scale for observed points had to be shifted (lengthened) by 50 seconds to obtain agreement with the calculated curve.

Reaction with Methanol.—No absorption at 425 mμ (peak for unsubstituted triphenylcarbonium ion) was detected when triphenylmethyl chloride, thiocyanate, acetate, benzoate or azide was solvolyzed in methanol or in benzene containing methanol or phenol, only ultraviolet absorption of the reactants or products with maxima in the region 230–290 mμ.

With trianisylmethyl chloride in benzene containing methanol (instead of pyrrole), the absorption at 498 mμ showed only a rise to an equilibrium value. For example, with 7×10^{-4} *M* chloride and 1.2×10^{-1} *M* methanol, optical densities at 0, 22, 42, 62, 102, 202, 502 and 942 sec. were 0.210, 0.450, 0.482, 0.505, 0.530, 0.560, 0.610 and 0.650, respectively. If pyridine, di-*n*-propylaniline or N,N-dimethyl-α-naphthylamine was added, discharge of the color was immeasurably fast, and if the amine was present initially no detectable color ever formed.

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α-Methylene-γ-phenyl-γ-butyrolactone

BY EUGENE E. VAN TAMELEN AND SHIRLEY ROSENBERG BACH[1]

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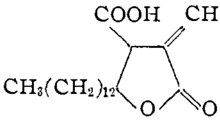
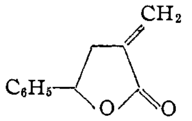
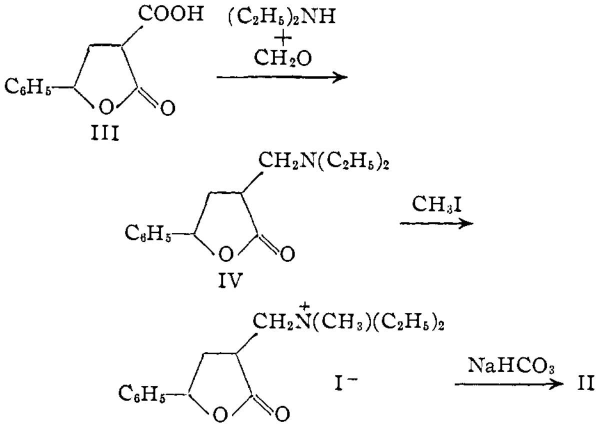
In anticipation of its application to the synthesis of certain natural products, *e.g.*, the labile protolichesterinic acid (I), we should like to disclose a selective and potentially general route to α-methylene lactones, exemplified by the preparation of α-methylene-γ-phenyl-γ-butyrolactone (II). α-Carboxy-γ-phenyl-γ-butyrolactone (III),[2] readily available by hydrolysis of the lactonic ester derived from diethyl malonate and styrene oxide, was allowed to react at room temperature with formaldehyde and diethylamine, whereby it was transformed, with decarboxylation, to α-diethylaminomethyl-γ-phenyl-γ-butyrolactone (IV). This Mannich product was obtained as a stable, distillable oil which could be readily converted to a crystalline methiodide (V). *Treatment of the methiodide with aqueous sodium bicarbonate at room temperature yielded the methylene lactone II.* This ready elimination may be viewed as conforming to the Hofmann type, but greatly facilitated by the lability of the α-hydrogen (*cf.* the transformation of tropinone methiodide to 2,4-cycloheptadienone).[3]



I

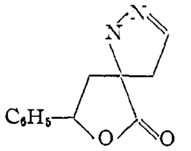


II

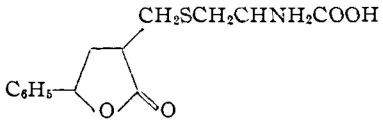


III IV V

Structure proof for II rests upon three pieces of evidence: (i) ultraviolet spectral comparison, the absorption in the 220–240 mμ region compares favorably with that of established α-methylene-γ-lactones (Table I), (ii) catalytic reduction to α-methyl-γ-phenyl-γ-butyrolactone, which was compared with an authentic sample, and (iii) production of formaldehyde by ozonolysis, a result which clearly indicates the exocyclic nature of the double bond. The lactone II was characterized by (i) conversion with diazomethane to a pyrazoline, and (ii) the preparation of the cysteine addition compound; these two products we consider to have the structures VI and VII, respectively.



VI



VII

TABLE I

Extinction coefficients	220 mμ	230 mμ	240 mμ
α-Methylene-γ-phenyl-γ-butyrolactone (II)[a]	4960	2170	990
α-Methylene-γ-butyrolactone[b]	..	2400	500
Protolichesterinic acid (I)[a]	7060	4620	..

[a] Measured with a Cary spectrophotometer; solvent, ethanol. [b] C. J. Cavallito and T. H. Haskell, THIS JOURNAL, **68**, 2332 (1946).

Experimental[4]

α-Diethylaminomethyl-γ-phenyl-γ-butyrolactone (IV).—Three and one-half grams of α-carboxy-γ-phenyl-γ-butyrolactone (m.p. 144.5–145.5°)[2] was added to 7.5 g. of diethylamine in a 50-ml. erlenmeyer flask, after which 3.7 g. of 30% formaldehyde solution was added slowly with swirling. During the addition process, the carboxylactone dissolved smoothly while the mixture effervesced and heat evolved. After standing for two days, the aqueous layer was saturated with potassium carbonate and the upper layer separated. After extracting once with ether, the ether solution was washed twice with water and evaporated *in vacuo*. Upon distillation of the residue at 116–118° (0.2 mm.), 1.6–1.7 g. (40–43%) of colorless α-diethylaminomethyl-γ-phenyl-γ-butyrolactone was obtained.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.51; N, 5.67. Found: C, 73.23; H, 7.82; N, 5.20.

In order to obtain the **methiodide V**, the basic lactone (2.36 g.) was treated with 10 ml. of *dry* methyl iodide. After about three minutes, pale yellow crystals of the quaternary salt began to precipitate rapidly. Upon completion of the reaction, the solid was triturated with ether, filtered, and dried. The crude salt, obtained in a yield of 3.0 g. (80%), was hygroscopic in that it rapidly became sirupy upon exposure to the atmosphere; in an attempted melting point determination, the solid merely foamed up in the capillary.

α-Methylene-γ-phenyl-γ-butyrolactone (II).—After the addition, with shaking, of 35 ml. of 5% sodium bicarbonate

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[1] Wisconsin Alumni Research Foundation Research Assistant, Feb.-June, 1953; du Pont Summer Research Assistant, 1953.

[2] G. Van Zyl and E. van Tamelen, THIS JOURNAL, **72**, 1357 (1950).

[3] G. Buchi, N. C. Yang, S. L. Emerman and J. Meinwald, *Chemistry and Industry*, 1063 (1953).

[4] All melting points are corrected.

to 6.55 g. of α-diethylaminomethyl-γ-phenyl-γ-butyrolactone methiodide, a thick, yellow oil separated. After standing for a day, the mixture was extracted with ether, and the ether layer was dried over sodium sulfate. The product was distilled in an atmosphere of nitrogen and weighed 2.40 g. (83%), b.p. 124–126° (0.3 mm.), n^{25}D 1.5547. The lactone exhibited characteristic bands in the infrared at 5.68, 6.01 and 6.23 μ.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.98; H, 5.95.

The pyrazoline derivative VI was obtained by the addition of ethereal diazomethane to a solution of the methylene lactone in ether. After the solvent had spontaneously evaporated, the orange oil remaining subsequently crystallized. Two crystallizations from aqueous acetic acid afforded colorless needles which melted with decomposition at 98.5–99.5°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60. Found: C, 66.54; H, 5.76.

The cysteine addition product VII was prepared through the addition of 0.5 g. of the lactone II in 1 ml. of ethanol to a solution of an equimolar amount of cysteine in 1.5 ml. of water adjusted to *p*H 6.5. The precipitate, which formed immediately, was removed by filtration after standing for 1 hr. and was recrystallized from ethanol, yielding crystals melting at 171–173° dec.

Anal. Calcd. for $C_{14}H_{17}NO_4S$: C, 56.90; H, 5.80. Found: C, 56.44; H, 5.67.

Hydrogenation of II.—One gram of α-methylene-γ-phenyl-γ-butyrolactone (II) in 100 ml. of glacial acetic acid was reduced over 300 mg. of 10% palladium-on-carbon at an initial hydrogen pressure of 38 lb. The calculated pressure drop for one molar proportion of hydrogen was 11.2 lb., whereas the observed value at the point where reduction ceased was 13.7 lb. After removal of the catalyst and evaporation of the solvent by distillation *in vacuo* at 40°, the product, an orange oil, was taken up in ether and distilled, b.p. 134–138° (2.0 mm.).

For the comparison with the hydrogenation product, authentic α-methyl-γ-phenyl-γ-butyrolactone was required. This previously reported[5] substance was obtained conveniently by the condensation of styrene oxide and diethyl methylmalonate followed by the alcoholic base cleavage of the unisolated α-carbethoxy-α-methyl-γ-phenyl-γ-butyrolactone. To a solution of 0.25 mole of the sodium salt of diethyl methylmalonate in 150 ml. of absolute ethanol was added dropwise with stirring during a one hour period an equivalent amount of styrene oxide. After standing overnight, during which time the cleavage[2] to α-methyl-γ-phenyl-γ-butyrolactone was completed, the clear, yellow solution was chilled to 15° and neutralized to litmus with cold glacial acetic acid. After removal of the excess alcohol under reduced pressure and at room temperature, 150 ml. of water was added and the oily layer which separated was removed from the aqueous phase. After extraction of the water solution with ether, the combined ether extracts were dried over sodium sulfate. A forerun boiling at 98–105° (1.0 mm.) was discarded, and the main fraction then distilled at 134–138° (0.9 mm.) (37 g., 91%).

The infrared spectra of authentic lactone and the product obtained by the hydrogenation of II were, within experimental error, identical. To confirm the identity of the two lactones, each was converted to the solid **α-methyl-γ-hydroxy-γ-phenylbutyramide**. The ammonolysis was accomplished by allowing a solution of the lactone in ethanolic ammonia (anhydrous) to stand for 24 hours. The mixture then was cooled in ice and the precipitated amide was removed by filtration. Crystallization from benzene–petroleum ether (b.p. 60–68°) afforded material with a m.p. 162.5–163° dec., which was not raised on subsequent crystallization from benzene–methanol.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.66; H, 7.85.

The mixed melting point of amides prepared separately from the two lactones was not depressed.

Ozonization of II.—One gram of II, dissolved in 50 ml. of glacial acetic acid, was subjected at room temperature to the action of excess ozone. The ozonide was decomposed with zinc dust and glacial acetic acid, after which the product was steam distilled, the distillate being collected in water. From the distillate, 0.76 g. (45%) of dimedone adduct of formaldehyde was obtained; the mixed melting point with authentic material was not depressed.

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[5] O. Mumm and K. Brodersen, *Ber.*, **56**, 2295 (1923).

COMMUNICATIONS TO THE EDITOR

A NEW CLASS OF BIOLOGICALLY ACTIVE CORTICOIDS

Sir:

We wish to report the preparation of a new class of corticosteroids which display varying degrees of glucocorticoid activity. The compounds described are derivatives of hydrocortisone and cortisone functionally substituted in the D-ring. Introduction of the various nuclear substituents was readily effected by chemical transformations of a dihydroxylated product obtained from the microbiological oxygenation of 11-desoxy-17α-hydroxycorticosterone.[1] This O_6-compound, shown below to be Δ^4-pregnene-11β,14α,17α,21-tetrol-3,20-dione (14α-hydroxyhydrocortisone) (I), is itself more active than hydrocortisone acetate in the thymus involution assay[2] and has been found to be an active anti-inflammatory agent in rheumatoid arthritis.[3]

Preliminary formulation of (I), m.p. 241–242°, $[\alpha]_D$ +183° (EtOH), λ^{alc}_{max} 241 mμ (log ε 4.23), Found: C, 66.5, H, 7.93; as a tertiary-hydroxylated derivative of hydrocortisone arose from two observations: (a) acetylation of (I) with acetic anhydride–pyridine afforded only a *monoacetate* (Ia), m.p. 211–212°, $[\alpha]_D$ +147° (EtOH), λ^{alc}_{max} 241 mμ (log ε 4.19), Found: C, 65.7; H, 7.70; and (b) this monoacetate (Ia) underwent oxidation with chromic anhydride yielding a dehydro compound (IIa), m.p. 262–263°, $[\alpha]_D$ +237° (dioxane), λ^{alc}_{max} 237 mμ (log ε 4.22), Found: C, 66.1; H, 7.21; the 21-alcohol (II) of which had m.p. 232–233° dec., $[\alpha]_D$ +210° (dioxane), λ^{alc}_{max} 237 mμ (log ε 4.20), Found: C, 66.8; H, 7.53; which displayed typical six-membered ring ketone absorption in the

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[1] (a) G. M. Shull, D. A. Kita, J. W. Davisson, U. S. Patent 2,658,023, November 3, 1953; (b) G. M. Shull and D. A. Kita, THIS JOURNAL, **77**, 763 (1955).

[2] Pharmacological activities were determined by Dr. S. Y. P'an who will report on his findings in a forthcoming publication.

[3] Reports on the clinical investigations of the anti-inflammatory activity of (I) will appear elsewhere.