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

# Synthesis of Cortisone-21 Phosphate

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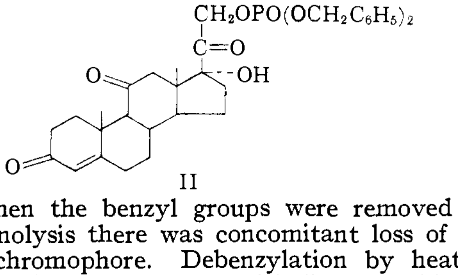
Cortisone-21 dihydrogen phosphate has been synthesized as outlined in the Chart. A more reproducible procedure for preparing silver dibenzyl phosphate is reported.

In the course of a program on the esters of cortisone, cortisone-21 dihydrogen phosphate was desired, in the hope that a stable water-soluble form retaining the full activity of cortisone could be achieved. A number of phosphate esters of other steroids has been reported. Desoxycorticosterone-21 dihydrogen phosphate has been prepared by a route involving the diazoketone. Testosterone dihydrogen phosphate has been prepared[2] by treatment of testosterone enol ethyl ether with phosphorus oxychloride followed by hydrolysis. A similar scheme was used to phosphorylate 5-androstene-3,17-diol 3-acetate[2] and is recorded in the patent literature as having been applied successfully to corticosterone.[3]

After many fruitless attempts at direct phosphorylation of cortisone, a number of indirect methods were studied. Success finally was achieved by use of the general scheme of Zervas[4] which employs the reaction of silver dibenzyl phosphate with a halide with subsequent displacement of the benzyl groups in the triester by catalytic hydrogenation.

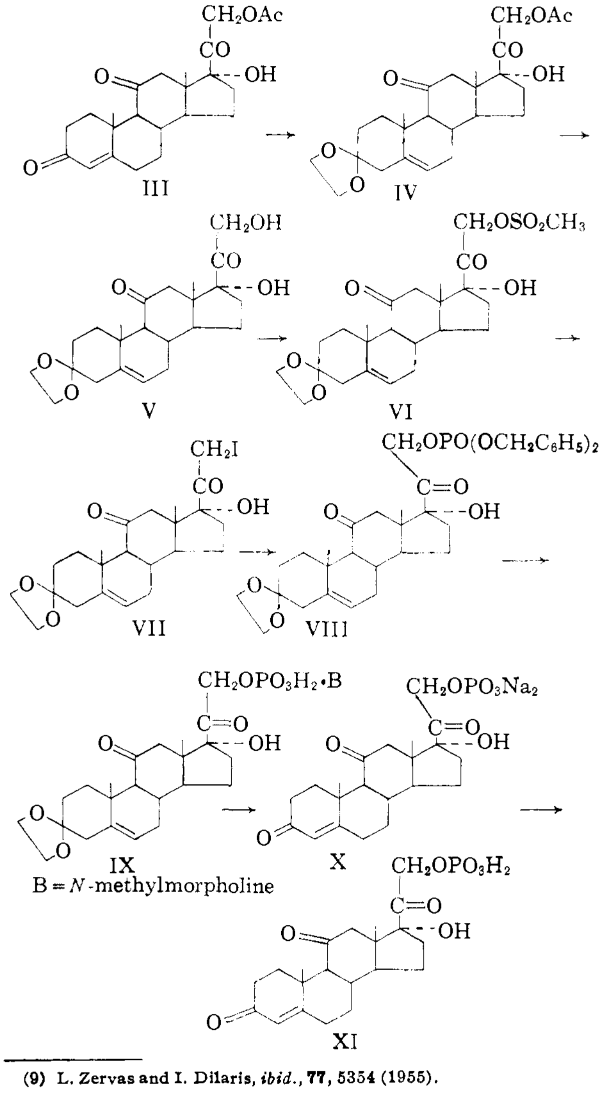
$$\begin{array}{l} RX + AgOPO(OCH_2C_6H_5)_2 \longrightarrow ROPO(OCH_2C_6H_5)_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad ROPO(OH) \end{array}$$

Initially, the halide used in our work was 21-iodo-4-pregnen-17α-ol-3,11,20-trione[5] (I), readily prepared from cortisone *via* the 21-methanesulfonate.[6] Reaction of I with silver dibenzyl phosphate in refluxing benzene readily gave the triester II. However, when the benzyl groups were removed by hydrogenolysis there was concomitant loss of the A-ring chromophore. Debenzylation by heating in pyridine[7] or by heating with lithium chloride in methyl or ethyl Cellosolve[8] failed to give tractable products. With lithium chloride in dimethylformamide, cleavage to the 21-chloro steroid occurred. This result is surprising in that benzyl chloride is normally eliminated in preference to the alkyl chloride from mixed esters. However, when II was treated with sodium iodide[9] in acetone monodebenzylation occurred.


II

Protection of the A-ring prior to hydrogenolysis appeared to be essential. The dioxolane grouping was found to give the necessary protection and for optimum over-all yield was best introduced into cortisone acetate (III). The entire ultimate sequence of reactions is summarized in the Chart.

CHART I



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(1) T. Reichstein and W. Schindler, *Helv. Chim. Acta*, **23**, 669 (1940).

(2) E. Müller, A. Langerbeck and W. Riedel, *Z. physiol. Chem.*, **281**, 29 (1944).

(3) T. Reichstein and E. Schlittler, U. S. Patent 2,183,589 (Dec. 19, 1939).

(4) L. Zervas, *Naturwissenschaften*, **27**, 317 (1939).

(5) P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955).

(6) *Cf.* P. Tannhauser, R. J. Pratt and E. V. Jensen, THIS JOURNAL, **78**, 2658 (1956); J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955).

(7) V. M. Clark and A. R. Todd, *J. Chem. Soc.*, 2023 (1950).

(8) V. M. Clark and A. R. Todd, *ibid.*, 2030 (1950); J. Lecocq and A. R. Todd, *ibid.*, 2381 (1954); M. Miyano, THIS JOURNAL, **77**, 3524 (1955).

(9) L. Zervas and I. Dilaris, *ibid.*, **77**, 5354 (1955).

Cortisone acetate (III) was converted to the dioxolane IV in 91% yield by application of the method of Dauben[10] involving exchange with 2-ethyl-2-methyl-1,3-dioxolane. The 21-acetoxy group was saponified with sodium methoxide in methanol affording V in 73% yield, including recrystallization. Treatment of the alcohol V with methanesulfonyl chloride, and then metathesis of the resulting methanesulfonate VI with sodium iodide in acetone, gave the 21-iodide VII in 85% yield from V. Reaction of the iodide with silver dibenzyl phosphate gave the triester VIII in 85% yield. Hydrogenolysis of VIII over palladium in the presence of N-methylmorpholine afforded the 21-phosphate IX as the monoamine salt in 77.5% yield. The dioxolane moiety was removed by slurrying a solution of IX in methanol with an ion exchange resin, IR-120, on the acid cycle. The product was isolated as the sodium salt X in nearly quantitative yield. The free acid XI could be isolated as a white crystalline powder by acidification of concentrated aqueous solutions of X.

Cortisone-21 disodium phosphate (X) is readily soluble in water. When administered to mice either orally or subcutaneously, the salt was as active on a molar basis as cortisone in the liver glycogen assay.

Some discussion of the preparation of silver dibenzyl phosphate is appropriate.[11] We chose the method of Lynen,[12] which involves reaction of phosphorus pentoxide with benzyl alcohol

$$3C_6H_5CH_2OH + P_2O_5 \longrightarrow (C_6H_5CH_2O)_2POOH + C_6H_5CH_2OPO(OH)_2$$

The mono- and dibenzylphosphoric acids after initially being heated in aqueous solution are separated by virtue of the difference in solubility of their barium salts. Treatment of the barium dibenzyl phosphate with silver nitrate gives the desired silver salt.

Our initial attempts gave poor yields of the barium salt and silver dibenzyl phosphate of poor quality. Sheehan and Frank[13] appear to have experienced similar difficulties.

A brief investigation of the reaction between benzyl alcohol and phosphorus pentoxide then was made along the lines reported by Cherbuliez and Weniger.[14] These authors also report a useful titration scheme which allows the simultaneous determination of mono- and dialkylphosphoric acids and phosphoric acid. By use of this tool it soon became apparent that the reaction did proceed essentially as indicated by Lynen but that dibenzylphosphoric acid was being hydrolyzed[15] rapidly under the conditions of work-up. Accordingly, the reaction time between benzyl alcohol and phosphorus pentoxide was prolonged to avoid possible incomplete alcoholysis of polyphosphate esters, and the reaction mixture was brought to *p*H 4 in the cold with barium carbonate. Further processing afforded the barium salt in improved yield and quality, and the direct conversion to pure silver dibenzyl phosphate was effected with no difficulty, following Lynen's original procedure.

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## Experimental

**4-Pregnene-17α,21-diol-3,11,20-trione 21-Dibenzylphosphate (II).**—To 625 ml. of benzene were added 10 g. of 21-iodo-4-pregnen-17α-ol-11,20-dione[5] and 9 g. of silver dibenzyl phosphate. The mixture was heated to the reflux temperature and 150 ml. of benzene was distilled to remove moisture. The suspension was heated at the reflux temperature overnight. A small amount of charcoal was added and the mixture was filtered from the charcoal and silver iodide. The filtrate was concentrated to a volume of 150 ml. and 600 ml. of petroleum ether was added slowly with cooling. The resulting crystals were collected and recrystallized once from acetone–petroleum ether. The material weighed 10.5 g. and melted at 161–162°, $\lambda_{max}$ 238 mμ (ε 16,700) (methanol).

*Anal.* Calcd. for $C_{35}H_{41}O_8P$: C, 67.73; H, 6.66; P, 4.99. Found: C, 67.13, 68.44, 68.52, 68.79; H, 6.57, 6.78, 6.75, 6.81; P, 4.76, 4.61, 4.61.

**Attempted Debenzylation of II. (a) By Hydrogenolysis.**—Hydrogenation of II over palladium in methanol or over 5% palladium-on-charcoal in ethanol containing N-methylmorpholine gave nearly complete loss of the A-ring chromophore, as indicated by ultraviolet spectra.

**(b) With Bases.**—When treated with potassium hydroxide or sodium methoxide in methanol at room temperature for a few minutes, II was cleaved to cortisone. When II was heated with pyridine or with N-methylmorpholine, well-defined acidic products could not be isolated.

**(c) With Lithium Chloride.**—A mixture of 62 mg. of II, 32 mg. of lithium chloride and 2 ml. of dimethylformamide was heated at the reflux temperature in a nitrogen atmosphere for 80 minutes. The mixture was cooled and diluted with 5 ml. of chloroform and the chloroform phase was extracted successively with 5-ml. portions of aqueous sodium bicarbonate, sodium carbonate and sodium hydroxide; the extracts possessed no significant ultraviolet absorption. The chloroform phase after washing with water and brine was evaporated to dryness yielding 38 mg. of crystals showing a strongly positive Beilstein halogen test. After recrystallization the compound was shown to be 21-chloro-17α-hydroxy-4-pregnene-3,11,20-trione by comparison with authentic material[16] by mixed m.p. and infrared spectra. When II was heated with lithium chloride in methyl or ethyl Cellosolve, no useful products could be isolated.

**(d) With Sodium Iodide.**—A mixture of 2.48 g. of II and 1.98 g. of sodium iodide in 40 ml. of acetone was refluxed for one hour. After removal of the solvent under reduced pressure, water was added and the solid material removed by filtration. The clear filtrate was acidified with concentrated hydrochloric acid to give a gum which solidified on rubbing. The solid was collected by filtration, washed with water (in which it is somewhat soluble) and ether. The product (1.66 g.) was purified *via* its sodium salt to give 1.625 g. of **17α,21-dihydroxy-4-pregnene-3,11,20-trione 21-monobenzylphosphate**, m.p. 175.5–180° dec. Recrystalli-

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(10) H. J. Dauben, Jr., B. Löken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954). A similar yield is reported by F. Sondheimer, O. Mancera and G. Rosenkranz, *ibid.*, **76**, 5020 (1954).

(11) For a recent review of methods of preparation of dibenzyl phosphate and its salts see ref. 9.

(12) F. Lynen, *Ber.*, **73**, 367 (1940).

(13) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **72**, 1312 (1950).

(14) E. Cherbuliez and H. Weniger, *Helv. Chim. Acta*, **28**, 1584 (1945).

(15) A detailed kinetic study of the hydrolysis of mono- and dibenzyl phosphates as a function of *p*H was published subsequently by J. Kumamoto and F. H. Westheimer, THIS JOURNAL, **77**, 2515 (1955). Their work could well serve to further refine the isolation of dibenzyl phosphate.

(16) W. J. Leanza, J. P. Conbere, E. F. Rogers and K. Pfister, 3rd, THIS JOURNAL, **76**, 1691 (1954).

zation once from methanol–chloroform and twice from methanol–ether gave an analytical specimen, m.p. 184–186° dec.

*Anal.* Calcd. for $C_{28}H_{35}O_8P$: C, 62.77; H, 6.59; equiv. wt., 530.6. Found: C, 62.39; H, 6.30; equiv. wt., 546.

**3-Ethylenedioxy-5-pregnene-17α,21-diol-11,20-dione (V).**—To a suspension of 22.5 g. of 3-ethylenedioxy-5-pregnene-17α,21-diol-11,20-dione 21-acetate[17] in 4400 ml. of methanol (purified by distillation from sodium hydroxide) under an atmosphere of nitrogen was added a solution of 3.41 g. of sodium methoxide in a small amount of methanol. The suspension was stirred at room temperature for two hours, during which time the solid nearly all dissolved. The sodium methoxide was neutralized by addition of a solution of 4.1 ml. of glacial acetic acid in 75 ml. of water. The mixture was filtered from 0.8 g. of starting material and the filtrate was sucked slowly into 1–2 l. of water maintained at near room temperature under reduced pressure. In this manner the crude product precipitated at once and the methanol was largely removed by distillation. After a cooling period, the product was collected, washed with water, and dried in a vacuum oven at 80°. The crude product weighed 19.4 g. (95%) and melted at 208–211° (sintering at 200°). It was recrystallized by dissolution in ethyl acetate (20 ml./g.), filtration while hot, concentration to one-third volume under reduced pressure, and chilling. Recovery was 77% and the material melted at 209–216°.

*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.03; H, 8.26.

**3-Ethylenedioxy-5-pregnene-17α,21-diol-11,20-dione 21-Methanesulfonate (VI).**—A solution of 28 g. of the alcohol V in 140 ml. of dry pyridine was cooled to 0–5°. Methanesulfonyl chloride (8.6 ml.) was added slowly over about 10 minutes, while the batch temperature was kept at 0–5°. The mixture was then held at 0–5° for one hour. Then 1680 ml. of water was added slowly with chilling causing crystallization. The suspension was kept cold for an hour, then filtered. The product was washed with water, cold methanol, and then ether, and air-dried. It weighed 33.15 g. and melted upon rapid heating at 199–201.5° dec. The material appears to be hydrated; it is suitable directly for use in the next step.

A sample was recrystallized from a mixture of acetonitrile and ether, whereupon it melted at 204–205°.

*Anal.* Calcd. for $C_{24}H_{34}O_8S$: C, 59.73; H, 7.10; S, 6.64. Found: C, 60.52, 60.65; H, 7.06, 7.17; S, 6.55.

**3-Ethylenedioxy-21-iodo-5-pregnen-17α-ol-11,20-dione (VII).**—To a solution of 33.15 g. of mesylate VI in 1 l. of acetone was added 16.5 g. of sodium iodide. The mixture was refluxed with agitation for 30 minutes while sodium methanesulfonate rapidly precipitated. Water (1 l.) was then added causing first dissolution of the sodium methanesulfonate and then crystallization of the iodo compound. The acetone now was removed from the batch by concentration under reduced pressure to a volume of about 1 l. The suspension of crystals was chilled, then filtered. The product was washed with water and rapidly dried at room temperature by drawing air through it. When dry the material weighed 32.17 g. (86.4%) and decomposed at about 130°. After a few days' storage discoloration and decomposition occurred.

*Anal.* Calcd. for $C_{23}H_{31}IO_5$: C, 53.70; H, 6.08. Found: C, 53.81; H, 5.80.

**3-Ethylenedioxy-5-pregnene-17α,21-diol-11,20-dione 21-Dibenzylphosphate (VIII).**—The iodo compound VII (32.17 g.) and silver dibenzyl phosphate (28.8 g.) were added to 4750 ml. of benzene in the dark. The suspension was heated to the boiling point with agitation and 1600 ml. was allowed to distil to dry the mixture. The mixture was stirred and heated at the reflux temperature in the dark for 21 hours. The mixture was filtered hot from the silver iodide, which was washed with a little benzene. The benzene filtrate was concentrated under reduced pressure to a volume of about 300 ml. Petroleum ether (Skellysolve B) was added slowly to the benzene solution, maintaining the solution at 50–65°. Under these conditions crystallization occurred nicely, while at lower temperatures a gelatinous precipitate formed. When no further turbidity developed, the suspension was cooled slowly to room temperature and filtered. The crystals were washed with Skellysolve B and ether and dried. The material weighed 33.31 g. (84.5%) and melted at 145°. Such material was suitable for the hydrogenolysis. After further recrystallization in the same manner, a sample melting at 150–151.5° was obtained.

*Anal.* Calcd. for $C_{37}H_{45}O_9P$: C, 66.85; H, 6.82; P, 4.66. Found: C, 66.66, 67.00; H, 6.48, 6.64; P, 4.56.

**3-Ethylenedioxy-5-pregnene-17α,21-diol-11,20-dione 21-Phosphate, Mono-N-methylmorpholine Salt (IX).**—A suspension of 5 g. of palladium oxide in 2130 ml. of absolute ethanol containing 42.6 ml. of N-methylmorpholine was reduced at 40 p.s.i. hydrogen until no further hydrogen was taken up. The solid phosphate ester VIII (21.3 g.) was added and the reduction was continued until two moles of hydrogen was absorbed. The catalyst then was removed by filtration, after first warming the batch to about 60° to redissolve the product. The solution was concentrated under reduced pressure to a volume of about 500 ml. The resulting suspension of crystals was chilled and filtered and the salt was washed with cold ethanol. When dry, the salt weighed 14.57 g. (77.5%) and melted at 203–205°.

*Anal.* Calcd. for $C_{28}H_{44}NO_{10}P$: N, 2.39. Found: N, 2.09.

**Cortisone-21 Disodium Phosphate (X).**—To a solution of 14.57 g. of the salt IX in 725 ml. of methanol was added 29 g. of IR-120 resin (acid cycle). The suspension was stirred overnight and then the resin was filtered off and washed with a little methanol. To the filtrate was added a solution of 4.2 g. of sodium bicarbonate in 33 ml. of warm water. The mixture was concentrated under reduced pressure and at a temperature of 20–25° to a volume of about 50 ml. Water (150 ml.) was added and the solution was extracted with 50 ml. of ethyl acetate and two 30-ml. portions of ether. The aqueous layer was freeze-dried. The solid residue was taken up in 500 ml. of methanol (a small portion of the material fails to dissolve), 2 g. of charcoal (Darco G-60) was added and the mixture was filtered. The filtrate was concentrated under reduced pressure and below 25° to a volume of about 100 ml. Ether (200 ml.) was added and the resulting suspension of the disodium salt was filtered. The salt was washed with ether and after drying weighed 12.37 g. (94.5% after allowing for a moisture content of 8%); $\lambda_{max}$ 238 mμ (ε 13,100) (methanol, dry basis), $[\alpha]^{24}D$ +117° (1% in methanol, dry basis).

*Anal.* Calcd. for $C_{21}H_{27}Na_2O_8P$: C, 52.07; H, 5.62; Na, 9.50; P, 6.40. Found (dry basis): C, 52.12, 52.46; H, 6.12, 6.30; Na, 9.23, 9.65, 10.15; P, 6.19.

**Cortisone-21 Dihydrogen Phosphate (XI).**—To a solution of 1 g. of the disodium salt X in 4 ml. of water was added dropwise and with stirring and chilling concentrated hydrochloric acid to excess. A few drops of chloroform were added and the mixture was stirred in the ice-bath for 30 minutes forming a suspension of crystals. The crystals were collected by filtration, washed with minimal amounts of water and chloroform and dried. The weight of cortisone phosphate obtained was 0.60 g., m.p. 190° dec.

The acid was purified for analysis by dissolution in methanol and precipitation with ether. It melted at 190–193.5° dec., $\lambda_{max}$ 238 mμ (ε 14,700) (methanol).

*Anal.* Calcd. for $C_{21}H_{29}O_8P$: C, 57.27; H, 6.64; P, 7.03; equiv. wt., 220.2. Found: C, 57.44; H, 6.66; P, 6.74; equiv. wt., 222.

**Hydrolysis of Dibenzyl Phosphate.**—A solution of 0.5 g. of dibenzyl phosphate, m.p. 77–80° (reported[18] m.p. 78–79°), in 20 ml. of water was heated at the reflux temperature. After one hour a 10-ml. sample was titrated according to the procedure of Cherbuliez and Weniger.[14] There was required 7.3 ml. of 0.1189 *N* sodium hydroxide to the methyl orange end-point, 5.9 ml. more to the phenolphthalein end-point, and 3.2 ml. more after the addition of calcium chloride. From the difference of the first two titers, the amount of dibenzyl phosphate remaining is 18.5%. From the difference in the second pair of titers, the amount of monobenzyl phosphate present is 35.7%. The final titer alone corresponds to 42.3% phosphoric acid. The total phosphorus accounted for (first titer) is 96.5%. These data point out the need for avoiding heating in the early stages of the preparation of barium dibenzyl phosphate.

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[17] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953); J. M. Constantin, A. C. Haven, Jr., and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953).

[18] W. Lossen and A. Köhler, *Ann.*, **262**, 211 (1891).

**Barium Dibenzyl Phosphate.**—A solution of 212 ml. of benzyl alcohol in 200 ml. of absolute ether was cooled to 0°. With agitation and cooling, there was added 90 g. of phosphorus pentoxide. The resulting solution was refluxed for 24 hours. Differential titration of an aliquot taken at this time indicated that the distribution of phosphorus was 49.5% as dibenzyl phosphate, 41.6% as monobenzyl phosphate and 3.8% as phosphoric acid. In a duplicate experiment the indicated yields were 50.6, 41.6 and 4.5%, respectively. The ether solution was then concentrated to a sirup under reduced pressure and the residue was poured into a slurry of 200 g. of barium carbonate and ice in water. Barium hydroxide solution was added until the *p*H rose from 4 to 11. The slurry then was heated to 60° with free steam and filtered hot from barium monobenzyl phosphate. The filtrate at this point amounted to about 4 liters. The cake was slurried with one liter of boiling water for 90 minutes and filtered. The combined filtrates were concentrated under reduced pressure. After distillation of about 1200 ml. a small amount of barium monobenzyl phosphate precipitated and was removed by filtration. Concentration was resumed and the barium dibenzyl phosphate began to crystallize. When the residual volume was about 1800 ml., the first crop of barium dibenzyl phosphate was collected and when dry weighed 79.5 g., m.p. 290–295°. Further concentration gave a second crop of 18.55 g., m.p. 293–296°.[19] The total yield (98 g.) corresponds to 45% of that indicated by titration.

**Silver Dibenzyl Phosphate.**—Barium dibenzyl phosphate (125 g.) was dissolved in 4350 ml. of boiling water. The solution was filtered hot from traces of insoluble material. With agitation and in the dark there was added to the solution a solution of 64.5 g. of silver nitrate in 100 ml. of water. The silver salt began to separate immediately. The suspension was protected from light and chilled. The silver dibenzyl phosphate was collected, washed successively with cold water and cold methanol and dried. The silver salt weighed 114.86 g. (82.5%) and melted upon rapid heating at 229–231°.[20] Titration with standard potassium thiocyanate indicated a purity of 99.7%.

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[19] On the same scale Lynen[12] reported a yield of 75 g., m.p. 255–261°.

[20] Lynen[12] reported m.p. 216° dec.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

# The Peracetic Acid Oxidation of Dehydronorcamphor

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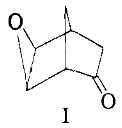
Peracetic acid reacts with dehydronorcamphor (II) to give a mixture of lactones (VI and IX) rather than the epoxide I. The mechanism of this transformation is discussed briefly, and some general conclusions regarding the oxidation of $\beta,\gamma$-unsaturated ketones with peracids are drawn.

In an attempt to prepare dehydronorcamphor epoxide (I), the reaction of dehydronorcamphor[1] (II) with peracetic acid has been investigated. Reaction conditions suitable for the conversion of norbornene to norbornene epoxide[2] were chosen, and a liquid transformation product, b.p. 131–132° (22 mm.), was obtained. Although the elementary analysis of this product corresponded to the expected formula ($C_7H_8O_2$), it soon became evident that the desired ketoepoxide I had not been formed. Thus, although the infrared spectrum of the product showed two clearly distinct carbonyl peaks at 5.65 and 5.80 $\mu$, no derivatives could be obtained with either semicarbazide or 2,4-dinitrophenylhydrazine. Since the product appeared to be non-ketonic, it was concluded that the peracetic acid had attacked the carbonyl group of II rather than the olefinic linkage.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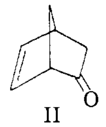
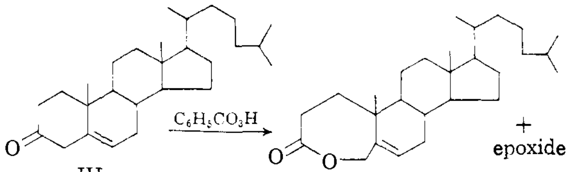

II

The transformation of cyclic ketones into lactones, using persulfuric acid, was described for the first time by Baeyer and Villiger in 1899[3]; closely related reactions involving organic peracids have since been quite extensively studied.[4] Although one might at first expect olefin epoxidation to take precedence over the Baeyer–Villiger type reaction, the oxidation of a $\beta,\gamma$-unsaturated ketone to an unsaturated lactone has been observed before. Thus, Mori and Mukawa[5] have shown recently that the so-called "$\alpha$-epoxide" derived from $\Delta^5$-cholestenone (III), first prepared by Ruzicka and Bosshard,[6] is in reality the lactone IV. In this case, an appreciable amount of the normal epoxide also is formed. However, in the case of dehydronorcamphor it is not hard to understand the reduced reactivity of the olefinic bond, since the carbonyl function is held in a position which is particularly suitable for electron withdrawal (see formula IIa), thus making the double bond unusually resistant to electrophilic attack. A similar phenomenon has been encountered and rationalized in this way by Woodward, *et al.*,[7] who found that the non-conjugated double bond in the lactone V could not be selectively epoxidized with perbenzoic acid, undoubtedly because of electron release from the double bond to the lactonic carbonyl group.



III IV

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[1] For a convenient preparation of II, see P. D. Bartlett and B. E. Tate, THIS JOURNAL, **78**, 2473 (1956).

[2] H. M. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5396 (1954).

[3] A. von Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899).

[4] For a convenient, although not encyclopedic, review of this reaction see C. H. Hassall's article in R. Adams, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 73–106.

[5] S. Mori and F. Mukawa, *Bull. Chem. Soc. Japan*, **27**, 479 (1954).

[6] L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937).

[7] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).