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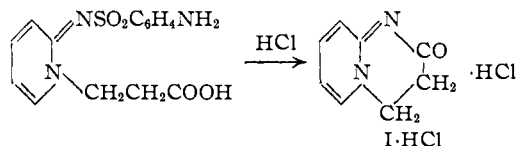
Reaction of Propiolactone with Heterocyclic Amines

BY CHARLES D. HURD AND SHIN HAYAO

RECEIVED JUNE 1, 1954

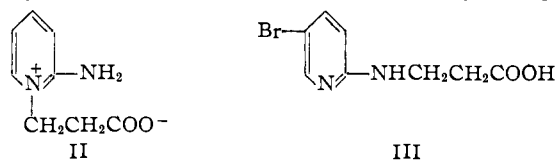
Propiolactone reacts with 2-aminopyridine, 2-amino-5-bromopyridine, 2-aminothiazole, 2-amino-4-methylthiazole and 2-amino-6-methylbenzothiazole to yield betaines or hetero bicyclic compounds depending on the conditions. There was no reaction with 2-amino-4,6-dimethylpyrimidine but the desired bicyclic compound could be made by use of 3-bromopropionic acid. This bromo acid also reacted similarly with 2-amino-4-phenylthiazole. The 2-amino and 2-imino types of tautomers in the betaines are discussed and evidence for both types is presented.

Magidson and Elina¹ have reported two syntheses of the hydrochloride of 3,4-dihydropyrido[1,2-a]pyrimidin-2-one (I). One was by hydrolysis of the reaction product of sulfapyridine and ethyl 3-bromopropionate with hot concentrated hydrochloric acid, with cleavage of sulfanilic acid



Their other synthesis was direct reaction of 2-aminopyridine and ethyl 3-bromopropionate in boiling alcohol solution. The hydrobromide separated (m.p. 293–294°), from which I·HCl (m.p. 275–276°) was obtained on reaction with silver chloride. Previously Kirpal and Wojnar² had synthesized I·HCl directly by heating a mixture of 2-aminopyridine and 3-chloropropionic acid.

Adams and Pachter^{3a} repeated Kirpal's experiment and also prepared I·HCl from 2-aminopyridine and ethyl 3-chloropropionate at 100°. They also prepared the free base I, m.p. 191–192°, by neutralizing the hydrochloride with alkali, and found that on refluxing this base with water they could effect the synthesis of 2-amino-1-(2-carboxyethyl)-pyridinium betaine (II). II readily changed



into I·HCl on heating with hydrochloric acid. II was formed also^{3b} by warming a mixture of 2-aminopyridine and glacial acrylic acid which contained 1% of *t*-butylcatechol.

In our work, we have found that both I and II may be prepared conveniently by reaction of 2-aminopyridine with propiolactone. This study is an extension of our previous report⁴ on the reaction of this β -lactone with several aniline derivatives.

The work of Gresham⁵ has established that heterocyclic bases such as pyridine or quinoline which contain no NH in the ring give rise to betaines, that from pyridine being 1-(2-carboxyethyl)-pyridinium betaine. If NH occurs in the ring, as in pyrrole or

(1) O. Y. Magidson and A. S. Elina, *J. Gen. Chem. (U.S.S.R.)*, **16**, 1933 (1946); *C. A.*, **41**, 6219 (1947).

(2) A. Kirpal and B. Wojnar, *Ber.*, **71**, 1261 (1938).

(3) (a) R. Adams and I. J. Pachter, *THIS JOURNAL*, **74**, 4906 (1952); (b) **74**, 5491 (1952).

(4) C. D. Hurd and S. Hayao, *ibid.*, **74**, 5889 (1952).

(5) T. L. Gresham, *et al.*, *ibid.*, **73**, 3168 (1951).

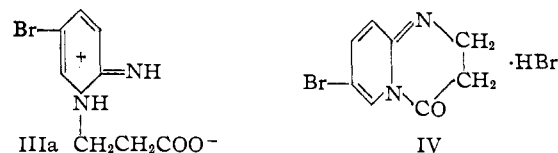
2-alkylindole, then the reaction proceeds to form C-substituted products.⁶ Pyrrole yields β -2-pyrrolyl-propionic acid, and 2-alkylindoles yield β -(2-alkyl-3-indolyl)-propionic acid.

In view of this, it is of interest to record the finding that propiolactone usually reacted at the hetero nitrogens of several 2-aminopyridines and 2-aminothiazoles rather than at the amino group. Reaction did occur at the amino group of 5-bromo-2-aminopyridine, however. This is reasonable providing one considers that resonance involving the bromine atom and the nucleus is at the expense of resonance involving the amino group.

Both hydrated (m.p. 156°,² 161–163°^{3a}) and anhydrous (m.p. 177.5–178.5° dec.^{3a}, 178° dec.^{3b}) forms of II are reported. As a matter of fact, we have found that both forms are obtainable, but there is no difference in their temperature of fusion. As ordinarily determined this is at 156°, but if the capillary tube is immersed in a bath at 160° then both melt at 165–166°. The only apparent difference is that the hydrate melts with evolution of gas (steam) whereas the anhydrous substance yields a clear melt. Nothing was ever obtained in the present work melting at 178°.

To make II from propiolactone, the reaction was conducted in acetone at 20–25°. If, instead, the reaction with 2-aminopyridine was performed in hot dilute hydrochloric acid, then I·HCl was obtained instead. The same salt could be made by passing hydrogen chloride gas into a suspension of II in acetone. I·HBr was formed similarly with dry hydrogen bromide.

2-Amino-5-bromopyridine reacts analogously, but the product is assigned structure III, N-(5-bromo-2-pyridyl)- β -alanine. 2-Amino-5-bromopyridine also reacts with 3-bromopropionic acid to yield 2,3-dihydro-7-bromopyrido[1,2-a]pyrimidin-4-one hydrobromide (IV). Thus, it is seen that 2-aminopyridine and 2-amino-5-bromopyridine elicit a dif-



ferent response from propiolactone. That II and III are of fundamentally different structures is evident since III may be titrated by alkali to give the correct equivalent weight, whereas II consumes no alkali. Instead, the phenolphthalein indicator becomes permanently red at the first drop of sodium hydroxide solution.

(6) J. Harley-Mason, *J. Chem. Soc.*, 2433 (1952).

Absorption spectra also support these structures. The ultraviolet absorption of II in 95% ethanol showed maxima at 234, 306 $m\mu$ ($\log \epsilon$ 3.79, 3.64, respectively), agreeing with data (231, 301 $m\mu$) reported by Adams and Pachter²⁶ who measured it in 0.001 *N* sodium hydroxide solution. Thus, alkali did not shift the peak to longer wave lengths. The absorption peak at 306 or 301 $m\mu$ supports structure II, since from measurements with 2-aminopyridine and 1,2-dihydro-1-methyl-2-iminopyridine any C=NH group would call for a peak closer to 350 $m\mu$.⁷

The infrared spectrum of II (Table I) showed a very strong, broad band at 6.35–6.45 μ , indicating carboxylate ion and aromatic unsaturation. Also, carboxylate ion was supported by a medium shoulder at 7.12 μ , the carboxyl group by a medium band at 6.05 μ , and the amino group by a medium band at 3.12 μ .

TABLE I

POSITION OF MAJOR BANDS IN INFRARED SPECTRA

Bands, μ , were of medium intensity unless marked w (weak), s (strong), v.s. (very strong), br. (broad). Samples of II, III, IV were prepared in powdered potassium bromide. The instrument used was a Baird double beam spectrophotometer.

II-H ₂ O	III	V-H ₂ O	2-Amino-5-bromopyridine (in CHCl ₃)
2.98	3.17	2.98 w.	2.97 w.
3.12	4.30 w., br.	3.08 w.	3.07 w.
3.48	5.39 w., br.	3.38	3.44 w.
6.05	5.50 w., br.	3.64 br.	3.51 w.
6.15	6.02 s.	6.12 w.	6.29 v.s.
6.35–6.45 v.s.	6.31 s.	6.22 w.	6.40
6.65	6.45	6.40 s.	6.49
6.89	6.65	7.12	6.85 s.
6.95	6.98 w.	7.32 s.	7.30 s.
7.12	7.26 v.s.	7.89 w.	7.73
7.30 s.	7.35 s., br.	7.99	8.05
7.98	7.52	8.48 w.	8.82
8.64	7.85 w.	8.63 w.	9.10
8.85	8.09	9.13 w.	10.05
9.30 w.	8.20 s.	9.70 w.	10.92 w.
9.63 w.	8.72	10.71 w.	12.30
9.80 w.	9.20	10.82 w.	
10.82 w.	9.95	12.05 w.	
11.60 w.	10.92 w.	12.50 w.	
12.50 w.	11.12 w.	13.42	
13.00	12.30 w.	13.75 w.	
14.66 br.	12.52	14.25 w.	
	14.43	15.50	
	15.50 w.		

These assignments are indicated: amino, 2.97, 3.07, 3.12, 3.17; -COOH, 6.02, 6.05, 6.10; aromatic unsaturation, 6.29, 6.31; carboxylate ion and/or aromatic unsaturation, 6.35–6.45; amino, 6.49; aromatic C=C, 6.85; carboxylate ion, 7.12; *cis* C=C, 7.26, 7.30; aromatic C-N-C, 7.52, 7.73, 7.98.

The ultraviolet absorption of III in 95% ethanol showed maxima at 252, 318 $m\mu$ ($\log \epsilon$ 4.14, 3.52, respectively). For comparison, 2-amino-5-bromopyridine in the same solvent showed maxima at 243, 313 $m\mu$ ($\log \epsilon$ 4.14, 3.52). The band at 313 $m\mu$ taken in alcohol agrees well with the reported

(7) I. C. Anderson and R. V. Seeger, *THIS JOURNAL*, **71**, 340 (1949).

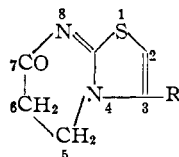
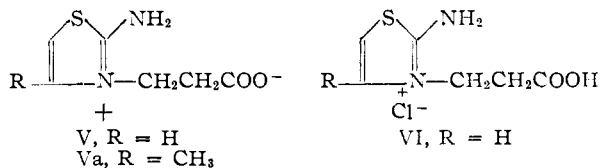
value⁸ of 307.6 $m\mu$ taken in heptane, if one applies the correction factor⁹ of +7 $m\mu$ for conversion of hexane (and presumably also of heptane) to ethanol. If III contained the C=NH structure (as in IIIa) then one would expect⁷ a peak near 350 $m\mu$ but this was missing. It could not have a structure like II because of its activity toward alkali.

Structure III is supported by the infrared spectrum (Table I). Absence of at least a medium shoulder at 7.12 μ speaks for the absence of carboxylate ion. The strong band at 6.31 μ represents aromatic unsaturation, comparable to the very strong band at 6.29 μ for 2-amino-5-bromopyridine (Table I).

The reactions of propiolactone with 2-aminothiazole and 2-amino-4-methylthiazole were studied also and the course was similar. The products were 2-amino-3-(2-carboxyethyl)-thiazolium betaine hydrate (V) and 4-methyl-2-amino-3-(2-carboxyethyl)-thiazolium betaine semihydrate (VIa), respectively. Not all aminothiazoles or related compounds react, however, for 2-amino-4-phenylthiazole, 2-acetamidothiazole and 2-amino-4,6-dimethylpyrimidine gave nothing with propiolactone and the amines were recovered. The betaine V was also prepared from 2-aminothiazole and 3-bromopropionic acid in the presence of an equivalent quantity of aqueous sodium hydroxide, or from 2-aminothiazole and acrylic acid in acetone. When V was heated in 48% hydrobromic acid there was obtained a cyclized product, 5,6-dihydrothiazolo[3,2-a]pyrimidin-7-one hydrobromide (VII·HBr), which was identical with the condensation product from 2-aminothiazole and 3-bromopropionic acid without solvent.

When V was heated in concd. hydrochloric acid two products were isolated and separated by fractional crystallization. They were 2-amino-3-(2-carboxyethyl)-thiazolium chloride (VI) and 5,6-dihydrothiazolo[3,2-a]pyrimidin-7-one hydrochloride (VII·HCl).

2-Aminothiazole reacted with methyl acrylate in the presence of hydroquinone to give 5,6-dihydrothiazolo[3,2-a]pyrimidin-7-one (VII). This free base was treated with dry hydrogen chloride to produce a salt identical with VII·HCl. Also, the betaine Va, when treated with dry hydrogen bromide, yielded a cyclized product, namely, 5,6-dihydro-3-methylthiazolo[3,2-a]pyrimidin-7-one hydrobromide (VIIa·HBr).



VII, R = H
 a, R = CH₃
 b, R = C₆H₅

(8) C. W. F. Spiers and J. P. Wibaut, *Rec. trav. chim.*, **56**, 573 (1937).

(9) G. Scheibe, G. Roessler and F. Backenkoelher, *Ber.*, **58**, 586 (1925).

treated with dry hydrogen chloride until all solids dissolved. Then the mixture was diluted with ether yielding 2.1 g. of white precipitate of m.p. 286° dec. One crystallization from methanol-ether gave 2.0 g. of pure salt of m.p. 288° dec. The picrate (m.p. 216–218°) was prepared from I by direct addition of alcoholic picric acid. Mixed melting points of the hydrochlorides and picrates from b and a were not depressed.

N-(5-Bromo-2-pyridyl)- β -alanine (III).—To a solution of 12.5 g. (0.072 mole) of 2-amino-5-bromopyridine¹⁶ in 100 ml. of acetone was added 11 g. (0.15 mole) of propiolactone. It was refluxed 13 hours before removing the solvent, then the residue was treated with aqueous sodium carbonate to remove 8.5 g. of insoluble starting material (m.p. 135–137°). The alkaline filtrate was extracted with ether to recover 0.35 g. more of it (total recovery, 70%). The alkaline layer was acidified to pH 7 (HCl) to cause precipitation of 1.57 g. of product. This is 30% yield based on the unrecovered amine. It was dissolved in base, boiled with Norit, and the filtrate acidified to pH 7 to give 1.0 g. of light tan powder of m.p. 221° dec. Further recrystallizations from aqueous methanol did not alter its m.p.

Anal. Calcd. for $C_8H_9BrN_2O_2$: C, 39.18; H, 3.67; N, 11.43; neut. equiv., 245. Found: C, 39.16; H, 3.74; N, 11.50; neut. equiv., 244.5.

2,3-Dihydro-7-bromopyrido[1,2-a]pyrimidin-4-one Hydrobromide (IV).—2-Amino-5-bromopyridine (5.1 g.) and 3-bromopropionic acid (6.1 g.) were mixed and heated at 100° for 4.5 hours to give a solid mass which was taken up in boiling methanol (Norit) and then precipitated by adding ether to give 5.4 g. (59% yield) of the amine hydrobromide, m.p. 322° dec.

Anal. Calcd. for $C_8H_9Br_2N_2O$: C, 31.07; H, 2.91; N, 9.06; neut. equiv., 308. Found: C, 31.18; H, 2.70; N, 8.95; neut. equiv., 307.

2-Amino-3-(2-carboxyethyl)-thiazolium Betaine Hydrate (V).—(a) One-tenth molar quantities of 2-aminothiazole and propiolactone were mixed in 100 ml. of acetone-ether mixture (1:1). Precipitation of the betaine started within a few minutes. The mixture was kept at 20–25° for 3 days and the betaine V was collected; yield 12.0 g. (70%). It was dissolved in 300 ml. of boiling water (Norit). The cooled filtrate was diluted with acetone; yield 7.2 g. The white powder was recrystallized twice from 50 ml. of water to give 5.0 g. of white plates, m.p. 164–165° dec. It was dried at 130° (1 mm.) for 4 hours, but no anhydrous product could be obtained. If 0.2 g. of this substance was treated with 0.1 N alkali a red color to phenolphthalein indicator appeared after 5 or 6 drops.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 37.89; H, 5.26; N, 14.74. Found: C, 38.03; H, 5.36; N, 15.13.

(b) 3-Bromopropionic acid (15.3 g.) was dissolved in 50 ml. of water containing 4.0 g. of sodium hydroxide. To this solution was added 10.0 g. of 2-aminothiazole. The clear solution was heated at 100° for an hour, treated with Norit and filtered. It was chilled to 0° and diluted with acetone to yield 8.8 g. of shiny plates of m.p. 154° dec. The sample was recrystallized from aqueous acetone to produce a white powder of m.p. 169° dec. after drying at 60° overnight.

(c) To a clear solution of 10 g. of 2-aminothiazole in 100 ml. of acetone was added 7.2 g. of glacial acrylic acid and about 0.01 g. of hydroquinone. The solution was refluxed for one hour, then was kept at 25° for 12 hours, diluted with 100 ml. of ether, and the 6.5 g. (38%) of precipitated betaine was collected, m.p. 158–159° dec. After one recrystallization from aqueous acetone the white sandy crystals melted at 168° dec. Mixtures of samples from a, b and c showed no depression of melting point.

5,6-Dihydrothiazolo[3,2-a]pyrimidin-7-one Hydrobromide (VII·HBr).—(a) Crude V (6.4 g.) of m.p. 159–159.5° was dissolved in 20 ml. of 48% hydrobromic acid and the solution was heated at 100° for 2 hours and kept at 25° for 2 days. This treatment caused separation of colorless solid. The mixture was diluted with acetone before filtering. The precipitated solid weighed 3.8 g. and it melted at 298° dec. Silver nitrate gave a positive test for ionic bromide. The analytical sample, after two crystallizations from methanol-ether, melted at 309° dec.

(16) H. W. T. Cadwell, F. T. Tyson and L. Lauer, *THIS JOURNAL*, **66**, 1479 (1944).

Anal. Calcd. for $C_8H_7BrN_2OS$: C, 30.63; H, 2.98. Found: C, 30.82; H, 3.08.

(b) A mixture of 5.0 g. of 2-aminothiazole and 7.7 g. of 3-bromopropionic acid was heated at 100° for 6 hours. The mixture first melted, then a solid mass separated. The latter was dissolved in hot methanol (Norit), filtered and the filtrate was concentrated and diluted with ether to give 1.9 g. of white crystals of m.p. 304° dec. One recrystallization from methanol-ether resulted in formation of 1.0 g. of product melting at 297–298° dec. A mixture with the material of m.p. 298° from (a) was not depressed in m.p.

2-Amino-3-(2-carboxyethyl)-thiazolium Chloride (VI) and 5,6-Dihydrothiazolo[3,2-a]pyrimidin-7-one Hydrochloride (VII·HCl).—A solution of the betaine V, 17.0 g., m.p. 162° dec., in 55 ml. of concd. hydrochloric acid was heated on the steam-bath for an hour and then evaporated to dryness at 15 mm. The remaining light brown sirup was triturated with acetone to give 18.3 g. of tan solid. It melted at 145°, darkened at 210° and then decomposed at 273–275°. For the purification and separation of two products, the following method was twice repeated. The crude product was dissolved in methanol and diluted with acetone to give 3.2 g. of pale tan crystals of m.p. 278–279° dec. After two recrystallizations from methanol-ether, the VII·HCl melted at 280° dec.

Anal. Calcd. for $C_8H_9ClN_2OS$: C, 37.80; H, 3.67; N, 14.70; neut. equiv., 190.5. Found: C, 37.95; H, 3.54; N, 15.09; neut. equiv., 191.9.

The filtrate from VII·HCl was concentrated and diluted with ether to give 8.4 g. of snow-white powder of m.p. 145.5–146°. This VI, after two recrystallizations from methanol-ether, melted at 149–150°.

Anal. Calcd. for $C_8H_9ClN_2O_2S$: C, 34.53; H, 4.32; neut. equiv., 208.5. Found: C, 34.60; H, 4.34; neut. equiv., 209.5.

5,6-Dihydrothiazolo[3,2-a]pyrimidin-7-one (VII).—A mixture of 10.0 g. of 2-aminothiazole, 9.5 g. of methyl acrylate and 0.1 g. of hydroquinone was heated on a steam-bath for 30 hours. Then, the dark brown oily solid was collected and washed with benzene, yielding 1.7 g. of product, m.p. 195–197°. One crystallization of this light tan solid from chloroform-hexane gave colorless prisms of m.p. 197°. The benzene washing was passed through an alumina-packed column without yielding any more solid.

Anal. Calcd. for $C_8H_8N_2OS$: C, 46.75; H, 3.90. Found: C, 46.62; H, 4.10.

Dry hydrogen chloride was passed into a solution of VII, (1.0 g.) in 20 ml. of methanol. The amine hydrochloride (VII·HCl) separated; yield 1.2 g., m.p. 280° dec.

4-Methyl-2-amino-3-(2-carboxyethyl)-thiazolium Betaine Semihydrate (Va) and 5,6-Dihydro-3-methylthiazolo[3,2-a]pyrimidin-7-one Hydrobromide (VIIa·HBr).—Three-tenths molar quantities of 2-amino-4-methylthiazole and propiolactone were dissolved in 200 ml. of a 1:1 mixture of acetone and ether. The clear solution was kept at room temperature for 3 days and the precipitated sticky solid was triturated with methanol-ether to give 12.6 g. (22.8% yield) of the betaine Va, m.p. 154.5–155° dec. It was recrystallized four times with methanol-ether to give a pale pink powder of m.p. 165° dec. after drying at 80° (10 mm.) for 3 hours.

Anal. Calcd. for $(C_7H_{10}N_2O_2S) \cdot \frac{1}{2}H_2O$: C, 43.07; H, 5.64; N, 14.35. Found: C, 43.23; H, 5.63; N, 14.44.

The filtrate was chilled and treated with dry hydrogen bromide for an hour. A yellow solid separated, yield 3.6 g. Two crystallizations from methanol-ether (Norit) resulted in 2.0 g. of canary yellow crystals of m.p. 308° dec.

Anal. Calcd. for $C_7H_9BrN_2OS$: C, 33.75; H, 3.61; neut. equiv., 249. Found: C, 33.87; H, 3.73; neut. equiv., 246.4.

The filtrate, after treatment with hydrogen bromide, was evaporated *in vacuo* to give 8.0 g. of 2-amino-4-methylthiazole hydrobromide of m.p. 182°. The neutral equivalent was 199.7 (calcd. 195).

5,6-Dihydro-3-phenylthiazolo[3,2-a]pyrimidin-7-one Hydrobromide (VIIb·HBr).—A solution of 3.0 g. of 2-amino-4-phenylthiazole and 2.6 g. of 3-bromopropionic acid in 100 ml. of chloroform was refluxed for 22 hours. Since no solid separated on cooling the solution was diluted with ether. A light yellow gum appeared (3.6 g.) which solidified on standing overnight. One recrystallization from methanol-

ether gave 0.6 g. of light yellow powder which decomposed at 277°. Two more recrystallizations resulted in a colorless powder of m.p. 281° dec. Silver bromide was precipitated when alcoholic solutions of this product and silver nitrate were mixed. From the first filtrate another 2.2 g. of the less pure substance was obtained of m.p. 275° dec.

Anal. Calcd. for $C_{12}H_{11}BrN_2OS$: C, 46.30; H, 3.54; N, 9.05. Found: C, 46.27; H, 3.84; N, 8.56.

3,4-Dihydro-6,8-dimethylpyrimido[1,2-a]pyrimidin-2-one Hydrobromide (VIII).—2-Amino-4,6-dimethylpyrimidine was prepared from guanidine carbonate and acetylacetone by adapting the procedure¹⁷ for the preparation of 2-amino-4-methyl-6-methoxypyrimidine. The yield was 88% and the pure sample melted¹⁸ at 150–151° (lit. 153°) after two recrystallizations from a mixture of chloroform and petroleum hexane.

When equivalent quantities (0.1 mole) of this amine and 3-bromopropionic acid were heated together on a steam-bath at first the mixture became a homogeneous melt. Then white solid began to appear and after 24 hours of heating the mixture became a hard mass. It was dissolved in 200 ml. of 90% methanol and its boiling point and then was diluted with excess ether to yield 5.7 g. of white powder which darkened at about 70° and melted with decomposition at 334–335°. One more crystallization from methanol-ether gave 4.0 g. of colorless needles (VIII) of m.p. 330° dec. Softening was noticed at about 245°.

Anal. Calcd. for $C_9H_{12}BrN_3O$: C, 41.85; H, 4.65; N, 16.28; neut. equiv., 258. Found: C, 41.95; H, 4.70; N, 16.03; neut. equiv., 256.

Processing of the first methanol-ether filtrate led to the recovery of 0.3 g. more of VIII and 3.3 g. of 2-amino-4,6-dimethylpyrimidine hydrobromide; m.p. 179–180°; neut. equiv., 209.6 (calcd. 204.0).

An attempt to effect interaction of 2-amino-4,6-dimethylpyrimidine and propiolactone in ether-acetone solution at 25° was negative. The clear solution turned dark brown in six days, but nothing precipitated. Actually, 99% of the pyrimidine was recovered.

3-(2,3-Dihydro-2-imino-6-methyl-3-benzothiazolyl)-propionic Acid.—2-Amino-6-methylbenzothiazole, m.p. 135–

(17) C. C. Price, N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **10**, 318 (1945).

(18) A. Combes and C. Combes, *Bull. soc. chim.*, [3] **8**, 788 (1892).

136° (lit.¹⁹ 142°), was prepared by the general procedure²⁰ for the preparation of 6-substituted benzothiazoles.

To a clear yellow solution of 16.4 g. of this compound in 100 ml. of acetone was added 8.0 g. of propiolactone. After the first hour of refluxing, 4.35 g. of pale yellow crystals separated, m.p. 131–133° dec. after rinsing with acetone. From the filtrate was obtained another 5.5 g. of product by heating it 3 hours longer and allowing it to stand overnight. The solid was insoluble in ether, acetone or cold water, but it dissolved in cold methanol, hot water, dilute hydrochloric acid and aqueous sodium carbonate.

The acetone filtrate was evaporated and the resulting sirup treated with sodium carbonate solution and ether extracted. The ether removed 3.85 g. of unreacted benzothiazole. The aqueous layer was heated with Norit, then was taken to pH 6 (dil. HCl) to yield a yellow sticky solid, but addition of chloroform did away with the stickiness. The pale yellow solid weighed 2.65 g., thus making a total yield of 12.5 g.

The recrystallizations of either this last product or the first product of m.p. 131–133° from aqueous methanol caused hydration and brought the m.p. to 168° dec. These were white crystals of practically identical solubility behavior as the material of m.p. 131–133°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S \cdot H_2O$: C, 52.0; H, 5.51; N, 11.0; neut. equiv., 254. Found: C, 52.35; H, 5.70; N, 11.0, 10.9; neut. equiv., 251.

The unpurified product of m.p. 131–133° probably contained a little of the original 2-amino-6-methylbenzothiazole. Its N content was 12.5–12.7% (calcd. for $C_{11}H_{12}N_2 \cdot O_2S$: N, 11.9).

Acknowledgments.—Microanalyses were performed by Mrs. C. White and Miss H. Beck. Propiolactone was generously furnished by B. F. Goodrich Chemical Company. One of us (S. H.) was holder of a Swift and Company fellowship during a portion of this work.

(19) G. M. Dyson, R. F. Hunter and R. W. Morris, *J. Chem. Soc.*, **130**, 1186 (1927).

(20) R. Q. Brewster and F. B. Dains, *THIS JOURNAL*, **58**, 1364 (1936).

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Chemistry of 2,5-Anhydro-L-arabinose¹

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Treatment of ethyl 5-O-tosyl- α -L-arabofuranoside (II, R = C_2H_5) with alkali affords ethyl 2,5-anhydro- α -L-arabofuranoside (III, R = C_2H_5); the corresponding anhydro methyl glucoside may be made in the same way. The structure of the 2,5-anhydro-L-arabinose was established by its transformation into 2,5-anhydro-L-arabitol, the enantiomorph of which was obtained from the known 3,6-anhydro-4,5-O-isopropylidene-D-mannitol. Although stable to alkali, the alkyl 2,5-anhydro-L-arabofuranosides are so sensitive to H^+ ions that they are hydrolyzed by distilled water giving 2,5-anhydro-L-arabinose (IV), which exists in the aldehydic form. Once the sugar ring is cleaved it would appear that it cannot be re-formed. methanolic hydrogen chloride, for example, affording the dimethyl acetal and not the methyl glycoside. The ease of conversion of 2,5-anhydro-L-arabinose into furfural by dilute acid favors the view that, in furfural formation, the hydrofuran ring is produced before unsaturation. It is also suggested that the enhanced reactivity at C_1 in III, induced by the strain of the 2,5-anhydro ring on the sugar ring, may parallel the manner in which an enzyme combines with and activates a substrate so that it may undergo facile cleavage.

The hydrofuranol (butylene oxide) type of ring system has been shown to have a marked effect upon the properties of hexose sugars and their derivatives. This deduction has been made as a result of investigation into 3,6-anhydro derivatives

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of D-galactose,^{2–4} D-glucose⁵ and D-mannose.⁶ The conclusion was reached⁵ that the anhydro ring assumes the character of the principal ring struc-

(2) W. N. Haworth, J. Jackson and F. Smith, *Nature*, **42**, 1075 (1938).

(3) W. N. Haworth, J. Jackson and F. Smith, *J. Chem. Soc.*, 620 (1940).

(4) P. A. Rao and F. Smith, *ibid.*, 229 (1944).

(5) W. N. Haworth, L. N. Owen and F. Smith, *ibid.*, 88 (1941).

(6) A. B. Foster, W. J. G. Jones and F. Smith, unpublished work.