The Action of Sulfur on Cyclic Amines[1]

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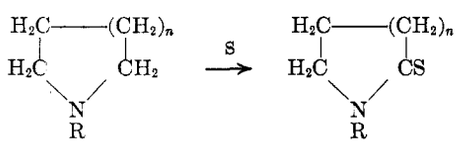
Pyrrolidines when treated with sulfur gave products which varied with the substituents present. 1-Methyl- and 1-butylpyrrolidine gave the corresponding thiopyrrolidones. Pyrrolidine, 1-ethyl-2-methylpyrrolidine, and 3-phenylpyrrolidine were converted to polymers. 2-Phenylpyrrolidine and 1-methyl-3-phenylpyrrolidine were converted to pyrroles and 1-methyl-2-arylpyrrolidines gave bis(1-methyl-5-aryl-2-pyrrolyl) disulfides. The pyrrole was not an intermediate in the formation of the disulfide since nicotyrine and sulfur gave a tetrathiocin. 1-Ethyl- and 1-butylpiperidines gave thiopiperidones. Piperidine and 4-methylpiperidine gave hydrosulfides.

The availability of pyrrolidines by the Hofmann–Loeffler reaction[2] suggested a study of the dehydrogenation of pyrrolidines by sulfur as a possible method for the preparation of pyrroles. This reaction, which may be involved in the formation of pyrroles in petroleum, has been applied in the past to only one pyrrolidine; nicotine has been reported to form a 2.5% yield of nicotyrine. The main product was represented as thiodinicotyrine.[3]

The action of sulfur on pyrrolidines was carried out by heating directly or in xylene as a solvent. In most examples evolution of hydrogen sulfide began at 50° or below. Continued heating at this temperature until the evolution of hydrogen sulfide had ceased required 2 to 3 days and gave polymeric materials. The conditions reported in the Experimental Section are those found to give the best yields and were determined by varying the temperature and time. Solvents such as toluene and pyridine and other sources of sulfur such as phosphorus pentasulfide proved less satisfactory. The results obtained were varied and depended on the substituents present on the ring.

1-Methylpyrrolidine (Ia) and 1-butylpyrrolidine (Ib) in the reaction shown gave the 2-thiopyrrolidones IIa and b. The structure of the products was based on their infrared and nmr spectra and comparison with an authentic sample.



Ia, $n = 1$; R = CH_3 — IIa, $n = 1$; R = CH_3
b, $n = 1$; R = C_4H_9 — b, $n = 1$; R = C_4H_9
c, $n = 2$; R = C_2H_5 — c, $n = 2$; R = C_2H_5
d, $n = 2$; R = C_4H_9 — d, $n = 2$; R = C_4H_9

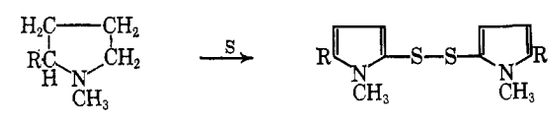
Pyrrolidine and 1-ethyl-2-methylpyrrolidine behaved differently when heated with sulfur and gave only polymeric materials.

To determine the generality of the formation of thioamides in other series a variety of cyclic amines was studied. 1-Ethylpiperidine (Ic) and 1-butylpiperidine (Id) behaved in a similar fashion to the 1-substituted pyrrolidines (I) and gave 2-thiopiperidones. Piperidine and 4-methylpiperidine gave extremely volatile and unstable products which proved to be the corresponding piperidine hydrosulfides. The best yield was obtained by adding a refluxing solution of sulfur in xylene to the amine in xylene. These products were identical with the products obtained by passing dry hydrogen sulfide into an ether solution of the piperidine.

1-Methylpiperidine, 1-methylmorpholine, 1-methylhexamethylenimine, 1,4-dimethylpiperazine, 3-azabicyclo[3.2.2]nonane, 1,4-diazabicyclo[2.2.2]octane, and N-butyl-3-azabicyclo[3.2.2]nonane using the methods described gave only polymers. In the last example a small amount of *n*-butylamine was isolated and suggested that a ring cleavage had occurred.

The majority of the phenyl-substituted pyrrolidines behaved differently in this reaction from the aliphatic examples. 2-Phenylpyrrolidine gave a 43% yield of 2-phenyl-Δ^1-pyrroline and a 22% yield of 2-phenylpyrrole. 2-Phenyl-Δ^1-pyrroline is an intermediate in the reaction since it is converted by sulfur to 2-phenylpyrrole in a 39% yield with a 50% recovery of the starting material. 3-Phenylpyrrolidine behaved like pyrrolidine and gave a polymer. Similar difficulties were encountered for this compound in its catalytic dehydrogenation over platinized asbestos.[4]

1-Methyl-2-phenylpyrrolidine (IIIa) when heated with sulfur gave bis(1-methyl-5-phenyl-2-pyrrolyl) disulfide (IVa). The result was not in agreement with



IIIa, R = C_6H_5 — IVa, R = C_6H_5
b, R = 3-C_5H_4N — b, R = 3-C_5H_4N

the reported reaction of nicotine (IIIb) and suggested a reinvestigation of the latter. The heating of nicotine with sulfur in toluene actually gave the disulfide (IVb) and not the sulfide as reported.[3] Better yields of the product were obtained by heating nicotine with sulfur directly. Evidence for the structure was the nmr spectrum, molecular weight, and elemental analysis. The prior assignment of structure[3] was based solely on molecular weight.

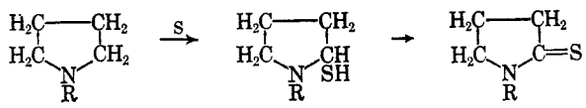
1-Methyl-3-phenylpyrrolidine when treated with sulfur behaved like 2-phenylpyrrolidine and gave 1-methyl-3-phenylpyrrole in a 17% yield.

The results obtained indicate that the thiopyrrolidones (IIa, b) and thiopiperidones (IIc, d) are formed by a mechanism similar to that proposed for the Willgerodt reaction. The latter reaction has been reported to occur in the aliphatic series with triethylamine and to form N,N-diethylthioacetamide.[5]

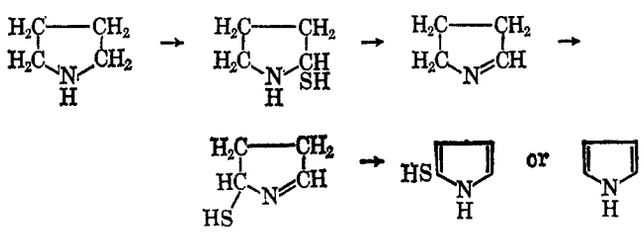
This behavior is apparently general since tributylamine gave N,N-dibutylthiobutyramide.

(1) Abstracted in part from the Ph.D. Thesis of G. R. Hansen.
(2) M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).
(3) A. A. Morton and D. Horvitz, *J. Am. Chem. Soc.*, **57**, 1860 (1935).
(4) H. P. L. Gitsels and J. P. Wibaut, *Rec. Trav. Chim.*, **59**, 1093 (1940).
(5) C. G. Moore and R. W. Saville, *J. Chem. Soc.*, 2082 (1954).

The precursor in the alicyclic series is probably the 2-mercaptopyrrolidine which is oxidized by sulfur to the 2-thiopyrrolidone. A similar mechanism has been sug-



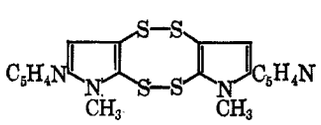
gested for the oxidation of secondary amines to thioamides.[5] Pyrrolidines with an alkyl group in the α position, *e.g.*, 1-ethyl-2-methylpyrrolidine, would lose hydrogen sulfide in the first step and form a Δ^2-pyrroline. Further reaction of this compound with sulfur could lead to a mercaptopyrrole or a pyrrole which would be polymerized by the sulfur. The absence of a substituent on the nitrogen as in pyrrolidine could cause formation of a Δ^1-pyrroline by the elimination of hy-



drogen sulfide from the 2-mercaptopyrrolidine. The resulting pyrroline would be converted further by sulfur to an easily polymerizable pyrrole. The latter sensitivity of simple pyrroles to sulfur has been verified with pyrrole and 1-methylpyrrole; both compounds were converted to polymeric materials by sulfur.

The formation of hydrogen sulfide occurs in all the reactions and introduces a complication with piperidine and 4-methylpiperidine by forming the very volatile and sensitive hydrosulfides.

Substitution of aryl groups on the pyrrolidine ring gives products which are more stable to the further action of sulfur. 3-Phenylpyrrolidine is an exception and behaves like pyrrolidine; only a polymeric material was isolated. 2-Phenylpyrrolidine gave the corresponding pyrrole. 1-Methyl-2-phenylpyrrolidine and nicotine form the 2-pyrrolyl disulfide (IV). The disulfide must be formed directly from the pyrrolidine and not from the pyrrole since nicotyrine when treated with sulfur gave 1,8-dimethyl-2,7-di(3-pyridyl)bispyrrolo[2,3-*c*; 3′,2′-*g*]-1,2,4,5-tetrathiocin (V) together with polymeric



V

material. Evidence for this structure was the nmr spectrum, molecular weight, and the formation of two polarographic reduction waves. The more symmetrical isomer (*trans*-methyls) would be expected to give only one polarographic wave. The infrared spectrum was nearly identical with that of nicotyrine.

The results obtained in this study do not eliminate the possible formation of pyrroles from pyrrolidines in petroleum since simpler reactions may occur under the dilute conditions involved.

Experimental Section[6]

General Procedure.—The pyrrolidine or piperidine (1 mole) and sulfur (2 g-atoms) were heated under nitrogen with stirring at temperatures which varied with the amine. Heating was continued until the evolution of hydrogen sulfide ceased. The resulting black mixture was distilled under reduced pressure and the volatile product was isolated and purified. The physical constants and yields are reported in Table I.

TABLE I

PRODUCTS FROM THE REACTION OF SULFUR AND N-ALKYLPYRROLIDINES AND -PIPERIDINES

Reactant	Product	Reacn time, hr	Temp, °C	Yield, %	Bp (mm), °C	$\nu_{max}^{C=S}$, cm^{-1}
Ia	IIa[a]	6.5	80	8.1	124–126 (7.3)[b]	1127[b]
Ib	IIb[c]	9	180	63	134–136 (6)	1136
Ic[d]	IIc[e]	9	140	29	126–127 (4)	1127
Id	IId	6	160	29	149–151 (5)[f]	1128

[a] The product was identical with a sample synthesized from 1-methyl-2-pyrrolidone and phosphorus pentasulfide using the general procedure of L. G. S. Brooker and D. W. Heseltine, U. S. Patent 2,882,158 (1955). Treatment of IIa with hydroxylamine followed by polyphosphoric acid gave 2-(1H)-tetrahydro-1-methylpyrimidone, mp 85–87°; J. J. Fox and D. V. Praag [*J. Am. Chem. Soc.*, **82**, 486 (1960)] gave mp 86–89°. [b] H. Eilingsfeld, M. Seefelder, and H. Weidinger [*Chem. Ber.*, **96**, 2671 (1963)] report bp 144–145° (15 mm). R. Mecke, R. Mecke, and A. Lutrringhaus [*ibid.*, **90**, 975 (1957)] report ν_{max} 1136 for C=S cm^{-1}. The nmr spectrum (CCl_4) showed a triplet at 2.88 (3-CH_2), quintet at 2.05 (4-CH_2), triplet at 3.79 (5-CH_2), and a singlet at 3.17 ppm (1-CH_3). [c] *Anal.* Calcd for $C_8H_{15}NS$: C, 61.09; H, 9.61; N, 8.91; S, 20.39. Found: C, 60.81; H, 9.42; N, 8.67; S, 20.18; $n^{20}D$ 1.5476; d^{20}_4 1.007. The nmr spectrum (CCl_4) showed a triplet at 2.90 (3-CH_2), multiplet at 2.08 (4-CH_2), triplet at 3.72 (5-CH_2 and α-CH_2), multiplet at 1.51 (β- and γ-CH_2), and triplet at 1.00 ppm (δ-CH_3). [d] Xylene was used as a solvent. [e] *Anal.* Calcd for $C_7H_{13}NS$: C, 58.68; H, 9.15; N, 9.28. Found: C, 59.01; H, 9.06; N, 10.03; $n^{18}D$ 1.5748; d^{18}_4 1.054. [f] J. Renault [*Compt. Rend.*, **232**, 77 (1951)] reports bp 152° (5 mm).

N,N-Dibutylthiobutyramide. A.—Tributylamine was heated with sulfur at 200° for 16 hr. Distillation gave a golden oil in a 30% yield, bp 108–109.5° (2.3 mm), $n^{23}D$ 1.5139, ν_{max} 1112 cm^{-1} (C=S).

B.—N,N-Dibutylbutyramide (29.9 g) and phosphorus pentasulfide (9.0 g) were refluxed in pyridine (100 ml) for 15 min. Distillation gave the thioamide (16.8 g). The nmr spectrum (liquid) gave a triplet at 2.70 ppm (S=CCH_2), triplet at 3.60 (CH_2N), triplet at 3.96 (CH_2N), multiplet at 1.61 for the remaining methylenes groups, and a triplet at 0.98 ppm (CH_3).

Anal. Calcd for $C_{12}H_{25}NS$: C, 66.91; H, 11.70; S, 14.89. Found: C, 66.06; H, 11.18; S, 15.41.

Traces of sulfur were difficult to remove from this compound and gave low carbon and hydrogen values. A similar purification problem was associated with N,N-diethylthioacetamide.[5]

Piperidine Hydrosulfide. A.—A refluxing solution of piperidine (25.6 g) in xylene (70 ml) was treated with a refluxing solution of sulfur (19.4 g) in xylene. The white, crystalline solid collected in the condenser was removed, washed with absolute ether, and stored at −20°. The solid was purified by sublimation under nitrogen, yield 11.3 g, mp 69–72° (sealed tube under nitrogen). Exposure to air caused decomposition with the evolution of hydrogen sulfide. Carbon and hydrogen values could not be obtained because of the instability of the compound. A suitable sulfur analysis was obtained by the Schoniger method.

Anal. Calcd for $C_5H_{13}NS$: S, 26.89. Found: S, 26.74.

The xylene solution gave only water-soluble polymers.

B.—Dry hydrogen sulfide gas was passed into a cold solution of piperidine in absolute ether. The white precipitate formed was filtered under dry hydrogen sulfide and purified by sublimitation, mp 68–72°.

(6) Melting points are corrected and boiling points are not. Infrared spectra were recorded on films using a Perkin-Elmer spectrophotometer. Nmr spectra were recorded on a Varian Model A-60 spectrophotometer using tetramethylsilane as an internal standard (δ = 0 ppm).

4-Methylpiperidine Hydrosulfide.—This compound was made by method A in a 70% yield and melted at 29–31°. A similar melting point was obtained using method B.

Anal. Calcd for $C_6H_{15}NS$: S, 23.89. Found: S, 24.06.

2-Phenylpyrrole. A.—2-Phenylpyrrolidine[7] (14.72 g) and sulfur (6.42 g) were heated at 120° for 5 hr and 160° for 0.5 hr. Distillation of the reaction mixture gave two fractions. The first fraction (6.24 g) boiled at 102° (6 mm), melted at 41–44°, and was identical with 2-phenyl-Δ^1-pyrroline.[8] The second fraction boiled at 140–50° (6 mm) and solidified upon standing. Recrystallization from 70% ethanol followed by sublimation gave 2-phenylpyrrole (3.14 g) melting at 128–129° (lit.[9] mp 129–130°).

B.—A mixture of 2-phenyl-Δ^1-pyrroline (45.9 g) and sulfur (11.1 g) was heated at 85° for 7 hr at which time the evolution of hydrogen sulfide had subsided. Distillation at reduced pressure gave starting material (23 g) and 2-phenylpyrrole (8.9 g). The nmr spectrum ($DCCl_3$) showed a singlet at 7.30 (NH), a multiplet at 7.16 for the phenyl hydrogens, doublets at 6.56 and 6.38 for the 5- and 3-pyrrole hydrogens, and a triplet at 6.20 ppm for the 4-pyrrole hydrogen.

Bis(1-methyl-5-phenyl-2-pyrrolyl) Disulfide (IVa).—1-Methyl-2-phenylpyrrolidine[10] (24.5 g) and sulfur (10.6 g) were heated at 125° for 11 hr. The dark, tarry product was dissolved in absolute ethanol (50 ml). Cooling gave a yellow solid melting at 147–51°. Repeated recrystallization from absolute ethanol gave 8.37 g of a yellow, crystalline solid, mp 148–150°. The nmr spectrum ($CDCl_3$) showed a singlet at 3.43 (CH_3N), doublets at 6.23 and 6.53 for 3- and 4-pyrrole hydrogens, and a multiplet at 7.22 ppm for the aromatic hydrogens.

Anal. Calcd for $C_{22}H_{20}N_2S_2$: C, 70.17; H, 5.35; N, 7.44; S, 17.03; mol wt, 376.6. Found: C, 70.47; H, 5.33; N, 7.75; S, 17.24; mol wt, 371 (vapor phase osmometer).

Bis[1-methyl-5-(3-pyridyl)-2-pyrrolyl] Disulfide (IVb).—A mixture of nicotine (25.0 g) and sulfur (9.9 g) was heated at 155° for 4 hr and 170° for 0.5 hr or until the evolution of hydrogen sulfide had ceased. The resulting dark green, viscous liquid was dissolved in absolute ethanol (2 l.) and allowed to cool. The resulting yellow solid after four recrystallizations from alcohol melted at 154–156° (lit.[3] mp 151.5–153.5°), yield 5.9 g. The nmr spectrum ($DCCl_3$) gave a singlet at 3.44 (CH_3), doublets at 6.12 and 6.56 for the 3- and 4-pyrrole hydrogens, respectively, doublet at 8.20 for the 6-pyridine hydrogen, multiplet at 8.36 for the 2-pyridine hydrogen, and a multiplet at 7.24 ppm for the 4- and 5-pyridine hydrogens.

Anal. Calcd for $C_{20}H_{18}N_4S_2$: C, 63.46; H, 4.79; N, 14.80; S, 16.94; mol wt, 378.5. Found: C, 63.69; H, 5.01; N, 14.96; S, 16.76; mol wt, 374 (vapor phase osmometer).

1-Methyl-3-phenylpyrrole.—1-Methyl-3-phenylpyrrolidine[11] (24.6 g) and sulfur (9.8 g) were heated at 105° for 16 hr. The dark tar when poured into hot absolute ethanol (600 ml) gave a dark orange polymeric solid (9.11 g). The alcoholic solution upon evaporation gave a dark oil. Distillation gave the pyrrolidine (2.49 g) and 1-methyl-3-phenylpyrrole (3.6 g), bp 140–144° (4.1 mm), mp 43.4° (from 30% ethanol). The nmr spectrum ($CDCl_3$) showed a singlet at 3.52 (NCH_3), multiplets at 6.95, 6.68, and 7.52 ppm for the 2-pyrrole hydrogen, 4- and 5-pyrrole hydrogens, and aromatic hydrogens, respectively.

Anal. Calcd for $C_{11}H_{11}N$: C, 84.03; H, 7.05; N, 8.91. Found: C, 84.18; H, 7.07; N, 9.07.

1,8-Dimethyl-2,7-di(3-pyridyl)bispyrrolo[2,3-*c*;3′,2′-*g*]-1,2,4,-5-tetrathiocin (V).—A mixture of nicotyrine (9.7 g) and sulfur (3.95 g) was heated at 140° for 4 hr, at which time evolution of hydrogen sulfide had ceased. The hot, tarry mixture was poured into 600 ml of absolute ethanol, and after cooling the liquid was decanted from the tar. This operation was repeated three times using 75% ethanol and finally gave a yellow, flocculent, hydrated solid, mp 125–128°. Recrystallization from absolute ethanol gave 1.06 g of the tetrathiocin (V) melting at 175–176°. The nmr spectrum ($CDCl_3$) gave a singlet at 3.76 (NCH_3), and 6.44 (3-pyrrole hydrogen), doublet at 7.30 for the 4-pyridine hydrogen, and multiplets at 7.66 and 8.56 ppm for the 5- and 2- and 6-pyridine hydrogens, respectively. The infrared spectrum was similar to that of nicotyrine.

Anal. Calcd for $C_{20}H_{16}N_4S_4$: C, 54.51; H, 3.67; N, 12.72; S, 29.11; mol wt, 440.6. Found: C, 54.53; H, 3.67; N, 12.54; S, 29.33; mol wt, 446 (vapor phase osmometer).

Polarographic studies were carried out in acetonitrile containing 0.2 *N* $(C_4H_9)_4NI$ with a mercury pool anode. The tetrathiocin (V) gave two waves at $E_{1/2} = -0.20$ v, $I_d = 5.23$ μa and $E_{1/2} = -0.76$ v, $I_d = 1.23$ μa. The disulfide (IVb) under the same conditions gave $E_{1/2} = -0.36$ v and $I_d = 4.74$ μa. The capillary used had a $m^{2/3}t^{1/6}$ of 1.54 $mg^{2/3}\ sec^{-1/2}$ at 42 cm.

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Sulfur-Containing Polypeptides. V. Studies on N-(2-Hydroxyarylidene) and Enamine Protective Groups[1,2]

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The synthesis of cysteine peptide derivatives using N-salicylidene and N-(1-benzoylisopropenyl) protective groups is described. The N-salicylidene group apparently can only be used with S-tritylcysteine or valine. The N-(1-benzoylisopropenyl) group is readily hydrolyzed and may be useful in specific synthetic situations.

The problem involving the choice of amino and carboxy protective groups compatible with various acid-labile sulfur protective groups for use in the synthesis of cystine peptides has been previously discussed.[1,4] In brief, the most desirable amino protective group would be one which could withstand the conditions of peptide bond formation and could later be removed under conditions mild enough to avoid hydrolysis of acid-labile esters or thioethers. Although the problem of devising such a group has not received a great deal of attention, at least two promising approaches have appeared; these include the proposed use of the N-(2-

(1) Part IV of this series, R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.*, **31**, 2178 (1966).
(2) Supported by Grant A-3416 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.
(3) Abstracted in part from a dissertation submitted by G. L. Southard to the University of North Carolina, Chapel Hill, in partial fulfillment of the requirements for the Ph.D. degree, June 1965.
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