form at the steam bath and the residue distilled under reduced pressure (approx. 1 mm.). Crude product (91 g., 86.5%) was collected at 160–165°. On redistillation at 0.7 mm., this product was still yellowish in color and had a b.p. of 137–145°. This distillate was crystallized from 2.5 l. of isopropyl ether to give 80 g. (77%) of white needles, m.p. 82–83°.

*Anal.* Calcd. for $C_{10}H_{20}O_2N_2$: C, 60.00; H, 10.00; N, 14.00. Found: C, 60.11, 60.34; H, 10.16, 10.06; N, 14.02, 14.06.

**Acknowledgment.**—The authors express their appreciation to M. E. Gibson and C. W. Patterson for radioassays.

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# A Direct Synthesis of Sulfonium Perchlorates

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*Received August 11, 1962*

A few examples of the synthesis of trialkylsulfonium salts by direct alkylation of organic sulfides with perchloric acid–alcohol mixtures have appeared in the literature.[1,2] Recently the utility of this reaction has been demonstrated in the synthesis of 5-dimethylsulfonium-2-pentanone perchlorate from 5-methylmercapto-2-pentanone and perchloric acid in methanol.[3] The renewed interest in such reactions reported by Overberger, *et al.*,[4] prompt us to report our findings.

When equimolar quantities of dibenzyl sulfide and 70% aqueous perchloric acid were heated in benzyl alcohol solution for 2.5 hours at 65–70°, dilution with ether afforded an excellent yield of tribenzylsulfonium perchlorate. This reaction was extended to a number of aliphatic alcohol-sulfide systems, and gave surprisingly good yields of pure sulfonium salts if the time, temperature, and most important, the water content of the system were properly adjusted. The products were obtained as colorless crystals of high purity, and were dried for elemental analysis without recrystallization. The properties of the salts are recorded in Table I.

TABLE I

SULFONIUM PERCHLORATES—$R_3S^{(+)}ClO_4^{(-)}$

| | | Carbon, % | | Hydrogen, % | |
|---|---|---|---|---|---|
| R | M.p. | Calcd. | Found | Calcd. | Found |
| Benzyl | 171.5–174°[a] | 62.29 | 62.58 | 5.23 | 5.27 |
| *n*-Butyl | 94–95°[b] | 47.25 | 47.37 | 8.99 | 8.99 |
| *n*-Propyl | 155–157° | 41.35 | 42.00 | 8.12 | 8.14 |
| Ethyl | 111.5–112.5° | 32.95 | 32.74 | 6.91 | 6.73 |

[a] Reported 178°; J. de Pascual Teresa, *Anales real soc. españ. fis. quim.*, **45B**, 235 (1949). [b] reported 94°; ref. 5.

## Discussion and Results

The initial attempts to prepare *n*-alkylsulfonium salts under the conditions used for the benzyl compound afforded only low yields. Even after heating the mixtures under reflux for 24 hours, the yields ranged from less than 1% (ethyl) through 24% (*n*-propyl) to 46% (*n*-butyl). A remarkable improvement was achieved when water was removed from the mixture by azeotropic distillation. Under these conditions tri-*n*-butylsulfonium perchlorate was obtained in a yield of 84%. The limited yield in the presence of water was in fact due to an equilibrium phenomenon. This was confirmed when the yields after 24 hours (46%) and 48 hours (45%) were shown to be the same. The equilibrium involved was not, however, reaction 1, since 92% of tri-*n*-butylsulfonium perchlorate was recovered unchanged after 24 hours of heating in butanol containing the same amount of water as was present under the conditions of synthesis.

$$Bu_3S^{(+)}ClO_4^{(-)} + H_2O \rightleftharpoons Bu_2S + BuOH_2^{(+)} + ClO_4^{(-)} \tag{1}$$

It was determined that one source of the variation in yields from the three aliphatic sulfides was the difference in boiling points of the alcohols used as solvents. A reaction carried out in a sealed vessel at 120° afforded 16% triethylsulfonium perchlorate without removal of water.

It is of interest to note the apparent total absence of carbon-skeleton rearrangement in the sulfonium salts. The tri-*n*-butylsulfonium perchlorate had a melting point identical with the previously reported value,[5] and the infrared spectra of all the compounds indicated them to be free of chain branching.

Several experiments were carried out without success in attempts to detect perchlorate ester formation by chemical means. A mixture of butanol and perchloric acid refluxed for 24 hours in the absence of dibutyl sulfide and titrated with potassium butoxide retained all of the original acid concentration. When water was azeotropically removed from such a mixture, only dark polymer was obtained. Another possible alkylating species is of course the alkyloxonium on $ROH_2^{(+)}$.[4]

If our conception of the reaction path is correct, it should be possible to accomplish direct synthesis of unsymmetrical sulfonium salts without the troublesome "alkyl scrambling" which frequently occurs in the synthesis of sulfonium salts from sulfides and alkyl halides.[6] Only the alkyl group corresponding to the alcohol should be introduced, and the non-nucleophilic nature of perchlorate ion as compared to halide ion should make the process irreversible. This possibility has been demonstrated in one case, the benzylation of dibutyl sulfide, which affords benzyldi-(*n*-butyl)-sulfonium perchlorate as a single product in 83.5% yield.

### Experimental

Dialkyl sulfides were Eastman Kodak White Label materials. Perchloric acid was Baker Analyzed reagent grade. Melting points are uncorrected and were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were by Dr. S. M. Nagy of the Microchemical Laboratory, Massachusetts Institute of Technology. Infrared spectra were obtained in potassium bromide pellets on a Perkin–Elmer Model 21 spectrophotometer by Mr. Walter Legsdin and his associates of these laboratories.

**Tribenzylsulfonium Perchlorate.**—A solution of dibenzyl sulfide (0.77 g., 3.59 mmoles) in 5 ml. of benzyl alcohol was mixed with 0.512 g. (3.59 mmoles) of 70% perchloric acid. The resulting

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(1) (a) O. Hinsberg, *Ber.*, **62**, 2167 (1929); (b) O. Hinsberg, *ibid.*, **69**, 492 (1936).

(2) J. de Pascual Teresa and H. Sanchez Bellido, *Anales real soc. españ. fis. quim.*, **50B**, 71 (1954).

(3) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960).

(4) C. G. Overberger, P. Barkan, A. Lusi, and H. Ringsdorf, *ibid.*, **84**, 2814 (1962).

(5) E. R. Kline and C. A. Kraus, *ibid.*, **69**, 814 (1947). We did not find our sample of this compound to be unstable.

(6) W. Steinkopf, "Die Methoden der Organischen Chemie," 3rd ed., J. Houben, ed., Vol. 3, Verlag George Thieme, Leipzig, 1930, p. 1261.

mixture was heated for 2.5 hr. at 60–70°, cooled to room temperature, diluted with ether, and filtered. The product was washed with ether and dried, leaving 1.32 g. (91%) of colorless plates which were analyzed directly.

**Trialkylsulfonium Perchlorates. (A) Without Removing Water.**—A solution of 5 mmoles of dialkyl sulfide in 5 ml. of the corresponding alcohol was mixed with 0.72 g. (5 mmoles) of 70% perchloric acid and heated under reflux for 24 hr. The mixture was cooled to room temperature, diluted with 50 ml. of ether, and filtered to collect any sulfonium salt formed. Under these conditions the following yields were obtained: *n*-butyl, 46% (45% after 48 hr. reflux); *n*-propyl, 24%; ethyl, < 1%. The yield of triethylsulfonium perchlorate was raised to 16% if the reaction was carried out in ethanol solution in a sealed vessel at 120° for 24 hr.

**(B) With Removal of Water.**—A solution of 0.73 g. (5 mmoles) of di-*n*-butyl sulfide in 15 ml. of *n*-butyl alcohol was mixed with 0.72 g. (5 mmoles) of 70% perchloric acid and refluxed under a condenser with provision for periodic removal of solvent by distillation. A total of 6 ml. of distillate was collected over a 24-hr. period. Near the end of the reflux period an insoluble oil appeared in the reaction flask. The mixture was cooled and poured into 50 ml. of ether, precipitating 1.27 g. (84%) of tri-*n*-butylsulfonium perchlorate.

**(C) Benzyldi(*n*-butyl)sulfonium Perchlorate.**—A mixture of di-*n*-butyl sulfide (0.53 g., 3.59 mmoles), 70% perchloric acid (0.52 g., 3.59 mmoles) and 5 ml. of benzyl alcohol was heated at 70–80° for 4 hr., cooled and diluted with ether. The white solid product (1.02 g., 83.5%) had m.p. 70–72°. Recrystallization from acetone/ether in a Dry Ice–acetone bath left the melting point (71–73°) essentially unchanged.

*Anal.* Calcd. for $C_{15}H_{25}ClO_4S$: C, 53.48; H, 7.48. Found for crude product: C, 54.05; H, 7.48. Found after purification: C, 53.25; H, 7.21.

Our product was identical with a sample synthesized by the reaction of benzyl bromide and dibutyl sulfide in ether at 25° followed by conversion to the perchlorate with perchloric acid; m.p. 70–72°, mixture m.p. 72.5–73.5°; found on elemental analysis C, 53.44; H, 7.36. Our directly synthesized product thus is a single compound of unambiguous structure.

The formation of the sulfonium salts under the conditions of synthesis was shown not to be a reversible process by refluxing 3.02 g. (10 mmoles) of tri-*n*-butylsulfonium perchlorate, 10.0 ml. of dry butanol, and 0.43 g. of water for 24 hr. These conditions duplicate the solvent composition in the synthetic reaction (46% yield), but 2.78 g. (92%) of the sulfonium salt was recoverable unchanged by dilution with ether.

A 0.5 *N* solution of potassium *n*-butoxide was prepared by dissolving cautiously 9.775 g. (0.25 g.-atom) of potassium metal in 500 ml. of *n*-butyl alcohol, previously distilled from sodium. This reagent, prepared and stored under nitrogen, was used to titrate the perchloric acid content of butanol solutions[7] after refluxing for 24 hr. in the absence of dialkyl sulfide. The reagent was standardized by titration against benzoic acid in butanol. It was shown that a solution of 14.4 g. (0.1 mole) of 70% perchloric acid in 100 ml. of butanol retained 101% of the original acid concentration after 24 hr. reflux. Unfortunately, azeotropic removal of water led to formation of a black polymer in the butanol mixture.

**Acknowledgment.**—The authors wish to thank Professor D. H. R. Barton for a helpful discussion of this work.

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(7) This is a modification of a standard method for the quantitative determination of potassium; see F. P. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. II, 9th ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 272.

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# O-Acylation of Tyrosine during Peptide Synthesis

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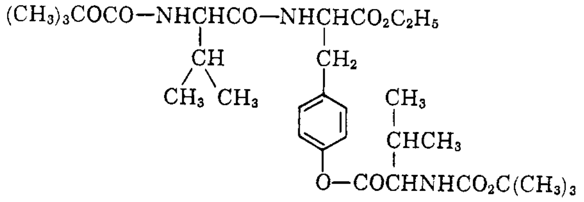
*Received July 6, 1962*

In the synthesis of angiotensin II amide-1 a great deal of difficulty was encountered in forming the valyl-tyrosine bond.[1,2] Only after many attempts were we able to obtain a 50% yield[2] (subsequently raised to 67%) of ethyl *t*-butyloxycarbonyl-L-valyl-L-tyrosinate (I) from N,N′-carbonyldiimidazole,[3,4] ethyl L-tyrosinate[5] and *t*-butyloxycarbonyl-L-valine.[6] The *N,N′*-dicyclohexylcarbodiimide,[7] tetraethylpyrophosphite,[8] and *p*-nitrophenyl ester[9] methods gave only intractable oils. The mixed anhydride method[10] gave a 65% yield of I as the two isomorphic forms (m.p. 139.5–141° and m.p. 151–152°) described earlier.[2] Dimorphism also occurred with N,N′-carbonyldiimidazole preparations but in an erratic fashion.

Since we were particularly interested in N,N′-carbonyldiimidazole, the formation of I was examined in more detail. A sample of a crude reaction mixture of I was separated on a silica gel column and ethyl N,O-bis(*t*-butyloxycarbonyl-L-valyl)-L-tyrosinate (II) was detected in a ratio of one part of II to eight parts of I. The structure of II was proved by synthesis from I and *t*-butyloxycarbonyl L-valine using N,N′-carbonyldiimidazole as the condensing agent. It was further confirmed by ultraviolet spectra studies.



II

Of the methods studied the mixed anhydride method gave the most easily purified dipeptide I. Replacing the *t*-butyloxycarbonyl group by a carbobenzoxy group, as in ethyl carbobenzoxy-L-valyl-L-tyrosinate, gave similar findings. Table I shows that the purest product again resulted from mixed anhydride coupling. The melting point was used as the criterion of purity.

TABLE I

PREPARATION OF Z·Val-Tyr·OEt

| Method | Yield, % | M.p. °C. |
|---|---|---|
| Mixed anhydride[a,b] | 64 | 155–157° |
| *p*-Nitrophenyl ester[a,c] | 67 | 145–147° |
| N,N′-Carbonyldiimidazole[d] | 22 | 152–154° |

[a] These literature results have been repeated and confirmed. [b] L. T. Skeggs, Jr., K. E. Lentz, J. R. Kahn, and N. P. Shumway, *J. Exptl. Med.*, **108**, 283 (1958). [c] R. Schwyzer, B. Iselin, H. Kappeler, B. Riniker, W. Rittel, and H. Zuber, *Helv. Chim. Acta*, **41**, 1273 (1958). [d] Worked up by the procedure cited in footnote *b*.

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(1) Reported at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 21, 1962.

(2) R. Paul and G. W. Anderson, *J. Org. Chem.*, **27**, 2094 (1962).

(3) H. A. Staab, *Ann.*, **609**, 75 (1957).

(4) G. W. Anderson and R. Paul, *J. Am. Chem. Soc.*, **80**, 4423 (1958); R. Paul and G. W. Anderson, *ibid.*, **82**, 4596 (1960).

(5) E. Fischer, *Ber.*, **34**, 433 (1901).

(6) G. W. Anderson and A. C. McGregor, *J. Am. Chem. Soc.*, **79**, 6180 (1957); L. A. Carpino, C. A. Giza, and B. A. Carpino, *ibid.*, **81**, 955 (1959); R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959). Using Carpino's reagent we obtained a 50% yield of crystalline *t*-butyloxycarbonyl-L-valine, m.p. 78.5–82°; $[\alpha]^{25}D$ −5.7° (*c* 1.2, acetic acid).

(7) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(8) G. W. Anderson, J. Blodinger, and A. D. Welcher, *ibid.*, **74**, 5304 (1952).

(9) M. Bodanszky, *Nature*, **175**, 685 (1955).

(10) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).