

Anal. Calcd. for $C_{12}H_{10}N_6 \cdot 3HCl$; C, 41.6; H, 3.7. Found: C, 41.9; H, 3.7.

4-Quinolylguanidine.—Ten grams (0.05 mole) of ethyl quinoline-4-carboxylate was added to a solution of guanidine (0.05 mole) in 30 ml. of ethanol. The solution was allowed to stand for about sixteen hours, during which time crystals were deposited slowly. The crystalline material, after filtration, weighed 8.2 g. On heating in a capillary tube it softened at 230° with darkening and melted at $267-274^\circ$. The melting point varies with the rate of heating.

Anal. Calcd. for $C_{11}H_{10}ON_4$; C, 61.6; H, 4.7. Found: C, 61.7; H, 4.8.

4'-Quinolylguanamine (2,4-Diamino-6-(4'-quinolyl)-1,3,5-triazine).—One gram of the above compound was heated in a test-tube in a metal-bath. Ammonia began to be evolved at about 200° and the solid turned a pinkish color. The temperature was kept at $200-230^\circ$ until no more ammonia was evolved. The residue was then washed with hot alcohol and dissolved in 5 ml. of concentrated hydrochloric acid. After addition of charcoal and filtration the solution was made alkaline with sodium hy-

droxide when the guanamine (0.1 g.) separated as a slightly pinkish crystalline powder, m. p. $318-322^\circ$ (dec.). It was shown to be identical with the condensation product of 4-cyanoquinoline and guanidine by melting point and ultraviolet absorption spectrum measurements.

The authors' thanks are due to S. Blackman and N. Martinez, Jr., for the microanalyses reported here.

Summary

Aromatic nitriles appear to react with guanidine to form acylimidoguanidines as primary products, but this reaction fails when the aromatic nucleus is substituted with certain electron donating groups. The acylimidoguanidines may react further, depending on electronic and steric factors, giving 2-amino-4,6-diaryl-1,3,5-triazines as the usual product, but in one instance an aryl-guanamine was isolated.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

The Chemistry of 2,2-Diphenyl-4-pentenoic and 2,2-Diphenyl-4-methyl-4-pentenoic Acids¹

BY PAUL N. CRAIG AND IVAN H. WITT²

Because of the recent availability of 2,2-diphenyl-4-pentenoic (I) and 2,2-diphenyl-4-methyl-4-pentenoic (II) acids^{3,4} these compounds were examined as starting materials for the synthesis of compounds which might show pharmacological activity. These acids are of particular interest because their bifunctional nature allows the possibility of effecting transformations through a single function or by reactions involving both functions simultaneously. The present paper deals with the basic chemistry of these two γ,δ -unsaturated acids.

1. Reduction.—Reduction with either platinum or palladium catalysts gave excellent yields of 2,2-diphenylpentanoic (III)⁵ and 2,2-diphenyl-4-methylpentanoic (IV) acids. This was the sole reaction thus far observed which affected only the double bond in I and II.

2. Ester Formation.—The methyl ester (VI) was prepared from the acid (I) by the action of dimethyl sulfate on the potassium salt (V). The methyl ester (XIII) was prepared from the acid (II) by diazomethane. Either method of esterification may be used for these acids.

3. Acid Chloride Formation.—The acid chloride (VII) was prepared from I by both thionyl chloride and phosphorus pentachloride; VII was characterized by preparation of the amide

(1) Allyldiphenylacetic and β -methylallyldiphenylacetic acids, respectively.

(2) Deceased.

(3) Arnold and Searles, *THIS JOURNAL*, **71**, 1150 (1949).

(4) Obtained from Research Dept., General Mills, Inc., Minneapolis, Minn.

(5) May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

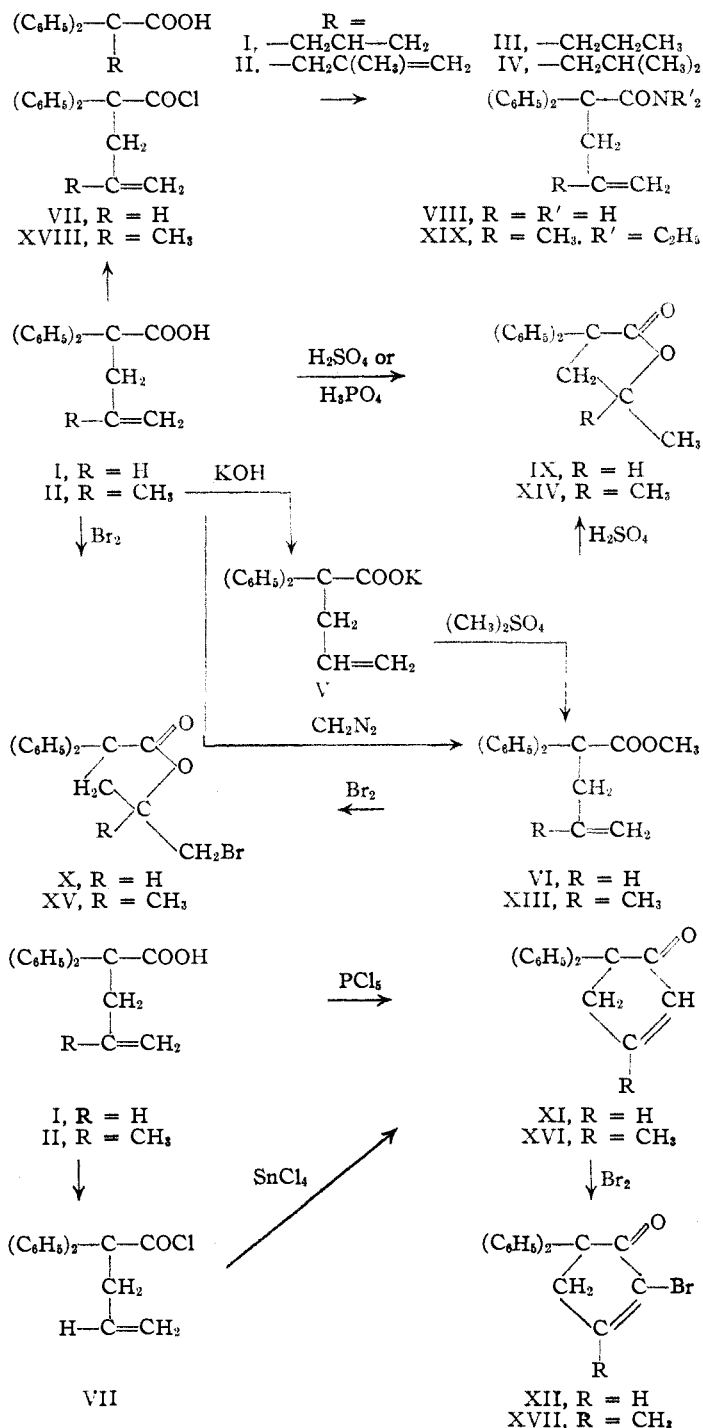
(VIII). When the 4-methylpentenoic acid (II) was treated with thionyl chloride, an anomalous reaction occurred (discussed in Section 4) unless pyridine was also employed as a reagent, in which case the corresponding acid chloride (XVIII) was readily prepared. The acid chloride (XVIII) was characterized by preparation of the diethylamide (XIX). The reaction of the 4-methylpentenoic acid (II) with phosphorus pentachloride did not yield the acid chloride, but led to the formation of a cyclopentenone (discussed below).

4. Lactone Formation.—When the unsaturated acids (I and II) were dissolved in sulfuric acid and then diluted with ice-water, lactonization occurred to give the valerolactones, IX and XIV, respectively. Lactonization occurred most readily with II, but excellent yields of both lactones were obtained. When the temperature exceeded 50° during the lactonization of the acid (I) with sulfuric acid, large amounts of water-soluble products were obtained.⁶ The best method for the lactonization of I utilized hot sirupy phosphoric acid.

Interaction of the 4-methylpentenoic acid (II) with thionyl chloride gave a mixture from which only the lactone (XIV) was isolated. Apparently the hydrogen chloride initially formed acted to lactonize the acid (II) in preference to the formation of the acid chloride (XVIII).

5. Bromolactone Formation.—Both of the pentenoic acids (I and II) reacted with bromine in the cold with evolution of hydrogen bromide

(6) Presumably this was due to the addition of sulfuric acid to the double bond, but this reaction was not further examined.



to give good yields of the bromovalerolactones (X and XV). These lactones were tentatively assigned the γ -lactone structure; degradative studies are now in progress.

In the preparation of the bromolactone from the 4-methylpentenoic acid (II), the hydrogen bromide formed initially during the reaction competed with the bromine for the unreacted

acid (II), resulting in the simultaneous formation of the lactone (XIV). To obtain the pure bromolactone (XV), it was necessary to add the acid to a large excess of bromine. No such difficulty was found in the preparation of the bromolactone (X) from the pentenoic acid (I). This emphasizes the greater ease of cyclization of II as compared to I, which was also found for the formation of the lactones, IX and XIV. An analogous situation as regards ease of lactonization was reported by Goering, Cristol and Dittmer⁷ for allylglycine and β -methallylglycine. The best preparation of the bromolactone (XV) involved the use of pyridine to remove the hydrogen bromide.

6. Cyclopentenone Formation.—In an attempted esterification of the 4-methylpentenoic acid (II) by a dialkylamino alcohol, utilizing phosphorus pentachloride in an attempt to prepare the acid chloride (XVIII), the α,β -unsaturated cyclopentenone (XVI) resulted. The latter was transformed to a bromoketone (formulated as XVII). The action of phosphorus pentachloride on I gave only traces of the acid chloride (VII) upon distillation. Instead, the cyclopentenone (XI) was obtained in poor yield. This ketone was obtained in slightly better yields by the cyclization of the acid chloride (VII) with stannic chloride. The cyclopentenone (XI) was transformed to a bromoketone (formulated as XII). No carbonyl derivatives could be obtained from either of the two cyclopentenones.⁸

The mechanism involved in the lactonizations of these olefinic acids is considered to be similar to that shown by Tarbell and Bartlett⁹ for dimethylmaleic and dimethylfumaric acids.

Further work is in progress with the allylic acids, and studies pertaining to the mechanism of formation of the bromolactones will be reported.

Acknowledgments.—The authors wish to acknowledge the helpful interest and many suggestions of Drs. Glenn E. Ullyot and Richard T. Arnold. Acknowledgment is also made to Drs. Ralph Manley and J. Opie of General Mills, Inc., for samples of the unsaturated acids.

(7) Goering, Cristol and Dittmer, Abstracts, Chicago Meeting A. C. S., April, 1948, 69 L.

(8) Compound XI was independently synthesized by Geissman and Horowitz (private communication), who definitely proved its structure and will report on this compound at a later date.

(9) D. S. Tarbell and P. D. Bartlett, THIS JOURNAL, 59, 407 (1937).

Experimental¹⁰

2,2-Diphenylpentanoic Acid (III).—2,2-Diphenyl-4-pentenoic acid (12.6 g., 0.05 mole), m. p. 141.5–143.5°, was dissolved in an excess of dilute sodium hydroxide solution. Reduction occurred within 2 minutes using a 10% palladium-charcoal catalyst and 3 atm. of hydrogen. On acidification, 2,2-diphenylpentanoic acid precipitated; after one recrystallization from alcohol and water, 11.4 g. was obtained (91%); m. p. 153.5–154.0° (lit. 150–152°). *Anal.* Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.13; neut. equiv., 254.3. Found: C, 80.17; H, 7.19; neut. equiv., 254.6.

2,2-Diphenyl-4-methylpentanoic Acid (IV).—2,2-Diphenyl-4-methyl-4-pentenoic acid (26.6 g., 0.10 mole), m. p. 120–121.5°, was dissolved in 250 ml. of ethanol. Reduction occurred in 45 minutes using 0.2 g. of platinum oxide catalyst and 3 atm. of hydrogen. On addition of water, 22.9 g. of 2,2-diphenyl-4-methylpentanoic acid was obtained (86%); m. p. 121.0–122.5°. A mixture with β -methallyldiphenylacetic acid melted at 105–109°. *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 80.56; H, 7.51; neut. equiv., 268.3. Found: C, 80.45; H, 7.61; neut. equiv., 270.8.

Methyl 2,2-Diphenyl-4-pentenoate (VI).—A solution of 20.0 g. (0.0793 mole) of 2,2-diphenyl-4-pentenoic acid and 5.25 g. of potassium hydroxide was prepared in 80 ml. by water. The water was removed by azeotropic distillation with xylene. Then 10.0 g. (0.0795 mole) of dimethyl sulfate was added and the mixture was stirred vigorously at reflux for two hours. Water was added, the layers were separated, and the xylene layer was washed with water. The combined organic layers were dried over calcium chloride and then distilled. The ester distilled at 154–161° (4 mm.); 15.0 g. (57%). *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81; sapon. equiv., 266.3. Found: C, 81.35; H, 7.16; sapon. equiv., 271.

Methyl 2,2-Diphenyl-4-methyl-4-pentenoate (XIII).—Diazomethane was prepared from 18 g. of nitrosomethylurea and extracted by 250 ml. of ether. To this solution was added a solution of 30.0 g. of 2,2-diphenyl-4-methyl-4-pentenoic acid in 200 ml. of ether. The volume was reduced on the steam-bath to 150 ml., and an extraction was made with 5% sodium bicarbonate solution. No acid was recovered on acidification of this extract. The ether was washed once with water and removed by evaporation *in vacuo*. The residue weighed 32.0 g. (100%). One gram of this ester was redistilled for analysis; b. p. 160–170° (5 mm.). *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19; neut. equiv., 280.35. Found: C, 80.78; H, 7.85; neut. equiv., 259. This ester was very difficult to saponify.

2,2-Diphenyl-4-pentenoyl Chloride (VII).—A mixture of 50.0 g. of 2,2-diphenyl-4-pentenoic acid (m. p. 141.5–143.5°) and 50 g. of thionyl chloride (Eastman Kodak Co. Pract.) was refluxed for 20 minutes on the steam-bath. Air was blown through the flask for another 20 minutes. The solution was cooled and dissolved in benzene. After a wash with 3% sodium bicarbonate, the benzene was removed on the steam-bath, and the residue was distilled; b. p. 148° (0.26 mm.); 48.7 g. (91%). *Anal.* Calcd. for $C_{17}H_{16}OCl$: C, 75.41; H, 5.58. Found: C, 75.56; H, 6.00.

2,2-Diphenyl-4-pentenamide (VIII).—A mixture of 25.2 g. (0.1 mole) of 2,2-diphenyl-4-pentenoic acid and 25 g. of thionyl chloride (0.2 mole) was heated on a steam-bath for one hour while a small stream of air was blown into the flask. The brown oil was poured into 100 ml. of concd. ammonia with stirring, and the mixture was allowed to stand at room temperature overnight. The crude amide was distilled from a sausage flask; b. p. 180–190° (0.8–1.2 mm.); 17.0 g., m. p. 75–77° (67%). An analytical sample was prepared by crystallization from benzene and petroleum ether; m. p. 77–78°. *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82. Found: C, 81.18; H, 7.20.

2,2-Diphenyl-4-methyl-4-pentenoyl Chloride and Diethylamide (XVIII and XIX).—A solution of 5.3 g. (0.02 mole) of 2,2-diphenyl-4-methyl-4-pentenoic acid and 4 g. (0.04 mole) of pyridine in 20 ml. of benzene was treated with 4 g. (0.03 mole) of thionyl chloride. An oil separated, and benzene and water were added. The benzene layer was washed twice with water, and dried by distilling one-half of the benzene. The acid chloride was not isolated, but was treated immediately with 5.0 g. of diethylamine. After refluxing the mixture for 15 minutes, ether was added; the resultant amine hydrochloride was removed by filtration. Distillation of the residue *in vacuo* gave 3 g. of a thick oil. Recrystallization from benzene and pet. ether (b. p. 45–60°) followed by recrystallization from ethanol-water gave 1.5 g. of needles; m. p. 83–84°. *Anal.* Calcd. for $C_{22}H_{27}ON$: C, 82.20; H, 8.47. Found: C, 82.02; H, 8.58.

2,2-Diphenyl-4-valerolactone (IX).—A mixture of 20.0 g. of 2,2-diphenyl-4-pentenoic acid (m. p. 141.5–143.5°) and 60 g. of 85% phosphoric acid was stirred vigorously at 160° for one and one-half hours. The contents were cooled and poured onto 250 cc. of lukewarm water. After chilling the mixture in an ice-bath, filtration afforded a light tan product which was washed with water, triturated with 5% sodium bicarbonate solution, and further washed with water; m. p. 107–112°. Recrystallization from ethanol gave 17.5 g. (87.5%) of colorless lactone; m. p. 113.5–114.5°. A mixed melting point with authentic lactone kindly furnished by Dr. E. M. Schultz of Sharp and Dohme, Inc., was not depressed.¹¹ The same lactone was obtained from methyl 2,2-diphenyl-4-pentenoate or 2,2-diphenyl-4-pentenoic acid on treatment with sulfuric acid at 40°.

2,2-Diphenyl-4-methyl-4-valerolactone (XIV).—A solution of 2.0 g. of 2,2-diphenyl-4-methyl-4-pentenoic acid in 8 g. of concd. sulfuric acid was swirled 5 minutes at 45° and cast onto ice. The precipitate was washed with water, triturated with 1 *M* sodium bicarbonate, and further washed with water. After one recrystallization from ethanol, 1.5 g. of lactone was obtained; m. p. 106–107°. *Anal.* Calcd. for $C_{19}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.97, 81.21; H, 6.99, 7.17. This lactone was obtained in 60% yield by the action of thionyl chloride on 2,2-diphenyl-4-methyl-4-pentenoic acid, as well as by the action of sulfuric acid on methyl 2,2-diphenyl-4-methyl-4-pentenoate.

2,2-Diphenyl-5-bromo-4-valerolactone (X).—A mixture of 30.0 g. (0.119 mole) of 2,2-diphenyl-4-pentenoic acid (m. p. 141.5–143.5°) and 180 ml. of carbon tetrachloride was stirred vigorously at 0 to 5° while 19.2 g. (0.012 mole) of bromine was added over a period of 15 minutes. The carbon tetrachloride was removed under reduced pressure at room temperature, and the residue was recrystallized from ethanol to give 35.1 g. (89%); m. p. 87–88°. *Anal.* Calcd. for $C_{17}H_{16}O_2Br$: C, 61.64; H, 4.56. Found: C, 61.64; H, 4.68.

Methyl 2,2-diphenyl-4-pentenoate formed this bromolactone when treated in the same manner with bromine in carbon tetrachloride.

2,2-Diphenyl-4-methyl-5-bromo-4-valerolactone (XV). (a) The following technique was devised to obtain the desired bromolactone free from 2,2-diphenyl-4-methyl-4-valerolactone. To a stirred solution of 60 g. of bromine in 100 ml. of carbon tetrachloride at 0° was added 60.0 g. of 2,2-diphenyl-4-methyl-4-pentenoic acid (m. p. 121–122°) in portions over a 10-minute period. The mixture was allowed to warm to room temperature slowly. The excess bromine and carbon tetrachloride were removed by blowing air through the flask, which was heated to 40°. The residue was recrystallized from 400 ml. of acetone; 44.5 g. (69%) of large, diamond-shaped crystals was obtained; m. p. 145–146°. A second fraction was obtained from the filtrate; 10.5 g. (16%) of m. p. 137–141°. Recrystallization of the first fraction gave an analytically pure bromolactone melting at 147.0–148.5°. When bromine was added to the acid, a product was obtained

(10) All melting points were open capillary and corrected. Analyses by Mrs. Lillian Shreve, Miss Ruth Savacool and Miss Rita Fox.

(11) Schultz, Robb and Sprague, *This Journal*, **66**, 2454 (1947)

which melted 10–25° below the m. p. of the pure bromolactone. *Anal.* Calcd. for $C_{18}H_{17}O_2Br$: C, 62.62; H, 4.96. Found: C, 62.69, 62.40; H, 5.27, 5.12.

(b) Bromination of 2,2-diphenyl-4-methyl-4-pentenoic acid by bromine in the presence of pyridine gave an excellent yield of this bromolactone; m. p. 148–149°. Methyl 2,2-diphenyl-4-methyl-4-pentenoate formed the same bromolactone when treated with bromine in carbon tetrachloride.

5,5-Diphenyl-2-cyclopentenone (XI). A.—The acid chloride of 2,2-diphenyl-4-pentenoic acid was prepared from 10.0 g. (0.04 mole) of acid and excess thionyl chloride. After removal of thionyl chloride at 100° *in vacuo*, the residue was dissolved in dry benzene. To this solution was added dropwise a solution of 11.5 g. (0.045 mole) of stannic chloride in dry benzene. Stirring at room temperature was continued for 15 minutes. A slight evolution of heat was noticed. The mixture was decomposed with water and hydrochloric acid, and the organic layer was washed with water. Extraction of the organic layer with 10% sodium hydroxide gave essentially no recovered acid. On distillation at 5 mm., 2.8 g. of product (b. p. 182–190°) was obtained as crystals; m. p. 80–82°. Three recrystallizations from acetic acid and water raised the melting point to 97–98.5°. *Anal.* Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.97; H, 6.25.

B.—Ten grams of 2,2-diphenyl-4-pentenoic acid and 8.5 g. of phosphorus pentachloride were warmed on the steam-bath for 15 minutes. Some of the phosphorus oxychloride was removed by evacuation at 100°, and the residue was distilled. Vigorous evolution of gas occurred at 150–200° at 10–20 mm. After the decomposition, distillation gave 3 g.; b. p. 155–185° (1 mm.). A large amount of polymer was left behind. A recrystallization of the 3 g. from benzene and pet. ether (b. p. 45–60°) gave 0.75 g. of crystals melting at 80–83°. A mixed melting point with the cyclopentenone obtained by method (A) was not depressed.

5,5-Diphenyl-2-bromo-2-cyclopentenone (XII).—To a solution of 100 mg. of 5,5-diphenyl-2-cyclopentenone (m. p. 80–82°) in 5 ml. of carbon tetrachloride was added dropwise a 5% solution of bromine in carbon tetrachloride until no more take-up of bromine occurred. After the solvent was removed by heating, the product melted at 87–88°. Two recrystallizations from ethanol and water gave an analytical sample; m. p. 100–101°. *Anal.*

Calcd. for $C_{17}H_{13}OBr$: C, 65.19; H, 4.19. Found: C, 65.22; H, 4.65.

5,5-Diphenyl-3-methyl-2-cyclopentenone (XVI).—A mixture of 2.7 g. of 2,2-diphenyl-4-methyl-4-pentenoic acid and 2.0 g. of phosphorus pentachloride was warmed on the steam-bath for 15 minutes. Then 1.5 g. of diethylaminoethanol was added, and after five minutes, 25 ml. of benzene was added. Filtration gave 1.5 g. of amine hydrochloride. Evaporation of the benzene left an oil, which was washed with 5% sodium hydroxide and 5% hydrochloric acid. Two recrystallizations of the resulting oil from ethanol gave crystals; m. p. 106.5–108.5°. A mixed melting point with 2,2-diphenyl-4-methyl-4-valerolactone was depressed to 75°. *Anal.* Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.00; H, 6.79.

5,5-Diphenyl-3-methyl-2-bromo-2-cyclopentenone (XVII).—A solution of 50 mg. of 5,5-diphenyl-3-methyl-2-cyclopentenone in 3 ml. of carbon tetrachloride was treated with 0.5 g. of bromine. Evaporation on the steam-bath left an oil, which was recrystallized from ethanol-water to give needles; m. p. 117–119°. *Anal.* Calcd. for $C_{18}H_{15}OBr$: C, 66.06; H, 4.26. Found: C, 66.15; H, 4.83.

Summary

The chemistry of 2,2-diphenyl-4-pentenoic acid and 2,2-diphenyl-4-methyl-4-pentenoic acid was examined. Hydrogenation of the two olefinic acids to the saturated acids was accomplished. The unsaturated acids readily lactonized with acidic reagents, and easily formed bromolactones with bromine. They both were cyclized to substituted cyclopentenones, which were converted to bromo derivatives. The acid chlorides of the allylic acids were prepared and from them amides were made.

The methyl esters of the two acids have been prepared by different methods, and have been found to form both the lactones and the bromolactones readily on treatment with acids or bromine.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY¹]

Separation of γ -Casein²

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Mellander³ observed that casein was composed of three electrophoretic components, which he named α -, β - and γ -casein in the order of decreasing mobility. He reported that the γ -casein component has a low phosphorus content, which suggests that γ -casein is similar to the alcohol-soluble, low-phosphorus casein isolated by Osborne and Wakeman.⁴ A method has been devised for separating γ -casein that consists in fractionation with 50% ethyl alcohol and with

water at pH 5.8. The γ -casein prepared in this manner has an isoelectric point of pH 5.8–6.0 and is electrophoretically homogeneous in solutions alkaline to the isoelectric point but inhomogeneous in acid solutions. The similarity between the composition and properties of γ -casein and those of the alcohol-soluble casein described by Osborne and Wakeman⁴ indicates that the two caseins are essentially the same.

Experimental

Preliminary experiments on the solubility of unfrac-tionated casein in water-alcohol solution showed that under a given set of conditions solubility was greatest at an alcohol concentration of about 50%. The temperature, pH and salt content also affected its solubility in alcohol. Thus, a 20% solution of casein could be made at pH 4.7 in 50% alcohol that contained a high concentration of in-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented before the Division of Biological Chemistry at the 117th Meeting of the American Chemical Society, Philadelphia, April, 1950.

(3) Mellander, *Biochem. Z.*, **800**, 240 (1939).

(4) Osborne and Wakeman, *J. Biol. Chem.*, **33**, 243 (1918).