flux in toluene (250 ml). Water was removed azeotropically and after 23 hr the theoretical amount had been collected. The reaction was cooled to room temperature and the crystalline precipitate of **21** (18.0 g) was removed by filtration. Additional **21** (6.9 g) was obtained by concentration of the filtrate. An analytical sample was obtained by recrystallization from acetone–water and then from ethyl acetate: mp 192–194°; ir (Nujol) 1600 cm^{-1} (strong); nmr [$(CD_3)_2SO$] δ 8.10 (s, 1, vinyl H), 8.15–7.85 (m, 2, ortho ArH), 7.75–7.45 (m, 3, ArH), 4.28–4.05 (narrow m, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_{10}H_{10}O_4S_2$: C, 46.50; H, 3.91. Found: C, 46.43; H, 3.87.

2,3-Dihydro-5-phenyl-*p*-dithiin 1,1,4,4-Tetroxide (22).—2,3-Dihydro-5-phenyl-*p*-dithiin[19] (1.80 g, 0.0093 mol) was dissolved in ethyl acetate (50 ml) and the solution was cooled to 5°. Monoperphthalic acid (0.041 mol) in ether (120 ml) was added and the reaction mixture was warmed to room temperature and allowed to react for 22 hr. The solvent was removed under reduced pressure and the solid residue was washed with 5% sodium bicarbonate solution (3 × 50 ml) and then water. The residue was chromatographed on silica gel. Elution with ethyl acetate gave 0.80 g (33%) of **22**. Recrystallization from propanol gave an analytical sample: mp 205–206°; nmr [$(CD_3)_2SO$] δ 7.70–7.40 (narrow m, 6, 5 ArH, vinyl H), 4.42 (s, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_{10}H_{10}O_4S_2$: C, 46.50; H, 3.91; S, 24.83. Found: C, 46.70; H, 3.78; S, 24.56.

Reaction of α,α-Dipiperidinotoluene with Bis(ethylsulfonyl)methane.—α,α-Dipiperidinotoluene[25] (6.45 g, 0.025 mol), bis(ethylsulfonyl)methane (5.0 g, 0.025 mol), and glacial acetic acid (0.1 ml) in benzene (100 ml) was heated under reflux for 40 hr. The mixture was cooled to room temperature, washed with water (125 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was crystallized from ether–hexane to give 3.68 g (53%) of α-(ethylsulfonyl)-β-piperidinostyrene (**10**).

Piperidine-Catalyzed Conversion of β,β-Bis(ethylsulfonyl)styrene (3) to (*E*)-α,β-Bis(ethylsulfonyl)styrene (1).—A solution of **3** (144 mg) and piperidine (15 mg) in benzene (10 ml) was heated under reflux for 48 hr. Thin layer chromatography on silica gel with development by 6:1 benzene–ethyl acetate showed **1** to be the major product.

Triethylamine-Catalyzed Condensation of Benzaldehyde and Bis(ethylsulfonyl)methane.—A mixture of benzaldehyde (5.3 g, 0.05 mol), bis(ethylsulfonyl)methane (5.0 g, 0.025 mol), triethylamine (0.5 ml), and benzene (35 ml) was heated at reflux for 16 hr. During this time water (0.42 ml) was removed with the aid of a Dean–stark trap. The reaction mixture was cooled to room temperature and the benzene was removed under reduced pressure. Trituration of the residue with hexane gave a mass of crystals which were purified by chromatography over silica gel and elution with 2:1 benzene–ethyl acetate, yielding 1.47 g (21%) of **3**.

Triethylamine-Catalyzed Conversion of (*E*)-α,β-Bis(ethylsulfonyl)styrene (1) to β-Ethyl-α-(ethylsulfonyl)styrene (13).—A solution of **1** (1.44 g) and triethylamine (0.60 g) in toluene (20 ml) was heated under reflux for 30 hr. The solution was cooled, concentrated under reduced pressure, and chromatographed over silica gel. Elution with 6:1 benzene–ethyl acetate gave **13** (180 mg, 16%).

Attempted Conversion of 7 to 1.—A solution of **7** (25 mg, 0.087 mmol) and piperidine (0.74 mg, 0.0087 mmol) was heated under mild reflux for 48 hr. Tlc and nmr analysis of the product mixture indicated the presence of a minor amount of **10**. However, the bulk of the product was unchanged **7**. No **1** was observed.

(25) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

Registry No.—**1**, 34407-76-6; **3**, 3363-77-7; **4**, 34407-78-8; **5**, 33987-87-0; **6**, 34407-80-2; **7**, 34417-84-0; **8**, 34407-81-3; **10**, 34407-82-4; **13**, 34407-83-5; **14**, 34407-84-6; **15**, 34407-85-7; **21**, 34407-86-8; **22**, 34407-87-9; piperidine, 110-89-4; benzaldehyde, 100-52-7; bis(ethylsulfonyl)methane, 1070-92-4.

Acknowledgment.—The authors would like to thank the Physical Analytical Chemistry staff of The Upjohn Company for the elemental analyses.

Metalated Carboxylic Acids. IV. Reactions of Metalated Carboxylic Acids with Epoxides. Substituted Steroidal Spiro γ-Lactones from Spiro β-Epoxides[1]

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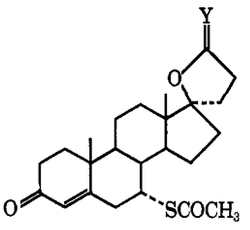
Attempts to convert spiro β-epoxide **2** to **5d** as a model for the preparation of substituted spiro lactones **5a–c** resulted in the observation that acetic acid can be metalated under mild conditions when treated with lithium diisopropylamide. Treatment of **2** with **6a** ($M^+ = Li^+$) successfully concluded the intended transformation. Extensions to homologous and functionally substituted examples established that the metalation of aliphatic carboxylic acids is a general phenomenon and use of these reagents permitted the preparation of **5a–c, f, g** in useful yields. The poor solubility and incomplete metalation of acetic acid were avoided by use of simple acetic acid derivatives in the same sequence. Some of these examples gave improved yields of epoxide cleavage products, **14a–c**. The reaction of metalated carboxylic acids with model epoxides served to illustrate an attractive route to γ-lactones, especially where the introduction of sterically bulky or geminal substituents is desired. When steroidal epoxides are treated with metalated carboxylic acids bearing bulky substituents, unequal amounts of C-21 substituted spiro lactones are obtained. The major isomers are assigned 21*S* stereochemistry which are related to the high field C-18 nmr absorption based on epimerization studies.

Large numbers of structurally diverse steroids have been studied with respect to their potential as aldosterone inhibitors.[2,3] Of those reported, **1a–c** have emerged as some of the more effective examples[3] capable of eliciting this type of biological response. These examples share as their most distinctive structural feature a five-membered spiro ring attached to C-17 of the steroid nucleus and it is this structural unit which provides the greatest synthetic challenge and the greatest biological interest. Correlations of biological activity with variations in the structure of the spiro ring indicate that the oxygen atom, if present, should be β oriented, that the oxidation state of the lactone carbonyl carbon of **1a** is not critical,[3b] and that substituent rings with more than five members

(1) Portions of this report have appeared in the following patents: (a) P. L. Creger, U. S. Patent 3,320,242 (1967); (b) U. S. Patent 3,413,288 (1968); (c) U. S. Patent 3,506,652 (1970).

(2) G. DeStevens, "Diuretic Chemistry and Pharmacology," Academic Press, New York, N. Y., 1963, Chapter 7.

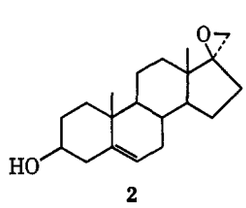
(3) (a) R. C. Tweit, E. A. Brown, S. Kraychy, S. Mizuba, R. D. Muir, and R. T. Nicholson, *Chem. Pharm. Bull.*, **12**, 859 (1964), and earlier papers in this series; (b) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963); (c) W. F. Johns and E. A. Brown, *J. Org. Chem.*, **31**, 2099 (1966); D. Bertin and J. Perronnet, *Bull. Soc. Chim. Fr.*, 564 (1964).



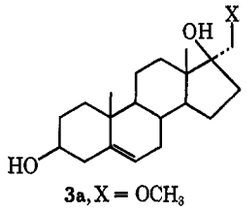
1a, Y = O
b, Y = H_2
c, Y = H,OH

display decreased activity.[3a,b] At the time the present study was initiated,[4] structures containing a spiro ring at C-17 with a β-oriented oxygen atom and fewer than five members were not known, although structures containing a spiro oxetane unit[5] have been described more recently.

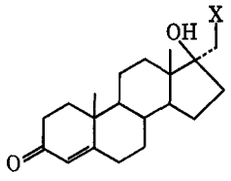
A logical approach to the synthesis of steroids containing spiro three-membered rings with a β-oriented oxygen atom (β-epoxides, *e.g.*, **2**) was made available when reactions of carbonyl compounds with sulfur ylides were described.[6] These reagents offered the attractive advantages of permitting use of available precursors and allowing construction of the spiro ring with stereochemistry which was not conveniently accessible by previous methods. Subsequently, reactions of these reagents with steroidal ketones were actively explored by several groups.[1b,7] Thus the preparation of **2** was established as the most immediate synthetic objective in the present work, and, depending on its success and stereospecificity, it could be carried on in a sequence of reactions as a logical precursor to substituted spiro lactones, **5**. Finally, standard procedures could be employed to manipulate the functionality in the A and B rings to produce **8–10** for biological evaluation. Attempts to convert **2** to **5** resulted in the observation that the metalation of carboxylic acids is a general phenomenon[8] and it was the use of these reagents with **2** that permitted construction of the spiro lactone rings. Later studies demonstrated the utility of metalated carboxylic acids for the preparation of trialkylacetic acids,[9a] dialkylacetic acids,[9b] alkylbenzoic acids,[9c] and β-hydroxy acids.[9d] The present report considers reactions of metalated carboxylic acids with epoxides, particularly **2**.



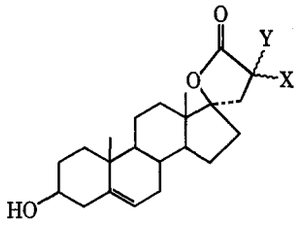
2



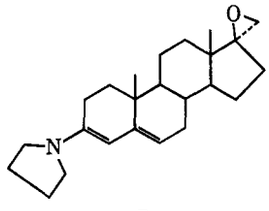
3a, X = OCH_3
b, X = N_3



4a, X = OCH_3
b, X = N_3



5a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3
d, X = H; Y = H
e, X = CN; Y = H
f, X = C_4H_9; Y = H
g, X = C_6H_5; Y = H
h, X = OCH_3; Y = H



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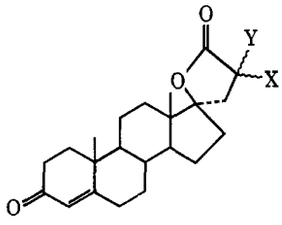
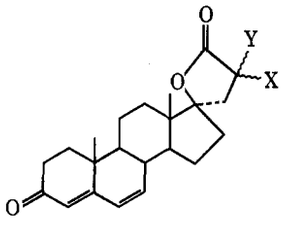
$[CR_2CO_2]^{2-}Li^+M^+$
6a, R = H
b, R = CH_3



8a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3
d, X = H; Y = H
e, X = C_4H_9; Y = H
f, X = C_6H_5; Y = H



9a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3

Results

Steroidal Epoxides.—The treatment of 3β-hydroxyandrost-5-en-17-one (acetate) with excess dimethylsulfonium methylide resulted in the formation of (17*S*)-spiro[androst-5-ene-17,2′-oxiran]-3β-ol (**2**) as the exclusive functional product[1a,10] isolated in 75–90% yields. The availability of **2** permitted consideration of the second objective, the preparation of **5**, but before proceeding, attempts were made to evaluate the reactivity of the relatively hindered epoxide ring toward simple nucleophiles. To illustrate ring cleavage, treatment of **2** with sodium methoxide in methanol or with methanolic sodium hydroxide yielded 17-(methoxymethyl)-androst-5-ene-3β,17β-diol[11] (**3a**), from which **4a** could be obtained by Oppenauer oxidation. Similarly, reaction of **2** with sodium azide gave 17-(azidomethyl)androst-5-

(4) Except for a few isolated experiments, the present work was completed in 1964–1965.

(5) E. A. Brown, *J. Med. Chem.*, **10**, 546 (1967); B. Singh and R. G. Christiansen, *J. Pharm. Sci.*, **60**, 491 (1971).

(6) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9, reviews the earlier literature.

(7) (a) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **65**, 3529 (1964); (b) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **33**, 2789 (1968); (c) D. Bertin and L. Nedelec, *Bull. Soc. Chim. Fr.*, 2140 (1964); (d) K. G. Holden, U. S. Patent 3,300,489 (1967). a–d describe examples using 17-keto steroids.

(8) Reactions of more than 50 carboxylic acids with various electrophiles have been studied.

(9) (a) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); *Org. Syn.*, **50**, 58 (1970); (b) *J. Amer. Chem. Soc.*, **92**, 1397 (1970); (c) *ibid.*, **92**, 1396 (1970); (d) G. W. Moersch and A. W. Burkett, *J. Org. Chem.*, **36**, 1149 (1971).

(10) 10–15% of **2** acetate was also isolated. None of the isomeric (17*R*)-spiro[androst-5-ene-17,2′-oxiran]-3β-ol was detected by nmr analysis. The ir spectra revealed no unreacted ketonic contaminants.

(11) G. Muller and M. Stefanovic, U. S. Patent 3,022,324 (1962); K. G. Holden, U. S. Patent 3,375,280 (1968).

ene-3β,17β-diol (**3b**), sequentially converted to **4b**. In contrast to the high yields experienced with simple azide and methoxide anions, diethyl sodiomalonate in tetrahydrofuran (THF) or dimethoxyethane failed to produce products expected from attack of the carbanion on the epoxide ring, although the latter transformation has been reported[7d] using different reaction conditions. The less hindered anion from ethyl cyanoacetate in the same solvent (THF) gave **5e** in low yield. In an effort to minimize steric hindrance in the carbanionic reagent and to reduce delocalization of the charge, carbanions with a single activating substituent were considered for use in the reaction. Sodium sodioacetate[12] seemed ideally suited for this purpose, but, on reaction with **2** in refluxing THF, no **5d** could be detected. In retrospect, the known properties[12,13] of sodium sodioacetate made it a poor choice for reaction with **2** because of its low solubility, high association, and extreme stability. Despite initial failures, the simplicity of the intended transformation demanded that it be given further serious consideration.

The relatively high acidity of acetate ion[14,15] ($pK_a \sim 24$) suggested that a variety of bases should be effective for removing a proton from the α carbon of a carboxylate salt and that the vigorous conditions used for the formation of sodium sodioacetate[12] were unnecessary. Further, no necessary relationship could be presumed to exist between the solubility of the metalated species and the solubility of the corresponding carboxylate salts, which made it possible to consider polar, aprotic, organic solvents for use as the reaction medium. Lithium diisopropylamide was ultimately selected as base because its steric bulk would minimize competitive side reactions between the amine, diisopropylamine, and an added electrophile. Additionally, the reagent was soluble in and did not react readily with coordinative, aprotic organic solvents and, like other metal amides, lithium diisopropylamide should be a more effective metalating agent[16] in proton transfer reactions than conventional organometallic agents, RM, many of which are capable of reacting with the carboxylate function. Finally, as cation, lithium should be more tightly associated with the anion[17] because it is a "harder" acid than sodium[18] and it could be expected to coordinate with the amine, diisopropylamine, with a presumed beneficial effect on the solubility of the complex in THF, which was chosen as solvent.

When acetic acid was added to 2 equiv of lithium diisopropylamide in THF, a colorless suspension of **6a** and unmetalated lithium acetate was produced. Following addition of **2**, the mixture was heated to reflux and **5d** was isolated in 55% yield. Repetitions which also used an excess of **6a** gave 50–60% of **5b** and the remainder of **2** was recovered. In these initial experiments, neither the product yields nor the homogeneity of the reaction mixture were consistently improved by use of hexamethylphosphoramide (HMP) as cosolvent[1b] and difficult removal from the steroid products discouraged its extensive use.

Spiro lactone **2** was easily isolated and identified. Addition of water afforded convenient separation of the intermediate carboxylate salt from unreacted **2**, and subsequent acidification of the aqueous extracts resulted in closure of the lactone ring. The nmr spectrum of **5d** revealed that reaction had occurred at the epoxide function by the absence of the well-defined AB quartet in **2** (ν_A δ 2.90, ν_B δ 2.61, J_{AB} = 5.5 Hz). The ir spectrum displayed ν(C=O) absorption at 1764 cm^{-1} suitable for a γ-lactone and the elemental analysis and other physical properties compared favorably with known values.[19] Similarly, treatment of **7**[1b] with **6a** ($M^+ = Li^+$) produced **8d** in 45% yield after hydrolysis of the enamine blocking group. Lower yields were experienced when metalated acetic acid was treated with other electrophiles. For example, reaction of **6a** ($M^+ = Li^+$) with benzophenone either in THF or THF–HMP mixtures (3:1 v/v) gave only 19% of 3,3-diphenylhydracyclic acid, and treatment with heptyl bromide gave only 12% of nonanoic acid.

The relatively mild conditions used with lithium diisopropylamide for the metalation of acetic acid indicated that other carboxylic acids should behave similarly. Ultimately, the addition of **2** to mixtures containing excess metalated propionic, butyric, hexanoic, phenylacetic, and isobutyric acids provided **5a–c, f, g** in yields ranging from 70 to 87%. The crude products consisted of mixtures of C-21 isomers which could not be separated easily by thin layer chromatography or by recrystallization. As an exception, recrystallization of **8f** allowed separation of the less soluble isomer, which was present in major amount. The minor isomer was not obtained pure. The major isomer was assigned a 21*R* configuration[20] based on its proportion in the reaction mixture, comparison of the C-18 chemical shifts in the nmr spectra,[21] and epimerization studies with related examples reserved for later discussion.

Alkylated spiro lactones **5a–c** were oxidized under Oppenauer conditions[22] to give **8a–c**. Further oxidation with chloranil in *tert*-butyl alcohol and later in toluene–acetic acid[23] gave **9a–c** in yields of 60–85% after chromatography. Finally, treatment of **9a–c** with thiolacetic acid[24] gave **10a–c** in 60–65% yields.

Metalation of methoxyacetic acid resulted in the formation of functionally substituted spiro lactone **5h** on reaction with **2**, but only in 19% yield. The low yield could be attributed to incomplete metalation of

(12) D. O. DePree and R. D. Closson, *J. Amer. Chem. Soc.*, **80**, 2311 (1958).

(13) H. Hopff and H. Diethelm, *Justus Liebigs Ann. Chem.*, **691**, 61 (1966).

(14) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).

(15) D. J. Cram, *Chem. Eng. News*, 92 (1963); D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 1; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 7. These present convenient comparative tables of pK_a values for a variety of carbon acids.

(16) R. Huisgen and J. Sauer, *Chem. Ber.*, **92**, 192 (1959); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 2000 (1964).

(17) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

(18) R. G. Pearson, *ibid.*, **85**, 3533 (1963); see B. Saville, *Angew. Chem., Int. Ed. Engl.*, **6**, 928 (1967), for a review.

(19) J. A. Cella, E. A. Brown and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

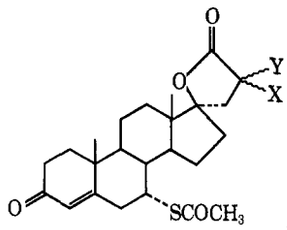
(20) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).

(21) (a) N. S. Bhacca and D. A. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, Chapter 2; (b) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 241 ff.

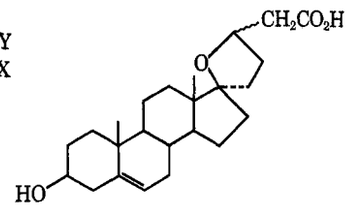
(22) C. Djerassi, *Org. React.*, **6**, 207 (1951).

(23) H. Specht, H. Jahn, and A. Stackowiak, East German Patent 41,938 (1965); *Chem. Abstr.*, **64**, 14245g (1966).

(24) R. M. Dodson and R. C. Tweit, *J. Amer. Chem. Soc.*, **81**, 1224 (1959); J. H. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959).



10a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3



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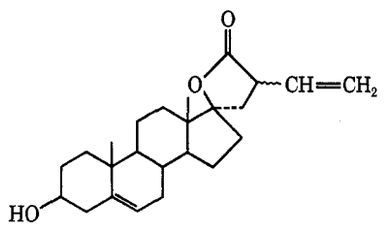

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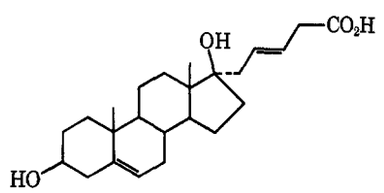

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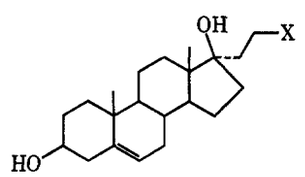
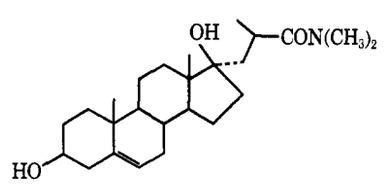


14a, X = CN
b, X = $CON(CH_3)_2$
c, X = $CON(CH_3)CH_2CH_2N(CH_3)_2$



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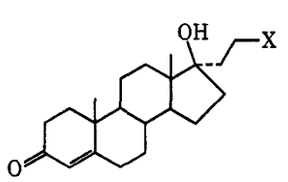
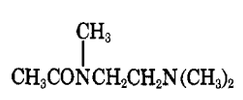


16a, X = $CON(CH_3)_2$
b, X = $CONHCH_3$



17

the carboxylate salt owing to poor solubility of the metalated intermediate or to the deactivating influence of the methoxy substituent,[25] which inhibited proton abstraction. Lower than average yields were also experienced in reactions of alkyl halides with other oxygenated acetic acids, such as phenoxyacetic acid[9b] and ethoxyacetic acid.[26]

(25) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **89**, 5911 (1967).
(26) Unpublished results.

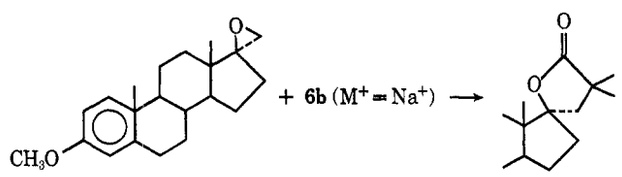
Anions generated from crotonic acid,[27] crotonic acid esters,[28] 3-butenoic acid,[29] or alkylidenemalonic acid esters[30] react almost exclusively at the carbon atom α to the carboxyl(ate) function(s) when treated with simple, unhindered alkyl halides. In contrast, if **2** is used as alkylating agent for metalated crotonic acid steric hindrance to approach at the α carbon of the crotonic acid dianion should make reaction at the terminal carbon more favorable. Terminal alkylation was observed, but the desired product, **11**, was not detected; instead, a mixture of **12** and **13** was obtained in addition to unreacted **2**. Lactone **12** was easily identified as a mixture of epimers. The ν(C=O) absorption (1757 cm^{-1}) established the presence of the lactone ring, and C-18 methyl absorption at δ 0.94 and 1.00 in the nmr spectrum provided evidence for epimeric vinyl substituents. Vinylic multiplets were centered at δ 5.05, 5.15, and 5.90. Carboxylic acid **13** displayed ν(C=O) and ν(C=C) absorptions at 1704 and 1655 cm^{-1}, respectively. The nmr spectrum displayed multiplets at δ 5.92 and 5.67 for vinyl protons and a multiplet at δ 3.63, which is appropriate for the methylene substituent adjacent to the carboxyl group and flanked by a vinyl substituent.

The relatively low yields experienced in the reaction of **2** with metalated acetic acid prompted use of simple acetic acid derivatives in the same sequence in order to overcome incomplete metalation and poor solubility of the carbanionic intermediate. The addition of acetonitrile at −60 or 0° to a THF solution containing 1 equiv of lithium diisopropylamide gave a homogeneous solution from which the carbanionic product soon precipitated.[1c,31] Addition of a THF solution of **2** gave 92% of nitrile **14a**. Similarly, after treatment with lithium diisopropylamide at 0°, *N*,*N*-dimethylacetamide gave 87% of **14b**, and treatment of **7**[1a-c] with *N*-methylacetamide gave 51% of **16b** following hydrolysis of the enamine blocking group. The reaction of acetamide with 2 equiv of lithium diisopropylamide at 40° resulted in its dehydration, a result not observed for simple carboxamides with unsubstituted alkali amides.[32] The acetonitrile which resulted was metalated and, on reaction with **2**, 65% of **14a** was produced when an excess of the reagents was used. To obtain a more soluble variant of the acyclic product, use of *N*-[2-(dimethylamino)ethyl]-*N*-methylacetamide (**17**) gave **14c** (70%) after acidification. In a similar manner, incomplete metalation of propionic acid was overcome by treating **2** with metalated *N*,*N*-dimethylpropionamide, which gave a higher (98%) yield of epoxide cleavage product (**15**) than was obtained using propionic acid.

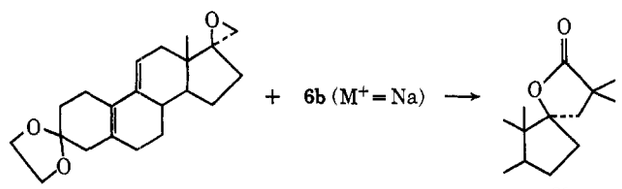
(27) A. J. Birch, *J. Chem. Soc.*, 1551 (1950).
(28) K. Sisido, K. Sie, and H. Nozaki, *J. Org. Chem.*, **27**, 2681 (1962); as an exception, C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **75**, 1068 (1953), report that *tert*-butyl crotonate condenses at the γ carbon with acetophenone.
(29) F. F. Blicke and H. Zinnes, *J. Amer. Chem. Soc.*, **77**, 4849, 6247 (1955), report that vinylacetic acid condenses at the γ carbon with cyclohexanone.
(30) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).
(31) K. Ziegler and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **495**, 84 (1932); D. N. Crouse and D. Seebach, *Chem. Ber.*, **101**, 3113 (1968); E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3402 (1968).
(32) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3317 (1966); E. M. Kaiser, R. L. Vaulx, and C. R. Hauser, *ibid.*, **32**, 3640 (1967); E. M. Kaiser, D. M. von Schriltz, and C. R. Hauser, *ibid.*, **33**, 4275 (1968).

The reaction of metalated acetic acid esters[33] with **2** promised to provide another alternative for the introduction of a two-carbon fragment. The principal attraction again was the improved solubility to be expected for the carbanionic intermediate as compared to metalated acetic acid, but the possibility of condensation reactions of the intermediate suggested use of a sterically hindered ester.[34] When *tert*-butyl acetate was treated with lithium diisopropylamide followed by **2** at ambient temperature, no epoxide cleavage products could be identified. In addition to unchanged **2**, the acetate of **2**, (17*S*)-spiro[androst-5-ene-17,2′-oxiran]-3β-ol acetate, was obtained in 19–42% yields depending on the length of the reaction period.

The generality of the reaction of metalated carboxylic acids with steroidal spiro epoxides was extended by treatment of 3-methoxy-(17*S*)-spiro[estra-1,3,5(10)-triene-17,2′-oxirane][26,35] (**18**) with metalated isobutyric acid (**6b**, $M^+ = Na^+$) to produce **19** (82%). In like manner, (17′*S*)-dispiro[1,3-dioxolane-2,3′-estra-5′(10′),-



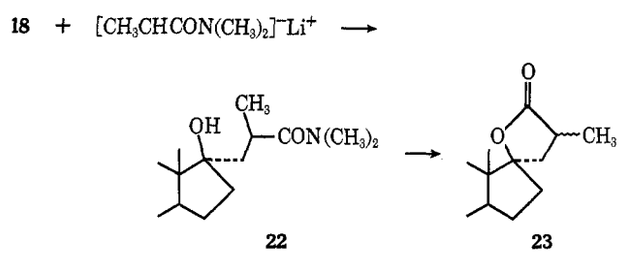
18 **19**



20 **21**

9′(11′)-diene-17′,2″-oxirane][26] (**20**) gave **21** as a noncrystalline solid (73%) which was identified from its spectra, but attempted acid hydrolysis of the ketal gave a mixture of noncrystalline double bond isomers which could not be separated and characterized. Finally, treatment of **18** with metalated *N*,*N*-dimethylpropionamide as an alternative to metalated propionic acid gave **22** (75%) and a substantial amount (25%) of **18** was recovered from a single trial.

Hydrolysis of the various amide or nitrile derivatives produced the desired lactones. For example,



22 **23**

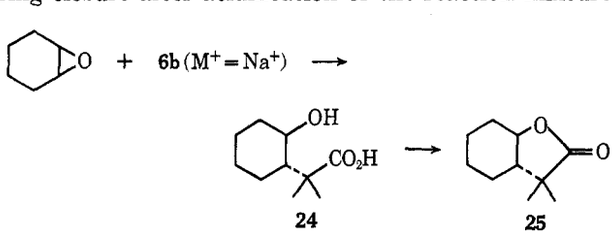
(33) (a) C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **73**, 2972 (1951); C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 1068 (1953); (b) K. Sisido, H. Nozaki, and O. Kurihara, *ibid.*, **74**, 6254 (1952); K. Sisido, Y. Kazama, H. Kodama, and H. Nozaki, *ibid.*, **81**, 5817 (1959); (c) M. W. Rathke, *ibid.*, **92**, 3222 (1970); M. W. Rathke and A. Lindert, *ibid.*, **93**, 2318 (1971); Y-N. Kuo, F. Chen, C. Ainsworth, and J. J. Bloomfield, *Chem. Commun.*, 136 (1971).

(34) Self-condensation may not be so serious as originally surmised.[33c]

(35) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **33**, 2789 (1968).

base hydrolysis of **14a** gave **5d** (75%) on acidification and similar treatment of **15** and **22** produced **5a** (70%) and **23** (99%), respectively. The reaction of C-17 steroidal spiro epoxides with anions generated from amide or nitrile derivatives of acetic or propionic acids followed by hydrolysis of the amide or nitrile products affords a satisfactory synthetic alternative to the use of metalated acetic and propionic acids by producing the desired lactones in higher overall yields.[1c]

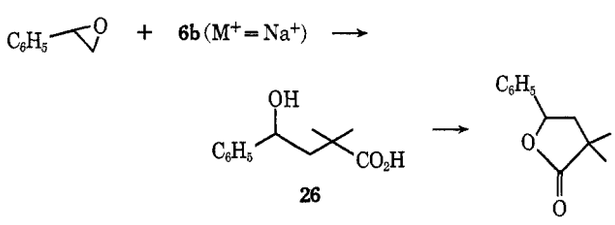
Model Epoxides.—Reactions of metalated carboxylic acids with epoxides of varying structure can be studied most easily by use of model compounds. As an example of a nonterminal epoxide, treatment of cyclohexene oxide with metalated isobutyric acid, **6b** ($M^+ = Na^+$), at 40° gave **24** (91%). The ir spectrum of the crude product failed to reveal evidence of spontaneous ring closure after acidification of the reaction mixture.



24 **25**

Cyclization was effected by heating a toluene suspension of the crude product with azeotropic water removal to give **25**. In contrast, cyclooctene oxide failed to react with **6b** ($M^+ = Na^+$) in THF either at 35° or at reflux. Similarly, metalated 3,3-dimethylbutyric acid failed to react with cyclohexene oxide at 50°. In each case, the epoxide and the carboxylic acid were recovered in high yield after the usual aqueous work-up. Likewise, metalation of methacrylic acid by either of the general procedures A or B (see Experimental Section) gave homogeneous solutions, but no epoxide cleavage products could be detected on treatment with cyclohexene oxide.

Styrene oxide reacted with **6b** ($M^+ = Na^+$) at the terminal, β carbon to give a hydroxy acid which could be isolated if sufficient care were exercised and for which structure **26** was proposed. Cyclization in refluxing benzene gave a lactone which was assigned



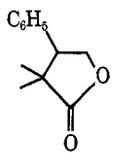
26 **27**

structure **27**. Styrene oxide is known to be subject to attack by anions at either carbon of the epoxide function, although sterically bulky anions can be expected to react at the terminal carbon.[36] Attack at the terminal carbon was concluded from the nmr spectrum. Hand calculations[37] of the well-defined ABX spin coupling pattern produced the following values: ν_A, δ

(36) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-membered Rings, Part One," A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter 1.

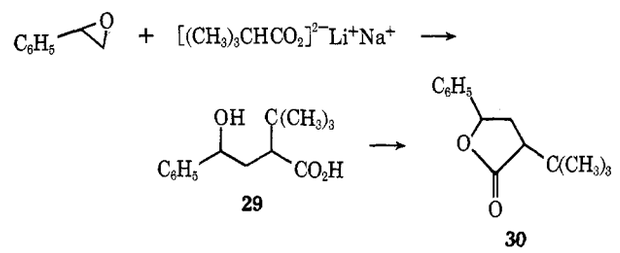
(37) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1965, pp 357 ff; D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press, New York, N. Y., 1967, p 85 ff.

2.44; ν_B, δ 1.98; ν_X, δ 5.43; $J_{AB} = -13.1$ Hz; $J_{AX} = 10.1$ Hz; $J_{BX} = 6.3$ Hz. The geminal coupling constant, J_{AB}, was assumed to be negative by analogy,[38] and line frequency and intensity calculations[37] indicated that J_{AX} and J_{BX} had identical although undefined signs. The chemical shift for the X proton at C-5 of structure **27** corresponds well with published examples,[39] and the geminal coupling constant, J_{AB}, closely corresponds to values reported[40] for geminal protons at C-4 of model γ-lactones. The alternative structure, **28**, would be expected[40] to display $J_{AB} \cong 9$–10 Hz, and, in addition, it should display considerably different chemical shifts for the A, B, and X protons.



28

Treatment of styrene oxide with metalated 3,3-dimethylbutyric acid gave a relatively stable hydroxy acid, **29**, whose structure was assigned by analogy with



29 **30**

26. Cyclization in refluxing toluene gave lactone **30** as a mixture of cis and trans isomers as determined from the doublets obtained for the *tert*-butyl (δ 1.05, 1.08) and phenyl (δ 7.35, 7.38) substituents in its nmr spectrum and the broad ν(C=O) band (1758 cm^{-1}) in its ir spectrum.

Discussion

Formation of Metalated Carboxylic Acids.—Inorganic carboxylate salts react with organometallic reagents with an outcome which is dependent both upon the structure of the carboxylic acid and upon the constitution of the organometallic agent. Simple organolithium reagents react cleanly with lithium carboxylates to produce ketones by a highly useful synthetic process.[41] The reaction proceeds without disturbing the stereochemical integrity of the α carbon of the lithium carboxylate when simple organolithium reagents are used, but examples with more reactive organolithium reagents are lacking.[41] An intermediate position between proton abstraction at the α carbon and nucleophilic addition at the carboxylate function is occupied by Grignard reagents.[42] Carboxylic acids with activating aryl or olefinic substituents attached to the α carbon display predominant proton abstraction and they produce highly useful Ivanov reagents.[43] Aliphatic carboxylic acids suffer varying degrees of nucleophilic addition. Similar results have been reported for alkali metal amides in ammonia, which react with olefinic[27] and aryl-[44] acetic acids by proton abstraction. Under more severe conditions, sodium amide,[12,45] sodium metal, and/or sodium hydride[46] react in the absence of solvent by proton abstraction with various sodium carboxylates including aliphatic examples to produce dianions with apparent limited synthetic utility.[13] Likewise, carboxylate salts of aliphatic carboxylic acids undergo proton abstraction in modest to satisfactory yields at the α carbon when treated with relatively ionic organosodium reagents[47] or with alkali metal radical anions.[48] Thus what is one of the first examples[47a] of an aliphatic metalated carboxylic acid resulted from carbonation studies of pentylsodium by Morton and coworkers. Extensions to other examples,[47b] clarification of the mechanism of the carbonation reaction,[49] and inclusion of a long-chain example[50] in addition to deuteration studies[51] indicated the existence of aliphatic carboxylic acid dianions. The low and variable yields observed for the formation of the dianions restricted synthetic applications. Use of sodium amide at high temperatures indicated that high yields of dianions were possible in selected cases, but documented results reveal poor reactivity toward added electrophiles.[12,13,45,46]

The use of lithium diisopropylamide as proton transfer agent in the present work or related lithium amides[26] permitted both formation of high yields of metalated carboxylic acids and suitable reactivity toward epoxides as electrophiles. Examples **5a–h**, **12**, and **13** suggest that formation of metalated carboxylic acids is reasonably general and that routine laboratory procedures may be used. The high yields enjoyed in these examples suggest further that lithium diisopropylamide is a base strong enough to abstract α protons from di- and monoalkylacetic acids, which by analogy with esters[14,52] should be considerably less acidic than acetate ion. Proton abstraction by a highly hindered base such as lithium diisopropylamide can be expected to proceed without initial addition to the carboxylate function, as was suggested for sodium amide.[12]

(38) Reference 21b, p 270.

(39) D. Savostianoff and M. Pfau, *Bull. Soc. Chim. Fr.*, 4162 (1967); see tabular examples **3**, **16**, and **26**.

(40) J. B. Lowry and N. V. Riggs, *Tetrahedron Lett.*, 2911 (1964).

(41) H. Gilman and P. R. Van Ess, *J. Amer. Chem. Soc.*, **55**, 1258 (1933); for an excellent review, see M. J. Jorgenson, *Org. React.*, **18**, 31 (1970).

(42) M. S. Kharasah and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 948 ff.

(43) B. Blagoev and D. Ivanov, *Synthesis*, 615 (1970).

(44) C. R. Hauser and W. J. Chambers, *J. Amer. Chem. Soc.*, **78**, 4942 (1956); W. J. Chambers, W. R. Brasen, and C. R. Hauser, *ibid.*, **79**, 879 (1957); P. J. Hamrick, Jr., and C. R. Hauser, *ibid.*, **82**, 1957 (1960).

(45) D. O. DePree, *ibid.*, **82**, 721 (1960).

(46) D. O. DePree and G. W. Mattson, *Ind. Eng. Chem., Prod. Res. Develop.*, **2**, 238 (1963).

(47) (a) A. A. Morton, W. J. LeFevre, and I. Heckenbleikner, *J. Amer. Chem. Soc.*, **58**, 754 (1936); (b) A. A. Morton and I. Heckenbleikner, *ibid.*, **58**, 1024, 1697, 2599 (1936); A. A. Morton, F. Fallwell, Jr., and L. Palmer, *ibid.*, **60**, 1426 (1938); A. A. Morton and F. Fallwell, Jr., *ibid.*, **60**, 1924 (1938); A. A. Morton, G. M. Richardson, and A. T. Hallowell, *ibid.*, **63**, 327 (1941); A. A. Morton, J. B. Davidson, and H. A. Newey, *ibid.*, **64**, 2240 (1942); for a review see A. A. Morton, "Solid Organoalkali Metal Reagents," Gordon and Breach, New York, N. Y., 1964, p 47 ff.

(48) J. F. Walker, U. S. Patent 2,171,871 (1940); *Chem. Abstr.*, **34**, 116 (1940); H. Normant and B. Angelo, *Bull. Soc. Chim. Fr.*, 810 (1962); B Angelo, *ibid.*, 1848 (1970); B. Angelo, *C. R. Acad. Sci., Ser. C*, 1471 (1970); S. Watanabe, K. Suga, T. Fujita, and K. Fujiyoshi, *Chem. Ind. (London)*, 1811 (1969).

(49) H. Gilman and H. A. Pacevitz, *J. Amer. Chem. Soc.*, **62**, 1301 (1940); H. Gilman, H. A. Pacevitz, and O. Blaine, *ibid.*, **62**, 1516 (1940).

(50) R. N. Meals, *J. Org. Chem.*, **9**, 211 (1944).

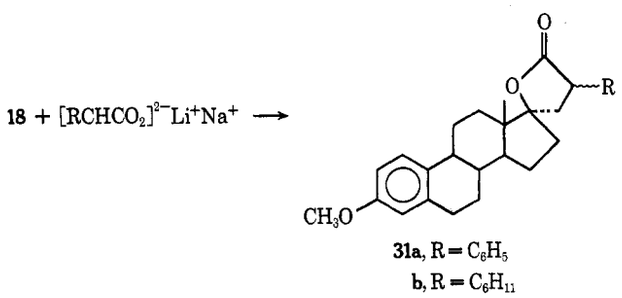
(51) P. Belanger, J. G. Atkinson, and R. S. Stuart, *Chem. Commun.*, 1067 (1969), and references cited therein; O. A. Reutov, "Fundamentals of Theoretical Organic Chemistry," Appleton-Century-Crofts, New York, N. Y., 1967, p 143 ff, reviews some of the early literature.

(52) W. G. Brown and K. Eberly, *J. Amer. Chem. Soc.*, **62**, 113 (1940); R. G. Pearson and J. M. Mills, *ibid.*, **72**, 1692 (1950).

Stereochemistry and Steric Hindrance.—The failure of cyclooctene oxide to react with metalated isobutyric acid and the failure of metalated 3,3-dimethylbutyric acid to react with cyclohexene oxide can be attributed to steric hindrance in each of the reactants. Forcing conditions above the reflux temperature of THF were not attempted. Under the conditions employed, recovered yields of the carboxylic acid and epoxide were high. Likewise, styrene oxide showed a preference for attack at the less hindered, terminal carbon with sterically hindered metalated carboxylic acids, as demonstrated by **27** and **30**. Steric effects also assume an important role in determining stereochemistry at C-21 in reactions of metalated carboxylic acids with steroid epoxide **2**.

Lactones **5** were obtained as inseparable mixtures of C-21 isomers. Oppenauer oxidation of **5g** gave **8f**. The predominant, less soluble isomer so formed was easily separated by crystallization. Nmr spectra of **5g** showed absorption at 59 Hz for the C-18 methyl resonance of one isomer of the mixture and superposition of the same resonance of the second isomer on C-19 at 62 Hz. Oxidation product **8f** revealed absorption at 65 (major) and 61 Hz (minor) for C-18 of the two isomers. Attempts to assign structure based on the shielding effect[53] resulting from the ring current of the C-21 phenyl substituent, however, proved to be inconclusive.

Attack of the metalated carboxylic acid at the steroidal epoxide can be rationalized in favor of preferential formation of either the 21*R* or 21*S* phenyl isomer. The more hindered 21*S* isomer should be capable of isomerization on base treatment, while the 21*R* isomer should be conformationally stable in the presence of a strong base. Conformational stability, or lack of it, permits correlations of structure with C-18 peak positions in the nmr spectra. A more suitable model was required because of the base sensitivity of the Δ^4-3-ketone functional combination present in the A ring of **8f**. Consequently, **31a**, which resulted from treatment

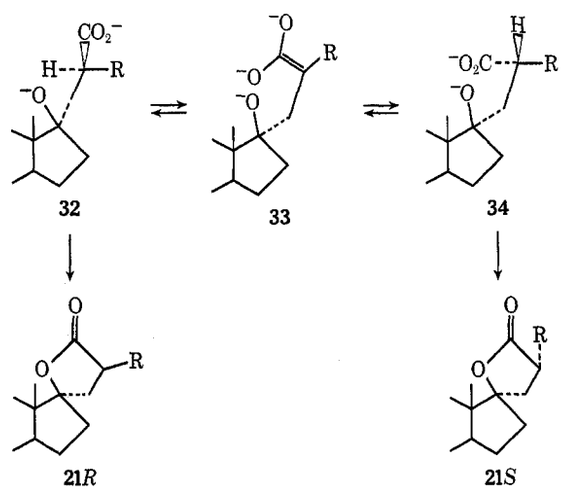


31a, R = C_6H_5
b, R = C_6H_{11}

of **18** with metalated phenylacetic acid, was used for this purpose. The ratio of the peak heights for C-18 methyl absorptions of the isomers of **31a** at 61 (major) and 65 Hz (minor) was 3.1:1. Treatment with *tert*-BuOK reversed peak intensities with C-18 absorptions at 61 Hz (minor) and 65 Hz (major) in the ratio 1:2.4. The logical conclusion may then be drawn that the high-field C-18 absorption is due to the 21*S* isomer and the low-field absorption is due to the 21*R* isomer. Structural similarities at C-18 in **5g** and **8f** allows an analogous conclusion—high field C-18 absorption relates to the 21*S* isomer. Finally, Oppenauer oxidation of **5g** in toluene caused isomerization at C-21 and the pure isomer of **8f** which was isolated can be characterized with 21*R* stereochemistry (C-18, 65 Hz).

Similar results were obtained when **18** was treated with metalated cyclohexylacetic acid. The isomeric mixture of **33b** obtained in 89% yield displayed two C-18 methyl absorptions in the nmr spectrum at 55 (major) and 59 Hz (minor) with peak intensities in the ratio 3.1:1. Since the cyclohexyl substituent approximates the steric bulk of phenyl, treatment with *tert*-BuOK could be expected to give a similar reversal of peak intensities, and this result was observed. The shift differences for the C-18 methyl absorptions in **33a** cannot then be attributed to differing influences of the ring current in the 21*S* isomer *vs.* the 21*R* isomer.

Stereochemistry and Anion–Dianion Equilibria.—Alkylation of metalated carboxylic acids with epoxides proceeds by monosubstitution. The ability of alkyl- or arylacetic acids to undergo twofold reaction with electrophiles depends upon the formation of the dianion of once-alkylated carboxylate anion. Treatment of **18** with 3 equiv of metalated phenyl- or cyclohexylacetic acids for 18 hr gave 21*S*-substituted spiro lactones, **31a,b**, on acidification as the predominant products. Attack by the metalated carboxylic acid from the least sterically hindered conformation of the reactants and accompanied by inversion at C-20 would produce **32**. If the reasonable assumption is made that the acidity of alkylated carboxylate anion differs



by only 1–2 pK_a units[14,52,54] from the parent carboxylate anion (phenyl or cyclohexyl acetate), then the excess metalated species could produce **33** as a long-lived,[55] delocalized[26] dianionic carboxylic acid. Long-lived carbanions can be expected to display a relatively small k_e/k_α value,[55] so that, if formed, **33** should invert given the favorable stereochemistry of the present system. On acidification, **34** would produce the 21*S* spiro lactones observed.

The observation that 21*S* spiro lactones **31a,b** are major products requires that inversion occur at C-21, and, hence, that formation of **33** is a significant process in the overall reaction. Formation of high yields of monosubstituted products and without detectable disubstitution can be accommodated by assuming steric

(53) Reference 21b, p 94 ff.

(54) W. L. Rellahan, W. L. Gumbry, and H. D. Zook, *J. Org. Chem.*, **24**, 709 (1959).

(55) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 92.

hindrance to the second alkylation step. This assumption draws support from the previous discussion, which cited the failure of metalated 3,3-dimethylbutyric acid to react with cyclohexene oxide and of the failure of metalated isobutyric acid to react with cyclooctene oxide. Thus, **33** is formed under the reaction conditions, but it fails to react further.

Experimental Section[56]

General Methods for the Preparation of Metalated Carboxylic Acids. Procedure A.—To a solution of 10.1 g (100 mmol) of diisopropylamine in 100–200 ml of anhydrous THF was added, by injection, 63 ml of a standard solution of *n*-butyllithium in heptane or hexane (1.60 *M*, 100 mmol) at a temperature below 10°. After 10 min at 0°, 50 mmol of the appropriate carboxylic acid in a small volume of anhydrous THF was added, and the mixture was warmed to 30–35° for 30 min to complete the metalation.

Procedure B.—A detailed procedure for the preparation of metalated carboxylic acids from preformed sodium carboxylates has been published.[9a] The procedure used with steroidal epoxides differed only by prior removal of the mineral oil from the sodium hydride by washing with heptane on a tared, sintered funnel.

Less reactive lithium hydride may be substituted for sodium hydride, but longer reaction periods are required for complete conversion of the acid to lithium carboxylate. In some cases, metalated intermediates prepared from lithium carboxylates are more soluble. Carbanionic intermediates prepared from alkylacetic acids *generally* produce heterogeneous mixtures in THF and those prepared from dialkylacetic acids are *generally* homogeneous.

I. Steroidal Epoxides. A. Exploratory Reactions of 2 with Simple Nucleophiles. 1. 17-(Methoxymethyl)androst-5-ene-3β,17β-diol (3a).—To a solution of 1.2 g (50 mg-atoms) of sodium in 100 ml of methanol was added 3.0 g (10 mmol) of **2**. After heating to reflux for 18 hr, the solution was acidified with excess acetic acid and the solvent was evaporated. The residue was taken up in chloroform–ether, the resulting solution was washed with water, then dried ($MgSO_4$) and evaporated, and the product was recrystallized from methanol, yielding a total of 2.80 g (85%) of **3a** in two crops: mp 160–163°; $[\alpha]^{24}D$ −97°; ir ($CHCl_3$) 3625 and 3575 cm^{-1}; nmr δ 0.90 (s, C-18), 1.03 (s, C-19), 3.38 (s, OCH_3).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.46; H, 10.15.

Oppenauer oxidation[22,57] of crude **3a** obtained from a repetition of the above procedure on a 7.5-mmol scale yielded 1.15 g (46%) of **4a** after chromatography and recrystallization from 50% ethanol: mp 118–119.5°; $[\alpha]^{24}D$ +66.6°; ir (KBr) 3500, 1685, and 1620 cm^{-1}; uv 241 nm (E_1^1 479); nmr δ 0.92 (s, C-18), 1.18 (s, C-19), 3.35 (s, OCH_3).

2. 17-(Azidomethyl)androst-5-ene-3β,17β-diol (3b).—A mixture of 3.0 g (10 mmol) of **2** in 50 ml of dioxane and 3.3 g (50 mmol) of sodium azide in 25 ml of water was stirred at reflux for 20 hr. The cooled mixture was diluted with 200 ml of ether and the aqueous layer was discarded. After washing with water, the solution was dried ($MgSO_4$) and evaporated. The crude product, 3.3 g (97%), mp 145–150°, displayed a single tlc spot on silica gel. Recrystallization from acetonitrile produced a sample for analysis: mp 149–152°; $[\alpha]^{24}D$ −88°; ir (KBr) 3400 and 2100 cm^{-1}; nmr δ 0.88 (s, C-18), 1.01 (s, C-19), 3.38 (q, J = 12 Hz, $-CH_2N_3$).

Anal. Calcd for $C_{20}H_{31}N_3O_2$: C, 69.52; H, 9.05; N, 12.17. Found: C, 69.42; H, 8.86; N, 12.37.

Oppenauer oxidation[22,57] of **3b** on a 10-mmol scale gave 3.00 g (91%) of crude **4b** and 1.75 g (52%) after column chromatography on alumina and recrystallization from 50% ethanol: mp 153–155°; $[\alpha]^{24}D$ +57.1°; uv 241 nm (E_1^1 444); ir 3430, 2100, 1654, and 1610 cm^{-1}; nmr δ 0.93 (s, C-18), 1.18 (s, C-19), 3.38 (q, J = 12 Hz, $-CH_2N_3$).

Anal. Calcd for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.24. Found: C, 69.87; H, 8.41; N, 12.37.

3. 4′,5′-Dihydro-3β-hydroxy-5′-oxo-(17*R*)-spiro[androst-5-ene-17,2′(3′*H*)-furan]-4′-carbonitrile (5e).—A solution of 5.7 g (50 mmol) of ethyl cyanoacetate in 10 ml of THF was added to 50 mmol of lithium diisopropylamide in 200 ml of THF. After 5 min at ambient temperature, 3.0 g (10 mmol) of **2** in 50 ml of THF was added and the mixture was stirred at reflux for 18 hr. The cooled mixture was treated with 6.0 g (100 mmol) of acetic acid and 100 ml of water. The organic layer was dried and evaporated and the residue was chromatographed, yielding 0.80 g (27%) of **2**, mp 165–175°. Further elution with benzene and benzene plus 20% ethyl acetate gave 0.50 g (14%) of **5e**, mp 200–215°. A sample for analysis was prepared by recrystallization from 50% ethanol, mp 212–223°, ir (KBr) 2260 and 1770 cm^{-1}.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46. Found: C, 74.31; H, 8.51.

B. Metalation and Reactions of Acetic Acid. 1. 4′,5′-Dihydro-3β-hydroxy-(17*R*)-spiro[androst-5-ene-17,2′(3′*H*)-furan]-5′-one (5d).—Metalated acetic acid was prepared on a 50-mmol scale in 200 ml of THF according to procedure A. A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the stirred mixture was heated to reflux for 18 hr. Water (100 ml) and ethanol were added to the cooled mixture; then it was acidified with excess 3 *N* hydrochloric acid. After stirring at ambient temperature for 0.5 hr, the phases were separated and the solvents were evaporated. The residue was taken up in chloroform–ether and the solution was washed with 2 *N* sodium hydroxide and brine, dried ($MgSO_4$), and evaporated. Chromatography gave 1.85 g (55%) of **5d**, mp 175–186°, on elution with benzene plus 20% ethyl acetate. Recrystallization from 40% ethanol showed mp 180–187°. The ir spectrum was identical with that of the same material obtained from base hydrolysis of **14a,b** (procedure I.D.2,3).

Repetitions of this procedure on a 20-mmol scale using 150 mmol of lithium diisopropylamide in 75 ml of hexamethylphosphoramide and 150 ml of THF gave a homogeneous mixture of **6a** (M^+ = Li^+) initially, but a precipitate soon formed. Crystallization of the product and chromatography of the residue gave 3.2–3.3 g (48%) of **5b**, mp 182–190°.

2. 4′,5′-Dihydro-(17*R*)-spiro[androst-4-ene-17,2′(3′*H*)-furan]-3,5′-dione (8d).—Metalated acetic acid was prepared on a 50-mmol scale in 200 ml of THF according to procedure A. A solution of 2.90 g (8.2 mmol) of **7**[1a-c] in 25 ml of THF was added and the mixture was stirred at reflux for 18 hr.

At the conclusion of the reaction period, 100 ml of water was added and the mixture was stirred at reflux for 2 hr. Another 100-ml portion of water was added to the cooled mixture and the aqueous layer was back-extracted with 100 ml of ether. Ethanol (100 ml) was added and the warm (50°) aqueous alcoholic solution was acidified to congo red with excess 6 *N* hydrochloric acid. Following 2 hr of stirring, the acidic mixture was extracted with chloroform and the extracts were combined, washed with water, dried, and evaporated. The crude **8d** amounted to 1.25 g (45%), mp 140–146°. Benzene elution of an alumina column containing the crude product gave several crystalline fractions. The homogeneity of each fraction was determined by tlc. The crystalline fractions were pooled and recrystallized from 50% ethanol to produce a sample for analysis: mp 166–167° (lit.[19] mp 163–165°); $[\alpha]^{25}D$ +81.5°; ir (KBr) 1778, 1675, and 1620 cm^{-1}; uv 240 nm (E_1^1 496); nmr δ 0.97 (s, C-18), 1.21 (s, C-19).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.28; H, 8.83.

3. 3,3-Diphenylhydracrylic Acid.—Procedure A was operated at 30° with 50 mmol of acetic acid in a solvent mixture consisting of 150 ml of THF and 50 ml of hexamethylphosphoramide. Benzophenone (9.1 g, 50 mmol) in 50 ml of THF was added and the homogeneous mixture was stirred at 20°. After 2 hr, the mixture was acidified with excess 2 *N* hydrochloric acid. The organic phase was separated, washed with water, dried ($MgSO_4$), and evaporated. When diluted with hexane, the residue deposited 2.3 g (19%) of product: mp 222–223° dec; nmr (pyridine) δ 3.65 (s, 2, $-CH_2-$); ir (KBr) 3480 and 1690 cm^{-1}.

(56) Melting points were determined on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. The nmr spectra were determined on a Varian A-60 spectrometer in deuteriochloroform solutions unless otherwise specified. Infrared spectra were obtained on Beckmann IR-7 and IR-9 spectrometers, and ultraviolet spectra were measured as methanol solutions on a Cary Model 11 instrument. Optical rotations were determined as 1.00% solutions in chloroform. Anhydrous tetrahydrofuran was obtained by passing commercial material through a column of basic alumina (Woelm, activity grade I). Diisopropylamine was stirred with and then distilled from calcium hydride. Column chromatography used neutral alumina (Woelm, activity grade III).

(57) J. F. Eastham and R. Teranishi, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 192.

TABLE I

Compd	Yield, %	Mp, °C	Nmr, δ C-18	Nmr, δ C-19	Ir ν(C=O), cm⁻¹	Uv λmax, nm (E_1^1)	[α]²⁵D, degree	Calcd, % C	Calcd, % H	Found, % C	Found, % H
5a[a]	70	214–220	0.92 0.98	1.02	1762		−103	77.05	9.56	77.04	9.39
5b	87	231–236	0.93 0.99	1.03	1753		−101	77.38	9.74	77.37	9.80
5f	76	215–218	0.92 0.99	1.02	1758		−98.4	77.95	10.06	77.50	10.08
5g	75	256–261	0.98	1.05	1750		−112	79.96	8.61	79.98	8.58
5h	19	177–181	0.92 0.97	1.03	1780		−103	73.76	9.15	73.69	9.12
8a	90	182–185	0.98 1.04	1.22	1770 1672	240.5 (464)	+66	77.50	9.05	77.40	9.17
8b	84	160–163	0.96	1.21	1760 1678	240 (448)	+63	77.80	9.25	77.72	9.10
8e	35	153–156	0.93 1.01	1.19	1776 1680	240 (422)	+52	78.35	9.61	78.36	9.64
8f	71	250–253	1.07	1.20	1778 1678	240 (370)	+53	80.35	8.19	80.16	8.18
9a	85	214–222	1.02 1.09	1.16	1770 1660	283 (730)	+1.7	77.92	8.53	77.89	8.49
9b	82	107–110	1.00 1.07	1.13	1766 1660	282 (714)	−12.8	78.22	8.75	78.00	8.57
9c	61	202–204	1.07	1.13	1768 1666	283 (741)	−23.8	78.22	8.76	78.12	8.84
10a[b]	64	138–140	0.98 1.05	1.26	1768 1690	238 (444)	−30.4	69.73	7.96	69.23	8.04
10b[c]	64	236–237	0.97	1.25	1768 1686	238 (432)	−10	70.23	8.16	69.98	8.17
10c[d]	61	242–244	1.00	1.22	1762 1680	239 (440)	−30	70.23	8.16	69.84	7.88

[a] $[\alpha]^{26}D$ −103° (*c* 0.32, $CHCl_3$). [b] S, 7.65; found, 7.68. [c] S, 7.22; found, 7.46. [d] S, 7.22; found, 7.67.

4. Nonanoic Acid.—Metalated acetic acid was prepared according to procedure A on a 200-mmol scale in 300 ml of methylal. Addition of 35.8 g (200 mmol) of 1-bromoheptane yielded, after stirring at 30° for 18 hr, 3.9 g (12%) of crude nonanoic acid. Distillation provided material of analytical quality,[58] bp 118–119° (5.0 mm), $n^{24}D$ 1.4312.

C. Metalation and Reactions of Substituted Acetic Acids. 1. 4′,5′-Dihydro-3β-hydroxy-4′,4′-dimethyl-(17*R*)-spiro[androst-5-ene-17,2′(3′*H*)-furan]-5′-one (5c).—Isobutyric acid (50 mmol) was metalated according to procedure A in 200 ml of THF, yielding a homogeneous solution of **6b** ($M^+ = Li^+$). A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the mixture was heated to reflux for 18 hr. After heating for a few minutes, the salt of the epoxide cleavage product began to separate.

At the conclusion of the reaction period, 250 ml of water was added to the cooled mixture. The organic layer was separated and washed with 50 ml of water. The aqueous layers were combined and back-extracted with 100 ml of ether. Ethanol (100 ml) was added and the warm (50°) solution was acidified to congo red with excess 6 *N* hydrochloric acid. After stirring for 3 hr, the spiro lactone was isolated by extraction with three 75-ml portions of chloroform. The chloroform extracts were freed of excess isobutyric acid by washing with two 50-ml portions of 2 *N* sodium hydroxide and brine, after which they were dried ($MgSO_4$) and evaporated, yielding 3.00 g (81%) of **5c**. Recrystallization from 80% ethanol produced a sample for analysis: mp 184–185.5°; $[\alpha]^{25}D$ −103°; ir (KBr) 1770 and 1742 cm^{-1}; nmr δ 0.99 (s, C-18), 1.03 (s, C-19), 1.27, 1.35 (s, C-21).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.18; H, 9.73.

The same procedure was used for several other examples, which are collected in Table I. Monosubstituted acetic acids produced heterogeneous mixtures of the metalated intermediate when either procedure A or B was used.

2. 4′,5′-Dihydro-4′,4′-dimethyl-(17*R*)-spiro[androst-4-ene-17,2′(3′*H*)-furan]-3,5′-dione (8c).—Oppenauer oxidation[57] of **5c** in toluene on a 5.1-mmol scale yielded 1.45 g (77%) of **8c** in two crops on recrystallization from 40% ethanol, mp 204–208°. Further recrystallization from ethyl acetate–hexane produced a sample for analysis: mp 209–211°; $[\alpha]^{23}D$ +51.5°; uv 240 nm (E_1^1 450); ir (KBr) 1758 and 1678 cm^{-1}; nmr δ 1.00 (s, C-18), 1.20 (s, C-19), 1.25, 1.35 (s, C-21).

Anal. Calcd for $C_{24}H_{36}O$: C, 77.80; H, 9.25. Found: C, 77.56; H, 9.12.

The products, **8a,b**, which resulted from the use of **5a,b** in the same procedure are listed in Table I.

3. 4′,5′-Dihydro-4′-methyl-(17*R*)-spiro[androsta-4,6-diene-17,2′(3′*H*)-furan]-3,5′-dione (9a).—A mixture of 4.70 g (13.1 mmol) of **8a** and 3.40 g (13.8 mmol) of chloranil and 47 ml [10:1 solvent (ml):steroid (g)] of a solvent mixture consisting of 8:2 toluene–acetic acic (v/v) was heated to reflux for 45 min. The dark, homogeneous solution was cooled and diluted with 100 ml of benzene. The precipitate of tetrachlorohydroquinone was removed; then it was washed with benzene, and the filtrates were washed with five 100-ml portions of 1 *N* sodium hydroxide and water. After drying ($MgSO_4$) the solvents were removed, leaving a brown, crystalline residue. Elution of an alumina column containing the product with benzene and benzene plus 10% ethyl acetate gave 3.95 g (85%) of **9a** in several fractions. Recrystallization from benzene–isopropyl ether produced a sample for analysis: mp 214–222°; $[\alpha]^{25}D$ +1.7°; uv 283 nm (E_1^1 730); ir (KBr) 1770, 1660, 1612, and 1582 cm^{-1}; nmr δ 1.02, 1.09 (d, C-18), 1.16 (s, C-19), 1.22, 1.34 (d, C-21).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.92; H, 8.53. Found: C, 77.89; H, 8.49.

The solvent system employed in this procedure[23] gave superior yields with **8a,b** than with use of more conventional[59] *tert*-butyl alcohol with **8c**. Data for **9b,c** are listed in Table I. The 7α-thioacetyl derivatives, **10a–c**, were prepared as described in existing procedures[24] and they are listed in Table I.

4. 4′,5′-Dihydro-3β-hydroxy-4′-vinyl-(17*R*)-spiro[androst-5-ene-17,2′-(3′*H*)-furan]-5′-one (12).—A solution of 100 mmol of lithium diisopropylamide in 200 ml of THF was prepared according to procedure A. A benzene solution containing 4.3 g (50 mmol) of crotonic acid was dried by azeotropic distillation

(58) Analytical and spectral data were obtained for this product.

(59) R. Owyang in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1963, Chapter 5.

and concentrated to 75 ml before it was added at 0–10° to the lithium diisopropylamide. The resulting solution was stirred at 30° for 0.5 hr; then 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the final solution was stirred at 40° for 18 hr.

Water (100 ml) and chloroform–ether (100 ml) were added to the cooled mixture. The organic layer was separated and washed with 50 ml of water. The aqueous layers were combined and back-extracted with 100 ml of ether, and the ether layer was combined with the original organic layer.

Ethanol (100 ml) was added to the aqueous solution and, after warming (50°), it was acidified to congo red with excess 6 *N* hydrochloric acid. After stirring for 3 hr, the acidic products were isolated with three 75-ml portions of chloroform. The chloroform extracts were freed of acidic products by washing with two 50-ml portions of 1 *N* potassium hydroxide. Finally, the chloroform solution was washed with brine, dried ($MgSO_4$), and evaporated. Crude **12** so obtained amounted to 1.10 g (28%). Recrystallization from 50% ethanol produced a sample for analysis: mp 228–235°; $[\alpha]^{25}D$ −125°; ir (KBr) 3515 and 1752 cm^{-1}; nmr δ 0.94, 1.00 (d, C-18), 1.03 (s, C-19), 5.65–6.28 (m, $-CH{=}CH_2$).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: 77.39; H, 9.16.

Acidification of the potassium hydroxide extracts with excess 6 *N* hydrochloric acid and extraction with three 75-ml portions of chloroform permitted isolation of **13** contaminated with excess crotonic acid. Trituration with acetone–hexane produced 0.20 g of solid which was recrystallized from 50% ethanol: mp 214–218°; $[\alpha]^{27}D$ −63° (*c* 1.01, dioxane); ir (KBr) 3420, 1704, 1655, and 960 cm^{-1}; nmr (DMSO) δ 0.80 (s, C-18), 0.98 (s, C-19), 3.63 (m, $C{=}CCH_2CO_2H$).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.20; H, 9.34. Found: C 73.96; H, 9.31.

The spectral data support **13** as the structure for this product. The nmr absorption at δ 3.63 corresponds to similar absorption at δ 3.08 (m, $=CCH_2CO_2H$) determined for vinylacetic acid for comparison. Assignment of the weak ir absorption at 960 cm^{-1} to a π (=CH) vibration for a trans-disubstituted carbon–carbon double bond is considered tenuous.

Evaporation of the washed and dried organic layer from the original reaction yielded 2.00 g (67%) of crude **2**, identified by tlc and ir comparison.

D. Metalation and Reactions of Acetic Acid Derivatives.

1. **3β,17-Dihydroxy-17α-pregn-5-ene-21-carbonitrile (14a).**—To a stirred solution containing 50 mmol of lithium diisopropylamide in 200 ml of THF was added 2.05 g (50 mmol) of acetonitrile in 10 ml of THF at 0°. After 5–10 min the carbanionic species began to separate. A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the mixture was stirred at ambient temperature for 18 hr. At the conclusion of the reaction period, 200 ml of water and 200 ml of ether were added. The organic layer was separated and washed successively with two 50-ml portions of 2 *N* hydrochloric acid and 50 ml of water. After being dried ($MgSO_4$) the solvents were removed, leaving 3.15 g (92%) of crude **14a**. Recrystallization from 80% ethanol yielded white crystals: mp 240–245°; $[\alpha]^{24}D$ −71° (*c* 1.02, dioxane); ir (KBr) 2260 cm^{-1}; nmr (pyridine) δ 1.03, 1.05 (C-18, C-19).

Anal. Calcd for $C_{22}H_{33}NO_3$: C, 76.92; H, 9.69; N, 4.07. Found: C, 76.87; H, 9.76; N, 4.07.

When acetamide was added to 2 equiv of lithium diisopropylamide and treated with **2**,[1a] **14a** (65%) was obtained, mp 238–239° after recrystallization. Spectra (ir and nmr) were identical with those determined for **14a** prepared from metalated acetonitrile.

2. **4′,5′-Dihydro-3β-hydroxy-(17*R*)-spiro[androst-5-ene-17,-2′(3′*H*)-furan]-5′-one (5d) by Hydrolysis of 14a.**—A mixture of 6.86 g (20 mmol) of **14a**, 5.6 g (100 mmol) of potassium hydroxide, and 50 ml of ethylene glycol was heated to reflux for 6 hr. The condenser was set down and the ethylene glycol was distilled at aspirator pressure. After cooling, 200 ml of water was added and the mixture was warmed until the solid dissolved, and then it was poured into 200 mequiv of dilute hydrochloric acid. The crude hydroxy acid was taken up in 200 ml of 80% ethanol and the solution was acidified with an arbitrary small volume of 6 *N* hydrochloric acid. After the warm solution was stirred for 1 hr, the ethanol was evaporated and the residue was taken up in chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated, yielding 6.8 g (99%) of crude **5d**, mp 173–181°. Elution of an alumina column with benzene–20% ethyl acetate gave 5.2 g (75%), mp 188–192°, in several fractions. Recrystallization from 60% ethanol gave white crystals: mp 191–194°; $[\alpha]^{25}D$ −98°; ir (KBr) 1766 cm^{-1}; nmr δ 0.95 (s, C-18), 1.03 (s, C-19).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.37. Found: C, 76.66; H, 9.47.

A similar hydrolysis with sodium hydroxide in aqueous ethanol for 6 hr gave 67% of **5d** after alumina chromatography, mp 190–192°, $[\alpha]^{25}D$ −96°.

3. **3β,17-Dihydroxy-*N*,*N*-dimethyl-17α-pregn-5-ene-21-carboxamide (14b).**—The carbanion of *N*,*N*-dimethylacetamide was prepared on a 50-mmol scale by the procedure described for metalated acetonitrile (I.D.1). A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the homogeneous solution was heated to reflux for 18 hr. After 20 min, the product began to separate.

At the conclusion of the reaction period, 100 ml of 1 *N* hydrochloric acid and 50 ml of chloroform were added at a temperature below 10°. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated, yielding 3.4 g (87%) of crude **14b**, mp 205–212° dec. Recrystallization from acetonitrile raised the melting point to 217–220° dec: $[\alpha]^{24}D$ −96.3°; ir (KBr) 1626 and 1598 cm^{-1}; nmr (CF_3CO_2H) δ 1.05 (s, C-18), 1.12 (s, C-19), 3.33, 3.40 [d, $N(CH_3)_2$].

Anal. Calcd for $C_{24}H_{39}NO_3$: C, 73.99; H, 10.09; N, 3.60. Found: C, 74.17; H, 10.07; N, 3.64.

4. **3β,17-Dihydroxy-*N*,*N*,21-trimethyl-17α-pregn-5-ene-21-carboxamide (15).**—A solution containing 100 mmol of the carbanion of *N*,*N*-dimethylpropionamide in 300 ml of THF was prepared at 0° according to the procedure described for acetonitrile (I.D.1). A solution of 6.0 g (100 mmol) of **2**[1a] in 100 ml of THF was added and the homogeneous solution was stirred at 60° for 18 hr.

Work-up as described for **14b** (I.D.3) gave 7.8 g (98%) of crude **15**, mp 205–213° dec. Recrystallization of a portion of the crude product from acetonitrile produced a sample for analysis: mp 217–220° dec; $[\alpha]^{25}D$ −106°; ir (KBr) 1624 and 1592 cm^{-1}; nmr δ 0.83 (s, C-18), 1.02 (s, C-19), 1.06, 1.18 (d, C-21), 2.92, 3.11 [d, $N(CH_3)_2$].

Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.39; H, 10.24; N, 3.47. Found: C, 74.31; H, 10.18; N, 3.37.

Hydrolysis of **15** with sodium hydroxide in aqueous ethanol for 6 hr gave 68% of **5a** after alumina chromatography. The melting point and ir spectrum were identical with those of the same product prepared by treating **2** with metalated propionic acid (Table I).

5. ***N*-[2-(Dimethylamino)ethyl]-3β,17-dihydroxy-*N*-methyl-17α-pregn-5-ene-21-carboxamide (14c).**—A mixture of 24.7 g (242 mmol) of *N*,*N*,*N*′-trimethylethylenediamine and 50 g (500 mmol) of acetic anhydride was stirred at ambient temperature for 18 hr. The mixture was poured into excess, dilute potassium hydroxide and the product was extracted with chloroform. Distillation of the residue remaining from the dried and evaporated extracts yielded 23.3 g (67%) of **17**: bp 91–92° (5.0 mm); $n^{25}D$ 1.4560; ir (film) 1644 cm^{-1}; nmr δ 1.93 (s, CH_3CO).

Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.43. Found: C, 58.47; H, 11.09; N, 19.37.

A solution containing 50 mmol of the carbanion of **17** in 300 ml of THF was prepared at 0° according to the procedure described for acetonitrile (I.D.1). A solution of 6.0 g (20 mmol) of **2**[1a] in 100 ml of THF was added and the homogeneous solution was stirred at 60° for 18 hr.

At the conclusion of the reaction period, 3.0 g (50 mmol) of acetic acid and 200 ml of water were added. The organic layer was separated; then it was washed with water and finally dried ($MgSO_4$) and evaporated. Recrystallization from ethyl acetate gave 5.9 g of **14c** and alumina chromatography of the filtrate residue gave 0.3 g of **14c** for a combined yield of 6.2 g (70%), mp 115–116.5°. Recrystallization from ethyl acetate produced a sample for analysis: mp 117–118°; $[\alpha]^{25}D$ −80°; ir 1620 cm^{-1}; nmr δ 0.98 (s, C-18), 1.01 (s, C-19), 2.25 [s, $N(CH_3)_2$].

Anal. Calcd for $C_{27}H_{46}NO_3$: C, 72.60; H, 10.38; N, 6.27. Found: C, 71.92; H, 10.22; N, 5.98.

6. **17-Hydroxy-*N*,*N*-dimethyl-3-oxo-17α-pregn-4-ene-21-carboxamide (16a).**—A solution containing 50 mmol of metalated dimethylacetamide in 200 ml of THF was prepared as described in procedure I.D.3. A solution of 2.70 g (7.7 mmol) of **7**[1a–c] in 50 ml of THF was added and the mixture was stirred at reflux for 18 hr. After cooling slightly, 12.0 g (200 mmol) of acetic acid and 30 ml of water were added, and the mixture was stirred for 3 hr without further heating. The solution was diluted with

ether (200 ml) and the organic layer was washed with 2 *N* hydrochloric acid, dried ($MgSO_4$), and evaporated. Recrystallization from 40% ethanol yielded 1.50 g (50%) of **16a** in two crops, mp 202–205° dec. Further crystallization from the same solvent gave a sample for analysis: mp 216–218° dec; $[\alpha]^{24}D$ +32°; uv 241 nm (E_1^1 414); ir 1680 and 1618 cm^{-1}; nmr δ 0.92 (s, C-18), 1.18 (s, C-19).

Anal. Calcd for $C_{24}H_{37}NO_3$: C, 74.38; H, 9.62; N, 3.62. Found: C, 74.29; H, 9.55; N, 3.58.

7. 17-Hydroxy-*N*-methyl-3-oxo-17α-pregn-4-ene-21-carboxamide (16b).—Substitution of *N*-methylacetamide for *N*,*N*-dimethylacetamide in the preceding experiment and use of 2 equiv of lithium diisopropylamide gave a heterogeneous mixture of the carbanionic intermediate. Recrystallization of the crude product from 50% ethanol gave 1.55 g (51%) of **16b** in two crops, mp 164–168° dec. Chloroform elution of an alumina column and crystallization from 50% ethanol produced an analytical sample: mp 208–210° dec; $[\alpha]^{25}D$ +46°; uv 241 nm (E_1^1 434); ir (KBr) 1675 and 1650 cm^{-1}; nmr (pyridine) δ 1.07 (s, C-18), 1.09 (s, C-19), 2.87, 2.94 (d, $NHCH_3$).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.40; H, 9.35; N, 3.80.

8. 17-Hydroxy-3-methoxy-*N*,*N*,21-trimethyl-19-nor-17α-pregna-1,3,5(10)-triene-21-carboxamide (22).—Substitution of **18**[26,35] for **2**[1a] in procedure I.D.7, but on a 30-mmol scale, gave 8.95 g (75%) of **22** after crystallization and alumina chromatography of the filtrate residue: mp 140–142°; $[\alpha]^{25}D$ +1.8°; ir (KBr) 1634 and 1617 cm^{-1}; nmr δ 0.88 (s, C-18), 1.12, 1.22 (d, C-21), 2.98, 3.14 [d, $N(CH_3)_2$].

Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.14; H, 9.33; N, 3.51. Found: C, 75.18; H, 9.42; N, 3.71.

9. 4′,5′-Dihydro-3-methoxy-4′-methyl-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (23).—Hydrolysis of **22** on a 14.2-mmol scale with potassium hydroxide in ethylene glycol following procedure I.D.2 gave 5.0 g (99%) of **23**. Recrystallization from acetonitrile gave white needles: mp 155–157°; $[\alpha]^{25}D$ +4.1°; ir (KBr) 1776 cm^{-1}; nmr δ 0.93, 1.00 (d, C-18), 1.22, 1.33 (d, C-21), 3.76 (s, OCH_3).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.13; H, 8.57.

10. (17*S*)-Spiro[androst-5-ene-17,2′-oxiran]-3β-ol Acetate.—To a solution of 50 mmol of lithium diisopropylamide in 200 ml of THF prepared according to general procedure A was added 5.8 g (50 mmol) of *tert*-butyl acetate at 0°. After stirring for 15 min, a solution of 3.0 g (10 mmol) of **2** in 50 ml of THF was added and the solution was stirred for 60 hr. During the reaction period the temperature gradually reached ambient temperature.

At the conclusion of the reaction period, 100 ml of water was added and the organic layer was washed with 2 *N* hydrochloric acid and 10% sodium carbonate. The residue recovered from the dried organic layer was chromatographed on alumina. Elution with benzene–hexane, benzene, and benzene plus 20% ethyl acetate yielded 1.60 g (53%) of **2** and 1.45 g (42%) of **2** acetate, mp 96–97°, identified by ir comparison. A shorter, 24-hr reaction period gave 19% of **2** acetate.

II. Model Epoxides. 1. *trans*-2-Hydroxy-α,α-dimethylcyclohexaneacetic Acid (24).—A solution of **6b** ($M^+ = Na^+$) was prepared in 200 ml of THF on a 300-mmol scale according to general procedure B. The solution was cooled to 0° and 29.4 g (300 mmol) of cyclohexene oxide was added over 10 min. The ice bath was retained for 1 hr, then the mixture was warmed to 40° for 18 hr.

At the conclusion of the reaction period, 400 ml of water was added at a temperature below 15°. The aqueous layer was separated and the reaction flask and the organic layer were washed with a mixture of 100 ml of water and 150 ml of ether. The aqueous layers were combined; then they were back-extracted with 100 ml of ether and acidified to congo red at a temperature below 10°. The crude product was taken up in chloroform, and the chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to yield 51 g (91%) of **24**, mp 113–115°. Recrystallization of a 5-g sample from acetonitrile gave white needles: mp 126–127°; ir (KBr) 3530 and 1695 cm^{-1}; nmr (DMSO-d_6) δ 0.98, 1.07 (*gem* CH_3), 3.17 (>CHO).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.63; H, 9.83.

2. *trans*-Hexahydro-3,3-dimethyl-2(3*H*)-benzofuranone (25).—The remaining 46 g (247 mmol) of **24** obtained in the preceding experiment was suspended in 300 ml of toluene and the mixture was stirred at reflux beneath a phase-separating head for 18 hr. The cooled solution was diluted with ether and washed successively with two 75-ml portions of 2 *N* sodium hydroxide and 100 ml of brine; then it was dried ($MgSO_4$) and evaporated, leaving 34.5 g (83%) of crude **25**. Recrystallization from 125 ml of hexane gave 25.9 g (62%) of white needles on refrigeration: mp 57–59°; ir (KBr) 1775 cm^{-1}; nmr (CCl_4) δ 1.00, 1.13 (gem CH_3), 3.78 (>CHO).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.14; H, 9.64.

3. 4-Hydroxy-2,2-dimethyl-4-phenylbutyric Acid (26).—Styrene oxide was substituted for cyclohexene oxide in procedure II.1. Crude **26** obtained from the acidified aqueous layers was collected, suspended in water for washing, and dried at 40° in a vacuum oven, yielding 43.6 g (70%) of crude **26**, mp 75–90°. The crude hydroxy acid was dissolved in 0.5 *N* sodium hydroxide and the solution was extracted with ether to remove contaminating lactone **27**. After charcoal treatment, the aqueous solution was cooled to 10°, and then it was acidified with 6 *N* hydrochloric acid and the solid was collected, washed with water, and dried at 30° in a vacuum oven: mp 107–108°; ir (KBr) 3360, 1705, and 1774 cm^{-1} (trace).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.71. Found: C, 69.03; H, 7.64.

4. Dihydro-3,3-dimethyl-5-phenyl-2(3*H*)-furanone (27).—Crude **26** obtained from repetition of procedure II.3 was dissolved in 200 ml of hot acetonitrile and cooled. In addition to 8.0 g (13%) of **26** which crystallized from the solution, evaporation of the filtrate gave 48 g (84%) of **27**. Distillation, bp 114–116° (20 μ), followed by recrystallization from hexane produced a sample: mp 45–46°; ir (KBr) 1773 cm^{-1}; nmr (CCl_4) 1.20, 1.27 (s, 3 each, *gem*-CH_3), 2.20 (m, 2, CH_2), 5.33 (m, 1, >CHO).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.02; H, 7.59.

5. 2-(β-Hydroxyphenethyl)-3,3-dimethylbutyric Acid (29).—A heterogeneous mixture containing 200 mmol of metalated 3,3-dimethylbutyric acid in 300 ml of THF was prepared according to general procedure B. To the cooled mixture was added 24.0 g (200 mmol) of styrene oxide over 5 min and the final suspension was warmed to 40° for 18 hr. After a brief period at 40°, a homogeneous solution was obtained.

At the conclusion of the reaction period, a total of 400 ml of water was added in two portions at a temperature below 15°. The aqueous layers were separated, combined, and back-extracted with ether and residual ether was removed on a rotary evaporator before charcoal treatment. The resulting solution was acidified to congo red with a small excess of 6 *N* hydrochloric acid at a temperature below 15° and the precipitated product was collected, suspended in ice water, and dried at 40° in a vacuum oven. There was obtained 34.4 g (73%) of **29**: mp 129–137°; ir (KBr) 3450, 1709, 1274, and 900 cm^{-1}; nmr (DMSO-d_6) δ 4.38 (m, 1, ArCHOH), 7.32 (s, 5, ArH). Two *t*-Bu absorption peaks at δ 0.82 and 0.92 indicated partial cyclization in the DMSO solution.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.44; H, 8.55.

6. 3-*tert*-Butyldihydro-5-phenyl-2(3*H*)-furanone (30).—A total of 22.9 g (97 mmol) of **29** was suspended in 200 ml of benzene and the stirred mixture was heated to reflux beneath a phase-separating head until water evolution was complete. Removal of the solvent on a rotary evaporator gave 21.8 g (100%) of **30**, mp 43–48°. Two recrystallizations from 100 ml of hexane gave white leaflets: mp 48–54°; ir (KBr) 1758 cm^{-1}; nmr δ 1.08 [s, 9, $C(CH_3)_3$], 1.6–2.8 (m, 3, >CHCH_2–), 5.1–5.6 (m, 1, ArOCHC), 7.35, 7.40 (d, 5, ArH).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.29.

III. Stereochemistry. 1. 4′,5′-Dihydro-3-methoxy-4′-phenyl-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (31a).—Metalated phenylacetic acid was prepared on a 60-mmol scale as a heterogeneous mixture in 150 ml of THF following general procedure B. A solution of 6.0 g (20 mmol) of **18**[26,35] in 50 ml of THF was added and the temperature of the stirred mixture was adjusted to 35° for 18 hr.

At the conclusion of the reaction period, 150 ml of water and 100 ml of ether were added at a temperature below 15°. The aqueous phase was separated and the reaction flask and the organic layers were washed with a mixture of 100 ml of water and 100 ml of ether. The aqueous layers were combined, back-extracted with 100 ml of ether, and then acidified with excess

6 *N* hydrochloric acid. Methanol (200 ml) was added and the mixture was stirred at 50° for 2 hr. The solid remaining after evaporation of the methanol was taken up in chloroform–ether and the solution was washed with two 50-ml portions of 2 *N* sodium hydroxide and brine. Crude **31a** obtained by evaporating the dried ($MgSO_4$) solution amounted to 9.1 g (>100%). Recrystallization from 70 ml of acetonitrile yielded 5.25 g (63%) of white needles: mp 180–188°; $[\alpha]^{25}D$ −52.5°; ir (KBr) 1774 cm^{-1}; nmr δ 1.00, 1.07 (d, C-18). C-18 peak heights appeared in the ratio 3.1:1.

Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.74; H, 7.74. Found: C, 80.97; H, 7.86.

A second crop of **31a** was obtained from 150 ml of ethanol amounting to 1.80 g (22%), mp 160–164°, with C-18 peak heights at δ 1.00 and 1.07 in the ratio 1:1.7. The combined yield amounted to 7.05 g (85%).

2. Isomerization of 31a with Potassium *tert*-Butoxide.—To a solution of 0.70 g (5 × 3.6 mg-atoms) of potassium in 50 ml of *tert*-butyl alcohol was added 1.50 g (3.6 mmol) of **31a** with C-18 nmr peaks at 60 and 64 Hz in the ratio 3.1:1. After heating to reflux under nitrogen for 16 hr, the cooled mixture was acidified with 2.1 g (10 × 3.6 mmol) of acetic acid and the solvent was evaporated. The residue was stirred with chloroform and water, and the dried chloroform solution was evaporated. Trituration with 15 ml of ethanol yielded 1.10 g (73%) of isomerized **31a**, mp 153–155°, with C-18 nmr peaks at 61 and 65 Hz in the ratio 1:2.4.

3. 4′-Cyclohexyl-4′,5′-dihydro-3-methoxy-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (31b).—Metalated cyclohexylacetic acid was prepared on a 60-mmol scale as a heterogeneous mixture in 150 ml of THF following general procedure B. A solution of 6.0 g (20 mmol) of **18** in 25 ml of THF was added and the stirred mixture was warmed to 45–50° for 18 hr.

At the conclusion of the reaction period, 150 ml of water and 100 ml of hexane were added to the homogeneous solution. The aqueous layer was separated and the reaction flask and organic layer were washed with a mixture of 100 ml of water and 100 ml of ether. The aqueous layers were combined, back-extracted with 100 ml of ether, and acidified with excess 6 *N* hydrochloric acid. Methanol (200 ml) was added and the warm (50°) mixture was stirred for 2 hr. The solids remaining after removal of the methanol were taken up in chloroform–ether and the solution was washed with two 50-ml portions of 2 *N* sodium hydroxide and brine. Crude **31b** obtained by evaporating the dried ($MgSO_4$) solution amounted to 7.5 g (89%). Recrystallization from ethanol gave white needles: mp 143–146°; $[\alpha]^{25}D$ −16.3°; ir (KBr) 1768 cm^{-1}; nmr δ 0.92, 0.98 (d, C-18). The peak heights appeared in the ratio 3.1:1.

Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.07. Found: C, 79.60; H, 8.80.

4. Isomerization of 31b with Potassium *tert*-Butoxide.—To a solution of 1.0 g (5 × 5 mg-atoms) of potassium in 50 ml of *tert*-butyl alcohol was added 2.1 g (5 mmol) of **31b** with C-18 nmr peaks at 55 and 59 Hz in the ratio 3.1:1. After heating to reflux under nitrogen for 18 hr, the cooled solution was acidified with 3.0 g (50 mmol) of acetic acid and the solvent was evaporated. The residue was stirred with chloroform and water, and the dried chloroform solution was evaporated. The pooled crystalline fractions obtained by eluting an alumina column with hexane–benzene amounted to 2.0 g (95%). The pooled material showed C-18 nmr peaks at 55 and 59 Hz in the ratio 1:4.3. The sample displayed mp 143–147° after recrystallization from 90% acetic acid: $[\alpha]^{25}D$ −14.7°; ir (KBr) 1770 cm^{-1}; nmr δ 1.08, 1.15 (d, C-18); peak height ratio, 1:9.4.

Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.07. Found: C, 79.58; H, 8.90.

Registry No.—**2**, 847-75-6; **2** acetate, 34414-55-6; **3a**, 19605-33-5; **3b**, 31552-58-6; **4a**, 19605-34-6; **4b**, 34414-59-0; **5a**, 34414-60-3; **5b**, 34414-61-4; **5c**, 16387-03-4; **5d**, 13934-61-7; **5e**, 34414-64-7; **5f**, 34414-65-8; **5g**, 34414-66-9; **5h**, 34414-67-0; **6a** (M^+ = Li^+), 31509-80-5; **8a**, 34414-69-2; **8b**, 34414-70-5; **8c**, 34414-71-6; **8d**, 976-70-5; **8e**, 34414-73-8; **8f**, 34440-55-6; **9a**, 34440-56-7; **9b**, 34440-57-8; **9c**, 34440-58-9; **10a**, 34440-59-0; **10b**, 34440-60-3; **10c**, 34440-61-4; **12**, 34440-62-5; **13**, 34440-63-6; **14a**, 34440-64-7; **14b**, 18290-18-1; **14c**, 34440-66-9; **15**, 34440-67-0; **16a**, 18290-22-7; **16b**, 34427-52-6; **17**, 20929-21-9; **22**, 34440-70-5; **23**, 34440-71-6; **24**, 34440-72-7; **25**, 34440-73-8; **26**, 34440-74-9; **27**, 20215-55-8; **29**, 34440-76-1; **30**, 34440-77-2; 21*R*-**3a**, 34440-78-3; 21*S*-**31a**, 34440-79-4; 21*R*-**31b**, 34440-80-7; 21*S*-**31b**, 34440-81-8; acetic acid, 64-19-7; lithium diisopropylamide, 34440-82-9.

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Stereoselective Alkylation Reactions. I. Organomagnesium and Organoaluminum Addition to 4-*tert*-Butylcyclohexanone. Unusual Stereoselectivity Involving Trimethylaluminum Alkylation in Benzene

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The stereochemistry of addition of methylmagnesium and methylaluminum compounds to 4-*tert*-butylcyclohexanone in several solvents has been studied. Specifically methylmagnesium fluoride, chloride, bromide, and iodide, dimethylmagnesium, and trimethylaluminum were allowed to react with 4-*tert*-butylcyclohexanone in hexane, benzene, diethyl ether, tetrahydrofuran, diphenyl ether, and triethylamine. Reactions involving organomagnesium compounds and trimethylaluminum in diethyl ether and tetrahydrofuran results in predominant equatorial attack to form the axial alcohol product (~73%) regardless of the halide and the mode of addition. In reactions involving trimethylaluminum in hydrocarbon solvent where the $(CH_3)_3Al$:ketone ratio is 1:1, similar results are observed. However, when the ratio is 2:1 or greater a drastic reversal of the stereochemistry is observed resulting in predominant axial attack to form the equatorial alcohol (~90%). The mechanism and stereochemistry of these reactions are discussed.

The steric course of organometallic alkylation and metal hydride reduction reactions involving cyclic ketones is a very fundamental problem in organic chemistry which does not seem to be well understood. It was originally proposed by Dauben and coworkers[1] that the course of hydride reduction reactions is de-

(1) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).