in seven times its volume of the same solvent. After the addition was complete, the mixture was allowed to stand for a period of 18–24 hr. Longer reaction times increased the amount of polymer formed. The precipitated hydrochloride was removed by filtration, the solvent and unchanged starting materials were stripped under reduced pressure, and the products were separated by vacuum distillation. Under these conditions the following yields of 1-N-disubstituted amino-2,3-epithiopropane (based on 50% of the amine used) were obtained for the indicated amine: dimethylamine, 0% (polymers only); diethylamine, 30–40%; dibutylamine, 72%; piperidine, 60–65%; and morpholine, 62.5%. Methanol as solvent appeared to give much faster reactions but also increased the amount of polymer formation. In one experiment with piperidine and a reaction time of only 5 hr., however, a yield of 75% of 1-piperidino-2,3-epithiopropane was obtained when methanol was the solvent.

B. In a Ratio of 2 Moles of Amine to 1 Mole of 1-Chloro-2,3-epithiopropane.—The same procedure was followed as described in A. The two types of products were separated by distillation. Yields of 1-N-disubstituted amino-2,3-epithiopropanes (based on the 1-chloro-2,3-epithiopropane used) varied from 30–48%, and the yields of 1,3-bis(N-disubstituted amino)-2-propanethiols (based on 25% of the amount of *amine* used) varied from 25–45%. With di-*n*-butylamine, no thiol-type product was formed, and with diethylamine the thiol-type product was formed in small per cent. The reaction with pyrrolidine appeared to be unusually fast, and, in one run in which the amine was added all at once in petroleum ether solution and the reaction period was only 5 hr., yields of 48.4% of the amino sulfide-type product and 34% of the thiol were obtained.

C. In a Ratio of 3 Moles or More of Amine to 1 Mole of 1-Chloro-2,3-epithiopropane.—In these experiments the sulfide solution was added dropwise with stirring to the excess of amine, but otherwise the procedure was the same as described in A. With dimethylamine and diethylamine both types of products were obtained, with piperidine and morpholine only the thiol. Yields were as follows: for dimethylamine, 37% amino sulfide and 33% thiol; for diethylamine, 35% amino sulfide and 50% thiol; for piperidine, 60–65% thiol; and for morpholine, 54% thiol.

Infrared Spectral Data for 1-N-Disubstituted Amino-2,3-epithiopropanes.—Infrared spectra were determined on a Beckman IR-5 spectrophotometer. Absorption bands which were *common* to all of the examples of this type of compound prepared were as follows: $\lambda_{max}^{CCl_4}$ 3.4, 3.6, 6.9, 7.2–7.3, and 9.6 μ. For comparison, 1-chloro-2,3-epithiopropane showed characteristic absorption bands at 3.35, 6.92, 7.95, 8.64, 9.18, 9.6, 13.96, and 14.9 μ.

Raney Nickel Desulfurizations in Structure Proofs.—Desulfurizations were carried out in absolute ethanol using commercial Raney nickel (No. 28 Raney Active Nickel, Raney Catalyst Co., Chattanooga, Tenn.) in an amount equal to ten times the amount of compound, and the mixtures were allowed to stand for about an hour at room temperature with frequent shaking. Evolution of heat was noticed. From the amino sulfide containing a piperidino group was obtained an amine which was immediately converted to a picrate derivative and this, after three recrystallizations from absolute ethanol, melted at 105–107°. This agrees with the m.p. 108° reported by Magnusson and Schierz[9] for N-*n*-propylpiperidine, whereas N-isopropylpiperidine picrate was reported melting at 153°.

From the diaminothiol product containing dimethylamine groups was obtained an amine which also was converted at once to the picrate and this, after one recrystallization from water, melted at 207–208°, after darkening and deformation from 205–207°. This agrees with the m.p. 207° reported by Clarke[10] for the picrate of N,N,N′,N′-tetramethyl-1,3-propanediamine, whereas N,N,N′,N′-tetramethyl-1,2-propanediamine picrate is reported[11] to melt at 190°.

Reactions of 1-Chloro-2,3-epithiopropane and Anhydrous Solutions of Chlorine and Bromine.—The general procedure described for other cyclic sulfides[3-5] was employed. Reaction with chlorine gave a 37% yield of liquid product, b.p. 157–160° (1 mm.), which, after two further distillations, crystallized in the receiver. Recrystallization from 95% ethanol gave colorless crystals, m.p. 67–69°. A mixture melting point of this product and the disulfide obtained by iodine oxidation of 2,3-dichloro-1-propanethiol prepared from reaction of 1-chloro-2,3-epithiopropane and concentrated hydrochloric acid showed no depression. The compound then is bis(2,3-dichloropropane) disulfide.

Anal. Calcd. for $C_6H_{10}Cl_4S_2$: C, 25.01; H, 3.50. Found: C, 24.89; H, 3.51.

Reaction with bromine gave a quantitative yield of slightly red solid which was recrystallized from 95% ethanol to give colorless crystals, m.p. 80–82.5°, assumed to be bis(2-bromo-3-chloropropane) disulfide.

Anal. Calcd. for $C_6H_{10}Br_2Cl_2S_2$: C, 19.11; H, 2.67. Found: C, 19.39; H, 2.64.

Reaction of 1-Chloro-2,3-epithiopropane and Aqueous Chlorine.—This reaction was carried out as described for other cyclic sulfides.[3-5] After one distillation, a yield of 47% was obtained. Redistillation gave a colorless liquid, b.p. 82.5–83.5° (1 mm.), $n^{20}D$ 1.5137, assumed to be 2,3-dichloro-1-propanesulfonylchloride.

Anal. Calcd. for $C_3H_5Cl_3O_2S$: C, 17.04; H, 2.38. Found: C, 17.36; H, 2.35.

Acknowledgment.—This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of this fund.

(9) H. W. Magnusson and E. R. Schierz, *Wyoming Univ., Publ.*, **7**, 1 (1940).

(10) H. T. Clarke, *J. Chem. Soc.*, **103**, 1699 (1913).

(11) R. Paul and S. Tchelitcheff, *Compt. rend.*, **238**, 2089 (1954).

Optical Resolution of (±)-1-Amino-2-propanethiol[1]

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Received December 3, 1963

The recently reported finding that (−)-2-(2-aminobutyl)-2-thiopseudourea hydrobromide is twice as effective in protecting mice against a single dose of lethal X-irradiation as the (+)-isomer[2] suggests that important differences may be found between other enantiomeric pairs of radioprotective agents previously evaluated as racemic mixtures. The optical resolution of (±)-1-amino-2-propanethiol [(±)-I] was selected for investigation because this compound has been reported to afford good radioprotection.[3]

The resolution of (±)-I was first approached *via* the crystalline salts of (±)-2-(benzylthio)propylamine with (−)-malic acid and (+)-tartaric acid, which were to be subsequently debenzylated; but optical enrichment was not attained by repeated recrystallization of these salts. The resolution was then undertaken by a method recently applied by Taguchi, *et al.*,[4] to the resolution of (±)-*trans*-2-aminocyclohexanethiol *via* the thiazolidine formed with D-glucose. The reported resolution suggests a general method, but the paucity of experimental details necessitated development of each step when applied to the resolution of (±)-I. The process that eventually evolved is outlined below.

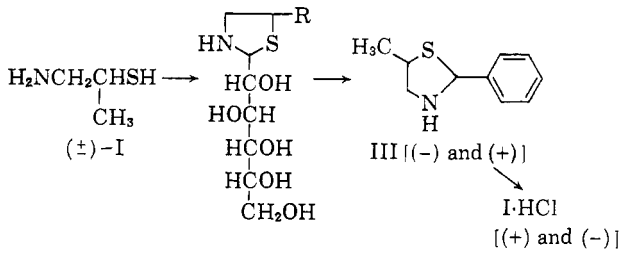
(1) This investigation was supported by the U. S. Army Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) D. G. Doherty and R. Shapira, *J. Org. Chem.*, **28**, 1339 (1963); see also Abstracts of Papers, International Congress of Radiation Research, Burlington, Vt., Aug. 10–16, 1958; *Radiation Res.*, **9**, 107 (1958).

(3) F. Yu. Rachinskii, A. S. Mozzhukhin, N. M. Slavachevskaya, and L. I. Tank, *Usp. Khim.*, **28**, 1488 (1959); J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p. 66.

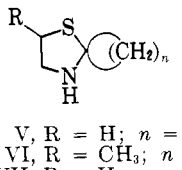
(4) T. Taguchi, T. Takatori, and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), **10**, 245 (1962).

Treatment of (±)-I hydrochloride with sodium methoxide in methanol gave the free aminothiol, which was purified by sublimation. Reaction of (±)-I with D-glucose in refluxing methanol gave 1-(5-methylthiazolidinyl)-D-*gluco*-1,2,3,4,5-pentanepentol, which was isolated from the reaction mixture in two forms (levorotatory IIa and optically inactive IIb) by fractional crystallization, each being subsequently purified further by recrystallization. An exchange reaction of the less soluble, higher melting IIa with benzaldehyde in aqueous ethanol produced (−)-5-methyl-2-phenylthiazolidine [(−)-III], and the same treatment of the more soluble, lower melting IIb afforded (+)-III. Hydrolysis of (−)-III in boiling 6 *N* hydrochloric acid gave (+)-I hydrochloride; that of (+)-III, (−)-I hydrochloride. Practical yields were obtained in each step, and optical purity of the enantiomeric pairs was attested by essentially equal specific rotation of opposite sign.



II (a and b), R = CH_3
IV, R = H

The major difference between the method described above and that reported by Taguchi, *et al.*,[4] is the use of benzaldehyde in the exchange step instead of cyclohexanone. After several unsuccessful attempts to effect the exchange of the glucose moiety of IIa with cyclohexanone in boiling cyclohexanone as solvent,[4] 1-thiazolidin-2-yl-D-*gluco*-1,2,3,4,5-pentanepentol[5] (IV) was used as a model in determining the optimal conditions (1-hr. reflux) that gave a 19% yield of 1-thia-4-azaspiro[4.5]decane[6] (V) and an even lower yield of the 2-methyl derivative VI when applied to IIIa. Cyclopentanone under similar conditions gave comparably impractical yields of 1-thia-4-azaspiro[4.4]nonane (VII). Direct generation of 2-aminoethanethiol from IV by acid hydrolysis was unsatisfactory (as in the case of



V, R = H; $n = 5$
VI, R = CH_3; $n = 5$
VII, R = H; $n = 4$

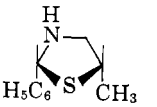
2-aminocyclohexanethiol[4]) because of the products of glucose decomposition. The action of phenylhydrazine hydrochloride on IV in hot aqueous solution resulted in the precipitation of D-glucose phenylosazone, but a practical isolation of 2-aminoethanethiol from the remaining nitroprusside-positive mixture was not devised.

(5) W. A. Bonner and W. Meyer zu Reckendorf, *Chem. Ber.*, **94**, 225 (1961).

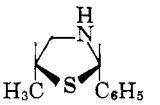
(6) A. H. Cook and I. M. Heilbron, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p. 957.

Difficult fractionation and purification problems were encountered in an exploratory preparation of II from (±)-I hydrochloride and D-glucose in the presence of triethylamine according to the procedure described[7] for a similar reaction of 3-aminopropanethiol hydrochloride. This difficulty was overcome by the use of the free amino thiol I as in the reported[5] reaction of D-glucose with 2-aminoethanethiol. It was also found that the presence of moisture in (±)-I made the isolation of IIb exceedingly tedious.

Four diastereoisomers can theoretically result from the reaction of a racemic amino thiolsuch as (±)-I with D-glucose, but only two forms of II were isolated, each being recrystallized to a constant specific rotation and melting point. The phenylthiazolidines (−)-III and (+)-III resulting from benzaldehyde exchange of IIa and IIb, respectively, are enantiomers; yet each has two asymmetric carbon atoms, whereas the corresponding cyclohexanone exchange products would have a single asymmetric carbon atom. This means that (−)-III and (+)-III are both *cis* or both *trans*[8] as



IIIx



IIIy

illustrated by the mirror image structures IIIx and IIIy and that the benzaldehyde exchange must have taken a stereospecific course. (The formation of exactly compensating mixtures is unlikely.) In order to confirm the implication that direct formation of a thiazolidine of this type would also be stereospecific, the product from (−)-I hydrochloride and benzaldehyde was examined and found to be virtually identical with (+)-III from which (−)-I hydrochloride was derived. The alternative nonspecific reaction would have resulted in a mixture of *cis* and *trans* isomers. These observations may then explain why only two forms of the D-glucose thiazolidine II were isolated.

Experimental[9]

(±)-2-(Benzylthio)propylamine. A. Free Base.—To a stirred mixture of (±)-1-amino-2-propanethiol hydrochloride[11] (6.38 g., 0.0500 mole) and anhydrous potassium carbonate (14.5 g., 0.105 mole) in *N*,*N*-dimethylformamide (50 ml.) was added a solution of α-chlorotoluene (6.58 g., 0.0520 mole) in the same solvent (15 ml.). The resulting mixture was stirred under nitrogen for 1 hr. (during this period the temperature of the mixture rose spontaneously to a maximum of 51°) and then heated at 50–60° for 2.5 hr. The product was isolated essentially as the previously described 2-(benzylthio)ethylamine[12]; the yield of racemic 2-(benzylthio)propylamine as a colorless oil was 5.66 g. (62%), b.p. 86° (0.3 mm.), $n^{25}D$ 1.5623.

Anal. Calcd. for $C_{10}H_{15}NS$: C, 66.24; H, 8.34. Found: C, 66.44; H, 8.50.

(7) R. Mani, W. Meyer zu Reckendorf, and W. A. Bonner, *Chem. Ber.*, **95**, 1000 (1962).

(8) See E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 5.

(9) Unless otherwise noted, melting points were determined with a Mel-Temp apparatus and are uncorrected. Specific rotations were determined with a Standard Model D Keston polarimeter attachment to a Beckman DU spectrophotometer, calibrated with standard sucrose solutions.[10] Subsequently some of the signs of rotation were confirmed with a Rudolph Model 80 high precision polarimeter.

(10) See K. G. Poulsen, *Anal. Chem.*, **32**, 410 (1960).

(11) Generously furnished by Dr. D. P. Jacobus, Walter Reed Army Institute of Research, Washington, D. C.

(12) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **28**, 1305 (1963).

B. Salt with (−)-Malic Acid.[13]—Equimolar amounts (5.00 mmoles) of the free base and (−)-malic acid were allowed to react in boiling ethanol (4 ml.) for a few minutes. The solution was cooled and and diluted with chloroform (15 ml.). The resulting solution was placed in a refrigerator, and after 4 days the acid salt had deposited as a white crystalline powder, which was collected, washed with ether, and dried *in vacuo* at 58° over phosphorus pentoxide. The yield was essentially quantitative, m.p. 95°.[14] Recrystallization of a 1.00-g. sample from 1-propanol resulted in 85% recovery of optically inactive salt (dried *in vacuo* at 78°); melting point was unchanged.

Anal. Calcd. for $C_{14}H_{21}NO_5S$: C, 53.31, H, 6.71. Found: C, 53.26; H, 6.58.

Further recrystallizations from 1-propanol, ethanol–chloroform, or ethanol–carbon tetrachloride did not affect the melting point. This salt is very soluble in cold methanol and ethanol.

C. Salt with (+)-Tartaric Acid.—Warm (50–60°) solutions of equimolar amounts (5.00 mmoles) of the free base and (+)-tartaric acid in ethanol (4 ml.) were combined. The initially clear solution rapidly deposited a white crystalline precipitate. The mixture was diluted with ether (20 ml.), and the white solid was collected and dried *in vacuo* at 78° over phosphorus pentoxide. The yield of acid tartrate was quantitative, m.p. 146–148°.[14] Repeated recrystallizations of this salt from widely varying volumes of methanol, ethanol, aqueous 1-propanol (96%), and water did not effect optical enrichment.

Anal. Calcd. for $C_{14}H_{21}NO_6S$: C, 50.74; H, 6.39. Found: C, 50.72; H, 6.41.

(±)-1-Amino-2-propanethiol [(±)-I].—A solution of (±)-1-amino-2-propanethiol hydrochloride[11] (54.8 g., 0.430 mole) in methanol (250 ml.) was added in a thin stream with vigorous stirring to a solution of an equimolar amount of sodium methoxide (from 9.89 g., 0.430 g -atom, of sodium) in methanol (250 ml.). Precipitated sodium chloride was removed by filtration, and the filtrate was evaporated at about 25 mm. with the bath temperature not exceeding 35°. The white residual solid was purified by sublimation under reduced pressure (bath 45–70° at 20–25 mm.); the yield of (±)-I was 32.6 g. (83%).

1-(5-Methylthiazolidin-2-yl)-D-*gluco*-1,2,3,4,5-pentanepentols (IIa and IIb).—A well-stirred mixture of (±)-1-amino-2-propanethiol (32.6 g., 0.358 mole), D-glucose (64.5 g., 0.358 mole), and methanol (530 ml.) was heated under reflux for 4.5 hr. (complete solution of the D-glucose occurred within 30 min.). The solution was transferred while still hot to a beaker, and crystallization was induced by scratching. The mixture was allowed to stand securely covered at room temperature for 48 hr. The heavy precipitate of short white needles was collected without the aid of additional methanol and was pressed as dry as possible on the funnel. (The filtrate was set aside for isolation of IIb.) The crude IIa, dried *in vacuo* at room temperature, weighed 32.6 g. and melted at 124–129°. Recrystallization from methanol afforded pure IIa, yield 24.7 g. (27%), m.p. 131–132°, $[\alpha]^{25}D$ −50.9 ± 1.0° (*c* 1.48 g./dl., water). Further recrystallization did not change the melting point or the specific rotation.

Anal. Calcd. for $C_9H_{19}NO_6S$: C, 42.67; H, 7.56. Found: C, 42.54; H, 7.59.

The filtrate set aside for isolation of IIb was concentrated by distillation at atmospheric pressure until 230 ml. of distillate had been collected. The residual solution was transferred to a beaker and allowed to stand securely covered at room temperature for 72 hr. A crop of hard colorless granules gradually deposited. This first crop of crude IIb was collected and dried *in vacuo* at room temperature (11.5 g., m.p. 105–109°). The filtrate was then concentrated to about 100 ml. and seeded with a powdered sample of the first crop. Precipitation of a second crop began immediately, and after 43 hr. at room temperature the crude second crop (27.0 g., m.p. 98–107°) was collected. The two crops were separately pulverized and recrystallized twice from minimum volumes of methanol. In the first recrystallization the samples were dissolved, respectively, in 30 and 75 ml. of boiling methanol, and after 4 days at room temperature the recrystallized samples were collected: (1) 8.17 g., m.p. 109–112°; and (2) 12.9 g., m.p. 108–112°. In the second recrystallization the respective volumes of solvent were 25 and 35 ml., and after 3 days at room temperature, the recrystallized samples were collected: (1) 5.65 g. and (2) 9.76 g. having the identical m.p. 110–112° (unchanged by further recrystallization). The pure IIb obtained, 15.4 g. (17%), was optically inactive.

Anal. Calcd. for $C_9H_{12}NO_5S$: C, 42.67; H, 7.56. Found: C, 42.62; H, 7.66.

(−)- and (+)-5-Methyl-2-phenylthiazolidines [(−)-III and (+)-III].—In a typical run IIa (17.3 g., 0.0683 mole) was dissolved in warm 50% (by weight) aqueous ethanol (35 ml.), and benzaldehyde (8.90 g., 84.0 mmoles) was added. The solution was refluxed with stirring for 18 hr. The cooled reaction mixture, which deposited (−)-III as white needles, was treated with 18% sodium bisulfite solution (150 ml.), and the resulting mixture was stirred at room temperature for about 2 hr. After the mixture had been refrigerated for 2–3 hr., the crude pale yellow product was collected and dried *in vacuo* at room temperature (8.20 g., m.p. 75–77°). Recrystallization from aqueous ethanol with Norit treatment afforded 7.52 g. (61%) of (−)-III as white needles, m.p. 77–79°. For analysis a small sample was recrystallized from cyclohexane, with melting point unchanged, $[\alpha]^{25}D$ −34.9 ± 1.1° (*c* 1.30 g./dl., chloroform) and −48.1 ± 1.01° (*c* 1.40 g./dl., 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}NS$: C, 66.98; H, 7.31. Found: C, 67.25; H, 7.43.

Application of the procedure described above to IIb afforded (+)-III in similar yield, m.p. 77–79°, $[\alpha]^{25}D$ +32.6 ± 1.4° (*c* 1.02 g./dl., chloroform) and +47.4 ± 1.4° (*c* 1.01 g./dl., 0.1 *N* HCl).

(+)- and (−)-1-Amino-2-propanethiol [(+)-I and (−)-I] Hydrochlorides.—A solution of (−)-III (13.62 g., 0.0760 mole) in 6 *N* hydrochloric acid (200 ml.) was heated to the boiling point in a simple distillation apparatus fitted with a Claisen head and a pressure-equalized dropping funnel, a continuously positive nitrogen pressure being maintained. The first drop of distillate contained benzaldehyde. Distillation was continued while additional 6 *N* hydrochloric acid (180 ml.) was gradually dripped into the boiling solution so as to maintain the volume at 190–200 ml. After about 200 ml. of distillate had been collected during 3 hr., the distillate had become clear. The residual solution was treated with Norit, and the filtrate was evaporated to dryness under reduced pressure. The residue, which crystallized readily, was dissolved in methanol (50 ml.); the solution was evaporated to dryness under reduced pressure. This dissolution and evaporation was repeated, the second solution being treated with Norit and filtered through a Celite mat. The resultant white crystalline solid was dissolved in boiling methanol (35 ml.). Addition of ether to the cool solution precipitated (+)-I hydrochloride as lustrous white platelets, which were collected under nitrogen and dried *in vacuo* at room temperature, yield 9.10 g. (94%), melting point not sharp (sintering at *ca.* 65°, melting completely at 80°), $[\alpha]^{25}D$ +35.3 ± 0.9° (*c* 1.46 g./dl., water).

Anal. Calcd. for $C_3H_9NS \cdot HCl$: C, 28.24; H, 7.90. Found: C, 28.44; H, 7.87.

Under the conditions described above, (−)-I was obtained from (+)-III in 95% yield and had the same melting characteristics as (+)-I, $[\alpha]^{25}D$ −36.4 ± 1.1° (*c* 1.27 g./dl., water).

Anal. Calcd. for $C_3H_9NS \cdot HCl$: C, 28.24; H, 7.90. Found: C, 28.17; H, 7.90.

(+)- and (±)-5-Methyl-2-phenylthiazolidines from (−)- and (±)-1-Amino-2-propanethiol Hydrochlorides and Benzaldehyde.—A solution of (−)-1-amino-2-propanethiol hydrochloride (1.28 g., 10.0 mmoles) and benzaldehyde (1.10 g., 10.4 mmoles) in 50% (by weight) aqueous ethanol was refluxed for 15 min., cooled, and evaporated under reduced pressure to a viscous oil. The residue was triturated in three 15-ml. portions of ether, the ethereal phase being removed by decantation. The ether-insoluble matter was then dissolved in water, and the solution was made basic by the dropwise addition of 10% sodium hydroxide solution. The white precipitate was dried *in vacuo* over phosphorus pentoxide, yield 1.42 g. (79%), m.p. 74–76°. Recrystallization from cyclohexane raised the melting point to 77–79°, which is identical with that of (+)-III made from IIb (and (−)-III made from IIa), $[\alpha]^{25}D$ +29.4 ± 2.3° (*c* 1.01 g./dl., chloroform) and +43.4 ± 2.3° (*c* 1.00 g./dl., 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}NS$: C, 66.98; H, 7.31. Found: C, 67.17; H, 7.33.

The procedure described above afforded a 94% yield of crude (±)-5-methyl-2-phenylthiazolidine (7.41 g., m.p. 62–66°) when applied to (±)-1-amino-2-propanethiol hydrochloride (5.62 g.). Successive recrystallizations from aqueous ethanol and cyclohexane raised the melting point to 67–69° (unchanged by further recrystallization from cyclohexane).

(13) The salt with (+)-10-camphorsulfonic acid was a sirup, which could not be induced to crystallize.

(14) Determined with a Kofler Heizbank.

Anal. Calcd. for $C_{10}H_{13}NS$: C, 66.98; H, 7.31. Found: C, 66.98; H, 7.47.

Acknowledgment.—The authors are indebted to Dr. B. L. Appleton for pointing out the Taguchi method of resolution, to Dr. J. A. Montgomery and Dr. Y. F. Shealy for helpful discussions, and to Dr. W. J. Barrett and associates of the analytical section of this Institute for microanalyses and specific rotations.

The Cleavage of Methylenebis(diphenylphosphine) by Phenyl Azide

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Received December 12, 1963

In connection with some work on organophosphorus systems containing nitrogen, we have had occasion to study the reaction of polymethylenebis(diphenylphosphines) with phenyl azide. The isolation of *p*-phenylenebis(diphenylphosphinimine) from the reaction of 1,4-bis(diphenylphosphino)benzene with phenyl azide was reported recently.[2]

It was found that an ether–tetrahydrofuran solution of phenyl azide and 1,2-ethylenebis(diphenylphosphine) in 2:1 mole ratio evolved nitrogen to give a product which exhibited an elemental composition, molecular weight, infrared spectrum, and n.m.r. spectrum expected for 1,2-ethylenebis(diphenylphosphinimine) (I, eq. 1).

$$2PhN_3 + (Ph_2PCH_2)_2 \longrightarrow [Ph_2P(NPh)CH_2]_2\ (I) \qquad (1)$$

Hydrolysis of I produced 1,2-ethylenebis(diphenylphosphine) dioxide as expected (eq. 2).

$$[Ph_2P(NPh)CH_2]_2 + 2H_2O \longrightarrow [Ph_2P(O)CH_2]_2 + 2PhNH_2 \qquad (2)$$

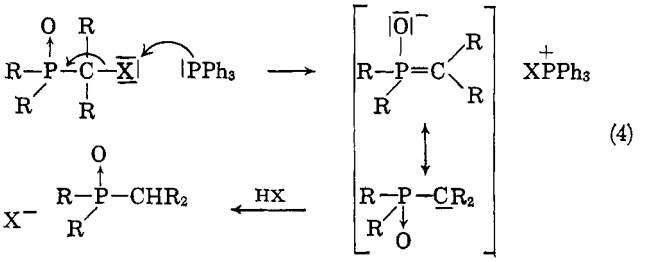
However, a 2:1 mole ratio of phenyl azide to methylenebis(diphenylphosphine) in ether did not lead to the isolation of a diphosphinimine. After a mildly exothermic slow gas evolution there occurred deposition of crystals of diphenylphosphinic acid anilide in 20.6% yield. The remaining solution gave more anilide when evaporated so that 78% was isolated. Column chromatography of the remaining sirup resulted in the isolation of methyldiphenylphosphine and its oxide in 64% yield as demonstrated by comparison with material produced from the reaction of lithium diphenylphosphide and methylchloride. Apparently the diphosphine was cleaved by phenyl azide (eq. 3).

$$(Ph_2P)_2CH_2 + PhN_3 \longrightarrow X \xrightarrow[H_2O]{air} Ph_2P(O)NHPh + Ph_2P(O)CH_3 \qquad (3)$$

The reaction was carried out under an atmosphere of prepurified nitrogen; therefore, the origin of the oxygen in the diphenylphosphinic acid anilide crystallizing out of the reaction solution poses a problem. Molecular oxygen and water were most probably present in very small amounts in the reagents and nitrogen used. Exposure to air after deposition of crystals and gas evolution had ceased did not cause any further gas evolution or precipitation. The significant fact, however, is that under similar reaction conditions essentially no cleavage of the ethylenebis compound occurred.

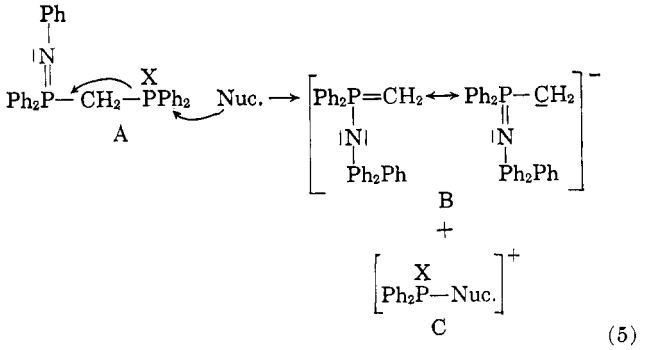
Although only 1 mole of phenyl azide appeared in the isolated products, an excess of azide helped in gaining cleavage. An equimolar solution of methylenebis(diphenylphosphine) and phenyl azide in ether evolved gas, but attempts at isolation of products resulted in the isolation of methylenebis(diphenylphosphine) dioxide (57%) and a small amount of diphenylphosphinic anilide. The presence of methyldiphenylphosphine oxide, determined by gas–liquid partition chromatography, presented further evidence that some cleavage of the diphosphine had occurred.

Horner, *et al.*, have shown that halogen atoms α to a phosphorus carrying a positive charge are not readily displaced by a nucleophile but can be replaced by a proton in the presence of triphenylphosphine.[3] Nucleophilic attack on the partially positive α-halogen with the concurrent displacement of a resonance stabilized carbanion can be proposed as an explanation (eq. 4).



(4)

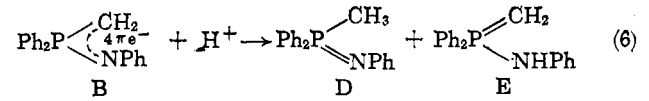
Methyldiphenylphosphine oxides are known to form anions in the presence of strong bases.[4,5] It is therefore reasonable to expect the monoimine or diimine of methylenebis(diphenylphosphine) (A) to cleave in the presence of a nucleophile (Nuc.) to give a resonance stabilized anion B (eq. 5).



(5)

X = NPh or a pair of electrons

The reaction of anion B with water (below) would result in a mixture of the N-phenylimine of methyldiphenylphosphine (D) and the tautomeric phosphinemethylene (E) (eq. 6). Further hydrolysis would be expected to lead to methyldiphenylphosphine oxide and aniline (eq. 7).



(6)

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