The entropy of fusion[1] for the molecules CF_4, CCl_4, CH_4, CBr_4, $C(CH_3)_4$, $C(CH_3)_3Cl$, $C(CH_3)_2Cl$ and $C(CH_3)Cl_3$, all of which rotate in the solid phase, is essentially constant with a value of 2.6 ± 0.4 e.u.[2] The entropy of transition for the molecules CF_4, CCl_4, CBr_4 and $C(CH_3)_4$, all of which have a symmetry number of 12, is essentially constant with a value of 4.6 ± 0.1 e.u. Thus it appears that the rotational contribution to the entropy change $\Delta S_t + \Delta S_f$ is constant for substituted methanes with equal symmetry numbers.

One obtains the following expressions by assuming the effect of the symmetry number can be calculated in a manner analogous to the symmetry number contribution to the rotational entropy of a gas:

$$\Delta S_{\sigma_1-\sigma_{12}} = -2.303R(\log 3 - \log 12) = 2.76 \text{ e.u.}$$
$$\Delta S_{\sigma_2-\sigma_3} = -2.303R(\log 2 - \log 3) = 0.81 \text{ e.u.}$$

Consequently, a substituted methane with a symmetry number of 3 should have a transitional entropy change of 7.4 e.u. if it is freely rotating, or a fusional entropy change of 10.0 e.u. if it does not rotate in the solid phase. The molecule $C(CH_3)Cl_3$, known to rotate in the solid phase, has a ΔS_t of 7.97 e.u. The molecules $CFCl_3$, CH_3Cl, $CHCl_3$, $CHBr_3$ and CHI_3 have an average ΔS_f of 9.7 ± 0.5 e.u. Thus it would not be expected that these molecules rotate in the solid phase. This is substantiated by the lack of any observed rotational transition points for these molecules, and the low dielectric constant values for solid CH_3Cl and $CHCl_3$, which indicate no molecular rotation, at least around any axis perpendicular to a carbon–halogen axis.[3] The molecule CH_3Br has a ΔS_t of 0.650 e.u. and a ΔS_f of 7.96 e.u. The observed transition point probably is not a rotational effect.

A substituted methane molecule with a symmetry number of 2 should have a transitional entropy change of 8.3 e.u. if it is freely rotating in the solid phase, or a fusional entropy change of 10.8 e.u. if it does not rotate in the solid phase. The molecule CH_2I_2 has a ΔS_t of 0.5 e.u. and a ΔS_f of 10.3 e.u. Again, the small entropy of transition probably is not a rotational effect. No transitions have been observed for the molecules CH_2Cl_2, CH_2Br_2 or CF_2Cl_2. In addition, the low dielectric constant value for solid CH_2Cl_2 again indicates no molecular rotation around any axis perpendicular to a carbon–halogen axis. However, the entropies of fusion are CH_2Cl_2 6 e.u., CH_2Br_2 4 e.u. and CF_2Cl_2 8.4 e.u. These values are too high to indicate complete rotation in the solid phase and too low to indicate no rotation in the solid phase. Admittedly, the data for CH_2Cl_2 and CH_2Br_2 are the most uncertain herein, but they would have to be considerably in error to fit the correlation either way. Then too, the value of 8.4 e.u. for the fusion of CF_2Cl_2 is more firmly experimentally established. Hence it would appear that these molecules possess a certain amount of rotation in the solid and have transition points with fairly large transitional entropy changes or the entropy of fusion data for these compounds are seriously in error.

This correlation for the type of series considered seems to fit the available data reasonably well and allows prediction of transitional entropy changes or fusional entropy changes, provided one or the other is known. The accuracy is generally better than one entropy unit. The correlation also provides information concerning the rotation of molecules in the solid phase.

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(1) All the data used herein were taken from *Selected Values of Chemical Thermodynamic Properties*, Circular of the National Bureau of Standards 500, Washington, D. C., 1950, except the data for $C(CH_3)_4$, $C(CH_3)_3Cl$, and $C(CH_3)_2Cl_2$, which were taken from A. Turkevich, and C. P. Smyth, THIS JOURNAL, **62**, 2468 (1940).

(2) All uncertainties used herein are average deviations.

(3) C. P. Smyth, *Chem. Revs.*, **19**, 329 (1936).

The Preparation and Properties of a Few ω-(N,N-Dialkylamino)-alkyl-2-thienyl Sulfide Hydrochlorides and 2-Thiophenethiol

BY WM. H. HOUFF AND ROBERT D. SCHUETZ

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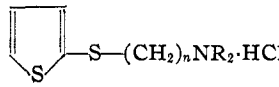
A recent report[1] indicated the possibility that there are differences between the physiological properties of 2- and 3-substituted thiophene isomers. The already known pronounced local anesthetic activity of a series of ω-(N,N-dialkylamino)-alkyl-3-thienyl sulfide hydrochlorides[2] prompted an investigation of their corresponding 2-thienyl analogs. The latter substances can be represented by the general formula



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These compounds were synthesized by the same general sequence of reactions as is described for the preparation of the 3-substituted isomers.[2] The reaction can be summarized as

$$R_2NH + Cl(CH_2)_nOH \xrightarrow[EtOH]{NaI} R_2N(CH_2)_nOH \quad \text{II}$$

$$\xrightarrow[CHCl_3]{SOCl_2} R_2N(CH_2)_nCl\cdot HCl \quad \text{III}$$

$$\xrightarrow[2.\ HCl]{1.\ C_4H_3SSH + NaOH} \text{(I)}$$

A secondary amine was allowed to react with the appropriate polymethylene chlorohydrin in ethanolic sodium iodide solution and the resulting ω-hydroxy alkyl amine (II) was converted to the corresponding chloro compound III by interaction with thionyl chloride in dry chloroform. The latter material was added to a refluxing solution of 2-thiophenethiol in aqueous sodium hydroxide and the oily ω-(N,N-dialkylamino)-alkyl-2-thienyl sulfide was converted to its hydrochloride salt I and characterized as such. A few properties of two tertiary amine derivatives of mixed thienyl alkyl sulfides not previously reported are listed in Table I.

Two new synthetic routes were investigated for the preparation of 2-thiophenethiol. One of these involved the interaction of sulfur and 2-thienylmagnesium bromide, and was similar to that used by

(1) E. Campaigne, Abstracts of Papers, Division of Medicinal Chemistry, American Chemical Society, Los Angeles, California, March 15, 1953, p. 7 L.

(2) W. H. Houff and R. D. Schuetz, THIS JOURNAL, **75**, 2072 (1953).

TABLE I

ω-(N,N-DIALKYLAMINO)-ALKYL-2-THIENYL SULFIDE HYDROCHLORIDES

$C_4H_3S—S(CH_2)_nN(R)(R)\cdot HCl$

2-Thienyl sulfide hydrochloride		β-Piperidinoethyl	γ-Morpholinopropyl
Formula		$C_{11}H_{18}ClNS_2$	$C_{11}H_{18}OClNS_2$
M.p., °C.		145–145.5	141.5–142
Yield, %		83	92
Nitrogen, %	Calcd.	5.00	5.31
	Found	4.95	5.23

Hurd and Kreuz[3] to prepare the corresponding hydroxy compound. The second method was carried out starting with the preparation of 2-thienylsulfonyl chloride and the reduction of this compound with zinc dust and sulfuric acid. The latter procedure was a combination of the method of Steinkopf and Hopner[4] for the preparation of 2-thiophenesulfonyl chloride and an adaptation of the reduction of benzenesulfonyl chloride described by Gilman.[5] By the first method, a yield of 67% was obtained while the second procedure afforded a 59% yield. Biedermann[6] prepared 2-thiophenethiol in a poor yield by a zinc dust reduction of 2-thiophenesulfonic acid.

Pharmacological Results.—The two ω-(N,N-dialkylamino)-alkyl-2-thienyl sulfide hydrochlorides were found to have very little local anesthetic activity in the guinea pig wheal test. This result is in sharp contrast to that of the 3-thienyl isomers which were equal or superior to procaine in activity.

Experimental

2-Thiophenethiol. Method A.—To 1500 ml. of dry ether in a three-necked flask fitted with a reflux condenser, stirrer and dropping funnel was added 31 g. (1.28 moles) of magnesium turnings. In the dropping funnel was placed 164 g. (1.0 mole) of 2-thienyl bromide and a small amount was allowed to enter the reaction flask. A crystal of iodine was added and the reaction proceeded vigorously. The remainder of the 2-thienyl bromide was added dropwise with stirring over a period of 1.5 hours. When the exothermic reaction had subsided the mixture was heated at reflux temperature for an additional half-hour to complete the reaction. The contents of the flask were then treated with 31.6 g. (0.99 mole) of powdered sulfur which was added at a rate sufficient to maintain gentle refluxing of the mixture. At the completion of the addition of sulfur, the reaction mixture was refluxed for an hour. The solution was cooled and 400 ml. of 6 *N* hydrochloric acid was added slowly with rapid stirring. The two layers were separated and the ether layer after filtering was extracted twice with 300 ml. of 10% potassium hydroxide solution. The combined basic extracts were made acidic causing the oily mercaptan to separate. This was taken up in ether and dried over anhydrous sodium sulfate. After removal of the ether, 78 g. (67%) of a crude yellow product remained which was distilled at reduced pressure; b.p. 54° (5 mm.). Since 2-thiophenethiol is easily oxidized by air to the disulfide, the product was stored under nitrogen in a brown bottle.

Method B.—A beaker containing 150 g. (1.29 moles) of chlorosulfonic acid was cooled to −15°. To this with rapid stirring was added 37 g. (0.44 mole) of thiophene over a period of 20 minutes. The contents of the beaker were immediately poured into a three-necked flask, fitted with an efficient stirrer and reflux condenser, containing 750 g. of crushed ice and 240 g. of concentrated sulfuric acid. The temperature of the mixture was kept at −5°, by means of an ice–salt-bath and 120 g. (1.65 moles) of zinc dust was added in portions with vigorous stirring, without allowing the temperature to rise above 0°. After being held at this temperature for an additional hour, the mixture was allowed to warm to room temperature with continuous stirring. A rather vigorous reaction took place and it was necessary to immerse the reaction vessel momentarily in a cold water-bath.

When the initial reaction had subsided, the mixture was heated for 4 hours at reflux temperature, the stirring being continued. The 2-thiophenethiol was steam distilled from the reaction mixture, taken up in ether and dried over anhydrous sodium sulfate. After removal of the ether, the product was distilled at reduced pressure. The yield of clear colorless product boiling at 50–51° (4 mm.) was 30.1 g. (59%).

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Vitamin B_{12}. XXII. Relation of α-Ribazole Phosphate to Vitamin B_{12}

BY EDWARD A. KACZKA AND KARL FOLKERS

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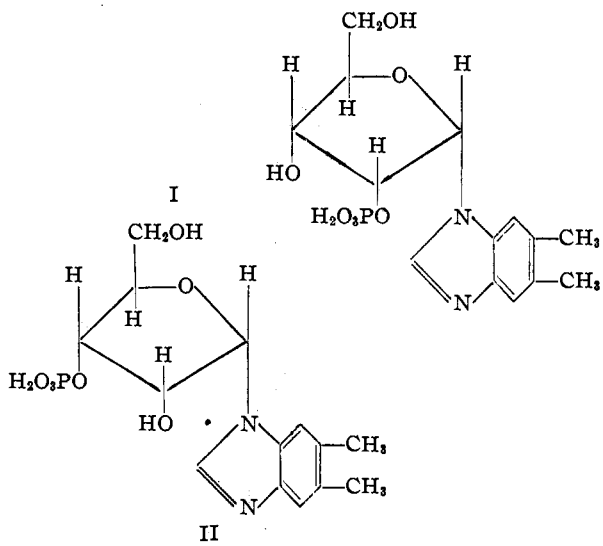
The crystalline α-ribazole phosphate (2′- or 3′-phosphate) obtained by degradation appears to exist as a moiety (a cyclic phosphoryl group not excluded) in the vitamin B_{12} molecule and may be α-ribazole-3′-phosphate (II).

We recently reported[1] the isolation of a crystalline phosphate of α-ribazole (1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole) as a degradation product of vitamin B_{12}. This crystalline phosphate was also obtained synthetically. The phosphate is ether α-ribazole-2′-phosphate (I) or α-ribazole-3′-phosphate (II).



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