The Reformatsky Reaction with Halolactones. I. Reaction with Nonsteroid Carbonyl Compounds

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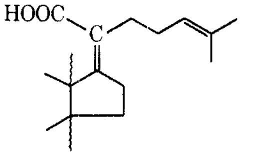
The classical Reformatsky reaction proceeds normally when α-bromolactones replace α-bromo esters. A variety of aromatic carbonyl compounds and one alicyclic ketone were condensed with α-bromo-γ-butyrolactone to yield both hydroxy and unsaturated addition products. 4,4′-Dimethoxybenzophenone and α-bromo-γ-butyrolactone reacted normally in benzene–ether solvents, but, when tetrahydrofuran was used as a solvent, a major product was tetrahydro-2,2-bis(*p*-methoxyphenyl)furan, derived by opening of the lactone followed by decarboxylation, dehydration, and ring closure. Not unexpectedly, the novel 2-bromo-6,6-dimethyl-ε-caprolactone did not react normally in two cases. Steric factors are of equal or greater importance when α-bromolactones are used instead of α-bromo esters in the Reformatsky reaction.

Three steroid antibiotics are known, helvolic acid,[3] cephalosphorin P_1,[4] and fusidic acid[5] which possess a common group at C_{17} as shown in **1**. It was of interest to attempt the synthesis of other steroids having this group at C_{17} from 17-keto steroids and the novel 2-bromo-6,6,-dimethyl-ε-caprolactone (**2**) by a conventional Reformatsky reaction. The normal product of such a reaction, on hydrolysis and dehydration, should afford a steroid having the partial structure **1**.



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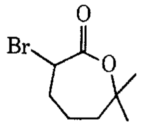

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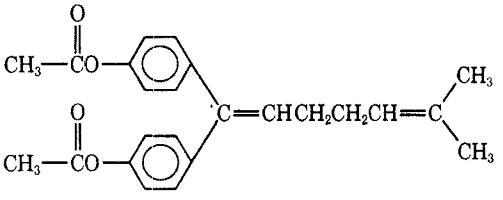

3

Preliminary to this it was necessary to establish that the classical Reformatsky reaction will proceed normally when α-bromolactones are used in place of α-bromo esters. Even though this appears to be an obvious extension of the scope of the reaction, surprisingly no such reactions are reported in the literature.[6] Furthermore, some of the products obtained were of potential interest for biological screening.

The desired 2-bromo-6,6-dimethyl-ε-caprolactone (**2**) was prepared from 2,2-dimethylcyclohexanone *via* bromination followed by a Baeyer–Villiger oxidation. The attempted condensation of the bromolactone **2** with dehydroisoandrosterone acetate did not appear to be fruitful, probably because of the hindered character of the 17 ketone or the instability of the starting lactone.

The Reformatsky-like condensation between bromolactone **2** and diacetoxybenzophenone was then attempted in ether–benzene containing a trace of iodine and boron trifluoride. The condensation occurred only in a very small yield and the reaction mixture was shown to have several components on tlc. By consecutive preparative layer chromatography separation a compound was isolated as a fairly pure oil. To this compound the structure **3** was assigned on the basis of nmr and mass spectroscopy (molecular ion *m/e* 378). Compound **3** is believed to have been produced from the normal Reformatsky adduct by lactone opening, decarboxylation and dehydration. No evidence was obtained for the presence of any unreacted bromolactone **2** in the reaction mixture. Instead, an acid was isolated, identified as 6-methyl-5-heptenoic acid on the basis of elemental analysis, ir, nmr, and mass spectra. Owing to hindrance at the sites of condensation the bromolactone **2** may have undergone a reductive loss of halogen to form 6,6-dimethyl-ε-caprolactone in much the same way that ethyl α-bromoisobutyrate is partially converted into ethyl isobutyrate.[7] The subsequent ring opening and dehydration of this lactone could yield 6-methyl-5-heptenoic acid.

Before any further investigation of the reaction involving the bromolactone **2** it was decided to examine the Reformatsky reaction with simpler bromolactones. We have found that α-bromo-γ-butyrolactone is indeed a suitable reactant in the Reformatsky reaction, although yields are generally lower than in reactions using α-bromo esters.

Reformatsky condensations with α-bromo-γ-butyrolactone were effected with several aromatic aldehydes and ketones and one aliphatic ketone, *trans*-1-decalone.[8] With the latter compound two isomeric products **4** were obtained. The compound eluted from a chromatographic column first, mp 118°, is presumably the product having an axial hydroxyl group.[9,10]

With benzaldehyde, the primary product was the hydroxy compound **5** which could be readily dehydrated. From the reaction mixture only one of the two possible *dl* pairs was separated, which on dehydra-

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(1) Decreased.

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(3) S. A. Waksman, E. S. Horning, and E. L. Spencer, *J. Bacteriol.*, **45**, 233 (1943).

(4) B. M. Baird, T. G. Halsall, E. R. H. Jones, and G. Lowe, *Proc. Chem. Soc.*, 257 (1961).

(5) W. O. Godfredsen and S. Vangedal, *Tetrahedron*, **18**, 1029 (1962).

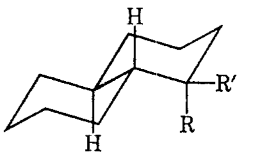
(6) U. S. Patent 2,361,968 reports the reaction of α- or β-halobutyrolactones with a few ketones but the products are not adequately characterized.

(7) W. R. Vaughn, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).

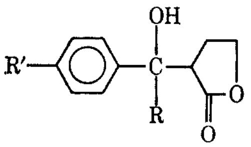
(8) Prepared by the procedure of W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(9) This assumption is made by analogy to the behavior of steroids; see I. E. Bush, "The Chromatography of Steroids," The Macmillan Co., New York, N. Y., 1961, p 91.

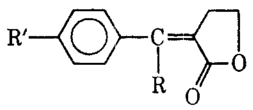
(10) Recently L. Rand and C. S. Rao [*J. Org. Chem.*, **33**, 2704 (1968)] reported that the Reformatsky reaction of *trans*-2-decalone with ethyl bromoacetate gave a mixture of the two epimeric hydroxy esters in a 1:1 ratio.



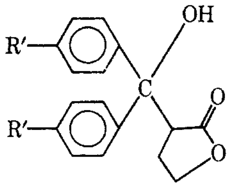
4a, R = α-(γ-butyrolactonyl); R' = OH
b, R = OH; R' = α-(γ-butyrolactonyl)



5, R, R' = H
6, R = CH_3; R' = H
7, R = CH_3; R' = OCH_3



8, R, R' = H
9, R = CH_3; R' = H
10, R = CH_3; R' = OCH_3



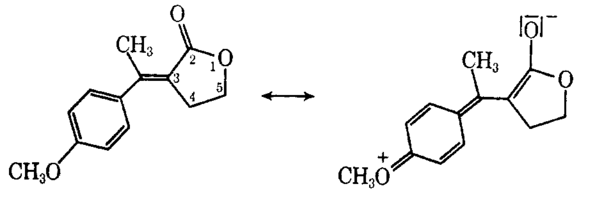
11, R' = H
12, R' = OCH_3
13, R' = $OCOCH_3$
14, R' = OH

tion afforded either *cis*- or *trans*-α-phenylmethylene-γ-butyrolactone, **8**. With benzophenone, the primary product isolated was again the normal undehydrated hydroxy compound **11** which could readily be dehydrated to α-(diphenylmethylene)-γ-butyrolactone, **15**.

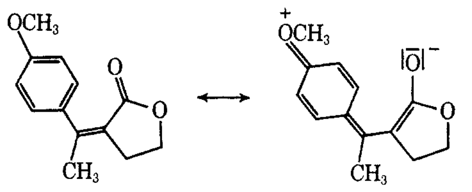
When acetophenone was condensed with α-bromo-γ-butyrolactone the crude product was a liquid. On vacuum distillation the main fraction gave a correct analysis for α-(α-methylbenzylidene)-γ-butyrolactone (**9**), but the nmr spectrum indicated that this substance was a mixture of **9** and its double-bond isomer containing a methylene, rather than a methyl, group. These structural assignments were made on the basis of methyl resonance at 152 cps (as required by **9**) and two singlets at 324 and 318 cps corresponding to the olefinic protons of the isomer. From the relative intensity of the singlets this isomer constitutes about 55% of the mixture. A crystalline hydrazide was prepared from the mixture, which on the basis of nmr was also a mixture of double-bond isomers, though enriched in the hydrazide of **9** by crystallization.

When the reaction was conducted with *p*-methoxyacetophenone the product of vacuum distillation was a mixture. By crystallization a solid was obtained which was a mixture of the *cis* and *trans* isomers **10a** and **10b**. The *trans* isomer **10a** could be purified by crystallization and the *cis* isomer **10b** was separated by chromatography. The structural assignments were made on the basis of ir, uv, and nmr spectra. With nmr the vinyl methyl and the C-4 protons across the double bond are expected to couple with one another. This coupling will be larger when the two interacting groups of protons are on the opposite side of the double bond (as in **10a**) than when they are on the same side (as in **10b**). Theoretically a difference of about 0.6 cps is expected. In fact, the methyl protons in both cases are triplets and the coupling constant is about 1.6 cps for **10b** and 2.2 cps for **10a**. Further support for this lies on the character of the uv spectra. Compound **10b** has an absorption band at 302 mμ (ε 7040) while compound **10a** shows an ε 14,810 for the same band (289 mμ). This is in agreement with the above assignment, since there is a much larger charge separation in **10a** than **10b**.

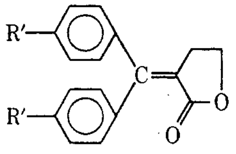
Unexpectedly from the reaction of 4,4'-dimethoxybenzophenone with α-bromo-γ-butyrolactone in tetrahydrofuran and in the presence of catalytic amount of iodine, compound **16** and two other products were obtained. One of these products was identified as tetrahydro-2,2-bis(*p*-methoxyphenyl)furan (**21**). The nmr spectrum of this compound showed a quintet for C-4 protons (δ 1.91 ppm) and two triplets for C-3 (δ 2.50 ppm) and C-5 (δ 4.03 ppm) protons with the coupling constants expected for this system. Furthermore, its mass spectrum indicated a molecular weight and fragmentation pattern consistent for this structure. The other product, an oil, was shown by nmr, ir, and mass spectral studies to have structure **20**. On refluxing with *p*-toluenesulfonic acid this substance is converted into the tetrahydrofuran derivative **21**, and not the "normal" product **16**. Clearly it is not the primary addition product **12**.



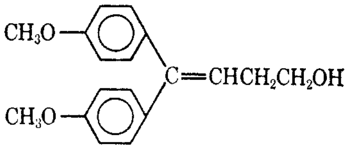
10a, *trans*



10b, *cis*



15, R' = H
16, R' = OCH_3
17, R' = $OCOCH_3$
18, R' = OH
19, R' = $OCH_2C{\equiv}CH$



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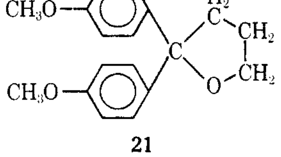

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In the absence of tetrahydrofuran in the solvent mixture, but using catalytic amount of iodine, neither the tetrahydrofuran derivative **21** nor the third product alluded to above (**20**) is present in the reaction mixture. When the reaction was repeated, with tetrahydrofuran and with catalytic amount of mercuric chloride in place of iodine, the main reaction product was **20**, which was converted by *p*-toluenesulfonic acid into the tetrahydrofuran **21**. On the basis of these experimental facts it would seem that lactone ring opening to yield structure **20** must precede cyclization to the tetrahydrofuran **21**. This would require a rather basic medium to open the lactone, and one possibility appears to be tetrahydrofuran.[11] In the absence of tetrahydrofuran reaction proceeds mainly to the unsaturated lactone **16**.

In contrast to this the Reformatsky condensation with diacetoxybenzophenone proceeds smoothly to furnish a crystalline primary addition product (**13**) in a much higher yield. This fact may be related to the greater tendency of acetoxy groups to withdraw electrons and thus contribute less to the stability of carbonium ion intermediates. By refluxing with phosphorous pentoxide in benzene, compound **13** was smoothly dehydrated to **17**. This in turn was readily deacetylated by acid to **18**. Compound **13** was also converted into **18** by treatment with hydrochloric acid in methanol at room temperature. The hydroxy derivative **14** expected from acid hydrolysis readily dehydrated and could not be isolated.

Several of the compounds reported herein are undergoing biological screening. The results of this evaluation will be reported elsewhere.

Experimental Section

Analyzed reagent grade zinc (30 mesh) was activated by heating with concentrated sulfuric acid containing a trace of nitric acid and was utilized immediately.[12] All equipment and solid reagents were vacuum-oven dried. The liquid reagents were A. R. grade except tetrahydrofuran which was distilled over lithium aluminum hydride. Ultraviolet spectra were taken by a Cary recording spectrophotometer, Model 11. The nmr spectra were recorded on a Varian Associates A-60 spectrometer; tetramethylsilane was used as internal reference and deuteriochloroform as solvent, unless otherwise stated.

2-Bromo-6,6-dimethyl-ε-caprolactone (**2**).—A mixture of 2,2- and 2,4-dimethylcyclohexanone[13] obtained from 1 mol of 2-methylcyclohexanone was subjected to bromination.[14] The resulting dark crude product was dissolved in hexane, decolorized with 1 g of alumina and crystallized by cooling. Recrystallization from hexane–ether yielded 93 g of 2-bromo-6,6-dimethylcyclohexanone, mp 156–157°.

Anal. Calcd for $C_8H_{13}BrO$: C, 46.84; H, 6.39; Br, 38.48. Found: C, 46.85; H, 6.40; Br, 38.56.

The ir and nmr spectra were consistent for the assigned structure.

The Baeyer–Villiger oxidation of 20.5 g (0.1 mol) of this product by a procedure similar to that of Smissman and Bergen[15] gave 31 g of crude oil. This was stirred overnight in hexane and the crystals formed were separated by filtration. Recrystallization from acetone–hexane gave 6.8 g of compound **2**: mp 97.5–98.5°; ir consistent; nmr δ 1.5 (s, 6, CH_3), 1.83–2.40 (m, 6, $CH_2CH_2CH_2$), and 4.80 ppm (t, 1, BrCH).

Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.47; H, 5.93; Br, 36.15. Found: C, 43.17; H, 5.92; Br, 36.04.

Reaction of Diacetoxybenzophenone with 2-Bromo-6,6-dimethyl-ε-caprolactone.—A solution of compound **2** (4.75 g, 0.021 mol) in benzene (50 ml) was added dropwise in 1 hr to a well-stirred mixture consisting of diacetoxybenzophenone (8 g, 0.027 mol), activated zinc (10 g), ether (100 ml), benzene (50 ml), and a crystal of iodine. The mixture was externally heated during this period and for an additional 2 hr. The physical state of the reaction mixture at this point indicated that no reaction occurred; so 100 mg of mercuric chloride and a few drops of boron trifluoride–ether complex (47% solution) were added; and the mixture was refluxed for 5 hr more. After cooling the unreacted zinc was removed by filtration through glass wool and the filtrate was mixed with 2 *N* HCl and ethyl acetate. The organic layer was washed with water, brine, and dried (Na_2SO_4) and evaporated under reduced pressure to obtain an oil which afforded 88% recovery of the starting diacetoxybenzophenone upon recrystallization from methanol.

The total mother liquor was subjected to an alkaline extraction with dilute potassium bicarbonate. The alkaline extract, after neutralization, extraction, and distillation, gave 6-methyl-5-heptenoic acid (*ca.* 2 g), bp 87–88° (0.8 mm), which was identified on the basis of elemental analysis, ir, nmr, and mass spectra (molecular ion *m/e* 142). The neutral extract was shown on tlc to be a mixture of several components. One of the major and the least polar components of this mixture (*ca.* 300 mg) was isolated by preparative layer chromatography as an oil. The ir, nmr, and mass spectra (*m/e* 378, molecular ion) of this compound were consistent with the structure **3**.

α-(**1-Hydroxy-*trans*-decahydronaphthyl**)-γ-**butyrolactone** (**4**).—A solution of *trans*-1-decalone (4.5 g, 0.03 mol) dissolved in benzene (20 ml) was added to a reaction flask containing dried and activated 30 mesh zinc metal (5 g). α-Bromo-γ-butyrolactone (4.95 g, 0.3 mol) was added at reflux temperature with stirring. After refluxing for a total of 3 hr the mixture was cooled and 2 *N* HCl (20 ml) was added. The benzene layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure, and the residue was chromatographed on acid-washed alumina. Elution with benzene yielded 0.4 g of **4b**, mp 118–120° (ether–benzene). Elution with benzene–ether mixtures afforded 1.2 g of **4a**, mp 160–165°. Ir spectra were consistent with the structure of **4**.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31; O, 2.14. Found (**4b**): C, 70.37; H, 9.36; O, 2.33. Found (**4a**): C, 70.58; H, 9.35; O, 2.31.

α-(**Phenylhydroxymethyl**)-γ-**butyrolactone** (**5**)—Reaction was carried out with benzaldehyde (16.3 g, 0.15 mol), α-bromo-γ-butyrolactone (20.9 g, 0.126 mol), and activated zinc (10 g) in benzene–ether (40 ml) according to the previous procedure (**4**). By a similar work-up a tan-colored oil (26 g) was obtained. A portion of the oil (13 g) was distilled *in vacuo* and the fraction boiling at 155–165° (0.3 mm) solidified on cooling. Recrystallization from ether–petroleum ether gave 3.5 g of **5**: mp 108–109.5°; ir consistent; uv max (EtOH) 280 mμ (ε 540); nmr δ 2.46 (m, 1, $CHCO_2$), 4.26 (m, 2, OCH_2), 5.39 ppm (d, 1, $J_{6,3}$ = 2.8 Hz, OCH), and aromatic signal (5 H).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.50; H, 6.32.

α-(**Benzylidene**)-γ-**butyrolactone** (**8**).—The other portion of the undistilled oil (13 g) obtained in **5** was dissolved in benzene and refluxed with *p*-toluenesulfonic acid hydrate (200 mg) with removal of water in a Dean–Stark trap. The benzene was evaporated under reduced pressure and the residue was distilled *in vacuo*. The fraction boiling at 145–150° (0.8 mm) was recrystallized from ether–ethyl acetate, yielding 4 g of **8**: mp 115.5–116.5°; ir consistent; uv max (EtOH) 282 (ε 24,900), 223 (ε 12,700), and 218 mμ (ε 14,600); nmr δ 3.23 (t, 2, $J_{4,5}$ = 7.3 Hz, $C{=}CCH_2$; d, $J_{4,6}$ = 3.0 Hz), 4.47 (t,2 $J_{5,4}$ = 7.3 Hz, OCH_2), 7.49 (m, 5, aromatic), and 7.65 ppm (t, 1, $J_{6,4}$ = 3.0 Hz, C=CH; $^1/_3$ is covered by Ph signal).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; O, 18.37. Found: C, 75.73; H, 5.95; O, 18.57.

α-(α-**Methylbenzylidene**)-γ-**butyrolactone** (**9**).—A reaction was carried out with acetophenone (55 g, 0.45 mol), α-bromo-γ-butyrolactone (80 g, 0.48 mol), activated zinc (35 g), a crystal of iodine and benzene (100 ml) in the usual manner The work-up as before afforded an oily crude product which was distilled *in vacuo* to give a 13 g mixture of **9** and its isomer having $C{=}CH_2$ instead of $C{=}CCH_3$: bp 130–135° (0.1 mm); ir consistent; nmr δ 2.53 ($={CCH_3}$), 5.31, and 5.40 ppm ($C{=}CH_2$). Relative intensity considerations indicated the presence of about 55% isomer.

On heating 1 g of this material with hydrazine, a crystalline hydrazide was obtained which was recrystallized to give 0.3 g solid enriched in the hydrazide of **9**: nmr (CF_3CO_2H) δ 2.64 ($C{=}CCH_3$), 5.25, and 5.70 ppm ($C{=}CH_2$). Relative intensity considerations indicated the presence of about 80% hydrazide of **9** and only 20% isomer.

Anal. Calcd for $C_{12}H_{26}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.11; H, 7.37; N, 12.92.

α-(α-**Methyl-4-methoxybenzylidene**)-γ-**butyrolactone** (**10**).—A reaction was carried out with *p*-methoxyacetophenone (35 g, 0.23 mol), α-bromo-γ-butyrolactone (40 g, 0.24 mol), activated

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[11] We have observed that the flask used as the receiver in distillation of THF over $LiAlH_4$ was covered, after repeated distillation, with a very thin solid film. The basic nature of this material, which was apparent from its solubility in dilute acids and its insolubility in water, could have been responsible for this effect. Moreover, the weakly basic character of THF and its higher boiling point and higher dielectic constant may have aided the reaction.

[12] M. B. Rubin and E. C. Blossey, *Steroids*, **1**, 453 (1963).

[13] E. E. King, T. J. King, and I. G. Topkiss, *J. Chem. Soc.*, 919 (1957).

[14] F. Ramirez and F. Kirby, *J. Amer. Chem. Soc.*, **74**, 4331 (1952).

[15] E. E. Smissman and J. V. Bergen, *J. Org. Chem.*, **27**, 2316 (1962).

zinc (18 g), and a crystal of iodine in benzene (50 ml) in the usual manner. Work-up as before gave a red-brown liquid which was distilled *in vacuo*. The fraction obtained at 165–175° (0.5 mm) was crystallized once from ether to give **14** g of solid, mp 78–100°. By several crystallizations from ether–petroleum ether 6.9 g of compound **10a** was obtained: mp 119.5–120.5°; ir consistent; uv max (EtOH) 220 (ϵ 13,120) and 289 mμ (ϵ 14,810); nmr δ 2.56 (t, 3, J = 2.2 Hz, $C{=}CCH_3$), 2.91 (m, 2, $C{=}CCH_2$), 3.84 (s, 3, OCH_3), 4.23 (t, 2, J = 7.2 Hz, OCH_2), and 7.11 ppm (m, 4, aromatic).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.57; H, 6.45.

The combined mother liquor was evaporated. A 2-g sample of this was chromatographed on silicic acid to afford about 1.3 g of **10b**: mp 95–96°; ir consistent; uv max (EtOH) 220 (ϵ 14,900) and 302 mμ (ϵ 7040); nmr δ 2.15 (t, 3, J = 1.6 Hz, $C{=}CH_3$), 3.00 (m, 2, J = 1.6 Hz, $C{=}CCH_2$), 3.80 (s, 3, OCH_3), 4.33 (t, 2, J = 7.4 Hz, OCH_2), and 7.04 ppm (m, 4, aromatic).

Anal. Found: C, 71.39; H, 6.33.

α-(**Diphenylhydroxymethyl**)-γ-**butyrolactone** (**11**).—A reaction was carried out with benzophenone (18.2 g, 0.10 mol), α-bromo-γ-butyrolactone (16.5 g, 0.10 mol), activated zinc (8 g), and a crystal of iodine in benzene (90 ml) as in the previous examples. The crude product obtained by the usual work-up procedure was recrystallized from ether to give 4.9 g of **11**: mp 150–155°; ir consistent; uv max (EtOH) 259 (ϵ 752) and 253 mμ (ϵ 724); nmr δ 2.15 (m, 2, CCH_2C), 4.12 (t, 2, OCH_2), 5.94 ppm (s, 1, OH), and aromatic signal (10 H).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; O, 17.89. Found: C, 75.71; H, 6.04; O, 17.77.

α-(**Diphenylmethylene**)-γ-**butyrolactone** (**15**).—Compound **11** was dehydrated according to the procedure given in **8**. Recrystallization of crude product from ether gave **15**: mp 175–176°; ir consistent; uv max (EtOH) 284 mμ (ϵ 11,650); nmr δ 3.10 (t, 2, $C{=}CCH_2$), 4.31 (t, 2, OCH_2), and 7.45 (m, 10, aromatic).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; O, 12.79. Found: C, 81.76; H, 5.75; O, 12.71.

α-[**Bis**(**4-Acetoxyphenyl**)**hydroxymethyl**]-γ-**butyrolactone** (**13**).—A solution of α-bromo-γ-butyrolactone (24.7 g, 0.15 mol) in benzene (30 ml) was added dropwise to a flask containing 4,4′-diacetoxybenzophenone (14.9 g, 0.05 mol), benzene (70 ml), ether (75 ml), freshly activated and dried zinc (25 g), and a crystal of iodine over 1 hr period. Heat was applied externally to maintain reflux for a total of 6 hr. The residue obtained by the usual work-up procedure was crystallized from methanol to yield 12.5 g of solid which was recrystallized three times from EtOAc to yield 7.2 g of **13**: mp 204–205°; ir consistent; uv max (EtOH) 222 mμ (ϵ 14,200); nmr δ 2.08 (m, 2, CCH_2C), 2.27 (s, 6, CH_3CO_2), 3.74 (t, 1, $CHC{=}O$), 4.16 (m, 2, OCH_2), and 7.26 ppm (m, 8, aromatic).

Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24. Found: C, 65.35; H, 5.14.

α-(**4,4′-Diacetoxydiphenylmethylene**)-γ-**butyrolactone** (**17**).—Compound **13** (2.8 g) in dry benzene was refluxed with P_2O_5 (1.5 g) for 1 hr. The crude dehydration product was crystallized from methanol to give 2.2 g of **17**: mp 159–160°; ir consistent; uv max (EtOH) 225 (ϵ 18,400), 286 mμ (ϵ 13,830); nmr δ 2.27 (s, 6, CH_3CO_2), 3.10 (t, 2, $C{=}CCH_2$), 4.30 ppm (t, 2, OCH_2), and aromatic signals (8 H).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 69.05; H, 4.98.

Reaction of 4,4′-Dimethoxybenzophenone with α-**Bromo**-γ-**butyrolactone** (16, **20**, **21**). **A.**—A reaction was carried out with α-bromo-γ-butyrolactone (24.7 g, 0.15 mol), activated zinc (20 g), 4,4′-dimethoxybenzophenone (12.1 g, 0.05 mol), THF (200 ml), and a crystal of iodine in the usual manner. The crude product was recrystallized from methanol giving a first crop which was unreacted dimethoxybenzophenone. The residue obtained from evaporation of the mother liquor was chromatographed on acid-washed alumina. The material eluted first was recrystallized from methanol to give 1.5 g of **21**: mp 66.5–67.5°; ir consistent; uv max (MeOH) 232 (ϵ 21,100), 275 (ϵ 3920), and 282 mμ (ϵ 3160); nmr δ 1.91 (m, 2, CH_2 ,C-4), 2.50 (t, 2, CH_2, C-3), 3.76 (s, 6, OCH_3), 4.03 (t, 2, OCH_2), and 7.10 ppm (m, 8, aromatic); mass spectrum (70 eV) *m/e* 284 (molecular ion).[16]

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.16; H, 7.07.

A trace of compound **21** in a solvent such as benzene forms an intense red complex with Lewis acids such as aluminum chloride and boron trifluoride. The color disappears upon addition of water or other hydroxylic solvents.

The second fraction, slightly more polar, was an oil which was further purified by preparative layer chromatography to give a noncrystalline material. The structure **20** was suggested for this: ir consistent; nmr δ 1.46 (s, 1, OH), 2.38 (m, 2, CCH_2C), 3.69 (t, 2, $J_{1,2}$ = 6.5 Hz, OCH_2), 4.20 (6, OCH_3), 5.97 ppm (t, 1, $J_{3,2}$ = 7.5 Hz, $C{=}CH$), and aromatic signal (8 H); mass spectrum (70 eV) *m/e* 284 (molecular ion). When this substance was refluxed with a small amount of *p*-toluenesulfonic acid in benzene for several hours the tetrahydrofuran derivative (**21**) was produced.

The third product eluted from the chromatogram was recrystallized from methanol to give 1.5 g of **16**: mp 182.5–183.5°; ir consistent; uv max (EtOH) 231 (ϵ 19,450) and 309 mμ (ϵ 16,100); nmr δ 3.12 (t, 2, $C{=}CCH_2$), 3.84 (s, 6, OCH_3), 4.31 (t, 2, OCH_2), and 7.06 ppm (m, 8, aromatic).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.82. Found: C, 73.50; H, 6.02.

B.—Somewhat a better yield of **16** was obtained when the similar reaction was carried out in ether–benzene, in which case none of **21** was obtained.

C.—When the similar reaction was carried out in THF with catalytic $HgCl_2$ only trace amounts of **21** and **16** were obtained. The major product which appeared to be compound **20** yielded **21** on acid treatment.

α-(**4,4′-Dihydroxydiphenylmethylene**)-γ-**butyrolactone** (**18**). **Procedure A.**—A 1.22-g sample of **17** was deacetylated by treating 3 hr at room temperature with 7 *N* aqueous HCl (20 ml) in methanol (100 ml). Water was added and the crystalline solid was collected by filtration, washed with water, and recrystallized from acetone–chloroform to give 0.6 g of **18**: mp 256.5–257.5°; ir consistent; uv max (EtOH) 230 (ϵ 16,100) and 310 mμ (ϵ 15,270); nmr (CF_3CO_2H) 3.32 (t, 2, $C{=}CCH_2$), 4.58 ppm (t, 2, OCH_2), and aromatic signal (8 H).

Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.75; H, 4.99.

Procedure B.—Compound **13** (1 g) was stirred in a mixture of methanol (20 ml) and 7 *N* hydrochloric acid (20 ml) for 4 hr. During this period the starting solid went into solution and another solid precipitated. Water was added and the crystalline solid was separated by filtration, washed with water, and recrystallized from benzene–acetone to yield 0.61 g of **18**: mp 256–257°; the ir, uv, and nmr spectra were consistent.

Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.71; H, 5.05.

α-[**4,4′-Bis**(**2-propynyloxy**)**diphenylmethylene**]-γ-**butyrolactone** (**19**). **Procedure A.**—A mixture of compound **15** (2.0 g, 0.007 mol), propargyl bromide (3.7 g, 0.031 mol), anhydride potassium carbonate (4 g), and acetone (50 ml) was stirred at room temperature for 20 hr. The inorganic solid was separated by filtration and washed with small portion of acetone. To the filtrate water was added and let stand to crystallize. The resulting solid material (2.2 g, mp 132–135°) was chromatographed on acid-washed alumina. Elution with 5% Et_2O in benzene gave, after recrystallization from methanol, 1.5 g of **19**: mp 134–134.5°; ir consistent; nmr δ 2.52, 2.53 (t, 2, J = 2.4 Hz, $C{\equiv}CH$), 3.11 (t, 2, J = 7.1 Hz, $C{=}CCH_2$), 4.30 (t, 2, J = 7.1 Hz, $CH_2OC{=}O$), 4.72 (d, 2, J = 2.4 Hz, $C{\equiv}CCH_2$), and 7.10 ppm (m, 8, aromatic).

Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.97; H, 5.26.

Procedure B.—A Reformatsky reaction was carried out with 4,4′-dipropargyloxybenzophenone (21.75 g, 0.075 mol, obtained from 4,4′-dihydroxybenzophenone and propargyl bromide according to the above procedure), α-bromo-γ-butyrolactone (26.12 g, 0.225 mol), activated zinc (40 g), and a crystal of iodine in 1:1 benzene–ether (300 ml) in the usual manner. The crude produce was chromatographed as in procedure A to give 1.1 g of **19**, mp 133.5–134.5°. The ir and nmr spectra were consistent.

Anal. Found: C, 77.27; H, 5.30.

Registry No.—2-Bromo-6,6-dimethylcyclohexanone,

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[16] Compound **21** has previously been obtained by a different route [P. D. Bartlett and J. D. McCollum, *J. Amer. Chem. Soc.*, **78**, 1441 (1956)].

21690-26-6; **2**, 21748-36-7; **4a**, 21690-24-4; **4b**, 21690-25-5; **5**, 21690-27-7; **8**, 6285-99-0; **9**, 21690-29-9; **10a**, 21690-30-2; **10b**, 21690-31-3; **11**, 21690-32-4; **13**, 21690-33-5; **15**, 21690-34-6; **16**, 21690-35-7; **17**, 21690-36-8; **18**, 21690-37-9; **19**, 21690-38-0; **21**, 21690-63-1.

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The Reformatsky Reaction with Halolactones. II. Reaction with Steroid Ketones

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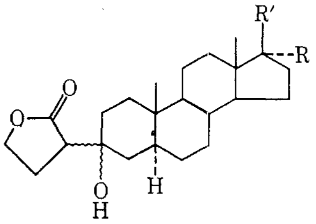
Steroids with 3-, 17- and 20-ketone groups have been condensed with α-bromo-γ-butyrolactone to form hydroxylactonyl addition products or the corresponding dehydrated substances. When Δ^4-3-keto steroids are condensed mixtures of the addition product and $\Delta^{3,5}$- and/or $\Delta^{3(3'),4}$-dienes are obtained. The $\Delta^{3(3'),4}$-diene is the end product of acid treatment. For obvious steric reasons, the C_{20}-ketone group of pregnenolone is totally unreactive, but 16-dehydropregnenolone reacts normally. The C_{17} ketone in steroids is also unreactive but low yields of a normal condensation product can be obtained.

It has been found that α-bromo-γ-butyrolactone is a suitable reactant, in place of α-bromo ester, in the Reformatsky reaction with aromatic carbonyl compounds.[3] In this paper we wish to report the condensation between α-bromo-γbutyrolactone and steroidal 3, 17, and 20 ketones.[4]

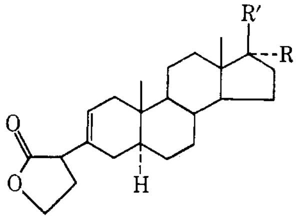
Condensations were carried out with two saturated 3-keto steroids, cholestanone, and 17α-methyldihydrotestosterone acetate. In both cases the primary addition products corresponding to structure **1** were isolated.

A priori it was expected that the bulky lactonyl group in **1a** and **1b** would be equatorial. The nmr spectrum of the dehydration product of **1a** showed the presence of an olefinic proton (δ 5.55 ppm) with an intensity equal to 0.35 that of CH_2–O (δ 4.31 ppm). This corresponds to 70% **2a** (or its Δ^3 isomer) and 30% **3a**. Structure **2a** would be expected from the epimer possessing an axial (3α) hydroxy group, while the 3β-hydroxy epimer would favor structure **3a**. Therefore, it seems justified to conclude either that the product (**1a**), as isolated, is a mixture of the two hydroxy epimers in which the 3α-hydroxy epimer predominates, or that **1a** is essentially only the 3α-hydroxy epimer, which yields an equilibrium mixture of **2a** and **3a** on dehydration.[5]

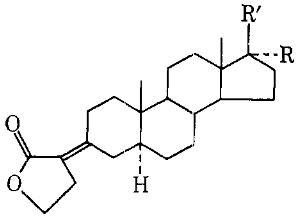
Reformatsky reactions carried out with steroids having a Δ^4-3-keto system were more complicated. When iodine was used to catalyze the reaction the hydroxy addition product **4** was partially or totally dehydrated, but with catalytic mercuric chloride instead of iodine less dehydration occurred. Three dehydrated products are possible (**5**, **6**, and **7**). No evidence for the



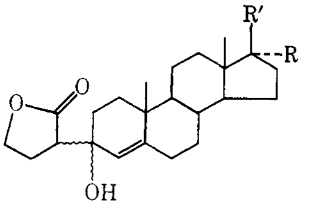
1a, R = H; R' = C_8H_{17}
b, R = CH_3; R' = $OCOCH_3$



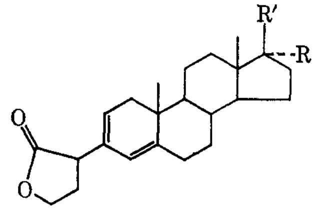
2a, R = H; R' = C_8H_{17}
b, R = CH_3; R' = $OCOCH_3$



3a, R = H; R' = C_8H_{17}
b, R = CH_3; R' = $OCOCH_3$



4a, R = H; R' = $OCOCH_3$
b, R = H; R' = $COCH_3$
c, R = CH_3; R' = $OCOCH_3$



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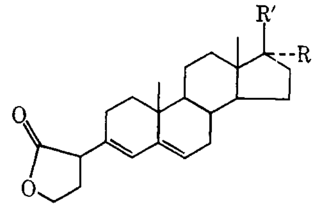
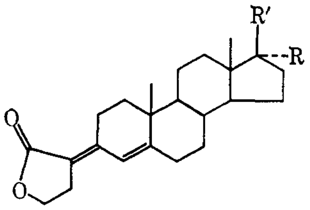
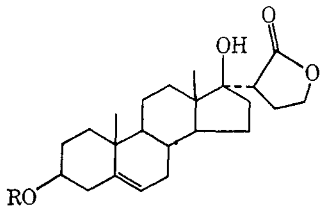


6a, R = H; R' = $OCOCH_3$
b, R = H; R' = $COCH_3$
c, R = CH_3; R' = $OCOCH_3$



7a, R = H; R' = $OCOCH_3$
b, R = H; R' = $COCH_3$
c, R = CH_3; R' = $OCOCH_3$



8a, R = $COCH_3$
b, R = H

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[3] H. Torabi, R. L. Evans, and H. E. Stavely, *J. Org. Chem.* **34**, 3792 (1969).

[4] R. L. Evans and H. E. Stavely, U. S. Patent 3,248,393 (1969).

[5] Since the preparation of this manuscript, L. Rand and C. S. Rao [*J. Org. Chem.*, **33**, 2704 (1968)] reported that the Reformatsky reaction of cholestanone with ethyl bromoacetate afforded a mixture of 3α- and 3β-hydroxy epimers in a 3:2 ratio.