4,5,6-Trimethoxyindane-2-carboxylic Acid (XIII).—Hydrogenation of the indene monoacid (XI) in acetic acid using a 5% palladium-on-charcoal catalyst proceeded readily at 50° and 40 lb. pressure and ceased after two hours with the absorption of 1.01 moles of hydrogen. After filtering, the solvent was distilled, and the residue, melting at 100–105°, was recrystallized from 50% ethanol to give a 92% yield of the indane acid as colorless fine crystals, m.p. 110–111°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.35. Found: C, 61.89; H, 6.38.

Infrared Spectrum.—Acid band was shown at 5.84 μ.

Attempted Preparation of 4,5,6-Trimethoxyindene-2,3-dicarboxylic Acid (VI).—A solution of the indene diester (VII) in acetic acid with a slight amount of hydrochloric acid[4] was warmed on the steam-bath for 30 minutes. A very small amount of crystalline precipitate, which separated from the dark red-brown reaction mixture, was collected. It melted at 132–135° with gas evolution, which apparently was caused by decarboxylation of the dicarboxylic to the monocarboxylic acid on heating.[4] No product could be isolated from the filtrate.

Ethyl α-Formyl-β-(3,4,5-trimethoxyphenyl)-propionate (X).—A suspension of potassium ethoxide was prepared by dissolving 2.4 g. of potassium in 20 ml. of absolute ethanol, removing excess solvent by heating under reduced pressure for 45 minutes and adding 30 ml. of dry ether. The mixture was cooled to −20° and a solution of 8 g. of ethyl β-(3,4,5-trimethoxyphenyl)-propionate and 4.6 g. of ethyl formate in 30 ml. of ether was added dropwise with stirring during a 30-minute interval. Stirring was continued for another 4 hours at −20°, then the reaction mixture allowed to stand at room temperature for 3 days. Cold water was added to dissolve the dark-reddish gum; the alkaline solution was acidified and the oil which separated extracted with ether, washed with water and dilute sodium bicarbonate solution, then dried over magnesium sulfate. Evaporation of the ether gave 5.1 g. (57%) of a clear reddish oil. This was used for the next preparation without further purification.

Ethyl 4,5,6-Trimethoxyindene-2-carboxylate (XII).—This indene monoester was obtained in the same manner as the analogous diester (VII) by cyclization of the formyl derivative (X) with two different agents. (a) A 3-g. sample of the above oil was added dropwise to a mixture of 10 ml. of concentrated sulfuric and 20 ml. of 85% phosphoric acid at 0° and, after stirring 5 minutes, the mixture was allowed to stand at room temperature for 1.5 hours. It was then poured into ice-water and the oily gum which separated was washed with water and dried; wt. 1.9 g. (68%). (b) Four grams of the oil was added to 40 g. of polyphosphoric acid at 10° with stirring. The mixture turned dark brown in a few minutes and was poured into ice-water after standing at room temperature for ten minutes. The oil which separated from the resulting emulsion solidified upon stirring. This solid was filtered; yield 3.4 g. (91%). The products from the two cyclization procedures were recrystallized separately from dilute ethanol to give similar colorless fine needles, m.p. 56–58°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.47. Found: C, 64.74; H, 6.18.

Infrared Spectrum.—Conjugated ester band was shown at 5.90 μ.

Hydrolysis of this ester with 15% alcoholic potassium hydroxide gave a 73% yield of the corresponding acid, which separated from dilute ethanol as colorless fine crystals, m.p. 169–170°. It was identical in melting point with the acid (XI) previously obtained from hydrolysis of diethyl 4,5,6-trimethoxyindene-2,3-dicarboxylate, and a mixed melting point with this acid showed no depression.

Ethyl 4,5,6-Trimethoxyindane-2-carboxylate (XIV).—A mixture of 1 g. of the indene ester (XII), 15 ml. of acetic acid and 1 g. of 5% palladium–carbon catalyst was hydrogenated at 60° and 5 lb. pressure. After 2.5 hours, 0.99 mole of hydrogen was absorbed. The catalyst was removed and the acetic acid evaporated under reduced pressure giving 0.93 g. (93%) of an oily product (XIV). All attempts to crystallize the oil were unsuccessful.

Saponification of the oil with 20% aqueous sodium hydroxide yielded the corresponding acid which separated from dilute ethanol in colorless fine crystals, m.p. 110–111°. It was proved to be identical with the sample (XIII) obtained by hydrogenation of 4,5,6-trimethoxyindene-2-carboxylic acid, by comparison of melting points and mixed melting point.

Acknowledgments.—The author wishes to express his thanks to Dr. J. L. Hartwell for his encouragement and to Dr. A. W. Schrecker for assistance in revising the manuscript. Analyses were carried out by the Microanalytical Laboratory under the direction of Dr. W. C. Alford.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Studies in Polyphosphoric Acid Cyclizations

BY JOHN KOO[1]

RECEIVED NOVEMBER 3, 1952

An extensive study of cyclizations with polyphosphoric acid (PPA) has been made and this acid has been found to be the reagent of choice in the synthesis of various 1-indanones, 1-tetralones, benzosuber-5-ones and anthraquinones from aryl-aliphatic and aroyl-aromatic acids. It has been further applied advantageously to the preparation of various substituted indenes from aryl-substituted aliphatic ketones. Improved and detailed experimental conditions and techniques required for PPA cyclizations have been described.

During the course of an investigation dealing with the synthesis of degradation products of colchicine and of some analogous compounds, it became necessary to develop procedures for the preparation of di- and trimethoxybenzosuberene derivatives by the cyclization of aryl-aliphatic carbonyl compounds.[2] In the original experiments, the appropriate α-ethoxalyl esters were treated with a mixture of concentrated sulfuric and 85% phosphoric acids to yield substituted benzosuberenecarboxylic anhydrides.[2a,b,c] This procedure was well suited for the preparation of indenes[3,4] and dihydronaphthalene,[5] but proved to be somewhat less satisfactory in the preparation of seven-membered ring compounds because of the sensitivity of the reaction product to the cyclizing agent or because of the occurrence of side-reactions,[2c] such as sulfonation or ester cleavage.

(1) Special Research Fellow of the National Cancer Institute, National Institutes of Health.

(2) (a) E. C. Horning and J. Koo, THIS JOURNAL, **73**, 5830 (1951); (b) J. Koo, *ibid.*, **75**, 720 (1953); (c) **75**, 723 (1953); (d) J. Koo and J. L. Hartwell, *ibid.*, **75**, 1625 (1953).

(3) E. C. Horning, J. Koo and G. N. Walker, *ibid.*, **73**, 5826 (1951).

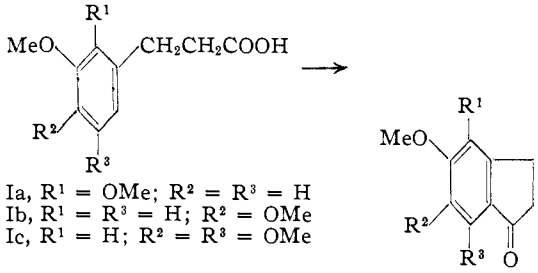
(4) J. Koo, *ibid.*, **75**, 1889 (1953).

(5) E. C. Horning and J. Koo, *ibid.*, **73**, 5828 (1951).

It was found subsequently that the cyclodehydration of substituted α-ethoxalyl-δ-phenylvalerates proceeded much more smoothly and in much higher yield when polyphosphoric acid (PPA)[6] was employed. Instead of benzosuberenecarboxylic anhydrides, the corresponding dicarboxylic esters were formed.[2d] It is noteworthy that PPA is such a mild dehydrating agent that ester cleavage (produced in the case of sulfuric–phosphoric acids) does not take place in its presence. Similarly, α-ethoxalyl-β-phenylpropionates were cyclized by PPA to indenedicarboxylates in excellent yield.[3,4] Starting with α-formyl rather than α-ethoxalyl esters, benzosuberenecarboxylates[2c,d] and indenecarboxylates[4] were obtained, depending on the length of the side chain. PPA again gave a higher yield than sulfuric–phosphoric acids, which also hydrolyzed the ester group in the case of the benzosuberene[2d] but not of the indene[3,4] derivatives. In another type of cyclodehydration leading to the formation of seven-membered ring compounds, 2,3,4-trimethoxybenzosuber-5-one was prepared from δ-(3,4,5-trimethoxyphenyl)-valeric acid in 94% yield with PPA,[2b] as compared to 64% and 84% yields, obtained with phosphorus pentoxide[7a] and phosphorus pentachloride–stannic chloride,[7b] respectively. These successes led us to investigate more fully the use of PPA in various types of ring closures, and the results form the subject of this paper.

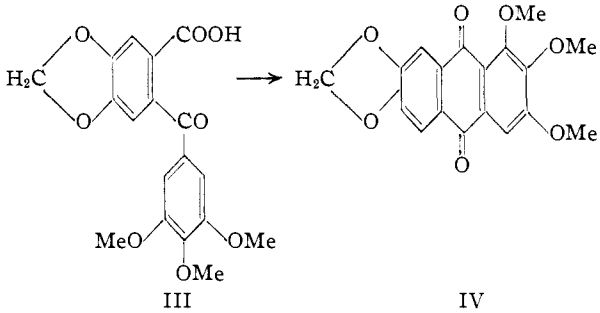
In the original reports on PPA cyclodehydrations, Snyder and Werber described the formation of harman and isoquinoline derivatives from α-acylamino-β-arylpropionic acids,[6a] and the cyclization of some hydrocinnamic, γ-phenylbutyric and *o*-benzoylbenzoic acids to the corresponding indanones, α-tetralone and anthraquinone, respectively.[6b] While PPA was the reagent of choice in the heterocyclic series (where it was used in conjunction with phosphorus oxychloride), they reported lower yields of α-hydrindone and α-tetralone than could be obtained by other methods.[8] The convenience of the experimental procedure, however, was considered to outweigh this factor. Thus the Friedel–Crafts method is laborious since it involves the preparation and purification of the intermediary acid chloride. It may be added that aluminum chloride frequently causes demethylation of phenolic ethers, while PPA does not. The action of hydrogen fluoride on the free acid generally affords good yields, but the reagent is hazardous. Sulfuric acid and also phosphorus pentoxide frequently promote ketone condensation reactions, with the result that the yields of the desired product are often low.[8]

By a modification of Snyder and Werber's experimental procedure,[6b] the yields of α-hydrindone and α-tetralone have now been increased to 94% and 93%, respectively, which are about as high or higher than the best ones reported in the literature. Extending the reaction to di- and trimethoxy derivatives, 4,5-dimethoxy- (IIa), 5,6-dimethoxy- (IIb) and 5,6,7-trimethoxy-1-indanone (IIc) were prepared in over 90% yields from the appropriate hydrocinnamic acids (I). 1,2,3-Trimethoxy-6,7-methylenedioxyanthraquinone (IV) was produced from 4,5-methylenedioxy-2-(3′,4′,5′-trimethoxybenzoyl)-



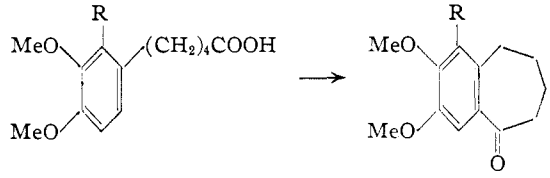
Ia, R^1 = OMe; R^2 = R^3 = H
Ib, R^1 = R^3 = H; R^2 = OMe
Ic, R^1 = H; R^2 = R^3 = OMe

IIa, R^1 = OMe; R^2 = R^3 = H
IIb, R^1 = R^3 = H; R^2 = OMe
IIc, R^1 = H; R^2 = R^3 = OMe



III IV

benzoic acid (III)[9] in 93% yield. The use of PPA in the preparation of 2,3,4-trimethoxybenzosuber-5-one has already been reported[2b]; similarly 2,3-dimethoxybenzosuber-5-one (VIa) and 1,2,3-trimethoxybenzosuber-5-one (VIb) have now been obtained from the substituted δ-phenylvaleric acids (V) in higher yields than with the previously employed[7] cyclizing agents.



Va, R = H
Vb, R = OMe

VIa, R = H
VIb, R = OMe

It has already been mentioned that, in the cyclodehydration of α-ethoxalyl and α-formyl esters, PPA gives higher yields than sulfuric–phosphoric acids and leaves the ester group intact. By extending the reaction to substituted acetoacetic esters, ethyl 3,4-dimethoxybenzylacetoacetate (VIIa) and the analogous 3,4-methylenedioxy derivative were both cyclized in over 80% yields to ethyl 5,6-dimethoxy-3-methylindene-2-carboxylate (VIIIa) and ethyl 5,6-methylenedioxy-3-methylindene-2-carboxylate. The yields of VIIIa and its 3,4-methylenedioxy analog using sulfuric–phosphoric acids were 47 and 48%, respectively.[10] Activation of the carbonyl group by a β-carbethoxy group was not required for successful cyclodehydration by means of PPA. Thus 3,4-dimethoxybenzylace-

(6) (a) H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2962 (1950); (b) **72**, 2965 (1950).

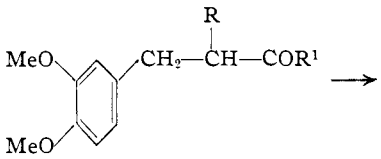
(7) (a) R. D. Haworth, B. P. Moore and P. L. Pauson, *J. Chem. Soc.*, 1045 (1948); (b) D. Caunt, W. D. Crow, R. D. Haworth and C. A. Vodoz, *ibid.*, 1631 (1950).

(8) W. S. Johnson, in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 114.

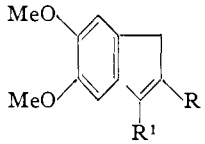
(9) Kindly supplied by Dr. Wilkins Reeve; *cf.* W. Reeve and W. M. Fareckson **111**, THIS JOURNAL, **72**, 5195 (1950).

(10) J. Koo, *ibid.*, **75**, 2000 (1953).

tone (VIIb) and 3,4-dimethoxybenzylacetophenone (VIIc) were cyclized to 5,6-dimethoxy-3-methylindene (VIIIb) (51–58% yield) and 5,6-dimethoxy-3-phenylindene (VIIIc) (100% yield). Sulfuric–phosphoric acids had given 52 and 91% yields, respectively.[10]



VIIa, R = CO_2Et; R^1 = CH_3
VIIb, R = H; R^1 = CH_3
VIIc, R = H; R^1 = C_6H_5



VIIIa, R = CO_2Et; R^1 = CH_3
VIIIb, R = H; R^1 = CH_3
VIIIc, R = H; R^1 = C_6H_5

Nearly all the experiments reported here were carried out in small quantities. It seems reasonable to believe that some of the compounds would have given still higher yields, if larger samples had been employed to reduce manipulative losses.

Experimental Conditions.—The chief factors influencing the yield in cyclizations with either sulfuric–phosphoric acids or PPA are the temperature and the reaction time. However, these factors have a somewhat greater variation in the case of PPA, which is the milder reagent. This is especially true for the reaction time, which in some instances can be varied by 10 to 30 minutes without any appreciable change in yield. The reaction takes place more readily as the reactivity of the carbonyl group increases, and it is also facilitated to a certain extent by the presence of alkoxyl groups in the aromatic ring. Thus the compounds cyclized by PPA fell into the following groups: (1) α-ethoxalyl and α-formyl esters are cyclized at 0 to 10° within 5 to 30 minutes; (2) acetoacetic esters and, less completely, methyl ketones are cyclized at room temperature in 30 minutes; (3) phenyl ketones and carboxylic acids react when heated at 60 to 70° for 30 to 60 minutes; (4) benzoylbenzoic acids require heating for several hours at temperatures ranging from 80 to 90°, depending on the substituents present. Another general experience is that low-melting or liquid compounds can be cyclized in the cold or at room temperature within a short time, while solid compounds require stronger conditions, the higher melting substances needing higher temperatures.

To determine the optimum temperature required for the cyclization of a given compound, a trace of substance is mixed with a few drops of PPA. If the mixture turns dark immediately, the reaction should be carried out in the cold; if the color changes gradually, room temperature is preferable; if only little color appears, heating is required. In the actual run, the optimum time for ending the reaction is determined most conveniently by observing the color changes that take place during the reaction. Most of the compounds give light yellow or light red colors in the beginning, turning to bright red and finally deep red. Two of the compounds (containing methylenedioxy groups) gave blue or purple colors, while a change from light to deep yellow was observed with some of the acids. It is best to stop the reaction as soon as a deep red, yellow or purple color is reached. This color change is easy to follow when the starting material is pure; otherwise it is obscured by a dark brownish discoloration. However, it does not appear necessary for a successful reaction as such to employ very pure compounds. In many cases, nearly pure products were obtained in the usual high yields from rather crude starting materials. An additional test for the completeness of the reaction is described in the Experimental section; it consists in diluting a small aliquot with ice-water and observing the appearance of the product.

In general, it is best to use five to ten grams of PPA for each gram of compound. If too little PPA is used, the yields tend to drop, while too large an amount requires a proportionally larger amount of water to dilute the reaction mixture. It was observed that PPA was quite hygroscopic, and in small-scale cyclizations which were carried out for several hours lower yields were obtained in open vessels than in vessels protected from moisture.

To conclude, the use of PPA in cyclodehydrations presents the following advantages: (1) a simple experimental set-up; (2) the reaction is easily followed; (3) yields are very high and products generally purer; (4) side reactions, such as demethylation, ester cleavage and sulfonation, are avoided; (5) the starting material need not be pure; (6) applicability to many types of cyclizations.

Experimental[11]

General Cyclization Procedure.—In most cases the reaction was conveniently carried out in a weighing bottle,[12] which was kept covered except while the mixture was stirred. In larger runs, an erlenmeyer flask protected from moisture with a cotton plug might be used. A three-necked round-bottomed flask fitted with an efficient mechanical stirrer, a thermometer and a calcium chloride tube was suitable for large-scale experiments carried out at elevated temperature. The compound to be cyclized should be finely ground, and the PPA prechilled, in case the temperature at which the reaction is to be performed is below that of the room.

In a typical run, 1 g. of the compound was added to 10 g. of PPA. The viscous mass was mixed thoroughly and the container covered and kept at the required temperature.[13] The mixture was well stirred every few minutes with a spatula or thermometer. The reaction was stopped as soon as a deep red, yellow, purple or blue color was reached. Additional evidence could be obtained by stirring a few drops of the reaction mixture into ice-water. Separation of colorless crystalline (in the case of higher melting products) or gelatinous material (for most low-melting esters) within a short while indicated completeness of the cyclization. If colorless gummy or oily material separated,[14] the cyclization was usually incomplete, while formation of a brownish gum indicated that the reaction had been carried out for too long a time.

The reaction mixture was then stirred into 20 ml. of ice-water, and the container rinsed with some more cold water.

(11) Melting points are corrected. Analyses were performed by the Microanalytical Laboratory under the direction of Dr. W. C. Alford.

(12) With outside ground cap, 30–45 ml. capacity.

(13) A constant-temperature bath or oven was found most convenient.

(14) This test is evidently not applicable when the reaction product is a liquid.

The combined aqueous solutions were then extracted with two 20-ml. and three 10-ml. portions of ether (or ethyl acetate); the organic extracts were washed with 10 ml. each of cold water, 10% sodium bicarbonate solution, and again water, then dried over magnesium sulfate. Evaporation of the solvent and drying to constant weight in a vacuum furnished the crude product, which in most cases was purified by crystallization from dilute ethanol or by vacuum distillation.

Alternatively, if the crude product separated in a crystalline or granular form when the reaction mixture was poured into ice-water, it could be collected on a filter after further dilution, washed with cold water, stirred thoroughly with 10% sodium bicarbonate solution, then washed again with water, and dried. When acids were cyclized, unchanged starting material could be recovered by acidification of the bicarbonate washings.

Cyclization Experiments. **α-Hydrindone.**—Hydrocinnamic acid (2 g.) was cyclized with 20 g. of PPA at 70° for 80 minutes, at which time the color was deep yellow. Isolation with ether yielded 1.65 g. (94%) of a pale yellow crystalline solid, m.p. 39.5–41°. No starting material was recovered from the bicarbonate extract. By the same method, Snyder and Werber[6b] reported a 62% yield of crude material, m.p. 35–37°. Also, starting with methyl hydrocinnamate Gilmore[15] obtained the same compound in 93% yield but no purity was indicated. The inverse Friedel–Crafts reaction (starting with purified hydrocinnamyl chloride) gave a product melting at 39–39.6° in 99% yield, and 94% recovery of pure ketone (m.p. 39.8–40.2°).[16]

α-Tetralone.—Cyclization of 20 g. of γ-phenylbutyric acid with 150 g. of PPA at 70° for 40 minutes, followed by isolation with ether gave an oil, b.p. 93° (1.3 mm.) (reported[6b] 96° (2 mm.)). The yield was 16.55 g. (93%). Previously, PPA cyclization had provided a 66%,[6b] and also a 72%[15] yield (starting with methyl ester of the acid), and the inverse Friedel–Crafts reaction a 90–91% yield.[16]

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.13; H, 5.51.

4,5-Dimethoxy-1-indanone (IIa).—A mixture of 1 g. of β-(2,3-dimethoxyphenyl)-propionic acid (Ia)[17] and 10 g. of PPA was heated at 60° for 20 minutes (dark red color). Isolation with ether provided a pale yellow oil (0.894 g., 99%), which crystallized rapidly. The crude material, m.p. 70–72°, was recrystallized once from ether–pentane and twice from dilute ethanol to give small colorless plates, m.p. 74–75° (reported[17] 82°). The compound had previously been prepared by cyclization with phosphorus pentoxide,[17] but no yield had been reported.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.28. Found: C, 68.90; H, 6.40.

5,6-Dimethoxy-1-indanone (IIb).—From 1 g. of β-(3,4-dimethoxyphenyl)-propionic acid (Ib)[3] and 10 g. of PPA, there was obtained similarly after 25 minutes at 65° a pale yellow product (0.812 g., 90%), m.p. 117–119° (reported[16] 118.8–119.5°). If heating was continued during 70 minutes, the yield dropped to 71%. Previously reported yields[16] were 88, 54 and 51%, with hydrogen fluoride, stannic chloride and phosphorus pentoxide, respectively.

5,6,7-Trimethoxy-1-indanone (IIc).—This compound was obtained from 0.8 g. of β-(3,4,5-trimethoxyphenyl)-propionic acid (Ic)[4] and 10 g. of PPA by heating at 60–70° for one hour (dark yellow color), and isolation with ether. The yield of crude solid, m.p. 111–113°, was 0.67 g. (91%). Recrystallization from dilute ethanol provided tiny colorless needles, m.p. 111.5–113.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.34. Found: C, 65.12; H, 6.26.

1,2,3-Trimethoxy-6,7-methylenedioxyanthraquinone (IV).—Reaction of 0.2 g. of 4,5-methylenedioxy-2-(3′,4′,5′-trimethoxybenzoyl)-benzoic acid (III)[9] with 4 g. of PPA at 80–85° for six hours (deep purple end-point), followed by isolation with ether–ethyl acetate, afforded 0.175 g. (93%) of yellow material, m.p. 194–196°, which crystallized from glacial acetic acid in bright yellow needles, m.p. 198–199°. The same compound was also prepared by heating a mixture of 0.2 g. of III, 3 ml. of concd. sulfuric and 1 ml. of 85% phosphoric acid at 75–80° for 50 minutes, and isolating the product similarly. The crude material (0.103 g., 54%) melted at 197–199°, and the pure substance at 198–199°.

Anal. Calcd. for $C_{18}H_{14}O_7$: C, 63.15; H, 4.12. Found: C, 62.89; H, 4.33.

2,3-Dimethoxybenzosuber-5-one (VIa).—δ-(3,4-Dimethoxyphenyl)-valeric acid (Va)[2a] (0.474 g.) was cyclized with 5 g. of PPA at 75° for one hour (brownish red color). The crude product (0.126 g., 84%, isolation with ether), m.p. 61–63°, crystallized from dilute ethanol as colorless needles, m.p. 63–64° (reported[7b] 63–64°). The product had previously[7b] been obtained by cyclization with phosphorus pentoxide (55% yield) and with phosphorus pentachloride–stannic chloride (79% yield).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.68; H, 7.38.

1,2,3-Trimethoxybenzosuber-5-one (VIb).—A pale yellow crude oil was obtained by treatment of 1 g. of δ-(2,3,4-trimethoxyphenyl)-valeric acid (Vb)[2a] with 10 g. of PPA at 70–75° for 50 minutes (deep orange color), followed by isolation with ether. Evaporative distillation at 173–186° (0.3 mm.) (reported[7a] 170° (0.3 mm.)) gave 0.84 g. (91%) of colorless oily ketone. This compound had been obtained in 60% yield by cyclization with phosphorus pentoxide.[7a] The colorless crystalline **oxime**, m.p. 122–124° (from dilute ethanol), was prepared in pyridine.

Anal. Calcd. for $C_{14}H_{19}O_4N$: C, 63.37; H, 7.21. Found: C, 63.52; H, 6.99.

Ethyl 5,6-Dimethoxy-3-methylindene-2-carboxylate (VIIIa).—Reaction of 2 g. of ethyl 3,4-dimethoxybenzylacetoacetate (VIIa)[10] with 20 g. of PPA at room temperature for 30 minutes (brownish-red color), followed by isolation with ether–ethyl acetate, yielded 1.85 g. (99.5%) of crystalline material, m.p. 128–133°. Two recrystallizations from dilute ethanol gave 1.58 g. (85%) of fine colorless crystals, m.p. 135.5–137° (reported[10] 136–136.5°). With sulfuric–phosphoric acids, the yield was 47%.[10]

Ethyl 5,6-Methylenedioxy-3-methylindene-2-carboxylate.—Starting with 1 g. of 3,4-methylenedioxybenzylacetoacetate,[10] the procedure used for the preparation of VIIIa (deep blue color after 30 minutes) provided, after one crystallization from dilute ethanol, 0.73 g. (80%) of colorless scales, m.p. 106–107°. Cyclization with sulfuric acid[10] gave a product, m.p. 107–108°, in 48% yield.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.72. Found: C, 68.20; H, 5.78.

5,6-Dimethoxy-3-methylindene (VIIIb).—A mixture of 1 g. of 3,4-dimethoxybenzylacetone (VIIb)[10] and 15 g. of PPA was kept at room temperature for 40 minutes (deep red color after ten minutes), then diluted with 150 ml. of ice-water. The colorless crystalline precipitate (obtained by the alternative general procedure) became gummy when dried. It was recrystallized from dilute ethanol to yield 0.46 g. (51%) of fine colorless crystals, m.p. 130–132° (reported[10] 132–133°, no mixed melting point depression). When the relative proportion of PPA was reduced (2 g. of ketone and 15 g. of PPA), the temperature rose to 40°, and the deep red color appeared within five minutes. The reaction was stopped after 25 minutes, the product isolated with ether as a crude oil (1.85 g.), and digested with 5 ml. of dilute ethanol. The crystalline residue (1.05 g., 58%) melted at 126–129°. In other experiments, the reaction mixture was heated at temperatures ranging from 60 to 90°, but a high-melting polymer was isolated instead of the expected product. A 52% yield of the compound had previously[10] been obtained by cyclodehydration with sulfuric–phosphoric acids.

5,6-Dimethoxy-3-phenylindene (VIIIc).—Treatment of 0.5 g. of 3,4-dimethoxybenzylacetophenone (VIIc)[10] with 10 g. of PPA at 60° for 50 minutes (deep red color), followed by dilution with 100 ml. of ice-water and chilling overnight, provided 0.465 g. (100%) of crude solid, m.p. 110–112°. Two recrystallizations from dilute ethanol gave 0.42 g. (93%) of small colorless scales, m.p. 113–114° (reported[10] 112–113°). The yield was 91% in a sulfuric–phosphoric acid cyclization.[10]

Acknowledgment.—The author wishes to express his appreciation to Dr. J. L. Hartwell for his generous encouragement and to Drs. A. W.

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BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AMHERST COLLEGE]

The Synthesis of Analogs of Penicillin.[1a] I

BY DAVID TODD[1b] AND SYLVIA TEICH

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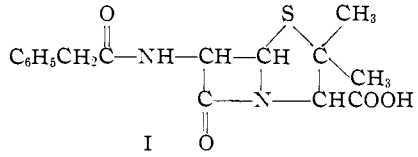
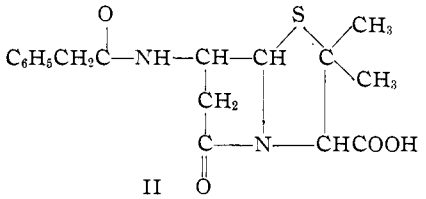
The condensation of L-cysteine and of DL-penicillamine with methyl γ-formylbutyrate gives the bicyclic thiazolidine lactams Va and Vb, whose structure is proved *via* nickel desulfurization. An attempt to prepare the vinylog IV of penicillin is described.

The chemical mechanism of the antibiotic action of penicillin (I) remains obscure in spite of the fact that much biological investigation[2] tends to show that penicillin may compete with glutathione in processes involving hydrogen transfer from –SH groups on molecules involved in the respiratory systems of many organisms. Because of the well-known instability of the β-lactam ring[3] in penicillin, it is not unreasonable to suppose that at some point in the metabolism of penicillin the β-lactam ring is opened. It is, therefore, of interest to modify this particular structural feature of penicillin in order to see if an easily-opened β-lactam ring is a *sine qua non* for its antibiotic action.

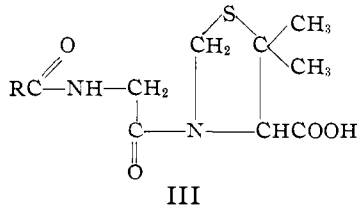
Two modifications of the β-lactam ring have already been reported, and in each case the resulting compound was found to be devoid of antibiotic action. du Vigneaud and Carpenter[4] have prepared the γ-lactam II, and Neher and co-workers[5] have prepared acylated thiazolidines of the type III in which the β-lactam ring has been formally hydrogenated open between the two asymmetric carbon atoms.



I

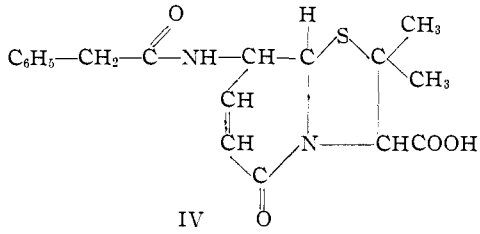


II

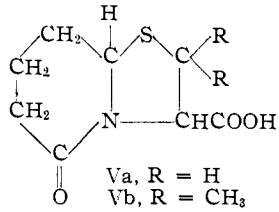


III

It seemed to us of interest to prepare compounds in which the β-lactam ring of penicillin is enlarged to a six-membered ring, and in particular the vinylog (IV) of penicillin. In this paper we report the synthesis of two δ-lactams, Va and Vb, and an attempt to prepare IV.

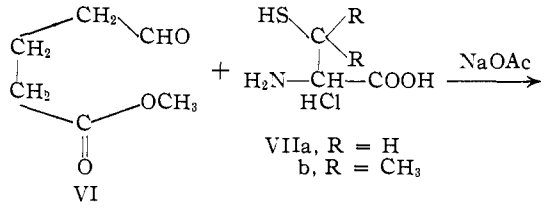


IV



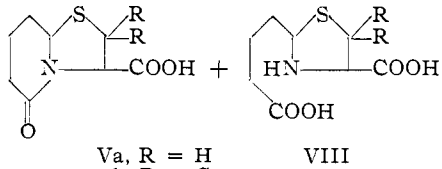
Va, R = H
Vb, R = CH_3

Methyl γ-formylbutyrate (VI) was condensed with L-cysteine hydrochloride (VIIIa) in an aqueous alcoholic solution containing sodium acetate or sodium hydroxide to give the bicyclic thiazolidine (Va) in 25–35% yield.



VI

VIIa, R = H
b, R = CH_3



Va, R = H
b, R = CH_3

VIII

The presumed intermediate amine-ester was never isolated, the cyclization to V occurring readily under mild conditions. However, under certain conditions, a second compound was isolated whose analysis corresponded to that of VIII. Since it could not be readily cyclized to Va it was not further characterized. Although attempts to convert Va

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(1) (a) This work was supported by the Office of Naval Research and by the Research Corporation. (b) Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

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