Infrared spectrum: ν_{CO} 1750 cm.$^{-1}$, $\nu_{N=N}$ 1565 cm.$^{-1}$; ultraviolet spectrum: λ_{max} 330, ϵ_{max} 180 (ethanol).

3-Acetoxy-3,5-dimethyl-1-pyrazoline.—By the same procedure using 4.9 g. (0.05 mole) of 3,5-dimethylpyrazoline, a bright yellow oil, b.p. 72–76° (0.3 mm.), $n^{20}D$ 1.4545, was obtained.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 55.05; H, 8.17; N, 17.97.

Infrared spectrum: ν_{CO} 1750 cm.$^{-1}$; $\nu_{N=N}$ 1568 cm.$^{-1}$; ultraviolet spectrum: λ_{max} 330, ϵ_{max} 186 (ethanol).

Synthesis of Cyclopropyl Acetates. A. From Azoacetates. 1,2,2-Trimethylcyclopropyl Acetate.—3,5,5-Trimethyl-3-acetoxy-1-pyrazoline (5.0 g., 0.03 mole) was heated under reflux (*ca.* 200°) until nitrogen evolution ceased (1 hr.). The residue was distilled to yield 2.5 g. (63%) of 1,2,2 trimethylcyclopropyl acetate (Table I).

B. From 2-Pyrazolines. 2-Phenyl-1-methylcyclopropyl Acetate.—A solution of 8.0 g. (0.05 mole) of crude 3-methyl-5-phenylpyrazoline in 25 ml. of methylene chloride was added to 25 g. (0.056 mole) of lead tetraacetate in 200 ml. of methylene chloride at 10–15° with good stirring. After the addition the mixture was allowed to warm to room temperature and stirred there for an hour. The mixture was diluted with water, the organic layer separated, and the aqueous layer extracted with two 50-ml. portions of methylene chloride. The combined organic extracts were washed with water and 5% sodium bicarbonate solution until the aqueous layer was free of acid. The organic extracts were dried over magnesium sulfate and concentrated. The residue was heated under reflux until gas evolution ceased. The crude product (8.9 g.) was distilled through a Holzman column to yield 5.8 g. (61%) of 2-phenyl-1-methylcyclopropyl acetate, b.p. 70° (0.35 mm.).

Vapor chromatography of the material on a Carbowax 20 M on Chromosorb column at 180° using an Aerograph Model 90 gas chromatograph resolved it into two components. The smaller component eluted first proved to be 1-methyl-*cis*-2-phenylcyclopropyl acetate; the predominant product was the *trans* isomer; ratio of isomers, 1:6 (Table I).

1,2-Diphenylcyclopropyl Acetate.—The crude pyrazoline prepared from 20.8 g. (0.1 mole) of benzalacetophenone and 40 ml. of 90% hydrazine was diluted with 50 ml. of methylene chloride and added at 10–15° to 49 g. (0.11 mole) of lead tetraacetate in 300 ml. of methylene chloride. The work-up procedure was the same as described for 2-phenyl-1-methylcyclopropyl acetate. The residual oil (20 g.) was induced to partially crystallize by addition of hexane. By further crystallizations of the oil a total of 7.5 g. (30%) of *cis*-1,2-diphenylcyclopropyl acetate, m.p. 52–53° (hexane) was obtained. The residual oil was distilled at 125° (0.4 mm.) to yield 8.8 g. (35%) of a viscous oil whose n.m.r. spectrum indicated that it was mainly the *trans* isomer, but which still contained substantial amounts of the *cis* isomer.

***trans*-1-Phenyl-2-methylcyclopropane.**—To a solution of iodomethylzinc iodide[17] prepared from 13.4 g. (0.05 mole) of methylene iodide, 0.05 g. of iodine, and the zinc–copper couple (4 g. of zinc) in 50 ml. of anhydrous ether was added 11.8 g. (0.1 mole) of *trans*-propenylbenzene[25] in 25 ml. of anhydrous ether. After stirring under reflux overnight, the mixture was worked up and the organic product distilled through a spinning-band column to yield 3.0 g. (53%) of *trans*-1-phenyl-2-methylcyclopropane, b.p. 76° (19 mm.), $n^{20}D$ 1.5215. From a mixture of *cis*- and *trans*-propenylbenzene, Simmons and Smith[17] obtained a mixture of phenylmethylcyclopropanes, b.p. 78–79° (20 mm.), $n^{25}D$ 1.5204. Since reduction of the reported[13] 1-phenyl-2-methyl-3,3-dichlorocyclopropane yielded *trans*-1-phenyl-2-methylcyclopropane, it must have the *trans* configuration.

***cis*-1-Phenyl-2-methyl-3,3-dichlorocyclopropane.**—A mixture of 18.2 g. (0.1 mole) of sodium trichloroacetate, 65 g. (0.5 mole) of *cis*-propenylbenzene,[26] and 75 ml. of ethylene glycol dimethyl ether was heated under reflux overnight. The dichlorocyclopropane was isolated by distillation, b.p. 60–62° (0.5 mm.), $n^{20}D$ 1.5405, yield 12.1 g. (61%).

Anal. Calcd. for $C_{10}H_{10}Cl_2$: C, 59.73; H, 5.01. Found: C, 59.65; H, 5.22.

***cis*-1-Phenyl-2-methylcyclopropane.**—A solution of 10 g. (0.05 mole) of *cis*-1-phenyl-2-methyl-3,3-dichlorocyclopropane in 200 ml. of ether was reduced with 23 g. (1 g.-atom) of sodium and 150 ml. of methanol containing 5 ml. of water. Distillation of the ether extracts yielded 2.4 g. (36%) of *cis*-1-phenyl-2-methylcyclopropane, b.p. 78–80° (20 mm.), $n^{20}D$ 1.5201.

Acknowledgment.—We are indebted to Dr. C. H. DePuy of Iowa State University for helpful correspondence concerning the spectra of cyclopropyl acetates.

(25) *trans*-Propenylbenzene of high purity may be obtained from Columbia Organic Chemicals Company. Their product was purified by gas chromatography on a Dow 710 silicone-on Chromosorb column at 125°. The properties of the purified material agreed in detail with those reported: R. Y. Mixer, R. F. Heck, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **75**, 4094 (1953).

(26) W. R. R. Park and G. F. Wright, *J. Org. Chem.*, **19**, 1435 (1954).

Factors Influencing the Separation of 4-Hydroxyproline Diastereomers by Ion-Exchange Chromatography

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On a preparative scale 4-hydroxy-DL-proline and allo-4-hydroxyproline were separated on ion-exchange resin. By working in alcoholic buffer systems, optimal conditions for accurate and rapid separation were elaborated. The method was applied to the preparation of pure diastereomers from mixtures obtained by two different synthetic pathways. The ratios of crystalline hydroxyproline to allohydroxyproline were 1:2 in the *intra*molecular cyclization of 2-amino-4-hydroxy-5-bromopentanoic acid, and 7:5 in the *inter*molecular reaction of 2,5-dichloro-γ-valerolactone with ammonia.

In the previous study[1] we reported on the preparation, separation, and quantitative determination of the diastereomers of hydroxyproline. The subject of this paper is the manipulation of the variables in the ion-exchange technique and an improved method for the rapid and quantitative separation of hydroxyproline diastereomers.

Reviewing the literature on the separation of the diastereomers of hydroxyamino acids, one notices that DL-threonine and DL-allothreonine[2] have been separated on Dowex 50 by elution with 1.5 *N* hydrochloric acid, the diastereomers of hydroxylysine by a buffer system of pH 5.0,[3] the diastereomers of β-hydroxy-DL-aspartic acid on Dowex 1 with dilute

(1) N. Izumiya and B. Witkop, *J. Am. Chem. Soc.*, **85**, 1835 (1963).

(2)(a) A. T. Shulgin, O. G. Lien, Jr., E. M. Gal, and D. M. Greenberg, *ibid.*, **74**, 2427 (1952); (b) throughout this paper the use of the name hydroxyproline refers to 4-hydroxy-DL-proline and its diastereomer.

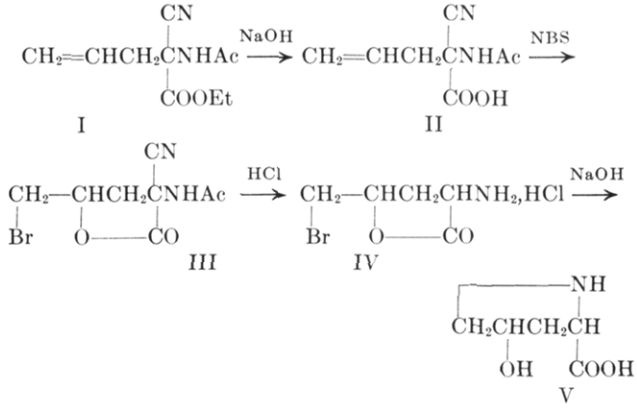
(3) P. G. Hamilton and R. A. Anderson, *J. Biol. Chem.*, **213**, 249 (1955).

formic acid,[4] the diastereomers of γ-hydroxyornithine on Dowex 50,[5] and D-leucyl-L-tyrosine and L-leucyl-L-tyrosine on Dowex 50 and a cellulose column.[6]

In a similar manner, the diastereomers of hydroxylysine, isoleucine, and hydroxyproline have been separated in aqueous buffer systems.[7] In the separation of the diastereomers of isoleucine and threonine, addition of ethanol was reported to be very effective for the separation of the diastereomers.[8] In addition, the same authors[8] have separated the diastereomers of hydroxyproline on a column of Amberlite CG-120 by elution with ethanolic aqueous ammonium acetate buffer,[9] a procedure which has been utilized to advantage for the preparation of 4-H^3-hydroxy- and 4-H^3-allohydroxy-L-proline.[10] These observations have been extended to a study of various solvents as they influence the separation of the diastereomers of threonine, isoleucine, and phenylserine.[11]

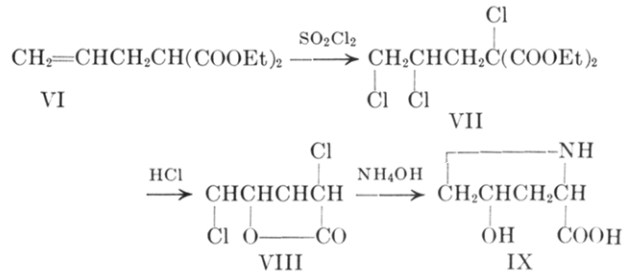
In this investigation we have studied the effects of organic solvents, buffer systems, and different resins in order to find optimal conditions for the separation of a representative example of a pair of diastereomeric hydroxyamino acids, such as hydroxyproline and allohydroxyproline, and found that a solvent system containing 40% methanol at pH 4.0 affords rapid and quantitative separation.

On a preparative scale the improved method has been applied to an easy separation of 4-hydroxy- and allo-4-hydroxy-DL-proline obtained by two different synthetic routes. One synthesis utilized ethyl allylacetaminocyanoacetate (I) rather than allylglycine[1] as an intermediate. By bromolactonization (III) of



the acid II, hydrolysis (IV), and ring closure (V) a 2:1 ratio of allohydroxyproline to hydroxyproline was obtained, indicative of the preponderant formation of the *cis*-disubstituted lactone as noted previously.[1]

The second synthetic route, VI–IX, is a modification of the method of Gaudry and Godin.[12] From the dichlorolactone VIII, hydroxyproline and allohydroxyproline were obtained in a ratio of 7:5 in an over-all yield of 60% of crystalline products.



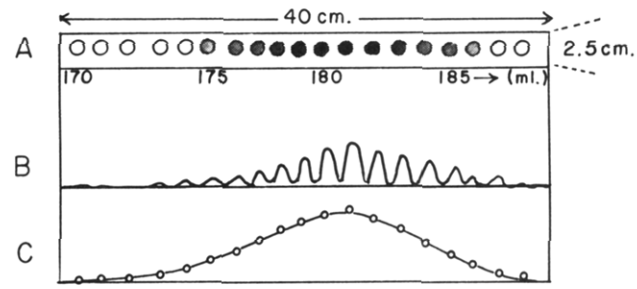


Fig. 1.—Separation and assay of mixtures of hydroxy-L- and allohydroxy-D-proline on Dowex 50W-X8: A, spotting of aliquots on filter paper strips by the isatin method; B, evaluation of color intensities with the aid of a densitometer; and C, integration of areas.

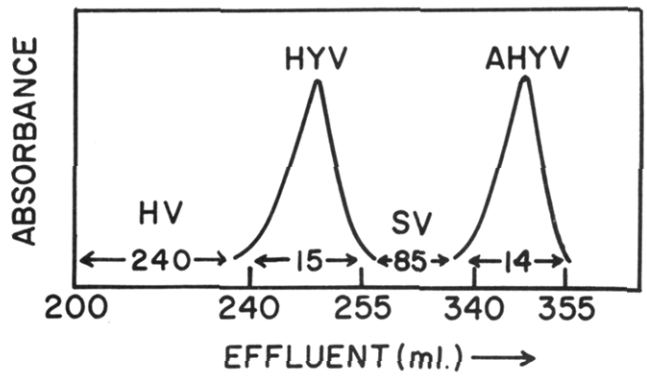


Fig. 2.—Elution pattern of mixtures of hydroxyproline and allohydroxyproline expressed in the four stages of HV (holdup volume), HYV (hydroxyprolone volume), SV (separation volume), and AHYV (allohydroxyproline volume).

Experimental

Separation Studies on Ion-Exchange Resins. A. Isatin Assay. Preparation of Column and Buffer Systems.—A column (1.8 × 110 cm.) was filled with Dowex 50W-X8 (200–400 mesh), NH_4^+ form, and washed with a solvent system prepared by the addition of acetic acid to 0.4 *M* ammonium hydroxide (2.5 l.) until the solution reached the desired pH. To the solution was then added the appropriate alcohol (1 or 2 l.) The solution was made up to 5 l. with water, and adjusted again to the desired pH by the addition of ammonium hydroxide or acetic acid. The final buffer solution was 0.2 *M* ammonium acetate containing 20 to 40% of alcohol at a chosen pH.

Chromatography of Model Mixtures.—Samples of 6.56 mg. (0.05 mmole) of hydroxy-L-proline and of allohydroxy-D-proline were dissolved in 1 ml. of water (total amino acid, 0.1 mmole), the solution applied to a column and eluted with the appropriate solvent system at room temperature (20–25°) and a flow rate of 4.5–5.5 ml./hr. One-milliliter fractions were collected, and 0.01 ml. from each tube was spotted on a strip of filter paper. The strip was put in an oven (100°) for 5 min., immersed in a trough with 0.2% isatin acetone solution for a moment, and again heated in an oven (100°) for 5 min. (Fig. 1A). The amounts of color

(4) M. L. Kornkuth and H. J. Sallach, *Arch. Biochem. Biophys.*, **91**, 39 (1960).

(5) B. Witkop and T. Beiler, *J. Am. Chem. Soc.*, **78**, 2882 (1956).

(6) S. Yanari, M. Volini, and M. A. Mitz, *Biochim. Biophys. Acta*, **45**, 595 (1960); S. Blackburn and P. Tetley, *ibid.*, **20**, 423 (1956).

(7) K. A. Piez, *J. Biol. Chem.*, **207**, 77 (1954).

(8) K. Michi, S. M. Birnbaum, and M. Winitz, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1959, p. 19C.

(9) S. M. Birnbaum, personal communication.

(10) A. V. Robertson, E. Katz, and B. Witkop, *J. Org. Chem.*, **27**, 2676 (1962).

(11) H. Aoyagi, H. Okai, M. Bessho, and N. Izumiya, *J. Chem. Soc. Japan*, in preparation.

(12) R. Gaudry and C. Godin, *J. Am. Chem. Soc.*, **76**, 139 (1954).

developed were determined by an Atago AG-4 densitometer (slit 1 × 18 mm., 440 mμ) (Fig. 1B), and the integrated areas were plotted on a graph (Fig. 1C). The terms of HV (holdup volume), HYV (hydroxyproline volume), SV (separation volume), and AHYV (allohydroxyproline volume) (Fig. 2) are used to describe the elution pattern. In all experiments we ascertained that HYV contained *hydroxyproline* and *allohydroxyproline*. The pH of the 20% alcoholic buffer system was 6.0 (see Table I). The

TABLE I

INFLUENCE OF VARIOUS ALCOHOLS ON THE SEPARATION OF HYDROXYPROLINE AND ALLOHYDROXYPROLINE

Alcohol, 20%	HV[a]	HYV[a]	SV[a]	AHYV[a]
No alcohol	149	13	28	16
MeOH	175	13	55	14
EtOH	141	19	31	20
n-PrOH	175	21	41	21
i-PrOH	152	28	38	21
t-BuOH	171	26	50	25

[a] In milliliters.

conditions were as described above. Among many alcohols tested, methanol and *t*-butyl alcohol most effectively separated the diastereomers. Cross-linked Dowex 50W-X2 and X8 gave about the same results, but X12 gave poorer separation (see Table II and III). Therefore, resin X8 was used exclusively in all our subsequent experiments.

TABLE II

EFFECT OF CROSS LINKAGE OF THE RESIN ON THE SEPARATION[a]

Dowex 50W (200–400 mesh)	HV[b]	HYV[b]	SV[b]	AHYV[b]
X2	200	28	44	27
X8	171	26	50	25
X12	92	18	20	17

[a] pH 6.0, 20% *t*-BuOH. [b] In milliliters.

TABLE III

ROLE OF CATION IN THE SEPARATION[a]

Cationic partner of the resin	Buffer system	HV[b]	HYV[b]	SV[b]	AHYV[b]
NH_4^+	0.2 *M* $AcONH_4$	171	26	50	25
Na^+	0.2 *M* $AcONH_4$	158	20	45	23
$NHEt_3^+$	0.2 *M* $AcONH_4$	112	11	14	11
Pyridinium$^+$	0.2 *M* pyridine–acetic acid	130	23	35	24

[a] pH 6.0, 20% *t*-BuOH. [b] In milliliters.

The effect of pH in buffer systems containing *n*-propyl alcohol or methyl alcohol is shown in Table IV. As noted in Table VI, 0.2 *M* pyridine–acetic acid buffer (pH 4.0) containing 40% methanol under somewhat different conditions effected better separation than the ammonium acetate buffer system. At lower pH, and especially in the presence of methanol, a better separation was achieved.

TABLE IV

EFFECT OF pH IN BUFFER SYSTEM pH 6

pH	HV	HYV	SV	AHYV
		20% *n*-PrOH		
7	154	28	33	15
6	175	21	41	21
4	196	25	67	21
		20% MeOH		
7	160	12	50	14
6	175	13	55	14
4	225	15	78	16

Concentration of Alcohol.—Among many conditions tested by us in a series of experiments, the solvent of pH 4.0 and 40% methanol gave best results (see Table V). The separation of the two pairs of diastereomers, DL-threonine and DL-allothreonine,

TABLE V

EFFECT OF CONCENTRATION OF ALCOHOL

Alcohol, %	HV[a]	HYV[a]	SV[a]	AHYV[a]
20[b]	171	26	50	25
40[b]	184	19	56	19
20[c]	225	15	78	16
40[c]	240	15	85	14

[a] In milliliters. [b] *t*-BuOH at pH 6.0. [c] MeOH at pH 4.0.

L-isoleucine and D-alloisoleucine, was tried and achieved under conditions similar to those described above. The use of ammonium acetate buffer (0.1, 0.2, and 0.3 *M*) with 20% *t*-butyl alcohol at pH 6.0 gave good separations. Variations in temperature (5, 25, and 45°) had little effect on the separation pattern.

B. Ninhydrin Assay.—Ten micromoles (1.31 mg.) each of hydroxy-L-proline and allohydroxy-D-proline was dissolved in 0.5 ml. of water. The resin, Dowex 50W-X8 (200–400 mesh), was in the NH_4^+ or pyridinium$^+$ form. The two buffer systems were 0.2 *M* ammonium acetate with 40% methanol at pH 4.0 and pyridinium acetate solvent—0.2 *M* pyridinium acetate with 40% methanol at pH 4.0. The flow rate was 4 ml./hr.; the temperature was 20–25°.

The sample solution (20 μmoles of the equimolar mixture) was passed through the column and eluted with the appropriate buffer. The effluent was collected in 1-ml. fractions; each fraction was analyzed by ninhydrin colorimetry[13] (440 mμ, in the case of pyridinium acetate buffer) or by densitometry as described above for the ammonium acetate buffer system. The results are shown in Table VI. The areas of the HYV and AHYV peaks were integrated to give the exact ratios of the two diastereomers. The results of experiment no. 2 were unaffected by a higher flow rate, such as 6 ml./hr. One such run will, therefore, be completed within less than 8 hr. when a column of 0.9 × 30 cm. is used.

Separation of Hydroxy-DL-proline and Allohydroxy-DL-proline Obtained from Ethyl Allylacetaminocyanoacetate.—To a suspension of ethyl allylacetaminocyanoacetate[14] (10.5 g., 0.05 mole) in water (50 ml.) was added 1.0 *N* sodium hydroxide (50 ml.) with stirring at room temperature. When stirring was continued for 2 hr. the suspension gradually became a solution. After addition of 1.0 *N* hydrochloric acid (50 ml.) the solution was evaporated *in vacuo*. The residue was extracted with hot acetone (total volume 150 ml.) and the acetone solution was evaporated *in vacuo* to a sirup (8.8 g.). The sirupy allylacetaminocyanoacetic acid in acetonitrile (100 ml.) and water (50 ml.) was treated with a solution of N-bromosuccinimide (NBS, 9.1 g.) in acetonitrile (100 ml.) and water (50 ml.) at room temperature. After standing for 1 hr. the solution was evaporated *in vacuo*. The residue, 2-acetamino-2′-cyano-4-hydroxy-5-bromopentanoic acid lactone, was dissolved in 6.0 *N* hydrochloric acid (100 ml.). The solution was refluxed for 5 hr. and evaporated *in vacuo* to dryness to the hydrochloride of 2-amino-4-hydroxy-5-bromopentanoic acid lactone. This salt was dissolved in water (100 ml.) and adjusted with 2.0 *N* sodium hydroxide at 50–55° to a final pH of 9.5–9.6.[1] Total volume of 2.0 *N* sodium hydroxide used was 135 ml. The solution was passed through a column (3 × 30 cm.) of Dowex 50W-X8 (100–200 mesh, H^+ form), washed with water, and eluted with 2 *N* NH_4OH. The ammonia-containing solution was evaporated *in vacuo*. The residue was dissolved in 20 ml. of water (solution A).

Half of solution A (10 ml.) was put on a column (1.8 × 110 cm.) of Dowex 50W-X8 (200–400 mesh, NH_4^+ form), previously washed with 0.2 *M* ammonium acetate containing 40% methanol, pH 4.0, and eluted with the same solvent at room temperature and a flow rate of 6 ml./hr. Each fraction (3 ml.) was tested on a paper strip by the isatin reaction. The results were HV, 174; HYV, 93; SV, 24; and AHYV, 138 ml. The other half of solution A was chromatographed and gave a similar ratio: 177, 96, 21, and 132 ml.

The two HYV fractions (93 + 96 ml.) were pooled and evaporated *in vacuo* to dryness. Most of the ammonium acetate was removed by sublimation *in vacuo* for about 2 hr. at 100°. The residue, dissolved in a small volume of hot water, on the addition of ethanol gave 1.31 g. of crystalline hydroxy-DL-proline. On recrystallization from water–ethanol 1.07 g. was obtained (16%

(13) H. Rosen, *Arch. Biochem. Biophys.*, **67**, 10 (1957).
(14) N. F. Albertson, *J. Am. Chem. Soc.*, **68**, 450 (1946).

TABLE VI

Expt. no.	Size of column, cm.	Buffer system	HV	HYV	SV	AHYV	Ratio of hypro-allohypro
1	0.9 × 50	Pyridinium acetate	33	9	18	11	49.8:50.2
2	0.9 × 30		20	9	7	10	49.7:50.3
3	0.9 × 20		14	9	2	9	49.9:50.1
4	0.9 × 50	Ammonium acetate	41	10	14	10	46:54

yield from ethyl allylacetaminocyanoacetate), m.p. 245–246° dec., lit. m.p. 247°.[12]

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.89; H, 6.83; N, 10.65.

The two AHYV fractions (138 + 132 ml.), processed as above, yielded 2.37 g. Further recrystallization with water–ethanol gave 2.11 g. (32%) of allohydroxy-DL-proline, m.p. 239–240° dec., lit.[12] m.p. 238°.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.70; H, 6.79; N, 10.52.

Separation of Hydroxy-DL-proline and Allohydroxy-DL-proline Obtained from Dichlorovalerolactone.—2,5-Dichloro-4-valerolactone was prepared by the action of sulfuryl chloride on diethyl allylmalonate. The dichlorolactone (13.5 g., 0.08 mole) dissolved in concentrated ammonium hydroxide (200 ml.) was left for 5 days at room temperature. This procedure was found more convenient than the ammonolysis at 100° in a pressure vessel.[12] The solution was evaporated *in vacuo*. The residue on paper chromatography (*n*-BuOH–AcOH–pyridine–H_2O = 4:1:1:2, v./v.) showed two ninhydrin-positive spots, one belonging to hydroxyproline (R_f 0.23, yellow), and another (R_f 0.16, purple) belonging to an unknown material, *not* proline amide, which disappeared after refluxing for 3 hr. in 100 ml. of 6.0 *N* hydrochloric acid. After evaporation to dryness the residue was dissolved in water (100 ml.), and the solution was passed through a column (3 × 30 cm.) of Dowex 50W-X8 (100–200 mesh, H^+ form), washed with water, and eluted with 2 *N* ammonium hydroxide.

TABLE VII

Expt. no.	HV[a]	HYV[a]	SV[a]	AHYV[a]
1	177	78	15	81
2	180	81	18	81
3	177	81	15	84

[a] In milliliters.

The ammonia solution was evaporated *in vacuo*, and the residue was made up to a volume of 30 ml. with water.

Each 10 ml. of the above solution was chromatographed as described above. The results obtained are shown in Table VII. The three HYV fractions were pooled and processed as described to yield 4.05 g. of hydroxyproline. Further recrystallization with water–ethanol gave 3.76 g. (35%) of pure hydroxy-DL-proline, m.p. 244–245° dec. By the same synthetic route and separation *via* the copper salts the yield of hydroxy-DL-proline was only 27%.[12]

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.77; H, 6.85; N, 10.61.

Similarly, the three portions yielded 2.85 g. of allohydroxyproline. Further recrystallization from water–ethanol gave 2.63 g. (25%), m.p. 238–239° dec. A yield of 27% of allohydroxyproline has been reported *via* the copper salts.[12]

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.81; H, 6.88; N, 10.73.

A Novel Method for the Preparation of Acid Anhydrides by Means of *trans*-Dibenzoylethylene and Tertiary Phosphines

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Reactions of *trans*-dibenzoylethylene with tertiary phosphines in the presence of carboxylic acids have been studied. When two equivalents of carboxylic acid were treated with *trans*-dibenzoylethylene and tertiary phosphine, the corresponding acid anhydrides were obtained in good yields, along with dibenzoylethane and phosphine oxide. Similar reactions were further extended to the phosphoric monoesters, and *sym*-pyrophosphates were obtained in good yields. The mechanism of the reaction is discussed.

It has recently been reported that the various carboxylic acids, phosphoric acids, and sulfonic acid were converted into the corresponding acid anhydrides in the course of oxidation–reduction reactions between diphenylmercury and tri-*n*-butylphosphine.[1]

$$(C_6H_5)_2Hg + 2RCO_2H + (n\text{-}C_4H_9)_3P \longrightarrow Hg + 2C_6H_6 + (RCO)_2O + (n\text{-}C_4H_9)_3P{=}O$$

In the present study, it was found that *trans*-dibenzoylethylene can be employed as a hydrogen acceptor in place of the diphenylmercury mentioned in the above experiments. When tri-*n*-butylphosphine was added to an anhydrous benzene solution of *trans*-dibenzoylethylene at room temperature, it assumed a red color with evolution of heat. After standing for 10 min., it was added to an anhydrous benzene solution of two equivalents of propionic acid and the mixture was refluxed for 2 hr.; propionic anhydride was obtained in 78% yield along with dibenzoylethane (77%) and tri-*n*-butylphosphine oxide (84%). Similar reaction was observed in the cases of the other carboxylic acids (see Table I).

$$C_6H_5COCH{=}CHCOC_6H_5 + (n\text{-}C_4H_9)_3P + 2RCO_2H \longrightarrow C_6H_5COCH_2CH_2COC_6H_5 + (n\text{-}C_4H_9)_3P{=}O + (RCO)_2O$$

Triphenylphosphine was likewise successfully used as an oxygen acceptor and propionic anhydride was obtained in 70% yield under the same condition.

The most probable pathway of this reaction may be sketched in the following manner. Initially, tri-*n*-butylphosphine reacts with *trans*-dibenzoylethylene to form an adduct (I),[2] which in turn is transformed into "phosphonium carboxylate" (II) in the presence of car-

(1) T. Mukaiyama, I. Kuwajima, and Z. Suzuki, *J. Org. Chem.*, **28**, 2024 (1963).

(2) Horner, *et al.*, reported that *trans*- and *cis*-dibenzoylethylene react with triethylphosphine to form an adduct similar to I in 95% and 65% yields, respectively: L. Horner and K. Klupfel, *Ann.*, **591**, 69 (1955).