from the evaporation of the mixed solvents was then crystallized from methanol, yielding 0.9 g. (47.4%) of pure product, melting at 171–172°.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 66.87; H, 5.26; N, 13.00. Found: C, 66.70; H, 5.40; N, 13.11.

2,6-Bis(4'-ethoxy-2'-pyridyl)-4-ethoxypyridine. To a cooled solution of 0.68 g. of sodium in 91 ml. of anhydrous ethanol was added 2.2 g. of 2,6-bis(4'-nitro-2'-pyridyl)-4-nitropyridine. After stirring for 4 hr. at 60–65°, solution was nearly complete. The filtered alcoholic solution was evaporated to dryness using an aspirator and extracted with chloroform. After evaporation to a volume of 45 ml., 9 ml. of phosphorus trichloride was added and the mixture refluxed for 3 hr. It was then poured on ice and made alkaline. The precipitate obtained, which was insoluble in ether and chloroform was dried and again treated with chloroform and phosphorus trichloride as before. After again pouring on ice and making alkaline, the product dissolved in ether and was recovered by evaporation of the mixed solvents; yield, 0.8 g. (42.1%) of pure product melting at 157–158°.

Anal. Calcd. for $C_{21}H_{22}N_3O_3$: C, 69.04; H, 6.30. Found: C, 68.96; H, 6.49.

2,6-Bis(4'-chloro-2'-pyridyl)-4-chloropyridine. To a suspension of 2 g. of 2,6-bis(4'-nitro-2'-pyridyl)-4-nitropyridine in 20 ml. of glacial acetic acid at 60° was added 12 ml. of acetyl chloride. After heating for 1 hr. on the steam bath, an additional 4 ml. of acetyl chloride was added and heating continued for 1 hr. The mixture was poured on ice and the solution neutralized with sodium bicarbonate. The crude oxide precipitating after separation by filtration and drying was suspended in 35 ml. of chloroform. To the cold mixture was added 4.5 ml. of phosphorus trichloride. After standing for 1 hr., it was refluxed for one hour on the steam bath, and then poured on ice and made alkaline. The resulting precipitate, after drying, was crystallized from benzene yielding 1.2 g. (75.0%) of product, m.p. 210–211°. An analytical sample melted at 212–213°.

Anal. Calcd. for $C_{15}H_8N_3Cl_3$: C, 53.51; H, 2.38. Found: C, 53.49; H, 2.24.

4,4'-Dihydroxy-2,2'-bipyridine. To 7.5 ml. of concd. sulfuric acid at 0° was added 0.95 g. of sodium nitrite. The mixture was allowed to warm to room temperature and then heated at 65° until a clear solution resulted. To this solution was then added a solution of 1.2 g. of 4,4'-diamino-2,2'-bipyridine in 5 ml. of concd. sulfuric acid at 0–5°. After standing for 15 min., the reaction mixture was poured on 40 g. of ice, and the solution was allowed to stand overnight whereupon considerable evolution of nitrogen was observed. On adjusting to *p*H 6 with sodium hydroxide, a precipitate formed which was separated and crystallized from water. The yield of pure hemihydrate melting at 342–343° was 0.7 g. (58.3%).

Anal. (sample dried at 100°). Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.26. Found: C, 63.69; H, 4.30. Calcd. for $C_{10}H_8N_2O_2 \cdot {}^1/_2H_2O$: H_2O, 12.56. Found: H_2O, 12.57.

2,6-Bis(4'-hydroxy-2'-pyridyl)-4-hydroxypyridine. The procedure for this preparation was the same as for that of 4,4'-dihydroxy-2,2'-bipyridine. From 1.2 g. of the triamino compound was obtained 1.2 g. of crude trihydroxy compound. The pure product was obtained as a dihydrate by crystallization from water, in which it is very sparingly soluble. It melts over 400°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3 \cdot 2H_2O$: C, 56.78; H, 4.73; H_2O, 11.36. Found: C, 56.92; H, 4.85; H_2O, 10.97.

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Piperidine Derivatives with a Sulfur-Containing Function in the 4- Position[1]

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A series of 1-methylpiperidines having a functional group containing sulfur at the 4- position was desired for screening as potential antiradiation compounds. The obvious approach to the synthesis of these compounds, the nucleophilic substitution of 1-methyl-4-chloropiperidine, failed to give the desired product.[3] An alternate route to 1-methyl-4-mercaptopiperidine (VIII) was suggested by the ease of formation of the hydrate of 1-methyl-4-piperidone hydrochloride,[4] which would suggest that the reaction of 1-methyl-4-piperidone with hydrogen sulfide should form a *gem*-dithiol with an ease similar to that observed with dibenzyl ketone.[5] The *gem*-dithiol thus formed could readily be converted to the corresponding mercaptan by reduction.

The reaction of 1-methyl-4-piperidone (I) with hydrogen chloride and hydrogen sulfide in ether, the procedure used for the conversion of dibenzyl ketone to the *gem*-dithiol,[5] failed to cause the introduction of sulfur, for the amine salt II precipitated before reaction with hydrogen sulfide occurred. By using a solvent, isopropyl alcohol, in which the amine salt would be soluble and precipitation of the product with ether the reaction led to a colorless, sulfur-containing product which released hydrogen sulfide on heating in aqueous solution. The color tests for sulfur-containing functional groups[6–8] were inconclusive; however, the elemental analyses corresponded to the formula of 1-methyl-4-thiopiperidone hydrochloride (V) which was assumed to be a trimer because of lack of color and analogy with polymerization of other thiones.[9] Molecular weight determinations on V were incon-

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(2) On leave from Extractos Curtientes y Productos Quimicos, S. A., Barcelona, Spain, 1959–1960, as Research Associate at the University of New Hampshire.

(3) Unpublished results, H. Barrera and R. E. Lyle. With the exception of potassium xanthate, nucleophiles led to cleavage of the heterocyclic ring of 1-methyl-4-chloropiperidine.

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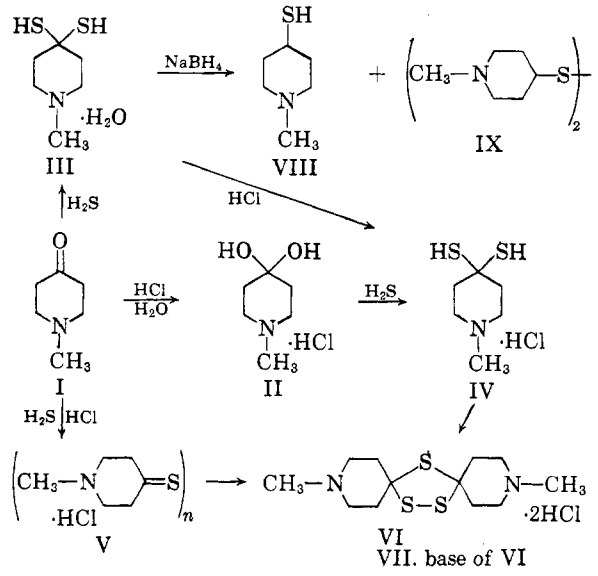

clusive due to the poor solubility characteristics and the salt character of V.

The recrystallization of polymeric 1-methyl-4-thiopiperidone hydrochloride (V) caused a partial conversion to a new salt (VI) which still contained sulfur but which gave negative results with the above-mentioned color-test reagents.[6-8] The elemental analyses and infrared spectrum of VI showed the salt to be hydrated; however, conversion of the salt VI to the base (VII) gave a solid which could be characterized as a dispiro-1,2,4-trithiolane (VII), formed by the autoxidation of the thio ketone V. Such structures have been reported as the product of the reaction of ketones with hydrogen sulfide, sulfur, and a secondary amine[10] and autoxidation of thio ketones.[11] The trithiolane (VII) was remarkably stable to heat and hydrolysis.

The reaction of hydrogen sulfide with the *gem*-diol, 1-methyl-4-piperidone hydrochloride hydrate (II), in isopropyl alcohol led to a good yield of a salt the properties of which showed it to be the desired 1-methyl-4,4-dimercaptopiperidine hydrochloride (IV). The *gem*-dithiol IV was very reactive, for it was converted to the trithiolane VI on attempted recrystallization from alcohols and eliminated hydrogen sulfide on dissolution in water.

A remarkable reaction was observed on treatment of the base 1-methyl-4-piperidone (I) with hydrogen sulfide in isopropyl alcohol, for a solid separated from solution with an analysis corresponding to 1-methyl-4,4-dimercaptopiperidine hydrate (III). The infrared spectra of III in chloroform solution gave evidence of the water of hydration and as a solid mull showed weak SH stretching bands at 2525 cm.$^{-1}$ and no evidence of ammonium hydrogen. These data are consistent with the molecule of water being associated with 1-methyl-4,4-dimercaptopiperidine. The reaction of III with hydrogen chloride gave a salt identical with 1-methyl - 4,4 - dimercaptopiperidone hydrochloride (IV). The formation of a *gem*-dithiol from a ketone in the absence of an acid catalyst is most unusual.

The 4-carbon atom of the *gem*-dithiol (III or IV) is in the same oxidation state as that of the thione. Thus it was assumed that in a reaction the unstable dithiol would be equivalent to the thione, and reactions anticipated for the thione could be obtained by using the *gem*-dithiol as starting material. The reaction of the *gem*-dithiol (III) with phenyllithium was investigated in an attempt to prepare 1-methyl-4-phenyl-4-mercaptopiperidine, but no pure product could be isolated. The reaction of the *gem*-dithiol with sodium borohydride in isopropyl alcohol was more successful. If the reaction product was isolated immediately so that the 1-methyl-4-mercaptopiperidine (VIII) which was formed was not allowed to stand in the alkaline medium, a good yield of VIII was obtained. The mercaptan VIII, however, was rapidly oxidized to the corresponding disulfide IX by air on standing in an alkaline medium.

In view of the anomalous cleavage reaction observed with nucleophilic reactions of 1-methyl-4-chloropiperidine,[3] the preparation of piperidines substituted in the 4- position with sulfur-containing functional groups requires an indirect route for synthesis. The most satisfactory preparation for 1-methyl-4-mercaptopiperidine (VIII) has thus been shown to be through the *gem*-dithiol.

EXPERIMENTAL

1-Methyl-4,4-dimercaptopiperidine hydrochloride (IV). A solution of 10.1 g. of freshly prepared 1-methyl-4-piperidone hydrochloride hydrate[12] (II) in 400 ml. of isopropyl alcohol was filtered and hydrogen sulfide was bubbled into the solution for 3 hr. After standing overnight, the solution deposited 9.2 g. (76%) of white 1-methyl-4,4-dimercaptopiperidine hydrochloride (IV), m.p. 145° with resolidification and remelting at 178–180°. The reaction of IV with nitrous acid[6] gave a green color, with lead acetate[7] an orange precipitate which darkened rapidly, and with Grote's reagent[8] a red color which turned green. These tests are consistent with the structure assigned.

Anal. Calcd. for $C_6H_{14}ClNS_2$: Cl, 17.75; N, 7.01; S, 32.10. Found: Cl, 18.12; N, 7.32; S, 32.27.

Concentration of the mother liquors from the isolation of IV gave the trithiolane (VI) *vide infra*.

1-Methyl-4,4-dimercaptopiperidine (III). A solution of 14.5 g. of 1-methyl-4-piperidone (I) in 100 ml. of isopropyl alcohol was cooled, and hydrogen sulfide was added over a period of 4 hr. The solution was allowed to stand overnight after

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(11) E. Campaigne and W. B. Reid, *J. Org. Chem.*, **12**, 807 (1959).

(12) Since the *gem*-dithiol could not be purified by recrystallization, an analytical sample of the *gem*-dithiol was prepared by starting with carefully purified 1-methyl-4-piperidone hydrochloride hydrate (II).

which time 6.4 g. of solid had been deposited. The mother liquors were treated with hydrogen sulfide for an additional 6 hr. to yield an additional 2 g. (36% total) of 1-methyl-4,4-dimercaptopiperidine hydrate (III), m.p. 48–50°.

Anal. Calcd. for $C_6H_{15}NOS_2$: C, 39.74; H, 8.34; S, 35.37. Found: C, 40.30, 40.59; H, 8.43, 8.66; S, 34.48, 34.27.

An isopropyl alcohol solution of 1-methyl-4,4-dimercaptopiperidine hydrate (II) was treated with hydrogen chloride to form the hydrochloride (IV), m.p. 142–144°, resolidified, m.p. 168–171°, identical in infrared spectrum with IV isolated from 1-methyl-4-piperidone hydrochloride hydrate (II).

Polymer of 1-methyl-4-thiopiperidone hydrochloride (V). A solution of 22 g. of 1-methyl-4-piperidone (I) in 180 ml. of isopropyl alcohol was saturated with anhydrous hydrogen chloride, and hydrogen sulfide was then passed into the solution for 5 hr. The addition of anhydrous ether caused the precipitation of an oil which partially crystallized on standing. The solid was removed by filtration and washed with isopropyl alcohol and ether. About 18 g. (55%) of V, m.p. 178–191°, was obtained, but it could not be purified by recrystallization due to decomposition. Fractional precipitation of V from the reaction mixture obtained with pure 1-methyl-4-piperidone (I) gave analytically pure V, m.p. 189–191°.

Anal. Calcd. for $(C_6H_{12}ClNS)_n$: C, 43.49; H, 7.30; S, 19.35; Cl, 21.40. Found: C, 43.40, 43.11; H, 7.32, 7.15; S, 20.15, 20.12; Cl, 21.43.

The reaction of V with nitrous acid gave a green color and V gave an orange precipitate which darkened rapidly on reaction with alcoholic lead acetate.[7] Grote's reagent[8] gave with V a red-purple color which changed to violet and finally blue.

Dispiro-1,2,4-trithiolane hydrochloride (VI). A solution of 1-methyl-4-piperidone hydrochloride hydrate (II) in isopropyl alcohol prepared from 28.3 g. of pure 1-methyl-4-piperidone (I) was saturated with hydrogen sulfide. The 1-methyl-4,4-dimercaptopiperidine hydrochloride (IV) which precipitated was removed by filtration. The filtrate was concentrated and 5.9 g. (13%) of VI, m.p. 225–227°, precipitated. Recrystallization of the solid from 95% ethanol gave VI, m.p. 233° dec.

Anal. Calcd. for $C_{12}H_{24}Cl_2N_2S_3$: C, 39.66; H, 6.66; Cl, 19.51; S, 26.47. Calcd. for $C_{12}H_{24}Cl_2N_2S_3 \cdot H_2O$: C, 37.78; H, 6.87; Cl, 18.59; S, 25.22. Found: C, 38.76, 38.67; H, 6.93, 7.07; Cl, 17.83; S, 27.14.

The base was prepared by neutralization of a solution of VI with potassium carbonate. Recrystallization of the base (VII) from ligroin gave colorless crystals, m.p. 78–80°.

Anal. Calcd. for $C_{12}H_{22}N_2S_3$: C, 49.61; H, 7.63; S, 33.11. Found: C, 49.85; H, 7.87; S, 32.96.

1-Methyl-4-mercaptopiperidine (VIII). To a suspension of 6.4 g. of sodium borohydride in 50 ml. of isopropyl alcohol, 20 g. of 1-methyl-4,4-dimercaptopiperidine hydrate (III) was added in portions. An additional 40 ml. of isopropyl alcohol was added and stirring was continued for 1 hr. The reaction mixture was heated at 58° on a water bath and stirred for 2 hr. Dilute hydrochloric acid was added until all of the solid dissolved, and the acidified solution was heated on the steam bath. The solution was neutralized with 20% potassium hydroxide until the addition of alkali caused no further clouding. The aqueous mixture was extracted several times with ether, and the ether extracts were dried. The ether was removed by distillation, and the residual oil was distilled under reduced pressure to give 10.1 g. (70%) of 1-methyl-4-mercaptopiperidine (VIII), b.p. 62° at 0.8 mm., and 2.5 g. (17%) of the corresponding disulfide (IX), b.p. 180°, at 0.8 mm. The two bases were converted to their hydrochlorides in isopropyl alcohol to give 1-methyl-4-mercaptopiperidine hydrochloride, m.p. 172–173°, and bis(1-methyl-4-piperidyl) disulfide hydrochloride, m.p. 237–238°.

Anal. Calcd. for $C_6H_{14}ClNS$: C, 42.97; H, 8.41; S, 19.12. Found: C, 43.21; H, 8.54; S, 18.20.

Anal. Calcd. for $C_{12}H_{26}Cl_2N_2S_2$: C, 43.23; H, 7.86; S, 19.24. Found: C, 43.17; H, 8.04; S, 18.17.

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Azasteroids. III[1,2]

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The preparation of 17β-acetoxy-19-nor-4-aza-androst-5-en-3-one (II) and its dehydrogenation to 4-azaestradiol 17β-acetate (V) has already been mentioned in a preliminary communication.[4] Further experiments have now demonstrated that II can be prepared in superior yields from 17β-acetoxy-19-nor-4-oxa-androst-5-en-3-one (I) by treatment of its benzene solution with ammonia, whereby II precipitates from the reaction mixture. Alkaline hydrolysis of II gives 17β-hydroxy-19-nor-4-aza-androst-5-en-3-one (III), which is oxidized to 19-nor-4-aza-androst-5-en-3,17-dione (IV) with chromic acid.

All the 3-keto-4-aza Δ^5-steroids have a strong ultraviolet absorption with an absorption maximum in the region of 230–235 mμ in neutral solution.

TABLE I

	λ_{max}	ϵ
4-Azacholest-5-en-3-one[4]	233	13,500
4-Azapregn-5-en-3,20-dione[4]	233	13,430
17β-Hydroxy-4-azaandrost-5-en-3-one[4]	233	13,790
17β-Acetoxy-4-azaandrost-5-en-3-one[4]	233	13,630
17β-Acetoxy-4-aza-19-norandrost-5-en-3-one[4]	234	9,630
4-Aza-4-methyl-5-cholesten-3-one	234	13,490[5]
4-Aza-4-methyl-5-pregnene-3,20-dione	234	13,180[5]
4-Aza-4-methyl-5-pregnen-20β-ol-3-one	234	13,490[5]
4-Aza-4,17α-dimethyl-5-androsten-17β-ol-3-one	234	13,490[5]

With increasing hydrochloric acid addition to the methanolic solution the maximum gradually disappears. This can be explained by the fact that the absorption is due to the form IX[6] and its disappearance to the formation of the protonated X.

Upon repeating[4] the oxidation of II with selenium dioxide in *tert*-butyl alcohol solution with a catalytic amount of either acetic acid or pyridine,

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(2) This study was supported by National Institute of Health Grant H-5266.

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(5) Dr. N. J. Doorenbos, private communication.

(6) NMR gives peaks for 1 H each, attached to N and C_6.