separated was taken up in ether and the ether solution dried over anhydrous calcium sulfate. After removal of the ether, the residue was distilled under reduced pressure to afford 20 g. (27%) of 1-propargylpyrrole, b.p. 70° (23 mm.), $n^{20}D$ 1.5095.

Anal. Calcd. for C_7H_7N: C, 80.0; H, 6.7; N, 13.3. Found: C, 80.0; H, 6.8; N, 13.2.

Hydrogenation of 1-Propargylpyrrole to 1-Allylpyrrole.—A solution of 10.0 g. (0.100 mole) of 1-propargylpyrrole in 50 ml. of ether, with 100 mg. of suspended platinic oxide, under a hydrogen pressure of 2 atm. was shaken in a standard Parr hydrogenation apparatus until 0.1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the ether by evaporation. Distillation of the residue under vacuum yielded 7 g. (60%) of 1-allylpyrrole, b.p. 49–50° (22 mm.), $n^{27}D$ 1.4950. The infrared spectrum of the product was identical with that of the 1-allylpyrrole prepared by pyrolysis of 3-(1-pyrryl)-propyl acetate.

2-Crotylpyrrole.—To a well-stirred, ice-cold solution of pyrrylpotassium, prepared from 40 g. (1.0 mole) of potassium and 268 g. (4.00 moles) of pyrrole, 102 g. (0.750 mole) of crotyl bromide was added dropwise. After addition was complete, the reaction mixture was refluxed for 1.5 hr., then cooled on an ice-bath and finally ice-cold water was added. The contents of the flask were transferred to a separatory funnel, the oil layer was removed and the water layer was extracted with an equal volume of ether. After drying of the combined extracts with magnesium sulfate, the ether was removed and the residue was distilled to give 55 g. (61%) of pure 2-crotylpyrrole, b.p. 90–92° (11 mm.), $n^{28}D$ 1.5088.

Anal. Calcd. for $C_8H_{11}N$: C, 79.2; H, 9.2; N, 11.6. Found: C, 79.2; H, 9.5; N, 11.5.

This reaction was repeated with 0.75-mole quantities of pyrrylpotassium and of crotyl bromide. The oil layer isolated from the reaction mixture was dried over magnesium sulfate and then hydrogenated catalytically in a Parr apparatus under a hydrogen pressure of 3 atm. in the presence of 100 mg. of platinic oxide. Careful fractional distillation of the residue, after removal of catalyst and solvent, yielded 0.45 mole (60%) of 2-butylpyrrole, b.p. 90–91° (25 mm.), and 0.057 mole (7.6%) of 1-butylpyrrole, b.p. 76–77° (24 mm.). The actual ratio of 2- to 1-alkylation in the reaction is therefore approximately 8:1.

Hydrogenation of 2-Crotylpyrrole to 2-Butylpyrrole.—Exactly 12.0 g. (0.1 mole) of 2-crotylpyrrole was dissolved in 50 ml. of ether, 100 mg. of platinic oxide was added and the suspension was shaken under a hydrogen pressure of 3 atm. until 0.1 mole of hydrogen had been absorbed (45 min.). The catalyst was filtered from the pale yellow solution and the solution was then dried over anhydrous calcium sulfate. Distillation of the ether-free residue yielded 11 g. (88%) of pure 2-butylpyrrole (IVa), b.p. 90–91° (24–25 mm.), $n^{28}D$ 1.4854. This product gave an infrared spectrum identical with that for a sample of 2-butylpyrrole (IVb) prepared by reaction of pyrrylmagnesium bromide with *n*-butyl bromide according to the general method of Hess.[4]

Hydrogenation of 2-Butylpyrrole to 2-Butylpyrrolidine.—Hydrogenation of 10 g. of IVa according to the procedure described for 2-propylpyrrole yielded 9.5 g. (94%) of 2-butylpyrrolidine, b.p. 170–171° (741 mm.), $n^{25}D$ 1.4479. Hydrogenation of IVb yielded the identical product.

Ozonolysis of 2-Crotylpyrrole.—A mixture of 5% ozone in oxygen was passed into a solution of 12.1 g. (0.10 mole) of 2-crotylpyrrole in 100 ml. of carefully purified methylene chloride at −60° until slightly more than 0.1 mole of ozone had been absorbed. Ozone absorption was complete during this period, with no ozone present in the exit gas.

The dark red solution containing the ozonide was warmed to 0°, transferred to an addition funnel equipped with a pressure equalizer and added cautiously, with stirring, to a solution of 22 g. (0.20 mole) of 30% hydrogen peroxide and 1 ml. of concentrated sulfuric acid in 100 ml. of distilled water. The methylene chloride was removed by distillation and the aqueous solution was refluxed for 15 minutes.

After being cooled to room temperature, the contents of the flask were extracted five times with a total of 1000 ml. of ether. The ether solution was extracted with 250 ml. of 10% aqueous sodium hydroxide. All the colored material was extracted into the aqueous layer during this operation.

After acidification with 10% sulfuric acid, the aqueous solution was re-extracted with 500 ml. of ether. The ether solution was dried and the ether removed under reduced pressure leaving a residue consisting of 1.5 g. of a liquid acid which formed a *p*-bromophenacyl ester, m.p. 86.1–87.3° (lit.[14] value for 3-pentenoic acid 87–88°) and an amide, m.p. 66.0–67.3° (lit.[14] 69–70°).

Attempted Rearrangement of 1-Allylpyrrole.—Rearrangement of 1-allylpyrrole was attempted as: (1) A mixture of 5 g. of potassium, 15 g. of 1-allylpyrrole and 250 ml. of toluene was refluxed for 4 hr. with stirring, then cooled, and cold water added cautiously. The oil layer was separated, the water layer extracted with an equal volume of ether, and the combined organic fractions were dried over anhydrous calcium sulfate. After removal of the ether, the residue was distilled under reduced pressure. (2) A mixture of 15 g. of potassium amide, 15 g. of 1-allylpyrrole and 100 ml. of benzene was treated as described for the mixture in (1). (3) A mixture of 15 g. of pyrrylpotassium, 5 g. of potassium bromide, 15 g. of 1-allylpyrrole and 100 ml. of benzene was treated as described for the mixture in (1).

In every case only 1-allylpyrrole was recovered; infrared spectra gave no evidence for the presence of any 2-allylpyrrole.

(14) K. V. Auwers, *Ann.*, **432**, 70 (1923).

LAWRENCE, KANSAS

[COMMUNICATION FROM THE B. F. GOODRICH RESEARCH CENTER]

The Synthesis and Reactions of Some Cyclic Imides[1]

BY C. M. HENDRY

RECEIVED AUGUST 20, 1957

The synthesis of simple five and six-membered cyclic imides through ring closure has been studied. A new catalyzed, low temperature ring closure was found and applied to the synthesis of 1,3-thiazanedione-2,4 and succinimide; these imides were prepared from β-thiocyanatopropionic acid and β-cyanopropionic acid, respectively. Some reactions of 1,3-thiazanedione-2,4 have been investigated. The previously reported acid-catalyzed, high temperature ring closure of β-cyanopropionic acid also was examined. β-Sulfopropionimide has been synthesized for the first time. The ease with which cyclic imides are formed depends upon the size and constitution of the ring.

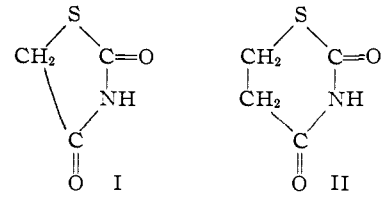
The reaction of carboxylic acids with nitriles to form imides is a general reaction.[2] This reaction as well as the reaction of carboxyamides with carboxyl groups may be employed to synthesize succinimide[3] (III); this type of ring closure requires high temperature and mineral acid catalysis. Five-membered cyclic imides containing a sulfide linkage, such as thiazolidinedione-2,4 (I), are much more easily formed than the succinimide ring, by

(1) Paper presented before the Division of Organic Chemistry at the National Meeting of the American Chemical Society, April 11, 1957.

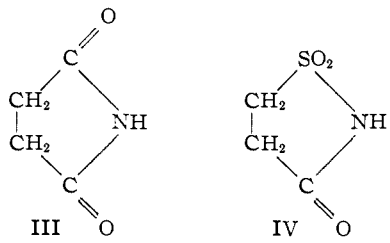
(2) F. C. Whitmore, "Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1937, p. 501.

(3) M. T. Bogert and D. C. Eccles, THIS JOURNAL, **24**, 20 (1902).

the reaction of a carbamoylthio group with a nitrile, carboxyl or carboxylic ester group.[4-6] These ring closures are effected by heating, or by hydrochloric acid treatment plus mild warming. Though the five-membered, sulfide-containing cyclic imides are well known, similar six-membered imides are much less common. 1,3-Thiazanedione-2,4 (II) has been reported by Langlet[7] who prepared it in undisclosed yield by treating xanthogenamide with β-iodopropionic acid in the presence of acetic anhydride. β-Sulfopropionimide (IV) is unknown, though an unsuccessful attempt at its preparation is reported by Bigelow, Sigmon and Wilcox.[8]



I II



III IV

The Preparation of Thiazolidinedione-2,4.—Thiazolidinedione-2,4 (I) is formed readily from thiocyanatoacetic acid. Hydration and ring closure both occur so readily that the cyclic imide as well as carbamoylthioacetic acid were isolated when sodium thiocyanatoacetate was treated with one equivalent of sulfuric acid with mild warming.

The Preparation and Reactions of 1,3-Thiazanedione-2,4.—β-Thiocyanatopropionic acid also was hydrated readily, β-(carbamoylthio)-propionic acid being formed even without heat or mineral acid catalysis. But β-thiocyanatopropionic acid did not cyclize to the cyclic imide nearly as readily as did thiocyanatoacetic acid. When heated, or treated with aqueous hydrochloric acid and warmed, β-thiocyanatopropionic acid yielded resins. Dry hydrogen chloride in an inert solvent was also ineffective in cyclizing the thiocyanato acid to II, but a low yield of this imide finally was achieved by heating sodium β-thiocyanatopropionate to 170°, in the presence of an excess of sulfuric acid.

A new catalyzed ring closure was discovered when β-thiocyanatopropionic acid was treated with small quantities of certain acid halides and metal halides. An exothermic reaction was initiated and II was obtained in excellent yield. The catalysts employed were thionyl chloride, phosphorus chlorides, phosphorus oxychloride and aluminum chloride. The optimum quantity of catalyst was about 5 to 10% by weight of the material to be cyclized. The quantity of catalyst required varied with the particular catalyst used; excess catalyst decreased imide yields. The reaction occurred spontaneously with certain of the catalysts, while others required external heat to initiate the cyclization. The optimum reaction temperature was the lowest temperature at which the reaction could be initiated and sustain itself as indicated by gas evolution.

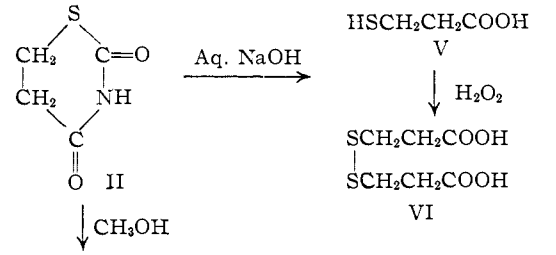
TABLE I

CONVERSION OF 0.2 MOLE OF β-THIOCYANATOPROPIONIC ACID TO 1,3-THIAZANEDIONE-2,4

Catalyst	Optimum quantity of catalyst, g.	Initiation temp., °C.	Reaction temp., °C.	Imide yields, %
$SOCl_2$	3.0	None	55	82.5
PCl_3	1.5	None	60	79
PCl_5	2.0	85	130	78
CH_3COCl	2.0	85	100	50
$POCl_3$	3.0	100	100	51
$AlCl_3$	1.0	175	175	26

This little known thiazane is a stable crystalline solid. Heating II with aqueous sodium hydroxide hydrolyzed the ring, mercaptopropionic acid (V) being a major product; V was oxidized to bis-(carboxyethyl) disulfide (VI) with hydrogen peroxide.

1,3-Thiazanedione-2,4 was essentially unchanged by boiling methanol, but when sodium methoxide was added to the alcohol solution, the imide apparently underwent a methanolysis to give a compound $C_5H_9O_3NS$. Compounds VIIa and VIIb are suggested as likely products of this methanolysis.



$H_2NOCCH_2CH_2SCOOCH_3$ or $H_2NOCSCH_2CH_2COOCH_3$

VIIa VIIb

The Preparation of Succinimide.—The new catalytic cyclization also has been applied to the synthesis of succinimide (III) from β-cyanopropionic acid. This imide was prepared using the same catalysts employed to cyclize β-thiocyanatopropionic acid; in this instance only aluminum chloride catalysis required external heat to initiate the reaction. Approximately the same catalyst-reactant ratio used in preparing 1,3-thiazanedione-2,4-prevailed as optimum, but the yields of succinimide were only 20 to 40%.

The details of the high temperature, acid-catalyzed cyclization of β-cyanopropionic acid have been little investigated. This reaction was examined and found to be superior to the new low temperature cyclization reported above. Sodium β-cyanopropionate was converted to succinimide in 74 to 78% yields by treatment with a slight excess of mineral acid at temperatures of 200–230°; at lower temperatures the yields were lower, while

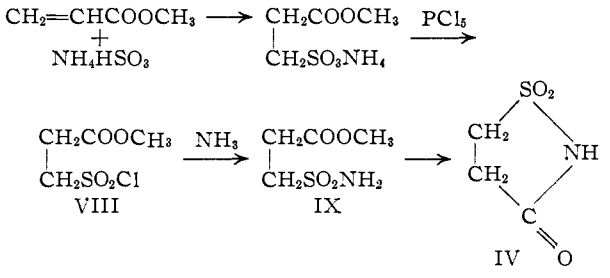
(4) W. Davies and J. A. Maclaren, *J. Chem. Soc.*, 2595 (1951).
(5) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **24**, 80 (1900).
(6) P. Klason, *Ber.*, **10**, 1349 (1877).
(7) N. A. Langlet, *ibid.*, **24**, 3851 (1891).
(8) L. A. Bigelow, H. W. Sigmon and D. H. Wilcox, THIS JOURNAL, **57**, 2521 (1935).

higher temperatures caused severe product discoloration. The mineral acid may be aqueous HCl or dry hydrochloric acid in ether, benzene or alcohol, but the preferred acid was sulfuric. Succinic acid or anhydride contaminated the product when too great an excess of mineral acid was employed. Some succinamic acid also was isolated when sufficient time for complete cyclization was not permitted before product isolation.

The Preparation of β-Sulfopropionimide.—Though β-sulfopropionimide (IV) has not been reported in the literature, it has essentially the same ring system present in saccharin, and there seemed to be no obvious reason why it could not be made. Bigelow, *et al.*,[8] reported the preparation of several derivatives but failed to isolate the imide itself.

A considerable variety of ring closures which had been successfully used to prepare cyclic dicarboxyimides also were utilized in attempts to synthesize β-sulfopropionimide, but without success; one unsuccessful cyclization involved the treatment of β-sulfopropionitrile with mineral acids.

A small quantity of IV finally was prepared in very low yield by the sequence



Ammonia failed to effect ring closure of the sulfonyl chloride (VIII). The ring closure proved to be the most difficult step in the synthesis. Methyl β-sulfamylpropionate (IX) was converted to the cyclic imide by warming with aqueous base, followed by neutralization, fractional distillation and recrystallization. β-Sulfopropionimide is a stable, crystalline solid which does not sublime as does succinimide and, unlike saccharin, it is not sweet.

Experimental

Thiazolidinedione-2,4 (I).—To monochloroacetic acid (94.5 g., 1.0 mole) in 200 cc. of water was added slowly sodium bicarbonate (84.0 g., 1.0 mole) with stirring. Sodium thiocyanate (81.1 g., 1.0 mole) was then added and the mixture was warmed on a steam-bath for one hour. The water was evaporated under aspirator vacuum while heating on a steam-bath. Recrystallization of the residue from ethanol gave 73.7 g. of sodium thiocyanatoacetate, m.p. 121°. A portion of this salt was dissolved in a large volume of water and treated with one equivalent of concentrated sulfuric acid, the mixture being cooled in an ice-bath. The water solution was then extracted with ether. Evaporation of the ether on a steam-bath left a solid, part of which was chloroform soluble. The chloroform-soluble portion yielded (I), which melted at 126–127° after ether recrystallization (lit. 125–126°).

Anal. Calcd. for $C_3H_3O_2NS$: C, 30.78; H, 2.56; N, 11.96; S, 27.35. Found: C, 31.06; H, 2.51; N, 11.93; S, 27.29.

Carbamoylthioacetic Acid.—The chloroform-insoluble portion from the preparation of I was recrystallized from ethanol–ether giving a solid melting at 134.5–135° (lit.[9] 139°).

Anal. Calcd. for $C_3H_5O_3NS$: C, 26.67; H, 3.70; N, 10.36. Found: C, 26.71; H, 4.04; N, 10.29.

(9) B. Holmberg and W. Rosen, *Ber.*, **58**, 1838 (1925).

β-Thiocyanatopropionic Acid and β-(Carbamoylthio)-propionic Acid.—Sodium β-thiocyanatopropionate was prepared in 85–88% yields by a variation of the method of Gresham, Jansen, Shaver, *et al.*[10] One mole of β-propiolactone was added to a solution of a mole of sodium thiocyanate in 250 cc. of ethanol at 25–40°; the product precipitated. β-Thiocyanatopropionic acid was obtained by treating the sodium salt with one equivalent of mineral acid and extracting the solution with chloroform. The chloroform extract was dried over anhydrous sodium sulfate for 3 to 4 hours and the solvent evaporated leaving β-thiocyanatopropionic acid melting at 5–6°. When water was not thoroughly eliminated, the β-thiocyanatopropionic acid was largely converted to β-thiolcarbamylpropionic acid during shelf storage for several months: the β-(carbamoylthio)-propionic acid melted at 150–152° (lit.[7] 147.5°).

Anal. Calcd. for $C_4H_7O_3NS$: C, 32.21; H, 4.70; N, 9.40; S, 21.48. Found: C, 32.37; H, 4.78; N, 9.37; S, 21.33.

1,3-Thiazanedione-2,4 (II). Method A.—Thionyl chloride (3.0 g.) was added to β-thiocyanatopropionic acid (26.2 g., 1.0 mole) with stirring. An exothermic reaction ensued and gas was evolved. The reaction was stirred continuously and occasionally cooled in ice to keep the reaction temperature at 50–55°. When the gas evolution had ceased, the mixture was warmed on a steam-bath for one hour with occasional stirring. The solid reaction mass was then extracted with 50 cc. of ethanol; concentrating and cooling the extract yielded 21.6 g. (82.5%) of yellow flakes melting at 159–161°. The product was recrystallized from ethanol and decolorized with Nuchar to give white plates, m.p. 163° (II) (lit.[7] 159°). The product can also be recrystallized from benzene, ether or water.

The infrared spectrum of 1,3-thiazanedione-2,4 was compared with those of thiazolidinedione-2,4 and 2-thiono-4-ketothiazane-1,3. The spectrum of II is very similar to that of the latter except for a broad carbonyl band at 5.80 to 6.10 μ for II, while 2-thiono-4-ketothiazane-1,3 has a sharp carbonyl maximum at 5.90 μ and a peak at 6.63 μ attributed to the thiono group.

Anal. Calcd. for $C_4H_5O_2NS$: C, 36.62; H, 3.82; N, 10.68; S, 24.42; mol. wt., 131. Found: C, 36.62; H, 3.85; N, 10.55; S, 24.64; mol. wt., 131.

Method B.—Sulfuric acid (120 g., 1.2 moles) was added to sodium β-thiocyanatopropionate (40 g., 0.26 mole). The mixture was heated to 170° for about 40 minutes. The sulfuric acid solution was neutralized with aqueous sodium hydroxide and then evaporated to dryness. The residue was then extracted with ethanol. Yellow flakes (5 g.) crystallized from ethanol, a 15% yield, m.p. 163°. The melting point was not depressed when this product was mixed with a sample of 1,3-thiazanedione-2,4 from method A.

Bis-(carboxyethyl) Disulfide (VI).—A 20-g. sample of 1,3-thiazanedione-2,4 was refluxed with 80 cc. of 20% aqueous sodium hydroxide for 4 hours. The resulting solution was titrated with hydrochloric acid to *p*H 6. The water solution was then extracted with ether and the ether solution evaporated leaving an oily residue with the odor of β-mercaptopropionic acid (V). A 10% water solution of this oil was warmed on a steam-bath with an excess of hydrogen peroxide for a few minutes. Cooling caused a white solid to precipitate, m.p. 154–155° (lit.[10] 150–152.2°). This product was identified as bis-(carboxyethyl) disulfide through mixture melting point with an authentic sample; there was no depression.

Basic Methanolysis of 1,3-Thiazanedione-2,4.—1,3-Thiazanedione-2,4 (13.1 g., 0.1 mole) was dissolved in 50 cc. of methanol, and sodium methoxide (5.4 g., 0.1 mole) added to the solution. After 2 hours of refluxing, a gray insoluble solid (4 g.) was filtered from the reaction; this solid failed to melt below 290°. The filtrate was evaporated to dryness and the solid residue was extracted with ether. The ether solution yielded 5.6 g. of white needles, m.p. 75–76° (VIIa or b). The ether-insoluble portion, 2.1 g., was treated with an alcoholic solution of hydrogen chloride and yielded more of the same solid previously isolated from the ether extract; the two ether-recrystallized solids gave no melting point depression when mixed.

(10) T. L. Gresham, J. E. Jansen, F. W. Shaver, *et al.*, THIS JOURNAL, **74**, 1323 (1952).

Anal. Calcd. for $C_5H_9O_3NS$ (VIIa or b): C, 36.80; H, 5.52; N, 8.59; S, 19.65; mol. wt., 163. Found: C, 36.92; H, 5.56; N, 8.58; S, 19.36; mol. wt., 158 (ebullioscopic).

Succinimide (III). Method A.—Sodium β-cyanopropionate was prepared in 75 to 78% yield by treating sodium cyanide with β-propiolactone in 50% aqueous ethanol, a variation of the procedure of Gresham, Jansen, Shaver, *et al.*[10] Recrystallized sodium β-cyanopropionate monohydrate (98 g., 0.705 mole) was mixed with 50% sulfuric acid (79 g., 0.805 mole). The mixture was heated until all of the water had been driven off and the temperature of the reaction mixture reached 200°. The flask was then fitted for distillation and heated at 200–230°, the pressure of the system being gradually reduced to about 200 mm. The succinimide sublimed and was collected in a chilled collection vessel. The sublimation was complete in 15 to 20 minutes. The sublimed material was recrystallized from 140 cc. of ethanol to give 54 g. (77%) of succinimide, melting at 124–125°. The mixture melting point of the reaction product with an authentic sample of succinimide was not depressed.

Methyl β-Chlorosulfonylpropionate (VIII).—Methyl acrylate (215 g., 2.5 moles) was treated with a 45% aqueous solution of ammonium bisulfite (550 g., 2.5 moles) adding the acrylate to the bisulfite solution at less than 50° with vigorous stirring. The mixture was then warmed at 80° for 30 minutes. Evaporation of the water and recrystallization of the product from ethanol gave 407.7 g. of ammonium β-carbomethoxyethanesulfonate melting at 203–204°. A portion of this salt (370 g.) was thoroughly mixed with phosphorus pentachloride (417 g., 2.0 moles), an exothermic reaction resulted and the mixture became fluid. The reaction mixture was heated and distilled, 203 g. (48%) of VIII distilling at 137–144° at 18 mm.

Anal. Calcd. for $C_4H_7O_4SCl$: C, 25.75; H, 3.76. Found: C, 25.75; H, 3.81.

Methyl β-Sulfamylpropionate (IX).—Methyl β-chlorosulfonylpropionate (55 g., 0.295 mole) was dissolved in 300 cc. of benzene and the solution was saturated with dry ammonia. The benzene solution was then evaporated to dryness and the residue was recrystallized from chloroform. The extract yielded 31.2 g. (63%) of IX as white plates melting at 69°.

Anal. Calcd. for $C_4H_9O_4NS$: C, 28.75; H, 5.39; N, 8.38. Found: C, 28.75; H, 5.74; N, 8.35.

β-Sulfopropionimide (IV).—Methyl β-sulfamylpropionate (6.16 g., 0.037 mole) was mixed with sodium hydroxide (1.47 g., 0.037 mole) in 50 cc. of water. The mixture was warmed on a steam-bath for one hour and neutralized with concentrated hydrochloric acid. The water solution was evaporated to dryness by warming on a steam-bath under aspirator vacuum. The residue was extracted with ethanol and the ethanol extract was distilled, after drying over anhydrous sodium sulfate. After the solvent was removed, and a milky forerun was discarded, the remainder of the material distilled at 230–250° (1.0 mm.) and solidified in the receiver. This solid was recrystallized from a small quantity of ethanol, cooling in Dry Ice and was then extracted with ether, from which was obtained 0.5 g. of white needles melting at 119° (IV).

The infrared spectrum of β-sulfopropionimide was compared with that of saccharin. The spectra are extremely similar and peaks are present to account for each functional group; the major differences are absorptions at 6.25, 6.88 and 13.16 μ for saccharin, attributed to the benzene ring, and a maximum at 7.02 μ for β-sulfopropionimide, this peak being attributed to the methylene group.

Anal. Calcd. for $C_3H_5O_3NS$: C, 26.70; H, 3.70; N, 10.37. Found: C, 26.69; H, 3.79; N, 10.35.

Acknowledgment.—The author wishes to thank A. K. Kuder and J. R. Kubik for the elemental analyses, and J. J. Shipman for the infrared interpretations.

BRECKSVILLE, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE]

The Reaction of Chloral Hydrate with Semicarbazides and the Synthesis of Semicarbazide-C^{14} and 6-Azauracil-2-C^{14} [1]

BY PAULINE K. CHANG AND T. L. V. ULBRICHT[2]

RECEIVED MARCH 27, 1957

Chloral hydrate reacts with semicarbazides to give chloral *hydrate* semicarbazones. The structure of these compounds is discussed in relation to the infrared spectrum of the thiosemicarbazone. Two syntheses of 6-azauracil (*asym*-triazine-3,5-dione) using chloral hydrate semicarbazones or their derivatives have been investigated. In one, heating an aqueous solution of chloral hydrate methylthiosemicarbazone gave azauracil directly. Two possible mechanisms for this unusual reaction are discussed. The other synthesis was used to prepare 6-azauracil-2-C^{14} from urea-C^{14} in an over-all yield of 30% *via* semicarbazide-C^{14}. The chlorination of 5-bromoazauracil and millimolar syntheses of potassium thiocyanate and thiosemicarbazide also are described.

6-Azauracil (*asym*-triazine-3,5-dione, I)[3] has been shown to inhibit the growth of certain strains of microörganisms[4,5] and a number of transplantable neoplasms[5,6] in mice. The ribofuranoside of this analog of uracil has been prepared recently[7] and, unlike free azauracil, this derivative inhibits the growth of sarcoma 180 cells in tissue culture.[8] To permit metabolic studies in these systems, a synthesis of C^{14}-labeled azauracil was developed.

Two recent four-step syntheses of azauracil from thiosemicarbazide and oxomalonic acid or its methyl ester, in over-all yields of 41[9] and 22%,[10] respectively, did not appear to be satisfactory for isotopic synthesis.

(1) This paper was presented, in part, at the 131st National Meeting of the A.C.S., Miami, Fla., April, 1957.

(2) This work was supported by a grant from the National Cancer Institute, Public Health Service.

(3) This designation is adopted in view of current practice (refs 4, 6, 7 and 9) and because it probably describes the structure better than does 3,5-dihydroxy-1,2,4-triazine.[10] However, the authors suggest (in view of the confusion caused in pyrimidine literature, particularly "Chemical Abstracts" [A. Bendich, "The Nucleic Acids," ed. by E. Chargaff and J. N. Davidson, Vol. 1, p. 83, Academic Press, Inc., New York, 1955] by calling compounds pyrimidones, pyrimidols and hydroxypyrimidines) that it might be preferable to name all compounds as derivatives of the aromatic ring system, without prejudice to the preferred tautomeric form.

(4) R. E. Handschumacher and A. D. Welch, *Federation Proc.*, **15**, 267 (1956); *Cancer Research*, **16**, 1965 (1956).

(5) F. Sorm, A. Jakobovic and L. Slechta, *Experientia*, **12**, 271 (1956).

(6) M. T. Hakala, L. W. Law and A. D. Welch, *Proc. Am. Assocn. Cancer Research*, **2**, 113 (1956).

(7) R. E. Handschumacher, *Biochim. et Biophys. Acta*, **23**, 428 (1957).

(8) R. Schindler and A. D. Welch, *Science*, **125**, 548 (1957).

(9) R. B. Barlow and A. D. Welch, THIS JOURNAL, **78**, 1258 (1956).

(10) E. A. Falco, E. Pappas and G. H. Hitchings, *ibid.*, **78**, 1938 (1956).