solution gave a yellow powder which, on recrystallization from n-heptane, afforded 2.0 g. of yellow-orange III oxide, whose infrared spectrum was identical to that of a second quantity of product isolated below. Evaporation of the mother liquor gave a hydrated, orange viscous liquid (B).

Extraction of solid A with boiling isopropyl alcohol, followed by evaporation of the solvent gave more of B. Oils B were taken up in isopropyl alcohol, and the solution diluted with water to form a stable emulsion. The emulsion was allowed to stand for a period of up to several days, after which 3.0 g. of III oxide, in the form of orange needles, were collected on a filter. Recrystallization from n-heptane gave orange needles, m.p. 163–165°; combined yield 5.0 g. (13%).

Anal. Calcd. for $C_{22}H_{19}FeOP$: C, 68.42; H, 4.96; Fe, 14.46; P, 8.02. Found: C, 68.37; H, 4.96; Fe, 14.16; P, 8.03.

Methyl iodide was added to a sample of phosphine III dissolved in benzene. After several minutes, the methiodide settled out as an orange, hydrated oil, which lost water and solidified on standing. The product was taken up in boiling isopropyl alcohol, and the solution concentrated and allowed to cool to room temperature. Black products separated and were removed by filtration and discarded. Dark orange crystals grew in the filtrate on standing, m.p. 187–188° dec., soluble in hot water.

Anal. Calcd. for $C_{23}H_{22}FeIP$: C, 53.93; H, 4.33; Fe, 10.90; I, 24.78; P, 6.05. Found: C, 54.64; H, 4.73; Fe, 10.55; I, 24.48; P, 5.95.

Alternately, the methiodide could be precipitated from the benzene extract of the water-washed solids above, by the addition of methyl iodide. The product settled out as the hydrated oil which solidified on standing overnight, with loss of water.

Infrared Spectra of the Tertiary Ferrocenylphenylphosphines and Derivatives.—Infrared spectra were obtained from Nujol mulls employing a Perkin–Elmer, Model 321, spectrophotometer.

Phosphines II and III, and their oxides and methiodides all show absorptions in the regions, 1310–1320 cm.$^{-1}$ and 1015–1045 cm.$^{-1}$, which were assigned earlier[2] to the ferrocenyl–phosphorus group. (The former range is now extended to include 1305 cm.$^{-1}$.) In addition, all spectra show a sharp band at 1440 cm.$^{-1}$ attributable to phenyl–phosphorus,[8] and the usual absorptions near 1110 and 1005 cm.$^{-1}$ characteristic of monosubstituted ferrocenes.[9] The band near 1005 cm.$^{-1}$, however, is often indistinguishable from the second phenyl–phosphorus absorption expected to appear near the same frequency (995 cm.$^{-1}$).[8]

The following are also common to all spectra: ferrocene C—H and C—C stretching bands in the regions, 3060–3100 cm.$^{-1}$ and 1410–1430 cm.$^{-1}$, respectively, and out-of-plane C—H bending bands in the region 810–830 cm.$^{-1}$[10]; two phenyl bands, one near 750 cm.$^{-1}$, the other in the region, 680–700 cm.$^{-1}$.[11]

Absorptions at 1180 cm.$^{-1}$ and 1200 cm.$^{-1}$ in the spectra of diferrocenylphenylphosphine (II) oxide and ferrocenyldiphenylphosphine (III) oxide, respectively, are assigned to phosphoryl stretching.[12] The latter oxide thus absorbs at nearly the same frequency as "unbonded" phosphoryl in triphenylphosphine oxide[11,13,14]; the former practically at the same frequency recently suggested for solid triferrocenylphosphine oxide.[2]

Phosphines II and III, and their methiodides absorb near 1190 cm.$^{-1}$ and in addition, the phosphines show a characteristic band near 1160 cm.$^{-1}$, all possibly due to ferrocene in-plane C—H bending.[2]

The oxide and methiodide of ferrocenyldiphenylphosphine (III) both show a strong band in the region, 1116–1120 cm.$^{-1}$, which in the case of triphenylphosphine oxide has been attributed[13] to in-plane C—H deformation of the phenyl ring. It is interesting to note that the band is absent from the spectra of ferrocenyldiphenylphosphine as well as triphenylphosphine itself, and from the spectra of diferrocenylphenylphosphine (II), its oxide, and methiodide.

As in the case of triphenylphosphine oxide,[11] the P—C (phenyl) band appears near 720 cm.$^{-1}$ in the spectra of II and III oxides, but is absent from this region in the spectra of the parent phosphines.

Acknowledgment.—The authors thank the Victor Chemical Works, Division of Stauffer Chemical Co., for generous samples of phenylphosphonous dichloride and diphenylphosphinous chloride.

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[8] L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).

[9] M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

[10] E. R. Lippincott and R. D. Nelson, *ibid.*, **77**, 4990 (1955).

[11] A. L. Geddes, *J. Phys. Chem.*, **58**, 1062 (1954).

[12] In making these assignments, it has been necessary to consider the spectra of solutions of the ferrocenylphenyl derivatives because of complicating, multiple absorptions in the region 1150–1220 cm.$^{-1}$ (II oxide: 1213, 1202, 1192, 1180, 1157 cm.$^{-1}$; III oxide: 1200, 1187, 1164 cm.$^{-1}$). A future paper will deal with this in more detail.

[13] M. Halmann and S. Pinchas, *J. Chem. Soc.*, 3264 (1958).

[14] R. A. Zingaro and R. M. Hedges, *J. Phys. Chem.*, **65**, 1132 (1961).

Total Synthesis of 19-Norsteroids. I. *d,l*-Estrone Methyl Ether

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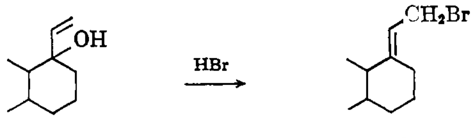
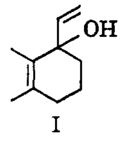
A four-step total synthesis of *d,l*-estrone methyl ether is described from 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol (II) and 2-methylcyclopentane-1,3-dione.

The base-catalyzed condensation of allyl bromides with cyclic β-diketones has been described by Nazarov and co-workers[1,2] and later by Newman and Manhart.[3] Cyclohexane-1,3-dione, 2-methylcyclohexane-1,3-dione, and 2-methylcyclopentane-1,3-dione have been used as the β-diketone component and various substituted allyl bromides as the alkylating agent.



Although a number of cyclic allylic bromides have been prepared from the readily available vinylcarbinols, Nazarov, Ananchenko, and Torgov[4] have found that bisvinylcarbinols of the type (I) described as intermediates for the synthesis of D-homo steroids, failed to yield the halides required for alkylation. These authors, however, succeeded in developing a new method for the synthesis of the desired steroid intermediates by condensing these bisvinylcarbinols directly with 2-methylcyclohexane-1,3-dione.[4] This



I

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[1] I. N. Nazarov, S. N. Ananchenko, and I. V. Torgov, *Zh. Obshch. Khim.*, **26**, 819 (1956).

[2] I. N. Nazarov, G. P. Verkholetova, S. N. Ananchenko, I. V. Torgov, and G. V. Aleksandrova, *ibid.*, **26**, 1482 (1956).

[3] Melvin S. Newman and Joseph H. Manhart, *J. Org. Chem.*, **26**, 2113 (1961).

[4] I. N. Nazarov, S. N. Ananchenko, and I. V. Torgov, *Izv. Akad. Nauk SSSR, Otd. Khim.*, 112 (1959).

novel, base-catalyzed condensation led to a series of compounds, which were key intermediates for the synthesis of *d,l*-D-homoestrone, which was subsequently converted into *d,l*-estrone.[5–7]

These considerations suggested a convenient four-step synthesis of *d,l*-estrone methyl ether and a three-step synthesis of *d,l*-8-isoestrone methyl ether from readily available starting materials.

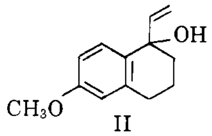
Triton B-catalyzed condensation of crude 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol II[8] with 2-methylcyclopentane-1,3-dione[9] afforded 2-(6-methoxy-1,2,3,4-tetrahydronaphthylideneethyl)-2-methylcyclopentane-1,3-dione (III) which on cyclization with *p*-toluenesulfonic acid in refluxing benzene, or more conveniently in formic acid at room temperature, afforded *d,l*-8,14-bisdehydroestrone methyl ether IV.[10] None of these products had to be purified by chromatography which is of advantage in view of their sensitivity.

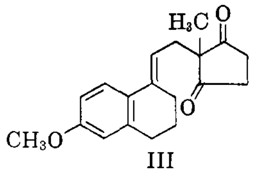
The smooth cyclization of III in formic acid prompted us to try to combine both the condensation and cyclization steps. However, reaction of II with formic acid in the presence of 2-methylcyclopentane-1,3-dione afforded only the dehydration product, the dimer of 3,4-dihydro-6-methoxy-1-vinylnaphthalene.

A similar reaction was observed by the Russian investigators who obtained this product from the vinylcarbinol and boron trifluoride.[7]

Compound IV is a key intermediate for the synthesis of 19-norsteroids. Its conversion to *d,l*-estrone methyl ether and *d,l*-8-isoestrone methyl ether has been described by Hughes and Smith.[11]

In our hands, partial hydrogenation[12] of IV with palladium on calcium carbonate in dioxane solution occurred extremely rapidly and pure *d,l*-8-dehydro-estrone methyl ether[10] could be crystallized directly from the reaction mixture. Reduction[11] with potassium in liquid ammonia retained the C-17 ketone essentially intact and afforded *d,l*-estrone methyl ether (VI).


II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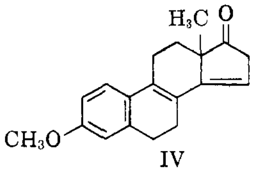
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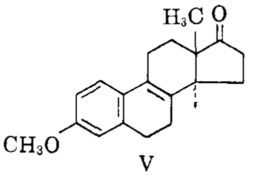
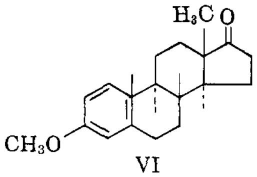
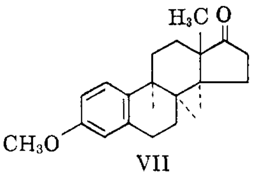

V


VI


VII

Complete hydrogenation of IV with palladium on charcoal, afforded *d,l*-8-isoestrone methyl ether.

Experimental

2-(6-Methoxy-1,2,3,4-tetrahydronaphthylideneethyl)-2-methylcyclopentane-1,3-dione (III).—A Grignard reagent was prepared from 6.70 g. of magnesium and 37 g. of vinyl bromide (commercial material from the Matheson Co.) using a total of 100 ml. of dry tetrahydrofuran.

This reagent reacted[8] with 13.40 g. of 6-methoxy-α-tetralone[13] dissolved in 25 ml. of tetrahydrofuran and 100 ml. of ether. The crude vinylcarbinol obtained (II) was dissolved in 53 ml. of xylene and 27 ml. of *t*-butyl alcohol, and 8.4 g. of 2-methylcyclopentane-1,3-dione was added. After stirring 15 min. at room temperature, 2.75 ml. of a 40% solution of Triton B in methanol was added and the mixture stirred and heated at the reflux temperature for 1.5 hr. After cooling, *ca.* 250 ml. of ether was added and the mixture stirred with cooling for 30 min. Some unchanged methylcyclopentanedione was separated by filtration and washed with ether. The combined ether filtrates were washed three times with a 5% potassium hydroxide solution and three times with water, dried over magnesium sulfate, and concentrated *in vacuo*. The oily residue was cooled overnight depositing 6.7 g. of crystalline material, m.p. 77–78°. One recrystallization from ethanol yielded 5.40 g. of 2-(6-methoxy-1,2,3,4-tetrahydronaphthylideneethyl)-2-methylcyclopentane-1,3-dione (III); m.p. 79–80°, ultraviolet $\lambda_{\max}^{\text{dioxane}}$ 268 mμ, ε 17,800; infrared in $CHCl_3$: two carbonyl peaks, 5.67 and 5.79 μ. The analytical sample was crystallized from ether–petroleum ether; m.p. 80°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.46; H, 7.40.

The combined filtrates were chromatographed on acid-washed alumina (225 g.). The eluates obtained from the fractions: benzene–petroleum benzene 4:6 to 6:4 yielded 3.75 g. of III, m.p. 79° after crystallization from ethanol. Total yield of III, calculated on the basis of methoxytetralone, was 40%.

d,l-**8,14-Bisdehydroestrone Methyl Ether (IV). Method A.**—A 24-mg. sample of *p*-toluenesulfonic acid was added to a solution of 500 mg. of III in 10 ml. of benzene. The flask was immersed in a hot oil bath and the mixture refluxed for 10 min. using a Dean–Stark water separator.

After cooling, the reaction product was washed first with a saturated bicarbonate solution, then with water, dried over magnesium sulfate, and treated with charcoal. The yellow solution which was obtained was concentrated *in vacuo*. On addition of ether, the residue crystallized. One recrystallization from ethanol, yielded 250 mg. of *d,l*-8,14-bisdehydroestrone methyl ether,[10] m.p. 112°; ultraviolet $\lambda_{\max}^{\text{dioxane}}$ 314 mμ, ε 28,900.

Method B.—A 5.45-g. sample of III was dissolved in 140 ml. of 98% formic acid and left standing for 3 hr. at room temperature. The greenish solution was then poured on an excess of ice and the crystalline product was filtered and washed liberally with water and small amounts of ice cold ethanol, which removed most of the colored by-products. After recrystallization from ethanol, *d,l*-8,14-bisdehydroestrone, methyl ether was obtained in approximately the same yield and quality as in the previous experiment.

d,l-**8-Dehydroestrone Methyl Ether** (V).—Hydrogenation of IV in dioxane solution in the presence of prereduced palladium-on-calcium carbonate catalyst, by the method of Hughes and Smith[11] afforded V by spontaneous crystallization from the filtered, concentrated reaction product. One recrystallization from ethyl acetate gave *d,l*-8-dehydroestrone methyl ether, m.p. 123°; ultraviolet $\lambda_{\max}^{\text{dioxane}}$ 280 mμ, ε 16,000; in nearly 50% yield. A further quantity of V could be obtained by chromatography of the filtrates.

d,l-**Estrone Methyl Ether** (VI).—Reduction[10] of V with potassium in liquid ammonia afforded *d,l*-estrone methyl ether in over 50% yield. Recrystallization from methanol gave a sam-

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[7] S. N. Ananchenko, Tao-Sen-Yeh, and I. V. Torgov, *Izv. Akad. Nauk SSSR, Otd. Khim.*, 298 (1962).

[8] I. N. Nazarov, I. V. Torgov, and G. P. Verkholetova, *Dokl. Akad. Nauk SSSR*, **112**, 1067 (1957).

[9] J. J. Panouse and C. S. Sannié, *Bull. soc. chim.*, 1036 (1955).

[10] H. Smith and G. A. Hughes, British Provisional Patent Applications 5.898/60 and 5.899/60.

[11] G. A. Hughes and H. Smith, *Chem. Ind.* (London), 1022 (1960).

[12] We wish to thank Dr. W. H. Jones and his associates for carrying out the hydrogenation experiments.

[13] G. Stork, *J. Am. Chem. Soc.*, **69**, 576 (1947).

ple with m.p. 142° which was characterized by comparing its infrared spectrum (in Chloroform solution) with the published[14] spectrum of *d,l*-estrone methyl ether and also with that of an authentic specimen of natural estrone methyl ether. All the spectra were found to be identical.

***d,l*-8-Isoestrone Methyl Ether (VII).**—Reduction[11] of IV in benzene solution with a palladium-on-charcoal catalyst afforded a 60% yield of *d,l*-8-isoestrone methyl ether, m.p. 151–152°, after filtration and crystallization from methanol. The infrared spectrum in chloroform solution of this compound was found to be identical with the published[14] spectrum.

Acknowledgment.—The authors wish to thank Mr. A. Kowalsky for the ultraviolet spectra, Mr. R. Walker for the infrared spectra, and Mr. R. Boos and his associates for the microanalyses.

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Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines. VII. The Preparation of Dihydroaromatics. A Comparison of the Lithium–Amine and Birch Reduction Systems

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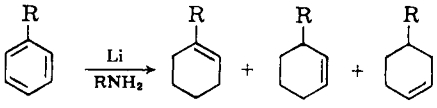
Four different aromatic compounds are reduced by lithium–methylamine–alcohol combinations as well as by sodium–ammonia–alcohol (Birch reduction). In each case unconjugated dienes (dihydroaromatics) are formed in comparable yields. Unlike the Birch method, wherein an excess of metal may be employed, it is shown that an excess of metal in the amine–alcohol system results in the formation of considerable amounts of monoölefins rather than dihydro products. Apparently the alcohol cannot prevent isomerization of the unconjugated dihydro products to conjugated dienes entirely under these circumstances. It is shown that at least two equivalents of water (based on aromatic) can be tolerated in the lithium–amine reduction of cumene. The reduction of both the aromatic and its diene intermediates is so rapid in this system that these organic materials compete successfully for electrons with the hydrogen of the water molecules.

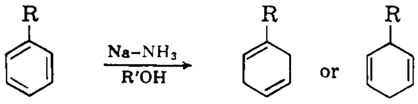
The blue solution which is formed by dissolving lithium in certain low molecular weight aliphatic amines is a potent reducing agent for aromatic ring systems.[1] The lithium–amine combination is presently the most convenient reagent for reducing an aromatic compound selectively to a monoölefin. When four equivalents of metal are used, a monosubstituted aromatic compound is reduced selectively to a mixture of the 1-, 3-, and 4-substituted olefins as shown in reaction 1. The 1-olefin usually predominates in the mixture, but the 3- and 4-isomers are formed in appreciable quantities. When a large excess of lithium is employed (*e.g.*, 6–8 equivalents based on aromatic compound) the 3- and 4-substituted olefins are reduced further in preference to the 1-isomer, and the 1-substituted olefin is obtained principally, admixed with completely saturated cyclohexanes.[1]



(1)

In order to increase the usefulness of the lithium–amine reducing agent in organic syntheses, it was deemed desirable to devise procedures whereby the selectivity of the reduction could be increased. It was found that this could be achieved quite successfully by the judicious choice of various solvent combinations for the reductions. In this paper we are reporting the effects of water and alcohols on the course of the reduction.

In an elegant series of papers by Birch[2] and his collaborators, it was shown that many aromatic ring systems could be reduced by a sodium–ammonia–alcohol combination to dihydro aromatics (reaction 2). This procedure was later modified by Wilds and Nelson[3] such that lithium was used instead of sodium and the addition of alcohol to the reaction was delayed.



(2)

We have found that, in the presence of alcohol,[4] the lithium–amine combination can be used quite successfully to form dihydro aromatics. A detailed study of the reduction of four different compounds was made, in which the Birch procedure (sodium–ammonia–alcohol) was compared with the newly discovered lithium–amine–alcohol combination. As will be noted in Table I, the results obtained by the two methods are quite comparable. Actually there are advantages to both procedures. The higher boiling methylamine makes for greater ease of handling than does liquid ammonia, and is to be recommended from this standpoint. However, as Table I indicates, the Birch method gives slightly higher yields of 2,5-dihydro products in some cases. There are probably at least two reasons for this. The sodium–ammonia–alcohol system is not capable of reducing an unconjugated double bond except in certain isolated circumstances.[5] The same is not true of the lithium–amine system,[6] which is capable of 1,2-reductions of olefins. Hence, with excess metal, the 2,5-dihydro products can suffer a slow reduction of one double bond in the lithium–amine system, thereby form-

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[1] R. A. Benkeser, J. J. Hazdra, R. F. Lambert, and P. W. Ryan, *J. Org. Chem.*, **24**, 854 (1959), and previous papers in this series.

[2] See A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); **12**, 17 (1958), for pertinent references.

[3] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

[4] We have yet to assess the importance of the kind of alcohol used in conjunction with the lithium and amine. Thus far we have employed ethanol, isopropyl alcohol and *t*-butyl alcohol indiscriminately. A detailed study of this point is presently underway.

[5] T. J. King, *J. Chem. Soc.*, 898 (1951).

[6] R. A. Benkeser, G. Schroll, and D. M. Sauve, *J. Am. Chem. Soc.*, **77**, 3378 (1955).