NOTES

The Preparation of 1-Methyl-4-phenyl-4-cyanopiperidine

By F. F. Blicke, J. A. Faust, John Krapcho and EuPhang Tsao

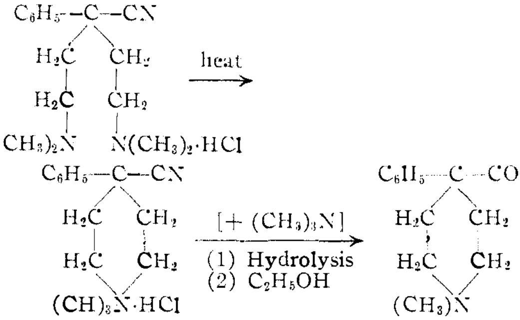
Prior to this investigation we know of no instance in which the direct pyrolysis of an acid salt[1] of a compound which contains two tertiary amino groups has been shown to yield a basic cyclic compound by the elimination of a tertiary amine.

In 1909 Le Sueur[2] heated a mixture of diethyl α,α'-dibromoadipate and monoethylaniline and obtained diethyl 1-phenylpyrrolidine-2,5-dicarboxylate in 62.5% yield. He stated that it is very probable that diethyl α,α'-di-(N-ethylanilino)-adipate was formed first and that this substance lost diethylaniline to form the pyrrolidine.

Le Sueur and Haas,[3] in 1910, heated a mixture of diethyl α,α'-dibromoadipate and diethylaniline and isolated the pyrrolidine mentioned above and ethyl bromide. In this instance we believe that the first reaction product may have been diethyl α,α'-di-(N-ethylanilino)-adipate diethobromide which lost ethyl bromide and then diethylaniline to produce the pyrrolidine. In this event, the reaction is entirely analogous to one which had been carried out a few years earlier by Willstätter[4] in which he found that when the dimethochloride of 1,4-di-(dimethylamino)-butane was heated, methyl chloride and trimethylamine were liberated and 1-methylpyrrolidine was the chief reaction product.

Clarke, *et al.*,[5] hoped to obtain ethyl 1-ethyl-4-phenylpiperidine-4-carboxylate by pyrolytic elimination of triethylamine from ethyl α,α-di-(β-diethylaminoethyl)-α-phenylacetate. However, since they could not obtain the latter ester by the method which they employed, this reaction was not carried out. Clarke and Mooradian[6] then attempted to eliminate triethylamine from α,α-di-(β-diethylaminoethyl)-α-phenylacetic acid. However, instead of triethylamine, diethylamine was evolved and α-diethylaminoethyl-α-phenylbutyrolactone was formed. Finally, they found that when α,α-di-(β-diethylaminoethyl)-α-phenylacetonitrile was heated at its boiling point (about 300°), triethylamine was not eliminated; the nitrile boiled unchanged.

Unaware of the experiments of Clarke, *et al.*, we heated α,α-di-(β-dimethylaminoethyl)-α-phenylacetonitrile at its boiling point in the hope that trimethylamine would be removed with the formation of 1-methyl-4-phenyl-4-cyanopiperidine, a compound which after hydrolysis and esterification with ethanol would yield ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (Demerol). The nitrile remained unchanged at its boiling point but when the solid monohydrochloride was heated to its melting point a vigorous evolution of trimethylamine took place; the residue consisted of the desired nitrile which, after purification, was isolated in 78.5% yield.



It was found that "Demerol nitrile" could also be obtained by pyrolysis of α,α-di-(β-dimethylaminoethyl)-α-phenylacetonitrile dihydrochloride in 55% yield and by pyrolysis of a mixture of equimolecular amounts of the nitrile base and the nitrile dihydrochloride in 71% yield.

Experimental Part

α,α-Di-(β-dimethylaminoethyl)-α-phenylacetonitrile. Mono- and Dihydrochloride.—A solution of 58.5 g. (0.5 mole) of phenylacetonitrile in 50 cc. of benzene was added, dropwise, to a cold (ice-bath), stirred suspension of 43.0 g. (1.1 moles) of pulverized sodamide in 150 cc. of benzene. The mixture was cooled and stirred for one hour, and β-dimethylaminoethyl chloride, obtained from 158.4 g. (1.1 moles) of the basic chloride hydrochloride, dissolved in 150 cc. of benzene was added, in portions, while the temperature was maintained below 40°. After the mixture had been refluxed for 3 hours it was cooled, diluted with 200 cc. of water, the organic layer separated, and the aqueous layer extracted with benzene. The solvent was removed from the combined benzene solutions, and the residue fractionated; b.p. 130–135° (1–2 mm.)[7]; yield 115 g. (89%).

Anal. Calcd. for $C_{16}H_{25}N_3$: N, 16.20. Found: N, 16.05.

The monohydrochloride was obtained when the water was removed, under reduced pressure, from a mixture of 129.3 g. (0.5 mole) of the base, 250 cc. of water and 90.0 g. (0.5 mole) of constant-boiling hydrochloric acid. A sample of the solid residue was dried to constant weight *in vacuo* over phosphorus pentoxide; it melted at 242–243° (dec.) after the bath had been preheated to 220°.

Anal. Calcd for $C_{16}H_{25}N_3 \cdot HCl$: Cl, 12.01. Found: Cl, 12.02.

In the presence of organic solvents the monohydrochloride undergoes transformation into the dihydrochloride. After the monohydrochloride had been ground under absolute ether, the chlorine content rose to 13.60%. The material was then dissolved in hot absolute alcohol, the solution cooled and the gelatinous precipitate filtered. The product then contained 18.43% chlorine and melted at 257–258° (dec.). In another experiment, after the alcohol treatment, the compound contained 21.04% chlorine and melted at 265–266° (dec.).

The dihydrochloride precipitated when an ethereal solution of the base was treated with hydrogen chloride; it melted at 268–269° (dec.) after the bath had been preheated to 260°.

Anal. Calcd. for $C_{16}H_{25}N_3 \cdot 2HCl$: N, 12.65; Cl, 21.41. Found: N, 12.55; Cl, 21.53.

---

(1) The term "acid salt" is used to differentiate the compound from a "quaternary salt."

(2) H. R. Le Sueur, *J. Chem. Soc.*, **95**, 273 (1909).

(3) H. R. Le Sueur and P. Haas, *ibid.*, **97**, 173 (1910).

(4) R. Willstätter and W. Huebner, *Ber.*, **40**, 3872 (1907).

(5) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, This Journal, **71**, 2821 (1949).

(6) R. L. Clarke and A. Mooradian, *ibid.* **71**, 2825 (1949).

(7) P. Lucas, U. S. Patent 2,510,784; *C. A.*, **44**, 8370 (1950).

Pyrolysis of α,α-Di-(β-dimethylaminoethyl)-α-phenylacetonitrile Monohydrochloride.—The monohydrochloride (29.6 g.) was placed in a 300-cc. flask, to which an air condenser was attached, and heated in a metal-bath which was maintained at 270–290°. As soon as the salt melted, trimethylamine was evolved. After about 6 minutes the salt had melted completely, and after ten minutes the evolution of gas had practically stopped. The cold, light brown, glass residue (the material becomes crystalline if rubbed under ether) was dissolved in a warm mixture of 20 cc. of water and 5 cc. of hydrochloric acid. The aqueous, acidic solutions, obtained from three experiments, were combined and the solution was made strongly alkaline. The precipitated nitrile was extracted with ether, the extract dried over magnesium sulfate, the solvent removed and the residue fractionated. The Demerol nitrile boiled at 119–122° (1–2 mm.); yield 47.1 g. (78.5%). The distillate solidified completely; m.p. 53°.[8] The hydrochloride melted at 222–224°[9] after recrystallization from absolute ethanol; mixed m.p. with an authentic sample 222–224°. The picrate melted at 247°[10] after recrystallization from methanol.

The evolved trimethylamine was passed into methyl bromide dissolved in chloroform, and the precipitated tetramethylammonium bromide (77%)[11] was analyzed.

Anal. Calcd. for $C_4H_{12}NBr$: Br, 51.87. Found: Br, 51.84.

Pyrolysis of a Mixture of Molecular Equivalent Amounts of the Base and the Dihydrochloride; Pyrolysis of the Dihydrochloride.—A mixture of 12.9 g. (0.05 mole) of the base and 16.5 g. (0.05 mole) of the dihydrochloride was heated in a bath at 260–280° (bath temperature) for 10 minutes and then at 280–310° for another 10 minutes. After the reaction mixture had been treated in the described manner, 14.2 g. (71%) of pure Demerol nitrile was obtained; m.p. 53°.

The dihydrochloride (22.5 g.) was heated in the manner described above. There was obtained 7.5 g. (55%) of Demerol nitrile. The hydrochloride melted at 222–224°.

---

[8] O. Eisleb (*Ber.*, **74**, 1433 (1941)), m.p. 53°.

[9] Reference 8, m.p. 221–222°.

[10] F. Bergel, A. L. Morrison and H. Rinderknecht (*J. Chem. Soc.*, 265 (1944)), m.p. 249–250°.

[11] A small amount of trimethylamine escaped from the solution.

College of Pharmacy
University of Michigan
Ann Arbor, Michigan
Received December 14, 1951

Wien Effect in Polyelectrolytes

By Frederick E. Bailey, Andrew Patterson, Jr., and Raymond M. Fuoss

Received November 24, 1951

If polyvinylpyridine is quarternized by the addition of butyl bromide, a typical polyelectrolyte is obtained. The statistical coil characteristic of the neutral polymer is distended by the intramolecular repulsion among the built-in cations; this is, however, partially screened by the counter ions which are held in the volume of the coil by the total cationic field. The equilibrium between free and associated counter ions is, of course, a dynamic one. (Here, we define free counter ions as those in the solvent between the polyions, and associated counter ions as those within the average radius of the polymer coil.) The associated counter ions do not contribute to anion current[1] and the conductance of a polyelectrolyte is therefore less than that of the corresponding monomeric salt at the same concentration. The polycation naturally has no sharp boundary, on account of intramolecular Brownian motion; we may, however, imagine a zone in which the potential energy of a cation is of the order of kT and define this zone as the periphery of the polycation. Inside this region, a counter ion will be considered as associated with the polycation. A small decrease in potential energy should therefore suffice to remove some of the peripheral counter ions, and thereby increase the population of free ions, and with it the conductance. We would then expect[2] a fairly large Wien effect[3] for polyelectrolytes. The purpose of this note is to present preliminary results which confirm this prediction and which presumably may be taken as additional evidence confirming our model.

A sample of poly-4-vinyl-N-*n*-butylpyridinium bromide[4] was used which has a degree of polymerization of approximately 2000. Strauss[4] found a reduced viscosity of about 12 at a concentration of 0.001 monomolar; the equivalent Einstein sphere would have a radius of the order of 500 Å. Conductances were measured by the Differential Pulse Transformer bridge method[5] over the range 9–18 kv./cm., at 25.00° at a concentration of 0.00105 monomolar in water. Pulse widths of 4, 6 and 11 μsec. were used; balancing was performed visually on single pulses. The experimental results are summarized in Fig. 1, where relative increase in specific conductance, $\Delta\kappa/\kappa_0$, is plotted against field strength in kv./cm. Here, κ_0 is conductance at low voltages and for all practical pur-

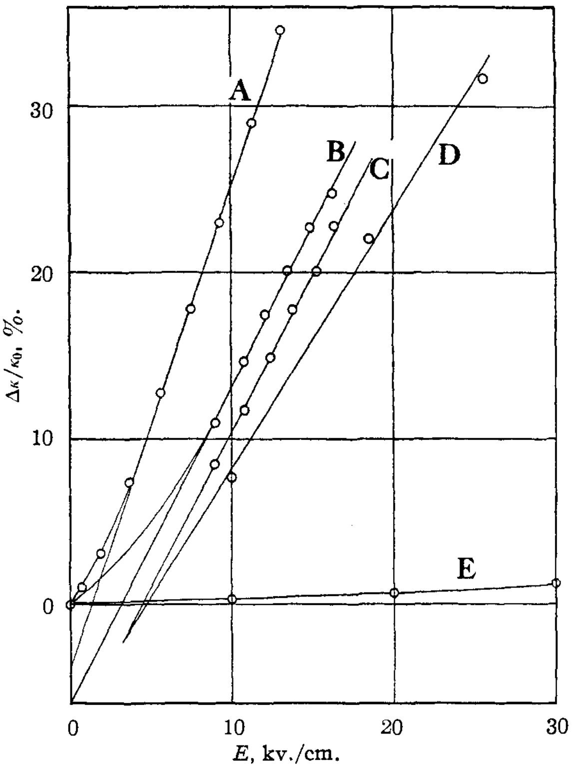


Fig. 1.—Wien effect of poly-4-vinyl-N-*n*-butylpyridinium bromide: A, $(Bz)_3NHPi$; B, 11 μsec.; C, 6 μsec.; D, 4 μsec.; E, $MgSO_4$.

---

[1] W. R. Huizenga, P. E. Grieger and F. T. Wall, This Journal, **72**, 2636 (1950).

[2] D. Edelson and R. M. Fuoss, *ibid.*, **72**, 306 (1950).

[3] H. C. Ekstrom and C. C. Schmelzer, *Chem. Revs.*, **24**, 367 (1939).

[4] R. M. Fuoss and U. P. Strauss, *Trans. N. Y. Acad. Sci.*, **51**, 836 (1949).

[5] J. A. Gledhill and A. Patterson, Jr., *Rev. Sci. Instruments*, **20**, 960 (1949).

poses equals the limiting conductance at zero field strength. It will be seen that a marked Wien effect is present; at only 10 kv./cm., the conductance is increased by 13%. For comparison, the lower curve is for 0.0001 molar magnesium sulfate[6] in water; this is a salt which is considered to have a fairly large Wien effect. By way of further contrast, the upper curve is for tribenzylammonium picrate[7] in toluene at 35°. We see that the polyelectrolyte in water gives about as large a Wien effect as does a 1-1 salt in a solvent whose dielectric constant is only 2.35. If we interpret our result as a second Wien effect in terms of Onsager's theory,[8] the polyelectrolyte is behaving approximately like a salt in which the cation has a charge of +33 (the ratio of the dielectric constants of water and toluene); in other words, the presence of about 1.7% of the counter ions in the peripheral zone mentioned above would be sufficient to account for our result.

The balance patterns (Fig. 2) observed on the oscilloscope for different pulse lengths are significant, if we consider the distances a bromide ion can travel during a pulse. At 10 kv./cm., a counter ion travels about 3000 Å. in 4 μsec. The balance patterns are tracings taken from the oscilloscope; a horizontal line coinciding with the center graticule marking is an indication of impedance balance. On the 11 μsec. tracing, balance was achieved after a preliminary excursion (*i.e.*, unbalance) lasting almost 5 μsec. On the shorter pulses balance was apparently not reached during the period of the pulse. Measurements taken with pulse lengths shorter than that necessary to give a steady state conductance value are accordingly only approximate estimates of the conductance. This behavior is, however, a clear indication of a time of relaxation effect in which the relaxation time is of the order of 1–5 microseconds. In such a time any free counter ions could travel several thousand Å. under the influence of a field of 10 kv./cm.

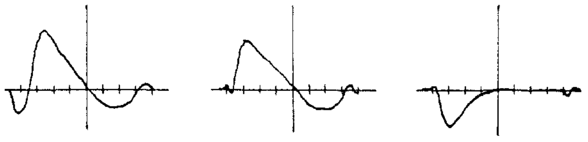

4 μsec. 6 μsec. 11 μsec.

Fig. 2.—Balance patterns.

In addition to this relaxation time phenomenon, it was noticed that the low field conductance of the solution was not regained instantaneously, as is usually the case with ordinary electrolytes. Figure 3 shows approximately the behavior observed. The low field conductance was regained slowly after the increase due to the high field, and then a decrease was observed, followed by a return to the normal low field conductance after a few minutes. This behavior was reproducible. On the other hand, two high field measurements made one immediately after the other were quite reproducible. The same phenomenon could be obtained with the application of a d.c. potential of 3 volts applied to the cell for a few seconds. In all cases the power dissipated in the cell was sufficient to raise the temperature of the electrolyte no more than 0.002°. The phenomenon of Fig. 3 is presumed to require more explanation than to ascribe it to electrode effects.

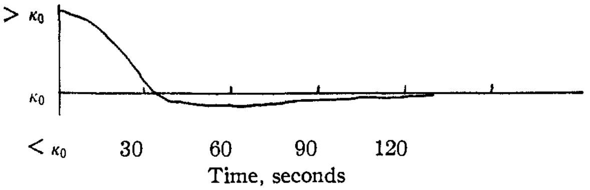


Fig. 3.—Time dependence of balance.

STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN 11, CONNECTICUT

Preparation and Properties of Some Unsaturated Sulfonium Salts[1]

BY GEORGE B. BUTLER AND BEN M. BENJAMIN

Ray and Levine[2] found that in the reaction between organic sulfides and alkyl halides, the sulfonium salt first formed can decompose in a variety of ways, the tendency being toward formation of the salt having the organic radicals of lowest molecular weight. The possibility exists that each alkyl radical may exist at some time as the alkyl halide. The final result is formation of the most stable product. These workers obtained trimethylsulfonium bromide by treating dimethyl sulfide with phenyl-2-fluorenylbromoethane and by treating phenyl-2-fluorenylmethylmethyl sulfide with methyl iodide, obtained trimethylsulfonium iodide.

In attempting to prepare unsaturated sulfonium halides, we have observed that when an alcohol is used as solvent, the alkyl radical of the alcohol may enter the sulfonium salt. Methanol[3] has been recommended as a suitable solvent for sulfonium salt formation. In attempting to prepare sulfonium halides of diallyl sulfide in methanol solution, only trimethylsulfonium halides were obtained. Methyl iodide, isopropyl iodide, phenacyl bromide and *p*-phenylphenacyl bromide were used as reactants. Diallyl-*p*-phenylphenacylsulfonium bromide has been reported[2]; however, in our attempts to prepare this compound, only trimethylsulfonium bromide was obtained. Dimethylallyl sulfide in methanol solution when treated with allyl iodide resulted in formation of trimethylsulfonium iodide. One previous unsuccessful attempt[4] to prepare triallylsulfonium salts has been reported, although allyldipropylsulfonium iodide was obtained. It has been stated[5] that dialkenyl sulfides, *e.g.*, diallyl sulfide, part with their sulfur when treated with excess of methyl iodide. In addition to diallyl-*p*-phenylphenacylsulfonium bromide[2] and allyldipropylsul-

---

(6) M. Wien, *Ann. Physik*, **85**, 795 (1928); F. E. Bailey, unpublished results.

(7) R. M. Fuoss, D. Edelson and B. I. Spinrad, THIS JOURNAL, **72**, 327 (1950).

(8) L. Onsager, *J. Chem. Phys.*, **2**, 599 (1934).

(1) This work was done under the sponsorship of the Office of Naval Research under Contract No. N7 onr-346.

(2) F. E. Ray and I. Levine, *J. Org. Chem.*, **2**, 267 (1937).

(3) R. W. Bost and H. C. Schultz, THIS JOURNAL, **64**, 1165 (1942).

(4) W. Steinkopf and R. Bessaritsch, *J. prakt. Chem.*, **109**, 230 (1925).

(5) P. D. Ritchie, "Chemistry of Plastics and High Polymers." Cleaver-Hume Press, Ltd., London, p. 186.

TABLE I

TRIALKYL SULFONIUM HALIDE MERCURIC HALIDE COMPLEXES

Compound	Formula	M.p., °C.	Analyses, % Carbon Found	Carbon Calcd.	Hydrogen Found	Hydrogen Calcd.	Decomposition upon standing at room temperature
Triallylsulfonium bromide mercuric iodide	$C_9H_{15}SBr \cdot HgI$	19–22	15.92	15.70	2.41	2.20	Slow but noticeable within an hour
Triallylsulfonium iodide mercuric iodide	$C_9H_{15}SI \cdot HgI_2$	64.5	14.85	14.67	2.23	2.05	None
Methyldiallylsulfonium iodide mercuric iodide	$C_7H_{13}SI \cdot HgI_2$	15–18	12.92	11.84	2.11	1.84	Noticeable within 15 hours
Triallylsulfonium iodide mercuric chloride	$C_9H_{15}SI \cdot HgCl_2$[a]	−47–−45	19.0	19.54	2.94	2.74	Starts immediately after isolation
Triallylsulfonium bromide mercuric chloride	$C_9H_{15}SBr \cdot HgCl_2$[b]	−46–−43	20.01	21.38	2.87	2.99	Noticeable within an hour
Ethylene-bis-(diallylsulfonium iodide) tetramercuric iodide	$C_{14}H_{24}S_2I_2 \cdot 4HgI_2$	84–84.7	7.26	7.23	1.28	1.04	Noticeable after two weeks
Ethylene-bis-(diallylsulfonium bromide) dimercuric iodide	$C_{14}H_{24}S_2Br_2 \cdot 2HgI_2$	25–28	12.79	12.71	1.94	1.83	Noticeable within an hour

[a] n^{25}_D 1.6814; d^{25}_4 2.4400. [b] n^{25}_D 1.6382; d^{25}_4 2.1849.

fonium iodide the only other unsaturated sulfonium salt located in the literature was acetylmethionineallylsulfonium bromide.[6] By treating diallyl sulfide with dimethyl sulfate in methanol solution, methyldiallylsulfonium methyl sulfate was obtained in this Laboratory.

Even though dialkyl sulfides and alkyl halides rarely are completely converted to sulfonium salts before the reaction reaches equilibrium,[7,8] in the presence of mercuric halides they combine more rapidly and completely.[9–11] These compounds retain the mercuric halide as part of the molecule. Even though unsaturated sulfides are very reluctant to form sulfonium salts, these compounds readily form sulfonium halide mercuric halide complexes. Even though these derivatives of saturated sulfides appear to be entirely stable, we have observed that in general, similar derivatives of the unsaturated sulfides decompose after standing for a short time. This decomposition appears to be accelerated by contact with light. For example, triallylsulfonium iodide mercuric chloride decomposes almost immediately after isolation to produce allyl chloride as one of the products. Other derivatives showed no signs of decomposition up to two weeks, while triallylsulfonium iodide mercuric iodide appears to be entirely stable.

When bis-(allylthio)-ethane was treated with allyl iodide and mercuric iodide, the product contained four mercuric iodide molecules. Substitution of allyl bromide in the above reaction resulted in the formation of a compound containing only two mercuric iodide molecules.

Some of the mercuric iodide complexes decomposed before they could be isolated. When diallyl sulfide, isopropyl iodide and mercuric iodide were mixed in acetone, the solution began to darken before all of the mercuric iodide dissolved. Only a black tarry mass could be isolated. The same was true when dimethallyl sulfide, methallyl chloride and mercuric iodide or chloride were mixed.

Experimental

Materials.—Diallyl sulfide was obtained from Eastman Kodak Company and used as received. Di-(2-methylallyl)-sulfide was prepared by the method described in the literature.[12] 2,4,6-Trithiane was prepared by the method o Chattaway and Kellett.[13] 2,4,6-Trimethyltrithiane was prepared by the method of Baumann and Fromm.[14] Ethylene mercaptan was prepared by the method of Meyer[15,16] and by reaction of ethylene bromide with potassium xanthate and basic hydrolysis of the product. The latter method gave better results.

1,2-Di-(allylthio)-ethane.—One mole of ethylene mercaptan was slowly added to two moles of potassium hydroxide in ethanol at 0°. To the suspended potassium mercaptide was added two moles of allyl bromide at 0°. The cooling bath was removed and the reaction mixture allowed to reach room temperature. Most of the alcohol was removed by distillation and the residue extracted with ether. After evaporating the ether, the oily liquid was distilled in vacuum, b.p. 109° (7 mm.), n_{25} 1.5345, d_{25} 0.9998. *Anal.* Calcd. for $C_8H_{14}S_2$: S, 36.78. Found: S, 36.64.

The methyl analog was prepared in a similar manner substituting methyl iodide for allyl bromide.

General Procedure for Preparing Sulfonium Salts.—One-hundredth mole of diallyl sulfide was dissolved in 10 ml. of dry methanol and placed in a heavy glass tube. To this was added 0.01 mole of methyl iodide and the tube was sealed, placed in a steam-cone, and heated with steam for three hours. The tube was cooled in Dry Ice–acetone and broken. To the contents was added dry ether until no more precipitation took place. The solid was purified by precipitating it from methanol solution with dry ether until constant melting. Analysis was performed by titration with standard silver nitrate. *Anal.* Calcd. for $C_7H_{13}IS$: I, 49.13. Found: I, 62.20.

This analysis and the melting point, 211°, correspond to trimethylsulfonium iodide which requires 62.19% I.

When the above mentioned reactants were refluxed for five hours the results were the same. A methanol solution of diallyl sulfide when treated with either methyl iodide or isopropyl iodide gave trimethylsulfonium iodide. Diallyl sulfide in methanol solution when treated with phenacyl bromide or *p*-phenylphenacyl bromide gave trimethylsulfonium bromide. Di-(2-methylallyl) sulfide, 2,4,6-trithiane and 2,4,6-trimethyltrithiane in methanol solutions when treated with allyl iodide or allyl bromide resulted in formation of the corresponding trimethyl sulfonium halide. 1,2-Di-(allylthio)-ethane did not react with allyl iodide or allyl bromide in the absence of a solvent. However, when its methanol solution was treated with methyl iodide, tetramethylethylenedisulfonium dibromide was obtained. *Anal.* Calcd. for $C_{10}H_{20}I_2S_2$, dimethyldiallylethylenedisulfonium dibromide: I, 53.6. Calcd. for $C_6H_{16}I_2S_2$: I, 62.3. Found: I, 59.5; m.p. 105–105.5° (dec.).

Methyldiallylsulfonium Methyl Sulfate.—To a methanol solution of 0.01 mole of diallyl sulfide was added 0.01 mole of dimethyl sulfate. The mixture was allowed to stand for five days in a sealed tube. The tube was broken and dry ether added to its contents. The light colored liquid which

---

(6) G. Toennies and J. J. Kolb, THIS JOURNAL, **67**, 1141 (1945).

(7) M. P. Balfe, J. Kenyon and H. Phillips, *J. Chem. Soc.*, 2554 (1930).

(8) S. Smiles, *ibid.*, 163 (1900).

(9) H. H. Cavell and S. Sugden, *ibid.*, 2572 (1930).

(10) F. H. Burstall and S. Sugden, *ibid.*, 229 (1930).

(11) P. C. Ray and N. Adhikary, *J. Indian Chem. Soc.*, **62**, 1752 (1940).

(12) M. Tamele, C. J. Ott, L. E. Marple and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

(13) F. D. Chattaway and E. C. Kellett, THIS JOURNAL, **53**, 2187 (1931).

(14) Baumann and Fromm, *Ber.*, **22**, 2602 (1889).

(15) V. Meyer, *ibid.*, **19**, 3263 (1886).

(16) H. Fasbender, *ibid.*, **20**, 461 (1887).

settled to the bottom was washed several times with dry ether and all residual ether removed in vacuum. The liquid did not crystallize even at −78°. The same result was obtained when no solvent was used. No precipitate formed upon addition of 2% barium chloride solution.

To an aqueous solution of the above liquid was added a few drops of chloroplatinic acid. A yellow solid immediately precipitated. This was removed by filtration and washed with alcohol; m.p. 145°. *Anal.* Calcd. for $C_{14}H_{26}Cl_6PtS_2$: Pt, 29.3. Found: Pt, 28.4. This shows that the compound is bis-(methyldiallylsulfonium)-chloroplatinate.

General Procedure for Preparing Mercuric Halide Complexes.—One-hundredth mole of mercuric iodide was placed in a flask with 20 ml. of acetone. To this was added 0.01 mole of allyl bromide and 0.01 mole of diallyl sulfide. The mixture was shaken and when all the mercuric iodide had dissolved, the acetone was evaporated in vacuum. Dry ether was then added and the solid product recrystallized from methyl isobutyl ketone; m.p. 64.5°. *Anal.* Calcd. for $C_9H_{15}I_3HgS$: C, 14.67; H, 2.05. Found: C, 14.85; H, 2.23.

The compound formed from 1,2-di-(allylthio)-ethane, allyl iodide and mercuric iodide was purified by adding dry ether to its acetone solution. The liquid members were isolated by evaporating the acetone in vacuum, adding and decanting ether, and evaporating all residual ether in vacuum.

The properties and analyses of seven of these compounds are recorded in Table I. In addition, isopropyldiallylsulfonium iodide mercuric iodide, *n*-butyldiallylsulfonium iodide mercuric iodide, and methallyldiallylsulfonium chloride mercuric chloride were prepared, but decomposed before they could be isolated from solution.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

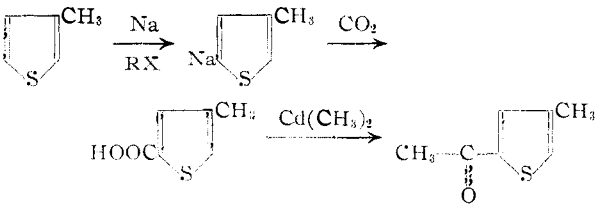
RECEIVED NOVEMBER 23, 1951

Alkylation During Transmetalation of 3-Methylthiophene

BY JOSEPH A. BLANCHETTE AND ELLIS V. BROWN

RECEIVED OCTOBER 31, 1951

In the course of our investigation of the Willgerodt reaction in the heterocyclic series,[1] it became necessary to prepare 4-methyl-2-acetylthiophene by a method which would circumvent the isomeric mixture of 3-methyl- and 4-methyl-2-acetylthiophenes obtained by the direct acetylation of 3-methylthiophene. One of the possible routes available for the synthesis of 4-methyl-2-acetylthiophene is shown by equation I.



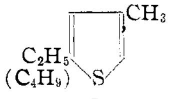
I

Schick and Hartough[2] reported that 3-methylthiophene metalated exclusively in the 5-position in the presence of alkyl or aryl halides such as ethyl chloride, bromobenzene or *n*-butyl bromide. On carbonation and acidification, they obtained a 42% yield of 4-methyl-2-thiophenecarboxylic acid with no trace of 3-methyl-2-thiophenecarboxylic acid being detected. The results obtained by us when this procedure of transmetalation was attempted with ethyl bromide and *n*-butyl bromide are shown in Table I.

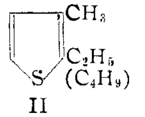
TABLE I

Alkyl or aryl halide	3-Methylthiophene recovered, %	4-Methyl-2-thiophenecarboxylic acid, %	Organic residue, %	B.p., °C.
Ethyl bromide	60	10	40	164–166, 46–48 (13 mm.)
n-Butyl bromide	46	21	60	198–202

It can be seen that the highest yield of 4-methyl-2-thiophenecarboxylic acid obtained was 21% with *n*-butyl bromide which does not approach the 42% reported by Schick and Hartough using ethyl chloride. With both *n*-butyl bromide and ethyl bromide, high boiling liquid organic residues remained after the unreacted 3-methylthiophene had been recovered by fractional distillation. It seemed probable that these organic liquids were alkylated 3-methylthiophenes with the formulas I or II formed by Wurtz–Fittig coupling of 3-methylthienylsodium and the alkyl halides.

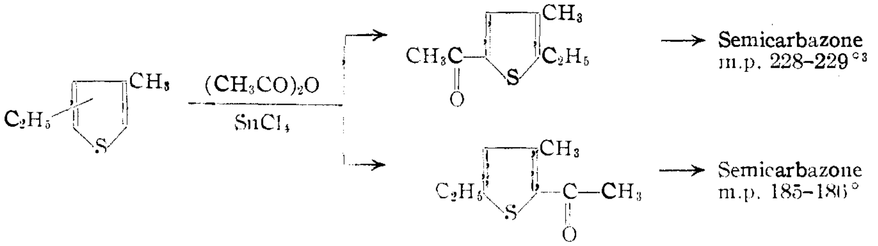


I



II

Since metalation takes place exclusively in the 5-position of 3-methylthiophene, as shown by the isolation of 4-methyl-2-thiophenecarboxylic acid after carbonation, I was the most probable and the scheme in equation II summarizes the experimental data which support this structure.



The two possible structures, I and II, are 2-ethyl-4-methylthiophene and 2-ethyl-3-methylthiophene. Acetylation would yield, either the known 2-ethyl-3-methyl-5-acetylthiophene, which can be converted to a known semicarbazone ($C_{10}H_{15}N_3OS$) with a melting point of 228–229°, or 2-ethyl-4-methyl-5-acetylthiophene. Acetylation of the compound obtained in this study gave a ketone whose semicarbazone had a melting point of 185–186° and analyzed for $C_{10}H_{15}N_3OS$. These results show that the original compound is a methylethylthiophene and seem to eliminate 2-ethyl-3-methylthiophene as a possibility. The structure is, therefore, most likely to be 2-ethyl-4-methylthiophene and, by analogy, the compound obtained with *n*-butyl bromide is 2-*n*-butyl-4-methylthiophene. A Willgerodt reaction on 2-ethyl-4-methyl-5-acetylthiophene gave the expected 2-ethyl-4-meth-

---

(1) J. A. Blanchette and E. V. Brown, THIS JOURNAL, **73**, 2779 (1951).

(2) J. W. Schick and H. D. Hartough, *ibid.*, **70**, 1645 (1948).

(3) W. Steinkopf, A. Merckoll and H. Strauch, *Ann.*, **545**, 45 (1940).

yl-5-thienylacetamide and the corresponding acid was obtained by hydrolysis.

Experimental

Attempted Transmetalation of 3-Methylthiophene.—A mixture of 23 g. (1 gram atom) of sodium sand, 250 ml. of anhydrous ether and 98 g. (1 mole) of 3-methylthiophene was refluxed and 68.5 g. (0.5 mole) of *n*-butyl bromide in 100 ml. of anhydrous ether was added dropwise with mechanical stirring. After the addition was completed the mixture was refluxed for an additional 2 hours and was carbonated with pieces of Dry Ice. Water was cautiously added, the alkaline aqueous layer was separated and acidified with concentrated hydrochloric acid whereupon 15 g. (21%) of 4-methyl-2-thiophenecarboxylic acid, m.p. 119–120°, was obtained.

There was also obtained from the ethereal layer 46% of 3-methylthiophene and 60% of a liquid, b.p. 198–202°. Using ethyl bromide as the alkyl halide there was obtained 10% of 4-methyl-2-thiophenecarboxylic acid, 60% of 3-methylthiophene and 40% of a liquid, b.p. 164–166°, 46–48° (13 mm.). For some unaccountable reason, when bromobenzene was used only a high recovery of 3-methylthiophene was observed.

2-Ethyl-4-methyl-5-acetylthiophene.—The organic liquid, b.p. 46–48° (13 mm.) obtained from the attempted transmetalation of 3-methylthiophene with ethyl bromide, was acetylated with acetic anhydride and stannic chloride by the method of Johnson and May.[4] From 16 g. (0.13 mole) there was obtained 15 g. (70%) of a colorless liquid, b.p. 125–126° (15 mm.). A semicarbazone was prepared in the usual manner and crystallized from alcohol, m.p. 185–186°.

Anal. Calcd. for $C_{10}H_{15}N_3OS$: C, 53.33; H, 6.66; N, 18.67. Found: C, 53.55; H, 6.60; N, 18.78.

The molecular formula, $C_{10}H_{15}N_3OS$, was calculated for the semicarbazone of a methylethylacetylthiophene. The semicarbazone of 5-ethyl-4-methyl-2-acetylthiophene is a known compound and has a m.p. of 228–229°. The ketone obtained is believed to be 2-ethyl-4-methyl-5-acetylthiophene.

2-Ethyl-4-methyl-5-thenylacetamide.—2-Ethyl-4-methyl-5-acetylthiophene was converted to 2-ethyl-4-methyl-5-thienylacetamide, m.p. 98–99°, in a yield of 35% by the Willgerodt reaction.[1]

Anal. Calcd. for $C_9H_{13}NOS$: N, 7.65. Found: N, 7.77.

Hydrolysis of this amide gave an oil which readily formed a solid *p*-bromophenacyl ester, m.p. 95–97°.

Anal. Calcd. for $C_{17}H_{17}BrO_3S$: C, 53.54; H, 4.46. Found: C, 53.82; H, 4.31.

---

[4] J. R. Johnson and C. E. May, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

DEPARTMENT OF CHEMISTRY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

Optical Rotation of Peptides. V. Alanine Tetra-, Penta- and Hexapeptides[1]

BY ERWIN BRAND, BERNARD F. ERLANGER AND HOWARD SACHS

Previous papers in this series dealt with the synthesis and specific rotation of alanine dipeptides[2] and tripeptides.[3] In this paper the syntheses and specific rotations (in 0.5 *N* HCl) of four isomeric alanine tetrapeptides,[4] pentaalanine (5L) and hexaalanine (6L) are presented. More detailed data on their specific rotations and on the *residue rotations*[5] of alanine residues will be reported subsequently.

Experimental

The synthesis and properties of most of the starting materials have been previously described: L- and D-alanine[2]; L- and D-alanine benzyl esters (ref. 2, Cmpds. 5, 6); carbobenzoxy-D-alanine hydrazide (ref. 2, Cmpd. 3); carbobenzoxydialanine hydrazide (Z.Ala-Ala.NHNH$_2$(2L), ref. 2, Cmpd. 17); and three isomeric carbobenzoxytrialanine hydrazides (ref. 3, Cmpds. 14–16).

The benzyl ester hydroiodides of di- and trialanine were used as intermediates in the synthesis of some of the higher peptides. These benzyl esters were prepared from their corresponding carbobenzoxy derivatives by reduction with phosphonium iodide, which removes the N-carbobenzoxy group more rapidly than the benzyl ester group.[6]

(1) **H.Ala-Ala.OBz.HI** (2L) ($C_{13}H_{18}O_3N_2$.HI, mol. wt. 378.2).—0.15 mole of Z.Ala-Ala.OBz (2L) (ref. 2, Cmpd. 13) is dissolved in 65 cc. of glacial acetic acid and warmed to 35–40°. Ph_4I (0.45 mole) is added and hydrogen passed through the solution for about two hours, when CO_2 evolution stops. The solution is evaporated *in vacuo*. Water is added and then distilled off *in vacuo*, in order to remove acetic acid; this treatment is repeated several times. The solution is finally distilled down to an oil, which is taken up in about 15 cc. of water and extracted with several portions of ether (caution—lachrymator!). The amount of H.Ala-Ala.OBz.HI (2L) present in this aqueous solution is determined by Van Slyke amino nitrogen determination. From this solution the free dipeptide benzyl ester is prepared in the usual fashion[2,3] for use in further synthesis.

Since neither the hydroiodide, the hydrochloride, nor the free dialanine benzyl ester is obtained in crystalline form, Compound 1 is identified by converting it into derivatives. Reaction of the free dialanine benzyl ester in ethyl acetate with an ethereal solution of carbobenzoxy-L-alanine azide yields a compound with the same melting point, mixed melting point (201°) and analysis as Z.Ala-Ala-Ala.OBz (3L), previously prepared by a different procedure (ref. 3, Cmpd. 9). Compound 1 is further identified by converting it into Z.Ala-(Ala)$_3$-Ala.OBz (5L) (*cf.* below, Cmpd. 7).

(2) **H.Ala-Ala-Ala.OBz.HI** (3L) ($C_{16}H_{23}O_4N_3$.HI, mol. wt. 449.3).—This compound is prepared from Z.Ala-Ala-Ala.OBz(3L)(ref. 3, Cmpd. 9) as described above for Compound 1. Since neither the hydroiodide nor the free trialanine benzyl ester is obtained in crystalline form, Compound 2 is identified by converting it into derivatives (*cf.* below, Cmpds. 6, 7 and 8).

Carbobenzoxytetraalanine Benzyl Esters (Compounds 3–6).—Compounds 3–5 are prepared by coupling the azide of a carbobenzoxytrialanine hydrazide[3] with free alanine benzyl ester essentially as described in detail for the synthesis of carbobenzoxydipeptide and -tripeptide esters.[2,3]

(3) **Z.Ala-(Ala)$_2$-Ala.OBz** (4L).—For the preparation of this compound, 0.1 mole of Z.Ala-Ala-Ala.NHNH$_2$ (3L) (ref. 3, Cmpd. 14) is dissolved in 150 cc. of glacial acetic acid, 12.5 cc. of 5 *N* HCl and 100 cc. of water. The solution is cooled to −5°, sodium nitrite (0.11 mole) added, and allowed to stand in an ice–salt-bath for three minutes, after which an additional 300 cc. of ice-cold water and 250 cc. of ice-cold ethyl acetate are added. The azide is extracted and washed with water, 3% aqueous $NaHCO_3$ and water (all ice-cold), dried over sodium sulfate and added in one portion to a cold, dry, ethereal solution of L-alanine benzyl ester[2] (previously prepared from 0.15 mole of its hydrochloride). After standing at room temperature for about 20 hours, the carbobenzoxytetraalanine ester is isolated and recrystallized from dioxane.

(4) **Z.Ala-(Ala)$_2$-Ala.OBz** (LDLL). (5) **Z.Ala-(Ala)$_2$-Ala.OBz** (LLDL).—For the preparation of these compounds, the carbobenzoxytrialanine azides are prepared from their respective carbobenzoxytrialanine hydrazides (ref. 3, Cmpds. 15, 16) by following exactly the procedure described for the preparation of carbobenzoxydialanine azides,[3] except that the carbobenzoxytrialanine azides are extracted with ethyl acetate instead of with ether–ethyl acetate. The azide solutions are then added in one portion to a 50% molar excess of free alanine benzyl ester in ether. After 20 hours the carbobenzoxytetraalanine benzyl esters are collected and recrystallized from 95% ethanol.

(6) **Z.Ala-(Ala)$_2$-Ala.OBz** (DLLL).—This compound is prepared by coupling 0.1 mole of carbobenzoxy-D-alanine azide[2] with 0.15 mole of H.Ala-Ala-Ala.OBz (3L) in ethyl

---

[1] Presented in part before the Division of Biological Chemistry at the 119th Meeting of the A. C. S., Boston, Mass., April, 1951.

[2] B. F. Erlanger and E. Brand, THIS JOURNAL, **73**, 3508 (1951).

[3] E. Brand, B. F. Erlanger, H. Sachs and J. Polatnick, *ibid.*, **73**, 3510 (1951).

[4] For abbreviations see Table I, footnote *a*.

[5] E. Brand and B. F. Erlanger, THIS JOURNAL, **72**, 3314 (1950).

[6] C. R. Harington and T. H. Mead, *Biochem. J.*, **30**, 1599 (1936).

TABLE I

TETRA-, PENTA- AND HEXAALANINE DERIVATIVES

No.	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. (cor.)	N, % Calcd.	N, % Found
3	Z.Ala-(Ala)$_2$-Ala.OBz (4L)	$C_{27}H_{34}O_7N_4$	526.6	246	10.6	10.7
4	Z.Ala-(Ala)$_2$-Ala.OBz (L-D-L-L)	$C_{27}H_{34}O_7N_4$	526.6	181.5	10.6	10.5
5	Z.Ala-(Ala)$_2$-Ala.OBz (L-L-D-L)	$C_{27}H_{34}O_7N_4$	526.6	213–214	10.6	10.6
6	Z.Ala-(Ala)$_2$-Ala.OBz (D-L-L-L)	$C_{27}H_{34}O_7O_4$	526.6	191–192	10.6	10.9
7	Z.Ala-(Ala)$_3$-Ala.OBz (5L)	$C_{30}H_{39}O_8N_5$	597.7	254	11.7	11.7
8	Z.Ala-(Ala)$_4$-Ala.OBz (6L)	$C_{33}H_{44}O_9N_6$	668.7	Decomp. >260	12.6	12.7

[a] The following abbreviations are used (*cf.* ref. 2, 3, Table I, footnote *a*): Z, carbobenzoxy, $C_6H_5CH_2OCO$; Ala, NH-$(CHCH_3)CO$; peptide linkage indicated by hyphen; Bz, $C_6H_5CH_2$; configuration follows compound in parentheses. *E.g.*, carbobenzoxy-L-alanyl-L-alanyl-L-alanyl-L-alanyl-L-alanyl-L-alanine benzyl ester: Z.Ala-(Ala)$_4$-Ala.OBz (6L); L-alanyl-D-alanyl-L-alanyl-L-alanine: H.Ala-(Ala)$_2$-Ala.OH (L-D-L-L).

TABLE II

TETRA-, PENTA- AND HEXAALANINE
ANALYTICAL DATA AND SPECIFIC ROTATION IN 0.5 *N* HCl

No.	Compound[a]	Molecular formula	Mol. wt.	Nitrogen, % Calcd.	Nitrogen, % Found	Amino N, % Calcd.	Amino N, % Found	$[\alpha]^{25}_{D}$ (c = 2)
9	H.Ala-(Ala)$_2$-Ala.OH.H$_2$O (4L)	$C_{12}H_{22}O_5N_4.H_2O$	320.3	17.5	17.6	4.4	4.5	−131.0
10	H.Ala-(Ala)$_2$-Ala.OH (L-D-L-L)[b]	$C_{12}H_{22}O_5N_4$	302.3	18.5	18.5	4.6	4.5	− 14.2[c]
11	H.Ala-(Ala)$_2$-Ala.OH (L-L-D-L)	$C_{12}H_{22}O_5N_4$	302.3	18.5	18.6	4.6	4.5	− 5.0
12	H.Ala-(Ala)$_2$-Ala.OH (D-L-L-L)	$C_{12}H_{22}O_5N_4$	302.3	18.5	18.3	4.6	4.5	−145.1[d]
13	H.Ala-(Ala)$_3$-Ala.OH (5L)	$C_{15}H_{27}O_6N_5$	373.4	18.8	18.8	3.8	3.8	−149.7[e]
14	H.Ala-(Ala)$_4$-Ala.OH (6L)	$C_{18}H_{32}O_7N_6$	444.5	18.9	18.7	3.2	3.1	−156.6[f]

[a] See Table I, footnote (*a*). [b] Neutralization equivalent = 303, obtained by titration in alcohol (Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April, 1950, Abstracts p.56C); the other peptides are too insoluble for this determination. [c] At 21°. [d] At 22°. [e] At 23°. [f] At 23°, c = 0.9

acetate (for the preparation of the free ester, *cf.* above under Compounds 1 and 2). The compound is isolated after 20 hours at room temperature and recrystallized from 95% ethanol.

The yield of pure carbobenzoxytetraalanine benzyl esters is 65–75%, based on the hydrazide used.

(7) **Z.Ala-(Ala)$_3$-Ala.OBz** (5L).—The carbobenzoxypentaalanine benzyl ester is prepared in two ways: (a) by coupling 0.1 mole of carbobenzoxydialanine azide (prepared[7] from Cmpd. 17, ref. 2) with 0.15 mole of trialanine benzyl ester in ethyl acetate (for the preparation of the free ester, *cf.* above Cmpds. 1 and 2); (b) by coupling 0.1 mole of carbobenzoxytrialanine azide (prepared as described above under Cmpd. 3) with 0.15 mole of dialanine benzyl ester (for the preparation of the free ester, *cf.* above under Cmpd. 1).

The carbobenzoxypentaalanine benzyl ester obtained by both procedures is insoluble in most organic solvents. It is purified by extracting with 95% boiling ethanol for 30 minutes, with a 75% yield of the pure product.

(8) **Z.Ala-(Ala)$_4$-Ala.OBz** (6L).—The carbobenzoxyhexaalanine benzyl ester is prepared by coupling 0.1 mole of carbobenzoxytrialanine azide (prepared as described above under Cmpd. 3) with 0.15 mole of trialanine benzyl ester (for the preparation of the free ester, *cf.* above under Cmpds. 1 and 2).

Compound 8 is insoluble in most organic solvents. It is purified by extracting with 95% boiling ethanol for 30 minutes, with a 75% yield of the pure product.

Peptides—Isomeric Tetraalanines (Compounds 9–12).—The carbobenzoxytetraalanine benzyl esters (Cmpds. 3–6) are hydrogenated in the usual way,[2] using 80% acetic acid as solvent. A volume of 180 cc. is used for 0.008 mole of Compound 3 and 150 cc. for 0.015 mole each of Compounds 4–6. The peptides are recrystallized from water–alcohol and dried in high vacuum at 56°. The yield of pure peptides is about 85%.

Tetraalanine (4L) (Cmpd. 9) is the only peptide obtained with one molecule of water. A previous preparation[8] from an α-halogen acid halide contained one molecule of water and gave $[\alpha]^{22}_{D}$ −122.5° (2.2% in 2 *N* HCl).

(13) **H.Ala-(Ala)$_3$-Ala.OH** (5L).—For the preparation of pentaalanine the corresponding carbobenzoxy benzyl ester is reduced in dimethyl formamide in the following way: 0.0045 mole of the ester (Cmpd. 7) is dissolved in 225 cc. of dimethyl formamide at 105°. The solution is cooled quickly to 45°, resulting in a fine suspension. About 1 g. of palladium black suspended in about 10 cc. of dimethyl formamide is added quickly and followed immediately by a rapid stream of hydrogen. After about 30 minutes, when the solution has cooled to about 25°, 2.5 cc. of 2 *N* HCl is added. After another 15 minutes, 50 cc. of water is added gradually over a 30-minute period to keep the reduced peptide in solution—care being taken not to precipitate unreduced material. After a total of about two hours, CO_2 evolution ceases and the solution is clear. Hydrogenation is continued for another two hours. Palladium black is filtered off and washed with 50 cc. of 0.1 *N* HCl. The peptide is precipitated by adding 2 cc. of pyridine to the combined filtrate and washings. After standing overnight in the ice-box, the peptide is filtered off and purified by dissolving in the calculated quantity of 0.25 *N* HCl, precipitating with pyridine, and washing thoroughly with alcohol and ether. For analysis it is dried in high vacuum at 100°. The yield of the pure peptide is 85%.

It was previously prepared[8] with $[\alpha]^{18}_{D}$ −136.4° (1.9% in 2 *N* HCl), containing one molecule of water which could not be removed in high vacuum at elevated temperature.

(14) **H.Ala-(Ala)$_4$-Ala.OH** (6L).—For the preparation of hexaalanine the corresponding carbobenzoxy benzyl ester is reduced in phenol in the following way: 0.0043 mole of the ester (Cmpd. 8) is dissolved in 175 cc. of phenol (saturated with water) by warming to 90°. The solution is then cooled rapidly to 40°. About 1 g. of palladium black suspended in about 10 cc. of phenol is added quickly to the slightly turbid solution, followed immediately by a rapid stream of hydrogen. After 20 minutes 2.5 cc. of 2 *N* HCl and 30 cc. of 95% ethanol are added. After hydrogenation has proceeded for one hour, 30 cc. of 50% ethanol is added to reduce the turbidity, and another 30 cc. after a second hour. At this point CO_2 evolution is negligible, and the solution becomes clear. Hydrogenation is continued for three more hours. Palladium black is then filtered off and washed with 50 cc. of a 1:1 (v./v.) mixture of 95% ethanol and 0.5 *N* HCl. An excess of pyridine is added to the combined filtrate and washings, followed by 250 cc. of 95% ethanol. After standing overnight in the ice-box, the gelatinous precipitate of the peptide is filtered off and washed

---

[7] As described previously[8] under "Carbobenzoxy Tripeptide Esters," except that ethyl acetate is used for extraction instead of ether–ethyl acetate.

[8] E. Abderhalden and W. Gohdes, *Fermentforschung*, **13**, 52 (1931).

with alcohol and ether. The peptide is purified by dissolving in 250 cc. of water containing a 50% molar excess of HCl, filtering, adding 150 cc. of absolute ethanol to the clear solution, and precipitating with pyridine. The precipitate is centrifuged off and washed repeatedly, first with absolute alcohol and then with ether. For analysis the material is dried *in vacuo* at 100°. The yield of pure peptide is about 78%. It was previously prepared[8] containing one molecule of water which could not be removed in high vacuum at elevated temperature; since the preparation was insoluble, no rotation was reported.[8]

This work was aided by a contract between the Office of Naval Research Department of the Navy and Columbia University (NR 122-260).

CORRECTION.—In Paper IV. Lysine Tripeptides, by E. Brand, *et al.*, THIS JOURNAL, **73**, 4026 (1951), Compound 5 in Table I should read Z.Ala-Z.Lys-Ala.OBz (L-L-D), and Compound 14 in Table II should read H.Ala-Lys-Ala.OH.HCl (L-L-D).

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY
NEW YORK 32, N. Y.
RECEIVED NOVEMBER 5, 1951

Optical Rotation of Peptides. VI. Tetra- and Pentapeptides Containing Alanine and Lysine[1]

BY ERWIN BRAND, BERNARD F. ERLANGER AND HOWARD SACHS

Previous papers in this series dealt with the synthesis and specific rotation of a number of alanine and lysine peptides.[2-5] In this paper the syntheses and specific rotations (in 0.5 *N* HCl) of two isomeric tetrapeptides and two isomeric pentapeptides containing lysine are presented. More detailed data on their specific rotations and on the *residue rotations*[6] of lysine and alanine residues in these peptides will be reported subsequently, as well as the action of certain proteolytic enzymes on these peptides.

Experimental[7]

The synthesis and properties of the starting materials have been previously described[8]: L-alanine[2]; L- and D-lysine[3]; Z.Ala-Z.Lys.NHNH$_2$ (2L and LD, ref. 3, Compds. 14, 15); Z.Ala-Z.Lys-Ala.NHNH$_2$ (3L, ref. 4, Compd. 10); benzyl ester hydroiodides of di- and tri-L-alanine (ref. 5, Cmpds. 1, 2).

Carbobenzoxytetrapeptide Benzyl Esters

(1) **Z.Ala-Z.Lys-Ala-Ala.OBz (4L).**—This compound is prepared by two different methods. (a) From a carbobenzoxy dipeptide azide and a dipeptide benzyl ester: 0.01 mole of Z.Ala-Z.Lys.NHNH$_2$ (2L, ref. 3, Cmpd. 14) is converted into the azide as described previously (ref. 4 under "Carbobenzoxy Tripeptide Esters") and added to an ethyl acetate solution of H.Ala-Ala.OBz (2L), prepared from 0.015 mole of the hydroiodide (ref. 5, Cmpd. 1). A white gelatinous precipitate forms almost immediately. The mixture is allowed to stand overnight at room temperature, the carbobenzoxytetrapeptide benzyl ester collected and recrystallized from absolute ethanol. The yield of pure product is 45%; m.p. 198° (all m.p. cor.).

Anal. Calcd. for $C_{38}H_{47}O_9N_5$ (717.8): N, 9.8. Found: N, 9.8.

(b) From a carbobenzoxy tripeptide azide and L-alanine benzyl ester: 0.006 mole of Z.Ala-Z.Lys-Ala.NHNH$_2$ (3L) (ref. 4, Cmpd. 10) is dissolved in 20 cc. of glacial acetic acid, 2 cc. of 5 *N* HCl and 120 cc. of water. The solution is cooled to −4°, and 0.006 mole of sodium nitrite dissolved in a small amount of water is added in one portion. The precipitated azide is extracted with ice-cold ethyl acetate, washed with ice-cold water and bicarbonate solution. If precipitation occurs in the ethyl acetate layer at this point, a small amount (10 cc.) of glacial acetic acid is added to it after removal of the aqueous bicarbonate layer. The clear ethyl acetate solution is then washed with ice-cold water, dried over sodium sulfate and added to L-alanine benzyl ester in ethyl acetate, prepared from 0.009 mole of the hydrochloride (ref. 2, Cmpd. 5). After standing overnight at room temperature, the carbobenzoxytetrapeptide benzyl ester is collected and recrystallized from absolute ethanol. Yield of pure product is 55%; m.p. 197°.

Anal. Calcd. for $C_{38}H_{47}O_9N_5$ (717.8): N, 9.8. Found: N, 9.8.

(2) **Z.Ala-Z.Lys-Ala-Ala.OBz (LDLL).**—The preparation of this compound is the same as that of Compound 1 (a), except that the isomeric (L-D) carbobenzoxy dipeptide hydrazide (ref. 3, Cmpd. 15) is used as one of the starting materials. The product is recrystallized from ethyl acetate. Yield of pure product is 45%; m.p. 166–167°.

Anal. Calcd. for $C_{38}H_{47}O_9N_5$ (717.8): N, 9.8. Found: N, 9.6.

TABLE I

TETRA- AND PENTAPEPTIDES CONTAINING ALANINE AND LYSINE ANALYTICAL DATA AND SPECIFIC ROTATION IN 0.5 *N* HCl
BASIS: FREE PEPTIDE

No.	Compound[a]	Molecular formula	Mol. wt.	Nitrogen, % Calcd.	Nitrogen, % Found	Amino N, % Calcd.	Amino N, % Found	HCl, % Calcd.	HCl, % Found	Neut. equiv.[b] Calcd.	Neut. equiv.[b] Found	$[\alpha]^{24}D$ (c 2)
5	**H.Ala-Lys-Ala-Ala.OH·2HCl (4L)**	$C_{15}H_{29}O_5N_5·2HCl$	432.4	16.2	16.0	6.5	6.5	16.9	16.6	144	147	− 78.0
6	**H.Ala-Lys-Ala-Ala.OH·HCl (LDLL)**	$C_{15}H_{29}O_5N_5·HCl$	395.9	17.7	17.5	7.1	7.1	9.2	9.1	198	190	− 18.6
7	**H.Ala-Lys-(Ala)$_2$-Ala.OH·HCl.H$_2$O (5L)**	$C_{18}H_{34}O_6N_6·HCl·H_2O$	485.0	17.3	17.1	5.8	5.8	7.5	7.3	243	244	−109.3[c]
8	**H.Ala-Lys-(Ala)$_2$-Ala.OH·HCl (LDLLL)**	$C_{18}H_{34}O_6N_6·HCl$	467.0	18.0	18.0	6.0	5.9	7.8	7.7	234	232	− 62.0[d]

[a] The following abbreviations are used (*cf.* refs. 2, 3 and 4, Table I, footnote *a*): Z, carbobenzoxy, $C_6H_5·CH_2OCO$; Ala, NH(CHCH$_3$)CO; Lys, NH(CHC$_4$H$_8$NH$_2$)CO; peptide linkage indicated by hyphen; Bz, $C_6H_5CH_2$; configuration follows compound in parentheses, *e.g.*, carbobenzoxy-L-alanyl-ε-carbobenzoxy-D-lysine hydrazide: Z.Ala–Z.Lys.NHNH$_2$ (L–D); carbobenzoxy-L-alanyl-ε-carbobenzoxy-L-lysyl-L-alanyl-L-alanine benzyl ester: **Z.Ala-Z.Lys-Ala-Ala.** OBz (4L); L-alanyl-D-lysyl-L-alanyl-L-alanyl-L-alanine monohydrochloride: H.Ala–Lys–(Ala)$_2$–Ala.OH.HCl (LDLLL). [b] Obtained by titration in alcohol (Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April, 1950, Abstracts, p. 56C). [c] At 23°. [d] At 27°.

Carbobenzoxypentapeptide Benzyl Esters

(3) **Z.Ala-Z.Lys-Ala-Ala.OBz (5L).**—The method of preparation of this compound is the same as that of Compound 1 (b). The carbobenzoxy tripeptide azide is coupled with the dipeptide benzyl ester, H.Ala-Ala.OBz (2L), prepared from a 50% molar excess of the hydroiodide (ref. 5, Cmpd. 1). Precipitation starts about 15 minutes after adding the azide solution to that of the dipeptide benzyl ester. After standing overnight at room temperature, the material is collected and recrystallized from glacial acetic acid-water. Yield of pure product is about 65%; m.p. 238–239°.

Anal. Calcd. for $C_{41}H_{52}O_{10}N_6$ (788.9): N, 10.7. Found: N, 10.5.

---

[1] Presented in part before the Division of Biological Chemistry at the 75th Anniversary Meeting of the A. C. S., New York, N. Y., September, 1951.

[2] B. F. Erlanger and E. Brand, THIS JOURNAL, **73**, 3508 (1951).

[3] B. F. Erlanger and E. Brand, *ibid.*, **73**, 4025 (1951).

[4] E. Brand B. F. Erlanger, J. Polatnick, H. Sachs and D. Kirschenbaum, *ibid.*, **73**, 4026 (1951).

[5] E. Brand, B. F. Erlanger and H. Sachs, *ibid.*, **74**, 1849 (1952).

[6] E. Brand and B. F. Erlanger, *ibid.*, **72**, 3314 (1950).

[7] We are indebted for analytical work to T. Zelmenis (total N) and to D. Kirschenbaum (amino N, HCl and neut. equiv.).

[8] For abbreviations see Table I, Footnote *a*.

(4) **Z.Ala-Z.Lys-Ala-Ala.OBz** (LDLLL).—The method of preparation of this compound is the same as that of Compounds 1 (a) and 2. The azide solution is prepared from Z.Ala-Z.Lys.NHNH$_2$ (LD, ref. 3, Cmpd. 15) and added to a solution of the tripeptide benzyl ester, prepared from a 50% molar excess of its hydroiodide (ref. 5, Cmpd. 2). A white gelatinous precipitate forms almost immediately. After standing overnight at room temperature, the material is collected and recrystallized from absolute ethanol. Yield of pure product is 62%; m.p. 213–214°.

Anal. Calcd. for $C_{41}H_{52}O_{10}N_6$ (788.9): N, 10.7. Found: N, 10.7.

Peptides (Compounds 5–8).—The peptides are isolated as hydrochlorides which are more or less hygroscopic (Cmpds. 6–8 as monohydrochlorides; Cmpd. 5 as dihydrochloride).

Hydrogenolysis of 0.005 mole of a carbobenzoxy peptide benzyl ester is carried out in 100 cc. of 85% acetic acid, containing 0.005 mole of *N* HCl (0.01 mole *N* HCl in the case of Cmpd. 1), with palladium black as catalyst in a rapid stream of hydrogen, as previously described.[3,4] Concentration of the filtrates *in vacuo* results in oils which crystallize upon dissolving in a small amount of absolute methanol and adding absolute ether. The compounds are recrystallized from a minimum amount of water by the addition of absolute alcohol followed by ether. The pure peptide hydrochlorides are obtained in 70–80% yield. For analysis and rotation measurements they are dried over P_2O_5 at 100° in high vacuum; the data are in Table I.

This work was aided by a contract between the Office of Naval Research, Department of the Navy, and Columbia University (NR 122-260).

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY
NEW YORK 32, N. Y.
RECEIVED DECEMBER 10, 1951

Chemistry of Technetium. II. Preparation of Technetium Metal[1]

BY J. W. COBBLE, C. M. NELSON, G. W. PARKER, W. T. SMITH, JR.,[2] AND G. E. BOYD

Recent large scale separations of technetium from fission product wastes at the Oak Ridge National Laboratory[3] have made chemical studies possible using readily weighable amounts.[4] The preparation of fractional gram quantities of pure metallic technetium was of interest since thus far only microgram amounts have been examined.[5,6] A tetraphenylarsonium perchlorate "process" precipitate containing coprecipitated pertechnetate was the starting material. This precipitate, which is quite stable toward common reagents, may be decomposed with difficulty by perchloric–sulfuric acid digestion. However, an electrolysis of its homogeneous solution in concentrated sulfuric acid afforded a convenient method.

About 0.2 g. of technetium together with 3–4 g. of tetraphenylarsonium perchlorate carrier in approximately one liter of sulfuric acid were electrolyzed for 24 hours with large platinum electrodes (C.D. = 10 ma./cm.^{2}, 2–3 volts). The black, technetium-containing solid which separated was filtered, dried, transferred to an all-glass distilling apparatus and then put into solution by gently warming with a mixture of five ml. each of concentrated nitric, perchloric and sulfuric acids. After the initially vigorous reaction subsided, the technetium was co-distilled with the perchloric acid and collected under dilute ammonium hydroxide. A variety of colors were noted in the acid distillate fractions, presumably owing to complexes similar to those postulated for manganese(VII)[7] and to those observed by us with rhenium(VII). The ammoniacal condensate was made slightly acid with HCl, bromine water was added and technetium sulfide (Tc_2S_7) precipitated with hydrogen sulfide. The coagulation of the slowly-forming, jet-black precipitate may be hastened by conducting operations on a water-bath at *ca.* 100°. The freshly precipitated sulfide dissolved readily in ammoniacal hydrogen peroxide and on evaporation to dryness NH_4TcO_4 and $(NH_4)_2SO_4$ were deposited. Technetium metal was prepared by hydrogen reduction of the latter mixture contained in a platinum boat. The initial reduction at low temperatures produced a black mass (TcO_2 ?) which prevented the loss of NH_4TcO_4 by sublimation. At the final higher temperature (500–600°) the $(NH_4)_2SO_4$ was volatilized leaving the technetium behind. Approximately 0.6 g. of spectrochemically pure metallic technetium has been isolated in the foregoing manner.

The metal, which shortly after reduction appeared as a silver-gray spongy mass, tarnished slowly in moist air. It did not dissolve in hot or cold, concentrated or dilute hydrochloric acid, nor was it attacked appreciably by alkaline hydrogen peroxide in agreement with Fried.[5] The metal did dissolve readily in nitric acid and aqua regia, and burned in oxygen to form Tc_2O_7.[4] Its atomic weight from previous chemical analyses on milligram quantities of the oxide was found to be 98.8 ± 0.1 which may be compared with the mass spectrometer value of 98.913.[8] Measurements on an X-ray diffraction pattern taken on the same preparation confirmed in detail the $\sin^2 \theta$ and intensity values of Mooney.[9,10]

Whereas the specific activity of pure technetium is not large (*ca.* 20 μc./mg.) it may constitute a radiation hazard in some circumstances. Pure, dry compounds have been found to show about 10 "R"/hr./100 mg. at their surfaces owing to the low energy beta particles emitted (300 kev. maximum energy). These radiations, however, are completely absorbed by ordinary glass laboratory equipment (*i.e.*, beakers, desiccators, etc.). Whether or not technetium is, in addition, a radiological poison is not known. Accordingly, small quantities should be handled with the foregoing facts in mind.

---

(1) This work was performed for the Atomic Energy Commission at Oak Ridge National Laboratory.

(2) University of Tennessee and Consultant, Oak Ridge National Laboratory.

(3) Hot Laboratory Group, Chemistry Division, G. W. Parker, Leader (W. J. Martin, G. M. Hebert, G. E. Creek and P. M. Lantz).

(4) G. E. Boyd, J. W. Cobble, C. M. Nelson and W. T. Smith, Jr., THIS JOURNAL, **74**, 556 (1952).

(5) S. Fried, *ibid.*, **70**, 442 (1948).

(6) R. C. L. Mooney, *Phys. Rev.*, **72**, 1269 (1947).

(7) W. M. Latimer and J. H. Hildebrand, "Reference Book of Inorganic Chemistry," The Macmillan Company, New York, N. Y., 1943, p. 374.

(8) M. G. Inghram, D. C. Hess, Jr., and R. J. Hayden, *Phys. Rev.*, **72**, 1269 (1947).

(9) The authors are indebted to Mr. R. D. Ellison of the Chemistry Division, ORNL, for this X-ray identification.

(10) R. C. L. Mooney, *Acta Cryst.*, **1**, 161 (1948).

CHEMISTRY DIVISION
OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENNESSEE AND
THE UNIVERSITY OF TENNESSEE
KNOXVILLE, TENNESSEE
RECEIVED DECEMBER 12, 1951

Separation of Keto-acids by Cellulose Columns[1]

BY FREDERICK D. DREW, LAWRENCE M. MARSHALL AND FELIX FRIEDBERG

Because of the instability of keto-acids the separation of these compounds as 2,4-dinitrophenylhydrazones becomes particularly useful. One such separation by column chromatography for biologically important keto-acids has been reported.[2] Cavallini, *et al.*,[3] suggested filter paper chromatography of 2,4-dinitrophenylhydrazones. In this report

---

(1) This investigation was supported in part by research grants from the National Cancer Institute and the United States Public Health Service, and from the Damon Runyan Memorial Fund.

(2) G. A. LePage, *Cancer Research*, **10**, 393 (1950).

(3) D. Cavallini, N. Frontali and G. Toschi, *Nature*, **163**, 568 (1949).

their method has been applied to column chromatography, using a cellulose product (Solka-Floc BW100, supplied by the Brown Company, Berlin, N. H.) and alcohols of different chain length. The order of emergence of the keto-acid derivatives agrees with the R_f values obtained by Cavallini, *et al.*[3] As the R_f values increase longer alcohol chains are needed for adequate resolution.

One to two grams of Solka-Floc was suspended in ammonia saturated *n*-amyl alcohol and introduced into a glass tube of 30-cm. length and 0.6-cm. diameter, the tip of which was plugged with a tuft of cotton. After the column had settled, 0.1 to 0.4 mg. of the hydrazones dissolved in 0.2 ml. of *n*-butanol or ethyl ether were introduced. As soon as the solution had entered the column completely the eluant was added. For satisfactory results, excess moisture must be avoided. Effluent fractions of 0.70 ml. per tube collected on a Technicon collector were diluted to 3.70 ml. with *n*-butanol, then hydrazone concentrations were measured by a Beckman spectrophotometer at 380 mμ. This method of reading hydrazone concentrations at this wave length was found to be not only simpler but 1.5 times more sensitive than alkalization and reading in the visible range.[2] Also, the color of the hydrazones in the butanol diluent was stable for several hours. Whenever there was present any free 2,4-dinitrophenylhydrazine in the sample, the acids were extracted into an ethyl ether and 0.2 ml. was placed on the column in order to effect an adequate separation of the reagent from the hydrazones.

Figure 1 shows the separation of pyruvic, oxalacetic and α-ketoglutaric acid hydrazones, using *n*-amyl alcohol saturated with ammonia as eluant. Figure 2 shows that of pyruvic, α-ketobutyric, and α-keto-γ-methiolbutyric acid hydrazones, using *n*-decyl alcohol saturated with ammonia as eluant.

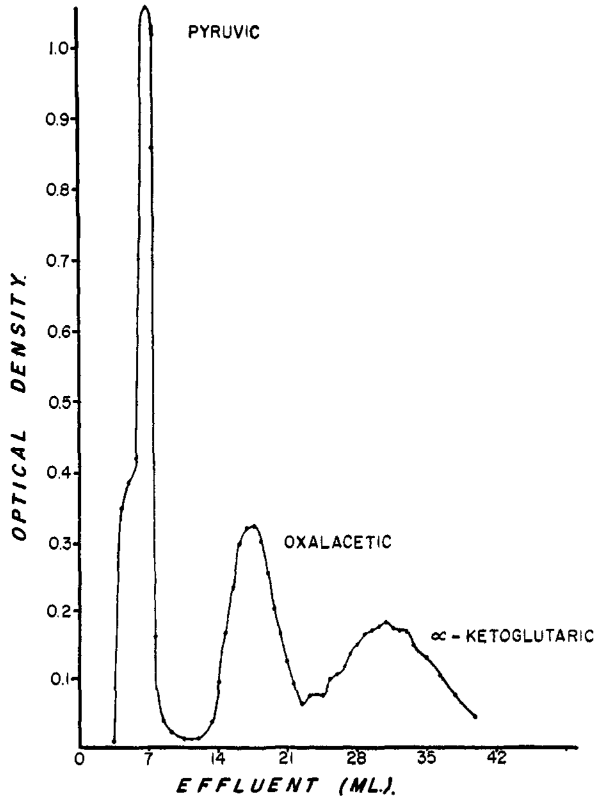


Fig. 1.—Chromatograph of pyruvic, oxalacetic and α-ketoglutaric acid hydrazones.

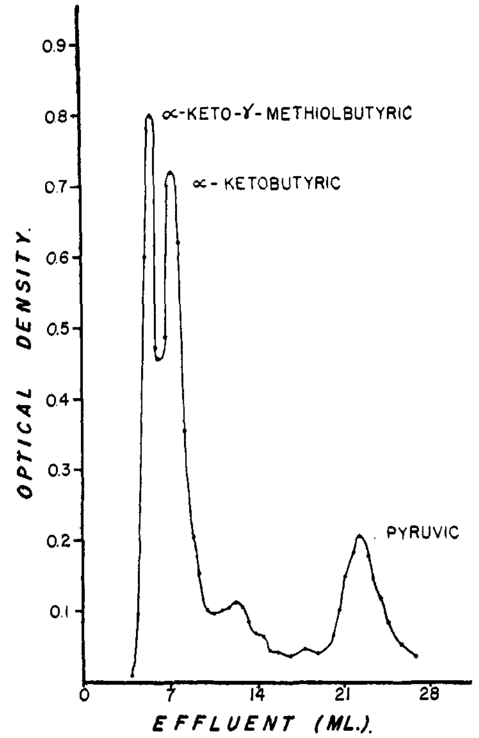


Fig. 2.—Chromatograph of pyruvic, α-ketobutyric and α-keto-γ-methiolbutyric acid hydrazones.

It was found that in conditions of best resolution, there was a separation of the pyruvic acid hydrazone into two bands, as reported by LePage.[2] All five acids may be separated on one chromatographic run by the use of a developing liquid delivered from a reservoir so arranged that the *n*-butyl-*n*-decyl alcohol mixture will gradually and automatically increase with respect to the concentration of the *n*-butyl alcohol.[4] The acids emerge in the following order: γ-methiol-α-ketobutyric, α-ketobutyric, pyruvic, oxalacetic and α-ketoglutaric. By this method, recovery of the hydrazones ranged from 75 to 90%, being highest for the pyruvic acid hydrazone. For identification, the emerging hydrazones were mounted on NaCl crystals and examined in the infrared spectrum between 1800 and 1400 cm.$^{-1}$

[4] K. Donaldson, V. Tulane and L. M. Marshall, *Anal. Chem.* (in press).

DEPARTMENT OF BIOCHEMISTRY
SCHOOL OF MEDICINE
HOWARD UNIVERSITY
WASHINGTON, D. C.

RECEIVED DECEMBER 6, 1951

The Photochemical Chlorination of Methylsilicones

BY J. R. ELLIOTT AND E. M. BOLDEBUCK

The photochemical reaction of ferric chloride with organic materials such as alcohols,[1] acids,[2] al-

---

[1] M. Prasad and P. S. Limaye, *J. Indian Chem. Soc.*, **10**, 91, 101 (1933).

[2] J. C. Ghosh and R. M. Purakayastha, *ibid.*, **6**, 827 (1929).

dehydes[3] and ethers,[3,4] has been described. In the case of ethyl ether,[4] the products of reaction are reported to include ferrous chloride dihydrate, di- and trichlorinated ether, and polymeric aldehydes.

We have found that methylsilicone solutions of anhydrous ferric chloride are stable in the dark but immediately reactive in sunlight. In an illuminated hexamethyldisiloxane solution, ferric chloride is converted completely to ferrous chloride. Half the chlorine available from the reduction of ferric chloride appears as hydrolyzable chlorine; the second half is non-hydrolyzable. Reaction products identified include hydrogen chloride, trimethylchlorosilane, water and chloromethylpentamethyldisiloxane. These products can all be accounted for if one assumes chlorination of a methyl group accompanied by formation of hydrogen chloride. Attack of the siloxane bond by hydrogen chloride would produce a chlorosilane and a silanol; water would then be formed by subsequent condensation of silanols.

Experimental

Procedure.—A weighed portion of reagent grade iron wire was quantitatively converted to ferric chloride by reaction with chlorine in a dry vacuum system, and was sublimed under chlorine into a Pyrex reaction tube. A weighed amount of previously degassed hexamethyldisiloxane was then distilled directly into the reaction tube. A portion of the resulting yellow solution appeared unchanged after standing two weeks in the dark.

The yellow solution, generally containing undissolved ferric chloride, was illuminated with a General Electric H-6 water-cooled mercury capillary arc until both the solution and the solid were colorless. The liquid product was then separated from the solid residue by vacuum distillation at room temperature. When the solid appeared dry, the system was brought to atmospheric pressure with dry nitrogen.

Analysis of Volatile Products.—Mass spectrometer analysis of various fractions of the volatile products of one run indicated that at liquid nitrogen temperature, no non-condensable gases except a trace of nitrogen were present; at room temperature hexamethyldisiloxane, trimethylchlorosilane and hydrogen chloride were indicated. Analysis of various fractions of the liquid by mass spectrometer and infrared absorption gave no indication of molecules containing C–C bonds.

Chlorine analyses from two preparations are listed in Table I.

TABLE I

DISTRIBUTION OF CHLORINE IN PRODUCTS

Prep. No.	Initial mole $FeCl_3$	Mole siloxane	Time of illum.	Mole hydrol. chlorine	Mole non-hydrol. chlorine
A	0.0013	0.45	45 min.	0.00062	....
B	.016	.69	6 hr.	.0078	0.0078

The distillate from A was hydrolyzed in an ether–ice mixture and titrated for acid directly. Distillate from B was hydrolyzed and washed with ice-water until the washings were neutral. Acid content of the aqueous phase was determined by titration. All chlorine originally present as hydrogen chloride or chlorosilane was thereby determined as aqueous hydrochloric acid.

Water-insoluble liquid from B was distilled in a small fractionating column of about 10 plates to remove unreacted hexamethyldisiloxane, boiling at 100°. A portion of the liquid residue, which contained undistilled hexamethyldisiloxane and a chlorinated material, was analyzed for chlorine by Parr bomb fusion. A micro-boiling point measurement of the residue reached a constant temperature at 150°, indicating the presence of chloromethylpentamethyldisiloxane (b.p. 152°). Since the silicon–carbon bond of chlorinated methyldisiloxanes is readily cleaved by alkali to give the corresponding chloromethanes,[5] the residue was heated at 80° with potassium hydroxide pellets. The exit gases were condensed in a Dry Ice, acetone-cooled trap; and were examined in the mass spectrometer. All possible fragments of methyl chloride were identified and, in addition, a trace of hexamethyldisiloxane; no di- or trichlorinated carbon derivative was found. It was thus assumed that the non-hydrolyzable chlorine was present exclusively in chloromethylpentamethyldisiloxane.

Analysis of Residue.—Aqueous solutions of the light gray, powdery residue gave strong tests for ferrous and chloride ions, a faint test for ferric ion. Iron content of the salt, after oxidation by bromine, was determined colorimetrically in 30% HCl at 4200 Å. by the use of the Beckman spectrophotometer. Chlorine was determined by the Volhard method.

Water content of the residue from B was determined by heating a portion of the residue to 200° in a stream of dry hydrogen chloride. Exit vapors were passed through a Dry Ice–acetone-cooled trap and the condensate was examined for water by the Karl Fischer method. Water content of the original hexamethyldisiloxane used in the reaction was less than 1% of that found in the products.

Results of analyses of the residue from preparations A and B are listed in Table II.

TABLE II

ANALYSES OF SOLID RESIDUE

Prep. No.	Iron, %	Chlorine, %	Wt. loss at 200°, %	H_2O, %	Calculated formula
A	38.6	49.3	..	...	$FeCl_{2.01}$
B	39.3	50.3	10.9	2.4	$FeCl_{2.02}\cdot 0.18H_2O$

A portion of the residue from preparation A was heated at 100° in the vacuum system at 10^{-4} mm. pressure. The small amount of distillate was composed of water and a carbon tetrachloride soluble phase. Examination of the carbon tetrachloride solution by infrared absorption showed no evidence of C–C bonds, but over the limited range of measurement gave the absorption curve of hexamethyldisiloxane.

Influence of Oxygen.—Sixty-five grams of a 1 mole % suspension of ferric chloride in hexamethyldisiloxane was prepared in the vacuum system as described above and dry oxygen was bubbled through the solution during a 40-minute period of illumination. Exit gases, which were collected in a liquid nitrogen-cooled trap, had a strong formaldehyde odor. Contents of the trap were dissolved in water and examined for formaldehyde by the standard hydrogen peroxide method.[6] A total of 5 mg. of formaldehyde was found.

Acknowledgment.—We are indebted to Dr. F. J. Norton for the mass spectrometer analyses; to Dr. D. J. Mead for infrared absorption measurements; and to Dr. E. H. Winslow and Mr. E. A. Beacham for chemical analyses.

---

[3] A. Benrath, *J. prakt. Chem.*, [2] **72**, 220 (1905).

[4] E. Puxeddu, *Gazz. chim. ital.*, **50**, 153 (1920).

[5] R. H. Krieble and J. R. Elliott, THIS JOURNAL, **68**, 2291 (1946).

[6] J. Assoc. Official Agr. Chem., Methods of Analysis. p. 75 (1916).

RESEARCH LABORATORY
GENERAL ELECTRIC CO.
SCHENECTADY, NEW YORK

RECEIVED DECEMBER 17, 1951

Chain Transfer of Styrene with Various Dihalides and the Preparation of Polystyrene Dihalides

BY J. A. GANNON, E. M. FETTES AND A. V. TOBOLSKY

One method for preparing chain molecules of low or intermediate molecular weight terminated on both ends by a halogen atom is to carry out a vinyl or diene polymerization in the presence of a dihalide which acts as a chain transfer agent. The polymeric dihalides thus produced (whose formula in a simple case would be $X(CH_2CHY)_nX'$) can then be used in further polymerizations, as for example in a polysulfide condensation. In all cases a heterogeneous distribution of molecular weights is obtained in the preparation of the polymeric dihalides which in the simplest case would be a "random" distribution.[1,2]

The most desirable chain transfer agent to be used in this connection is one whose chain transfer constant is close to unity. In this case the number average and weight average molecular weights should be approximately independent of conversion and the distribution of molecular weights at high conversion should be much less heterogeneous than is the case when the chain transfer constant differs appreciably from unity.

We investigated numerous dihalides as chain transfer agents for styrene polymerization in an attempt to select several whose chain transfer constants were close to unity. The data for chain transfer constant were obtained in most cases at 60° and in some cases at 80°. The experimental procedure used was identical with that reported by Gregg and Mayo[3,4] using intrinsic viscosity to obtain number average degree of polymerization.

To check our experimental accuracy we redetermined the values for the chain transfer constant of carbon tetrachloride with styrene at 60°. Our value was 0.0087 compared with the Gregg–Mayo value[3] of 0.0093.

The following observations should be pointed out: (1) In using the Gregg–Mayo method, it is very necessary to produce polymers of very low conversion. (2) In certain cases we used thermal initiation and in other cases we used benzoyl peroxide as an initiator. The results are independent of the form of initiation. (3) When large quantities of the most active dihalides were used an important retardation of polymerization was observed in the presence or absence of catalyst. (4) The molecular weight distributions to be expected when symmetrical dihalides are used as transfer agents is different from the simpler case when one halogen atom is very active to chain transfer and the other is relatively inert. (5) When dichlorides are used as the transfer agent we believe that very often hydrogen atoms rather than chlorine atoms are abstracted which, of course, does not produce polymers with a chlorine atom at each end. On the other hand, when dibromides or diiodides are used, polystyrene molecules are formed with a bromine or iodine atom at each end. (6) A certain fraction of the chains, corresponding to those that were initiated by catalyst fragments, or possibly by the thermal initiation, have bromine or iodine atoms at only one end. This fraction is small when active chain transfer agents are used in large concentrations. (7) At high conversions important transfer occurs with the halide terminated polymer as well as with the original dihalide molecules.

Table I shows the chain transfer constants for various purified dihalides with styrene obtained under the indicated conditions.

The results indicate that for comparable molecules iodides are more active than bromides and bromides more active than chlorides. Allylic or benzylic halides are exceptionally active, which has been previously noted for hydrocarbons.[4] The halogen atom on an acid halide is also extremely active.

TABLE I

CHAIN TRANSFER CONSTANTS FOR STYRENE WITH VARIOUS DIHALIDES

Dihalide	Temp., °C.	Weight % benozyl peroxide	Chain transfer constant
Bischloroethylformal	80	0.0165	0.00060
Methylene dichloride	80	.0165	.00095
Ethylene dichloride	80	.0165	.00098
1,4-Dichlorobutene-2	80	.0165	.0051
Chloroacetyl chloride	60	None	.330
Methylene dibromide	60	None	.011
p-Xylylene dibromide	60	None	.015
Styrene dibromide	60	None	.195
Stilbene dibromide	60	None	.302
Bromoacetic acid[b]	60	None	.043
Acetyl bromide[a,b]	60	None	.86
Methylene diiodide	60	None	.071

[a] Value somewhat uncertain due to partial hydrolysis. [b] Monohalides.

Acknowledgment.—The authors express their appreciation to the Engineer Research and Development Laboratories and the Research and Development Branch, Quartermaster Corps for financial support for this research.

THIOKEL CORPORATION
TRENTON, N. J., AND
DEPARTMENT OF CHEMISTRY
PRINCETON UNIVERSITY
PRINCETON, N. J.

RECEIVED DECEMBER 3, 1951

---

[1] H. Mark and A. V. Tobolsky, "The Physical Chemistry of High Polymeric Systems," Interscience Publishers, Inc., New York, N. Y., 1950, pp. 410–416.

[2] R. C. Fettes, A. V. Tobolsky and D. H. Johnson, Plastics Laboratory Report No. 17A, March 15, 1950. Available on request from Plastics Lab., Princeton University.

[3] R. A. Gregg and F. R. Mayo, THIS JOURNAL, **70**, 2373 (1948).

[4] R. A. Gregg and F. R. Mayo, *Discussions of the Faraday Soc.*, **2**, 328 (1947).

Reduction of an Amidine with Lithium Aluminum Hydride

BY R. T. GILSDORF AND F. F. NORD

Because of the structural similarity existing between amidines and amides, interest in the former class of compounds was fostered in these laboratories[1a,b] when reports[2,3] appeared in the literature on the reduction of amides with lithium aluminum hydride. An investigation was undertaken to ascertain whether amidines would behave analogously to amides when similarly treated. Study of the literature revealed that, in general, amidines in the free state are quite prone to hydrolysis to the corresponding amides, thus rendering them unsuitable for comparison with amides since the products could not be established as arising from the reduction of the amidine or the amide generated from the amidine by hydrolysis.

However, one class of amidines, *i.e.*, those which are N,N-disubstituted aromatic derivatives, seem

---

[1] (a) R. T. Gilsdorf and F. F. Nord, *J. Org. Chem.*, **15**, 807 (1950); (b) R. T. Gilsdorf and F. F. Nord, THIS JOURNAL, **74**, 1837 (1952).

[2] R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948).

[3] A. Uffer and E. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

to be stable toward hydrolysis. Therefore, a typical representative of this group, N,N-diethylbenzamidine, was subjected to the action of an excess of lithium aluminum hydride, and its reduction was found to be analogous to that of N,N-diethylbenzamide, the former yielding benzylamine, the latter, benzyl alcohol.[2]

Experimental[4]

Benzylamine.—N,N-Diethylbenzamidine (13.5 g., 0.0767 mole) in 50 ml. of absolute ether reacted with lithium aluminum hydride (3.8 g., 0.1 mole) in 200 ml. of absolute ether in the usual way.[2] After the completion of the addition, reflux was continued on the steam-bath for 20 hours. Hydrolysis of the organometallic complex was carried out with 200 ml. of 5% sodium hydroxide. Rectification afforded 1.1 g. (15.4%) of benzylamine, b.p. 60° (7 mm.), and 9.8 g. (72.5%) of N,N-diethylbenzamidine, b.p. 114° (7 mm.).

Phenylthioureide.—The reaction of benzylamine with phenyl isothiocyanate[5] gave the phenylthioureide. The product was recrystallized from 95% ethanol to yield white crystals, m.p. 153–154°, as recorded in the literature.[6]

Anal. Calcd. for $C_{14}H_{14}N_2S$: N, 11.56. Found: N, 11.40.

Picrate.—When benzylamine was treated with picric acid in 95% ethanol, a yellow precipitate was obtained on standing overnight. Washing with 95% ethanol afforded a product of m.p.[7] 194–195°.

Anal. Calcd. for $C_{13}H_{12}N_4O_7$: N, 16.66. Found: N, 16.65.

---

(4) All m.ps. and b.ps. are uncorrected.

(5) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 206.

(6) K. N. Campbell, B. K. Campbell and S. J. Patelski, *Proc. Ind. Acad. Sci.*, **53**, 119 (1943).

(7) R. Boudet, *Bull. soc. chim.*, [5] **15**, 390 (1948), reported 195–196°.

CONTRIBUTION NO. 246 FROM THE DEPARTMENT OF
ORGANIC CHEMISTRY AND ENZYMOLOGY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.
RECEIVED OCTOBER 26, 1951

Cleavage of Tetraphenylsilane and Benzyltriphenylsilane by Potassium Amide[1]

BY CHARLES R. HANCE AND CHARLES R. HAUSER

It was shown recently[2] that the benzyl-, diphenylmethyl- and triphenylmethyltrimethylsilanes are cleaved by potassium amide in liquid ammonia to form toluene, diphenylmethane and triphenylmethane, respectively. It has now been found that even tetraphenylsilane is cleaved readily by this base, benzene being isolated in 62% yield. The reaction may be represented by equation 1. As with other tetrasubstituted silanes,[2] the mechanism involves presumably the displacement of the hydrocarbon anion from silicon accompanied by the acquisition of a proton from the medium to form the hydrocarbon.

$$(C_6H_5)_3Si—C_6H_5 \xrightarrow[NH_3]{K^+NH_2^-} C_6H_6 + \text{silicate} \quad (1)$$

Similarly, benzyltriphenylsilane was cleaved by potassium amide in liquid ammonia, both benzene and toluene apparently being formed. This tetrasubstituted hydrocarbon silane was synthesized in 51% yield from triphenylchlorosilane and benzylmagnesium chloride.

Experimental

Triphenylchlorosilane (practical grade), obtained from Anderson Laboratories, Inc., was purified by distillation at 2 mm. followed by several recrystallizations from benzene and petroleum ether (b.p. 30–60°); the product then melted at 88–90°. Tetraphenylsilane, also obtained from Anderson Laboratories, was recrystallized once from benzene; the product then melted at 231–233°.

Benzyltriphenylsilane.—To a stirred solution of benzylmagnesium chloride (prepared from 0.31 mole of benzyl chloride and 0.29 mole of magnesium) in 500 ml. of anhydrous ether was added 29.4 g. (0.1 mole) of triphenylchlorosilane in 100 ml. of ether. The mixture was refluxed 13 hours and allowed to stand 40 hours. The ether was removed and the residue heated on the steam-bath 11 hours. After adding ether again, the mixture was decomposed with 200 ml. of 25% (by volume) hydrochloric acid. The ether phase was washed several times with water and 10% sodium bicarbonate, dried over anhydrous sodium sulfate, and the solvent removed. The residue was taken up in petroleum ether (b.p. 30–60°) and the solution washed successively with concentrated sulfuric acid, water and 10% sodium bicarbonate. After drying over sodium sulfate, the solution was concentrated to one-fourth its volume to precipitate 17.7 g. (51%) of benzyltriphenylsilane (m.p. 96–98°). Recrystallization from 95% ethanol gave the pure compound melting at 98–99.5°.

Anal.[3] Calcd. for $C_{25}H_{22}Si$: C, 85.68; H, 6.33. Found: C, 85.55; H, 6.40.

Cleavages by Potassium Amide.—Tetraphenylsilane (9.4 g., 0.028 mole) was stirred one hour with 0.0665 mole of potassium amide in 200 ml. of liquid ammonia. After neutralizing the muddy brown mixture with excess (10 g.) ammonium chloride, ether (100 ml.) was added and the ammonia allowed to evaporate. The mixture was filtered and the insoluble salts washed with ether. The filtrate and washings were fractionated through a 30-cm. glass helices-packed column to give 5.4 g. (62%) of benzene boiling at 78–80°, $n^{24}D$ 1.4890; *m*-dinitro derivative, m.p. and mixed m.p. 88–89°. The solid salts were treated with water leaving undissolved a granular material (1.9 g.) which appeared to be an inorganic silicate.

Similarly, benzyltriphenylsilane (3.90 g., 0.0111 mole) was stirred one hour with 0.048 mole of potassium amide in 200 ml. of liquid ammonia. The orange-red mixture was decomposed with ammonium chloride, the liquid ammonia replaced by ether and the mixture filtered. Fractionation of the filtrate gave 0.6 g. of material, b.p. 89–100°, having the characteristics of a mixture of benzene and toluene. None of the original silane was recovered. There was obtained from the solid a granular material (0.5 g.) which appeared to be an inorganic silicate.

---

(1) This work was supported by a grant from the Duke University Research Council.

(2) C. R. Hauser and C. R. Hance, THIS JOURNAL, **73**, 5846 (1951).

(3) Analysis by Clark Microanalytical Laboratory, Urbana, Ill.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, N. C.
RECEIVED DECEMBER 17, 1951

The Synthesis of Doubly Labeled Parathion

BY R. E. HEIN AND R. H. MCFARLAND

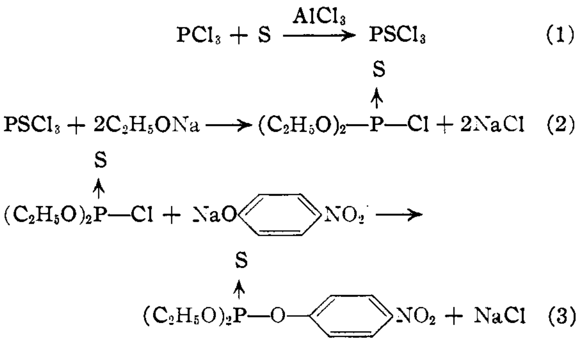
As an aid in studying the mode of action and metabolism of O,O-diethyl O-*p*-nitrophenyl thiophosphate (parathion), the synthesis of a labeled compound was undertaken. The synthesis of parathion starting with either thiophosphoric trichloride[1] ($PSCl_3$) or phosphorus pentasulfide[2] (P_2S_5) has been described previously. Phosphorus trichloride may also be utilized as a starting material. The direct

---

(1) J. H. Fletcher, J. C. Hamilton, I. Hechenbleikner, E. I. Hoegberg, B. J. Sertl and J. T. Cassaday, THIS JOURNAL, **72**, 2461 (1950).

(2) J. H. Fletcher, J. C. Hamilton, I. Hechenbleikner, E. I. Hoegberg, B. J. Sertl and J. T. Cassaday, *ibid.*, **70**, 3943 (1948).

combination of sulfur and phosphorus trichloride in the presence of anhydrous aluminum chloride produces thiophosphoric trichloride[3] in 97% yield. The steps in the synthesis of parathion are



$$PCl_3 + S \xrightarrow{AlCl_3} PSCl_3 \quad (1)$$

$$PSCl_3 + 2C_2H_5ONa \longrightarrow (C_2H_5O)_2\overset{\overset{S}{\uparrow}}{P}\text{—}Cl + 2NaCl \quad (2)$$

(3)

While the insecticide may be tagged with C^{14}, P^{32} or S^{35}, from the radiation detection standpoint, cost and waste disposal, it seemed advisable in this preliminary experimentation to label with P^{32}. Although not previously reported in the literature, if labeled phosphorus trichloride could be produced by neutron bombardment of phosphorus trichloride, the starting material could be obtained in this manner. Complicating factors in this procedure are the production of S^{35} by a (n,p) reaction on Cl^{35} isotopes in the phosphorus trichloride molecule and the subsequent recoil energies given to the molecule both by this reaction and the (n,γ) reaction producing P^{32}. As the recoil energies are sufficient to break the phosphorus-chlorine bonds, the production of labeled phosphorus trichloride depends on the recombination of fragments. Experimentally, one gram of phosphorus trichloride irradiated in the Oak Ridge reactor for three weeks did contain labeled phosphorus trichloride. Further, either the chemical form of S^{35} was such as to be incorporated in the thiophosphoric trichloride in step I or trace amounts of labeled thiophosphoric trichloride were synthesized by the recombination of fragments during bombardment. In any event, the insecticide was labeled with both P^{32} and S^{35}.

Since the preparation of labeled parathion was to be carried out on a semi-micro basis (1 g. PCl_3 starting weight), several syntheses were performed with inactive materials on this scale. When consistent, although low yields, for the individual steps and over-all process (25% based on starting weight of PCl_3) had been attained and the purity of the product established by the standard colorimetric method,[4] radioactive parathion was synthesized from the irradiated PCl_3. An over-all yield of 26% was obtained with a specific activity of 2 microcuries/mg. of parathion.

The chemical purity of the active parathion was established by the method of Averell and Norris[4] and found to be 94% parathion. The radiochemical purity of the insecticide was established by absorption of the emitted radiations in aluminum. Analysis of this information indicated that only P^{32} and S^{35} were present in the final product.

As a result of the covalent bonding of the phosphorus atom in parathion, it is unlikely that exchange would take place between that atom and other phosphorus atoms. However, this possibility was tested by shaking mixtures of inactive parathion and P^{32}-labeled phosphate ion in the presence of various radiation sources for periods of several hours. No exchange took place. In similar tests with the radioactive parathion, no exchange of the labeled phosphorus or sulfur atoms with the substrate occurred.

Experimental

Thiophosphoric Trichloride.—Anhydrous aluminum chloride (0.1–0.2 g.) was added to 1 g. of phosphorus trichloride and 0.24 g. of powdered sulfur. On heating in a water-bath to the b.p. of phosphorus trichloride (74°) the reaction proceeded rapidly (30 sec.) particularly with 0.2 g. of aluminum chloride. After the solution was cooled, the aluminum chloride was extracted in 0.3 ml. of water and the thiophosphoric trichloride layer dried with calcium chloride. The thiophosphoric trichloride was then distilled (at 124–126°) into the second reaction vessel. The average yield for three runs with inactive materials for this step was 78%. The yield with active phosphorus trichloride was 61%.

O,O-Diethyl Chlorothiophosphate.—The method of synthesis for the trial runs and active compound was very similar to that described by Fletcher and colleagues.[1] Because of the semi-micro scale the organic layer was transferred by capillaries rather than filtering. The average yield on this step for two inactive runs was 42.5%. Because of better stirring techniques the yield with active thiophosphoric trichloride was 69%.

Parathion.—The general procedure for *p*-nitrophenyl thiophosphates as reported by Fletcher, *et al.*,[2] was followed in this step with the exception again that the transferring of the active compound was done by capillaries. The average yield for two inactive runs was 51% and for the active material a 69% yield was obtained.

Acknowledgment.—The authors are grateful to E. W. Robb, P. A. Dahm and F. C. Fountaine for their interest and aid in this problem. This work was supported in part by funds from the American Cyanamid Company.

DEPARTMENTS OF CHEMISTRY AND PHYSICS
KANSAS STATE COLLEGE
MANHATTAN, KANSAS

RECEIVED NOVEMBER 8, 1951

---

(3) F. Knotz, *Osterr. Chem. Z.*, **50**, 128 (1949).

(4) P. R. Averell and M. V. Norris, *Anal. Chem.*, **20**, 753 (1948).

Cholesteryl Laurate[1]

BY DAVID KRITCHEVSKY AND MARGARET E. ANDERSON

Several isomorphic modifications of cholesteryl laurate have been reported. Page and Rudy[2] prepared the ester, m.p. 91°, $[\alpha]_D$ −27.6°, by heating cholesterol and lauric acid in a current of carbon dioxide; Jaeger[3] used the same method to obtain an ester m.p. 100°; Cataline and co-workers[4] heated the sterol and acid in benzene in the presence of benzene sulfonic acid to obtain this compound m.p. 92° and Abderhalden and Kautzsch[5] heated a chloroform solution of cholesterol and lauroyl chloride to obtain a product sintering at 78°, m.p. 110°; $[\alpha]_D$ −31.3°. In our hands, heating a pyridine solution of the sterol and acid chloride[6] yielded an

---

(1) This work was sponsored by the U. S. Atomic Energy Commission.

(2) I. H. Page and H. Rudy, *Biochem. Z.*, **220**, 304 (1930).

(3) F. M. Jaeger, *Rec. trav. chim.*, **25**, 334 (1906), quoted by Page and Rudy.

(4) E. L. Cataline, L. Worrell, S. F. Jeffries and S. A. Aronson, *J. Am. Pharm. Assoc.*, **33**, 107 (1944).

(5) E. Abderhalden and K. Kautzsch, *Z. physiol. Chem.*, **65**, 69 (1910).

(6) D. Kritchevsky, THIS JOURNAL, **65**, 480 (1943).

ester, m.p. 78–78.5°; $[\alpha]^{21}D$ −30.3°. Two other preparations of this ester following the methods of Page[2] and of Cataline[4] gave material melting at 75–76° and 74–75°, respectively. Crystallizations from acetone, ethanol or chloroform–methanol did not alter the melting point in any case. A sample of our material maintained at 75° for 100 hours melted over the range 75–85°. Another sample, maintained at 80° for 100 hours melted, after solidification, over the range 60–78°.

Our preparation would appear to be a hitherto unreported isomorphic modification of cholesteryl laurate.

Experimental[7]

Starting Materials.—Cholesterol (Amerchol), m.p. 141–143°; Lauric Acid (Eastman Kodak), m.p. 37°. The acid chloride gave quantitative yields of the amide, m.p. 99° (lit.[8] 98°) and anilide, m.p. 75° (lit.[8] 76°) when treated with ammonium hydroxide and aniline, respectively.

Cholesteryl Laurate.—A solution of 28 g. of cholesterol and 17.5 g. of lauroyl chloride in 25 cc. of pyridine was heated to boiling, and, after one minute, allowed to cool. The brown solid obtained on cooling was dissolved in ether, washed free of excess pyridine and acid and the ether dried over anhydrous sodium sulfate. Distillation of the ether left a tan solid, m.p. 73–76°. Three crystallizations from chloroform–methanol yielded 33 g. (80%) of white needles, m.p. 78–78.5°, $[\alpha]^{21}D$ −30.3° ($CHCl_3$).

Anal.[9] Calcd. for $C_{39}H_{68}O_2$: C, 82.33; H, 12.05. Found: C, 82.21; H, 11.99.

Cholesteryl Laurate.[2]—Lauric acid (4 g.) and cholesterol (2 g.) were heated in a stream of carbon dioxide at 200° for 3 hours. After removal of excess acid the ester was obtained as white needles from chloroform–methanol, m.p. 75–76°; $[\alpha]^{19}D$ −30.2° ($CHCl_3$). Mixed melting point with first preparation, 75–76°.

Cholesteryl Laurate.[4]—A solution of 5.8 g. of cholesterol, 3 g. of lauric acid and 0.13 g. of *p*-toluenesulfonic acid in 75 cc. of benzene was allowed to reflux, under constant water take-off, for 3 hours. After removal of all acidic material, the ester was crystallized from chloroform–methanol, m.p. 74–75°, $[\alpha]^{21}D$ −28.8° ($CHCl_3$). Mixed melting point with the initial preparation, 74–75°; mixed melting point with the second preparation, 75–76°.

---

[7] All melting points corrected.

[8] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 223.

[9] Analysis by Mr. V. Tashinian of the microanalytical laboratory, University of California, Berkeley.

RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA
RECEIVED NOVEMBER 21, 1951

Trifluoromethyl Substituted Biphenyls and Diphenyl Ethers

BY MOUSHY MARKARIAN

The recent interest in trifluoromethyl substituted biphenyls and diphenyl ethers[1,2] prompts us to report the syntheses of 3,3′-bis-(trifluoromethyl)-biphenyl, 4,4′-bis-(trifluoromethyl)-biphenyl, 3-trifluoromethyl diphenyl ether, 3-trifluoromethyl-4′-chlorodiphenyl ether, 3-trifluoromethyl 3′-ethyldiphenyl ether and 3-trifluoromethyl phenyl-α-naphthyl ether; the two bis-(trifluoromethyl)-biphenyls were prepared by coupling the appropriate Grignard reagent with either silver bromide[1] or cupric chloride.[3] For the preparation of 4,4′-bis-(trifluoromethyl)-biphenyl, the necessary starting material is *p*-bromobenzotrifluoride,[4] and we have developed a simple two-step preparation of this material. The *m*-bromobenzotrifluoride was obtained by the method of Simons and Ramler.[5]

The trifluoromethyl diphenyl ethers were all prepared by the method of Ullman and Sponagel.[6]

Experimental[7]

3,3′-Bis-(trifluoromethyl)-biphenyl.—*m*-Bromobenzotrifluoride (225 g.) was reacted with magnesium turnings (24.5 g.) and anhydrous cupric chloride (140 g.) in dry ether (750 cc.). After refluxing for two hours, the reaction mixture was poured onto ice and treated with excess concentrated hydrochloric acid to dissolve the copper chloride. The ether layer was washed with water and dilute sodium hydroxide and dried over anhydrous magnesium sulfate. The ether was removed and the residue was fractionated at 1 mm. pressure to yield 62 g. (42.7%) of colorless liquid; b.p. 79–80°; $n^{20}D$ 1.4899.

Anal. Calcd. for $C_{14}H_8F_6$: C, 57.92; H, 2.78. Found: C, 58.00, 57.88; H, 2.90, 2.78.

***p*-Bromobenzotribromide.**—Bromine (48 g.) was added dropwise to *p*-bromotoluene (17.1 g.) heated to 120–130° and illuminated with a 150-watt bulb. The temperature was gradually increased during the course of the addition and attained 210° when the bromine addition was completed. This final temperature was maintained another 10 minutes. The reaction mixture was then cooled and poured into an evaporating dish where it solidified to a crystalline mass; m.p. 72–76°; yield 38 g. (93%). Recrystallization from hexane raised the m.p. to 81–82°.

Anal. Calcd. for $C_7H_9Br_4$: C, 20.62; H, 0.99. Found: C, 20.71, 20.50; H, 1.00, 0.82.

***p*-Bromobenzotrifluoride.**—*p*-Bromobenzotribromide (175 g., 0.43 mole) and antimony trifluoride (89.4 g., 0.50 mole) were ground together in a mortar and placed in a 250-cc. flask equipped with a condenser for distillation. The mixture was heated with a free flame until reaction took place with distillation, and heating was maintained until distillation became negligible. The distillate and benzene extracts of the flask residue were steam distilled and then distilled at atmospheric pressure to yield 59 g. (60.9%) of *p*-bromobenzotrifluoride; b.p. 153–155°; $n^{25}D$ 1.4705.

4,4′-Bis-(trifluoromethyl)-biphenyl.—The Grignard reagent prepared from 6.2 g. of *p*-bromobenzotrifluoride was treated with 6.2 g. of anhydrous silver bromide and stirred overnight at room temperature. The ether solution was filtered, washed with water, and dilute sodium hydroxide and dried over anhydrous magnesium sulfate. The ether was removed to give 3 g. of solid, m.p. 75–85° which on recrystallization from methanol gave 1 g. (25%), m.p. 91–92°.

Anal. Calcd. for $C_{14}H_8F_6$: C, 57.92; H, 2.78; F, 39.30; mol. wt., 290. Found: C, 57.78, 57.90; H, 2.95, 2.72; F, 39.32, 39.53; mol. wt. (Rast), 310.

3-Trifluoromethyl Diphenyl Ether.—Phenol, 118 g. (1.25 moles) and 85% potassium hydroxide, 56 g. (0.85 mole) were placed in a one-liter three-neck flask equipped with stirrer, reflux condenser with Dean and Stark trap, and thermometer. Stirring was started and the mixture was heated to 140–150° until all of the potassium hydroxide had dissolved. The mixture was then cooled to 110° and 1 g. of copper powder was added, followed by 225 g. (1 mole) of *m*-bromobenzotrifluoride. The temperature of the reaction mixture was gradually raised until refluxing began with separation of water in the Dean and Stark trap. The water was periodically removed and the *m*-bromobenzotrifluoride returned to the reaction. As the reaction progressed, the temperature gradually rose to 190° with separation of potassium bromide and the amount of water separating became negligible. The reaction mixture was maintained at 190°

---

[1] C. K. Bradsher and J. B. Bond, THIS JOURNAL, **71**, 2659 (1949).

[2] J. K. Wolfe, U. S. Patent 2,547,679.

[3] J. Krizewsky and E. E. Turner, *J. Chem. Soc.*, **115**, 559 (1919).

[4] For another preparation of *p*-bromobenzotrifluoride see R. G. Jones, THIS JOURNAL, **69**, 2346 (1947).

[5] J. H. Simons and E. O. Ramler, *ibid.*, **65**, 389 (1943).

[6] F. Ullman and P. Sponagel, *Ber.*, **38**, 2211 (1905).

[7] The microanalyses are by Dr. Carl Tiedcke.

for two hours, then cooled and poured into 1 liter of water containing 30 g. of sodium hydroxide. The mixture was steam distilled, the product separated from the aqueous layer and dried over anhydrous magnesium sulfate and redistilled at reduced pressure to obtain 184 g. (77.5%) of 3-trifluoromethyl diphenyl ether, b.p. 81° (1 mm.), n^{20}_{D} 1.5118.

Anal. Calcd. for $C_{13}H_9F_3O$: C, 65.53; H, 3.81. Found: C, 65.18, 65.04; H, 3.86, 3.98.

Three other trifluoromethyl substituted ethers were prepared as above.

3-Trifluoromethyl 4′-Chlorodiphenyl Ether.—From 169 g. (0.75 mole) of *m*-bromobenzotrifluoride and 121 g. (0.94 mole) of *p*-chlorophenol was obtained 75 g. (36.8%) of 3-trifluoromethyl 4′-chlorodiphenyl ether, b.p. 94–95° (1 mm.), n^{20}_{D} 1.5278.

Anal. Calcd. for $C_{13}H_8F_3ClO$: C, 57.30; H, 2.96. Found: C, 56.85, 57.04; H, 3.00, 3.10.

3-Trifluoromethyl 3′-Ethyldiphenyl Ether.—From 118 g. (0.525 mole) of *m*-bromobenzotrifluoride and 64 g. (0.525 mole) of *m*-ethylphenol was obtained 106 g. (76%) of 3-trifluoromethyl-3′-ethyl diphenyl ether, b.p. 89° (1 mm.), n^{20}_{D} 1.5100.

Anal. Calcd. for $C_{15}H_{13}F_3O$: C, 67.68; H, 4.92. Found: C, 67.32, 67.50; H, 5.16, 4.89.

3-Trifluoromethyl Phenyl-α-naphthyl Ether.—From 232 g. (1.03 moles) of *m*-bromobenzotrifluoride and 240 g. (1.87 moles) of α-naphthol was obtained 52.5 g. (17.7%) of 3-trifluoromethyl phenyl-α-naphthyl ether, b.p. 157–158° (3 mm.), n^{20}_{D} 1.5784, with recovery of half the *m*-bromobenzotrifluoride unchanged.

Anal. Calcd. for $C_{17}H_{11}F_3O$: C, 70.08; H, 3.85. Found: C, 70.65, 70.48; H, 3.85, 3.98.

SPRAGUE ELECTRIC COMPANY
NORTH ADAMS, MASSACHUSETTS

RECEIVED NOVEMBER 16, 1951

Internal Rotation. VII. The Energy Difference between the Rotational Isomers of Some Halogen Substituted Ethanes

BY F. E. MALHERBE[1] AND H. J. BERNSTEIN

Liquid 1,1,2-tribromoethane is considered to consist of different isomeric forms.[2] This view is supported by the fact that certain bands, *e.g.*, those at 1183 and 1001 cm.$^{-1}$ which are present in the infrared spectrum of the liquid are absent in the spectrum of the solid tribromoethane (see Table III). In the course of an investigation, by the dilute solution method,[3] of the temperature dependence of the intensity of bands belonging to different rotational isomers anomalous results were obtained, and it was in fact possible to obtain a spurious value for ΔH by investigating a pair of bands belonging to the same isomeric species. This apparent temperature dependence led us to reinvestigate 1,1,2-trichloroethane and 1,1,2,2-tetrachloroethane which had been done previously by the dilute solution method.[3] An attempt was made also to determine a value for the energy difference between the isomeric forms in liquid 1,1,2-trichloroethane, 1,1,2-tribromoethane and 1,1,2,2-tetrabromoethane.

Experimental

The infrared spectra were obtained on a Perkin–Elmer Model 12c infrared spectrometer with a Brown electronic recorder. Absorption bands at frequencies above 2000 cm.$^{-1}$ were recorded with a LiF prism, frequencies between 2000 and 660 cm.$^{-1}$ with a NaCl prism, frequencies between 660 and 420 cm.$^{-1}$ with a KBr prism and those below 420 cm.$^{-1}$ with a KRS-5 prism. In the region below 420 cm.$^{-1}$ the liquids only were investigated. The experimental technique and principles of the method have been described previously.[3] Here, a new furnace capable of more accurate temperature control, was used.

The 1,1,2,2-tetrachloroethane was an Eastman Kodak product, distilled through a Stedman column, of 40 theoretical plates, b.p. 146 ± 0.2° at 760 mm.

The 1,1,2,2-tetrabromoethane and 1,1,2-tribromoethane were also Eastman Kodak products, redistilled; b.p. 151 ± 0.2°, 188.4 ± 0.2°, respectively.

The 1,1,2-trichloroethane was a Carbide and Carbon Chemicals product redistilled; b.p. 113 ± 0.2° whereas the sample used in the earlier work[2] had been prepared by a well known method.[4]

Results

1,1,2,2-Tetrachloroethane.—Reinvestigation of the temperature dependence of the pairs of bands at 1279 and 1243 cm.$^{-1}$, respectively, which had been used in the previous work,[3] as well as their behavior on freezing the liquid, led to the conclusion that they belong to the same isomeric form. The apparent temperature dependence of the bands, giving the straight line of Fig. 13 in the earlier paper,[3] is due largely to underestimating the experimental error and perhaps, also to temperature effects which are being investigated in more detail at the present moment in this Laboratory. No suit-

TABLE I

INFRARED SPECTRA OF 1,1,2-TRICHLOROETHANE

Frequencies in cm.$^{-1}$; relative spectral densities in parentheses; (sh) indicates shoulder; frequencies of prominent bands in liquid spectrum which are absent in the solid spectrum are underlined

Liquid (0.025 mm. cell)	Solid (approx. 0.005 mm. layer)	Vapor (10 cm. cell, 100 mm.)
2998 (3)		2943 (3)
2873 (1)		2810 (1)
1430 (7)	1424 (3)	1437 (7)
1308 (5)	1305 (1)	1306 (5)
1264 (7)	1259 (2)	1260 (9)
1237 (5)		
1212 (9)	1212 (5)	1204 (10) doublet
1162 (3)	1162 (1)	1161 (3)
1124 (2)	1120 (1)	
1086 (sh)	1058 (1)	
1050 (3)	1050 (1)	1050 (3)
1010 (2)		
940 (sh)		941 (10)
933 (9)	932 (9)	932 (10)
890 (1)	887 (0)	890 (0)
875 (2)	873 (1)	881 (0)
857 (0)		
849 (0)		
785 (sh)	781 (sh)	796 (10)
777 (7)	770 (8)	787 (10)
730 (10)	727 (10)	736 (10)
700 (5)		
662 (7)	667 (8)	668 (10)
640 (3)	637 (sh)	
613 (0)	613 (0)	
586 (0)	586 (sh)	
569 (0)		
545 (sh)		
524 (3)		
(0.2 mm. cell)		
388 (6)		
330 (3)		

---

[1] N. R. C. Post-doctorate Fellow 1950–1951.

[2] L. Kahovec and J. Wagner, *Z. physik. Chem.*, **B47**, 48 (1940).

[3] J. Powling and H. J. Bernstein, THIS JOURNAL, **73**, 1815 (1951).

[4] M. S. Kharasch and M. C. Brown, *ibid.*, **61**, 2142 (1939).

able pair of bands was found so that there is no value for ΔH by the dilute solution method forthcoming for this molecule.

1,1,2-Trichloroethane.—The sample of trichloroethane used in this work was found to be different from that used in the previous investigation[3] in one important respect, namely, that one of the bands (at 547 cm.$^{-1}$), whose temperature dependence relative to the band at 524 cm.$^{-1}$ had been measured, was absent in the infrared spectra of the liquid and solid material. The other pair of bands (at 1050 and 1010 cm.$^{-1}$) was present, however, in the spectrum of the liquid and it was confirmed that they belonged to different species, since of the pair only the band at 1050 cm.$^{-1}$ is present in the spectrum of the solid trichloroethane. The temperature dependence of this pair of bands was measured in the liquid and the plot of log (ratio of peak heights) *vs.* $1/T$ is shown in Fig. 1; the value found for ΔH was approximately 0.1 cal. The infrared spectra of 1,1,2-trichloroethane in the liquid, solid and vapor state are given in Table I.

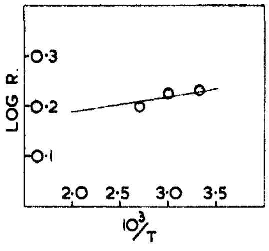


Fig. 1.

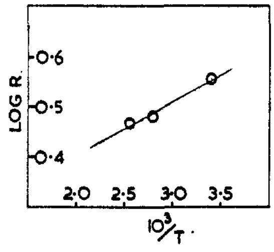


Fig. 2.

1,1,2,2-Tetrabromoethane.—No suitable pair of bands was found in the infrared spectrum of liquid tetrabromoethane. The spectrum of the liquid shows three bands at 636, 614 and 584 cm.$^{-1}$, respectively, whereas of these only the band at 614 cm.$^{-1}$ is present in the spectrum of the solid. The attempt to investigate the temperature dependence of the pair of bands at 614 and 584 cm.$^{-1}$ in the pure liquid and in solution proved unsatisfactory, owing to the large amount of overlap of the bands. The spectra of 1,1,2,2-tetrabromoethane in the liquid and solid states are given in Table II.

TABLE II

INFRARED SPECTRA OF 1,1,2,2-TETRABROMOETHANE (*cf.* TABLE I)

Liquid	Solid	Liquid	Solid
2986 (8)	2986 (9)	925 (0)	927 (0)
2430 (1)		895 (1)	903 (0)
2260 (2)	2264 (3)	828 (4)	831 (2)
1932 (1)	1938 (0)	788 (4)	794 (1)
1355 (1)	1358 (1)	761 (4)	766 (2)
1304 (1)	1310 (1)		748 (sh)
1275 (sh)		707 (9)	707 (8)
1240 (9)	1243 (9)	636 (6)	
1194 (6)	1198 (5)	614 (8)	614 (8)
1135 (10)	1135 (9)	584 (4)	
1073 (1)	1065 (0)		562 (1)
1006 (8)	1009 (6)	536 (4)	533 (8)
		449 (2)[a]	449 (3)

[a] 0.2 mm. cell.

1,1,2-Tribromoethane.—In the infrared spectrum of liquid tribromoethane there is a pair of bands at 1041 and 1000 cm.$^{-1}$, respectively, which belong to different isomeric forms, since again, of this pair, only the band at 1041 cm.$^{-1}$ is present in the spectrum of the solid tribromoethane. The temperature dependence of this pair of bands was measured in the liquid state, and the plot of log (ratio of peak heights) *vs.* $1/T$ is shown in Fig. 2; the value of ΔH for the liquid is approximately 0.5 cal. The infrared spectra of the 1,1,2-tribromoethane in the liquid and solid state are given in Table III.

TABLE III

INFRARED SPECTRA OF 1,1,2-TRIBROMOETHANE (*cf.* TABLE I)

Liquid	Solid	Liquid	Solid
	3548 (1)	1142 (10)	1145 (8)
3021 (10)		1119 (9)	1124 (6)
3002 (9)		1041 (4)	1042 (4)
2960 (6)	2979 (3)		1022 (sh)
2924 (sh)		1000 (1)	
2821 (1)			895 (sh)
2773 (1)		879 (10)	880 (10)
2534 (0)			847 (0)
2484 (0)		812 (1)	812 (0)
2456 (0)		769 (0)	767 (0)
2420 (0)		752 (0)	
2290 (2)		720 (0)	
2094 (0)	2130 (sh)		695 (sh)
2073 (0)	2062 (0)	686 (8)	682 (5)
1413 (9)	1415 (5)		642 (sh)
1315 (sh)	1306 (0)	609 (8)	605 (8)
1269 (9)	1272 (10)	562 (8)	560 (8)
1258 (8)		525 (2)	547 (1)
	1245 (1)	479 (0)	
1213 (10)	1214 (10)	426 (1)	
1181 (9)		334 (3) 0.2 mm. cell	

Discussion

It is apparent that the latitude of error in the infrared methods for measuring the energy difference between the isomeric forms is wider than previously reported.[3] In making measurements on pure liquids the greatest difficulty is the correct positioning of the background, since the scattering in an empty cell is greater than in one containing liquid between the plates. Furthermore, the effect of temperature and solvent on the shapes of bands requires further investigation and work along these lines is in progress in this Laboratory. In the previous dilute solution technique,[3] the peak heights of bands have been taken as a measure of their concentrations and further investigation is in progress to determine whether this is adequate or not.

In obtaining the infrared spectra of compounds in the solid state extreme care has to be taken to ensure that one has the true crystalline solid, rather than a glassy solid, the formation of which has been previously reported.[5,6] In many cases, especially for volatile liquids, the most satisfactory solids are obtained by condensation of the vapor in a Hornig-type cell,[6] and allowing the glassy solid to heat up slowly until it crystallizes.

---

(5) J. K. Brown and N. Sheppard, *Discus. Farad. Soc.*, **9**, 144 (1950); *J. Chem. Phys.*, **19**, 976 (1951); F. E. Malherbe and H. J. Bernstein, *ibid.*, **19**, 1607 (1951).

(6) E. L. Wagner and D. F. Hornig, *ibid.*, **18**, 296 (1950).

DIVISION OF CHEMISTRY
NATIONAL RESEARCH COUNCIL
OTTAWA, CANADA

RECEIVED DECEMBER 10, 1951

The Infrared Spectra of Some Allenic Compounds

BY JOHN H. WOTIZ AND WALTER D. CELMER

The characteristic allenic bond (C=C=C) absorption band is usually listed near 1970 cm.$^{-1}$.[1] This bond is of considerable analytical value as it is

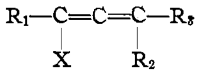
---

(1) R. B. Barnes, R. C. Gore and R. W. Stafford, *Anal. Chem.*, **20**, 402 (1948).

usually strong and occurs in a relatively unobscured infrared region. A number of new allenic compounds became available recently and the study of their spectra now reveals that the very strong allenic absorption band is near 1940 cm.$^{-1}$ and that it often splits into two strong bands near 1930 and 1950 cm.$^{-1}$, respectively. In Table I are listed the compounds studied and the position and intensities of the allenic absorption band(s). The upper curve in Fig. 1 is an example of a compound showing the doublet whereas the lower curve illustrates the single allenic absorption band.

With the exception of compounds I, VIII and XI the compounds studied are solids at room temperature. Their spectra were determined in carbon tetrachloride or nujol suspensions. It was observed that the doublet is especially noticeable when carbon tetrachloride was used as solvent, whereas it is not as apparent in nujol suspensions. We also found that compounds which often showed a broad band near 1940 cm.$^{-1}$ when studied with the Baird I. R. Spectrograph using a sodium chloride prism, showed a sharp doublet with a Perkin–Elmer instrument using a calcium fluoride prism. Thus we resolved the broad band near 1950 cm.$^{-1}$ of VIII in the recently published spectrum[2] into a doublet. We have also tried to determine the Raman spectrum of compound IV, but were unsuccessful due to absorption and (or) fluorescence in the region of 4358 Å.

Table I



$$R_1—\underset{\displaystyle X}{\overset{}{C}}=C=\underset{\displaystyle R_2}{C}—R_3$$

Comp.	R_1	X	R_2	R_3	Synthesis reference	Allenic absorption band, cm.$^{-1}$ 1930	1940	1950
I	C_4H_9	H	H	H	*a*	−	++	−
II	H	CO_2H	H	H	*d*	+	−	+
III	C_3H_7	CO_2H	H	H	*b*	+	−	+
IV	C_4H_9	CO_2H	H	H	*b*	+	−	+
V	C_5H_{11}	CO_2H	H	H	*b*	+	−	+
VI	C_4H_9	CO_2H	H	CH_3	*c*	−	++	−
VII	C_4H_9	CO_2H	CH_3	CH_3	*c*	−	++	−
VIII	C_4H_9	CO_2CH_3	H	H	*b*	+	−	+
IX	C_3H_7	$CONH_2$	H	H	*b*	+	−	+
X	C_4H_9	$CONH_2$	H	H	*b*	+	−	+
XI	C_4H_9	CH_2OH	H	H	*e*	−	++	−

+ Strong. ++ Very strong. − Missing. [a] H. Wotiz, This Journal, **73**, 693 (1951). [b] Reference 2. [c] J. H. Wotiz and R. J. Palchak, This Journal, **73**, 1971 (1951). [d] J. H. Wotiz, J. S. Matthews and J. A. Lieb, *ibid.*, **73**, 5503 (1915). [e] J. H. Wotiz and P. Mosso, unpublished results.

On the basis of the above listed findings we now have available a convenient method for the identification of compounds containing a carboxy, an amide or an ester grouping directly attached to an allenic bond. Such compounds containing a terminal allenic linkage show a doublet whereas the allenic bond inside the chain shows a single absorption band. The reason for such spectroscopic behavior is not apparent to us. We anticipate that other negative groups (electron attracting) will influence the allenic absorption band in the same manner as the groups listed above.

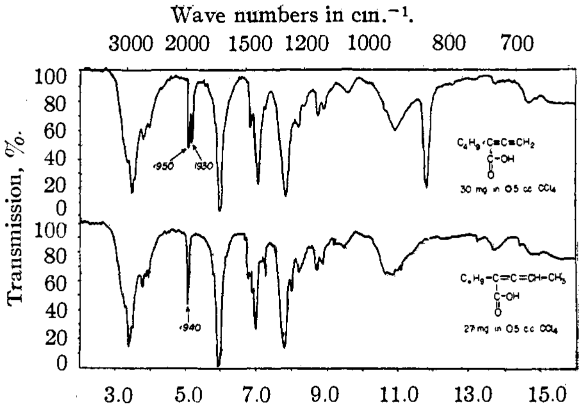


Fig. 1.

We wish to thank Dr. F. A. Miller and Mr. Robert Bauman of the Mellon Institute and Mr. G. B. Hess of Chas. Pfizer and Co. for the determination of the spectra used in this study.

Contribution No. 835 from the
Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania, and the
Research Laboratories
Chas. Pfizer & Company
Brooklyn, New York
Received November 5, 1951

---

[2] J. H. Wotiz, This Journal, **72**, 1639 (1950)

The Reduction of Cyclohexanone Cyanohydrin by Lithium Aluminum Hydride

By Harold R. Nace and Bill B. Smith[1]

Received November 12, 1951

The preparation of 1-aminomethyl-cyclohexanol by catalytic hydrogenation (Adams platinum) of cyclohexanone cyanohydrin has been reported by Tchoubar[2a,b] and Goldberg and Kirchensteiner.[2c] The hydrogenation was difficult to perform, and, consequently, unsatisfactory for the preparation of the aminoalcohol. Dauben, *et al.*,[3] developed a more convenient synthesis by reducing the corresponding nitroalcohol, 1-nitromethylcyclohexanol, to the aminoalcohol.

Difficulties with the hydrogenation of the cyanohydrin were also experienced in this Laboratory, and a second alternative synthesis, reduction of the cyanohydrin with lithium aluminum hydride, was developed.

Nystrom and Brown[4] reported the reduction of mandelonitrile (benzaldehyde cyanohydrin) in 48% yield using slightly more than one mole of hydride for two moles of cyanohydrin, and suggested that the use of a greater excess of hydride might improve the yield. Heusser, *et al.*,[5] reported the re-

---

[1] Research Corporation Fellow, 1951–1952. This paper is based on a portion of the thesis to be submitted by Bill B. Smith in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Brown University.

[2] (a) B. Tchoubar, *Compt. rend.*, **205**, 54 (1937). (b) B. Tchoubar, *Bull. soc. chim. France*, **216**, 160, 164, 169 (1949). (c) M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta*, **26**, 288 (1943).

[3] H. J. Dauben, H. J. Ringold, R. H. Wade and A. G. Anderson, This Journal, **73**, 2359 (1951).

[4] R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948).

[5] H. Heusser, P. th. Herzig, A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

duction in unspecified yield (product isolated as oxazolidine) of 3(β),17(β)-diacetoxy-17-iso-$\Delta^{5,6}$-etiocholenic acid nitrile with lithium aluminum hydride in ether. Amundsen and Nelson[6] found that maximum yields of amines from nitriles were obtained when the molar ratio of hydride to nitrile was one to one, lower yields being obtained when less hydride was used.

In the reduction reported here, the use of one and a half moles of hydride to one of cyanohydrin gave yields of 62–67%, and increasing the amount of hydride to two moles increased the yield to 76%. The method is convenient and requires no special equipment, and should prove to be a useful synthetic method for the preparation of aminoalcohols from cyanohydrins.

Experimental

1-Aminomethyl-cyclohexanol.—Cyclohexanone cyanohydrin was prepared from potassium cyanide and the bisulfite addition product of cyclohexanone according to the method of Tchoubar.[2b] Using 150 g. (1.53 moles) of cyclohexanone, the cyanohydrin (b.p. 112–115° (11 mm.)) was obtained in 70–79% yield.

A solution of 125 g. (1.0 mole) of cyclohexanone cyanohydrin in 200 ml. of absolute alcohol-free ether was added dropwise over a period of one hour to a well stirred slurry of 76 g. (2.0 moles) of lithium aluminum hydride (Metal Hydrides, Inc.) in 2 liters of ether in a three-necked, 5-liter flask (cooled in an ice-bath throughout the addition) fitted with an efficient reflux condenser, dropping funnel, and mercury-sealed Hershberg stirrer. After the addition, the mixture was stirred overnight at room temperature, and then the addition complex was decomposed by adding dropwise 50 ml. of water, 40 ml. of 20% sodium hydroxide solution, and finally 150 ml. of water. The resulting mixture was filtered, the filtrate dried over anhydrous sodium sulfate, the ether removed, and the residue distilled to yield 69 g. (53.5%) of 1-aminomethylcyclohexanol, b.p. 95–115° (22 mm.) (major portion 110–115°). The filter cake was digested with 600 ml. of hot benzene, and the benzene solution was dried and distilled to yield an additional 28.7 g. of aminoalcohol, b.p. 93–115° (20 mm.), total yield 97.7 g. (75.5%). The hydrochloride melted at 214.5–215.5° dec. (cor.) (reported[2] 215–216°) and the picrate at 169.5–171° (cor.) (reported[2] 168–170°).

The infrared spectra of the aminoalcohol prepared by the above method agreed in every respect with that of a sample of 1-aminomethylcyclohexanol prepared by the hydrogenation of cyclohexanone cyanohydrin. The strong band at 1700 cm.$^{-1}$ (unassigned) and the medium band at 2232 cm.$^{-1}$ (C≡N) of the cyanohydrin were absent in the aminoalcohol prepared above, thus assuring its purity. All spectra were taken on a modified Perkin–Elmer Model 12B infrared spectrometer in which a double beam rearrangement replaced the original single beam optical system.[7] Samples of the pure liquid were compressed between sodium chloride windows. A calcium fluoride prism was used.

---

[6] L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

[7] D. F. Hornig, G. E. Hyde and W. A. Adcock, *J. Optical Soc. Am.*, **40**, 497 (1950).

METCALF CHEMICAL LABORATORIES
BROWN UNIVERSITY
PROVIDENCE, RHODE ISLAND

Comparative Ease of Cleavage of Some Phenyl Alkyl and Phenyl Aralkyl Sulfides

BY D. S. TARBELL AND DONALD P. HARNISH[1]

The present study was undertaken to find out how the ease of cleavage of the carbon–sulfur bond varies, in a series of phenyl alkyl and phenyl aralkyl sulfides, with the structure of the sulfide, and to obtain data for a comparison of the corresponding sulfur and oxygen compounds.[2]

The behavior of the sulfides listed in the table was examined toward a variety of agents of varying degrees of effectiveness; the results with aluminum bromide in chlorobenzene and with aqueous hydrobromic acid, which allow the most general comparison of activity, are tabulated. It is clear that, as would be expected, the rate of cleavage of the sulfides, C_6H_5SR, to form C_6H_5SH, follows the order $(C_6H_5)_3C > (C_6H_5)_2CH > C_6H_5CH_2 > C_6H_5CH_2CH_2$. This order is emphasized by further observations that $C_6H_5SC(C_6H_5)_3$ is converted by alcoholic iodine (even at room temperature) to triphenylcarbinol, diphenyl disulfide and ethyl trityl ether, but $C_6H_5SCH(C_6H_5)_2$ is unaffected by this reagent, even on boiling. The trityl sulfide is cleaved by aluminum bromide in ether or nitrobenzene, which, being strong donor solvents, completely prevent cleavage of benzyl phenyl sulfide by aluminum bromide.[2a] The trityl and benzhydryl sulfides are both cleaved by alcoholic silver nitrate.[3]

The slower rate of cleavage of sulfides in comparison with the corresponding ethers, is shown by the rapid splitting of benzyl phenyl ether by hydrogen bromide in acetic acid at room temperature,[4] and by the splitting of phenyl trityl ether by hydrogen chloride in acetic acid in the cold.[5] The deactivating effect toward electrophilic substitution in an aromatic ring of sulfur, compared to oxygen,[2d] is indicated by the isolation, after iodine oxidation of the reaction mixture, of diphenyl disulfide from the aluminum bromide catalyzed cleavage of the benzyl, benzhydryl and trityl phenyl sulfides; the analogous oxygen compounds give much nuclear alkylation under comparable conditions.[2a,6]

In the series C_6H_5SR, the ease of cleavage follows the expected order[7] $C(CH_3)_3 > CH(CH_3)_2 > CH_3$. *t*-Butyl phenyl sulfide is not, however, affected by alcoholic iodine or alcoholic silver nitrate, in contrast to the benzhydryl and trityl compounds. The thermal[8] and aluminum chloride[8,9] catalyzed cleavage of $C_6H_5OC(CH_3)_3$ lead to *p*-*t*-butylphenol, and the action of boron fluoride on isopropyl aryl ethers leads to isopropylphenols[10]; these carbon–oxygen cleavages appear to take place far more rapidly than the carbon–sulfur cleavages listed in the table. In agreement with this, it has been found[11] that ani-

---

[1] Beaunit Mills Fellow, 1947–1948.

[2] Preceding papers on this topic: (a) D. P. Harnish and D. S. Tarbell, THIS JOURNAL, **70**, 4123 (1948); (b) *Anal. Chem.*, **21**, 968 (1949); (c) H. F. Wilson and D. S. Tarbell, THIS JOURNAL, **72**, 5200 (1950); (d) D. S. Tarbell and J. C. Petropoulos, *ibid.*, **74**, 244 (1952); (e) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

[3] D. C. Gregg, H. A. Iddles and P. W. Stearns (*J. Org. Chem.*, **16**, 246 (1951)) found that phenyl trityl sulfide was cleaved by methanolic mercuric chloride at room temperature.

[4] B. W. Tronow and L. W. Ladigina, *Ber.*, **62**, 2844 (1929).

[5] A. Baeyer, *ibid.*, **42**, 2626 (1909).

[6] H. A. Iddles, *et al.*, THIS JOURNAL, **62**, 2757 (1940); **64**, 3154 (1942); J. Van Alphen, *Rec. trav. chim.*, **46**, 287, 803 (1927).

[7] J. F. Norris and G. W. Rigby, THIS JOURNAL, **54**, 2088 (1932), showed that the rates of cleavage of ethyl butyl ethers by concentrated hydrochloric acid followed the order *t*-butyl > *s*-butyl > *n*-butyl.

[8] R. A. Smith, *ibid.*, **55**, 3718 (1933).

[9] T. W. Evans and K. R. Edlund, *Ind. Eng. Chem.*, **28**, 1188 (1936).

[10] F. J. Sowa, H. D. Hinton and J. A. Nieuwland, THIS JOURNAL, **54**, 2019 (1932); **55**, 3402 (1933).

[11] J. C. Petropoulos, unpublished observation.

sole is split completely to phenol by aluminum bromide in chlorobenzene after 18 hours at 60° (for the sulfur analog, see Table).

During this work several new aryl sulfides were prepared, which are described in the experimental part. It was found, however, that aluminum bromide caused hydrogen sulfide evolution from *p*-thiocresol, *β*-thionaphthol, and 4-phenylthiophenol, and hence kinetic runs could not be made on sulfides derived from these thiols. It was shown that aluminum bromide in chlorobenzene solution formed biphenyl from 4-phenylthiophenol.

$$p\text{-}C_6H_5C_6H_4SH \xrightarrow[C_6H_5Cl]{AlBr_3} C_6H_5C_6H_5$$

In benzene solution the products appeared to be biphenyl and diphenyl sulfide.

The carboxy sulfides in the table were found to be unaffected even by aluminum bromide–acetyl bromide, a combination which gives very rapid cleavage of benzyl phenyl sulfide.[2a]

Experimental[12]

The amount of cleavage was determined by the consumption of 0.02 *N* alcoholic iodine solution either directly as mercaptan or after hydrolysis of the thiol ester.[2b]

The sulfides below were prepared in the usual manner by adding alkyl halide to a solution of the thiophenol in alcoholic potassium hydroxide.

Sulfide	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Biphenylyl benzyl sulfide[a]					
p-$C_6H_5C_6H_4SCH_2C_6H_5$	127.5–128.5	82.56	82.18	5.83	5.77
4-Biphenylyl ethyl sufide					
p-$C_6H_5C_6H_4SCH_2CH_3$	74–75	78.46	78.20	6.58	6.56
β-Naphthyl benzyl sulfide					
β-$C_{10}H_7SCH_2C_6H_5$	88.5–89	81.56	81.33	5.64	5.76

[a] The sulfoxide was prepared from the reaction of bromine water on a solution of the sulfide in *t*-butyl alcohol[2b]; m.p. 198–199°. Calcd. for $C_{19}H_{16}OS$: C, 78.05; H, 5.51. Found: C, 77.84; H, 5.40.

CLEAVAGE OF SULFIDES, C_6H_5SR

R	AlBr$_3$[a] Time. hr.	AlBr$_3$[a] Cleavage, %	HBr[b, c, d] Time. hr.	HBr[b, c, d] Temp., °C.	HBr[b, c, d] Cleavage, %
$C_6H_5CH_2$	5	85	6[b]	200	Decomp.
	73(0°)	42	24[c]	150	30
$C_6H_5CH_2CH_2$	18	0			
	2(79°)	10–20			
$(C_6H_5)_2CH$	0.2	86[e]	4[d]	Reflux	0
	0.2(0°)	64	0.2[c]	Reflux	10–20
$(C_6H_5)_1C$	18	≫50[e]	0.02[b]	Reflux	>5
	0.2(0°)	>50	1[h]	Reflux	>5
CH_3	24	0[h]			
	24(93°)	0			
$(CH_3)_2CH$	18	0[f]			
	6(72°)	5–10			
$(CH_3)_3C$	0.2	5–10			
CH_2COOH	4(50°)	0[g]			
	0.2(reflux)	0			
CH_2CH_2COOH	4(50°)	0			
	0.2(reflux)	0			

[a] Chlorobenzene as solvent; 28° unless otherwise stated. [b] 32% aqueous solution. [c] 32% solution in acetic acid. [d] 48% aqueous solution. [e] Diphenyl disulfide isolated from the reaction. [f] AlBr$_3$ without solvent gave 50–60% cleavage after 24 hours at 28°. [g] No cleavage when fused with AlBr$_3$ in absence of solvent. [h] Dilute aqueous hydrochloric acid.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, N. Y.

RECEIVED DECEMBER 5, 1951

---

[12] Analyses by Mrs. G. Sauvage; melting points are corrected.

Arsenicals Containing Quinoline and Quinazoline Nuclei

BY YAO-HUA WU AND CLIFF S. HAMILTON

For a number of years various workers in this Laboratory have been employing the Bart reaction[1] to prepare different aromatic and heterocyclic arsonic acids as possible therapeutic agents. This reaction has now been utilized to synthesize 4-hydroxyquinoline- and 4-hydroxyquinazolinearsonic acids.

6-Amino-4-hydroxyquinoline, 6-amino-4-hydroxy-2-methyl-quinoline, 5-amino-4-hydroxyquinazoline, 6-amino-4-hydroxyquinazoline and 7-amino-4-hydroxyquinazoline were prepared by the reduction of the corresponding nitro compounds. The arsonic acids were obtained by diazotizing these amines and subsequent coupling with sodium arsenite. Some of these arsonic acids were reduced to their arsenoso derivatives by the action of sulfur dioxide and hydriodic acid.

The condensation of heterocyclic compounds containing an "active" halogen with aminoarylarsonic acids has been studied extensively by Banks and co-workers[2] and Hamilton and co-workers.[3] In most cases an aqueous suspension containing a trace of hydrochloric acid was used. Banks[2] pointed out that the trace of hydrochloric acid is necessary because the reaction rate in aqueous solution or suspension is increased by an increase in the hydrogen ion concentration. Because of the instability of the 4-haloquinolines and 4-haloquinazolines in aqueous acid solutions, the condensation with *p*-arsanilic acid was accomplished in N-dimethylformamide as a solvent.

Experimental

6-Amino-4-hydroxyquinolines.—6-Amino-4-hydroxyquinoline was prepared according to the direction of Albert, Brown and Duewell.[4] 6-Amino-4-hydroxy-2-methylquinoline was obtained by the method of Kermack and Weatherhead.[5]

Amino-4-hydroxyquinazolines.—The 4-hydroxynitroquinazoline (3.8 g.) was added gradually in portions to a warm solution of stannous chloride ($SnCl_2 \cdot 2H_2O$, 20.3 g.) in concd. hydrochloric acid (30 ml.). After all the solid had been added, the solution was heated gently under reflux for 1 hour. The hot solution was diluted with water and care-

TABLE I

Compound	Yield, %	M.p., °C. Liter.	M.p., °C. Found
5-Amino-4-hydroxyquinazoline	76.4	235–236[6]	236
6-Amino-4-hydroxyquinazoline	67.0	318[7]	316
7-Amino-4-hydroxyquinazoline[a]	53.7	......	315

[a] *Anal.* Calcd. for $C_8H_7ON_3$: C, 59.61; H, 4.38; N, 26.07. Found: C, 59.86; H, 4.25; N, 25.98.

---

(1) H. Bart, German Patent 250,264 (1910) [*Chem. Zentr.*, **83**, IV, 882 (1912)].

(2) C. K. Banks, O. M. Gruhzit, E. W. Tillitson and J. Controulis. THIS JOURNAL, **66**, 1771 (1944); C. K. Banks and J. Controulis, *ibid.*, **68**, 944 (1946).

(3) E. J. Cragoe, Jr., and C. S. Hamilton, *ibid.*, **67**, 536 (1945); R. J. Andres and C. S. Hamilton, *ibid.*, **67**, 946 (1945); I. H. Witt and C. S. Hamilton, *ibid.*, **67**, 1078 (1945); B. Elpern and C. S. Hamilton, *ibid.*, **68**, 1436 (1946).

(4) A. Albert, D. J. Brown and H. Duewell, *J. Chem. Soc.*, 1284 (1948).

(5) W. O. Kermack and A. P. Weatherhead, *ibid.*, 563 (1939).

(6) M. T. Bogert and V. S. Chambers, THIS JOURNAL, **28**, 207 (1906).

(7) O. W. Magidson and E. S. Golovchinskaya, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1797 (1938).

TABLE II

Name	Color	M.p., °C.	Yield, %	Formula	As analyses, %[8]	
					Calcd.	Found
4-Hydroxyquinoline-6-arsonic acid	White	>320	29.7	$C_9H_8O_4NAs$	27.84	27.97
4-Hydroxy-2-methylquinoline-6-arsonic acid	White	>320	31.6	$C_{10}H_{10}O_4NAs$	26.46	26.48
4-Hydroxyquinazoline-5-arsonic acid	White	>320	48.3	$C_8H_7O_4N_2As$	27.74	27.89
4-Hydroxyquinazoline-6-arsonic acid	White	>320	22.2	$C_8H_7O_4N_2As$	27.74	27.82
4-Hydroxyquinazoline-7-arsonic acid	White	>320	42.2	$C_8H_7O_4N_2As$	27.74	27.70
6-Arsenoso-4-hydroxyquinoline	White	317	53.2	$C_9H_6O_2NAs \cdot H_2O$	29.60	29.90
6-Arsenoso-4-hydroxy-2-methylquinoline	White	310	75.1	$C_{10}H_8O_2NAs \cdot H_2O$	27.97	27.80
7-Arsenoso-4-hydroxyquinazoline	White	295	69.1	$C_8H_5O_2N_2As \cdot H_2O$	29.49	29.41
4-(4′-Arsonoanilino)-8-nitroquinoline	Yellow	288	30.2	$C_{15}H_{12}O_5N_3As$	19.25	19.08
4-(4′-Arsonoanilino)-2-methylquinoline	Light gray	285	33.2	$C_{16}H_{14}O_3N_2As$	20.95	21.06
4-(4′-Arsonoanilino)-2-methyl-6-nitroquinoline	Yellow	288	50.1	$C_{16}H_{14}O_5N_3As$	18.58	18.39
4-(4′-Arsonoanilino)-quinazoline	Light gray	>320	58.0	$C_{14}H_{12}O_3N_3As$	21.71	21.66

fully neutralized with calcium carbonate. The mixture was then heated to boiling and filtered through a hot-water funnel. The undissolved portion was repeatedly extracted with boiling water. From the combined filtrate and washings the amino-4-hydroxyquinazoline crystallized in long white needles on cooling.

4-Hydroxyquinolinearsonic Acids and 4-Hydroxyquinazolinearsonic Acids.—A solution of 3.5 g. of the amine in 35 ml. of 2 *N* hydrochloric acid was cooled to a temperature below 5° and diazotized with sodium nitrite solution. The diazonium solution was poured with mechanical stirring into a water solution composed of sodium arsenite (5 g.), sodium hydroxide (3 g.) and a few crystals of copper sulfate. After being stirred for 2 hours and having stood overnight, the mixture was warmed at 80° for 10 minutes, and filtered to remove the dark tarry impurity. The filtrate was neutralized with hydrochloric acid, treated with charcoal, filtered and the filtrate was made acidic to congo red paper with hydrochloric acid. The crude arsonic acid separated as white needles and was purified by dissolving in 5% sodium bicarbonate solution and reprecipitating with the addition of 1 *N* hydrochloric acid until acid to congo red paper.

Arsenoso-4-hydroxyquinolines and Arsenoso-4-hydroxyquinazolines.—One gram of the pure arsonic acid was dissolved or suspended in 35 ml. of 1.5 *N* hydrochloric acid containing a trace of potassium iodide. The solution was cooled in an ice-bath and saturated with sulfur dioxide for two hours. After remaining in a refrigerator overnight, the solution was neutralized with concd. ammonium hydroxide. The white precipitate was filtered and dissolved in 1 *N* sodium hydroxide. The arsenoso derivative was isolated as white needles by passing carbon dioxide into the alkaline solution.

Condensation of 4-Chloroquinolines and 4-Chloroquinazolines with *p*-Arsanilic Acid.—The 4-chloroquinoline or the 4-chloroquinazoline (0.005 mole) and *p*-arsanilic acid (0.0045 mole) were dissolved in 5 ml. of dimethylformamide at 50°. The solution was heated at 80–90° for 3–4 hours. A solid product usually separated after 2–3 hours of heating. A less pure product could be recovered from the mother liquor by neutralizing with ammonium hydroxide. The crude product was purified by dissolving in hot 5% sodium bicarbonate solution and reprecipitating with the addition of 2 *N* hydrochloric acid. The condensation products are hygroscopic.

---

(8) Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

AVERY LABORATORY
THE UNIVERSITY OF NEBRASKA
LINCOLN, NEBRASKA

RECEIVED NOVEMBER 14, 1951

Attempted Preparation of Thorium(III) Fluoride[1a,b]

BY JAMES C. WARF[2]

An attempt to prepare a lower fluoride of thorium was undertaken to aid in clarifying the role of thorium as an actinide element. While the presence of an f electron in thorium is not essential to the general actinide hypothesis,[3] a trifluoride, isostructural with uranium(III) fluoride, would be predicted on the basis of an electron in the 5 f orbital, paralleling the cerium(III) ion with a 4 f electron.

The method employed involved the reduction of thorium(IV) fluoride by thorium metal, following a technique successful in the analogous synthesis of uranium(III) fluoride.[4] The thorium tetrafluoride, prepared by hydrofluorination of the oxide, was analyzed by pyrohydrolysis.[5] Calcd. for ThF_4: Th, 75.33; F, 24.67. Found: Th, 75.37; F, 24.60. Its freezing point was 1068 ± 2°. The thorium metal, prepared by bomb reduction, contained approximately 0.1% ThO_2 and 0.2% zinc.

Two attempts to carry out the reaction

$$Th + 3ThF_4 = 4ThF_3$$

were made using platinum boats. Thorium (1 g.) was converted to its hydride by heating to 750° in hydrogen (purified over uranium at 700°), and ground intimately with the stoichiometric quantity of thorium tetrafluoride. The mixture in a platinum boat was heated in a quartz tube by means of a platinum-wound resistance furnace. An atmosphere of helium purified over uranium powder at 800° was maintained at all times. A temperature of 1175° was reached in the first run, and 1280° in the second. In both cases the platinum boats were attacked, being reduced to metallic globules of a thorium–platinum alloy in the second case. The gray residues were examined by X-ray diffraction, and all the lines in both cases could be accounted for by the presence of Th, ThF_4 and ThH_2.

Another run was made as above using a boat fashioned from 1-mm. rolled thorium sheet. A temperature of 1290° was maintained 30 minutes. Practically all of the thorium tetrafluoride had volatilized away, and the boat had been etched. An X-ray diffraction pattern of the dark residue could be interpreted on the basis of the Th, ThF_4 and ThO_2.

Finally, two bombs were fabricated from thorium metal; each was tapped, and sealed with a threaded thorium plug. The first was charged with 10 g. of intimately ground stoichiometric Th–ThF_4 mixture, and heated to 1600° in vacuum in an induction furnace. The bomb was sawed open lengthwise, which revealed that the thorium powder had settled to the bottom, and that the inside wall was attacked. X-Ray analysis showed Th and ThF_4 only. The second bomb was filled with thorium tetrafluoride alone,

---

[1] (a) Based on work done in 1946–1947, Ames Laboratory of the Atomic Energy Commission, declassified as AECD-2654 on July 14, 1949. (b) Presented at the Chicago, Illinois, Meeting of the American Chemical Society, September, 1950.

[2] Department of Chemistry, University of Southern California, Los Angeles 7, California.

[3] See G. T. Seaborg, "The Transuranium Elements," "NNES," Div. IV, Vol. 14 B, McGraw-Hill Book Co., Inc., New York, N. Y., 1949, pp. 1492–1524.

[4] J. Warf, Plutonium Project Report CC-1525 (March 14, 1944) (AECD-2523); also J. J. Katz and E. Rabinowitch, "The Chemistry of Uranium," "NNES," Div. VIII, Vol. 5, McGraw-Hill Book Co., Inc., New York, N. Y., 1951, p. 349 ff.

[5] J. Warf, "Analytical Chemistry of the Manhattan Project," "NNES," Div. VIII, Vol. 1, McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 729 ff.

heated to 1600°, quenched in mercury, and sawed open. The walls had been attacked somewhat, and in the interior of the solidified thorium tetrafluoride a few gray areas of finely divided thorium metal were found.

No evidence for the existence of a lower fluoride of thorium was found. There was some indication however, that thorium dissolves slightly in its fluoride at high temperature, a behavior similar to that of uranium in its tribromide,[6] the alkaline earth metals in their halides,[7] or cerium in its chloride.[8]

Mention should be made of the preparation of thorium(III) and thorium(II) halides[9-11] prepared by reduction of the tetrahalides, especially the iodide, by the metal. These lower iodides were observed to parallel the corresponding halides of zirconium and hafnium in physical and chemical properties. Similarly a brown thorium(III) and silvery thorium(II) sulfide are known[12] whose properties indicate the presence of no f electrons.

---

(6) C. D. Thurmond, Plutonium Project Report CC-2522 (Dec. 20, 1944).

(7) D. D. Cubicciotti and C. D. Thurmond, THIS JOURNAL, **71**, 2149 (1949).

(8) D. D. Cubicciotti, *ibid.*, **71**, 4119 (1949).

(9) E. Hayek and Th. Rehner, *Experientia*, **5**, 114 (1949).

(10) E. Hayek, Th. Rehner, and A. Frank, *Monatsh.*, **82**, 575 (1951).

(11) J. S. Anderson and R. W. D'Eye, *J. Chem. Soc.*, (Suppl. Issue No. 2), S 244 (1949).

(12) E. D. Eastman, *et al.*, THIS JOURNAL, **72**, 4019 (1950).

CONTRIBUTION NO. 52 FROM THE
INSTITUTE FOR ATOMIC RESEARCH
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED OCTOBER 30, 1951

COMMUNICATIONS TO THE EDITOR

THE REACTION OF DI-ISOPROPYL FLUOROPHOSPHATE WITH TYROSINE

Sir:

We have been engaged for some time on a comparative study of the action of di-isopropyl fluorophosphate (DFP) and di-isopropyl chlorophosphate (DClP) on amino-acids under "physiological" conditions in the hope of finding some clear-cut difference which might parallel the marked difference between the biochemical activities of these two compounds[1] (DFP is toxic and inhibits choline-esterase and other enzymes whereas DClP is not markedly toxic). The appearance of the recent paper of Wagner-Jauregg, O'Neill and Summerson[2] on a similar subject prompts us to make this preliminary communication of our positive findings.

Wagner-Jauregg, O'Neill and Summerson[2] studied the action of non-polar DFP and DClP on a number of amino-acid esters and amines in that DClP is the more reactive solution and uniformly observed the latter to be the more reactive[3]; they were unable to phosphorylate amino-acids in slightly alkaline aqueous media with DFP although they observed, but do not describe in detail, reaction between DFP and phenol in aqueous potassium carbonate.

We have been more fortunate and have been able to demonstrate a marked difference in the reactivity of DFP and DClP toward tyrosine. Using 0.02 *M* halophosphate and 0.005 *M* tyrosine in 0.08 *M* sodium bicarbonate at 38° and following the disappearance of free phenolic hydroxyl by the colorimetric method of Thomas[4,5] we obtained the following results

Time hr.	3	4	9	24
% Reaction of (DFP)	43	49	52	56
phenolic OH. (DClP)	-	7	10	8

Clearly DFP reacts readily, under these conditions, with the phenolic hydroxyl group of tyrosine whereas DClP does not. The reaction product from DFP, O-di-isopropylphosphoryl-tyrosine (I), was isolated from the reaction mixture, by chromatography on deactivated charcoal,[6] as needles, m.p. 158–160° (dec.), from aqueous acetone (Found N, 4.1; $C_{15}H_{24}O_6NP$ requires N, 4.1), and, more easily, as its N-2,4-dinitrophenyl derivative, needles, m.p. 159–160°, from methanol (Found C, 49.4; H, 5.1; N, 7.9; $C_{21}H_{26}O_{11}N_3P$ requires C, 49.3; H, 5.1; N, 8.2). The structure of (I) was confirmed by its chromatographic recognition in the hydrogenation product of its amorphous *p*-bromocarbobenzoxy derivative (Found C, 49.7; H, 5.0; N, 2.8; $C_{23}H_{29}O_2NBrP$ requires C, 49.5; H, 5.2; N, 2.5), obtained by treating DFP similarly with N-*p*-bromocarbobenzoxytyrosine, m.p. 156–157° (Found: C, 51.7; H, 4.1; N, 3.4; $C_{11}H_{16}O_5NBr$ requires C, 51.8; H, 4.1; N, 3.55).

This marked difference in the chemical behavior of the two halophosphates suggests, although it does not prove, that the reaction of DFP with choline-esterase and other sensitive enzymes involves reaction at a tyrosine side-chain; it is of interest that chymotrypsin, which is sensitive to DFP, has been

---

(1) E. C. Webb, *Biochem. Soc. Symp.*, **2**, 50 (1948); H. G. Cook, B. C. Saunders and F. E. Smith, *J. Chem. Soc.*, 635 (1949).

(2) T. Wagner-Jauregg, J. J. O'Neill and W. H. Summerson, THIS JOURNAL, **73**, 5202 (1951).

(3) *Cf.* B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 695 (1948).

(4) L. E. Thomas, *Arch. Biochem.*, **5**, 175 (1944).

(5) The absorptiometer used was purchased with the aid of a grant from the Central Research Fund of the University of London for which we express our thanks.

(6) Schramm and J. Primosigh, *Ber.*, **76**, 373 (1943).