Anal. Calcd. for $C_{11}H_{16}N_4O$: N, 25.43. Found: N, 25.68.

Ethyl N-*n*-Hexylthioureidomethylenecyanoacetate.—N-*n*-Hexylthiourea (16 g. or 0.1 mole), ethyl orthoformate (17 g. or 0.115 mole) and ethyl cyanoacetate (11.3 g. or 0.1 mole) were mixed together and heated to refluxing temperature for 30 minutes. The mixture was concentrated under reduced pressure to obtain the solid product. This was recrystallized from ethyl acetate; yield 11.5 g. or 41%, m.p. 152°.

Anal. Calcd. for $C_{13}H_{21}N_3O_2S$: S, 11.33. Found: S, 11.42.

N-Cyclohexylureidoacrylic Acid.—N-Cyclohexylurea (14.2 g. or 0.1 mole), ethyl orthoformate (20 g. or 0.135 mole) and malonic acid (10.4 g. or 0.1 mole) were mixed and heated at refluxing temperature for 2 hours. The solution was concentrated and the cyclohexylureidoacrylic acid allowed to crystallize; yield 16 g. or 75%, m.p. 182° (dec.).

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: N, 13.45. Found: N, 13.29.

N-Cyclohexylureidomethylenemalonic Acid.—Cyclohexylurea (14.2 g. or 0.1 mole) and malonic acid (10.4 g. or 0.1 mole) were added to 100 ml. of ethyl orthoformate and stirred mechanically. After 5 minutes the mixture became cool, the reactants dissolved and the product began separating from solution. The stirring was continued overnight. The solid was filtered off and washed white with ether; yield 23 g. or 92%. An analytical sample was prepared by reprecipitation from bicarbonate solution; m.p. 180° (dec.).

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: N, 10.92. Found: N, 10.89.

Diethyl N-Cyclohexylureidomethyleneoxalacetate.—N-Cyclohexylurea (71 g. or 0.5 mole), ethyl orthoformate (74 g. or 0.5 mole) and freshly distilled diethyl oxalacetate (94.0 g. or 0.5 mole) were mixed and allowed to stand at room temperature. After 0.5 hour the reaction mixture had become completely solid. This was allowed to stand overnight and then dissolved in a minimum amount of warm alcohol. Water was added to the warm alcohol solution to incipient turbidity. Diethyl N-cyclohexylureidomethyleneoxalacetate crystallized as a beautiful white product; yield 137 g. or 88%, m.p. 127–128°.

Anal. Calcd. for $C_{16}H_{24}N_2O_6$: C, 56.45; H, 7.06. Found: C, 56.44; H, 7.11.

5-Carbethoxycytosine.—Sodium (46 g. or 2.0 g. atoms) was added to 750 ml. of absolute ethanol in a 2-l. flask fitted with a reflux condenser. After the sodium had completely reacted ethyl ureidomethylenecyanoacetate was added and the mixture agitated. A vigorous reaction occurred and the contents of the flask became solid. Ethanol (300 ml.) was added and the solid was broken into small lumps. The flask was heated under reflux for one-half hour. The alcohol was removed by filtration and the remaining solid dissolved in 8 l. of cool water. This solution was filtered and acidified with glacial acetic acid. The precipitated product was collected on a buchner funnel and sucked dry, washed with alcohol and then with ether, yield 176 g. or 96.3%. The 5-carbethoxycytosine decomposed slowly at 260–270°.[13]

3-*n*-Amyl-5-cyanocytosine.—N-*n*-Amylureidomethylenemalononitrile (41.2 g. or 0.2 mole) was added to 250 ml. of methanol. Sodium methylate (10.8 g. or 0.2 mole) was added and the mixture stirred until the solids were dissolved. The flask was stoppered and allowed to stand at room temperature. After 5 days the alcohol was removed and 500 ml. of cold water was added to dissolve the residue. The water solution was made neutral by the addition of dilute acetic acid. The precipitated solid was collected and recrystallized from ethanol; yield 29 g. or 71%, m.p. 209°. An analytical sample was prepared by repeated recrystallization from alcohol, m.p. 210°.

Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.35; H, 6.84; N, 27.18. Found: C, 58.40; H, 7.07; N, 26.99.

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(13) H. L. Wheeler and C. O. Johns, *Am. Chem. J.*, **38**, 601 (1907).

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Synthetic Hypoglycemic Agents. I[1]

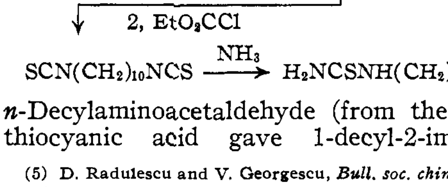
BY HARRY L. YALE

RECEIVED AUGUST 20, 1952

A number of heterocyclic sulfhydryl containing compounds have been synthesized for possible application as hypoglycemic agents.

There appears to be a relationship between the free sulfhydryl available in the tissues and diabetes. The work of Houssay and others has indicated that various sulfhydryl containing compounds increase the available –SH in certain tissues and thereby provoke a strong resistance to the diabetogenic effects of alloxan or subtotal pancreatectomy.[2] In an attempt to correlate chemical structure with hypoglycemic activity,[3] a number of sulfur containing organic compounds were synthesized. Houssay, Lott and Martinez[4] have reported on the activities of several of these compounds in alloxan and pancreatic diabetes. This paper will be concerned only with the synthesis of these compounds.

1,4-Dimercaptophthalazine was prepared by the reaction of 1,4-dichlorophthalazine and sodium hydrosulfide[5]; 2,4-dichloroquinazoline and sodium hydrosulfide gave 2,4-dimercaptoquinazoline. 1,10-Decamethylenebis-2-thiourea was synthesized by the sequence of reactions[6]



$$\mathrm{NC(CH_2)_8CN \xrightarrow{LiAlH_4} H_2N(CH_2)_{10}NH_2}$$
$$\xrightarrow[\mathrm{2,\ EtO_2CCl}]{\mathrm{1,\ CS_2 + NaOH}}$$
$$\mathrm{SCN(CH_2)_{10}NCS \xrightarrow{NH_3} H_2NCSNH(CH_2)_{10}NHCSNH_2}$$

n-Decylaminoacetaldehyde (from the acetal) and thiocyanic acid gave 1-decyl-2-imidazolethiol;

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(1) Presented before the Division of Medicinal Chemistry at the 121st Meeting of the American Chemical Society, Milwaukee, Wis., March 31–April 3, 1952.

(2) For reviews on this subject, see B. A. Houssay, *Am. J. Med. Sci.*, **219**, 353 (1950), and C. Martinez, *Acta Physiol. Latinoamericana*, **2**, 135 (1951).

(3) The earlier literature on the hypoglycemic activity of organic sulfur compounds has been reviewed by C. E. Braun, M. B. Mason and C. L. Brown, *J. Chem. Education*, **15**, 261 (1938). See, also, A. Loubatiers, *Compt. rend. soc. biol.*, **138**, 766, 830 (1944); *Arch. internat. physiol.*, **54**, 58 (1946); K. K. Chen, R. C. Anderson and N. Maze, *Proc. Soc. Exptl. Biol.*, **63**, 483 (1946); and D. Bovet and P. Dubost, *Compt. rend. soc. biol.*, **138**, 764 (1944).

(4) B. A. Houssay, W. A. Lott and C. Martinez, *Rev. soc. argentina biol.*, **26**, 335 (1950); *Compt. rend. soc. biol.*, **145**, 591 (1951).

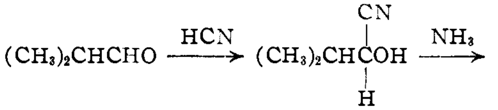
(5) D. Radulescu and V. Georgescu, *Bull. soc. chim.*, **37**, 881 (1925), (*C. A.*, **20**, 184 (1926)) prepared this compound by the reaction of 1,4-dihydroxyphthalazine and P_2S_5. In our hands this method gave a very impure product which was difficult to purify.

(6) The procedure followed was modeled after that described in *Org. Syntheses*, **21**, 81 (1941).

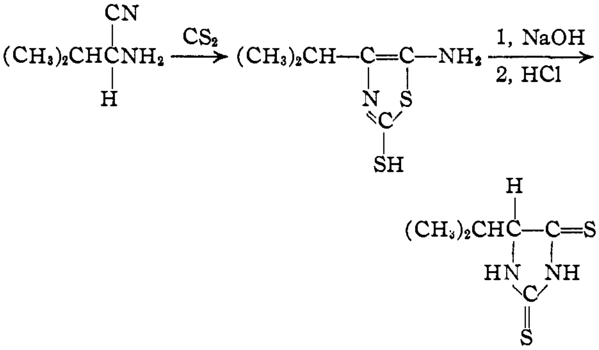
hexamethylenebisaminoacetaldehyde acetal could not be obtained analytically pure but when hydrolyzed to the aldehyde and treated with thiocyanic acid, there was obtained 1,1′-hexamethylenebis-(2-imidazolethiol).[7] 2,2′-Decamethylenebis-(2-thiopseudourea) dihydrobromide was obtained by the reaction of decamethylene bromide and thiourea. Sebacyl chloride and thiosemicarbazide reacted to give 5,5′-octamethylenebis-(2-amino-1,3,4-thiadiazole); although this compound formed a diacetyl derivative and a dihydrochloride, attempts to condense it with *p*-acetamidobenzenesulfonyl chloride or *p*-nitrobenzenesulfonyl chloride were unsuccessful. 4-Mercapto-2-methylquinazoline was prepared by the condensation of *o*-aminobenzonitrile and thiolacetic acid. 2-Thiouracil, phosphorus pentasulfide and liver of sulfur in boiling xylene gave 2,6-dithiouracil.

The compounds of greatest interest were those related to 5-isopropylidene-2,4-dithiohydantoin.[8] This compound was one of those synthesized for this screening program and was the compound found by Houssay to be most effective in decreasing the incidence of diabetes due to alloxan or sub-total pancreatectomy.[4] Attempts to prepare homologs of the isopropylidene derivative by using other ketones in place of acetone were unsuccessful. In searching for an alternative synthetic approach, it was found that 2-thiohydantoin condensed readily with aldehydes and ketones at room temperature in the presence of piperidine or a pyridine–piperidine mixture to give 5-alkylidene-2-thiohydantoins; under these conditions, 1-acetyl-2-thiohydantoin did not condense.[9] It was of interest, too, that the 5-alkylidene-2-thiohydantoins could not be acetylated even by refluxing for eight hours with acetic anhydride.[10] Several attempts were made unsuccessfully to convert these 5-alkylidene-2-thiohydantoins to the corresponding 2,4-dithiohydantoin derivative by reaction with phosphorus pentasulfide and liver of sulfur in toluene or xylene.

Efforts to prepare 5-isopropyl-2,4-dithiohydantoin were also unsuccessful employing the following sequence of reactions, since the intermediate, 2-mercapto-4-isopropyl-5-aminothiazole, could not be obtained pure. A related compound, 1,3-diacetyl-5-octyl-2,4-dithiohydantoin, was prepared employing Nonylaldehyde Cyanohydrin[11] as the starting material in the synthesis.



$(CH_3)_2CHCHO \xrightarrow{HCN} (CH_3)_2CH\overset{CN}{\underset{H}{C}}OH \xrightarrow{NH_3}$



5-Isopropyl-2-thiohydantoin[12] and phosphorus pentasulfide in xylene gave apparently 5-isopropyl-2,4-dithiohydantoin, but this compound could not be obtained analytically pure. The reduction of 5-isopropylidene-2,4-dithiohydantoin with red phosphorus in glacial acetic acid[13] also gave a product which analyzed low in sulfur content.

Acknowledgments.—The author is indebted to Mr. W. A. Lott for his great interest and encouragement in this program and to Mr. Thomas Buckley for technical assistance. The microanalyses were carried out by Mr. J. F. Alicino.

Experimental Part

1,4-Dimercaptophthalazine.—Phthalazine[5] and POCl$_3$ at 190° gave an 88% yield of 1,4-dichlorophthalazine, m.p. 160–162°.[14] *Anal.* Calcd. for $C_8H_4Cl_2N_2$: Cl, 35.63. Found: Cl, 35.26. To a warm solution of 48.5 g. (0.86 mole) of sodium hydrosulfide in 800 ml. of 95% ethanol was added 21.5 g. (0.11 mole) of 1,4-dichlorophthalazine in small portions. A vigorous reaction occurred and the mixture became dark green in color. Subsequently, the mixture was refluxed four hours, cooled and filtered. The filtrate was diluted with an equal volume of water and acidified with 10% hydrochloric acid. The precipitated yellow solid was air-dried and weighed 23 g. It was recrystallized from 2 liters of boiling toluene to give 16 g. (83% yield) of product, yellow needles, m.p. 262–264°.[15]

Anal. Calcd. for $C_8H_6N_2S_2$: N, 14.42; S, 33.01. Found: N, 14.29; S, 33.74.

2,4-Dimercaptoquinazoline.—2,4-Dichloroquinazoline (m. p. 120–121°,[16] 32 g., 0.16 mole) was added in small portions with stirring to 95 g. (1.7 mole) of sodium hydrosulfide in 1 l. of 95% ethanol at room temperature. The mixture was refluxed four hours and filtered hot. The filtrate was cooled, 1 kg. of ice was added, and the mixture made acid with 10% hydrochloric acid. The yellow solid which separated was filtered and redissolved in an excess of 10% sodium hydroxide; the alkaline solution was filtered from a small amount of solid and the filtrate was acidified. The precipitated solid was filtered, washed with water, and

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(7) The procedure was that of R. G. Jones, E. C. Kornfeld, K. C. McLaughlin and R. C. Anderson, THIS JOURNAL, **71**, 4000 (1949).

(8) 5-Isopropylidene-2,4-dithiohydantoin was first prepared by A. H. Cook, I. M. Heilbron and A. L. Levy, *J. Chem. Soc.*, 201 (1948), by the reaction of aminoacetonitrile, carbon disulfide and acetone in the presence of pyridine. These authors report no other homologs and none was found in the literature.

(9) 1-Acetyl-2-thiohydantoin has been condensed with 1-methylimidazole-5-carboxaldehyde in pyridine–diethylamine or a pyridine–piperidine mixture at 100° to give 5-(1-methyl-5-imidazolylmethylene)-2-thiohydantoin (W. Sakami and D. W. Wilson, *J. Biol. Chem.*, **154**, 215 (1944)) or with benzaldehyde in pyridine or piperidine to give 5-benzal-2-thiohydantoin (W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 542 (1935)). A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 2342 (1949), have condensed benzaldehyde with 1,3-dimethyl-2-thiohydantoin by refluxing one hour in a pyridine–morpholine mixture.

(10) 2,4-Dithiohydantoin and acetic anhydride react spontaneously at room temperature to give 1,3-diacetyl-2,4-dithiohydantoin (A. H. Cook, I. Heilbron and A. L. Levy, *ibid.*, 201 (1948)). Our studies on the acetylation of thiohydantoins will be reported in a later publication from these laboratories.

(11) This material was generously supplied by Rohm and Haas Co. It consists of a mixture of isomers, of which $(CH_3)_3CCH_2CH(CH_3)$-$CH_2CH(OH)CN$ predominates.

(12) M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar and S. Archer, THIS JOURNAL, **70**, 2884 (1948).

(13) A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 2342 (1949), reduced 5-benzylidene-3-phenyl-1-methyl-2-thiohydantoin to the 5-benzyl derivative in 80% yield by this method. The stability of this derivative may be due to the replacement of both =NH hydrogen atoms so that the compound exists only in the dithio form.

(14) The method is described in German Patent 481,650.

(15) Reference 5. These authors report a m.p. of 262–265°.

(16) F. H. S. Curd, J. K. Landquist and F. L. Rose, *J. Chem. Soc.*, 775 (1947), reported a m.p. of 118°. The material used here was recrystallized from heptane.

recrystallized from *n*-butanol to give 14.1 g. (44% yield) of product, m.p. 313° (dec.).

Anal. Calcd. for $C_8H_6N_2S_2$: C, 49.45; H, 3.11; N, 14.42; S, 33.01. Found: C, 48.76; H, 2.99; N, 14.70; S, 33.00.

1,10-Decamethylenebis-2-thiourea.—Sebaconitrile, 41 g. (0.25 mole) in 500 ml. of dry ether was added dropwise to a mixture of 18 g. of $LiAlH_4$ in 600 ml. of dry ether. Subsequently, the mixture was refluxed for 12 hours, cooled, hydrolyzed with water, made strongly alkaline with 300 ml. of 10% NaOH and extracted with ether. The dried ether extracts were concentrated and distilled to give 21.5 g. (50% yield) of decamethyleneamine, b.p. 110–115° (4 mm.), m.p. 62–64°.[17] To a mixture of 35 ml. of carbon disulfide, 22.0 g. of sodium hydroxide and 150 ml. of water at 10–15°, was added in small portions 46.1 g. (0.27 mole) of decamethyleneamine. From this point on, the method described in reference 18 was followed except that the 1,10-decamethylenebisisothiocyanate was extracted with ether. Subsequent to the evaporation of the ether, the crude isothiocyanate was treated with 140 ml. of concentrated aqueous ammonia. The yield of product was 42.5 g. (54%), m.p. 173–175° after recrystallization from boiling water and from acetonitrile.

Anal. Calcd. for $C_{12}H_{26}N_4S_2$: C, 49.62; H, 9.02; N, 19.29. Found: C, 50.22; H, 8.84; N, 19.20.

1-Decyl-2-imidazolethiol. 1-Decylaminoacetaldehyde Diethyl Acetal.—A mixture of 76.3 g. (0.49 mole) of decylamine and 30.5 g. (0.2 mole) of ethyl chloroacetal was heated 20 hours at 145°, cooled and poured into a stirred mixture of 20 g. of sodium hydroxide in 100 ml. of water and 500 ml. of ether. The ether layer was separated, dried, concentrated and distilled to give 19.8 g. (36% yield) of product, b.p. 128–129° (2 mm.), n^{26}D 1.4360.

Anal. Calcd. for $C_{16}H_{35}NO_2$: N, 5.12. Found: N, 5.18.

The **acetal**, 19.8 g., 9.5 g. of sodium thiocyanate and 50 ml. of 50% ethanol were treated with 10 ml. of concentrated hydrochloric acid and the mixture heated five hours on the steam-bath. The cooled reaction mixture was made alkaline with 10% sodium hydroxide, the alkaline solution was treated wth Darco, filtered and the filtrate acidified. The oil which separated was extracted with ether, the dried ether extracts were concentrated and the residue dissolved in warm acetonitrile. On standing in the cold, a solid separated. The yield of crude product was 8 g. (33%); the pure product, m.p. 57–59°, was obtained by recrystallization from heptane.

Anal. Calcd. for $C_{13}H_{24}N_2S$: C, 64.95; H, 10.07; N, 11.61; S, 13.28. Found: C, 65.03; H, 10.03; N, 11.40; S, 13.06.

1,1'-Hexamethylenebis-(2-imidazolethiol). Hexamethylenebisaminoacetaldehyde Diethyl Acetal.—When a mixture of 11.6 g. (0.1 mole) of hexamethylenediamine and 30.5 g. (0.2 mole) of ethyl chloroacetal was heated 20 hours at 145° and the mixture worked up as in the preceding example, no definite product was isolated. The same reactants and 13.2 g. (0.2 mole) of 85% potassium hydroxide in 75 ml. of absolute ethanol were heated 16 hours at 140° the mixture was cooled, filtered and distilled giving 19.3 g. of colorless liquid, b.p. 128–184° (3 mm.). Since no definite cut could be obtained by refractionation, the crude acetal was dissolved in 100 ml. of 50% ethanol and the solution treated with 19 g. (0.23 mole) of sodium thiocyanate and 20 ml. of concentrated hydrochloric acid. The mixture was heated for five hours on the steam-bath, maintaining the volume constant by adding water. The solid product was filtered, dissolved in 10% sodium hydroxide, the alkaline solution was treated with Darco, filtered and the filtrate acidified to give the crude product. The pure product, m.p. 245–247°, 2.7 g. (11% yield), was obtained after two recrystallizations from acetonitrile and one recrystallization from absolute ethanol.

Anal. Calcd. for $C_{12}H_{18}N_4S_2$: C, 51.03; H, 6.43; N, 19.84; S, 22.70. Found: C, 51.43; H, 6.36; N, 19.35; S, 22.21.

To obtain larger amounts of the acetal, a mixture of 80 g. (0.69 mole) of hexamethylenediamine, 112 g. (0.7 mole) of 85% potassium hydroxide, 214 g. (1.4 mole) of ethyl chloroacetal and 800 ml. of 2-ethylbutanol was stirred and refluxed for five hours. The cooled mixture was filtered and the filtrate was distilled. The product cuts were the following: (a) 32 g., b.p. 148–150° (5 mm.), n^{23}D 1.4480 and (b) 68.3 g., b.p. 150–175° (5 mm.), n^{23}D 1.4535. Cut (a) appeared to be 6-aminohexamethyleneaminoacetaldehyde diethyl acetal.

Anal. Calcd. for $C_{12}H_{28}N_2O_2$: C, 62.02; H, 12.15; N, 12.06. Found: C, 62.26; H, 11.91; N, 12.21.

When Cut (b) was refractionated, only the highest boiling fraction, 23 g., b.p. 180–195° (1.2 mm.), $n^{24.5}$D 1.4478, when treated as above with thiocyanic acid gave 1,1'-hexamethylenebis-(2-imidazolethiol). The yield of product was 9 g. (20%), m.p. 245–247°. When the lower boiling fractions were similarly treated, none of this product was obtained.

2,2'-Decamethylenebis-(2-thiopseudourea) Dihydrobromide.—A mixture of 48 g. (0.16 mole) of decamethylene bromide, 24.3 g. of thiourea and 30 ml. of absolute alcohol was refluxed five hours on the steam-bath. The mixture turned solid after one hour. The mixture was cooled, filtered and the solid recrystallized from absolute alcohol-ether to give 57.7 g. (80% yield) of product, m.p. 160–162°.

Anal. Calcd. for $C_{12}H_{28}Br_2N_4S_2$: N, 12.39; S, 14.18. Found: N, 12.12; S, 13.98.

5,5'-Octamethylenebis-(2-amino-1,3,4-thiadiazole).—To 264.0 g. (2.9 moles) of powdered thiosemicarbazide, with stirring and ice-cooling, was added 167 g. (0.7 mole) of sebacyl chloride. The mixture was stirred eight hours at 0°, then heated on the steam-bath for eight hours. The reaction product was leached with 750 ml. of boiling 5% hydrochloric acid, filtered, the acid extracts were made alkaline with 10% sodium hydroxide and the precipitated solid filtered. The solid was extracted with 5 liters of boiling water to remove unreacted thiosemicarbazide (73 g. recovered) and the water-insoluble material was extracted with hot glacial acetic acid and filtered. The hot glacial acetic acid filtrate was diluted with water to make a 75% acetic acid solution, and cooled. The yield of crude product was 36.1 g. (16%). Three recrystallizations from 70% acetic acid gave the pure product as colorless microcrystals which sinter at 243° and melt at 252–253° (dec.).

Anal. Calcd. for $C_{12}H_{20}N_6S_2$: C, 46.13; H, 6.45; N, 26.90. Found: C, 45.94; H, 6.42; N, 26.17.

A small portion of the free base was heated to boiling with 5% hydrochloric acid and the hot solution filtered. The filtrate on cooling deposited the **dihydrochloride**, white crystals, m.p. 234–236° (dec.).

Anal. Calcd. for $C_{12}H_{20}N_6S_2 \cdot 2HCl$: Cl, 18.40. Found: C, 18.06.

A small portion of the free base was refluxed for two hours with a mixture of acetic anhydride and glacial acetic acid. On cooling a pale yellow solid separated. It sintered at 262° and melted at 270–271°. One recrystallization from glacial acetic acid gave the pure **diacetyl derivative**, which sintered at 265° and melted at 272–273°.

Anal. Calcd. for $C_{16}H_{24}N_6O_2S_2$: C, 48.46; H, 6.10. Found: C, 48.32; H, 6.40.

A suspension of 3.13 g. (0.01 mole) of the free base in 80 ml. of dry pyridine was treated gradually at room temperature with 4.44 g. (0.02 mole) of recrystallized *p*-nitrobenzenesulfonyl chloride. Heat was evolved and the temperature rose to 40° but the free base did not dissolve. There was incomplete solution even after 14 hours heating and stirring at 60°. The mixture was cooled and filtered. The insoluble material weighed 1.41 g. and was unreacted amine. From the filtrate no product could be identified.

A reaction was carried out between 1.57 g. (0.005 mole) of the amine, 2.34 g. (0.01 mole) of *p*-acetamidobenzenesulfonyl chloride and 80 cc. of pyridine at 95–100° for 24 hours. The recovery of unreacted amine was 1.2 g.

4-Mercapto-2-methylquinazoline.—The condensation of *o*-aminobenzonitrile and thiolacetic acid was reported by Bogert, Breneman and Hand.[19] A mixture of 11.8 g.

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(17) A freezing point of 60° is reported in *Org. Syntheses*, **27**, 18 (1947).

(18) *Ibid.*, **21**, 81 (1941).

(19) M. T. Bogert, H. C. Breneman and W. F. Hand, THIS JOURNAL, **25**, 372 (1903), mention this preparation but give no details. They report a m.p. of 218–219°.

(0.1 mole) of *o*-aminobenzonitrile and 10 cc. of thiolacetic acid was heated in a sealed tube at 100–110° for two hours, the tube was cooled and the crude product recrystallized from 20% ethanol gave 15.8 g. (90%) of pure product. The m.p. varied with the rate of heating; sometimes the compound melted at 216–218°, at other times it melted at 160°, solidified, and then remelted at 211–212°.

Anal. Calcd. for $C_9H_8N_2S$: N, 15.90; S, 18.19. Found: N, 15.52; S, 18.35.

2,6-Dimercaptopyrimidine.—A mixture of 60 g. (0.47 mole) of thiouracil, 60 g. (0.27 mole) of phosphorus pentasulfide, 60 g. of pulverized liver of sulfur and 500 ml. of xylene was stirred and refluxed for 18 hours and filtered hot. The xylene-insoluble material was stirred with 500 ml. of water, the mixture made strongly alkaline with 20% sodium hydroxide, the alkaline solution was treated with Darco, filtered and the filtrate acidified with 20% hydrochloric acid. The precipitated solid was filtered, mixed with Hyflo, extracted with 6 liters of water. The solid which separated from the cooled extract was recrystallized from boiling water to give 52.4 g. (77% yield) of product, m.p. 281–284° (with decomposition).[20]

Anal. Calcd. for $C_4H_4N_2S_2$: N, 19.43; S, 44.46. Found: N, 19.30; S, 44.68.

1,3-Diacetyl-5-octyl-2,4-dithiohydantoin.—Redistilled Nonylaldehyde Cyanohydrin (Rohm and Hass, b.p. 125° (1 mm.), 50 g., 0.29 mole) in 50 ml. of absolute ethanol was added to 100 ml. of liquid ammonia and the ammonia allowed to evaporate overnight at room temperature. The ethanol and residual ammonia were removed *in vacuo* at room temperature, the residual oil was dissolved in ether, the ether solution was dried and excess ethereal HCl added. The white solid which separated was filtered and melted at 185° (dec.). Recrystallization from amyl acetate gave 45 g. (63% yield) of **α-aminodecanonitrile hydrochloride,** sinters at 175°, m.p. 185° (dec.).

RELATED DERIVATIVES: 5-SUBSTITUTED-2-THIOHYDANTOINS

5-Substituent	Method	M.p., °C.	Recrystn. solvent	Yield, %	Analyses, % Calcd. C	H	N	Found C	H	N
2-Pentylidene	B	151–152	Toluene	81	52.14	6.57	15.21	51.88	7.19	15.34
2-Methylpropylidene	B	174–176	50% EtOH	80	49.39	5.92	16.47	49.46	5.83	16.27
2-Hexylidene	B	112–114	Toluene	81	54.51	7.12	14.13	54.64	7.30	14.07
2-Heptylidene	B	114–115	Toluene	60	56.57	7.60	13.20	56.63	7.77	13.24
Cyclohexylidene	A	263–265	*n*-PrOH	52	55.06	6.14	14.28	55.23	6.20	14.12
4-Methylcyclohexylidene	B	245–247	*i*-PrOH	55	57.12	6.71	13.33	57.16	6.93	13.57
3-Methylcyclohexylidene	B	240–242	*i*-PrOH	43	57.12	6.71	13.33	57.49	6.56	13.08
Nonylidene[11]	B	183–185	Toluene	30	59.97	8.39	11.66	59.72	8.43	11.98
Benzylidene[21]	A	256–257	*n*-PrOH	58	58.80	3.95	13.72	59.02	4.25	13.59

Anal. Calcd. for $C_{10}H_{21}ClN_2$: Cl, 17.32; N, 13.68. Found: Cl, 17.40; N, 13.84.

The above hydrochloride, 45 g. (0.22 mole) was decomposed with aqueous sodium bicarbonate and the free base extracted with hexane. The hexane solution was distilled under nitrogen until no more hexane–water azeotrope distilled, the dry solution was cooled to 0° and treated with 19.8 g. (0.26 mole) of carbon disulfide dissolved in 100 ml. of hexane. The reaction mixture was kept under nitrogen and at 0°. After about two hours a yellow crystalline solid began to separate. The mixture was kept cold overnight, the solid was filtered and recrystallized from heptane to give 27 g. (50% yield) of 5-amino-2-mercapto-4-octylthiazole, m.p. 136–137°.

Anal. Calcd. for $C_{11}H_{20}N_2S_2$: C, 54.05; H, 8.25; N, 11.47. Found: C, 53.88; H, 8.18; N, 11.00.

To 90 ml. of 2 *N* NaOH at 70–80° was added 27 g. (0.11 mole) of the 5-amino-2-mercapto-4-octylthiazole, the mixture was maintained at this temperature for 10 minutes, cooled to 0° and acidified with 10% hydrochloric acid. The precipitated crude 5-octyl-2,4-dithiohydantoin was filtered and dried. It could not be obtained analytically pure; consequently, the crude product was dissolved in refluxing acetic anhydride, the mixture was refluxed for 10 minutes and the excess acetic anhydride removed *in vacuo*. The residual gummy solid was washed with water, dissolved in boiling acetonitrile, the hot acetonitrile solution was treated with Darco, filtered and concentrated. The solid which separated was recrystallized from acetic anhydride to give 5 g. (14% yield) of 1,3-diacetyl-5-octyl-2,4-dithiohydantoin, m.p. 188–189°.

Anal. Calcd. for $C_{15}H_{24}N_2O_2S_2$: C, 54.86; H, 7.37; N, 8.53. Found: C, 54.39; H, 7.11; N, 8.67.

5-(2-Propylidene)-2-thiohydantoin. Method A.—A mixture of 11.6 g. (0.1 mole) of 2-thiohydantoin, 25 ml. of Reagent Grade pyridine, 5 ml. of piperidine and 15 ml. of acetone reacted spontaneously with the evolution of heat to form a clear solution from which a yellow crystalline solid began to separate after several minutes. The mixture was kept overnight and filtered to give 15 g. (96% yield) of product, m.p. 256–258°. Recrystallization from 300 ml. of absolute ethanol raised the m.p. to 258–260°.

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.94. Found: C, 46.40; H, 5.03; N, 17.93.

5-(2-Butylidene)-2-thiohydantoin. Method B.—A mixture of 23.2 g. (0.2 mole) of 2-thiohydantoin, 10 ml. of piperidine, 30 ml. of pyridine and 30 ml. of methyl ethyl ketone was kept at room temperature for three days. No solid had separated. The volatiles were removed from the steam-bath *in vacuo* and the viscous residue triturated with 50 ml. of 5% hydrochloric acid until the product solidified. The crude product weighed 37.6 g. and was recrystallized from 1220 ml. of toluene to give 28 g. (82% yield) of product, m.p. 188–190°.

Anal. Calcd. for $C_7H_{10}N_2OS$: C, 49.39; H, 5.92; N, 16.46. Found: C, 49.41; H, 5.78; N, 16.35.

1-Acetyl-2-thiohydantoin and Acetone in the Presence of Pyridine and Piperidine.—When 15.9 g. (0.1 mole) of 1-acetyl-2-thiohydantoin was added to a mixture of 20 ml. of pyridine, 5 ml. of piperidine and 15 ml. of acetone a clear solution formed first, heat was evolved, a solid separated and then gradually redissolved. The mixture stood at room temperature for 24 hours and was concentrated *in vacuo* from the steam-bath. The residue solidified and was identified as unreacted 1-acetyl-2-thiohydantoin, m.p. 156°.

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 37.99; H, 3.82; S, 20.27; N-acetyl, 21.71. Found: C, 37.60; H, 4.20; S, 20.36; N-acetyl, 20.43.

Further identification was established by boiling the above product with 10% hydrochloric acid which gave 2-thiohydantoin, m.p. 228–230° alone or mixed with an authentic specimen of 2-thiohydantoin.

5-Isopropyl-2-thiohydantoin and Phosphorus Pentasulfide.—A mixture of 20 g. (0.126 mole) of 5-isopropyl-2-thiohydantoin, 20 g. (0.09 mole) of phosphorus pentasulfide and 500 ml. of dry xylene was stirred and refluxed 48 hours under nitrogen. The insoluble material was filtered, dissolved in 10% sodium hydroxide, the alkaline solution was treated with Darco, filtered and the filtrate acidified. The precipitated product was filtered, dried in air and recrystallized from glacial acetic acid to give 2.3 g. of product, m.p. 237–239° (dec.).

Anal. Calcd. for $C_6H_{10}N_2S_2$: N, 16.08; S, 36.80. Found: N, 16.55; S, 33.12, 32.87.

The above product was recrystallized again from glacial acetic acid. The m.p. was unchanged.

Anal. Found: N, 15.51; S, 29.03, 28.70.

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[20] H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908), prepared this compound from 2,6-dichloropyrimidine and KSH and reported a m.p. above 270° (with decomposition).

[21] Reference 13. These authors report a m.p. of 258°.