Heteroalicyclic Analogs of 2- and 3-Aminoalkanethiols[1,2]

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Heteroalicyclic analogs of 2- and 3-aminoalkanethiols have been synthesized from the alkanols Ia–Va *via* the corresponding halogenoalkylamine hydrohalides for evaluation as antiradiation drugs. The analogs described have mercapto (or potential mercapto) groups on a side chain two or three carbon atoms removed from the secondary amino groups of pyrrolidine, piperidine, thiomorpholine, and piperazine. The bicyclic dithiocarbamates VIII and IX resulted from the reaction of carbon disulfide with 2-(chloromethyl)pyrrolidine hydrochloride (Ib) and 2-(2-chloroethyl)piperidine hydrochloride (IIIc), respectively. The synthesi of VIII elucidated the structure of the water-insoluble product formed concurrently with 2-pyrrolidinylmethyl dimethyldithiocarbamate hydrochloride (Id) from Ib and sodium dimethyldithiocarbamate.

2-Aminoethanethiol and several of its *S*-substituted derivatives,[3-5] such as *S*-2-aminoethyl thiosulfuric acid,[6] are well known radioprotectors of experimental animals, as are the corresponding *S*-3-aminopropyl derivatives.[3,7] The need for effective drugs possessing lower toxicity and longer duration of protective action has prompted the synthesis and study of structural variations of these known active compounds. In this report we describe the synthesis of analogous heteroalicyclic-substituted methane- and ethanethiols and a number of *S*-substituted derivatives of these and similar thiols, which are, in effect, *N*,2- or *N*,3-disubstituted derivatives of 2- or 3-aminoalkanethiols.

The heteroalicyclic-substituted alkanols Ia–Va in which secondary amino groups of the ring moiety are two or three carbon atoms removed from primary hydroxyl groups served as starting materials. The conversion of these amino alcohols to the corresponding halogenoalkylamine hydrohalides, which in turn were allowed to react with various thioanions, was the key step in the synthesis of the title compounds and their derivatives. The amino alcohols whose hydrohalides are soluble in chloroform (Ia, IIa, IIIa) were converted to halogenoalkyl derivatives by the conventional treatment of chloroform solutions of the appropriate preformed hydrohalides with thionyl chloride or phosphorus tribromide: thus formed were 2-(chloromethyl)-pyrrolidine hydrochloride (Ib), 2-(bromomethyl)piperidine hydrobromide (IIb), 2-(2-bromoethyl)piperidine hydrobromide (IIIb), and 2-(2-chloroethyl)piperidine hydrochloride (IIIc). The piperidine IIb was also prepared by prolonged boiling of a solution of IIa in 48% hydrobromic acid, but this method was ineffective when applied to 3-thiomorpholinemethanol (IVa) and 2-piperazinemethanol dihydrobromide (Va): Va was recovered completely unchanged after a solution of it in 48% hydrobromic acid had been heated in a sealed tube at 175° for five hours. The action of phosphorus tribromide on a suspension of IVa hydrobromide in *o*-dichlorobenzene up to 150° afforded an excellent yield of 3-(bromomethyl)thiomorpholine hydrobromide (IVb), but similar variations of common methods did not effect the conversion of the piperazine Va: (1) no conversion occurred when Va was suspended in solutions of phosphorus tribromide or thionyl bromide in indifferent solvents at temperatures up to 150°, and (2) either no conversion or the formation of resinous matter occurred when Va was treated with pure phosphorus tribromide at various temperatures. 2-(Bromomethyl)piperazine dihydrobromide (Vb) was ultimately prepared *via* 1,4-di(*p*-tolylsulfonyl)-2-piperazinemethanol (VI), the intermediate immediately preceeding Va in the synthetic scheme. Thus the action of thionyl bromide on VI in appropriate solvents provided 2-(bromomethyl)-1,4-di(*p*-tolylsulfonyl)piperazine (VII) which was readily detosylated in boiling 48% hydrobromic acid containing phenol to give Vb; in the absence of phenol VII was virtually unchanged after six hours.

Each of the halogenoalkyl-substituted compounds described above (Ib–Vb) was converted to the respective *S*-substituted thiosulfuric acids (Ic, IIc, IIIg, IVd, Vd, inner salts) by reaction with sodium thiosulfate in aqueous solution. It is interesting that the product isolated from Vb dihydrobromide was a hydrobromide [*S*-2-piperazinylmethyl thiosulfuric acid hydrobromide (Vd)] although the reaction was carried out in the presence of sodium acetate in order to avoid acidic decomposition of the sodium thiosulfate and the product.

Three of the halogenoalkyl derivatives (IIIb, IVb, and Vb) were converted to air-sensitive free thiols by the action of sodium hydrosulfide in methanol: 2-piperidineëthanethiol (IIId) was isolated as such, but the distilled 3-thiomorpholinemethanethiol and 2-piperazinemethanethiol were immediately converted to the more stable hydrobromide IVc and dihydrobromide Vc, respectively. Consideration was first given, however, to the basic hydrolysis of isothiuronium salts as a means of obtaining thiols in this series, but failure of 2-(chloromethyl)pyrrolidine hydrochloride (Ib) to give an isolable isothiuronium salt prompted the preparation of 2-pyrrolidinylmethyl dimethyldithiocarbamate hydrochloride (Id), another potential source of the thiol. The reaction of Ib with sodium dimethyldithiocarbamate in *N*,*N*-dimethylformamide gave, in addition to the expected dithiocarbamate Id, a water-insoluble product that was shown by synthesis from Ib and carbon disulfide in *N*,*N*-dimethylformamide containing potassium carbonate to be hexahydropyr-

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(2) Presented at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 26–29, 1962.

(3) D. G. Doherty and W. T. Burnett, Jr., *Proc. Soc. Exptl. Biol. Med.* **89**, 312 (1955).

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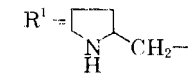
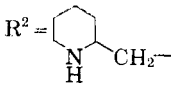
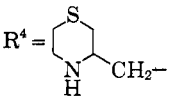
Ia. R^1OH
b. $R^1Cl \cdot HCl$
c. R^1SSO_2OH
d. $R^1S(C{=}S)N(CH_3)_2 \cdot HCl$

IIa. R^2OH
b. $R^2Br \cdot HBr$
c. R^2SSO_2OH

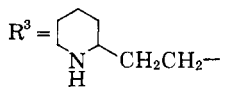
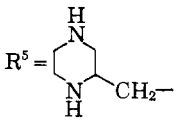



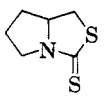
IIIa. R^3OH
b. $R^3Br \cdot HBr$
c. $R^3Cl \cdot HCl$
d. R^3SH
e. $R^3S(C{=}O)CH_3 \cdot HBr$
f. $R^3SCN \cdot HBr$
g. R^3SSO_2OH
h. $R^3SSR^3 \cdot 2HCl$
i. $R^3SC(=NH)NH_2 \cdot 2HBr$
j. $R^3SC(=S)N(CH_3)_2 \cdot HBr$
k. $R^3SC(=S)N(CH_3)_2 \cdot HCl$

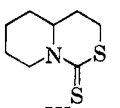
IVa. R^4OH
b. $R^4Br \cdot HBr$
c. $R^4SH \cdot HBr$
d. R^4SSO_2OH



Va. $R^5OH \cdot 2HBr$
b. $R^5Br \cdot 2HBr$
c. $R^5SH \cdot 2HBr$
d. $R^5SSO_2OH \cdot HBr$


VIII


IX

rolo[1,2-*c*]thiazole-3-thione (VIII), the lack of an NH stretching band in the infrared absorption spectrum supporting the assigned structure. The formation of VIII concurrent with Id apparently occurred after a partial acidic decomposition of the sodium dimethyldithiocarbamate had released carbon disulfide and dimethylamine. In contrast, 2-(2-bromoethyl)piperidine hydrobromide (IIIb) and the chloro hydrochloride IIIc, when allowed to react with sodium dimethyldithiocarbamate, gave only the expected dithiocarbamates IIIj and IIIk, respectively. Ring closure was achieved, however, by the reaction of IIIc with carbon disulfide in *N*,*N*-dimethylformamide in the presence of potassium carbonate, and octahydropyrido[1,2-*c*][1,3]thiazine-1-thione (IX) was isolated in high yield. This bicyclic dithiocarbamate was found to be highly resistant to acid hydrolysis; it remained virtually unchanged after four days in boiling hydrochloric acid.

The halides IIIb and IIIc were accessible in large amounts because of the commercial availability of IIIa; therefore, several model conversions of these compounds to other *S*-substituted derivatives of IIId were carried out. The preformation of potassium thioacetate from thioacetic acid and potassium bicarbonate in *N*,*N*-dimethylformamide proved convenient in the synthesis of the thioacetate IIIe. The thiocyanate IIIf and the isothiuronium salt IIIi (formed by prolonged boiling of a solution of IIIa and thiourea in 48% hydrobromic acid) interestingly showed no tendency to undergo intramolecular cyclization.[8]

(8) *Cf.* D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957); J. X. Khym, R. Shapira, and D. G. Doherty, *ibid.*, **79**, 5663 (1957); J. X. Khym, D. G. Doherty, and R. Shapira, *ibid.*, **80**, 3342 (1958); A. Schöberl, M. Kawohl, and R. Hamm, *Chem. Ber.*, **84**, 571 (1951); A. Schöberl, M. Kawohl, and G. Hansen, *Ann. Chem.*, **614**, 83 (1958).

Experimental[9]

2-(Chloromethyl)pyrrolidine Hydrochloride (Ib).—A solution of 2-pyrrolidinemethanol[10] (Ia) (9.30 g., 92.0 mmoles) in 55 ml. of chloroform was saturated with external cooling with dry hydrogen chloride. The stirred solution was chilled to 0°, and thionyl chloride (13.5 ml., 0.186 mole) was added dropwise during 30 min. with the temperature maintained 0–3°. The resulting solution was allowed to warm to room temperature during 1 hr. and was then refluxed 2 hr. Removal of the solvent and excess thionyl chloride by evaporation under reduced pressure left a black sirup. This residue was taken up in methanol, and the solution was repeatedly treated with Norit until a pale yellow filtrate was obtained. Removal of the methanol left an orange-yellow crystalline residue. Recrystallization from ethanol (Norit) gave 10.3 g. (72%) of Ib as colorless crystals, m.p. 141–142°.

Anal. Calcd. for $C_5H_{10}ClN \cdot HCl$: C, 38.48; H, 7.10; N, 8.98. Found: C, 38.76; H, 7.25; N, 8.98.

***S*-2-Pyrrolidinylmethyl Thiosulfuric Acid (Ic).**—An aqueous solution of equimolar amounts of Ib and sodium thiosulfate was boiled 1 hr., and the solution was evaporated to dryness under reduced pressure. The dry solid residue was taken up in *N*,*N*-dimethylformamide and filtered. Addition of ether to the filtrate precipitated the product. Repeated reprecipitations from *N*,*N*-dimethylformamide by addition of ether eventually gave pure Ic (m.p. 188–192° dec.) in 38% yield.

Anal. Calcd. for $C_5H_{11}NO_3S_2$: C, 30.44; H, 5.62; S, 32.51. Found: C, 30.80; H, 5.90; S, 32.43.

2-Pyrrolidinylmethyl Dimethyldithiocarbamate Hydrochloride (Id) and Hexahydropyrrolo[1,2-c]thiazole-3-thione (VIII).—Compound Ib (0.78 g., 5.0 mmoles) was gradually added during 15 min. to a cold (0–2°), stirred solution of 0.78 g. (5.1 mmoles) of sodium dimethyldithiocarbamate hemihydrate in 12 ml. of *N*,*N*-dimethylformamide.[5] The mixture was stirred in the cold 15 min. longer and finally at room temperature for 1 hr. The mixture was then poured into 40 ml. of water, and the solid precipitate that formed immediately was collected and washed with cold water. The filtrate was set aside for the isolation of Id. Recrystallization of the water-insoluble product from ethanol provided 0.33 g. of VIII as white needles, m.p. 132–133°. The aqueous *N*,*N*-dimethylformamide filtrate was evaporated to dryness under reduced pressure, and the residue was taken up in 20 ml. of hot acetonitrile. The mixture was filtered, and the filtrate was concentrated to 5 ml. Addition of ether precipitated Id which was recrystallized from acetonitrile–ethyl acetate and finally from pure acetonitrile; yield 0.18 g. (15%), m.p. 172°.

Anal. Calcd. for $C_8H_{16}N_2S_2 \cdot HCl$: C, 39.90; H, 7.12; N, 11.63; S, 26.63. Found: C, 39.88; H, 7.07; N, 11.80; S, 26.53.

Hexahydropyrrolo[1,2-*c*]thiazole-3-thione (VIII) was also prepared in the following direct manner. A stirred solution of Ib (0.78 g., 5.0 mmoles) and carbon disulfide (1.5 g., 19.7 mmoles) in 10 ml. of *N*,*N*-dimethylformamide was gradually treated at room temperature with potassium carbonate (1.50 g., 10.9 mmoles). The mixture was stirred 2.5 hr. longer at room temperature and was then poured into 30 ml. of cold water. Excess carbon disulfide was dispelled by passing nitrogen through the stirred mixture. The white precipitate was collected and recrystallized from ethanol as white needles; yield 0.70 g. (88%); melting point, mixed melting point, and infrared spectrum identical with the water-insoluble product obtained by reaction of Ib with sodium dimethyldithiocarbamate.

Anal. Calcd. for $C_6H_9NS_2$: C, 45.24; H, 5.70; N, 8.80; S, 40.26. Found: C, 45.20; H, 5.69; N, 8.79; S, 40.16.

2-(Bromomethyl)piperidine Hydrobromide (IIb).—A solution of 1.00 g. of 2-piperidinemethanol[11] (IIa) in 48% hydrobromic acid (initially 10 ml.) was boiled for about 24 hr. under a 10-cm. Metro Vigreux column equipped for distillation. A total of 8 ml. of distillate was removed in four 2-ml. portions after 2, 4, 20, and 22 hr. The residue was dissolved in 20 ml. of 10:1 acetone–ether solution, and, after the resulting solution was cooled and stirred for a few minutes, a precipitate of short white needles deposited. Recrystallization from acetonitrile gave 1.30 g. (58%) of IIb as white needles, m.p. 192–193° dec.

(9) Melting points were determined on a Kofler Heizbank (unless noted otherwise) and are corrected.

(10) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta* **31**, 1617 (1948).

Anal. Calcd. for $C_6H_{12}BrN \cdot HBr$: C, 27.82; H, 5.06; Br, 61.71. Found: C, 27.59; H, 4.94; Br, 61.80.

***S*-2-Piperidylmethyl Thiosulfuric Acid (IIc).**—A solution of 12.3 g. (47.5 mmoles) of 2-(bromomethyl)piperidine hydrobromide and 11.8 g. (47.5 mmoles) of sodium thiosulfate pentahydrate in 30 ml. of water was heated at 90–95° for 1 hr. The resulting solution was evaporated to dryness, and the white solid residue was dried *in vacuo* at 78° over phosphorus pentoxide. The dried powder was extracted in a Soxhlet apparatus with anhydrous acetonitrile (300 ml.) for 12 hr. The white solid in the cooled extract was collected, washed with ethanol, and stirred for 3–4 hr. with two 50-ml. portions of ethanol. The remaining insoluble portion amounted after being dried to 5.66 g. (56%) and was free of bromide ion. Dissolution in warm methanol followed by filtration and precipitation by addition of ether afforded 5.30 g. (53%) of white crystalline product, m.p. 205–210° dec.

Anal. Calcd. for $C_6H_{13}NO_3S_2$: C, 34.10; H, 6.20; S, 30.35. Found: C, 34.12; H, 6.20; S, 30.5.

2-(2-Bromoethyl)piperidine Hydrobromide (IIIb).—A solution of 50.0 g. (0.386 mole) of 2-piperidineëthanol[12] (IIIa) in 400 ml. of chloroform was saturated with external cooling with dry hydrogen bromide. The resulting solution was chilled to 0°, and a solution of 38.4 g. (0.142 mole) of phosphorus tribromide in 50 ml. of chloroform was added during 40 min. with the temperature maintained 0–3°. Stirring in the cold was continued 1 hr. longer. The solution was then allowed to stand at room temperature for 1 hr., and was finally boiled under reflux for 1 hr. Complete removal of the solvent left a yellow crystalline residue that was recrystallized from ethanol (Norit) to give 68.0 g. (64%) of IIIb as white needles, m.p. 166–167°.

Anal. Calcd. for $C_7H_{14}BrN \cdot HBr$: C, 30.79: H, 5.54. Found: C, 30.59; H, 5.58.

2-Piperidineëthanethiol (IIId).—A methanolic solution of sodium hydrosulfide was prepared by treating a solution of sodium methoxide (from 0.300 g.-atom of sodium in 520 ml. of methanol) with hydrogen sulfide gas at 0° until the solution was saturated. While a slow current of hydrogen sulfide was passed through the stirred solution, powdered IIIb (41.0 g., 0.150 mole) was gradually added during 1 hr. with the temperature maintained 0–5°. Stirring in the cold was continued 1 hr. longer, and the mixture was allowed to warm to room temperature. The hydrogen sulfide flow was stopped, the openings in the apparatus were closed, and the mixture was left standing overnight. The methanol was removed under reduced pressure, and the residue was stirred under nitrogen with warm (50°) acetonitrile (*ca.* 375 ml.). Fractionation of the filtered extract gave 16.1 g. (74%) of IIId as a colorless oil, b.p. 60° (1 mm.), that solidified after being stored under nitrogen in the refrigerator; m.p. 40–41° (sealed capillary).

Anal. Calcd. for $C_7H_{15}NS$: C, 57.86; H, 10.41; N, 9.64; S, 22.07. Found: C, 57.76; H, 10.42; N, 9.25; S, 22.00.

***S*-2-(2-Piperidyl)ethyl Thioacetate Hydrobromide (IIIe).**—A mixture of 4.40 g. (43.9 mmoles) of potassium bicarbonate and 3.34 g. (43.9 mmoles) of freshly distilled thioacetic acid in 100 ml. of *N*,*N*-dimethylformamide was stirred under nitrogen for 2 hr. The resulting clear yellow solution was chilled to 0°, and 12.0 g. (43.9 mmoles) of IIIb was added in portions during 15 min. Stirring in the cold was continued 15 min. longer. The solvent was then distilled at 0.5 mm. with the aid of a warm (up to 65°) water bath. The residue was taken up in 200 ml. of boiling acetonitrile. The filtered extract was concentrated by boiling at atmospheric pressure to *ca.* 75 ml. volume and refiltered while hot. The white needles that deposited from the slowly cooled filtrate were collected, washed with a little cold acetonitrile, and dried *in vacuo* at 78°; yield 9.50 g. (80%); m.p. 144°. Another recrystallization from acetonitrile did not change the melting point.

Anal. Calcd. for $C_9H_{17}NOS \cdot HBr$: C, 40.30; H, 6.76; N, 5.23; S, 11.95. Found: C, 40.58; H, 6.82; N, 5.48; S, 11.96.

2-(2-Piperidyl)ethyl Thiocyanate Hydrobromide (IIIf).—A solution of 1.00 g. (3.66 mmoles) of IIIb and 0.36 g. (3.7 mmoles) of potassium thiocyanate in 10 ml. of water was boiled for 30 min. The solution was evaporated to dryness under reduced pressure, and the residue was taken up in 20 ml. of boiling acetonitrile. The mixture was filtered, and the filtrate was evaporated to a volume of 5 ml. and refiltered while hot. The cooled filtrate deposited 0.73 g. (81%) of pure IIIf as white crystals; m.p. 177–178°; $\tilde{\nu}_{max}^{KBr}$ (cm.$^{-1}$) 2160 (—SCN),[13] very sharp.

Anal. Calcd. for $C_8H_{14}N_2S \cdot HBr$: C, 38.35; H, 6.76; N, 8.94; S, 20.47. Found: C, 38.50; H, 6.89; N, 8.99; S, 20.49.

***S*-2-(2-Piperidyl)ethyl Thiosulfuric Acid (IIIg).**—A solution of 15.0 g. (81.4 mmoles) of 2-(2-chloroethyl)piperidine hydrochloride[14] (IIIc) and 20.2 g. (81.4 mmoles) of sodium thiosulfate pentahydrate in 120 ml. of water was refluxed for 1 hr. The solution was evaporated to dryness under reduced pressure, and the residual sirup solidified when stirred with 40 ml. of boiling acetonitrile. The solid was collected and dried *in vacuo* at 78° over phosphorus pentoxide. The dried powder was extracted in a Soxhlet apparatus with anhydrous acetonitrile (500 ml.) for 24 hr. The white crystalline product filtered from the cooled extract contained a considerable amount of chloride ion as evidenced by qualitative test. The crude product was dried [yield 14.7 g. (80%)], and the extraction process was repeated in exactly the same manner as described above. The product obtained in this manner amounted, after being dried, to 12.0 g. (65%) and was nearly free of chloride ion as evidenced by a faintly positive qualitative test. A small sample was further purified for analysis by recrystallization from a large volume of acetonitrile; m.p. 195–200° dec.

Anal. Calcd. for $C_7H_{15}NO_3S_2$: C, 37.31; H, 6.71; N, 6.22; S, 28.47. Found: C, 37.58; H, 6.76; N, 6.27; S, 28.72.

2-(2-Piperidyl)ethyl Disulfide Dihydrochloride (IIIh).—A solution of 10.6 g. (57.6 mmoles) of IIIc and 14.3 g. (57.6 mmoles) of sodium thiosulfate pentahydrate in 90 ml. of water was refluxed 1 hr. The solution was cooled slightly below the boiling point, and a total of 7.30 g. (28.7 mmoles) of iodine was gradually added during 30 min. The resulting colorless solution was chilled in an ice–water bath and was made basic by the addition of cold 20% sodium hydroxide solution. The yellow oil that precipitated was extracted with benzene (3 × 100 ml.). The benzene was washed with water and dried over magnesium sulfate. The benzene was removed under reduced pressure, and the residual yellow oil was treated with methanolic hydrogen chloride until the solution was acidic. The solution was treated with Norit, and the filtrate was evaporated under reduced pressure to a pale yellow sirup. The sirup was thinned with 5 ml. of ethanol, and portions of acetonitrile were gradually added with vigorous mixing until a total of 60 ml. had been added. The white crystalline solid that formed was collected and dissolved in 25 ml. of hot ethanol. Boiling acetonitrile (75 ml.) was added, and the resulting solution gradually deposited 8.20 g. (79%) of pure IIIh as a white crystalline powder, m.p. 201–202° dec.

Anal. Calcd. for $C_{14}H_{28}N_2S_2 \cdot 2HCl$: C, 46.52; H, 8.37; N, 7.75; S, 17.75. Found: C, 46.60; H, 8.39; N, 7.48; S, 17.82.

2-[2-(2-Piperidyl)ethyl]-2-thiopseudourea Dihydrobromide (IIIi). Method A.—A solution of 25.8 g. (0.200 mole) of IIIa and 15.2 g. (0.200 mole) of thiourea in 100 ml. of 48% hydrobromic acid was refluxed for 72 hr. The solution was then chilled in an ice–salt bath. The white crystalline solid that separated was collected with the aid of cold ethanol and was washed on the funnel with cold ethanol, acetone, and ether. The dried material weighed 36.5 g., m.p. 200–202° dec. Concentration of the filtrate to *ca.* 50 ml. volume and similar workup afforded an additional 12.5 g. of material with the same melting point. The two crops were combined and dissolved in 1650 ml. of boiling ethanol. The resulting solution was distilled until 1150 ml. of ethanol had been recovered. Slow cooling of the residual solution provided 37.0 g. (53%) of IIIi as short white needles, m.p. 202–204° dec.

Anal. Calcd. for $C_8H_{17}N_3S \cdot 2HBr$: C, 27.51; H, 5.49; N, 12.04; S, 9.19. Found: C, 27.79; H, 5.64; N, 11.86; S, 9.05.

Method B.—Compound IIIb (540 mg., 1.97 mmoles) was added to a warm solution of thiourea (150 mg., 1.97 mmoles) in 5 ml. of ethanol. The resulting solution was refluxed 1 hr. and then allowed to cool. Tiny white needles separated; yield 520 mg. (75%); m.p., mixed m.p., and infrared spectrum identical with that of the product obtained by method A.

(11) F. F. Blicke and C. J. Lu, *J. Am. Chem. Soc.*, **77**, 29 (1955).

(12) Aldrich Chemical Co., Milwaukee 10, Wis.

(13) L. S. Luskin, G. E. Gantert, and W. E. Craig, *J. Am. Chem. Soc.*, **78**, 4965 (1956).

(14) E. R. Lavagnino, R. R. Chauvette, W. N. Cannon, and E. C. Kornfeld, *ibid.*, **82**, 2609 (1960); *cf.* M. S. Toy and C. C. Price, *ibid.*, **82**, 2613 (1960).

2-(2-Piperidyl)ethyl Dimethyldithiocarbamate Hydrobromide (IIIj).—Compound IIIb (2.73 g., 10.0 mmoles) was gradually added during 15 min. to a cold (0–2°) stirred solution of 1.55 g. (10.2 mmoles) of sodium dimethyldithiocarbamate hemihydrate in 25 ml. of *N,N*-dimethylformamide. The mixture was stirred in the cold 15 min. longer and finally at room temperature for 1 hr. The solvent was removed *in vacuo*, and the residual yellow sirup was taken up in 100 ml. of boiling acetonitrile. The hot solution was treated with Norit, and the filtrate was concentrated to 50-ml. volume and refiltered while hot. White needles separated from the cooled filtrate; yield 2.53 g. (81%); m.p. 177–178°. A second recrystallization from acetonitrile did not change the melting point.

Anal. Calcd. for $C_{10}H_{20}N_2S_2 \cdot HBr$: C, 38.35; H, 6.76; N, 8.94; S, 20.47. Found: C, 38.50; H, 6.89; N, 8.99; S, 20.49.

2-(2-Piperidyl)ethyl Dimethyldithiocarbamate Hydrochloride (IIIk).—2-(2-Chloroethyl)piperidine hydrochloride (IIIc) reacted with sodium dimethyldithiocarbamate in the same manner as 2-(chloromethyl)pyrrolidine hydrochloride (Ib). When the reaction mixture was poured into water a trace amount of sticky precipitate formed. The mixture was clarified by filtration, and the filtrate was evaporated to dryness under reduced pressure. The hydrochloride IIIk, m.p. 177–178°, was isolated in the same manner as IIIj.

Anal. Calcd. for $C_{10}H_{20}N_2S_2 \cdot HCl$: C, 44.67; H, 7.87. Found: C, 44.63; H, 7.80.

Octahydropyrido[1,2-*c*][1,3]thiazine-1-thione (IX).—This compound was prepared by reaction of IIIc with carbon disulfide and potassium carbonate in *N,N*-dimethylformamide using the procedure described for the preparation of VII; yield 91% (white plates from ethanol); m.p. 81–82° (capillary).

Anal. Calcd. for $C_8H_{13}NS_2$: C, 51.30; H, 7.00; N, 7.48; S, 34.24. Found: C, 51.18; H, 6.91; N, 7.25; S, 34.08.

3-Thiomorpholinemethanol (IVa).—A stirred mixture of 3.2 g. (85 mmoles) of lithium aluminum hydride in 200 ml. of ether was treated dropwise during 30 min. with a solution of 14.0 g. (80.0 mmoles) of ethyl 3-thiomorpholinecarboxylate[15] in 75 ml. of ether. After being stirred 1 hr. at room temperature, the mixture was refluxed 30 min. The mixture was then chilled in an ice–water bath, and 3.5 ml. of water was cautiously added followed by 8 ml. of 15% sodium hydroxide solution and finally 8 ml. more water. The resulting mixture was stirred at room temperature for 30 min. and was then filtered. The solid on the funnel was washed with two 250-ml. portions of ether and with two 100-ml. portions of chloroform. The original filtrate and the washings were combined and dried over magnesium sulfate. Complete removal of the solvents left an orange oil that crystallized on standing. Recrystallization from ethyl acetate afforded 5.88 g. (55%) of yellow crystals, m.p. 90–91°. (This material was sufficiently pure for the subsequent use.) Sublimation at 77° and less than 1 mm. followed by recrystallization from benzene gave the analytical sample as white needles, but the melting point was unchanged.

Anal. Calcd. for $C_5H_{11}NOS$: C, 45.08; H, 8.33; S, 24.07. Found: C, 45.27; H, 8.35; S, 24.0.

The hydrobromide was prepared in ethanol by use of anhydrous hydrogen bromide and was precipitated quantitatively as white needles, m.p. 148°, by addition of ether.

Anal. Calcd. for $C_5H_{11}NOS \cdot HBr$: C, 28.05; H, 5.93. Found: C, 27.95; H, 5.65.

3-(Bromomethyl)thiomorpholine Hydrobromide (IVb).—A mixture of 14.0 g. (65.4 mmoles) of IVa hydrobromide and 14.0 g. (51.6 mmoles) of phosphorus tribromide in 330 ml. of *o*-dichlorobenzene was stirred at room temperature for 3 hr. The mixture was then heated during 20 min. to 150° and was stirred at 145–150° for 30 min. After the mixture had cooled to room temperature, the solvent was removed by filtration or decantation. The remaining orange solid was washed with several portions of ether. Recrystallization from ethanol (Norit) provided 15.7 g. (87%) of IVb as white crystals, m.p. 156–157°.

Anal. Calcd. for $C_5H_{10}BrNS \cdot HBr$: C, 21.68; H, 4.00; N, 5.06. Found: C, 21.57; H, 4.21; N, 5.03.

3-Thiomorpholinemethanethiol Hydrobromide (IVc).—Compound IVb reacted with sodium hydrosulfide in methanolic solution as described in the preparation of IIId. The solvent was removed, and the free base was distilled directly from the sodium bromide as a colorless oil [b.p. 72–80° (0.3–0.4 mm.)] in 70% yield. This material was immediately converted to its hydrobromide by treatment with ethanolic hydrogen bromide followed by precipitation by addition of ether. The yield of white crystalline precipitate, m.p. 120–122°, corresponded to quantitative conversion of the distilled material.

Anal. Calcd. for $C_5H_{11}NS_2 \cdot HBr$: C, 26.09; H, 5.26; S, 27.86. Found: C, 26.24; H, 5.24; S, 27.9.

***S*-3-Thiomorpholinylmethyl Thiosulfuric Acid (IVd).**—An aqueous solution of 3.73 g. (13.5 mmoles) of IVb and 3.35 g. (13.5 mmoles) of sodium thiosulfate pentahydrate in 6.7 ml. of water was heated at 90–95° for 1 hr. After the solution had been chilled in an ice bath, slow crystallization commenced and was completed by allowing the mixture to stand overnight in the refrigerator at 4°. The precipitated crystals were collected, washed with a small volume of ice-cold water, and dried at 78° *in vacuo* over phosphorus pentoxide; yield 1.58 g. (52%); m.p. 230–235° dec.

Anal. Calcd. for $C_5H_{11}NO_3S_3$: C, 26.19; H, 4.84; S, 41.96. Found: C, 26.37; H, 4.87; S, 41.9.

***N,N'*-Ethylenebis-*p*-toluenesulfonamide.**—A stirred solution of 12.4 g. (0.206 mole) of ethylenediamine in 50 ml. of *N,N*-dimethylformamide was treated dropwise with mild external cooling (room temperature water bath) with a solution of 38.2 g. (0.200 mole) of *p*-toluenesulfonyl chloride in 80 ml. of *N,N*-dimethylformamide at such a rate that the reaction temperature did not exceed 40° (*ca.* 45 min.). The reaction mixture was stirred 45 min. longer at room temperature and was poured into 600 ml. of water. The precipitated product amounted to 31.7 g. (86%) of white crystalline powder (dried at 100° *in vacuo* over phosphorus pentoxide); m.p. 162–163° (lit.,[16] m.p. 162–163°).

1,4-Di(*p*-tolylsulfonyl)-2-piperazinemethanol[17] (VI).—To a stirred solution of sodium ethoxide, prepared from 21.5 g. (0.935 g.-atom) of sodium and 2 l. of absolute ethanol, 171.6 g. (0.466 mole) of *N,N'*-ethylenebis-*p*-toluenesulfonamide and 23 g. of potassium hydroxide pellets were added. The thick mixture was stirred for 30 min., and 129.0 g. (0.592 mole) of 2,3-dibromo-1-propanol was added. The resulting mixture was refluxed with stirring for 18 hr. The crude product precipitated when the hot mixture was poured into 5 l. of water. Recrystallization from ethanol gave 116.6 g. (51%) of short white needles, m.p. 173–175°. This material was sufficiently pure for the subsequent use. For analysis a sample was recrystallized from ethanol to its ultimate m.p. 177°.

Anal. Calcd. for $C_{19}H_{24}N_2O_5S_2$: C, 53.76; H, 5.70; N, 6.60. Found: C, 53.50; H, 5.39; N, 6.34.

2-(Bromomethyl)-1,4-di(*p*-tolylsulfonyl)piperazine (VII).—A stirred mixture of 206 g. (0.485 mole) of VI, 2 l. of 1,2-dibromoethane, 500 ml. of carbon tetrachloride, and 170 g. (0.816 mole) of thionyl bromide[18] was heated to boiling during 1 hr. The resulting solution was refluxed for 3 hr., cooled to room temperature, and 50 ml. of water was added dropwise. The mixture was stirred at room temperature for 30 min., treated with Norit, and heated to boiling. The hot mixture was filtered, and the solvents were removed under reduced pressure. Three recrystallizations of the initially dark orange residue from 1–1.2 l. of 2-methoxyethanol gave 107 g. (45%) of VII as short white needles (dried at 110° *in vacuo* over phosphorus pentoxide); m.p. 205–206°.

Anal. Calcd. for $C_{19}H_{23}BrN_2O_4S_2$: C, 46.81; H, 4.75; Br, 16.40; N, 5.75. Found: C, 46.66; H, 4.61; Br, 16.39; N, 5.49.

2-(Bromomethyl)piperazine Dihydrobromide (Vb).—A mixture of 50.0 g. (0.103 mole) of VII, 50 ml. of 88% phenol, and 500 ml. of 48% hydrobromic acid was refluxed with vigorous stirring for 3 hr. Most of the hydrobromic acid (*ca.* 80%) was then distilled under reduced pressure, and the residue was treated with 600 ml. of acetone. The acetone-insoluble product was filtered from the purple solution and was washed virtually white by repeated washings with acetone. The material thus obtained was stirred with 200 ml. of boiling acetone for 1 hr. The white product, dried *in vacuo* over phosphorus pentoxide at 110°, weighed 32.6 g. (93%) and melted at *ca.* 230° dec.

Anal. Calcd. for $C_5H_{11}BrN_2 \cdot 2HBr$: C, 17.62; H, 3.84; N, 8.22; Br, 70.33. Found: C, 17.68; H, 3.86; N, 8.24; Br, 70.03.

(15) B. Belleau, *J. Med. Pharm. Chem.*, **2**, 553 (1960).

(16) J. Meisenheimer, *Ann. Chem.*, **438**, 235 (1924).

(17) This compound was previously prepared as an uncharacterized intermediate in the synthesis of Va [F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Am. Chem. Soc.*, **79**, 2221 (1957)]. The free base of Va was recently described as the product of a direct cyclization [V. Prey and W. Unger, *Ann. Chem.*, **651**, 154 (1962)].

(18) K & K Laboratories, Jamacia 33, N. Y.

2-Piperazinemethanethiol Dihydrobromide (Vc).—Reaction of Vb (33.0 g., 96.7 mmoles) with sodium hydrosulfide (0.290 mole) was carried out in the manner described for the preparation of IIId. The reaction mixture was left standing at room temperature for 18 hr. and was then boiled under reflux for 1 hr. in a nitrogen atmosphere. In each subsequent operation the product was protected from air as well as conveniently possible. Removal of the methanol left a white solid residue, from which the product was extracted by two 150-ml. portions of hot acetonitrile. Removal of the acetonitrile gave a semisolid residue that distilled at 140–160° under variable vacuum from a water pump. The slightly yellow crude distillate, which crystallized rapidly, weighed 9.65 g. (75%).

The hygroscopic, air-sensitive free base was dissolved in a solution consisting of 18 ml. of 48% hydrobromic acid in 30 ml. of methanol. When the resulting warm solution was allowed to cool, a copious precipitate deposited; precipitation was completed by addition of acetone. The crude dihydrobromide thus obtained (15.4 g.) was dissolved in 30 ml. of water, the solution was treated with Norit, and the product was precipitated from the filtrate by addition of acetone. This reprecipitation process was repeated and afforded 13.1 g. (47% over-all) of white crystalline powder (dried at 80° *in vacuo* over phosphorus pentoxide); m.p. 220° dec.

Anal. Calcd. for $C_5H_{12}N_2S \cdot 2HBr$: C, 20.42; H, 4.80; N, 9.53; S, 10.90. Found: C, 20.57; H, 4.72; N, 9.29; S, 10.64.

S-2-Piperazinylmethyl Thiosulfuric Acid Hydrobromide (Vd).—A solution of 9.22 g. (27.0 mmoles) of Vb, 3.68 g. (27.0 mmoles) of sodium acetate trihydrate, and 6.70 g. (27.0 mmoles) of sodium thiosulfate pentahydrate in 13.5 ml. of water was heated at 90–95° for 2 hr. After the solution had stood at room temperature for 3 days, a slight amount of crystallization had occurred. The mixture was chilled to 0°, and 150 ml. of cold ethanol was added. The white powder that precipitated was collected and stirred overnight with 50 ml. of methanol. The methanol-insoluble solid was collected (weight 3.00 g.) and stirred 2 hr. in 25 ml. more methanol. The white powder thus obtained was dissolved in 4.0 ml. of hot water, and the solution was filtered with the aid of 2.0 ml. of hot water. The cooled filtrate deposited a small amount of white crystalline precipitate; addition of ethanol completed the precipitation. The white crystalline powder was collected and dried at 78° *in vacuo* over phosphorus pentoxide; yield 2.54 g. (32%); m.p. *ca.* 255° dec.

Anal. Calcd. for $C_5H_{12}N_2O_3S_2 \cdot HBr$: C, 20.48; H, 4.47; S, 21.87. Found: C, 20.52; H, 4.76; S, 22.0.

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Alkylidene Phthalides and Dihydrophthalides from Celery

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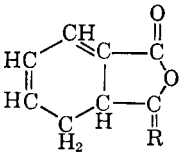
The isolation and characterization of 3-isobutylidene-3a,4-dihydrophthalide (I), 3-isovalidene-3a,4-dihydrophthalide (II), 3-isobutylidene phthalide (III), and 3-isovalidene phthalide (IV) are described. The compounds are believed to be primarily responsible for the flavor and odor of celery.

During the course of investigations on the flavor of the stem and leaf portion of the celery plant, two phthalide and two dihydrophthalide compounds were isolated with the strong characteristic odor of celery. It is proposed that these are 3-isobutylidene-3a,4-dihydrophthalide (I), 3-isovalidene-3a,4-dihydrophthalide (II) and their aromatic analogs.

Following the identification of sedanolide and sedanonic anhydride by Ciamician and Silber[2] as the principal odor constituents of the essential oil of celery seed, Berlingozzi and co-workers[3] undertook a study of the chemistry and odor characteristics of alkyl- and alkylidene phthalides. Working with $\Delta^{2,6}$-dihydrophthalides, Δ^{6}-tetrahydrophthalides,[4] and hexahydrophthalides, they found that when one of the γ-carbon hydrogens was replaced by an alkyl group, a celery odor was noted. When both were replaced by alkyl groups, the odor was less intense. They note that celery odor was most intense when the γ-carbon hydrogens were replaced by an alkylidene group. Intensity was found to increase as the number of carbons in the group was increased from 1 to 4. The last observation was repeated by Kariyone and Shimizu.[5] The presently reported compounds are naturally occurring materials with structures similar to those of Berlingozzi and co-workers.



I. R = CH·CH(CH$_3$)$_2$
II. R = CH·CH$_2$·CH·(CH$_3$)$_2$

The compounds were distilled from celery juice under vacuum and the neutral fraction of the distillate extract was chromatographed on silica gel. Final purification was effected by gas chromatography. The compounds gave positive spot tests for the ester group and for unsaturation.[6]

The molecular weight of dihydro compound (I) was found to be 190 using a Mechrolab Osmometer and confirmed by mass spectrometry.[7] The empirical formula was determined as $C_{12}H_{14}O_2$.

The compound was saponified with 10% ethanolic potassium hydroxide. The neutralized solution was partitioned between ether and aqueous sodium bicar-

(1) Specific mention of particular products or firms does not constitute endorsement by the Department of Agriculture over other products or firms of similar nature.

(2) G. Ciamician and P. Silber, as cited by E. Guenther and D. Althausen, "The Essential Oils," Vol. 2, D. Van Nostrand Co., Inc., New York, N. Y., 1949, pp. 609, 694.

(3) (a) S. Berlingozzi and F. P. Mazzo, *Gazz. chim. ital.*, **56**, 88 (1926); (b) S. Berlingozzi and L. Cione, *ibid.*, **57**, 243 (1927); (c) S. Berlingozzi, *ibid.*, 248 (1927); (d) S. Berlingozzi and G. Lupo, *ibid.*, 255 (1927); (e) S. Berlingozzi, *ibid.*, 264 (1927).

(4) According to current numbering, these would be 5,6-dihydro- and 3a,4,5,6-tetrahydrophthalides.

(5) T. Kariyone and S. Shimizu, *J. Pharm. Soc. Japan*, **73**, 336 (1953).

(6) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Company, New York, N. Y., 1956, pp. 237, 308.

(7) Petroleum Analytical Research Corporation, 8213 Gulf Freeway, Houston Tex.