% alcohol at its boiling point for two hours. We obtained 4 g. of pure  $\beta$ amino acid melting without any further purification at 216°. The above proportions were increased five-fold and the reaction applied, but without any decrease in the yield.

Anal. Calcd. for  $C_9H_{11}O_2N$ : N, 8.49. Found: N, 8.24, 8.48.

 $\beta$ -(p-Methoxyphenyl)- $\beta$ -aminopropionic Acid, CH<sub>3</sub>O- $C_6H_4CH(NH)_2CH_2COOH$ . Anishydramide as the Source of Anisic Aldehyde and Ammonia.--- A 50% yield of this  $\beta$ -amino acid is easily obtained as follows. Thirty grams of anishydramide and 18 g. of malonic acid are dissolved in 150 cc. of 98% alcohol saturated in the cold with pmethoxycinnamic acid. This mixture was then heated to boiling for seven hours when the evolution of carbon dioxide had ceased and the reaction was complete. The crude reaction mixture of  $\beta$ -amino acid and p-methoxycinnamic acid was washed with hot ethanol to remove the cinnamic acid, and the  $\beta$ -amino acid further purified by crystallization from boiling water. It melted at 232° with decomposition. The presence of methoxycinnamic acid led to an increase in yield of  $\beta$ -amino acid. The yield of amino acid was not improved by using absolute ethanol as a solvent. Rodionov<sup>5d</sup> has prepared this  $\beta$ -amino acid by the action of anisaldehyde on malonic acid in alcoholic ammonia solution.

Anal. Caled. for  $C_{10}H_{13}O_8N$ : N, 7.18. Found: N, 7.10, 7.14.

#### Synthesis of Dihydrouracils

(a) Preparation of  $\beta$ -Ureidopropionic Acids.—The two  $\beta$ -amino acids used in this research, namely,  $\beta$ -phenyl- $\beta$ -aminopropionic and  $\beta$ -(p-methoxyphenyl)- $\beta$ -aminopropionic acids, were converted into their corresponding  $\beta$ -ureido acids by the action of potassium cyanate in warm aqueous solution or by combining them in alkaline solution with the required amount of alkyl or aryl isocyanate. The thioureido acids were prepared by a similar technique using isothiocyanates as reactants. The various isocyanates and isothiocyanates used in our work are recorded in Chart I. The yields were good in every case.

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		pu	67	12.54	40	11.65	9.83	9.76	10.41	1	9.37		8.82		8.58	7.95		13.16	11.95	8.67	7.84	13.86	11.90	9.33	8.43	ydroura	bromo	oxyphe	nyl-ura	Corres	comine	-(3-bro	nation.	
	еп. %	Four	14.	12.52	13.	11.62	9.87	9.64	10.36	4	9.Z0		8.72		8.69	7.99		13.24	11.84	8.61	7.97	13.88	12.02	9.40	8.37	, 5-dih	-4-(3-	t-meth	ayphe	acil.	by br	enyl-4	bromit	
	Nitroe	Calcd.	14.74	12.73	13.60	11.86	9.93	9.87	10.53		9.46	đ	9.03		8.86	8.09		13.50	12.32	8.86	8.09	13.73	11.97	9.52	8.64	bromo-4	o-Tolyl- bromo- 4-metho	hydrou	tacked	Nitropl further				
	Dihydro- uracil	т. р., °С	$217^{b}$	228	238°	228	243	231-232	$226^d$		210	) Not forme	181		240-241	256-257		253 - 254	268 - 269	192 - 193	218-219	$149-151^{b}$	138	170	188	B, β-	B, $\beta$ - DURNAL,	razkova,	ther and	. 01,4-	heating	romo-4-	enyl)-5-	
	Condensing	agent	HCI, 10%	(CH <sub>2</sub> CO) <sub>2</sub> O	HCI	HCI	HC1, 20%	(CH <sub>3</sub> CO) <sub>2</sub> O	HCI, 20%	(CH2CO)2O	(CH <sub>3</sub> CO) <sub>2</sub> O	$HCI + (CH_{3}CO)_{3}C$	(CH3CO)20		(CH2CO)2O	(CH <sub>2</sub> CO) <sub>2</sub> O		(CH3CO)20	(CH <sub>a</sub> CO) <sub>2</sub> O	(CH <sub>3</sub> CO) <sub>2</sub> O	(CH <sub>3</sub> CO) <sub>2</sub> O	HCI	(CH2CO)2O	(CH3CO)2O	(CH <sub>8</sub> CO) <sub>2</sub> O	opropionic acid;	Johnson, THIS J	todionov and Vy	16 (1934). <sup>°</sup> Fisc	oxvphenvl)-uracil	promic acid by	<sup>4</sup> 1-Phenyl-4-(3-b	mo-4-methoxyph	mo-4-methoxypl
		acid <sup>a</sup> propionic acid, Nitrogen, % m. p. °C. Caled. Found	:	11.62			9.28	9.17	9.67		8.71	9.32	8.33		8.26	7.53		12.60	11.29		7.51	7.44 7.51 10.95 7.96 8.04	8.04	8-amin	ns and	). <sup>d</sup> R	28, 27	-metho	hvdrol	acil.	-(3-Bro	,		
	() []		:	11.51			9.22	8.19	9.64	5	8.82	9.35	8.38		8.14	7 43		12.63	11.23	11.40	7.44		10.		7.96	henyl-	<sup>b</sup> Eval	(1905)	C. A.:	romo-4	loses	nenylur	enyl-4	•
	Nite		:	11.76			9.33	8.48	9.86		8.92	9.40	8.54		8.38	7 69		12.77	11.70		7.69		11.11		8.19	<b>A</b> , β-p	<b>A</b> , β-p acid. , 2324 933);	4-(3-B	which	4-dip	ud−l,			
	o B-Ureido-		1926	193	Not isolated	Not isolated	158	146	174 <sup>d</sup>	•	167-168	172	180-181		201	101	101	202 - 203	171-172	$184 - 186^{d}$	178	Not isolated	168 - 169	Not purifd.	163	nino acid:	Designation of <i>P</i> -amino acid: tethoxyphenyl)- <i>P</i> -aminopropionic 1933 (1930). * Posner, <i>Ber</i> , <b>38</b> <i>en. Chem.</i> (U. S.S. R.), <b>3</b> , 628 (1	(1001)	(1901). <sup>1</sup> 4 ydrouracil w		drouracil.			
	8-Amin		۷	<b>a</b>	<	1 4	4	1	<		æ	۷	B		V	<u>م</u>		A	۲ ۲		В	V	B	V	B	$\beta$ -am		3751	4.5-dil	- Liou	pom- dihyc	•		
	, ,	Isocyanate or isothiocvanate	HNCO	HNCO	SJNH	SUNH	CALNES	Centrol	Centration		C <sub>6</sub> H <sub>6</sub> NCO	0-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NCO	0-CH2C6H4NCO		A-C.,H-NCO	P C.H-NCO		P-NO-CAHANCO	0. NO CHINCO	w-CuH-NCO	o-CinHaNCO	CHANCO	CHINCO	o-CHaCaHANCS	0-CH3C6H4NCS	besignation of		m Chow (11 !	er Rer 34	envl-5-hromo-4	its melting	e its melting xyphenyl)-4, <sup>5</sup>		
		Expt.	-	- 64		9 4	1.4		) F	-	80	6	10		11	1 -	4	13	14	12	91	17	8	2	20	η,	)(u-q)	52.4		Doord	Dinh	ahove	meth	

are characterized by their behavior on heating, all decomposing with violent effervescence. The alkali salts are easily soluble in cold water and on treatment with cold hydrochloric acid are decomposed with precipitation of the  $\beta$ -ureidopropionic acids, which are difficultly soluble in water.

(b) Conversion of  $\beta$ -Ureidopropionic Acids into the Corresponding Dihydrouracils .-- Two reagents served for condensing our  $\beta$ -ureido acids to dihydrouracils, hydrochloric acid and acetic anhydride. In some cases hydrochloric acid was the more effective condensing or dehydrating agent, while in others, it could not be used as it brought about a complete deaminization of the  $\beta$ -ureidopropionic acid with formation of the corresponding cinnamic acid. The dehydration result was also dependent on the concentration of hydrochloric acid used. Where cyclization of  $\beta$ -ureidopropionic acids to dihydrouracils could not be accomplished by means of hydrochloric acid we resorted to the use of acetic anhydride. Digestion with this reagent generally led to the production of the desired dihydrouracils in good yields. In some cases, however, involving substitution on nitrogen of the  $\beta$ -ureidopropionic acid we were unable to effect cyclization to dihydrouracil by digestion with either hydrochloric acid or acetic anhydride. In Chart I are recorded the particular condensing agents which led to the desired result in our various experiments.

#### Conversion of 4,5-Dihydrouracils into Uracils

The success of our method of operating for the preparation of uracil derivatives is dependent on the successful formation of 5-bromohexahydropyrimidines by the action of bromine on dihydrouracils. This procedure was first developed by Fischer, 10,13b and applied with success for the synthesis of uracil, thymine and 4-phenyluracil. All the dihydrouracils used in our research were soluble in glacial acetic acid, and, therefore, this solvent was used in all our bromination experiments. The temperature for favorable bromination varied from 75 to  $105^{\circ}$  and the reactions were generally complete within a heating period of two hours. The 5-bromohexahydropyrimidines prepared were all sufficiently stable to permit of their crystallization from alcohol. Conversion to true uracils can be accomplished in different ways. Fischer utilized dilute alkali or pyridine as the reagents for removing hydrobromic acid from the 5bromohexahydropyrimidines. In some cases simple heating leads to smooth degradation of the 5-bromo derivative with evolution of hydrobromic acid and formation of the uracil compound. In our work we found pyridine the most useful reagent for accomplishing this change. The aromatic substituted uracils resemble the dihydrouracils in many of their properties. They are well-crystallized compounds having sharp melting points and are soluble in acetone, glacial acetic acid, pyridine and alcohol, but insoluble in acids, water, benzene, ether and chloroform. The analytical results and melting points of the different aromatic substituted uracils prepared in our work are recorded in Chart I.

2-Methylmercapto-4-phenyl-4,5-dihydrouracil, NHC-(SCH<sub>3</sub>)==NCHC<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CO.—This compound (not recorded in Chart I) was obtained by alkylation of the corresponding 2-thiopyrimidine in alcoholic sodium ethylate solution with methyl iodide. The yield, however, was very small. The pyrimidine crystallized from alcohol in prismatic crystals melting at 163.5°.

Anal. Calcd. for  $C_{11}H_{12}ON_2S$ : N, 12.73. Found: N, 12.52.

### Summary

1. An improvement in the technique of preparing  $\beta$ -amino acids from malonic acid has been reported.

2. The factors influencing cyclization of certain  $\beta$ -amino acids to their corresponding  $\beta$ -ureido acids have been studied. This investigation has been confined to  $\beta$ -amino acids containing aromatic groups in the  $\beta$ -position.

3. The Fischer method of converting 4,5-dihydrouracils into uracil compounds has been investigated and new applications of this principle have been made. Structural conditions have been revealed which limit its successful application.

New Haven, Conn.

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