Table I. Oxidosteroid Ring Opening by Dichlorobis(benzonitrile)palladium(II) in Benzene

starting compd	registry no.	chlorohydrin	registry no.	mp, °C found	mp, °C lit.	yield, %
(I) 2α,3α-oxido-5α-cholestane	1753-61-3	2β-Cl, 3α-OH	14287-32-2	120	120[6]	95
(II) 3-acetoxy-5α,6-oxido-5α-cholestane	68974-60-7	6β-Cl, 5α-OH	68974-63-0	188	189[12]	90
(III) 3-acetoxy-5β,6-oxido-5β-cholestane	68974-61-8	5α-Cl, 6β-OH	68974-64-1	197	196[13]	95
(IV) 3-acetoxy-5α,6-oxido-5α-androstan-17-one	68974-62-9	6β-Cl, 5α-OH	68974-65-2	204	205[14]	90
(V) 17β-acetoxy-4α,5-oxido-5α-androstan-3-one	5178-01-8	4β-Cl, 5α-OH	68950-33-4	202	204[15]	85
(VI) 4β,5-oxido-5β-cholestan-3-one	1975-34-4	4α-Cl, 5β-OH	68950-34-5	137–139		90
(VII) 4ξ,5ξ-oxidopregnane-3,20-dione		4α-Cl, 5β-OH	68950-35-6	143–144		95
(VIII) 17β-hydroxy-4β,5-oxido-5β-androstan-3-one	2189-83-5	4α-Cl, 5β-OH	68950-36-7	181–182		90

behavior of Grignard reagents).[7,8] Other reagents such as CrO_2Cl_2 and $TiCl_2$ open the oxirane ring to give the corresponding alkene.[9]

The use of $Pd(PhCN)_2Cl_2$ is particularly valuable in the opening of 4,5-oxido-3-ketosteroids. 17β-Acetoxy-4α,5-oxido-5α-androstan-3-one (V), 4β,5-oxido-5β-cholestan-3-one (VI), 4ξ,5ξ-oxidopregnane-3,20-dione (VII), and 17β-hydroxy-4β,5-oxido-5β-androstan-3-one (VIII) are reported to react with hydrochloric acid in acetone to give the corresponding 4-halo-4-ene-3-keto derivatives through the rapid (especially for VII and VIII) elimination of water from the initially formed halohydrins.[10,11] Camerino et al. found that isolation of the halohydrins from oxides VII and VIII by the use of HCl was unsuccessful also under controlled conditions.[16]

In the reactions promoted by dichlorobis(benzonitrile)-palladium(II), only the expected 4-chloro-5-hydroxy-3-keto compounds were isolated in excellent yields (Table I). In the opening of 4,5-oxidopregnane-3,20-dione, two halohydrins were isolated, the 4α-chloro-5β-hydroxypregnane-3,20-dione as major product (80%) together with 4β-chloro-5α-hydroxypregnan-3,20-dione (20%). This result is in agreement with the view that the epoxide from progesterone is a mixture of isomers with the β form predominating.[11] The NMR spectrum of this mixture suggests that the two oxides are in a ratio of 4:1.

In conclusion, it appears that owing to the mild reaction conditions, the quantitative yields, and the general interest toward the halogenated steroidic hormones, dichlorobis-(benzonitrile)palladium(II) may be usefully employed in the opening of oxidosteroids containing acid-sensitive functions.

Experimental Section

The steroid epoxides were prepared by the literature methods and characterized by infrared and NMR spectra and melting points. Dichlorobis(benzonitrile)palladium(II) was prepared by the method of Kharasch.[17]

The standard procedure for the preparation of the steroid halohydrins was as follows. The epoxide and coordination compound (2-mmol amounts) were allowed to react in 6 mL of benzene for 8–10 h. The mixture was then hydrolyzed with water and extracted with ether. The aqueous phase was evaporated to dryness to recover the palladium salt. The evaporated ether extracts were chromatographed on a SiO_2 column by eluting with 1:4 hexane–ether. For compound III, the experimental conditions (1 day, 25 °C) were found to be important for a quantitative yield owing to the decomposition of the reaction product.

The reaction products were characterized by IR and NMR spectra, which were found to be in agreement with the reported configurations. Halohydrins VI–VIII gave satisfactory elemental analyses (±0.2% for C and H).

Registry No.—4β,5β-Oxidopregnane-3,20-dione, 17597-24-9; 4α,5α-oxidopregnane-3,20-dione, 17503-05-8; dichlorobis(benzonitrile)palladium(II), 14220-64-5.

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Alkylation of Styrylacetic Acid Systems Using Lithium Diisopropylamide–Hexamethylphosphoramide. Effect of Temperature Variation

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In connection with a program directed toward the study of hypocholesteremic agents containing a styrylacetic acid system, we became interested in the potential utility of the lithium diisopropylamide–hexamethylphosphoramide (LDA–HMPA) complex for the preparation of certain α-methylated derivatives. We had previously attempted to prepare (*E*)-2,3-dimethyl-4-phenyl-3-butenoic acid (1) by dehydration and saponification of the corresponding β-hydroxy ester (Reformatsky product). This procedure, however, led to a complex mixture of isomeric olefins, **2** (apparently containing all five of the possible isomers), from which we were unable to isolate **1** in pure form although it was the major isomer present. We therefore became interested in possible methods for isomerizing the double bond exclusively into the β,γ position.

It had been previously reported that in the anions derived from α,β- or β,γ-unsaturated aliphatic esters[1] and the dianions of the corresponding acids[2] the charge is predominantly localized at the α position, and electrophilic reagents (e.g., H^+

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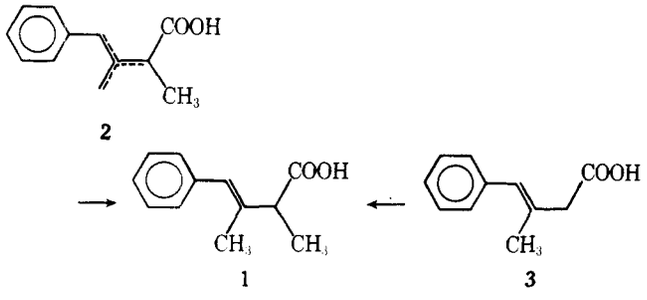
and RX) react nearly exclusively at this position, producing little or none of the isomeric products expected from attack at the γ position. Kende and co-workers[3] studied the effect of the presence of a sulfur atom on the γ position of γ,β-unsaturated carbonyl systems and again found that mono- and dialkylation occurred exclusively at the α position. Apparently, the inductive effect of the heteroatom did not significantly shift the localization of charge in the anion away from the α position. It was anticipated that selectivity for attack at the α position might, however, be reduced by the presence of the aromatic ring on the γ carbon, which could stabilize a negative charge at the position by a resonance effect and might enhance delocalization. This report describes the effect of a phenyl substitutent at the γ position and the possibility of incorporation of the charge into an aromatic system as well as the influence of temperature variation on the regioselectivity of the alkylation. Such an investigation was considered to be of importance in more clearly defining the scope of this synthetic tool. As an initial exploration into this question, we decided to apply this technique to our mixture of olefinic acids.

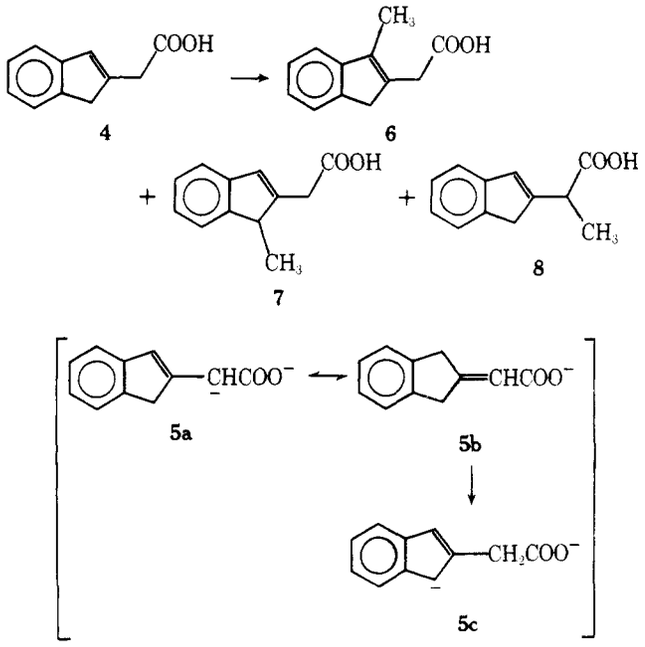
The mixture was first treated with KO-*t*-Bu and HO-*t*-Bu–Me_2SO (2:1) in order to isomerize the nonconjugated olefin.[4] Treatment of the resulting mixture of olefins in which the double bond was conjugated with either the phenyl ring or carboxyl group with 2 equiv of the LDA–HMPA complex at −5 to 0 °C followed by quenching with dilute HCl after 30–40 min afforded a mixture consisting of 85–90% **1** (NMR analysis) along with small amounts of the nonconjugated olefin and what appeared to be the *Z* isomer of **1**.



Approximately the same mixture was obtained by treatment of **3** with 2 equiv of LDA–HMPA followed by addition of MeI at −30 °C. We were unable to detect (NMR analysis) any compounds produced as a result of alkylation at the benzylic position in this mixture or in the product obtained by repeating the methylation procedure a second time (producing the known 2,2,3-trimethyl derivative[4]). These results suggest that the presence of the aromatic ring at the γ position does not substantially effect the nature of the dianion system and that, as suggested by Pfeffer and Silbert,[2] the negative charge is not delocalized by the π-bond system.

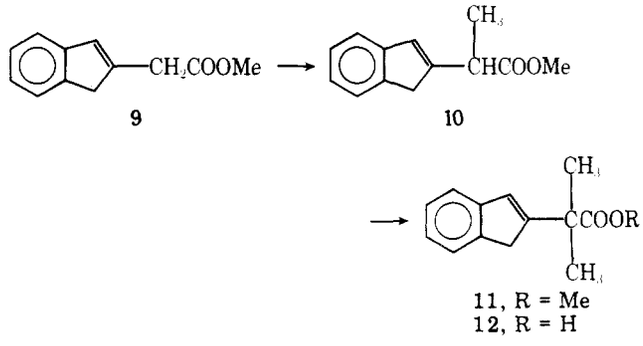
In order to further examine the apparent resistance of the α-anion toward delocalization, we applied the reaction to indenyl-2-acetic acid (**4**) and some interesting results were observed which were not readily predictable on the basis of previous studies on this reaction. It was rationalized that if a sufficient degree of delocalization were present in dianion **5**, an isomerization might occur such that the charge would be located in an aromatic system, **5c**, and reaction would necessarily occur in the γ position (i.e., ring methylation). Alternatively, initial proton abstraction could conceivably occur to give **5c** directly (however, see below).

Reactions were then conducted using 2 equiv of LDA–HMPA at three temperatures. At −5 to 0 °C the major product (~75% of the crude mixture based on NMR analysis) of the reaction was **6**,[5] apparently arising by alkylation of **5c** and subsequent double-bond migration. At −30 to −35 °C a mixture was obtained which appeared to be composed of



primarily **7**[6] and **8** with a smaller amount of **6**. At −78 °C the major product (>75%) was **8**, although significant amounts of **6** and **7** were also present. The decreasing extent of products resulting from ring alkylation as the temperature is lowered indicates that **5c** probably arises by isomerization of the initially formed α-anion rather than direct abstraction of a ring proton.

Based on the assumption that the monoanion generated by reaction of 1 equiv of LDA–HMPA with an ester of **4** should have less tendency to isomerize, we subjected methyl ester **9** to the methylation conditions. At either −30 or −78 °C, near quantitative yields of **10** were obtained. A second alkylation



(−30 °C) afforded the *gem*-dimentyl homologue **11**, which has hydrolyzed (HOAc–concentrated HCl, 4:1) to give **12** in about 75% overall yield from **9**. These results further emphasize the marked tendency for nondelocalization in α-anions of carboxylate systems, but they also demonstrate that selectivity for electrophilic addition to this position is also dependent upon the temperature of the reaction and the character of the γ position.

Experimental Section[7]

General Procedure. Diisopropylamine (1.0 equiv) in an amount of dry THF to provide a final concentration of ~1 M was placed in a four-neck round-bottom flask equipped with a low temperature thermometer, mechanical stirrer, addition funnel, reflux condenser, and $CaCl_2$ drying tube. The whole apparatus was previously flame-dried and cooled to dry nitrogen. The internal temperature was

maintained by use of an appropriate cooling bath: 0 to −5 °C in an ice–salt bath, −30 to −35 °C in a CH_3CN–liquid N_2 slush bath,[8] and −78 °C in a dry ice–acetone bath. *n*-Butyllithium (1.0 equiv)[9] in hexane was placed in the addition funnel via syringe and added dropwise to the reaction mixture followed by addition of HMPA (1.1 equiv). The mixture was stirred for 30–40 min, and a THF solution of the unsaturated acid (0.5 equiv) or unsaturated ester (1.0 equiv) was added dropwise over 10 min. The resulting mixture was stirred for an additional 10 min followed by the addition of MeI (1.0 equiv). After being stirred for 30 min, the mixture was allowed to warm to −10 °C and was quenched by the addition of water. The resulting mixture was acidified with dilute HCl and extracted with Et_2O. The combined Et_2O extracts were washed with saturated NaCl, dried (Na_2SO_4), and evaporated to give the crude product.

3-Methylindene-2-acetic Acid (6). 2-Indeneacetic acid[10] (0.96 g, 5.5 mmol) was methylated as described above at 0 to −5 °C, affording 0.80 g (79%) of a mixutre of methylated products as described in the text. Two recrystallizations from hexane afforded an analytical material: mp 113–115 °C; NMR ($CDCl_3$) δ 2.02 (3, m, CH_3), 3.41 (4, m, $2CH_2$), 7.18 (4, m, aromatic), 9.70 (1, s, COOH).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.72; H, 6.51.

α-Methyl-2-indeneacetic Acid (8). 2-Indeneacetic acid (3.0 g, 17.2 mmol) was treated according to the general procedure at −78 °C, affording 3.1 g (96%) of a yellow oil which solidified on standing. Recrystallization from hexane after treatment with charcoal afforded an analytical sample: mp 104–106 °C (lit.[10] mp 106–106.5 °C); NMR ($CDCl_3$) δ 1.43 (3, d, J = 7 Hz, CH_3), 3.38 (2, s, CH_2), 3.54 (1, q, J = 7 Hz, CH), 6.69 (1, s, vinyl H), 7.25 (4, m, aromatic), 11.0 (1, s, COOH).

α,α-Dimethyl-2-indeneacetic Acid (12). Ester **9**[10] (1.0 g, 5.3 mmol) was treated according to the general procedure twice in succession. The resulting yellow oil (1.02 g) was then heated at gentle reflux for 16 h in 20 mL of a 4:1 mixture of HOAc and concentrated HCl. The resulting mixture was cooled to ambient temperature, poured onto ice, and filtered when the ice had melted, affording 0.77 g (72%) of crude acid after vacuum drying. Three recrystallizations from hexane afforded an analytical sample: mp 143–146 °C; NMR ($CDCl_3$) δ 1.57 (6, s, $2CH_3$), 3.49 (2, s, CH_2), 6.78 (1, s, vinyl H), 7.05–7.55 (4, m, aromatic), 10.5 (1, br s, COOH).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.25; H, 7.00.

Registry No.—**4,** 57932-05-5; **6,** 69381-20-0; **7,** 69381-21-1; **8,** 24040-29-7; **9,** 24040-30-0; **10,** 24040-28-6; **11,** 69381-22-2; **12,** 69381-23-3.

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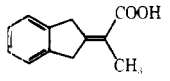

i

in HO-*t*-Bu–Me_2SO, as would be anticipated from results obtained with the phenylbutenoic acids.
(6) The presence of **7** in the reaction product mixture was assigned on the basis of the NMR spectrum. After substraction for spectral characteristics equivalent to those for **6** and **8,** an additional doublet was seen at δ 1.73 and the total integration of the methyl region (δ 2.5–1.0) was found to be equivalent to about three protons relative to the aromatic and downfield (acid) protons. The total integration of the vinyl resonance and the region from δ 3.0 to 4.2 was four protons with the vinyl region (broad singlet) accounting for about 0.75 proton.
(7) Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. NMR spectra were recorded with a Hitachi Perkin-Elmer Model R-24 spectrometer, using Me_4Si as an internal standard.
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Alkyl Nitrite–Metal Halide Deamination Reactions. 6. Direct Synthesis of Arenediazonium Tetrafluoroborate Salts from Aromatic Amines, *tert*-Butyl Nitrite, and Boron Trifluoride Etherate in Anhydrous Media

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Arenediazonium tetrafluoroborate salts have been prepared by a wide variety of methods.[3] The most commonly employed procedures involve diazotization of aromatic amines with sodium nitrite in 40–50% aqueous fluoroboric acid[4] or diazotization in aqueous hydrochloric or sulfuric acid followed by addition of sodium tetrafluoroborate or fluoroboric acid to precipitate the arenediazonium tetrafluoroborate salt.[5] Although these procedures generally give good yields of water-insoluble diazonium salts, a large excess of fluoroboric acid or sodium tetrafluoroborate is required to precipitate the tetrafluoroborate salts and the process for obtaining the anhydrous salt is laborious. In addition, aromatic amines that do not dissolve in aqueous mineral acid are not amenable to these procedures. In these instances, alternate processes that employ either sodium nitrite in concentrated acids[6] or nitrosonium tetrafluoroborate in anhydrous solvents[7] have been advanced. Modified procedures for the preparation of arenediazonium tetrafluoroborates that are appreciably soluble in water have also been described.[8]

We have recently reported that nitrosyl chloride and nitrosyl bromide are formed by an efficient halide–alkoxide exchange between titanium tetrahalides and alkyl nitrites.[1] Although titanium tetrafluoride is unreactive with alkyl nitrites, boron trifluoride is not similarly limited and when combined with alkyl nitrites provides convenient access to nitrosyl fluoride. When in situ generated nitrosyl fluoride is produced in the presence of an aromatic amine and excess boron trifluoride, arenediazonium tetrafluoroborate salts are formed in high yield (eq 1).

$$ArNH_2 \xrightarrow[BF_3]{RONO} ArN_2^+BF_4^- \qquad (1)$$

The diazotization reactions are performed under mild conditions in an anhydrous solvent, usually methylene chloride. Excess boron trifluoride, employed as the conveniently handled etherate complex, traps the alcohol and water produced in this diazotization procedure, and the arenediazonium tetrafluoroborates precipitate from the reaction solution as they are formed. The anhydrous tetrafluoroborate salts are obtained following simple filtration (Table I). The physical (decomposition temperature) and spectral (^1H NMR and IR) characteristics of the isolated salts are consistent with those previously reported in the literature.[3,9,10]

As seen from the yield data for isolated diazonium salts in Table I, the use of methylene chloride has significant yield advantages over other solvents. Ethers are susceptible to hydride abstraction by nitrosonium tetrafluoroborate,[11] and although their use as solvents for the preparation of arenediazonium tetrafluoroborate salts under aqueous conditions has been shown to improve the yields and purity of these salts,[8a] the present results do not indicate any unique advantage of ether solvents over methylene chloride in reactions performed under anhydrous conditions. However, amines such as the aminobenzoic acids that are insoluble in methylene chloride are preferably diazotized in the more polar ether solvents, and the isolated yields of the resulting arenediazonium tetrafluoroborate salts are superior to those reported

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