ethanol. Decomposition of a sample of the complex by passage over alumina afforded the crystalline hydrocarbon (m.p. 40°) and identity was established by mixture melting point and infrared comparison with samples of the hydrocarbon and its trinitrofluorenone complex synthesized according to procedure (a).

DETROIT, MICH.

[CONTRIBUTION FROM THE MONSANTO CHEMICAL COMPANY, PLASTICS DIVISION]

4-Imidazolidinethiones

JOHN D. CHRISTIAN[1]

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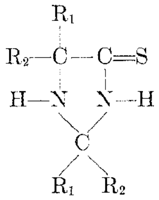
The isolation of 2,2,5,5-tetramethyl-4-imidazolidinethione from the reaction of acetone cyanohydrin with carbon disulfide and ammonium hydroxide has been verified. High yields of this and other substituted 4-imidazolidinethiones were obtained by the reaction of ketones with ammonium sulfide and either HCN or alkali cyanide.

The literature pertaining to 4-imidazolidinethiones has never been placed in order and the relevant findings of several investigators have been left uncorrelated. Gatewood and Johnson[2] investigating the action of hydrogen sulfide on α-aminoacetonitrile and α-aminopropionitrile found that dithiopiperazines were produced. α-Aminoisobutyronitrile, however, yielded a well defined crystalline material, melting at 153–155°, with the empirical formula $C_7H_{14}N_2S$. Upon acid hydrolysis this product gave α-aminoisobutyric acid. From these results they assigned structure I to the product. This is the earliest report of a 4-imidazolidinethione in the literature.

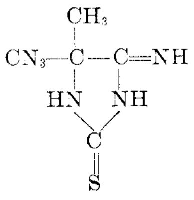
Abe[3] reported that methyl ethyl ketone by successive treatment with hydrogen cyanide, ammonia, and hydrogen sulfide produced "4-thio-2,5-dimethyl-2,5-diethyldesoxyhydantoin," II, melting at 67°. Similar treatment of alkyl aryl ketones was reported to produce α-aminothioamides while aryl ketones yielded dibenzohydryl disulfides.

Bucherer and Brandt[4] reacted cyclohexanone cyanohydrin and freshly prepared ammonium sulfide to obtain a compound, m.p. 225°, to which they assigned structure III. They assigned structure I to a similar product, melting at 155–156° which they obtained from acetone cyanohydrin and ammonium sulfide. Methyl ethyl ketone cyanohydrin and ammonium sulfide yielded a product $C_6H_{18}N_2S$ (II), m.p. 58–63°.[5] Later, Bucherer and Lieb[6] reported that they had obtained by reacting cyclohexanone cyanohydrin with carbon disulfide and 25% ammonium hydroxide in ethanol an unidentified product melting at 225°.[6] In the absence of ethanol, these reactants produced a compound, m.p. 261–265°.[7] Cyclohexanone cyanohydrin, carbon disulfide and gaseous ammonia gave products melting at 223°[8] and 195°.[9] Acetone cyanohydrin, carbon disulfide, and ammonium hydroxide were found to yield a compound $C_7H_{14}N_2S$, m.p. 154–155°;[10] gaseous ammonia gave this compound and another, m.p. 297°.[11]



Compound	R_1	R_2	Nomenclature
I	CH_3	CH_3	2,2,5,5-tetramethyl-4-imidazolidinethione
II	CH_3	C_2H_5	2,5-diethyl-2,5-dimethyl-4-imidazolidinethione
III	$—(CH_2)_5—$		7,14-diazadispiro-(5.1.5.2)pentadecane-15-thione

Carrington[12] prepared a series of "5,5-disubstituted-2,4-dithiohydantoins" which were found to react with ammonia to give the corresponding "4-imino-2-thiohydantoin." It was his opinion that "4-imino-5,5-dimethyl-2-thiohydantoin" (IV), m.p. 300–302° dec., was the unidentified material melt-



(IV)

4-imino-5,5-dimethyl-2-imidazolidinethione

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(1) Present address: Grace Chemical Co., Box 4906, Memphis 7, Tenn.

(2) Gatewood and Johnson, *J. Am. Chem. Soc.*, **50,** 1424 (1928).

(3) Abe, *Science Repts. Tokyo Bunrika Daigaka*, Sect. A, 2, 1 (1934); through *Chem. Abstr.*, **28,** 4383.

(4) Bucherer and Brandt, *J. prakt. Chem.*, **140,** 129 (1934).

(5) The difference in melting points from that reported by Abe may be due to a separation of stereoisomeric pairs.

(6) Bucherer and Lieb, *J. prakt. Chem.*, **141,** 5 (1934).

(7) Probably V.

(8) Probably III.

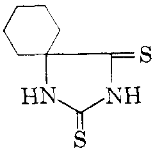
(9) Probably VI.

(10) Probably I.

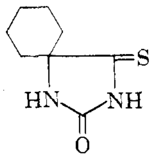
(11) Probably IV.

(12) Carrington, *J. Chem. Soc.*, 681, 684 (1947).

ing at 297° reported earlier by Bucherer and Lieb. Carrington further reported "5,5-pentamethylene-2,4-dithiohydantoin" (V), m.p. 267°, and "5,5-pentamethylene-2-thiohydantoin" (VI), m.p. 192° but failed to associate these compounds with other unidentified materials in the earlier work by Bucherer and Lieb.



1,3-diazaspiro[4.5]decane-2,4-dithione
(V)



1,3-diazaspiro[4.5]decane-2-one-4-thione
(VI)

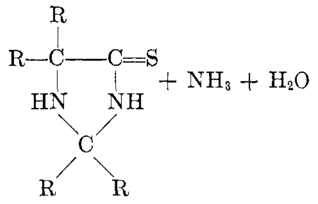
In order to establish the identity of the material produced by Bucherer and Lieb which was presumed to be 2,2,5,5-tetramethyl-4-imidazolidinethione, the reaction of acetone cyanohydrin with carbon disulfide and ammonium hydroxide was reinvestigated. The product which was obtained from the reaction in low yield was verified by derivative and mixture melting point with an authentic sample as I. Although this method of synthesis is obviously inefficient for the synthesis of 4-imidazolidinethiones, the investigation served to identify a material which had not previously been characterized.

Since the stoichiometry of Bucherer and Brandt's reaction of ammonium sulfide with acetone cyanohydrin indicated that HCN or a derivative therefrom might be a by-product of their synthesis, there appeared to the writer the possibility that half of the acetone cyanohydrin could be replaced with acetone without sacrifice of yield. This was verified by the finding that 2.0 moles of acetone cyanohydrin with an excess of acetone and ammonium sulfide yielded 1.8 moles of 2,2,5,5-tetramethyl-4-imidazolidinethione. This technique was also successful in preparing III in good yields from cyclohexanone cyanohydrin and cyclohexanone. These results are not surprising as the reaction is conducted under alkaline conditions, and a portion of the cyanohydrin can easily eliminate hydrogen cyanide to form the ketone needed to complete the formation of the imidazolidine ring.

Since the conditions of the reaction permit the elimination of hydrogen cyanide, an effort was made to completely circumvent the preformed cyanohydrin and supply the stoichiometric amounts of ketone and hydrogen cyanide as a stabilized nonalkaline mixture. This technique had been found satisfactory in other cases where a cyanohydrin would normally be reacted under alkaline conditions.[13] The procedure was successful in this instance and afforded 4-imidazolidinethiones from cyclopentanone and cyclohexanone in 73 and 92% yields, respectively. 6,12-Diazadispiro[4.1.4.2]tridecane-13-thione, prepared from cyclopentanone by this technique, is a compound not previously reported in the literature. Where liquid hydrogen cyanide is available this technique eliminates a prior preparation of the cyanohydrin and is an excellent process for producing large quantities of these compounds.

In the course of this investigation a technique of broader applicability was developed wherein it was found that an alkali metal cyanide could replace hydrocyanic acid in the reaction. Inclusion of an ammonium salt in the reaction mixture obviates possible difficulties from increasing alkalinity as cyanide ion is consumed. The reaction thus proceeds according to the equation:

$$2\ R_2CO + NH_4^+ + CN^- + (NH_4)_2S \rightarrow$$



Through this technique, cyclohexanone readily produced a 94% yield of 7,12-diazadispiro[5.1.5.2]pentadecane-15-thione in a one-step process.

The procedures outlined in this work cannot be assumed to be limited to the production of 2,2,5,5-tetrasubstituted products from ketonic starting materials. Although Abe claimed only aliphatic ketones produced "deoxythiohydantoins," Gatewood and Johnson reported a small amount of by-product from glycinonitrile and hydrogen sulfide which may have been the parent compound of the series, 4-imidazolidinethione. Brief efforts by the writer, however, to produce 4-imidazolidinethione (from glycolonitrile and ammonium sulfide) and 2,5-dimethyl-4-imidazolidinethione (from lactonitrile and ammonium sulfide) gave only red resinous materials.

The apparent incapacity of aldehydes to form a 2,5-dialkyl derivative was interpreted as a reluctance to enter into only one position of the ring under the conditions of the reaction. To test this hypothesis an effort was made to produce a trimethyl-4-imidazolidinethione from lactonitrile, acetone, and ammonium sulfide. A low yield of product was obtained which after several recrystallizations produced a material melting at 160–161° and analyzing correctly for $C_6H_{12}N_2S$, the empirical formula for either the 2,2,5-trimethyl or the 2,5,5-trimethyl derivative. An infrared spectrogram was similar to the previously prepared series of imid-

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[13] Rogers, U. S. Patent **2,391,799**.

azolidinethiones. Proof of structure was established by acid hydrolysis of the product followed by reaction with potassium cyanate. This action produced 5-methylhydantoin as a derivative, thereby establishing the product from the reaction as 2,2,5-trimethyl-4-imidazolidinethione.

EXPERIMENTAL

2,2,5,5-Tetramethyl-4-imidazolidinethione from acetone, acetone cyanohydrin, and ammonium sulfide. A mixture of acetone cyanohydrin (170 g.) and acetone (170 g.) was slowly fed with stirring into a solution of commercial ammonium sulfide (602 g. of a 22.6% solution) and water (1 l.). The addition was carried out over a period of 2.25 hr. during which time the solution temperature rose from 25° to a maximum of 47°. After all of the reactants had been brought together the mixture was maintained at 45–50° for an additional 1 hr. by external heating. A solid white crystalline product which had formed during the course of the above procedure was filtered and dried (209 g., m.p. 152–154°[14]). Evaporation of the reaction liquor yielded 70 g. of product melting 152–154°, followed by 4.1 g. melting 146–152°. Total product from all fractions (283 g.) represented an 89.5% yield of 2,2,5,5-tetramethyl-4-imidazolidinethione.

2,2,5,5-Tetramethyl-4-imidazolidinethione through the reaction of acetone cyanohydrin, carbon bisulfide, and ammonium hydroxide. A mixture of carbon disulfide (19 g.) and acetone cyanohydrin (21.3 g.) was added with stirring to a round bottomed flask containing conc. ammonium hydroxide (136 ml.) over a period of 1.5 hr. The heat of reaction raised the solution temperature from 24° to about 35° toward the end of the addition. Partial evaporation of the reaction mixture produced a deposit (7.2 g.) of white crystals, m.p. 145–149°. After several recrystallizations from ethanol, the melting point of this material was raised to 153–154°. A mercury salt derivative, prepared by heating of an ethereal solution of the product with mercuric oxide, melted at 174–176° (reported 175° by Gatewood and Johnson[2]). A mixture melting point of this material with 2,2,5,5-tetramethyl-4-imidazolidinethione prepared above was not depressed.

7,14-Diazadispiro[5.1.5.2]pentadecane-15-thione from cyclohexanone, cyclohexanone cyanohydrin, and ammonium sulfide. Cyclohexanone (20 g.), cyclohexanone cyanohydrin (25 g.) and ammonium sulfide (60.2 g. of a 22.6% solution) in substantially the same procedure as above produced III (43 g., m.p. 224.5–225.5°) in 90% yield.

Anal.[15] Calcd. for $C_{13}H_{22}N_2S$: C 65.49; H 9.31; N 11.75; S 13.45. Found: C 65.50; H 9.54; N 11.82; S 13.65.

6,12-Diazadispiro[4.1.4.2]tridecane-13-thione from ammonium sulfide, cyclopentanone, and hydrogen cyanide. Liquid hydrogen cyanide (13.5 g.) stabilized with phosphoric acid and cyclopentanone (89.1 g.) were mixed and slowly fed into a stirred solution of ammonium sulfide (225 g. of a 22.6% solution) and ethanol (250 ml.) over a period of 1.5 hr. After all of the reactants had been brought together the mixture was heated and maintained at 50–60° for 1 hr. Cooling of the reaction mixture to room temperature resulted in the deposition of white crystals, 61.6 g., m.p. 191°. Evaporation of the mother liquor yielded additional crystalline product, 14 g., m.p. 190–191°. A portion of the product was recrystallized three times from methanol to obtain a sample melting 195–196° for analysis.

Anal. Calcd. for $C_{11}H_{18}N_2S$: C 62.83; H 8.61; N 13.33; S 15.23. Found: C 63.24; H 8.46; N 13.24; S 15.58.

The product obtained from the reaction represented 73.5% yield of 6,12-diazadispiro[4.1.4.2]tridecane-13-thione.

7,14-Diazadispiro[5.1.5.2]pentadecane-15-thione from ammonium sulfide, cyclohexanone, and hydrogen cyanide. By the procedure outlined above, a stabilized mixture of cyclohexanone (522 g.) and hydrogen cyanide (71.9 g.) was fed into stirred solution of ammonium sulfide (884 g. of a 22.6% aqueous solution) and methanol (1080 ml.) over 1.5 hr. A maximum temperature of 58° was reached toward the end of the addition. The stirred reaction mixture was maintained at 60° for an additional hour by the application of heat, then allowed to cool. The cream colored crystalline product isolated from the liquor (585 g., m.p. 231°) represented a 92% yield of III.

2,2,5,5-Tetramethyl-4-imidazolidinethione from ammonium sulfide, acetone and hydrogen cyanide. Using the above procedure, a stabilized mixture of acetone (407 g.) and hydrogen cyanide (97 g.) was reacted with ammonium sulfide (1200 g. of a 22.6% aqueous solution) to produce I (480 g., melting at 156°) in 84% yield.

7,14-Diazadispiro[5.1.5.2]pentadecane-15-thione from cyclohexanone, ammonium sulfide, and potassium cyanide. Cyclohexanone (196 g.) was added with stirring over a 45 min. period to a mixture of potassium cyanide (65 g.), ammonium sulfide (450 g. of a 22.6% solution), ammonium chloride (54 g.) and methanol (250 ml.). The formation of solids in the reaction mixture was noted after about half of the ketone had been added. After all of the reactants had been brought together, the mixture was maintained at 60° for an additional 1 hr. Cooling of the reaction mixture yielded a white crystalline product (201 g.) melting at 231–232°. Evaporation of the mother liquor yielded additional light yellow crystals (24 g.) m.p. 228–232°. The combined fractions represented a 94% yield of III.

Preparation and proof of structure of 2,2,5-trimethyl-4-imidazolidinethione. A mixture of lactonitrile (71 g.) and acetone (58 g.) were introduced gradually over a period of 50 min. into a stirred reaction flask containing ammonium sulfide (300 g. of a 22.6% solution) and lactonitrile (7.1 g.). The reaction mixture was maintained at 50° during the period of addition and thereafter for an additional 2 hr. Several fractions of crystalline product were obtained by evaporating the reaction mixture under a slow stream of air:

	G.		MELTING AT:
(a)	33	White crystals	157–160°
(b)	37	Yellowish white crystals	105–110°
(c)	12	Light yellow crystals	115–130°
(d)	21	Yellow brown crystals	105–120°
(e)	4	Brown amorphous solid	95–112°
Residue	48	Black tar	

A sample of the first crystalline fraction was recrystallized several times from methanol to obtain a product for analysis, m.p. 160–161°.

Anal. Calcd. for $C_6H_{12}N_2S$: C 49.97; H 8.40; N 19.43; S 22.21. Found: C 49.89; H 8.38; N 19.30; S 22.24.

Attempts to obtain pure material from the low melting fractions were unsuccessful.

A 5 g. portion of the analytical sample from above was refluxed in 20% aqueous hydrochloric acid for 4 hr. The mixture was evaporated to dryness and the residue taken up in 20 ml. water and treated with 10 g. potassium cyanate on a steam bath for 1.5 hr. The solution was then acidified to pH 2 with conc. hydrochloric acid, heated for ten min., and evaporated almost to dryness. The residue was extracted with methanol and the alcohol allowed to evaporate. White crystals, 2.3 g., obtained from the alcoholic extract melted 143.5–145.5°. This material failed to depress the melting point of an authentic sample of 5-methylhydantoin. It was concluded from these results that the material subjected to elemental analysis was 2,2,5-trimethyl-4-imidazolidinethione.

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(14) Melting points reported are corrected.

(15) Nitrogen analyses were by the Kjeldahl method in the Monsanto Texas City Laboratory. Carbon, hydrogen, and sulfur analyses were by the Galbraith Laboratory, Knoxville, Tenn.

Acknowledgments. The writer wishes to acknowledge the capable assistance of Mr. Tom F. Davenport in conducting this investigation and to express appreciation to Monsanto Chemical Co. for permission to publish the work.

TEXAS CITY, TEX.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH, WYETH LABORATORIES, AND THE DEPARTMENT OF CHEMISTRY, TEMPLE UNIVERSITY]

Synthesis of Azacycloheptane Derivatives Related to Piperidine Analgesics[1,2]

JULIUS DIAMOND,[3] WILLIAM F. BRUCE, AND FLOYD T. TYSON

Received October 11, 1956

A synthesis of seven-membered ring compounds related to meperidine was effected by the stepwise reaction of 2-phenyl-4-dimethylaminobutyronitrile with trimethylene halides. The initial cyclization products, 1-methyl-4-phenyl-4-cyanoazacycloheptane methohalides, lost methyl halide at elevated temperatures to yield the tertiary aminonitrile, which was converted to the carboxylic acid, amide, ester, ketone, and amine derivatives. *dl*-1-Methyl-4-phenyl-4-carbethoxyazacycloheptane was resolved into its optical antipodes.

Seven-membered ring analogs of the piperidine analgesic meperidine[4] and a number of its derivatives were synthesized in a study of the effect of structure on analgesic activity.[5]

The azacycloheptane ring[6] was formed by the reaction of 2-phenyl-4-dimethylaminobutyronitrile (I) with trimethylene chlorobromide (II), bromide (IIa), or chloride (IIb).[7,8] Highest yields were obtained by a stepwise reaction with the chlorobromide. I was converted to its sodio derivative (Ia) by sodamide in toluene or ether at 35°. When II was added dropwise to the solution of Ia at about −20°, the product was almost exclusively 1-dimethylamino-3-phenyl-3-cyano-6-chlorohexane (III). At temperatures of 0° to +10°, some of the 1,6-aminobromide (IIIa) was also formed. Moreover, at these higher temperatures preferential formation of III was favored by low concentrations of Ia which were obtained by reversing the order of addition of the reactants, *i.e.*, by adding Ia to II. This cumbersome operation was avoided by conducting the "direct addition" alkylation at −20°.

The intramolecular cyclization of III to 1-methyl-4-phenyl-4-cyanoazacycloheptane methochloride (IV) was carried out without isolating III. This was accomplished by replacing the toluene or ether of the alkylation mixture with such polar solvents as nitrobenzene, *o*-nitrotoluene, benzonitrile, or 2-nitropropane, and heating the solution at 100° until no more quaternary salt (IV) precipitated. Use of a high dilution was unnecessary and the yield of IV from I was 65 to 80%. The preferred dilution in the polar solvent for the best yields of pure IV was approximately $1M$. When the cyclization of III was attempted in toluene at 100° and about $1M$ concentration, an impure preparation of IV was obtained. From those experiments in which Ia was alkylated by II at 0° to +10°, subsequent cyclization led to a mixture of quaternary salts IV and IVa. Trimethylene chloride (IIb) was also used to produce IV from I, but the yield was 24%.

1 - Methyl - 4 - phenyl - 4 - cyanoazacycloheptane methobromide (IVa) was formed in low yields by the reaction of Ia with trimethylene bromide (IIa). Alkylation of Ia by IIa, even at low temperatures, led to a bis-amine as well as the desired 1,6-aminobromide (IIIa). Formation of the bis-amine was favored when the alkylation was conducted in more concentrated solutions. Cyclization of IIIa to IVa went poorly because IIIa underwent intermolecular polymerization (probably to the linear polymeric salt IVb) more readily than III. To overcome this effect, the cyclization of IIIa required greater dilution. IVa was obtained from I in 26% yield by heating an approximately $0.1M$ solution of IIIa in nitrobenzene at 100° for 1 hr. Longer heating diminished the purity of IVa in the same manner as observed when the cyclization of IIIa was conducted at higher concentrations.

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(1) Taken in part from the dissertations of J. Diamond submitted to the Temple University Graduate Council in partial fulfillment of the requirements for the degrees of Master of Arts (1953) and Doctor of Philosophy (1955).

(2) Presented before the Organic Division at the Delaware Valley Regional Meeting of the AMERICAN CHEMICAL SOCIETY, Philadelphia, Pa., February 16, 1956.

(3) Present address: Wallace Laboratories Division, Carter Products, Inc., New Brunswick, N. J.

(4) Generic name for ethyl 1-methyl-4-phenylpiperidine-4-carboxylate.

(5) (a) This portion of our work had been completed when Blicke and Tsao (ref. 5b) reported a similar study in which several of the present compounds were synthesized by modifications of our procedure.

(b) Blicke and Tsao, *J. Am. Chem. Soc.*, **75**, 3999 (1953).

(6) Hexahydro form of azepine, also named hexamethylenimine, Patterson and Capell, *Ring Index*, Reinhold Publishing Corp., New York, N. Y., 1940, p. 60.

(7) Diamond and Bruce, U. S. Patent 2,666,050 (1954) [*Chem. Abstr.*, **49**, 4031 (1955)].

(8) Kaegi and Miescher, *Helv. Chim. Acta*, **32**, 2489 (1949), employed ethylene halides in a synthesis of meperidine and its derivatives.