[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY]

2,6-Dicyanopiperidines

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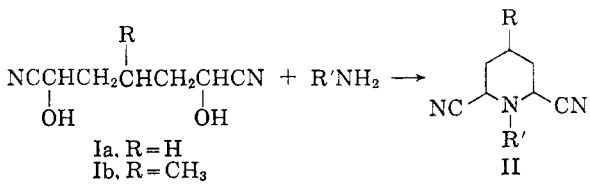
The reaction of the dicyanohydrins of glutaraldehyde and 3-methylglutaraldehyde with various primary amines, ammonia, and hydrazine yields *N*-substituted-2,6-dicyanopiperidines. 2,6-Diaminopimelonitrile derivatives are obtained when aniline and secondary amines are employed in the reactions. Hydrolysis of several of these nitriles is reported.

Prior to the report of Henry,[1] the reaction of glutaraldehyde with ammanium cyanide or the equixalent reaction of glutaraldehyde dicyanohydrin with ammonaia to give 2,6-dicyanopiperidine had not been investigated. 1-Amino-2,6-dicyano-2,6-dimethylpiperidine and its 4-methyl derivative, however, had been prepared earlier by the reaction of the 2,6-heptanediones with hydrazine and hydrogen cyanide; both of these compounds lost the primary amino function upon treatment with nitrous acid to give the corresponding piperidines unsubstituted at the 1- position.[2,3] The present communication describes, in general, some reactions of the dicyanohydrins of glutaraldehyde (1a) and 3-methylglutaraldehyde (Ib) with amines. The related reaction of glutaraldehyde with hydrazine and hydrogen cyanide also is reported.

When I and primary aliphatic amines are allowed to react at 25–50° in aqueous solution, *N*-alkyl-2,6-dicyanopiperidines (II) are formed:

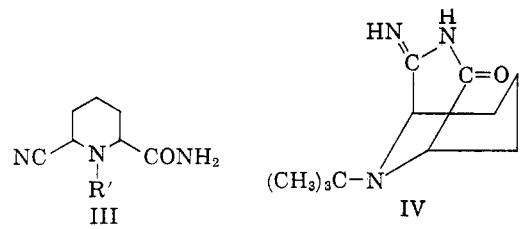


Ia, R = H
Ib, R = CH_3

Yields range from 50% in the case of ammonia to about 90% for some amines.

No attempt was made to establish the configuration of the reaction products, although it does appear that a single isomer is predominantly favored. In those piperidines where R′ is H, methyl, ethyl, and similar nonbulky substituents, the *cis* configuration is probably the more stable, as both nitrile groups can assume equatorial positions with a minimum of crowding from the *N*-substituents. When R′ = *t*-butyl, there exists no apparent favorable conformations and on this basis no structural assignment can be made with confidence. Stewart and Li[4] have shown that in the formation of α-aminonitriles from cyanohydrins and amines, equilibrium is rapidly established between the two as well as with the starting aldehyde. The configuration of the piperidines is then, most probably, the more stable one, as it is equilibrium controlled.

Of particular interest is the formation of the by-product monoamides III (R′ = CH_3,C_2H_5) from the reaction of I with at least methyl and ethylamines and of 2 - keto - 4 - imino - 9 - *t* - butylbicyclo[3.3.1]-3,9-diazanonane (IV) from I and *t*-butylamine. The structure of III (R′ = CH_3) was



III IV

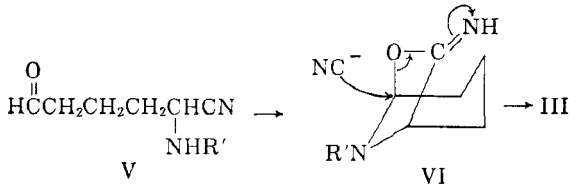
established from its elemental analysis, neutralization equivalent, infrared spectrum (λ_{CONH_2} 3.0, 3.15, 6.05, 6.25 μ; λ_{CN} 4.51 μ) and identity with an authentic sample prepared by the partial hydrolysis of the dicyanopiperidine II (R′ = CH_3).

The bicyclic structure IV is supported by its infrared spectrum (λ_{CONHR} 3.05, 6.1 μ; $\lambda_{C=N}$ 6.6 μ; and no λ_{CN}), ultraviolet spectrum (λ_{max} 240 mμ, ε 2.12 × 10^3),[5] and hydrolysis with hydrochloric acid to piperidine-2,6-dicarboxylic acid hydrochloride. Treatment of II (R′ = *t*-C_4H_9) with hydrochloric acid also produces this diacid.

As III and IV apparently are produced simultaneously with II, it is of interest to speculate on the mechanism of their formation. Davis and Levy[6] found that acetone reacts with α-aminonitriles to yield 4-imino-2,2-dimethyloxazolidines which can be converted to α-amino acid amides by treatment with acetic acid. Similarly, cyclization of the aldehyde V (or other comparable interme-

(1) R. A. Henry, *J. Org. Chem.*, 24, 1363 (1959).
(2) C. G. Overberger and B. S. Marks, *J. Am. Chem. Soc.*, 77, 4097 (1955).
(3) C. G. Overberger, G. Kesslin, and P. Hwang, *J. Am. Chem. Soc.*, 81, 3779 (1959).
(4) T. D. Stewart and C. Li, *J. Am. Chem. Soc.*, 60, 2782 (1938).
(5) There are apparently no examples of the ultraviolet spectra of suitable models. Acetamidine and biguanide have maxima at 224 and 231 mμ (ε 4000 and 9000), respectively [J. C. Gage, *J. Chem. Soc.*, 221 (1949)]. The ultraviolet absorptions of a number of imidazolines also fall in his region (λ_{max} 230 mμ, ε 2250–7000) [R. J. Ferm, J. L. Riebsomer, E. L. Martin, and G. H. Daub, *J. Org. Chem.*, 18, 645 (1953)].
(6) A. C. Davis and A. L. Levy, *J. Chem. Soc.*, 3479 (1951).

diates[4]) may give a bicyclic oxazolidine VI which is transformed into the monoamide III upon reaction with cyanide. The formation of IV is readily

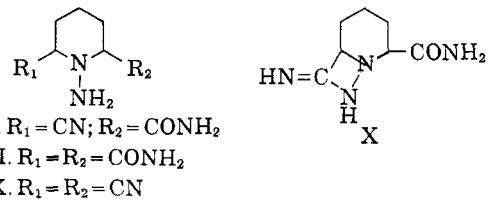


V VI

rationalized if III (R′ = *t*-C_4H_9) is considered an intermediate. The steric requirements of the *t*-butyl group are such as to cause the nitrile and carboxamido groups to assume polar conformations where they are in a favorable position to interact. Both III and structures similar to IV also may have been formed from I and other amines but, if so, were not readily isolable.

The low (50%) yield of II (R′ = H) is not due to the formation of 2,6-diaminopimelonitrile; acidic hydrolysis of the reaction mixture, after removal of the piperidine derivative, under conditions which would be expected to produce 2,6-diaminopimelic acid[7] did not yield any of this substance.

Treatment of an aqueous solution of hydrazine and hydrogen cyanide with glutaraldehyde resulted in a rapid precipitation of 1-amino-2-carboxamido-6- cyanopiperidine (VII). Stirring the reaction mixture at room temperature for several days caused conversion of VII into 1-amino-2,6-dicarboxamidopiperidine (VIII). The corresponding dinitrile IX was obtained *via* the reaction of Ia with hydrazine in ethanol solution.



VII. $R_1 = CN$; $R_2 = CONH_2$
VIII. $R_1 = R_2 = CONH_2$
IX. $R_1 = R_2 = CN$

X

Again, the ease with which these amides were formed *in situ* was unexpected. The sequence V → VI → III may be used as a model to explain the formation of VII, and it is postulated that a cyclic amidine X acts as the intermediate in the facile formation of VIII. It is possible that VII is formed in this manner also from 1-amino-2,6-dicyanopiperidine. Derivatives of VII with acetone and benzaldehyde were easily prepared, suggesting that VII could be a useful reagent in the characterization of aldehydes and ketones.

Reaction of Ia with dimethylamine and dibenzylamine produced the corresponding pimelonitrile derivatives. Aniline, too, gave the pimelonitrile derivative. Judging from the melting point range of these materials, a mixture of *dl*- and *meso*-isomers probably was obtained, but they were not readily separable.

2,6-Dicyanopiperidine was readily hydrolyzed to piperidine-2,6-dicarboxylic acid in aqueous hydrochloric acid and was isolated as its sparingly soluble hydrochloride. 1-Methyl-2,6-dicyanopiperidine (II. R = CH_3) required sulfuric acid for the hydrolysis, and it was necessary to perform the reaction under conditions tht would first partially hydrolyze the nitriles to amides. Neither *N,N,N′,N′*-tetrabenzyl- nor *N,N,N′,N′*-tetramethyl-2,6-diaminopimelonitrile could be converted to the pimelic acids; dibenzylamine hydrochloride was recovered in good yield by treatment of the first with hydrochloric acid and no identifiable products were isolated from the latter. 2,6-Dianilinopimelonitrile gave the expected pimelic acid upon hydrolysis.

EXPERIMENTAL[8]

Glutaraldehyde dicyanohydrin (Ia). To 3027 g. (7.6 moles) of a 25% aqueous glutaraldehyde solution containing 8 ml. of pyridine was added 432 g. (16 moles, 626 ml.) of liquid hydrogen cyanide. The addition was made over a 1-hr. period at temperatures below 30°. After stirring an additional hour at 25–30°, 5 ml. of phosphoric acid was added, and all water was removed by distillation under reduced pressure to leave 1172 g. (100%) of a light-yellow viscous liquid. The small amount of solids present were conveniently removed by filtering the product at about 80°.

2,6-Dicyanopiperidines and 2,6-diaminopimelonitriles. General procedure. To a stirred 10–20% aqueous solution of 1.2 moles of amine (2.2 moles for the pimelonitrile derivatives) was added 1 mole of the dicyanohydrin. For the less water-soluble amines it was found advantageous to use enough alcohol to at least partially dissolve the amine. The temperature was held between 30–50°, and the product was generally completely precipitated after several hours. The solid product was then collected by filtration, washed well with water, and dried. Yields and physical properties of these nitriles are tabulated in Table I.

Piperidine-2,6-dicarboxylic acid. To 500 ml. of 28% ammonium hydroxide was added 77 g. (0.50 mole) of Ia. The mixture was stirred 1 hr. at 25° during which time a precipitate of 2,6-dicyanopiperidine had formed. The complete reaction mixture was then evaporated to dryness under reduced pressure to provide 79 g. of semi-solid residue. Four hundred milliliters of concentrated hydrochloric acid was added to the residue and the mixture allowed to stir at 25° overnight, followed by a 4-hr. reflux period. The precipitated solids were collected, washed with a minimum amount of water, and dried to give 33 g. (41%) of the diacid hydrochloride as colorless microcrystals, m.p. 287–289°, dec. (reported[9] 290–295° and[10] 284–285°).

The filtrate from the above preparation was evaporated to dryness under reduced pressure and the residue dissolved in 200 ml. of water. This solution was adjusted to *p*H 6 with lithium hydroxide and lithium acetate and diluted with 1.5 l. of ethanol.[7] No diaminopimelic acid precipitated.

1-Methylpiperidine-2,6-dicarboxylic acid. To 150 g. of concentrated sulfuric acid was added 36 g. (0.24 mole) of 1-

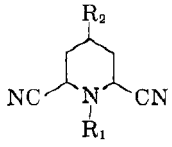
(7) E. Work, S. M. Birnbaum, M. Winitz, and J. P. Greenstein, *J. Am. Chem. Soc.*, **77**, 1916 (1955).

(8) Melting points are corrected. Infrared spectra were recorded with a Perkin Elmer Model 21 spectrophotometer and ultraviolet spectra with a Cary Model 14 spectrophotometer.

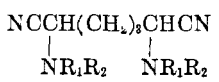
(9) K. Hess and F. Wissing, *Ber.*, **48**, 1907 (1915).

(10) N. Anderson and T. O. Soine, *J. Am. Pharm. Assoc.*, **39**, 403 (1950).

TABLE I



(A) 2,6-DICYANOPIPERIDINES



(B) 2,6-DIAMINOPIMELONITRILES

Structure	R_1	R_2	M.P.	% Yield	Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
A[a]	H	H	114–115	50	$C_7H_9N_3$	—	—	—	—	—	—
A	CH_3	H	128–130	78	$C_8H_{11}N_3$	64.40	7.43	28.17	64.60	7.47	27.97
A	C_2H_5	H	88–89	60	$C_9H_{13}N_3$	66.26	8.03	25.75	66.14	8.10	25.75
A	$CH(CH_3)_2$	H	98–99	86	$C_{10}H_{15}N_3$	67.76	8.53	23.71	67.50	8.60	23.68
A	$C(CH_3)_3$	H	125–126	72	$C_{11}H_{17}N_3$	69.07	8.96	21.97	69.24	8.81	21.98
A	n-$C_{18}H_{37}$	H	62–64	99	$C_{25}H_{45}N_3$	77.46	11.70	10.84	77.35	11.66	10.56
A	$CH_2CH{=}CH_2$	H	87–88	78	$C_{10}H_{13}N_3$	68.54	7.48	23.98	68.32	7.93	23.81
A[b]	$CH_2CH_2CH_2$	H	175–180	93	$C_{17}H_{22}N_6$	65.78	7.14	27.08	65.62	7.15	26.83
A	NH_2	H	101–103	40	$C_7H_{10}N_4$	55.98	6.71	37.31	56.23	6.61	36.98
A[c]	H	CH_3	127–128	51	$C_8H_{11}N_3$	64.40	7.43	28.17	64.57	7.48	28.11
A	CH_3	CH_3	122–123	64	$C_9H_{13}N_3$	66.22	8.03	25.75	65.97	8.17	25.71
B[d]	C_6H_5	H	117–139	24	$C_{19}H_{20}N_4$	74.94	6.62	18.41	75.16	7.01	18.40
B	CH_3	CH_3	63–65	59	$C_{11}H_{20}N_4$	63.42	9.68	26.90	63.66	9.66	26.58
B	$C_6H_5CH_2$	$C_6H_5CH_2$	125–150	99	$C_{35}H_{36}N_4$	81.99	7.08	10.93	81.84	7.00	11.03

[a] Reported,[1] m.p. 114–115°. *N*-Nitroso derivative, m.p. 143–145° (reported,[1] 143.5–144.5°). *N*-Acetyl derivative, m.p. 130–131°. *Anal.* Calcd. for $C_9H_{11}N_3O$: N, 23.72; found: N, 23.94. [b] From 1,3-diaminopropane. [c] *N*-Nitroso derivative, m.p. 107–109°. *Anal.* Calcd. for $C_8H_{10}N_4O$: N, 31.45; found: N, 31.17. [d] Diacid, m.p. 178–185°. *Anal.* Calcd. for $C_{19}H_{22}N_2O_4$: N, 8.18; found: N, 8.19.

methyl-2,6-dicyanopiperidine, and the mixture was allowed to stir at 25° for 18 hr. After adding to 150 ml. of water, it then was refluxed for 6 hours, cooled to 5°, neutralized to pH 1.5–2.0 with concentrated ammonium hydroxide, and the precipitated material collected by filtration. The product was dried to give 23 g. (47%) of the desired diacid as its hydrate. Crystallization from water afforded colorless blunt needles, m.p. 220–225°, dec. (reported[9] 225°).

Isolation of 1-alkyl-2-carboxamido-6-cyanopiperidines III. (A) (R′ = C_2H_5). The preparation of 1-ethyl-2,6-dicyanopiperidine (II. R′ = C_2H_5) from 72 g. (0.5 mole) of Ia was performed as described in the general procedure to yield 57 g. (70%) of product, m.p. 82–86° with some crystals remaining to 140°. All of this material was dissolved in hot ethanol and allowed to cool to 15°. The precipitate (6 g.) was collected as colorless microcrystals, m.p. 160–183°. Further crystallizations from ethanol produced an analytical sample, m.p. 189–190°, λ_{max} 2.96, 3.13, 4.5, 6.03, 6.15 μ. The ultraviolet spectrum exhibited no maximum above 220 mμ.

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19; Neut. equiv. 181. Found: C, 59.62; H, 8.56; N, 23.04; Neut. equiv. 182 (perchloric acid titration in acetic acid).

(B) (R′ = CH_3). This preparation was conducted as described above employing 231 g. (1.5 moles) of Ia in the reaction. The precipitated dicyanopiperidine did not contain any of the desired amide, and the filtrate was evaporated under reduced pressure. The resulting amber sirup (82 g.) was covered with *i*-propanol; after allowing it to stand for several days, crystals appeared and were collected (3.5 g., m.p. 185–192°). Crystallization from methanol afforded an analytical sample as small colorless needles, m.p. 197–199°, λ_{max} 3.0, 3.15, 4.51, 6.05, 6.25 μ. A mixed m.p. with an authentic specimen of the expected product (see below) was undepressed, and the infrared spectra of the two were identical.

Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.35; H, 8.05; N, 25.07.

1-Methyl-2-carboxamido-6-cyanopiperidine (III. R′ = CH_3). The piperidine II (R′ = CH_3) (30 g., 0.2 mole) was added to 200 ml. of concentrated hydrochloric acid and the orange solution was kept at 25–30° for 4 hr. Water and hydrochloric acid were removed by evaporation under reduced pressure and the remaining syrup mixed with about 200 ml. of water. Six grams of the starting nitrile precipitated, m.p. 130–132°, and the supernatant was neutralized with ammonium hydroxide. Evaporation of the solution in a stream of air caused the product (10 g.) to precipitate. The colorless crystals, m.p. 193–195°, exhibit considerable water-solubility. A sample, crystallized from toluene, m.p. 197–199°, was identical in all respects to the material obtained as a by product in the preparation of II (R′ = CH_3).

2-Keto-4-imino-9-t-butylbicyclo[3.3.1]-3,9-diazanonane (IV). The filtrate from a standard preparation of II (R′ = *t*-C_4H_9) was allowed to stand at about 25° for 18 hr. Eleven grams (from 0.47 mole of Ia) of material precipitated, m.p. 280–286°, dec., which was obtained after crystallization from alcohol as colorless microcrystals, m.p. 282–297°, dec., λ_{max}^{EtOH} 240 mμ, ϵ 2,120; λ_{max} 3.05, 6.1, 6.6 μ.

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.12; H, 9.15; N, 20.08. Found: C, 62.98; H, 9.28; N, 19.80.

Hydrolysis of IV *to piperidine-2,6-dicarboxylic acid.* A 504-mg. sample of IV was dissolved in 5 ml. of concentrated hydrochloric acid and boiled under reflux for 2.5 hr. The mixture was cooled and the precipitated solids collected and washed with a small amount of water to give 153 mg. of colorless piperidine-2,6-dicarboxylic acid hydrochloride, m.p. 289–291°, dec. The infrared spectrum of this material was identical to the spectrum of an authentic sample. A mixture of 48 g. of the dinitrile II (R′ = *t*-C_4H_9) and 300 ml. of concentrated hydrochloric acid reacted similarly to give 18 g. of piperidine-2,6-dicarboxylic acid, m.p. 293–295°, dec.

1-Amino-2-carboxamido-6-cyanopiperidine (VII). To a solution of 98 g. (1.0 mole) of sulfuric acid in 200 ml. of water was added 118 g. (2.0 moles) of 85% hydrazine hydrate followed by a solution of 200 g. (4.0 moles) of sodium cyanide in 600 ml. of water. This solution was cooled to 0° and 800 g. (2.0 moles) of a 25% aqueous solution of glutaraldehyde was added over a period of 1 hr. A dense precipitate soon formed, and after stirring the mixture for an additional hour at 0°, the product was collected by filtration. A yield of 375 g. of colorless solids was obtained and found to

contain 30% inorganic material by trituration with ethanol. An analytical sample of VII was obtained as colorless needles from ethanol, m.p. 245–247°, dec., λ_{max} 2.95, 3.17, 4.46, 6.04, 6.20 μ.

Anal. Calcd. for $C_7H_{12}N_4O$: C, 50.00; H, 7.14. Found: C, 49.85; H, 7.38.

The benzal derivative was obtained as colorless feathery needles in 66% yield by reaction with benzaldehyde in dilute aqueous hydrochloric acid. The compound was crystallized from 80% aqueous ethanol, m.p. 188–189°.

Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.60; H, 6.25; N, 21.88. Found: C, 65.42; H, 6.03; N, 22.06.

The isopropylidene derivative was prepared similarly and obtained as colorless needles in 32% yield, m.p. 209–210° (from ethanol).

Anal. Calcd. for $C_{10}H_{16}N_4O$: C, 57.73; H, 7.69; N, 26.92. Found: C, 57.61; H, 7.78; N, 27.06.

1-Amino-2,6-dicarboxamidopiperidine (VIII). A reaction mixture identical to that described for the preparation of VII was allowed to stir at 25° for 3 days. During this time a granular precipitate replaced the original dense slurry of material. The product was collected by filtration, washed with a small amount of cold water, and dried to give 193 g. (52%) of colorless microcrystals, m.p. 247–253°, dec. An analytical sample was obtained as colorless needles, m.p. 246–250°, dec., after several crystallizations from water.

Anal. Calcd. for $C_7H_{14}N_4O_2$: C, 45.18; H, 7.52; N, 30.08. Found: C, 44.94; H, 7.61; N, 29.90.

Acknowledgment. The authors wish to thank C. R. McClure and F. G. Bollinger for their able assistance and Q. Quick and his associates for microanalyses and spectral data.

SOUTH CHARLESTON, W. VA.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORIES, MICHIGAN STATE UNIVERSITY]

A New Synthesis of Thiophene- and Thianaphthenethiols

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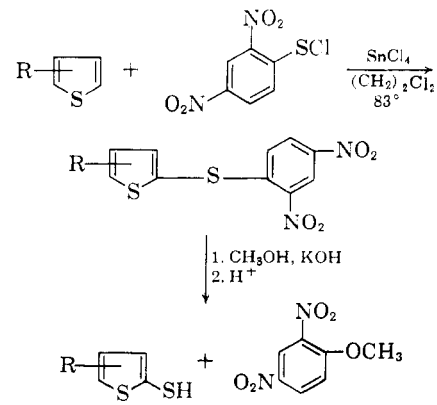
The thiols, 2-thiophenethiol, 5-methyl-2-thiophenethiol, 2,5-dimethyl-3-thiophenethiol, and 2-methyl-3-thianaphthenethiol were prepared by a simple synthesis involving the Friedel-Craft reaction of 2,4-dinitrobenzenesulfenyl chloride with the sulfur heterocyclic nucleus followed by basic cleavage of the resulting sulfide to obtain the heterocyclic mercaptan. The mercaptan, 2-thianaphthenethiol was also prepared by a reaction in which 2-methylthiirane was desulfurized by interaction with 2-thianaphthyllithium.

Relatively few thiophene- and thianaphthenethiols have been reported in the literature. Challenger and Harrison[2] prepared 2-ethyl-3-thiophenethiol by reducing thieno[3,2-*b*]thiophene with sodium in alcohol. Caesar and Branton[3] obtained 3-thiophenethiol by treating 3-thienylmagnesium iodide with sulfur followed by acid hydrolysis. This thiol was also obtained by these investigators through the destructive distillation *in vacuo* of the tarry material produced during the commercial production of thiophene from the dehydrogenation and cyclization of butane with sulfur at high temperatures. More recently, Schuetz and Houff[4] obtained 2-thiophenethiol by the zinc dust-sulfuric acid reduction of 2-thiophenesulfonyl chloride. Schuetz and Fawcett[5] reported the preparation of 2,5-dimethyl-3-thiophenethiol by the lithium aluminum hydride reduction of the corresponding sulfonyl chloride. These same investigators also prepared 5-(1′-cyclohexenyl)-2-thiophenethiol by reduction of the corresponding disulfide with lithium aluminum hydride. Schuetz and Heyd[6] reported the synthesis of both the 2- and 3-thianaphthenethiols. The former was obtained by treating 2-benzo[*b*]thienyllithium with sulfur followed by acidification, and the 3 isomer by interaction of 3-benzo[*b*]thienylmagnesium bromide with sulfur and acidification of the organometallic complex.

The present study was undertaken to determine the feasibility of preparing thiophene- and thianaphthenethiols via preparation and subsequent basic hydrolysis of thienyl and thianaphthyl (2,4-dinitrophenyl) sulfides.

The reaction sequence is,



(1) Abstracted in part from the Masters thesis of W. L. Fredericks, 1959.

(2) F. Challenger and J. B. Harrison, *J. Inst. Petroleum Technol.*, **21**, 135 (1935).

(3) P. D. Caesar and P. D. Branton, *Ind. Eng. Chem.*, **44**, 122 (1952).

(4) R. D. Schuetz and W. H. Houff, *J. Am. Chem. Soc.*, **75**, 6316 (1953).

(5) R. D. Schuetz and R. J. Fawcett, Abstracts of Papers, Am. Chem. Soc. Meeting, San Francisco, Calif., April 13–18, 1958, p. 48-N.

(6) R. D. Schuetz and C. E. Heyd, Abstracts of Papers, Am. Chem. Soc. Meeting, Miami, Fla., April 7–12, 1957, p. 84-O.