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Syntheses of Hormones from 5,6-Dichloro Steroids. II. Introduction of 17α-Hydroxyl

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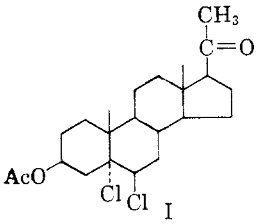
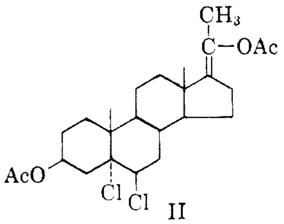
Enol acetylation of 5α,6β-dichloro-3β-acetoxy-pregnan-20-one followed by treatment with peracetic acid and hydrolysis has given 5α,6β-dichloro-3β,17α-dihydroxy-pregnan-20-one in 80% yield. The peracid–enol acetate reaction is shown to be bimolecular and its rate constant is greater than those observed with the mono- and dienol acetates of 3α-acetoxypregnane-11,20-dione.

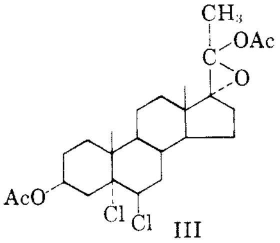
In the preceding paper[1] we described the addition of chlorine to 3β-acetoxy-5-pregnen-20-one and indicated that the product, 5α,6β-dichloro-3β-acetoxypregnan-20-one (I), obtained in 84% yield, was useful in the synthesis of Reichstein's Substance S. In the present paper we wish to record our experience in introducing the 17α-hydroxy group *via* the general method of Gallagher[2] involving preparation of the enol acetate II, epoxidation with peracid, and hydrolysis of the epoxide III to 5α,-6β-dichloro-3β,17α-dihydroxypregnan-20-one IV. Certain details of this work have already appeared in the form of patents.[3]



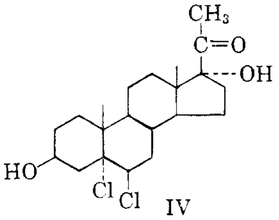
I



II



III



IV

When the enol acetylation of I was attempted by the original method[4] involving continuous distillation of acetic anhydride at atmospheric pressure in the presence of *p*-toluene sulfonic acid, some loss of halogen was observed. However, at steam bath temperature loss of halogen did not occur. Crude kinetic experiments indicated that the enol acetylation was essentially complete in a few hours. The enol acetate II was ordinarily not isolated in solid form, but could be chromatographed to give crystalline material; however, most cuts were broad melting, suggesting mixed *cis* and *trans* isomers. The initial fraction, m.p. 158–161.5°, may be one isomer in nearly pure form.[5]

The epoxidation of the enol acetate was effected with perbenzoic acid,[3] monoperphthalic acid,[3] and peracetic acid. Of these, peracetic acid was the most convenient because of its commercial availability.[6] A procedure for its direct use is described in the Experimental.

It was also possible to extract peracetic acid into benzene in a simple manner and to study the epoxidation in some detail. The crystalline enol acetate, even though an apparent mixture of isomers, was useful in this work. We were gratified to find that merely determining the amount of peracid consumed as a function of time afforded data which responded well to kinetic analysis. When the data are plotted in conformity with a bimolecular reaction between the enol acetate and peracetic acid, it is found that a straight line is obtained to over 80% conversion, as may be seen from Fig. 1. The second-order rate constant in benzene at 27° is found to be 4.1 l./mole-hour.

It became of interest to compare this rate with those of two other enol acetates: 3α,20-diacetoxy-17(20)-pregnen-11-one (V),[7] and 3α,11,20-triacetoxy-9(11),17(20)-pregnadiene (VI).[9] Each of these was allowed to react with peracetic acid in benzene at 27° and again second-order kinetics were fol-

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[1] F. A. Cutler, Jr., L. Mandell, D. Shew, J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1621 (1959).

[2] T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

[3] F. A. Cutler and J. M. Chemerda, U. S. Patents **2,786,856–7** (Mar. 26, 1957), **2,884,417** (Apr. 28, 1959).

[4] C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948).

[5] Enol acetylation of 5,6-dichloro-3β-acetoxypregnan-20-one in the presence of ketene has been reported to give an enol acetate melting at about 155°; A. Middelbeek, E. M. De Graaf, and P. Modderman, German Patent **1,021,844** (June 12, 1958).

[6] Treatment of steroidal enol acetates with commercial 40% peracetic acid in the presence of sodium acetate has been described by Anderson *et al.*[7] Its use without the addition of base to neutralize the sulfuric acid present has also been described.[8]

[7] H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan, and J. A. Hogg, *J. Am. Chem. Soc.*, **76**, 743 (1954).

[8] E. P. Oliveto and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 5167 (1954).

[9] T. H. Kritchevsky, D. L. Garmaise, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 483 (1952).

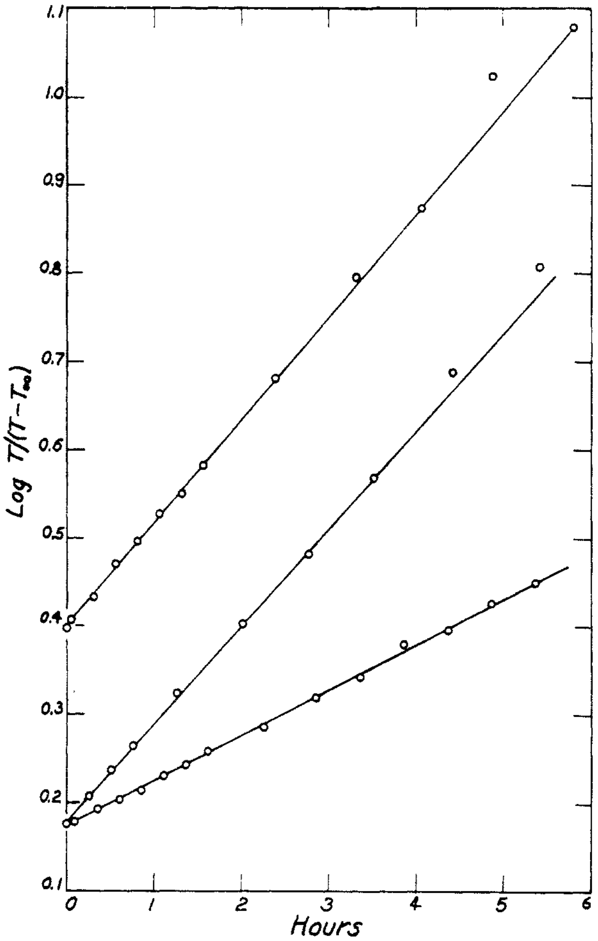
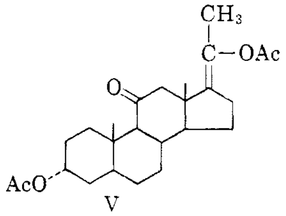
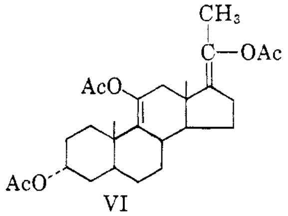


Fig. 1. Second-order curves for reaction of peracetic acid with enol acetates in benzene at 27°. Upper curve, with 3α,11,20-triacetoxy-9(11),17(20)pregnadiene (VI); middle curve, with 5α,6β-dichloro-3β,20-diacetoxy-17(20)pregnene (II); lower curve, with 3α,20-diacetoxy-17(20)pregnen-11-one (V)



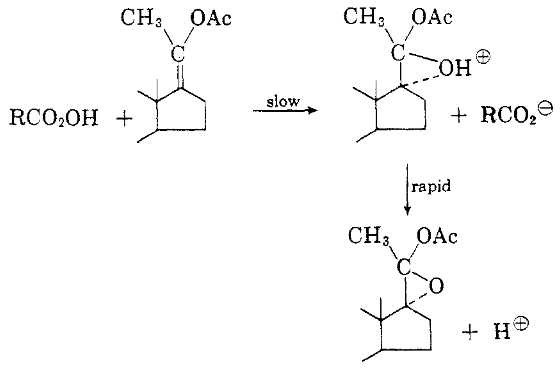
V



VI

lowed, based on the consumption of one mole of peracid.[10] The data are likewise plotted in Fig. 1. The specific rate constants are 1.95 and 2.5 l./mole-hour for V and VI, respectively. Apparently the enol acetylation of the 11-carbonyl slightly increases the rate of reaction at 17(20). In each case the rate of reaction is considerably lower than with II.

Since simple second-order kinetics are observed in the epoxidation of enol acetates, it follows that the reaction is not catalyzed by the by-product acid produced.[11] The reaction is kinetically similar to that between simple olefins and peracids.[12] The reaction probably involves direct attack by the peracid on the 17(20)-double bond rather than prior dissociation of peracid into OH^+ and RCO_2^-.[13]



The direct product III of the epoxidation was not fully characterized. Its melting range indicated that it was a mixture of isomers. Attempts to hydrolyze III at room temperature with potassium hydroxide were complicated by solubility problems. These could be overcome by hydrolyzing instead with potassium bicarbonate in aqueous methanol at the reflux temperature. The product, 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (IV) proved to be an easily isolated, stable compound. By operating without isolation of intermediates, it was possible to convert I to IV in 80% yield. No loss of halogen was observed at any point.

EXPERIMENTAL[14]

5α,6β-Dichloro-3β,20-diacetoxy-17(20)-pregnene (II). The enol acetylation was conducted in a 250-ml. three-neck round-bottom flask fitted with an agitator and thermometer and connected through a spray trap to a condenser and receiver. Ten g. of 5α,6β-dichloro-3β-acetoxypregnan-20-one (I), 1.34 g. of *p*-toluenesulfonic acid monohydrate, and 52.5 ml. of acetic anhydride were charged to the flask and the solution was heated on the steam bath to 97–98°. A vacuum of 10–11 in. was applied to the receiver to eliminate air from the system and the reaction was maintained at this tempera-

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[10] Had the dienol acetate VI reacted appreciably at the 9(11) double bond, considerable deviation from a straight line would have resulted. Moreover, Anderson *et al.*,[7] have shown that treatment of VI with peracetic acid gives after hydrolysis a 78.5% yield of 3α,17α-dihydroxypregnane-11,20-dione, demonstrating that attack was limited largely to the 17(20) double bond. Hydrolysis of our product at the termination of the run confirmed this.

[11] The Baeyer-Villiger cleavage of ketones with peracids constitutes an example in which the reaction is catalyzed by the acid produced; M. F. Hawthorne and W. D. Emmons, *J. Am. Chem. Soc.*, **80**, 6398 (1958).

[12] J. Böeseken and J. Stuurman, *Rec. trav. chim.*, **56**, 1034 (1937).

[13] C. G. Overberger and R. W. Cummins, *J. Am. Chem. Soc.*, **75**, 4250 (1953), regard the bimolecular oxidation of organic sulfides to sulfoxides with perbenzoic acid as a nucleophilic attack on a cyclic hydrogen-bonded form of the peracid with elimination of molecular benzoic acid. A similar mechanism could prevail in the present case rather than the indicated stepwise elimination of the acid as its ions.

[14] Melting points were measured with total immersion thermometers and are not corrected.

ture and vacuum for 2 hr.[15] The vacuum was then increased to 25–26 in. until slow, continuous distillation occurred, while the batch temperature was maintained at 90–94°. Distillation was continued under these conditions for 2.5 hr., leaving a sirup. A 29-in. vacuum was applied for 10 min. followed by pumping at about 50° with an oil pump in order to remove most of the residual acetic anhydride. The dark gummy residue was dissolved in 150 ml. of benzene and the benzene solution was cooled, washed with two 50-ml. portions of cold 10% sodium carbonate solution and 50 ml. of water. Halogen ion was not detectable in the washes. The benzene solution was concentrated to dryness under reduced pressure, finally with the use of an oil pump. The crude amorphous enol acetate was ordinarily used in the next step without further purification.

Crystalline enol acetate was obtained as follows: A solution of the foregoing amorphous enol acetate in 11 ml. of benzene and 110 ml. of light petroleum ether was chromatographed over 220 g. of acid-washed alumina. Crystalline material first appeared in the 5 to 1 petroleum ether: benzene eluates and after crystallization from methanol melted at 158–161.5° and showed $[\alpha]_D^{25}$ $-36.5°$ (c = 1, chloroform); $-64°$ (c = 1, benzene).

Anal. Calcd. for $C_{25}H_{36}Cl_2O_4$: C, 63.69; H, 7.70; Cl, 15.04. Found: C, 64.14, 64.36; H, 7.50, 8.00; Cl, 14.51.

Later chromatographic fractions were progressively lower melting (to about 140–146°) but their infrared spectra were only slightly different from the spectrum of the initial material.

Preparation of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (IV). (a) *Using monoperphthalic acid.* To the amorphous enol acetate (23.2 mm.) prepared as described hereinbefore was added 45.5 ml. of 0.777*M* monoperphthalic acid (150% of that theoretically required) in ethyl acetate.[16] The solution was allowed to stand overnight at room temperature.[17] The solution was washed free of peracid with four 50-ml. portions of cold 1*N* sodium hydroxide and to neutrality with water. No ionic halogen was detectable in the washes. Backwashing with ethyl acetate was necessary to avoid losses. Evaporation of the ethyl acetate and trituration with methanol left a crystalline residue of epoxide III, not purified further. A specimen was found to melt at 130–160° and probably is a mixture of isomers.

The crude epoxide was suspended in 210 ml. of methanol and a solution of 6.46 g. of potassium bicarbonate in 21 ml. of water was added. The mixture was heated to reflux, complete dissolution occurring in 5 min. Reflux was continued for 3 hr. more, the entire operation being carried out under a nitrogen atmosphere. Water (84 ml.) was added slowly, crystallization occurring. The methanol was removed under reduced pressure, and the suspension was chilled and filtered. No ionic halogen was observed in the filtrate. The crude product after washing and drying weighed 9.0 g.; m.p. 188–194° (dec.). The material was dissolved in 680 ml. of boiling benzene, filtered from traces of colored material, and concentrated at atmospheric pressure until approximately 80 ml. of solvent remained, crystallization occurring in the process. After chilling, the product was collected, washed with benzene, and dried; weight, 7.28 g. (77.5% from I); m.p. 199–204° (dec.). For analysis the compound was recrystallized from benzene and melted at 201–206° (dec.) (bath heated at 6° per min.; insertion at 190°); $[\alpha]_D^{21}$ $-72°$ (c = 1, chloroform).

Anal. Calcd. for $C_{21}H_{32}Cl_2O_3$: C, 62.52; H, 8.00; Cl, 17.58. Found: C, 63.07; H, 8.07; Cl, 17.36, 17.69.

(b) *Using peracetic acid.* The enol acetylation was conducted on five-fold the scale described earlier. The benzene solution of the enol acetate after the washes with sodium carbonate solution and water was concentrated to a volume of 345 ml. The solution was cooled to 10° and 14.6 g. of anhydrous sodium sulfate (powder) and 4.1 g. of sodium bicarbonate were added. The suspension was stirred for about 3 min. at 10° and 29 ml. of commercial 40% peracetic acid[18] was added slowly, maintaining the temperature at 10°. The mixture was then allowed to warm to 20° and was stirred for about 18 hr. at 20–23°. The mixture was then cooled to 10° and a cold solution of 12.4 g. of sodium bisulfite and 20.7 g. of sodium hydroxide in 104 ml. of water was slowly added, keeping the temperature below 23°. After the addition, the mixture was stirred further for 15 min. The mixture was transferred to a separatory funnel with the aid of additional benzene and water and the benzene phase was separated and washed with two 100-ml. portions of water. Evaporation of the benzene left a sirupy residue which was hydrolyzed in a mixture of 625 ml. of methanol, 35 g. of potassium bicarbonate, and 115 ml. of water for 2 hr. The crude product was slurried in 460 ml. of boiling benzene to give after chilling 37.8 g. (80.5%) of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (IV), m.p. 202–205° (dec.).

Kinetic experiments. General. It was convenient in this work to express the second-order rate expression in the following form:

$$\log T/(T - T_\infty) = 0.4343(1 - 1/r)Mkt + \log r$$

where *T* represents ml. of thiosulfate solution required to titrate iodometrically an aliquot of the reaction mixture, T_∞ represents *T* at infinite time, *r* represents the initial ratio of peracid to enol acetate, and *M* is the initial molarity of the peracid. If second-order kinetics are obeyed, a plot of $\log T/(T - T_\infty)$ against time (*t*) gives a straight line from whose slope the rate constant *k* may be calculated:

$$k = \frac{(\text{slope})}{0.4343(1 - 1/r)M}$$

In practice T_∞ could not be determined precisely from experiment, and was calculated instead from the titration at zero time, T_0, by the following equation:

$$T_\infty = T_0(r - 1)/r$$

Temperature was maintained at 27 ± 0.5° during the runs.

Preparation of peracetic acid solution.[19] A suspension of 10 g. of anhydrous sodium sulfate (powder)[20] and 10 g. of sodium bicarbonate in 100 ml. of benzene was cooled with stirring to 5°. Commercial 40% peracetic acid (8.4 ml.) was added and the mixture was stirred for 5 min. at 5°.[21] The benzene layer containing the peracetic acid was immediately decanted through glass wool. The molarity of the peracetic acid was determined by adding 2 ml. to a solution of sodium iodide (about 3 g.) and acetic acid (1–2 ml.) in water (about 25 ml.) and titrating the liberated iodine

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[15] In studies of the enol acetylation in which the rotation of aliquots was observed with time, it was found that the enol acetylation was essentially complete under these conditions after two hours. Analysis of the data from a kinetic viewpoint was difficult because of color at high conversions. The reaction appeared to be pseudo first order in steroid, as was found by Anderson, *et al.*[7] The rate was also found to be roughly proportional to the concentration of catalyst. These findings are in accord with the mechanism of enol acetylation proposed by Barton *et al.* [D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954)].

[16] Prepared by a modification of the method of M. A. Stahmann and M. Bergmann, *J. Org. Chem.*, 11, 586 (1946).

[17] The second-order rate constant for this reaction in ethyl acetate at 25° was estimated from a kinetic study to be 1.35 l./mol.-hr.

[18] From Buffalo Electro-Chemical Co., Buffalo, N. Y.

[19] We are indebted to Dr. H. E. Mertel of these laboratories for this procedure.

[20] Granular sodium sulfate gives poorer results..

[21] Longer times lead to lower final molarity.

with $0.1N$ sodium thiosulfate. The molarity was generally about 0.2. Aliquots in the kinetic runs were titrated in a similar manner.

Kinetic run with 5α,6β-dichloro-3β,20-diacetoxy-17(20)-pregnene (II). A specimen of II obtained by chromatography and melting at 140–150° was dissolved in the required amount of peracetic acid in benzene solution. The initial molarity of the peracetic acid was 0.187 and the peracid:enol acetate ratio, *r*, was 1.5. The titration data are plotted in Fig. 1. Excellent linearity is observed to over 80% conversion at 3.5 hr. The upward deviation beyond that time reflects lack of blank corrections. From the slope of the line (0.111 unit per hour) the rate constant, *k*, is calculated to be 4.1 l./mol.-hr.

Kinetic run with 3α,20-diacetoxy-17(20)-pregnen-11-one (V). A specimen of V melting at 118–125° (lit.,[7] 130.5–131.5°) was used. The initial molarity of the peracetic acid was 0.182 and *r* was 1.5. Small blank corrections were applied after 3 hr. A straight line (Fig. 1) is obtained for more than 5 hr. (72% conversion). From the slope (0.0515) the rate constant, *k*, is calculated to be 1.95 l./mol.-hr.

Kinetic run with 3α,11,20-triacetoxy-9(11),17(20)-pregnadiene (VI). A specimen of VI melting at 196–200° (lit.,[9] 200–201°) was used. The initial molarity of the peracetic acid was 0.181 and *r* was 2.5 to allow for possible reaction at both double bonds. Small blank corrections were applied throughout the run. Linearity (Fig. 1) is good through 4 hr. (77% conversion) and fair to 5.8 hr. (86% conversion). The slope (0.118) gives a rate constant, *k*, of 2.5 l./mol.-hr.

After 22 hr. total time, the steroid remaining was recovered and hydrolyzed to give 3α,17α-dihydroxypregnane-11,20-dione, m.p. 200.5–205°, in 85% yield.

Acknowledgments. We wish to thank the Physical and Inorganic Research Department for microanalyses and infrared spectra. We also thank Dr. George Krsek for the benefit of his experience in related work and Dr. Leon Mandell for many stimulating discussions.

RAHWAY, N. J.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Syntheses of Hormones from 5,6-Dichloro Steroids. III. Progesterone, 17α-Hydroxyprogesterone, and Reichstein's Substance S Acetate

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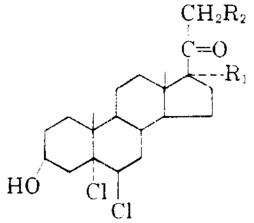
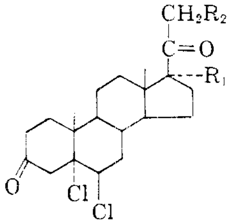
5α,6β-Dichloro-3β,17α-dihydroxypregnan-20-one has been converted to Substance S acetate in 72% yield by bromination at position 21, metathesis to the 21-acetoxy derivative, oxidation to the 3-ketone, and dechlorination with chromous chloride. Progesterone and 17α-hydroxyprogesterone have likewise been prepared by dechlorination of the appropriate ketones.

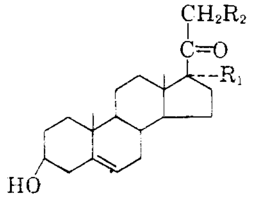
In the preceding papers of this series[1,2] the addition of chlorine to pregnenolone acetate and conversion of the dichloride to 5α, 6β-dichloro-3β, 17α-dihydroxypregnan-20-one (I) were described. In the present paper we wish to discuss the conversion of I to Reichstein's Substance S acetate, and to indicate some of the other transformations possible with various intermediate compounds.



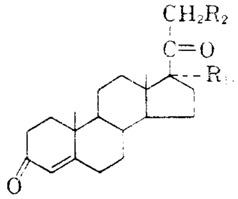
I. R_1 = OH, R_2 = H
II. R_1 = OH, R_2 = Br
III. R_1 = OH, R_2 = OAc
VI. $R_1 = R_2$ = H



IV. R_1 = OH, R_2 = OAc
IX. R_1 = OH, R_2 = H
VII. $R_1 = R_2$ = H



XI. R_1 = OH, R_2 = H
XII. R_1 = OH, R_2 = OAc



V. R_1 = OH, R_2 = OAc
VIII. $R_1 = R_2$ = H
X. R_1 = OH, R_2 = H

The bromination of I was carried out in hot chloroform with 1.12 moles of bromine and afforded in 92% yield crude 21-bromide II which was easily purified by recrystallization from methanol. Small amounts of the 21,21-dibromide were also isolated.

The pure 21-bromide II gave the corresponding 21-acetoxy compound III in good yield on treatment with potassium acetate in refluxing acetone. However, for practical purposes, the acetoxylation was better carried out in the presence of sodium iodide[3] and a small amount of acetic acid.[4] The

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[1] F. A. Cutler, Jr., L. Mandell, D. Shew, J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, (Paper I).

[2] F. A. Cutler, Jr., J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, (Paper II).

[3] G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).