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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(3) C. D. Hurd and K. L. Kreuz, THIS JOURNAL, **72**, 5543 (1950).
(4) W. Steinkopf and T. Hopner, *Ann.*, **501**, 174 (1933).
(5) H. Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 504.
(6) A. Biedermann, *Ber.*, **19**, 1615 (1886).

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

BY EDWARD A. KACZKA AND KARL FOLKERS

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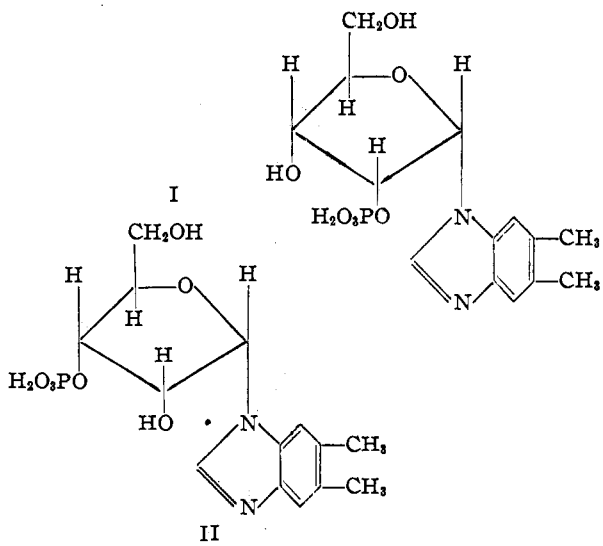
The crystalline α-ribazole phosphate (2′- or 3′-phosphate) obtained by degradation appears to exist as a moiety (a cyclic phosphoryl group not excluded) in the vitamin B_{12} molecule and may be α-ribazole-3′-phosphate (II).

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).



(1) E. A. Kaczka, D. Heyl, W. H. Jones and K. Folkers, THIS JOURNAL, **74**, 5549 (1952).

Evidence has now been obtained which indicates that the isomeric phosphate which was obtained is that isomer which occurs as a moiety in the vitamin B_{12} molecule.

The ease of phosphoryl migration in the purine and pyrimidine nucleotides brought about by acids has been observed.[2] The conditions of acid hydrolysis, which were applied to vitamin B_{12} for its degradation to α-ribazole phosphate, might have given a mixture of the 2′- and 3′-phosphates, but only one isomer was isolated by the purification procedures used.

A study of the reaction of vitamin B_{12} with 6 *N* hydrochloric acid at 25°, with time as a variable, was made. The formation and isomerization of α-ribazole phosphate was determined by paper chromatography.

The results of these experiments show that, after a reaction time of 5–16 hours, only one isomer of α-ribazole phosphate was detectable in the reaction mixture; this phosphate and the isolated crystalline phosphate are identical. Furthermore, it was shown that, when the residue from one of the above reactions which contained only one isomer of α-ribazole phosphate was refluxed with 80% acetic acid, an equilibrium mixture of approximately equal parts of the two isomers was obtained. This mixture when chromatographed on paper strips gave two fluorescent spots with R_f values of 0.73 and 0.78 which corresponded to the R_f values for the isomers obtained from the isomerization[1] of the crystalline phosphate.

If the isolated phosphate does not exist as a moiety in the vitamin B_{12} molecule and is the result of a structural rearrangement of the phosphoryl group, then the rearrangement must have been essentially quantitative and not detectable by the methods used. If the isolated phosphate is the result of a partial hydrolysis of a 2′-3′-cyclic phosphate, then the hydrolysis must likewise have been essentially quantitative and unidirectional and undetected. The adenylic acids *a* and *b* have been identified[3] as the adenosine-2′- and 3′-phosphates and have R_f values of 0.74 and 0.67, respectively, in the system described below. The R_f values (0.78, 0.73) of the two α-ribazole phosphates have a magnitude and differential which are comparable with the R_f values of adenosine-2′- and 3′-phosphates. Adenosine-3′-phosphate has the lower R_f value; it is noted that the crystalline α-ribazole phosphate which appears to exist as a moiety in vitamin B_{12} has the lower R_f value and by analogy would be α-ribazole-3′-phosphate (II); this deduction is only tentative.

Experimental

Two and one-half mg. of cyanocobalamin was dissolved in *ca.* 2 ml. of 6 *N* hydrochloric acid, and after *ca.* 16 hours at 25°, the solution was evaporated *in vacuo* to dryness. Paper strip chromatography of this residue and the crystalline phosphate, using the system[4] 5% aqueous disodium hydrogen phosphate–isoamyl alcohol, gave one fluorescent spot for each, with identical R_f values of 0.73. One-half of the above acid hydrolysis residue and *ca.* 0.5 mg. of the crystalline phosphate were each dissolved in *ca.* 5 ml. of 80% acetic acid, and the two solutions were heated at reflux for 15 minutes. The solutions were evaporated to dryness *in vacuo* and chromatographed as described.[1] In each case, two fluorescent spots of similar visual intensities were obtained with identical R_f values of 0.73 and 0.78.

The fluorescent spots were detected under a mineralite lamp after the dried paper chromatograms were sprayed with a 2% acetic acid solution. The spots were of greater intensity when the paper was still wet with the acetic acid solution.

There were slight variations in the R_f values with different ascending chromatograms which appeared to be due mainly to the relative distance between the position of the applied spots on the paper strip and the surface of the mixed solvent system.

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(2) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 52 (1952).

(3) J. X. Khym, D. G. Doherty, E. Volkin and W. E. Cohn, THIS JOURNAL, **75**, 1262 (1953).

(4) C. E. Carter, *ibid.*, **72**, 1466 (1950).

The Addition of Dithiols to Dibenzalketones[1]

BY C. S. MARVEL AND HERMAN WEXLER

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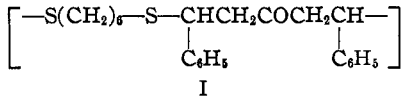
Recently it was reported[2] that a polymer could be obtained by the base-catalyzed addition of hexamethylenedithiol to dibenzalacetone in an emulsion system. We have now studied this polymer-forming reaction further to determine its limitations and possible usefulness.

The addition of hexamethylenedithiol to dibenzalacetone takes place readily in benzene solution at 30° with piperidine as the catalyst. Emulsion systems do not seem as successful as solution systems perhaps due to some addition of water to stop the growth of the polymer. Free radical initiators which are effective for the addition of dithiols to non-conjugated diolefinic hydrocarbons do not function with these conjugated systems. The highest molecular weight polymers as judged by inherent viscosity were obtained in 18 hours at 50° or 36 hours at 30°. After longer periods there was degradation in molecular weight. Exact balance of reacting monomers is very essential to the success of the reaction.

The addition polymer apparently has the expected structure I since the elementary analysis



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agrees with this composition and the infrared spectrum shows strong carbonyl bands at 1715–1722 cm.$^{-1}$ and 1722–1729 cm.$^{-1}$ and strong bands for the grouping $-CH_2CO-$ at 1410 cm.$^{-1}$.[3] It is believed that the end groups are neither mercaptan nor olefin double bond. No infrared bands for the conjugated carbon–carbon double bond could be found. No evidence for mercaptan end groups could be obtained either in the spectrum or by oxidation experiments. It seems probable that some side reaction involves addition

(1) The work discussed herein was performed as a part of the research project sponsored by the Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the Government Synthetic Rubber Program.

(2) C. S. Marvel and A. H. Markhart, Jr., *J. Polymer Sci.*, **6**, 711 (1951).

(3) We are indebted to the Anderson Physical Laboratories, Champaign, Ill., for these infrared data.