The Synthesis of 4,6-Dihydrothieno[3,4-*b*]thiophene[1]

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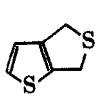
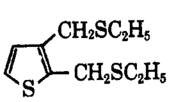
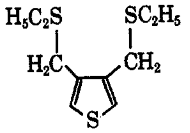
In continuation of our studies[2] of the effect of ring strain (Mills-Nixon effect[3]) on the properties of five-membered heterocyclic aromatics, we have now synthesized the title compound, I. Biochloromethylation of methyl 2-thiophenecarboxylate using chlorodimethyl ether, ring closure with sodium sulfide, followed by hydrolysis and decarboxylation gives the title compound, I. The nmr and ultraviolet spectra of I are compared with those of an appropriate open model compound.

In an earlier publication,[2] we have described the synthesis of 1H,3H-thieno[3,4-*c*]thiophene (III), and of 3,4-bis[(ethylthio)methyl]thiophene (IV). The ultraviolet and nmr spectra of III and IV appeared to indicate that the saturated five-membered ring in the thienothiophene III has perturbed the aromaticity of the thiophene ring.[2] Although the effects are not large, the perturbation caused by fusing a five-membered ring to a five-membered heterocyclic system is larger than in the case of indane derivatives.[3]


I


II

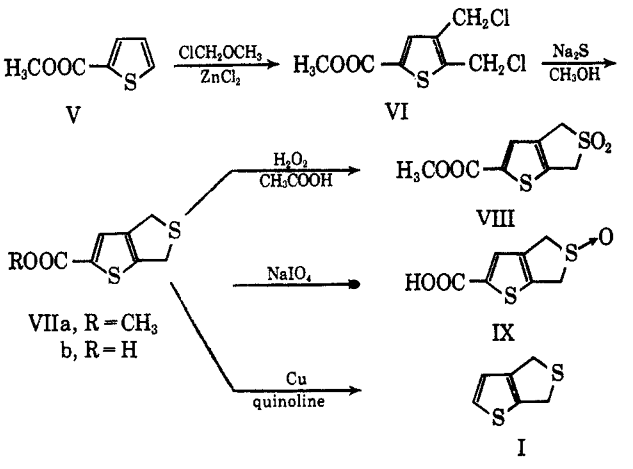

III


IV

This paper described the synthesis of a thiophene ring, with a five-membered ring in the 2,3 position, namely 4,6-dihydrothieno[3,4-*b*]thiophene (I). In order to be able to compare the spectral properties of I with those of an appropriate model compound, 2,3-bis[(ethylthio)methyl]thiophene (II) was also prepared.

The synthesis of I is outlined in Scheme I.

SCHEME I



A number of different conditions and reagents have been described for the chloromethylation of thiophenes.[4–7]

We obtained methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (VI) in 85% yield from methyl 2-thiophenecarboxylate (V), chlorodimethyl ether, and zinc chloride as a catalyst. The structure of VI, mp 72–72.5°, was supported by elementary analysis and its nmr spectrum (see the Experimental Section).

The bischloromethyl product (VI) could be cyclized to methyl 4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylate (VIIa) using a freshly prepared sodium sulfide solution in anhydrous methanol. The thienothiophene (VIIa) was a white solid, mp 94–95°, and was obtained in 66% yield. A derivative of VIIa was prepared by oxidation with hydrogen peroxide in acetic acid solution. The methyl 4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylate 5,5-dioxide (VIII), mp 149–150°, was obtained in 70% yield. After hydrolysis of the thienothiophene (VIIa) to the carboxylic acid (VIIb), the sulfoxide (IX) was prepared by the method of Leonard and Johnson,[8] using sodium metaperiodate in water. The yield of 4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylic acid 5-oxide (IX), mp 225° dec, was 74%. The differences in the nmr absorption of the methylene protons of the sulfide (VIIa), sulfoxide (IX), and sulfone (VIII) are striking.. The first shows two broad singlets, the second four clear doublets, and the third (VIII) two sharp singlets (see the Experimental Section). The two methylene positions differ from one another in all structures. Moreover in the sulfoxide (IX) the protons on each methylene carbon also become magnetically nonequivalent, since the S→O bond projects out of plane of the ring. Thus the nmr spectra of the sulfoxide and sulfone are completely in accordance with expectation. In the sulfide the two methylene absorptions are markedly broadened which we attribute to a long-range coupling between the methylene protons. Presumably a minor variation in the C–H dihedral angle causes a significant difference in this long-range coupling in the sulfide (VIIa) and the sulfone (VIII).

The carboxylic acid (VIIb) was decarboxylated, using copper powder and quinoline[2,9] to furnish 4,6-dihydrothieno[3,4-*b*]thiophene (I), in a yield of 63%, bp 70–71° (0.2 mm), mp approximately −20°.

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(1) (a) Part III in the series, "Steric Effects in Heterocyclic Systems." For part II, see H. Wynberg and A. Kraak, *J. Org. Chem.*, **29**, 2455 (1964). (b) Presented in part at the Second Organic Sulphur Symposium, Groningen, The Netherlands, May 1966.

(2) H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

(3) W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1930). For a review of the Mills-Nixon effect, see L. d'Albis, *Chim. Mod.*, **5**, 209 (1960); *Chem. Abstr.*, **55**, 17585 (1961). See also ref 6 and 7 and ref 14–29 in ref 2. Some recent literature on the Mills-Nixon effect: W. Koch and H. Zollinger, *Helv. Chim. Acta*, **48**, 1791 (1965); G. Eigenmann and H. Zollinger, *ibid.*, **48**, 1795 (1965); J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, **21**, 1665 (1965).

(4) L. Lukes, M. Janda, and K. Kefurt, *Collection Czech. Chem. Commun.*, **25**, 1058 (1960).

(5) M. Janda, *ibid.*, **26**, 1891 (1961).

(6) Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR Otdl. Khim. Nauk*, 495 (1956); *Chem. Abstr.*, **50**, 16745 (1956).

(7) S. Gronowitz, *Arkiv Kemi*, **8**, 441 (1955).

(8) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(9) I. J. Rinkes, *Rec. Trav. Chim.*, **51**, 1134 (1932).

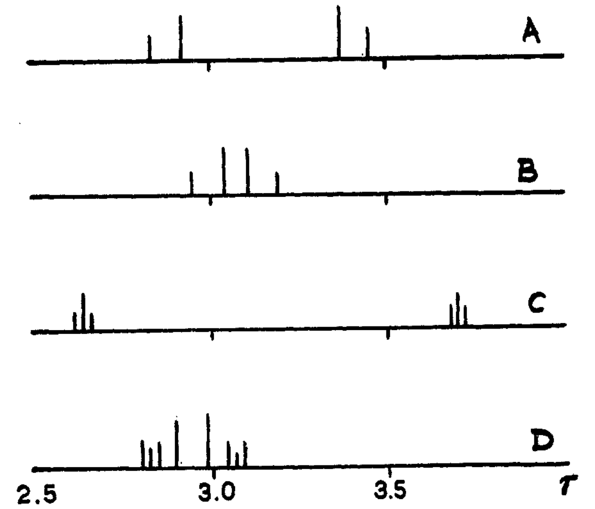


Figure 1.—Nmr spectra (aromatic protons) of A, 4,6-dihydrothieno[3,4-*b*]thiophene (I); B, 3,4-bis[(ethylthio)methyl]thiophene (IV); C, furan; D, thiophene.

The structure of I is supported by the elementary analysis, the nmr spectrum in carbon tetrachloride (two doublets at τ 2.83, 2.92, 3.36, 3.44, and a complex multiplet 5.88–6.17, area ratio 1:1:4) and the ultraviolet spectrum [$\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 233 mμ (ε 4200)].

The instability of I compared to that of III is striking. 4,6-Dihydrothieno[3,4-*b*]thiophene (I) blackens within a few hours on exposure to air, although at −20° it appeared to be stable for at least 1 month.

The spectral properties of I were compared with those of the model compound, 2,3-bis[(ethylthio)-methyl]thiophene (II). The latter was prepared from VI with ethyl mercaptan and sodium methoxide in methanol, with subsequent hydrolysis and decarboxylation.

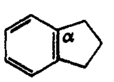
Discussion

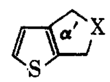
The most notable difference in physical properties of the two compounds is seen in the nmr spectrum (Figure 1) of the thienothiophene (I) and its open-chain analog (II). In the spectrum of the latter the two doublets at τ 2.95, 3.02 and 3.10, 3.18, attributable to the α and β aromatic protons, show a coupling constant of 5 cps. The coupling constant and the difference in the chemical shifts are nearly the same as that reported for the α and β protons of thiophene itself (see Figure 1).

The nmr spectrum of the thienothiophene (I, two doublets at τ 2.83, 2.92 and 3.36, 3.44, and a coupling constant of 5 cps for the aromatic α and β protons) more nearly resembles that of furan (see Figure 1) in that the absorption due to the α and β protons shows a considerably increased difference in their chemical shift. It seems reasonable to interpret this in terms of an increase in the effect of the thiophene sulfur atom on the anisotropy of the α and β protons, this in turn being caused by a diminished delocalization in this strained thiophene ring.

The ultraviolet spectra of I, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 233 mμ, (ε 4200) and of II, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 2405 mμ (ε 8300), are also consistent with the hypothesis that the five-membered ring in thienothiophene has influenced the aromaticity of the thiophene ring.

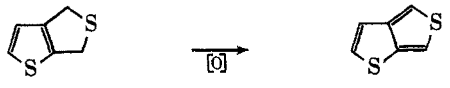
Even a cursory comparison between the hydrindan and cyclopentanothiophene, or thienothiophene (X = S) ring systems clearly reveals that a considerable angle deviation and thus ring strain may be expected. In





hydrindan the external C–C–C angle α is about 110°, a 10° deviation from the 120° C–C–C angle in *o*-xylene. In the thienothiophene angle α′ may be assumed to be 110° also. This is a 13° deviation at C-3 and a 18° deviation at C-2 from the known[10] C–C–H angles. Since the energy varies as the square of the angular deflection ($E = \Sigma\ 17.5\theta^2$, where θ is the angular deflection in degrees[11]), this increase in angular strain may amount to as much as 4–5 kcal. Although several assumptions are involved in the calculation of such strain energy (is the angle strain divided over several carbon atoms?), reasonable internal consistency is maintained when similar systems such as hydrindans, cyclopentanothiophenes and -furans are compared. Using this reasoning it is predicted that the furan analog of I will show even greater ring strain effects than have been observed in the thiophene (I).

The apparent thermal (and light) instability of I may be due to an oxidative transformation to XI. A number of pathways for this transformation might be imagined.[12]



I XI

The ring system XI, the only one of the three unsubstituted thiophthenes which is still unknown, would not be expected to be very stable, in view of the known instability of 4,6-dimethylthieno[3,4-*b*]thiophene[13] and of isothianaphthene.[14]

Experimental Section

All melting points and boiling points are uncorrected. Nmr spectra were determined in carbon tetrachloride, unless stated otherwise, on a Varian A-60, using tetramethylsilane (TMS, τ 10) as internal standard, ultraviolet spectra in 95% alcohol using a Zeiss P.M.Q. II, and infrared spectra on a Perkin-Elmer Infracord. Microanalyses were carried out in the analytical section of our department under the direction of Mr. W. M. Hazenberg.

Methyl 2,3-Bis(chloromethyl)thiophene-2-carboxylate (VI).—A solution of 60.0 g (0.423 mole) of methyl 2-thiophenecarboxylate [V, bp 89.5–90.5° (13 mm), $n^{20}\mathrm{D}$ 1.5420 [lit.[15] bp 40° (0.5 mm), $n^{20}\mathrm{D}$ 1.5420], in 50 ml of chlorodimethyl ether (Fluka T 52107, $n^{20}\mathrm{D}$ 1.397) was dropped in 15 min into a stirring suspension of 57.5 g (0.423 mole) of water-free zinc chloride in 500 ml of chlorodimethyl ether. The temperature rose during the addition to about 50°. After the addition was complete the reaction mixture was gently boiled under reflux for 6 hr. The reaction mixture went from colorless to deep red. The red solution was cooled to room temperature and then poured with

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(10) For the angles in thiophene, see B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Anderson, *J. Mol. Spectry.*, **7**, 58 (1961).

(11) F. H. Westheimer, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 533.

(12) H. Wynberg and H. van Driel, *J. Am. Chem. Soc.*, **87**, 3998 (1965).

(13) O. Dann and W. Dimmling, *Ber.*, **87**, 373 (1954).

(14) R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.*, **20**, 244 (1963).

(15) B. Weinstein, *J. Am. Chem. Soc.*, **77**, 6709 (1955).

stirring into 1000 g of crushed ice. The resulting mixture was stirred for about 1 hr. The formed yellow solid was removed by filtration, washed with cold water, and dried in a rotary vacuum evaporator at 40°, cooling the receiver in ice. The dried solid was crystallized from petroleum ether (bp 40–60°) and this furnished 86.0 g (85%) colorless needles, mp 71–71.5°. The analytical sample melted at 72–72.5° after further crystallizations from petroleum ether (bp 40–60°); ultraviolet absorption showed λ_{max} 263 mμ (ε 11,300); nmr spectrum showed four sharp singlets at τ 2.36, 5.24, 5.42 and 6.15, area ratio 1:2:2:3.

Anal. Calcd for $C_8H_8Cl_2O_2S$ (239.12): C, 40.18; H, 3.37; Cl, 29.66; S, 13.41. Found: C, 40.5, 40.4; H, 3.4, 3.4; Cl, 29.4, 29.7; S, 13.6, 13.4.

Methyl 4,6-Dihydrothieno[3,4-*b*]thiophene-2-carboxylate (VIIa).—A solution of dry sodium sulfide in methanol was prepared in the following manner. Sodium (27.6 g, 1.2 g-atoms) was dissolved in 600 ml of methanol. One-half of the solution was saturated with dry hydrogen sulfide from a cylinder (about 6 hr was required). This solution of sodium hydrogen sulfide was added to that of sodium methylate (the other half of the original solution). The resulting mixture was refluxed for 1 hr. After cooling to room temperature, the volume was brought up to 1500 ml with methanol, to dissolve all the sodium sulfide.[16] By means of titration with 1 *N* hydrochloric acid, the concentration of the remaining solution was found to be 0.397 mole/l.[17]

To 600 ml of boiling methanol was added in 5 hr, under stirring, 9.6 g (0.04 mole) of VI in 400 ml of methanol and 105 ml (brought up to 400 ml with methanol) of the sodium sulfide solution. After cooling of the reaction mixture, the precipitate was filtered off. The filtrate was concentrated to 500 ml and poured into water (800 ml). After cooling, the precipitate was collected and recrystallized from water–alcohol (1:1). The yield was 5.2 g (66%) of light yellow needles, mp 94–95.5°. An analytical sample was obtained after three recrystallizations from water, mp 94–95°; the ultraviolet spectrum showed two maxima at λ 249 mμ (ε 9100) and 290 mμ (ε 7000); nmr spectrum showed two sharp singlets at τ 2.60 and 6.17, two broad singlets at 5.89 and 5.94 (methylene protons), area ratio 1:3:2:2.

Anal. Calcd for $C_8H_8O_2$ (200.28): C, 47.97; H, 4.03; S, 32.02. Found: C, 47.9, 48.0; H, 4.1, 4.0; S, 31.5, 31.4; mol wt, 196.1, 199.1 (ethyl acetate).

The free carboxylic acid (VIIb) was obtained upon hydrolyzing the ester (VIIa) by refluxing for 4 hr with potassium hydroxide solution. The acid was obtained in 92% yield, mp 240° dec.

Methyl 4,6-Dihydrothieno[3,4-*b*]thiophene-2-carboxylate 5,5-Dioxide (VIII).—A solution of 4.72 g (0.02 mole) of VIIa and 7.2 ml of 30% hydrogen peroxide in 250 ml of acetic acid was heated at 90° for 1 hr. After cooling to 50°, the reaction mixture was concentrated *in vacuo* to 50 ml. Upon addition of water VIII was precipitated. Recrystallization of the solid (4 g, 70% yield, mp 147–149°) from petroleum ether (bp 120–160°) furnished the sulfone (VIII) as colorless needles, mp 149–150°; infrared spectrum (Nujol) showed sulfone peaks at 1328 and 1158 cm^{-1}; ultraviolet spectrum showed two maxima at λ 252.5 mμ (ε 10,300) and 277.5 mμ (ε 9300); nmr spectrum (chloroform) showed four sharp singlets at τ 2.36, 5.60, 5.71, and 6.10; area ratio 1:2:2:3.

Anal. Calcd for $C_8H_8O_4S_2$ (232.28): C, 41.37; H, 3.48; S, 27.60. Found: C, 41.4, 41.0; H, 3.5, 3.5; S, 26.8, 27.1; mol wt, 223.8, 227.7 (ethyl acetate).

4,6-Dihydrothieno[3,4-*b*]thiophene-2-carboxylic Acid 5-Oxide (IX).—To 12 ml (6 mmoles) of a 0.5 *M* solution of sodium metaperiodate at 0° was added 930 mg (5 mmoles) of 4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylic acid and 600 mg (5.6 mmoles) of sodium carbonate. The mixture was stirred at ice-bath temperature for 16 hr. The precipitated sodium iodate was removed by filtration. The filtrate was acidified with 4 *N* hydrogen chloride solution (pH 7). The precipitate was collected and dried, yielding 750 mg (74%).

Recrystallization from alcohol furnished the analytical sample, mp 225° dec; infrared spectrum (KBr) showed sulfoxide peaks at 990 and 1000 cm^{-1}; the ultraviolet spectrum showed two maxima at λ 250 mμ (ε 9400) and 280 mμ (ε 8300); nmr spectrum ($CDCOCD_3$) showed one singlet at τ 2.40, four doublets at 5.34 and 5.63, 5.53 and 5.79, 5.94 and 6.23, and 6.14 and 6.40, respectively, area ratio singlet, four doublets 1:4.

Anal. Calcd for $C_7H_6O_3S_2$ (202.25): C, 41.57; H, 2.99; S, 31.71. Found: C, 41.7, 41.6; H, 3.1, 3.1; S, 31.2, 31.5.

4,6-Dihydrothieno[3,4-*b*]thiophene (I).—A mixture of 7.44 g (0.04 mole) of the carboxylic acid (VIIb), 1.7 g of copper powder, and 50 ml of quinoline (bp 235–237°) was heated at 220°, until the carbon dioxide evolution stopped (about 15 min). The reaction mixture was cooled quickly, taken up in ether, and then filtered to remove the copper powder. The ether solution was extracted several times with excess hydrochloric acid to remove the quinoline. After extraction of the ether solution with sodium bicarbonate solution, the ether solution was dried over magnesium sulfate. The ether was removed under diminished pressure and the residue (still containing quinoline) was passed over an acid alumina column (petroleum ether, bp 40–60°, and benzene as solvents).

The solvents were removed *in vacuo* and distillation of the residue furnished 3.51 g (62%) of I, bp 78–79° (1.2 mm), $n^{20}D$ 1.6370. The analytical sample was recrystallized from petroleum ether (bp 40–60°) at low temperature (−70°), under a nitrogen atmosphere (melting point of I was approximately −20°); ultraviolet spectrum showed one maximum at λ 233 mμ (ε 4200); nmr spectrum showed two doublets at τ 2.83, 2.92, 3.36 and 3.44, and a complex multiplet τ 5.88–6.17, area ratio 1:1:4.

Anal. Calcd for $C_6H_6S_2$ (142.24): C, 50.66; H, 4.26; S, 45.08. Found: C, 50.6, 50.5; H, 4.3, 4.3; S, 45.1, 44.9.

Methyl 2,3-Bis[(ethylthio)methyl]thiophene-5-carboxylate (Xa).—The sodium salt of ethylmercaptan was prepared by adding under ice cooling, 4.65 g (0.075 mole) of ethylmercaptan (bp 36–37°) to a solution containing 1.7 g (0.075 g-atom) of sodium in 75 ml of absolute methanol. A solution of 7.2 g (0.03 mole) of methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (VI) in 100 ml of dry benzene was added in the cold. After the addition was complete (70 min), the solution was heated under reflux for 1.5 hr. The methanol and benzene were evaporated and the residue was taken up in ether and in water. The *ether solution* was dried over magnesium sulfate and furnished after distillation 5.2 g (60%) of methyl 2,3-bis[(ethylthio)methyl]thiophene-5-carboxylate (Xa), bp 139–146° (0.1 mm), $n^{20}D$ 1.5830. The analytical sample was redistilled, bp 182–184° (0.9 mm), $n^{20}D$ 1.5830; ultraviolet spectrum showed two maxima at λ 257 mμ (ε 7400) and 289 mμ (ε 9000); nmr spectrum showed one singlet at τ 2.44, two singlets at 6.13, 6.33, one singlet at 6.19, two quadruplets partial falling over each other at 7.28, 7.39, 7.49, 7.53, 7.56, 7.62, 7.64, 7.73, and one triplet at 8.64, 8.76, 8.88, area ratio 1:2:2:3:4:6.

Anal. Calcd for $C_{12}H_{18}O_2S_3$ (290.46): C, 49.62; H, 6.25; S, 33.11. Found: C, 49.7, 49.5; H, 6.3, 6.3; S, 33.2, 33.1.

The *water solution* was acidified with hydrochloric acid. The solid (2 g, 23%) was collected. The infrared spectrum of this compound (Xb) was identical with that obtained after hydrolysis of the methyl ester (Xa).

2,3-Bis[(ethylthio)methyl]thiophene (II).—A mixture of 6 g (0.022 mole) of the carboxylic acid (Xb), 1.4 g of copper powder, and 45 ml of quinoline (bp 235–237°) was heated at 220°, until the carbon dioxide evolution stopped. Removal of the quinoline with hydrochloric acid and distillation furnished 3.8 g (72%) of II, bp 182–184° (13 mm), $n^{20}D$ 1.5840. For an analytical sample the liquid was redistilled, bp 143–144° (3 mm), $n^{20}D$ 1.5848; ultraviolet spectrum showed one maximum at λ 240.5 mμ (ε 8300); nmr spectrum showed two singlets at τ 6.15, 6.34, two doublets at 2.95, 3.02, 3.10, 3.18, one triplet at 8.67, 8.79, 8.92, and two quadruplets at 7.33, 7.46, 7.54, 7.60, 7.62, 7.67, 7.69, 7.78, area ratio 2:2:1:1:6:4.

Anal. Calcd for $C_{10}H_{16}S_3$ (232.43): C, 51.67; H, 6.95; S, 41.38. Found: C, 51.9, 51.4; H, 6.9, 7.1; S, 41.4, 41.3.

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(16) This preparation is similar to the preparation of sodium sulfide in ethanol from R. W. Bost and M. W. Conn, *Org. Syn.*, **15**, 72 (1935). The solution could be held in the dark at −20°.

(17) The titration of the sodium sulfide solution was similar to that of sodium carbonate: F. P. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1945, pp 498, 499. The equivalence points of sodium hydrogen sulfide and hydrogen sulfide are 9.52 and 4.02, respectively (phenolphthalein and methyl orange or congo red were used as indicators). It was necessary to add some sodium methylate, in order to get a solution of sodium sulfide not containing sodium hydrogen sulfide.