Experiments with benzaldehyde are summarized in Table I. The *triethylbenzylidene phosphonoacetate* obtained in experiment No. 4, b.p. 140°/0.01 mm., n_D^{20} = 1.520–1.524, had the correct analysis.

Anal. Calcd. for $C_{15}H_{21}O_5P$: C, 57.7; H, 6.77. Found: C, 57.2; H, 7.1.

The cinnamic acid obtained from all experiments was identified by melting point and mixed melting point of the substance itself and by its *p*-bromophenacyl bromide derivative, m.p. 147.[8]

The substance obtained in experiment No. 2 had the correct analysis for *benzylidenebis(triethyl)phosphonoacetate*), $C_6H_5CH[CH(COOC_2H_5)PO(OC_2H_5)_2]_2$, IV.

Anal. Calcd. for $C_{23}H_{38}O_{10}P_2$: C, 51.57; H, 7.09. Found: C, 51.67; H. 6.85.

No attempt was made to establish the structure of this compound, but its analysis and the fact that it gave cinnamic acid on hydrolysis are strong evidence for its constitution.

The reaction of p-nitrobenzaldehyde with triethyl phosphonoacetate. In a representative experiment, 6 g. (0.0398 mole) of *p*-nitrobenzaldehyde and 5.5 g. (0.0246 mole) of triethyl phosphonoacetate were refluxed for 5 hr. in 60 ml. of pure ethanol containing 0.4 g. of piperidine. After removal of most of the solvent *in vacuo*, the residue solidified and melted at 80–85°. After one recrystallization from dilute ethanol, the substance melted at 86–87° (fast heating) and 90–91° (slow heating). After the second recrystallization the substance melted at 86° (fast heating) and at 138° (slow heating). After the third recrystallization the melting point was 138°, both on fast and slow heating.

The *cis*-ethyl *p*-nitrocinnamate is not described in the literature; the *trans*-ester melts at 138°.[4]

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.8; H, 4.98; N, 6.34. Found: C, 60.2; H, 5.4; N, 6.3.

On hydrolysis the substance yielded *trans-p*-nitrocinnamic acid, m.p. 285° dec., showing no depression with an authentic sample.

Attempted reaction of benzophenone with triethyl phosphonoacetate. Using the same conditions as in the above experiment, over 85% of the benzophenone was recovered unchanged and no other product could be isolated from the reaction mixture.

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Substituted γ-Lactones. V.[1] Synthesis of Certain α,β-Disubstituted γ-Lactones. A Route to Lignans of the α, β-Dibenzylbutyrolactone Class

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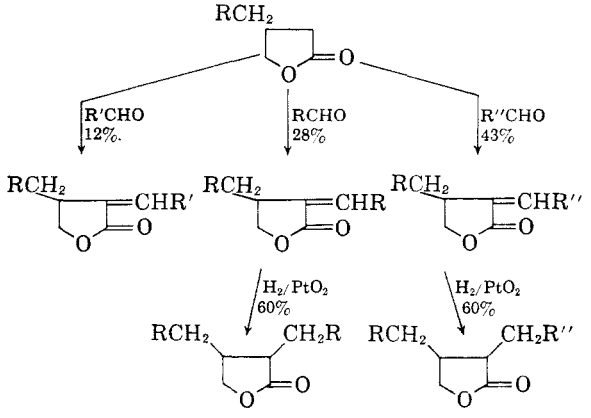
Received December 28, 1959

In our investigations dealing with substituted γ-lactones[3a–c] we became interested in the synthesis of α,β-disubstituted γ-butyrolactones, especially α,β-unsymmetrically substituted γ-butyrolactones. This type of butyrolactones occurs in nature as a class of lignans.[4,5] These are compounds which, at least formally, could be derived from substituted *n*-propylbenzenes which are dimerized by joining the β-carbon atoms of the side chain. Haworth and Woodcock[6] gave a synthesis of such a compound, namely, matairesinol (I), and its dimethylether (II).

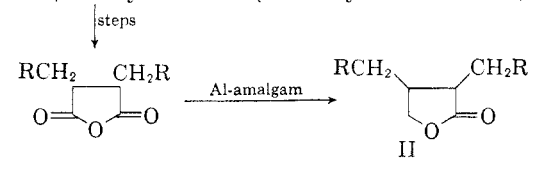
In paper III[3a] of this series we described a method which is generally applicable for the synthesis of β-benzyl-γ-butyrolactones. In paper I[3b] of this series we showed that γ-butyrolactone condenses with a large variety of aldehydes to yield α-benzylidene-γ-butyrolactones. A combination of these two methods resulted in a convenient procedure for synthesizing symmetrically and unsymmetrically α,β-disubstituted γ-butyrolactones. We tested this method in the synthesis of II as a member of a natural occurring lignan and in the synthesis of α-(4-dimethylaminobenzyl)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone as an example for an α,β-unsymmetrically substituted γ-butyrolactone.

The following chart illustrates the route of the syntheses.



R = 3,4-dimethoxyphenyl
R′ = 3,4-dioxymethylenephenyl
R″ = 4-dimethylaminophenyl

2 RCHO + diethyl succinate (Route by Haworth *et al.*[6])



II

II was converted into a dinitro derivative. II and its dinitro derivative synthesized by this route were identical in melting points and infrared spectra with II and dinitro-II prepared by Haworth's method. Both compounds gave no depressions when mixed melting points were determined.

(1) Paper IV of this series, Hans Zimmer, J. Rothe, and Dolores Gracian, *J. Org. Chem.*, in press.

(2) Chattanooga Medicine Company Post-doctorate Research Fellow, 1956–1958. Recipient of a Fulbright Travel Grant.

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As is shown in the condensation between piperonal and β-veratryl-γ-butyrolactone this method is not restricted to a few aldehydes but is obviously a general one for the synthesis of α,β-disubstituted γ-butyrolactones.

We are presently engaged in applying this route in the preparation of other lignans of the α,β-benzylbutyrolactone class.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany.

The infrared spectra were taken in nujol mulls on a Baird double-beam spectrophotometer.

dl-α-(3,4-Dimethoxybenzylidene)-β-(3,4-dimethoxybenzyl)-butyrolactone. Two grams (8.5 millimoles) of β-(3,4-dimethoxybenzyl)butyrolactone,[3] 1.4 g. (8.5 millimoles) of veratraldehyde, 0.5 g. (9 millimoles) of sodium methoxide, and 16 ml. of benzene were kept in a stoppered bottle for 6 days with occasional shaking. Sulfuric acid, 25 ml. of 2*N*, was added; after some agitating, the layers were separated. The aqueous layer was once more extracted with benzene and the combined organic phase was washed successively with 10% sodium bisulfite and 2*N* sodium carbonate solutions, then with water. After removal of the solvent a brownish oil remained which was taken up in methanol-ether. The compound crystallized after standing in the refrigerator for about 10 days; in later experiments, the process could be accelerated by seeding. The crude first fraction (0.5 g.; m.p. 130–131°) was brownish but could easily be washed colorless with a small amount of methanol. By working up the filtrates, an additional 0.4 g. (m.p. 127–128°) of the compound was obtained; total yield 0.9 g. (28%). The analytical sample melted at 131–131.5°; microcrystalline powder from methanol. The infrared spectrum was as follows: 5.77 μ and 6.08 μ (lactonic C=O, C=C double bond).

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.57; H, 6.19.

dl-α,β-Bis(3,4-dimethoxybenzyl)butyrolactone (dl-Matairesinol dimethyl ether) (II). A. One gram of α,β-bis(3,4-dimethoxybenzyl)succinic anhydride (m.p. 109–111°; lit., m.p. 110–112°) was reduced with amalgamated aluminum according to Haworth and Woodcock.[6] The work-up procedure was changed as follows: After filtration, the alumina was extracted (Soxhlet, 24 hr.) with chloroform; evaporation of the combined extract and filtrate yielded an oil which was refluxed with 5% methanolic potassium hydroxide solution (10 ml.) for 30 min. The methanol was removed, the residue taken up in water (10 ml.), the aqueous solution washed twice with methylene chloride, acidified with hydrochloric acid, and heated on a water bath for 1 hr. The cooled mixture was extracted with chloroform, the extract washed with sodium bicarbonate solution and water, dried (sodium sulfate), and the solvent removed. The residue was taken up in methanol to give 420 mg. (43%) of the lactone, m.p. 111–113°. One recrystallization from methanol raised the melting point to 112–114° (lit., 113–115°).

B. The preceding unsaturated lactone (2.60 g.) was hydrogenated in methanol with platinum oxide (50 p.s.i.). The crude product (2.52 g.) was an almost colorless oil; its methanolic solution did not deposit any crystals, even after standing in the refrigerator for 1 year. Crystallization could easily be induced, however, by seeding with a sample prepared by procedure A; 1.56 g. (60%) of short white prisms, m.p. 102–107°, were obtained. Two recrystallizations from methanol gave material melting at 112–114°, unchanged when mixed with a sample prepared by procedure A. The infrared spectra (5.67 μ) were identical.

The *dinitro derivative* was prepared according to Haworth and Woodcock[6]: (1) from the reduction product of the anhydride (yellow needles from chloroform-methanol, m.p. 193–194°; lit.: 191–192°), and (2) from the crude hydrogenation product (yellow needles from dioxane-methanol, m.p. 190.5–191.5°). Mixed melting point of the two specimens was 191–193°. The infrared spectra (5.69μ) were identical.

Anal. Calcd. for $C_{22}H_{24}N_2O_{10}$: C, 55.46; H, 5.08; N, 5.88. Found: C, 55.45; H, 5.14; N, 5.89.

dl-α-(p-Dimethylaminobenzylidene)-β-(3,4-dimethoxybenzyl)-butyrolactone was obtained from β-(3,4-dimethoxybenzyl)-butyrolactone and *p*-dimethylaminobenzaldehyde as above, with a yield of 43% as pale-yellow short needles from dioxane-methanol, m.p. 193–193.5°; infrared spectrum: 5.74 β and 6.12 β.

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.00; H, 6.73; N, 3.99.

dl-α-(p-Dimethylaminobenzyl)-β-(3,4-dimethoxybenzyl)-butyrolactone was prepared by hydrogenation of the preceding compound in 60% yield, as colorless blocks from methanol, m.p. 115–115.5°. The infrared spectrum was as follows: 5.64 μ (no peak at ~6.1 β, no C=C-unsaturation).

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.76; H, 7.47; N, 3.84.

dl-α-(3,4-Methylenedioxybenzylidene)-β-(3,4-dimethoxybenzyl)butyrolactone was prepared from β-(3,4-dimethoxybenzyl)butyrolactone and piperonal as above, yield 12% as pale-yellowish short needles from methanol, m.p. 97–97.5°. The infrared spectrum showed the following bands: 5.75 and 6.10 μ.

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; Found: C, 68.40; H, 5.44.

Acknowledgment. The authors appreciate the skillful assistance of Mr. Horst Schmank.

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Esters and Ketones Related to Diphenylacetic Acid

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Received January 4, 1960

In order to study the pharmacological properties of ketones and basic esters related to diphenylacetic acid, the preparation of a number of such compounds (Table I) was required. These molecules are of interest since they are structurally related to substances possessing antispasmodic, local anesthetic, anti-adrenal, and analgetic activities.

Most of the final compounds prepared in the present study possess nuclear amino groups. 2,2-Bis(*p*-nitrophenyl)propionic acid (I) and 2,2-bis(*p*-nitrophenyl)acetic acid (II)[1,2] were prepared by acid hydrolysis of the respective methyl esters.[3] The reported[1] facile decarboxylation of II

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