Studies in the Total Synthesis of Steroids and Their Analogs. III. Addition Products of *trans*-2-(Alkoxyaryl)-5-oxocyclopentaneacetic Acids

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An addition to the keto group of a *trans*-2-(alkoxyaryl)-5-oxocyclopentaneacetic acid gives a mixture of hydroxy acid and lactone. When the reagent is sodium borohydride, the hydroxy acid predominates, indicating that the reaction is product development controlled. When a Grignard or a Reformatsky reagent is applied, a greater proportion of the lactone is formed. The enhanced formation of the lactone in the latter reactions is shown to be due in part to the ready isomerization of the hydroxy acid.

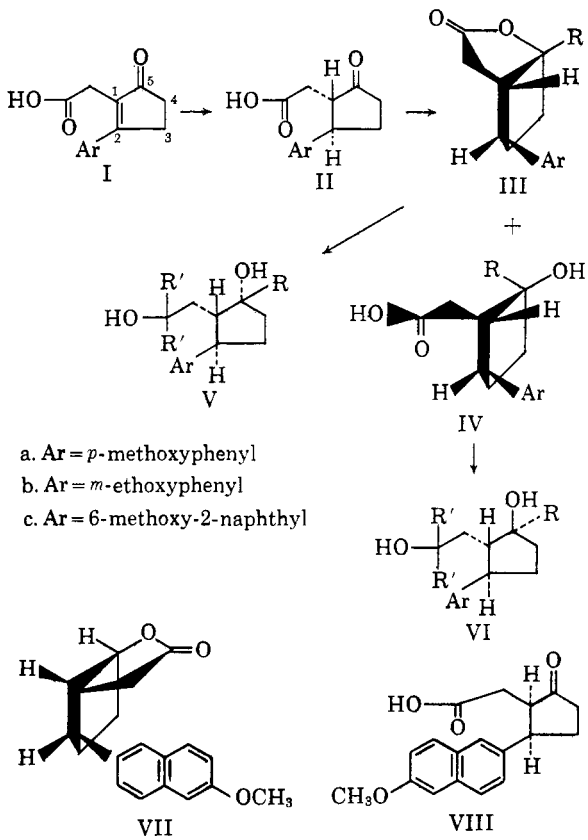
Compounds whose structures simulate those of the steroids have been synthesized in our laboratory for biological evaluation. Among the compounds prepared are the *trans-anti-* and the *trans-syn*-2-(alkoxyaryl) - 5 - hydroxycyclopentaneethanols,[1] which are obtained from the corresponding *trans*-2 - (alkoxyaryl) - 5 - oxocyclopentaneacetic acids (II). The latter acids, prepared according to the procedure of Robinson,[2] are assigned the *trans*-configuration since hydrogenation of their immediate precursors, I, is carried out in the presence of a base, which should facilitate equilibration to yield the more stable acid as the major product in each reduction.[3]

Grinenko and Maksimov[4] previously reported that the reduction of 2-(*p*-methoxyphenyl)-5-oxo-1-cyclopenteneacetic acid (Ia) over palladium-on-calcium carbonate in an alkaline or a neutral medium affords *trans*-2-(*p*-methoxyphenyl)-5-oxocyclopentaneacetic acid (IIa) as the predominant product.

Similarly, we found that hydrogenation of methyl 2-(6-methoxy-2-naphthyl)-5-oxo-1-cyclopenteneacetate (Ic, methyl ester)[2b] over palladium-on-charcoal in methanol, followed by treatment of the reaction mixture with a dilute solution of sodium methoxide, affords methyl *trans*-2-(6-methoxy - 2 - naphthyl) - 5 - oxocyclopentaneacetate (IIc, methyl ester), methyl *cis*-2-(6-methoxy-2-naphthyl)cyclopentaneacetate, and *cis-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetic acid lactone (VII) in yields of 84%, 0.2%, and 4%, respectively.

The addition to the keto function of each of the acids, II, gives a lactone, III and a hydroxy acid, IV. The lactones, III, are assigned the *trans-syn*-configuration[1,4] on the basis that the preferred

CHART I



fusion of two five-membered rings is *cis*[5] and on the assumption that no epimerization occurs at C-2 during the reaction. The acids, IV, are assigned the epimeric *trans-anti*-configuration[1,4] since the diols, VI, obtained from them are isomeric with the diols, V, obtained from the lactones, III.

Grinenko and Maksimov[4] noted that borohydride reduction of IIa yields a mixture of *trans-syn* - 2 - (*p* - methoxyphenyl) - 5 - hydroxycyclopentaneacetic acid lactone (IIIa. R = H) and

(1) Throughout this paper the configuration is assigned in the order of the relative spatial orientation of the alkoxyaryl group at C-2, the hydroxyalkyl or the acetic acid group at C-1, and the hydroxyl group at C-5.

(2) (a) R. Robinson, *J. Chem. Soc.*, 1390 (1938); (b) A. Koebner and R. Robinson, *J. Chem. Soc.*, 1994 (1938).

(3) Y. Amiel, A. Loffler, and D. Ginsburg, *J. Am. Chem. Soc.*, **76**, 3625 (1954).

(4) G. S. Grinenko and V. I. Maksimov, *Proc. Acad. Sci. U.S.S.R.*, **112**, 1059 (1957) [*Chem. Abstr.*, **51**, 14769b (1957)].

(5) (a) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934); (b) W. Hückel and W. Gelmroth, *Ann.*, **514**, 233 (1934); (c) W. E. Grigsby, J. Hind, J. Chanley, and F. W. Westheimer, *J. Am. Chem. Soc.*, **64**, 2606 (1942); (d) E. E. van Tamelen, *J. Am. Chem. Soc.* **73**, 3444 (1951).

trans - anti - 2 - (*p* - methoxyphenyl) - 5 - hydroxycyclopentaneacetic acid (IVa. R = H) in a ratio of 1:3, which we substantiated. In addition, we observed that *trans-anti*-2-(*m*-ethoxyphenyl)-5-hydroxycyclopentaneacetic acid (IVb. R = H) and *trans - anti* - 2 - (6 - methoxy - 2 - naphthyl) - 5 - hydroxycyclopentaneacetic acid (IVc. R = H) are likewise the major products of *trans*-2-(*m*-ethoxyphenyl)-5-oxocyclopentaneacetic acid (IIb) and *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid (IIc), respectively.

These results indicate that borohydride reduction of the keto function in II proceeds preferably from the more hindered side and is product development controlled.[6]

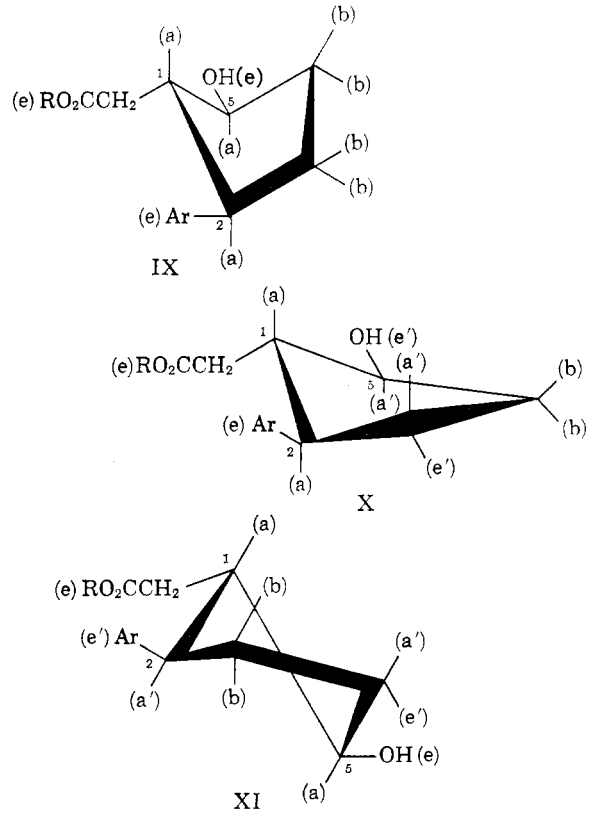
A priori the *trans-anti*-arrangement is more stable than the *trans-syn*-. In the former all three substituents are staggered while in the latter arrangement two of them eclipse one another when the planar structure is adopted for the cyclopentane ring.[7]

When *trans-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetic acid lactone (IIIc. R=H) is kept at 200° for eighteen hours in sodium ethoxide, conditions which promote equilibration of epimeric alcohols,[8] the *trans-anti*-hydroxy acid IVc (R = H) is obtained in 18% yield after acidification.

Although the *trans-syn*-lactone IIIc (R = H) is recovered in 26% yield, the results from a similar study with *cis-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetic acid lactone (VII) (*vide infra*) indicate the preponderant presence of IIIc (R = H) to be due to the failure of the reaction to attain the expected equilibrium under these conditions.

When the *cis-syn*-lactone VII is heated with sodium ethoxide and the reaction mixture worked up as before, the *trans-anti*-acid IVc (R = H) is isolated in 12% yield, the *cis-syn*-lactone VII is recovered in 38% yield and none of the *tran-syn*-lactone IIIc (R = H) is obtained. These results point to the greater stability of the *trans-anti*-arrangement relative to the *trans-syn*-.

CHART II



a = axial
a′ = pseudo-axial
e = equatorial
e′ = pseudo-equatorial
b = bisectional

The equilibration of epimeric alcohols involves an intermediate carbonyl compound.[8] In the alkaline medium the conjugate base of *cis*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid (VIII), the intermediate in the equilibration of the *cis-syn*-lactone VII, isomerizes to the conjugate base of the more stable *trans*-keto acid IIc, from which the *trans-anti*-acid IVc (R = H) is derived.

Although borohydride reduction of the keto acid II gives the hydroxy acid IV (R = H) as the major product, a Grignard or a Reformatsky[9] reaction yields a greater proportion of the lactone III (R ≠ H) and in several instances as the predominant product. While it is reasonable to attribute the apparent difference in the stereochemical course of addition to the greater bulk of the reacting Grignard and Reformatsky species relative to the borohydride entity and to conclude, therefore, that the Grignard and Reformatsky reactions, irrespective of whether or not a cyclic chelated intermediate[10] is involved in the mechanism, are steric approach controlled,[6] this interpretation is vitiated by the observation that the

(6) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(7) The greater stability of the *trans-anti*-arrangement in terms of potential energy can also be demonstrated when the ring is puckered [(a) J. G. Aston, H. L. Fink, and S. C. Schumann, *J. Am. Chem. Soc.*, **65**, 341 (1943); (b) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959); (c) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959)]. Of the several nonplanar conformations possible, the preferred ones, from the standpoint of minimized nonbonded interactions, are IX, X, and XI (see Chart II). In IX, the "C_S" (envelope) form, all three substituents are attached to equatorial bonds. In X and XI, the two "C_1" (half-chair) forms, two of the substituents are on equatorial bonds and the third is on a pseudo-equatorial bond. Inversion at C-5 of the *trans-anti*-arrangement to the *trans-syn*-arrangement would result in the hydroxyl group being on a less stable bond (axial in IX and XI and pseudo-axial in X).

(8) See W. von E. Doering, G. Cortes, and L. H. Knox, *J. Am. Chem. Soc.*, **69**, 1700 (1947); W. von E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, **71**, 838 (1949); **75**, 393 (1953) for a detailed discussion of the mechanism of the reaction and for leading references.

(9) The Reformatsky reaction with methyl bromoacetate was actually carried out on methyl *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetate (IIc, methyl ester) rather than on the acid IIc.

(10) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).

tertiary hydroxyl group at C-5 is extremely labile towards acid and because of the participation of the carboxyl group, isomerization readily occurs at C-5.

When *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneacetic acid (IVc. R = CH_3) is allowed to stand at room temperature for one hour in 3.6 *N* sulfuric acid, it is completely converted into *trans-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneacetic acid lactone (IIIc. R = CH_3). Hence, the lactone III (R ≠ H) may in part be formed from the hydroxy acid IV (R ≠ H) during the work-up of the Grignard and Reformatsky reactions and in the isolation of the products, and the extent of its formation cannot alone be adduced as evidence for the stereochemical course of addition of the Grignard and Reformatsky reagents to the keto function of the acids II and their esters.

Several years ago Bentley[11] reported that the reaction of ethyl 2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetate of unspecified configuration with lithium aluminum hydride gives a diol, m.p. 130°, in nearly 80% yield and that when this keto ester is treated with methylmagnesium iodide a trimethyldiol, m.p. 147°, is obtained.

Although neither the properties nor the manner in which it was prepared was described, it seemed likely to us that Bentley's keto-ester had the *trans*-configuration (IIc, ethyl ester). Our results suggested that his lithium aluminum hydride product had the *trans-anti*-configuration VIc (R = R′ = H) while the product from the Grignard reaction could have the *trans-syn*-configuration Vc (R = R′ = CH_3).

Subsequently, we found that *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneethanol (VIc. R = R′ = H) obtained from the lithium aluminum hydride reduction of methyl *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetate (IVc. R = H, methyl ester) melts at 135–137° while the *trans-syn*-diol Vc (R = R′ = H) prepared from the *trans-syn*-lactone IIIc (R = H) melts at 105–108°.

When methyl *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneacetate (IVc. R = CH_3, methyl ester) is treated with methylmagnesium bromide, *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentane-α,α-dimethylethanol (VIc. R = R′ = CH_3), m.p. 170–171°, is obtained. A similar reaction on the *trans-syn*-lactone IIIc (R = CH_3) gives the *trans-syn*-trimethyldiol Vc (R = R′ = CH_3), whose melting point of 169–171°, although nearly identical with that of the *trans-anti*-isomer, is markedly depressed when the two diols are admixed.

In an attempt to reproduce Bentley's trimethyldiol melting at 147°, we found that when methyl *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetate (IIc, methyl ester) is treated with methylmagnesium bromide, the *trans-syn*-trimethyldiol Vc (R = R′ = CH_3), identified by mixed melting point and a comparison of the infrared spectra, is obtained in 51% yield while none of the *trans-anti*-trimethyldiol VIc (R = R′ = CH_3) can be isolated. Assuming the *trans*-configuration for Bentley's starting keto ester, we are unable to explain the discrepancy in melting points of our product and that of Bentley.

In preparing *trans-syn*-2-(*p*-methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneethanol (Va. R = HC≡C, R′ = H), we observed that lithium aluminum hydride reduction of *trans-syn*-2-(*p*-methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneacetic acid lactone (IIIa. R = HC≡C) results also in the partial reduction of the triple bond, for the product is a mixture of *trans-syn*-2-(*p*-methoxyphenyl)-5-hydroxy-5-vinylcyclopentaneethanol (Va. R = H_2C=CH, R′ = H) and the desired *trans-syn*-ethynyldiol Va (R = HC≡C, R′ = H), in which the former predominates.

The presence of the vinyldiol in the mixture was established by a paper chromatography comparison[12] with an authentic sample prepared by the lithium aluminum hydride reduction of the *trans-syn*-vinyl lactone IIIa (R = H_2C=CH), which in turn is obtained from the ethynyl lactone IIIa (R = HC≡C) by hydrogenation. Reduction of IIIa (R = HC≡C) with sodium borohydride[13] instead gives the ethynyldiol Va (R = HC≡C, R′ = H) as the reduced product exclusively.

Since lithium aluminum hydride may partially reduce the ethynyl group of an ethynylcarbinol,[14] for the preparation of *trans-anti*-2-(*p*-methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneethanol (VIa. R = HC≡C, R′ = H) the hydroxyl group at C-5 of methyl *trans-anti*-2-(*p*-methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneacetate (IVa. R = HC≡C, methyl ester) was acetylated before reduction, which then proceeded to give the expected ethynyldiol VIa (R = HC≡C, R′ = H) in 76% yield.

Experimental[15]

2-(*m*-Ethoxyphenyl)-5-oxo-1-cyclopenteneacetic Acid (Ib).—The general procedure developed by Robinson[2a] was employed. *m*-Ethoxyacetophenone was condensed with 2-furaldehyde to afford in 89% yield 3-(2-furyl)-*m*-ethoxyacrylophenone as a viscous yellow liquid, b.p. 163–165° (0.25 mm.); $\lambda_{max}^{CH_3OH}$ 340 mμ (ε 22,700).

(11) K. W. Bentley, *J. Chem. Soc.*, 2398 (1955).

(12) We are indebted to Dr. E. G. Daskalakis and members of our paper chromatography staff for making the comparison.

(13) M. L. Wolfrom and H. B. Wood, *J. Am. Chem. Soc.*, **73**, 2933 (1951).

(14) R. Ahmad, F. Sondheimer, B. C. L. Weedon, and R. J. Woods, *J. Chem. Soc.*, 4089 (1952); N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956, p. 968.

(15) All compounds described in this paper which possess centers of asymmetry are racemic.

TABLE I

R = H

Starting Keto Acid	Products	% Yield	M.P.	Formula	Calcd. C	Calcd. H	Found C	Found H
IIa	IIIa	19[a]	140–140.5°[b]					
	IVa	75[c]	83.5–84.5°[d]					
IIb	IIIb	6	Oil, distilled at 170° (bath temp.), 0.1 mm.					
	IVb	60	96–97°	$C_{15}H_{20}O_4$	68.16	7.63	67.86	7.67
IIc	IIIc	13	177–182°	$C_{18}H_{18}O_3$	76.57	6.43	76.53	6.27
	IVc	61[e]	138–140°	$C_{18}H_{26}O_4$	71.98	6.71	71.88	6.77

[a] Yield of product melting at 135–139°. [b] Reported (ref. 4) m.p. 141–142°, yield 24%. [c] Consists of 69% of product melting at 80–84°, and 6% of product melting at 78–82.5°. [d] Reported (ref. 4) m.p. 86–87°, yield 73.6%. [e] Consists of 50% of product melting at 138–140° and 11% of less pure product.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.23; H, 6.09.

Acid cleavage of the furan ring gave in a yield of 54% crude 4,7-dioxo-7-(*m*-ethoxyphenyl)heptanoic acid, m.p. 80–84°, which crystallized from ethyl acetate–cyclohexane as light tan needles, m.p. 86.5–87°; $\lambda_{max}^{CH_3OH}$ 249 mμ (ε 8350).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.78; H, 6.69.

Cyclization of the diketoheptanoic acid afforded Ib, m.p. 93–95°, in quantitative yield. On crystallization from ether–carbon tetrachloride Ib was obtained as light brown prisms, m.p. 96–97°; $\lambda_{max}^{CH_3OH}$ 272 mμ (ε 16,300).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.23; H, 6.48.

***trans*-2-(*m*-Ethoxyphenyl)-5-oxocyclopentaneacetic Acid (IIb).**—A solution of 20.9 g. (0.08 mole) of Ib in 250 ml. of water containing 4.5 g. of potassium hydroxide was hydrogenated over 5 g. of 5% palladium-on-charcoal in a low pressure hydrogenation setup. After the calculated amount of hydrogen was absorbed over a period of 22 hr., the reaction mixture was freed of the catalyst by filtration and acidified. The resulting oil solidified on standing. The solid was collected, washed with water, and dried; yield 19.0 g. (90%), m.p. 88.5–90°. Crystallization from carbon tetrachloride–cyclohexane gave IIb as tan prisms, m.p. 89.5–90.5°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.91; H, 6.78.

Hydrogenation of Methyl 2-(6-Methoxy-2-naphthyl)-5-oxo-1-cyclopenteneacetate (Ic, Methyl Ester).[2b]—A solution of 87.5 g. (0.281 mole) of Ic (methyl ester) in 1 l. of anhydrous methanol was hydrogenated over 5 g. of 5% palladium-on-charcoal at 2.5 atm. and 70°. After 108% of the calculated amount of hydrogen was absorbed in 1.5 hr., the catalyst was removed by filtration. The filtrate was allowed to cool to room temperature, and a solution of sodium methoxide, prepared from 0.5 g. of sodium and 100 ml. of methanol, was added. In a short time crystallization began. The mixture was cooled to 0–5° after which the crystalline product was collected, washed with cold methanol, and dried; yield 73 g., m.p. 103–105°. Crystallization from acetone–hexane gave 68.5 g. (78%) of methyl *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetate (IIc, methyl ester), m.p. 106–107°.[16]

The methanolic filtrate was acidified with 36 *N* sulfuric acid and added to the acetone–hexane mother liquor. The resulting solution was concentrated under reduced pressure to 500 ml. After treatment with charcoal the solution was diluted with an equal volume of water, affording a gummy precipitate. The mixture was cooled to 0–5°, and the supernatant liquid was decanted. The gummy residue was dissolved in 250 ml. of benzene. The benzene solution was washed with water, dried over anhydrous sodium sulfate, and concentrated to *ca.* 100 ml. The solution was adsorbed on 500 g. of a silica gel column. The column was eluted with ethyl acetate in benzene. Elution with 2% ethyl acetate in benzene gave 0.40 g. of a product, which crystallized from hexane to yield 0.17 g. (0.2%) of methyl *cis*-2-(6-methoxy-2-naphthyl)cyclopentaneacetate, m.p. 80.4–81.2°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.47; H, 7.43. Found: C, 76.50; H, 7.32.

Continued elution with 2% ethyl acetate in benzene gave 4.5 g. of another product, which was crystallized from methanol to afford 3.2 g. (4%) of *cis-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetic acid lactone (VII), m.p. 138–142°. Recrystallization of VII from methanol raised the m.p. to 143–144°; infrared (chloroform): 5.62, 6.10, 6.22 μ.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.58; H, 6.43. Found: C, 76.79; H, 6.64.

Further elution of the column with 5% ethyl acetate in benzene gave after two crystallizations from methanol an additional 5.2 g. (6%) of the *trans*-keto ester IIc (methyl ester), m.p. 106–107°.

Sodium Borohydride Reduction of *trans*-2-(Alkoxyaryl)-5-oxocyclopentaneacetic Acid (II).—The reduction of each of the acids IIa, b, and c was carried out essentially in the following manner. To a solution of 4.00 g. of the acid II in 160 ml. of a 5% solution of sodium hydroxide was added 2.0 g. of sodium borohydride. The reaction mixture was stirred at room temperature for 15–18 hr. after which it was carefully decomposed with glacial acetic acid and acidified with 12 *N* hydrochloric acid. The acidified mixture was extracted with ether or ethyl acetate. The combined organic extracts were washed with water and then extracted with a 5% solution of sodium bicarbonate. The sodium bicarbonate extracts were acidified with 6 *N* hydrochloric acid to afford the crude *trans-anti*-2-(alkoxyaryl)-5-hydroxycyclopentaneacetic acid (IV. R = H). The organic phase was further washed with water and a satu-

(16) Koebner and Robinson (ref. 2b) reported that the hydrogenation of Ic (methyl ester) yields methyl 2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetate of unspecified configuration melting at 61–62°. Subsequently, they reported [*J. Chem. Soc.*, 566 (1941)] that this ester probably has the *cis*-configuration, for saponification of this ester and remethylation of the resulting acid, m.p. 147°, gives an isomeric ester, m.p. 101–102°, to which they assigned the *trans*-configuration as the probable configuration.

rated solution of sodium chloride, dried over anhydrous sodium sulfate, and evaporated or distilled to dryness under reduced pressure to yield the crude *trans-syn*-2-(alkoxyaryl)-5-hydroxycyclopentaneacetic acid lactone (III. R = H).

Conversion of IIIc (R = H) to IVc (R = H).—To a solution of sodium ethoxide prepared by dissolving 1.0 g. (0.0435 g.-atom) of sodium in 15 ml. of absolute ethanol was added 1.000 g. (0.00354 mole) of *trans-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetic acid lactone (IIIc. R = H), m.p. 178–182°. The reaction mixture was distilled to dryness under reduced pressure, and the residue was maintained at 200 ± 5° (bath temperature) at one atmosphere for 16 hr. Air was excluded from entering into the system by connecting the reaction vessel to a mercury trap.

The reaction mixture was diluted with water and acidified with 1.7 *N* hydrochloric acid. After it was cooled to 0–5°, the semisolid product was collected and washed with water. The semisolid turned into an oil on standing at room temperature. The oil was dissolved in ether. The ethereal solution was in turn extracted successively with water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solution was evaporated to dryness to afford 0.245 g. of a colorless crystalline product, m.p. 153–172°. It was crystallized from ethyl acetate to afford 0.111 g. (11%) of the *trans-syn*-lactone IIIc (R = H), m.p. 178.5–181.5°, undepressed when admixed with the starting material. From the mother liquor an additional 0.037 g. (4%) of IIIc, m.p. 172.5–181.5°, was obtained.

The combined bicarbonate extracts were acidified with 6 *N* hydrochloric acid. The resulting brown solid was collected, washed well with water, and dried; yield 0.544 g., m.p. *ca.* 64–95°. It was chromatographed on 20 g. of silica gel. Elution of the column with 10% ethyl acetate in benzene gave, after crystallization from ethyl acetate, 0.070 g. (7%) of the lactone IIIc (R = H), m.p. 181.5–186.5°, and 0.036 g. (4%) of the same lactone, m.p. 170–181.5°.

Further elution with 30–50% ethyl acetate in benzene gave 0.395 g. of a product, which was crystallized from ether–pentane to yield 0.187 g. (18%) of the *trans-anti*-acid IVc (R = H), m.p. 140.5–141.5°, undepressed when admixed with an authentic sample of IVc.

Conversion of VII to IVc (R = H).—The epimerization study with 1.000 g. (0.00354 mole) of *cis-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxycyclopentaneacetic acid lactone (VII), m.p. 141–142°, was carried out as described in the conversion of IIIc (R = H) to IVc (R = H).

The neutral (bicarbonate-insoluble) fraction was crystallized from methanol to yield 0.342 g. (34%) of the *cis-syn*-lactone (VII), m.p. 137–140°, undepressed when admixed with the starting lactone.

The combined bicarbonate extracts were cooled to 0–5° and acidified with 12 *N* hydrochloric acid. The resulting brown solid was collected, washed well with water, and dried; yield 0.352 g. It was chromatographed on 15 g. of silica gel. The column was eluted with 10% ethyl acetate in benzene to yield 0.037 g. of a solid, which according to paper chromatography analysis consisted of the *cis-syn*-lactone (VII) to the extent of *ca.* 95%.

Further elution of the column with 40% ethyl acetate in benzene gave 0.169 g. of a semisolid, which was crystallized from ether–pentane to yield 0.095 g. (9%) of the *trans-anti* acid IVc (R = H), m.p. 141–143°, whose structure was established through mixed m.p. and a comparison of infrared spectra. From the mother liquor an additional 0.028 g. (3%) of IVc (R = H), m.p. 137–143°, was obtained.

The presence of the *trans-syn*-lactone IIIc (R = H) in the reaction products could not be detected.

***trans-syn*-2-(*p*-Methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneacetic Acid Lactone (IIIa. R = HC≡C) and *trans-anti*-2-(*p*-methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneacetic Acid (IVa. R = HC≡C).**—One hundred fifty milliliters of tetrahydrofuran (purified by distillation from methylmagnesium bromide) was stirred and saturated with acetylene over a period of 1 hr. To the mixture was then added during the course of 2.5 hr. a solution of 150 ml. of 1 *M* ethylmagnesium bromide in tetrahydrofuran with continuous stirring and passage of acetylene. The reaction mixture was cooled in an ice bath, and while acetylene was continually being passed into the mixture, a solution of 4.00 g. (0.0161 mole) of the *trans*-keto acid IIa in 50 ml. of purified tetrahydrofuran was added over a period of 1 hr. After the addition funnel was rinsed with an additional 20 ml. of purified tetrahydrofuran, which was added to the reaction mixture, passage of acetylene was continued for an additional 2 hr. The reaction mixture was stirred and allowed to warm to room temperature over the course of 15 hr. Then it was concentrated under reduced pressure until a solid appeared. The residue was treated with *ca.* 100 ml. of 7 *N* sulfuric acid to dissolve the solid and then extracted with ether. The ethereal solution was in turn extracted with water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed by distillation under reduced pressure to afford 1.68 g. of a semiviscous brown oil, which was chromatographed on 60 g. of silica gel. Elution of the column with 1% ethyl acetate in benzene gave the *trans-syn*-ethynyl lactone IIIa (R = HC≡C), which crystallized from ether–pentane as slightly yellow, heavy plates, m.p. 69–70°; yield 0.74 g. (18%); infrared (potassium bromide): 3.07, 4.72, 5.64, 6.21, 6.33, and 8.07 μ.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.39; H, 6.18.

The combined bicarbonate extracts were acidified with 12 *N* hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure to yield 3.18 g. of a semiviscous yellow-brown oil, which was chromatographed on 80 g. of silica gel. Elution of the column with 5% ethyl acetate in benzene gave an additional 0.73 g. (18%) of the *trans-syn*-ethynyl lactone IIIa (R = HC≡C), m.p. 65–70.5°. Elution of the column with 10% ethyl acetate in benzene yielded 1.49 g. (34%) of the *trans-anti*-ethynyl acid IVa (R = HC≡C) as a colorless, viscous oil; infrared (chloroform): 2.84, 3.02, 5.72, 5.83, 6.20, 6.31 μ.

Methyl *trans*-*anti*-2-(*p*-Methoxyphenyl)-5-acetoxy-5-ethynylcyclopentaneacetate.—To a solution of 1.04 g. (0.0038 mole) of the aforementioned *trans-anti*-ethynyl acid IVa (R = HC ≡ C) in 10 ml. of ether, cooled in an ice bath, was added carefully 12 ml. of a chilled ethereal solution of diazomethane [prepared from 1.2 g. (0.0116 mole) of *N*-nitrosomethylurea].[17] The reaction mixture was maintained at 5° for 2.5 hr. and then evaporated to dryness to afford the methyl ester as a viscous yellow oil.

A 1.05-g. (0.00364 mole) sample of this oil was dissolved in 10 ml. of pyridine and 10 ml. (0.11 mole) of acetic anhydride and kept at 60° for 4 days. The brown reaction mixture was then poured into a mixture of ice and water. The resulting oil solidified on rubbing. The tan solid was collected, washed well with water, and dried. Crystallization from ether gave 0.79 g. (66%), m.p. 119.5–121.5°, and 0.10 g. (8%), m.p. 117–121°, of the acetoxy methyl ester.

The analytical sample of methyl *trans-anti*-2-(*p*-methoxyphenyl)-5-acetoxy-5-ethynylcyclopentaneacetate was obtained as colorless rhombs from ether–pentane, m.p. 121.5–124°; infrared (potassium bromide): 3.07, 4.73, 5.76, 6.21, 6.31, 8.03 μ.

(17) W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 38 (1942).

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.47; H, 6.90.

trans-syn-2-(*p*-Methoxyphenyl)-5-hydroxy-5-vinylcyclopentaneacetic Acid Lactone (IIIa. R = H_2C=CH).—A solution of 2.52 g. (0.0098 mole) of the ethynyl lactone IIIa (R = HC≡C) in 153 ml. of 95% ethanol containing 17 ml. of pyridine was hydrogenated over 1.3 g. of 5% palladium-on-calcium carbonate. After the calculated amount of hydrogen had been absorbed over a period of 1 hr., the catalyst was removed by filtration. The reaction mixture was evaporated to dryness, and the residual oil was dissolved in ether. The ethereal solution was in turn successively washed with 1.7 *N* hydrochloric acid, water, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solution was evaporated to dryness to yield the vinyl lactone IIIa (R = H_2C=CH) as a yellow-brown, viscous oil.

trans-syn-2-(6-Methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetic Acid Lactone (IIIc. R = HC≡C) and *trans-anti*-2-(6-Methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetic Acid (IVc. R = HC≡C).—The ethynylation of 20.00 g. (0.067 mole) of *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid (IIc) was carried out essentially as described for the *p*-methoxyphenyl series (*vide supra*) except proportionately larger quantities of reagents and solvents were employed. The neutral (bicarbonate-insoluble) fraction was chromatographed on 1 kg. of silica gel. Elution of the column with 2% ethyl acetate in benzene gave 8.20 g. (40%) of the ethynyl lactone IIIc (R = HC≡C) which melted at 87–95° after trituration with a slight amount of ether–pentane. The acid (bicarbonate-soluble) fraction was chromatographed on 1.7 kg. of silica gel. Elution of the column with 5% ethyl acetate gave an additional 3.10 g. (15%) of the ethynyl lactone IIIc (R = HC≡C), m.p. 71–84°. Further elution of the column with 15% ethyl acetate in benzene gave 7.07 g. (34%) of the ethynyl acid IVc (R = HC≡C) melting in the range of 124–129° and 132–136°.

The analytical sample of the lactone IIIc (R = HC≡C) was obtained after several crystallizations from ether–pentane, m.p. 92.5–94.5°; infrared (potassium bromide): 3.06, 4.72, 5.62, 6.12, 6.22 μ.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.79; H, 5.92.

The analytical sample of the acid IVc (R = HC≡C) was obtained as colorless, densely packed platelets, m.p. 133–135°; infrared (potassium bromide): 3.00, 5.79, 6.08, 6.18 μ.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.22; H, 6.10.

trans-syn-2-(*p*-Methoxyphenyl)-5-hydroxy-5-methylcyclopentaneacetic Acid Lactone (IIIa. R = CH_3) and *trans-anti*-2-(*p*-Methoxyphenyl)-5-hydroxy-5-methylcyclopentaneacetic Acid (IVa. R = CH_3).—To a stirred solution of 4.00 g. (0.0161 mole) of IIa in 200 ml. of anhydrous ether was added over a period of 15 min., 50 ml. of 0.72 *M* methylmagnesium bromide in ether. The reaction mixture was stirred at room temperature for 2.5 hr. and then decomposed with the successive addition of water and 1.7 *N* hydrochloric acid. The ethereal phase was separated and then extracted successively with 1.7 *N* hydrochloric acid, water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ethereal solution was distilled to dryness under reduced pressure to afford 0.411 g. (10%) of what is presumed to be the lactone IIIa (R = CH_3) exclusively.

The combined bicarbonate extracts were acidified with 6 *N* hydrochloric acid and extracted with ether. The ether extracts were combined and washed in succession with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure to yield a viscous oil. The oil was chromatographed on 150 g. of silica gel. Elution of the column with 5–10% ethyl acetate in benzene gave *ca.* 1.15 g. (29%) of lactone IIIa (R = CH_3), which after crystallization from ether–pentane amounted to 0.98 g. (25%), m.p. 59–62°.

Further elution of the column with 15–20% ethyl acetate in benzene gave after crystallization from ether–pentane 0.45 g. (11%) of IIa, m.p. 108.5–111°, undepressed when admixed with the starting ketoacid.

Elution of the column with 20% ethyl acetate in benzene gave IVa (R = CH_3), which was crystallized from ether–pentane to afford a total of 1.19 g. (28%) of the acid as colorless platelets melting in the range of 123.5–124.5° and 125.5–126.5°.

The analytical sample of the lactone IIIa (R = CH_3) was obtained as colorless, dense, massive crystals, m.p. 58.5–60°, from ether–pentane.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.31; H, 7.31.

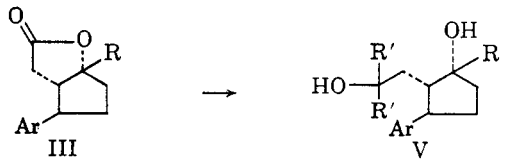
The analysis of the acid IVa (R = CH_3) was performed on the sample melting at 125.5–126.5°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.19; H, 8.05.

trans-syn-2-(6-Methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentane-acetic Acid Lactone (IIIc. R = CH_3) and *trans-anti*-2-(6-Methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneacetic Acid (IVc. R = CH_3).—To a solution of 20 ml. of 3 *M* methylmagnesium bromide in diethyl ether and 50 ml. of tetrahydrofuran stirred and heated under reflux was added over a period of 10 min. a solution of 5.00 g. (0.0168 mole) of *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid in 60 ml. of tetrahydrofuran. After the addition was complete, 40 ml. more of tetrahydrofuran was added to the reaction mixture. The ether was removed by distillation, and the reaction mixture was stirred and heated under reflux for 1 hr. Then it was decomposed with a large volume of water. The *p*H of the reaction mixture was adjusted to 8 with the addition of 1.7 *N* hydrochloric acid. The tetrahydrofuran was removed by distillation under reduced pressure. The residue was acidified with 1.7 *N* hydrochloric acid, resulting in the deposition of an oil. Upon the addition of ether to the mixture the oil solidified. The solid was collected, washed well with ether, and dried; yield 1.48 g., m.p. 170–176.5°. The solid exhibited characteristics of an acid; *e.g.*, it was soluble in a 5% sodium bicarbonate solution. It was dissolved in 20 ml. of methanol. To the solution was added 5 ml. of 6 *N* hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 2.5 hr. whereupon a crystalline product resulted. The solid was collected and washed with ether. It amounted to 0.42 g. (9%) and proved to be the *trans-syn*-lactone IIIc (R = CH_3), m.p. 128–134.5°. The filtrate was diluted with a large volume of water and extracted with ethyl acetate. The ethyl acetate extracts were in turn successively extracted with water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ethyl acetate solution was distilled to dryness under reduced pressure to afford a viscous brown oil. Crystallization of this oil from ether–pentane gave an additional 0.15 g. (3%) of IIIc (R = CH_3), m.p. 128–132°. The combined lactone IIIc (R = CH_3) was crystallized from ethyl acetate–pentane, yield 0.54 g., m.p. 132.5–134°.

The ethereal phase of the original filtrate from which the 170–176.5° solid was obtained was separated and then extracted successively with water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. It was then dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure. The residual oil was fractionally crystallized from ether to give 0.14 g. (3%) of the lactone IIIc, m.p. 129–133°, as the more soluble component. The less soluble component was recrystallized from acetone–pentane to yield 0.10 g. (3%) of a diol, m.p. 166–169°, undepressed when admixed with an authentic sample of *trans-syn*-2-(6-methoxy-2-naphthyl)-

TABLE II



a. Ar = *p*-methoxyphenyl
b. Ar = *m*-ethoxyphenyl
c. Ar = 6-methoxy-2-naphthyl

R′ = H

Starting Lactone		Product				Calcd.		Found	
	R		R	M.P.	Formula	C	H	C	H
IIIa	H	Va	H	100.5–102°	$C_{14}H_{20}O_3$	71.16	8.53	71.33	8.44
IIIb	H	Vb	H	101–101.5°	$C_{15}H_{22}O_3$	71.97	8.86	72.28	8.74
IIIc	H	Vc	H	105–108°	$C_{13}H_{22}O_3$	75.49	7.75	75.25	7.43
IIIa	CH_3	Va	CH_3	94.5–95°	$C_{15}H_{22}O_3$	71.97	8.86	72.06	8.69
IIIa	C_2H_5	Va	C_2H_5	87.5–88°	$C_{16}H_{24}O_3$	72.69	9.15	72.77	9.33
IIIa	HC≡C	Va	HC≡C (15%)	[a] Mixture, m.p. 69.5–80°					
		Va	H_2C=CH (85%)						
IIIa	H_2C=CH	Va	H_2C=CH	86–87°	$C_{16}H_{22}O_3$	73.25	8.46	73.57	8.54

[a] Proportion estimated from analysis of crude mixture by paper chromatography (see footnote 12).

5-hydroxy-5-methylcyclopentane-α,α-dimethylethanol (Vc. R = R′ = CH_3) (*vide infra*). From the acetone–pentane mother liquor an additional 0.06 g. (1%) of the lactone IIIc (R = CH_3), m.p. 131–135°, was obtained.

The combined bicarbonate extracts of the ethereal phase of the original filtrate were acidified with 6 *N* hydrochloric acid to yield a solid. The solid was collected, washed well with water, and dried; yield 1.70 g. It was chromatographed on 130 g. of silica gel. The column was eluted with ethyl acetate in benzene and afforded in succession the lactone IIIc (R = CH_3) [0.78 g. (16%) after crystallization from ethyl acetate–hexane, m.p. 135–136°], the starting keto acid IIc [0.04 g. (1%) after crystallization from ether, m.p. 142–145.5°, undepressed with authentic starting material], and the *trans-anti*-acid IVc (R = CH_3) [0.32 g. (6%) after crystallization from ethyl acetate–hexane, m.p. 157–158.5°].

The analysis of the lactone IIIc (R = CH_3) was performed on a sample melting at 131–133°; infrared (potassium bromide): 5.67, 6.13, 6.23 μ.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.07; H, 6.80. Found: C, 77.11; H, 6.79.

The acid IVc (R = CH_3) crystallized from ethyl acetate–hexane as colorless heavy platelets; infrared (chloroform): 2.68, 2.73, 2.83, 5.83, 6.09, 6.22 μ.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.96; H, 7.44.

Conversion of IVc (R = CH_3) to IIIc (R = CH_3).—A solution of 0.800 g. (0.00254 mole) of *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneacetic acid IVc (R = CH_3), m.p. 155–158.5°, in 27 ml. of tetrahydrofuran and 3 ml. of 36 *N* sulfuric acid was allowed to stand at room temperature for 1 hr. The orange reaction mixture was poured into a mixture of ice and water. The colorless solid was collected, washed well with water, and dried; yield 0.660 g. (88%), m.p. 125–129°.

Crystallization from ethyl acetate–hexane gave 0.627 g. (83%) of the *trans-syn*-lactone IIIc (R = CH_3), m.p. 132.5–134°, whose structure was unequivocally established by a comparison of its infrared spectrum with that of an authentic sample of IIIc (R = CH_3).

***trans-syn*-2-(*p*-Methoxyphenyl)-5-ethyl-5-hydroxycyclopentaneacetic Acid Lactone (IIIa. R = C_2H_5) and *trans-anti*-2-(*p*-Methoxyphenyl)-5-ethyl-5-hydroxycyclopentaneacetic Acid (IVa. R = C_2H_5).**—The synthesis of IIIa (R = C_2H_5) and IVa (R = C_2H_5) from 4.00 g. (0.0161 mole) of IIa was carried out in the same manner as described for the preparation of their lower homologs IIIa and IVa (R = CH_3), except that ethylmagnesium bromide was used in place of methylmagnesium bromide. The neutral (bicarbonate-insoluble) oil amounted to 0.94 g. [22%, assuming it consisted of the lactone IIIa (R = C_2H_5) exclusively].

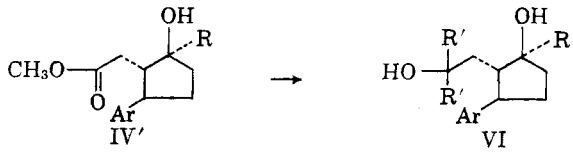
The acidic (bicarbonate-soluble) fraction was an oil, which was chromatographed on 160 g. of silica gel. Elution of the column with 5% ethyl acetate in benzene gave an additional 1.38 g. (33%) of the lactone IIIa (R = C_2H_5) as a viscous oil; infrared (chloroform): 5.66, 6.21, 6.32 μ. Elution of the column with 10% ethyl acetate in benzene gave 0.52 g. (13%) of the starting keto acid IIa, which after crystallization from ether–pentane amounted to 0.34 g., m.p. 107.5–109°, undepressed when admixed with the starting material. Continued elution of the column with 10% ethyl acetate in benzene yielded 0.50 g. (11%) of the acid IVa (R = C_2H_5) as a viscous oil.

***trans-syn*-2-(6-Methoxy-2-naphthyl)-5-hydroxy-5-methoxycarbomethylcyclopentaneacetic Acid Lactone (IIIc. R = $CH_3O_2CCH_2$) and Methyl *trans-anti*-2-(6-Methoxy-2-naphthyl)-5-hydroxy-5-methoxycarbomethylcyclopentaneacetate (IVc. R = $CH_3O_2CCH_2$, Methyl Ester).**—The procedure was essentially that described by Johnson, Christiansen, and Ireland.[18] A mixture of 4.00 g. (0.0153 mole) of methyl *trans*-2-(6-methoxy-2-naphthyl-5-oxocyclopentaneacetate (IIc, methyl ester), 2 ml. (*ca.* 0.02 mole) of methyl bromoacetate, 60 ml. of anhydrous ether, 60 ml. of anhydrous benzene, and 4 g. of 20 mesh zinc pellets (activated by treatment with 7 *N* hydrochloric acid) was stirred and heated under reflux for 11 hr. The reaction was initiated with the addition of small quantities of iodine. During the first 7 hr. an additional 3 ml. (*ca.* 0.03 mole) of methyl bromoacetate and 12 g. of the activated zinc pellets were added in three 1-ml. and three 4-g. portions, respectively. After the reaction mixture had stood at room temperature for 11 hr., it was acidified with glacial acetic acid. The solution was decanted from the residual zinc and diluted with ether. The ethereal solution was successively extracted with water, dilute ammonium hydroxide, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solution was distilled to dryness under reduced pressure to afford a viscous brown oil, which was chromatographed on 200 g. of silica gel.

The combined aqueous extracts were acidified with 6 *N* hydrochloric acid to yield 0.29 g. of a brown resin, which was not further investigated.

(18) W. S. Johnson, R. G. Christiansen, and R. E. Ireland, *J. Am. Chem. Soc.*, **79**, 1995 (1957).

TABLE III



a. Ar = *p*-methoxyphenyl
b. Ar = *m*-ethoxyphenyl
c. Ar = 6-methoxy-2-naphthyl

R′ = H

Starting Ester			Work-up Procedure	Product				Calcd.		Found	
	R	State			R	M.P.	Formula	C	H	C	H
IV'a	H	Oil	B	VIa	H	75–77.5°	$C_{14}H_{20}O_3$	71.16	8.53	71.29	8.72
IV'b	H	Oil	B	VIb	H	88–89°	$C_{14}H_{22}O_3$	71.97	8.86	72.19	8.68
IV'c	H	Solid, m.p. 73–77°	A	VIc	H	135–137°	$C_{18}H_{22}O_3$	75.49	7.75	75.50	7.45
IV'a	CH_3	Oil	A	VIa	CH_3	120–124.5°	$C_{15}H_{22}O_3$	71.97	8.86	72.41	8.82
IV'a	C_2H_5	Oil	A	VIa	C_2H_5	49–55°	$C_{16}H_{24}O_3$	72.69	9.15	72.55	9.29

Elution of the column with 10% ethyl acetate in benzene gave 2.50 g. (46%) of the lactone IIIc (R = $CH_3O_2CCH_2$), which after washing with ether amounted to 2.16 g., m.p. 99.5–101°. Several crystallizations from methanol raised the m.p. to 101.5–102.5°; infrared (potassium bromide): 5.63, 5.73, 6.10, 6.19, 8.05 μ.

Anal. Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.95; H, 5.93.

Continued elution of the column with 10% ethyl acetate in benzene gave 0.71 g. (18%) of the diester IVc (R = $CH_3O_2CCH_2$, methyl ester). A 0.41-g. sample of the diester was crystallized from ether, m.p. 136.5–137.5°; yield 0.14 g. Several more crystallizations of the diester from ether gave colorless laths, m.p. 142–143°; infrared (potassium bromide): 2.83, 5.75, 5.83, 6.10, 6.22, 8.30 μ.

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. Found: C, 68.29; H, 6.53.

Lithium Aluminum Hydride Reduction of the *trans-syn*-Lactones III.—The reduction was carried out by adding an ether or a tetrahydrofuran solution of the lactone to a mixture of lithium aluminum hydride in ether heated under reflux. The reaction mixture was heated under reflux for 2 hr., cooled, and decomposed with the alternate additions of water and 20% sodium hydroxide until a paste or a granular solid resulted.[19] The solution was decanted, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure to afford the crude diol V which was purified by crystallization.

Sodium Borohydride Reduction of *trans-syn*-2-(*p*-Methoxyphenyl) - 5 - ethynyl - 5 - hydroxycyclopentaneacetic Acid Lactone IIIa (R = HC≡C).—To a solution of 1.00 g. (0.00375 mole) of IIIa (R = HC≡C) in 20 ml. of isopropyl alcohol was added 1.00 g. (0.00264 mole) of sodium borohydride. The reaction mixture was stirred at room temperature for 15 hr. Then it was decomposed with the successive addition of glacial acetic acid, water, and 1.7 *N* hydrochloric acid. The acidified mixture was concentrated under reduced pressure to remove the alcohol. The residue was extracted with ether. The ethereal extracts in turn were washed with successive portions of water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ether solution was evaporated to dryness to afford 1.04 g. of a pale yellow oil. The oil was chromatographed on 30 g. of silica gel. Elution of the column with 3–5% ethyl acetate in benzene gave 0.22 g. (22%) of the starting lactone, which was crystallized from ether–pentane, m.p. 67–70°, undepressed when admixed with the starting material.

(19) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

Further elution of the column yielded 0.53 g. (52%) of the ethynyldiol, m.p. 79–81.5°. The analytical sample of *trans-syn*-2-(*p*-methoxyphenyl)-5-ethynyl-5-hydroxycyclopentaneethanol (Va. R = HC≡C, R′=H) was obtained as colorless stout needles and rods, m.p. 82.5–83.5°; infrared (potassium bromide): 2.95, 3.04, 6.19, 6.31 μ.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.75. Found: C, 74.01; H, 7.58.

Paper chromatography[12] indicated it was a homogeneous substance, uncontaminated with the vinyl lactone Va (R = H_2C=CH, R′=H).

Lithium Aluminum Hydride Reduction of *cis-syn*-2-(6 - Methoxy - 2 - naphthyl) - 5 - hydroxycyclopentaneacetic Acid Lactone (VII).—A solution of 1.00 g. (0.00354 mole) of the *cis-syn*-lactone VII in 25 ml. of tetrahydrofuran and 100 ml. of ether was added to a slurry of 0.20 g. (0.00527 mole) of lithium aluminum hydride in 50 ml. of ether. The reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 2 hr. The excess hydride was decomposed with ethanol, and the mixture was washed successively with 1.7 *N* hydrochloric acid, water, a 5% solution of sodium bicarbonate, and water again. After drying over anhydrous magnesium sulfate, the organic solution was evaporated to dryness. The residue was crystallized from benzene to yield 0.87 g. (85%) of *cis-syn*-2-(6-methoxy - 2 - naphthyl) - 5 - hydroxycyclopentaneethanol. The analytical sample melted at 171–172° after another crystallization from benzene.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.75. Found: C, 75.71; H, 7.72.

Lithium Aluminum Hydride Reduction of the *trans-anti*-Hydroxy Esters IV (Methyl Ester).—Each of the acids IV was methylated in the usual manner with diazomethane.[17] The methyl ester IV′ was reduced in ether with excess lithium aluminum hydride and the reaction mixture was freed of the inorganic products either by the alternate additions of water and a 20% solution of sodium hydroxide (procedure A)[19] or by extraction with dilute hydrochloric acid after prior decomposition with acetone and water (procedure B). After the ethereal solution was dried over anhydrous sodium sulfate, removal of the solvent gave the *trans-anti*-diol VI (R′=H), which was purified by crystallization.

Lithium Aluminum Hydride Reduction of Methyl *trans-anti* - 2 - (*p*- Methoxyphenyl) - 5 - acetoxy - 5 - ethynylcyclopentaneacetate.—A 0.25-g. (0.00075 mole) sample of the diester, m.p. 119.5–121.5°, was reduced with 0.40 g. (0.0106 mole) of lithium aluminum hydride in 85 ml. of anhydrous ether. The reaction mixture was worked up according to procedure A as described in the previous series of experiments. The crude diol was crystallized from ether–pentane to afford 0.15 g. (76%) of *trans-anti*-2-(*p*-methoxyphenyl)-

5-ethynyl-5-hydroxycyclopentaneethanol (VIa. R = HC≡C, R′ = H), m.p. 90–93°. Recrystallizations of VIa (R = HC ≡ C, R′ = H) from ether–pentane gave colorless plates, m.p. 97.5–99.5°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.75. Found: C, 74.03; H, 7.87.

***trans-anti*-2-(6-Methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentane-α,α-dimethylethanol (VIc. R = R′ = CH_3).**—To 10 ml. of 3 *M* methylmagnesium bromide in ether stirred and heated under reflux, was added a solution of methyl *trans-anti*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneacetate, prepared from 0.31 g. (0.000985 mole) of the corresponding acid IVc (R = CH_3), in 35 ml. of anhydrous ether. After the addition was complete, an additional 25 ml. of ether was added. The reaction mixture was stirred and heated under reflux for 3 hr. Then it was decomposed with the successive addition of water and 1.7 *N* hydrochloric acid. The ether phase was separated and washed successively with water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ether solution was concentrated to a small volume under reduced pressure. During the concentration, crystallization of the product began. The residue was cooled to 0–5°, and the diol was collected, m.p. 166–170°; yield 0.22 g. (68%). The analytical sample of the *trans-anti*-trimethyldiol VIc (R = R′ = CH_3) was obtained as colorless laths after two more crystallizations from ether, m.p. 170–171°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.32; H, 8.48.

***trans-syn*-2-(6-Methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentane-α,α-dimethylethanol (Vc. R = R′ = CH_3).**—To a solution of 35 ml. of 1 *M* methylmagnesium bromide in ether, stirred and heated under reflux, was added over a period of 5 min. a solution of 0.14 g. (0.000472 mole) of the *trans-syn*-lactone IIIc (R = CH_3) in 50 ml. of anhydrous ether. After the addition was complete, an additional 25 ml. of ether was added. The reaction mixture was stirred and heated under reflux for 5 hr. Then it was decomposed with the successive addition of water and 1.7 *N* hydrochloric acid. The ether phase was separated and extracted successively with water, a 5% solution of sodium hydroxide, water again, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ether solution was distilled to dryness under reduced pressure to yield a semisolid product. Crystallization of the semisolid from ether–pentane gave 0.13 g. (84%) of the *trans-syn*-trimethyldiol Vc (R = R′ = CH_3), m.p. 167–172°. The diol was further crystallized from acetone–pentane to afford colorless rhombs, m.p. 169–171°. Admixed with the *trans-anti*-trimethyldiol VIc (R = R′ = CH_3), it melted at 152–163°. Their infrared spectra were very dissimilar.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.55; H, 8.49.

Reaction of Methyl *trans*-2-(6-Methoxy-2-naphthyl)-5-oxocyclopentaneacetate (IIc, Methyl Ester) with Methylmagnesium Bromide.—To a solution of 70 ml. of 1 *M* methylmagnesium bromide in ether was added over a period of 15 min. a solution of 0.80 g. (0.00268 mole) of the keto ester IIc (methyl ester) in 100 ml. of anhydrous ether. After the addition was complete, an additional 100 ml. of ether was added. The reaction mixture was stirred and heated under reflux for 5 hr. Then it was decomposed with the successive addition of water and 1.7 *N* hydrochloric acid. The ether phase was separated and extracted successively with water, a 5% solution of sodium bicarbonate, water again, and a saturated solution of sodium chloride. The ether solution was dried over anhydrous sodium sulfate and then distilled to dryness under reduced pressure. The semisolid residue was crystallized from acetone–pentane to afford a total of 0.45 g. (51%) of *trans-syn*-2-(6-methoxy-2-naphthyl)-5-hydroxy-5-methylcyclopentaneethanol (Vc. R = R′ = CH_3) melting in the range of 165–167° to 168–170.5°. All fractions melting in this range had identical infrared spectra. The sample melting at 168–170.5° showed no depression in melting point when admixed with an authentic sample of the *trans-syn*-trimethyldiol Vc (R = R′ = CH_3). Their infrared spectra, determined in potassium bromide, were identical.

The presence of the epimeric *trans-anti*-trimethyldiol VIc (R = R′ = CH_3) in the reaction mixture could not be established.

Studies in the Total Synthesis of Steroids and Their Analogs. IV. Nonsteroid Mineralcorticoid Antagonists

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The syntheses of two substances, which are not related to the steroidal spirolactones, yet which are capable of blocking the effects of cortexone acetate in adrenalectomized rats, are described.

The isolation of aldosterone (I)[1] and the elucidation of its structure[2] have given rise to the hope that an approach based upon the competitive inhibition of this potent mineralcorticoid can be found to alleviate the edematous state of patients suffering from congestive heart failure, nephrosis, or cirrhosis of the liver. As a result of an intensive screening program, steroidal 17-spirolactones II were found to block the sodium-retaining effects of the mineralcorticoids.[3]

These spirolactones bear a superficial resemblance to aldosterone in that in both I and II a

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