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Reagents for Organic Synthesis

VOLUME SIX

Reagents for Organic Synthesis

VOLUME 6

Mary Fieser

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PREFACE

This volume covers literature for the most part from August 1974 through December 1975. It includes references to about 400 reagents previously discussed in this series and to about an equal number of reagents that are included for the first time. Of course we realize that few of these newer reagents will become as valuable as, say, Grignard reagents, but we have tried to include reagents that open new vistas in organic synthesis. For example, we have included for the first time a reagent based on the lanthanide ytterbium, because, with the exception of cerium, this area has been rather neglected by organic chemists.

We are again indebted to colleagues who have furnished suggestions or additional information. We are particularly grateful to the following chemists who have again been most helpful in the preparation of the book: Professors John A. Secrist and Robert H. Wollenberg, Dr. William Moberg, Dr. Mark A. Wuonola, Dr. James V. Heck, Dr. Oljan Repič and Dr. Rick Danheiser. We acknowledge with gratitude the help for the first time of Dr. Ving Lee, Dr. May Lee, Dr. David Hesson, David Wenkert, Homer Pearce, Peter Ulrich, William Roush, Howard Simmons, III, Donald W. Landry, John Lechleiter, Stephen Kamin, Janice Smith, and Dale Boger. The photograph on the dust cover was taken by Mary Hanlon-Wollenberg.

We thank the Chemistry Department of Harvard University for use of an office and for limited access to the library.

MARY FIESER
LOUIS F. FIESER

Belmont, Massachusetts
November 1976

Reagents for Organic Synthesis

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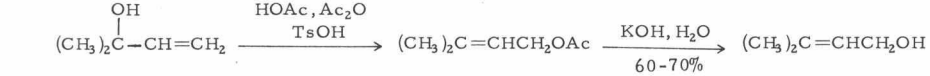
A

Acetic acid–Acetic anhydride.

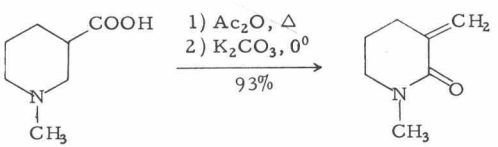
Isomerization of vinylcarbinols to allylic alcohols.[1] Treatment of a tertiary vinylcarbinol, available by the reaction of a ketone with a vinylmagnesium halide, with acetic acid–acetic anhydride and a trace of *p*-toluenesulfonic acid at ~20° (cooling) for several hours results in isomerization to the acetate of the isomeric primary allylic alcohol. An example is the preparation of 3,3-dimethylallyl alcohol from 2-methyl-3-butene-2-ol.



[1] J. H. Babler and D. O. Olsen, *Tetrahedron Letters*, 351 (1974); J. H. Babler, D. O. Olsen, and M. Turner, *Org. Syn.*, submitted (1975).

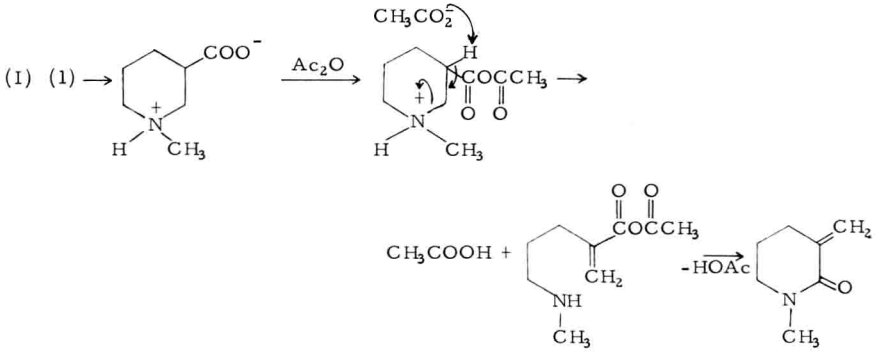
Acetic anhydride, 1, 3; **2**, 7–10; **5**, 3–4.

α-Methylenelactam rearrangement. Ferles[1] and Rueppel and Rapoport[2] have reported that treatment of 1-methylnipecotic acid (1) with refluxing acetic anhydride for several hours and then with potassium carbonate at 0° leads to 1-methyl-3-methylene-2-piperidone (2) in high yield. Actually, before their work this rearrangement had been carried out with lysergic acid and derivatives,[3] but

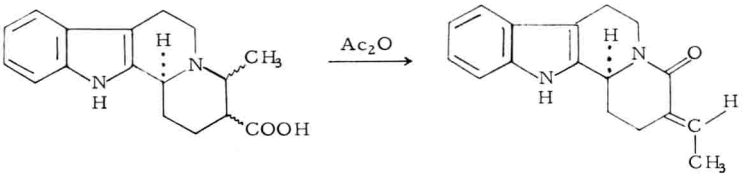


(1) (2)

had attracted little notice. Rapoport *et al.*[4] have recently shown that this rearrangement is a general reaction for five- and six-membered cyclic β-amino acids and have established the mechanism shown in equation I. The rearrangement involves formation of a mixed anhydride, β-elimination, and, finally, recyclization.

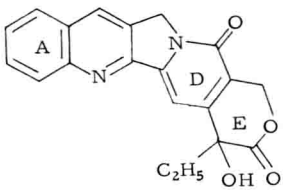


Substituents on nitrogen and at the α- and α′-positions to nitrogen have little effect on the reaction. The high selectivity of the rearrangement is shown by the fact that the four isomers of the acid (3) yield exclusively the same unsaturated lactam (4), which has the thermodynamically more stable *trans*-configuration with respect to the carbonyl group.[5]



(3, four isomers) (4)

The rearrangement has been used by Rapoport *et al.*[6] to obtain the fused pyridone–lactone DE ring system in a total synthesis of *dl*-camptothecin (5).

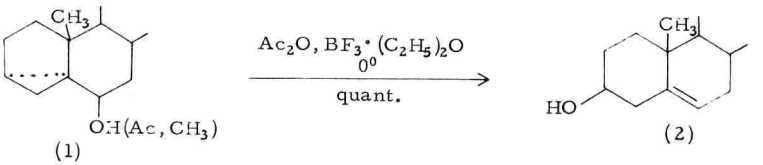


(5)

[1] M. Ferles, *Czech. Commun.*, **29**, 2323 (1964).
[2] M. L. Rueppel and H. Rapoport, *Am. Soc.*, **94**, 3877 (1972).
[3] W. A. Jacobs and L. C. Craig, *ibid.*, **60**, 1701 (1938); A. Stoll, A. Hofmann, and F. Troxler, *Helv.*, **32**, 506 (1949).
[4] D. L. Lee, C. J. Morrow, and H. Rapoport, *J. Org.*, **39**, 893 (1974).
[5] D. Thielke, J. Wegener, and E. Winterfeldt, *Angew. Chem. internat. Ed.*, **13**, 602 (1974).
[6] J. T. Plattner, R. D. Gless, and H. Rapoport, *Am. Soc.*, **94**, 8613 (1972); C. Tang and H. Rapoport, *ibid.*, **94**, 8615 (1972).

Acetic anhydride–Boron trifluoride etherate.

Regeneration of Δ^5-steroids from 3α,5-cyclosteroids. The 5,6-double bond of steroids is often protected by conversion to the *i*-steroid (1). The 3β-ol-Δ^5-steroid was regenerated in recent research by reflux in acetic acid with



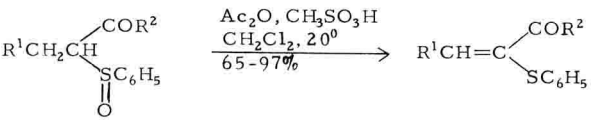
(1) (2)

fused zinc acetate or by treatment with a large quantity of alumina. Indian chemists[1] report that the conversion of (1) to (2) can be carried out in quantitative yield by treatment with acetic anhydride and BF_3 · etherate at 0° for about 15 min. Simultaneous attack of the reagents on the cyclopropane ring is considered to be involved.

[1]C. R. Narayanan, S. R. Prakash, and B. A. Nagasampagi, *Chem. Ind.*, 966 (1974).

Acetic anhydride–Methanesulfonic acid.

Pummerer rearrangement (5, 3–4). 2-Phenylsulfonyl ketones (1)[1] can be converted into (2) by a Pummerer rearrangement using acetic anhydride and a catalytic amount of methanesulfonic acid in CH_2Cl_2 at 20°.[2] The rearrangement provides a general synthesis of α-phenylthio-α,β-unsaturated ketones (2).

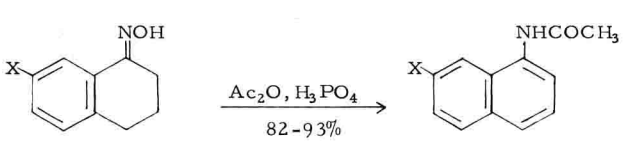


(1) (2)

[1]H. J. Monteiro and J. P. de Souza, *Tetrahedron Letters*, 921 (1975).
[2]H. J. Monteiro and A. L. Gemal, *Synthesis*, 437 (1975).

Acetic anhydride–Phosphoric acid.

Aromatization of α-tetralone oximes (1).[1] When the oximes (1) are heated in acetic anhydride and anhydrous phosphoric acid (**1**, 860) for 30 min. at 80°, *N*-(1-naphthyl)acetamides (2) are obtained in 82–93% yields. Lower yields have



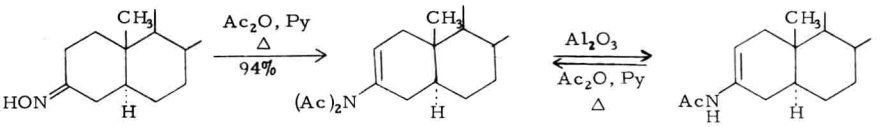
(1, X = H, CH_3, Cl) (2)

been obtained with acetic acid–acetic anhydride containing hydrogen chloride or hydrogen bromide.

[1] M. S. Newman and W. M. Hung, *J. Org.*, **38**, 4073 (1973).

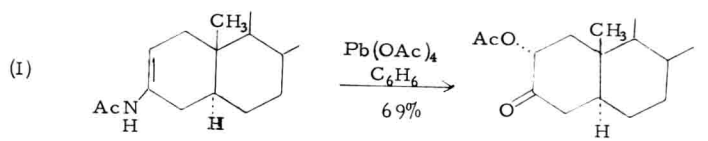
Acetic anhydride–Pyridine.

Enamides.[1] Treatment of an aldoxime with refluxing acetic anhydride and a base affords the corresponding nitrile. Ketoximes under these conditions are converted into enamides or enimides. Thus cholestanone oxime (1), when refluxed in acetic anhydride and pyridine for 10 hr., is converted into the enimide (2) in high yield. When (2) is chromatographed on alumina, it is converted quantitatively into the enamide (3).

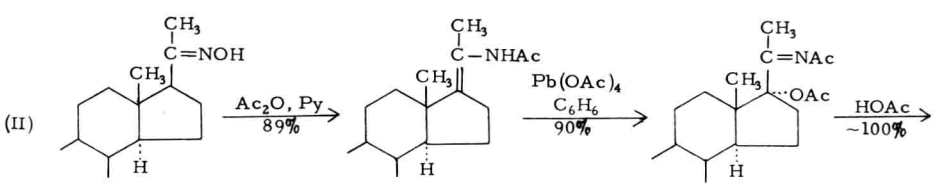


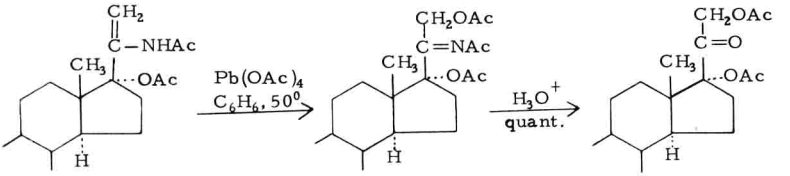
Enamides can also be obtained in comparable yields by the reaction of ketoximes with acetic anhydride, DMF, and chromium(II) acetate or titanium(III) acetate at room temperature. Under these conditions the enamides are not further acetylated. However, Boar and Barton consider acetic anhydride in pyridine to be the reagent of choice for reductive acetylation of ketoximes.

Corticosteroid side-chain synthesis. The paper[1] reports a potentially useful reaction of enamides. Thus the enamide (3) is oxidized by lead tetraacetate in benzene to 2α-acetoxy-5α-cholestane-3-one (4) in 69% yield. This reaction has

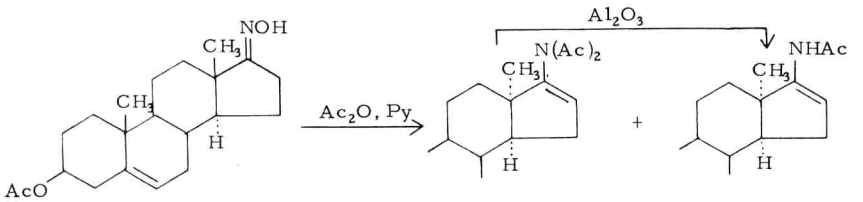


been developed into a one-pot synthesis of the corticosteroid side chain from 20-keto steroids as formulated in equation II[2]:





13-epi-*Steroids.*[3] Treatment of the oxime of 3β-acetoxyandrostene-5-one-17 (1) with acetic anhydride and pyridine (prolonged reflux) gives a mixture of (2) and (3). If the reaction mixture is chromatographed on alumina, (3) is ob-



(1) (2) (3)

tained as the only product (85% yield). These products are 13-*epi*-steroids, previously obtained less conveniently by irradiation of 17-ketosteroids with ultraviolet light.[4]

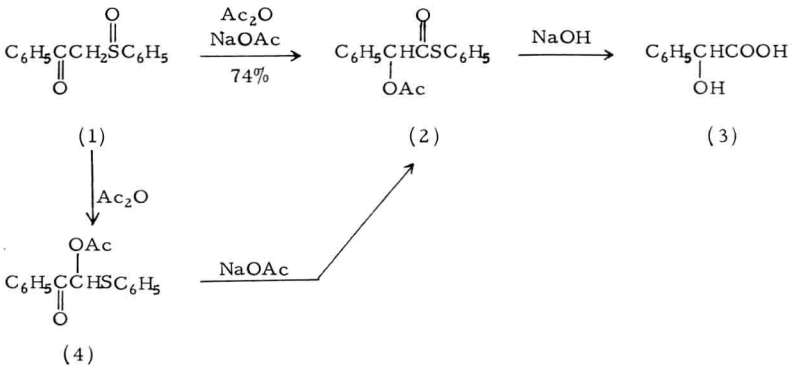
This reaction, which involves ring opening and reclosing, provides evidence for a radical mechanism for the acetic anhydride–pyridine reaction.

Reduction of (1) with chromous acetate in the presence of acetic anhydride gives the normal enamide with no epimerization of the 13-methyl group.

[1]R. B. Boar, J. F. McGhie, M. Robinson, D. H. R. Barton, D. C. Horwell, and R. V. Stick, *J.C.S. Perkin I,* 1237 (1975).
[2]R. B. Boar, J. F. McGhie, M. Robinson, and D. H. R. Barton, *J.C.S. Perkin I*, 1242 (1975).
[3]R. B. Boar, F. K. Jetuah, J. F. McGhie, M. S. Robinson, and D. H. R. Barton, *J.C.S. Chem. Comm.*, 748 (1975).
[4]L. F. Fieser and M. Fieser, *Steroids*, Rheinhold, New York, 1959, p. 464.

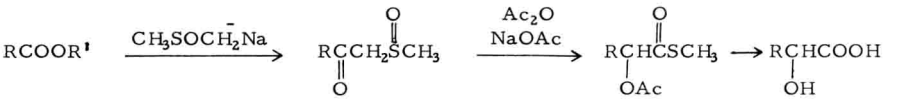
Acetic anhydride–Sodium acetate.

Pummerer rearrangement (5, 3–4). The Pummerer rearrangement of β-hydroxy sulfoxides to derivatives of α-hydroxy aldehydes has been extended to the rearrangement of β-keto sulfoxides.[1] Thus rearrangement of (1) with acetic anhydride–sodium acetate in toluene under reflux gives the S-aryl thioester (2) in 74% yield. The ester is hydrolyzed by base to mandelic acid (3). In the absence of sodium acetate the normal product of the Pummerer rearrangement



(4) is formed. This is converted into (2) by sodium acetate or pyridine. Therefore in the modified reaction an intramolecular oxidation–reduction is involved.

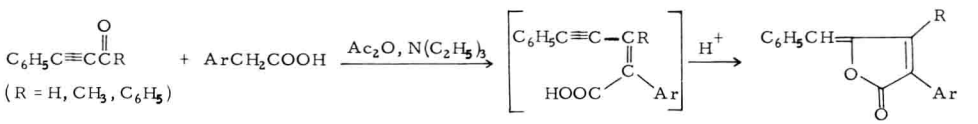
Note that β-keto sulfoxides are readily available by the reaction of esters with dimsylsodium (**1**, 310–311). The reaction thus constitutes a method for preparation of one-carbon homologated α-hydroxy acids from esters.



[1] S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, *Am. Soc.*, **97**, 596 (1975).

Acetic anhydride–Triethylamine, 5, 4.

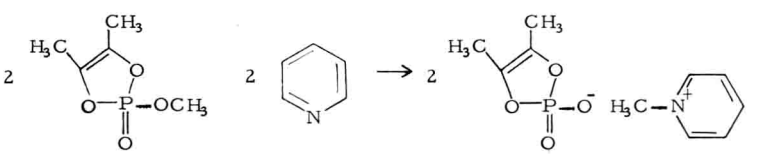
α-Aryl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolides.[1] These substances can be obtained in 40–85% yield by heating phenylpropargyl aldehydes or ketones with arylacetic acids in the presence of acetic anhydride and triethylamine at 150° for 18 hr. followed by treatment with acid.

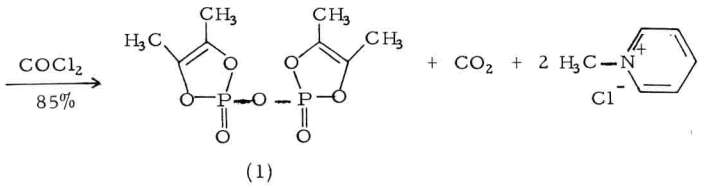


[1] Y. S. Rao and R. Filler, *Tetrahedron Letters*, 1457 (1975).

Acetoinenediolcyclopyrophosphate [Di-(4,5-dimethyl-2-oxo-1,3,2-dioxaphospholenyl)oxide] (1). Mol. wt. 282.13, m.p. 84–86°.

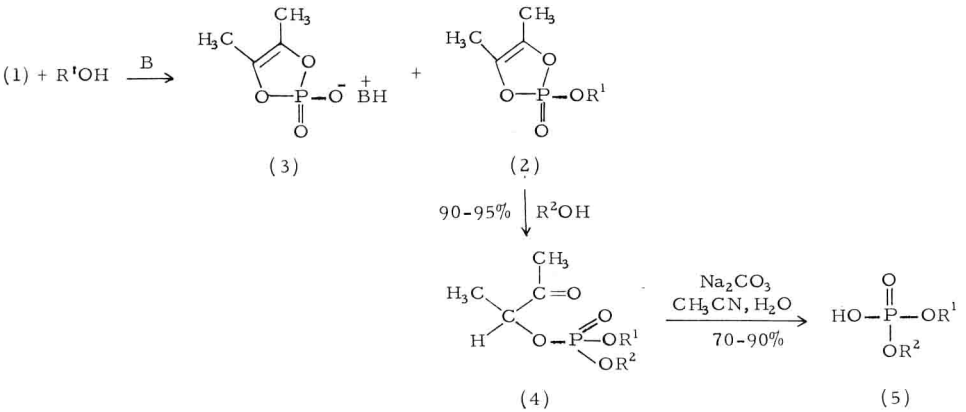
Preparation:





(1)

Phosphodiesters.[1] The pyrophosphate (1) reacts with alcohols or phenols in the presence of 1 eq. of a base (2,4,6-collidine) to give (2) and the collidinium salt (3). The product (2) can react with another alcohol in the absence of a base to give dialkylacetoinyl phosphates (4) in yields of about 95% (**4**, 536). The

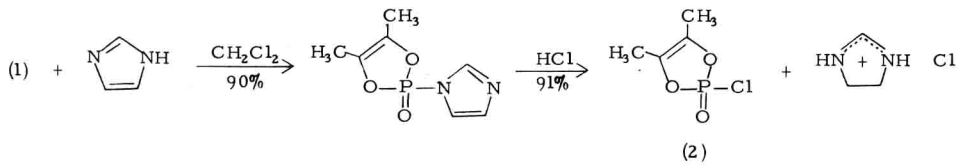


(3) (2) (4) (5)

acetoinyl blocking group can be removed from (4) by sodium carbonate in water–acetonitrile or by triethylamine in aqueous pyridine.

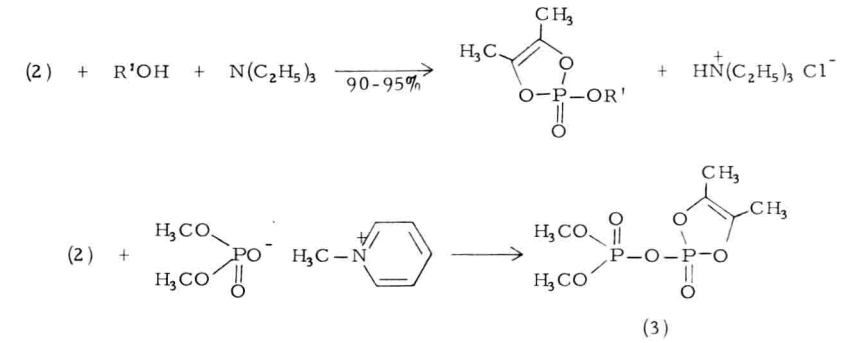
If one of the two alcohols is a primary, secondary diol the reagent reacts selectively with the primary hydroxyl group.

4,5-Dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphole (2). This new reagent for phosphorylative coupling of two different alcohols can be prepared from (1) in 82% overall yield as formulated. This new reagent undergoes displacement



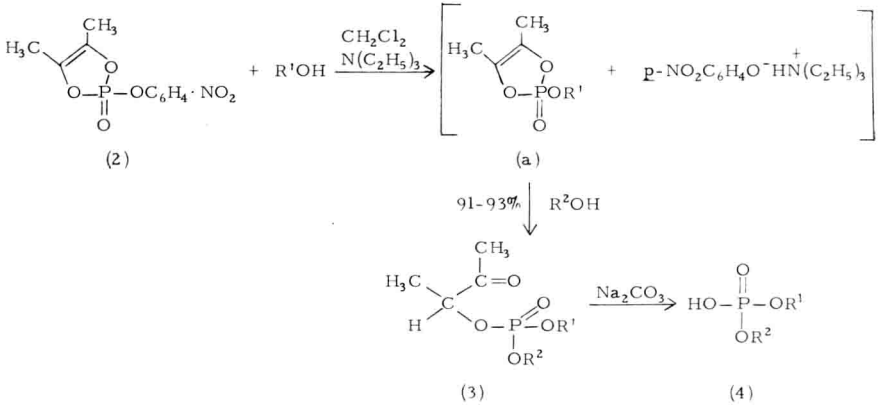
(2)

with alcohols in the presence of a base (triethylamine or pyridine) in yields of 90–95%. It has been used for the synthesis of a pyrophosphate (3).[2]



(3)

One-flask phosphorylative coupling to unsymmetrical dialkyl phosphates (4). Ramirez and Marecek[3] have developed a convenient method for the preparation of dialkylacetoinyl phosphates (3) without isolation of intermediates. The reagent is the *p*-nitrophenyl(1,2-dimethylethenylenedioxy)phosphate (2), prepared by the reaction of *p*-nitrophenol with (1).[4] The reaction is carried out in CH_2Cl_2 by dropwise addition of R^1OH and triethylamine (1 eq. of each) to



(2); after 15–30 min. at 25°, R^2OH (1 eq.) is added, and the reaction is allowed to proceed for 1–2 hr. at 25°. The final step involves the usual hydrolysis of the triester (3). This one-flask procedure is possible because the phenolic salt formed in the first step catalyses the reactions involving both R^1OH and R^2OH. Aryl phosphates are not formed because electron-withdrawing substituents decrease the reactivity of phenols toward both (2) and the intermediate (a).

[1]F. Ramirez, J. F. Marecek, and I. Ugi, *Synthesis*, 99 (1975); *Idem, Am. Soc.*, **97**, 3809 (1975).

[2]F. Ramirez, H. Okazaki, and J. F. Marecek, *Synthesis*, 637 (1975).

[3]F. Ramirez and J. F. Marecek, *J. Org.*, **40**, 2849 (1975).

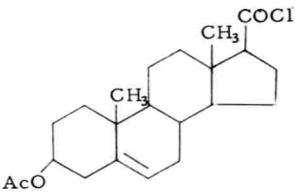
[4]The corresponding phosphate in which the aryl group is C_6F_5 was also used with comparable results.

Acetone, CH_3COCH_3.

Ketones can be recovered in acceptable yields from hydrazones and oximes by exchange with acetone in a sealed tube at 50–80° (*cf.* **Pyruvic acid, 1**, 974).[1]

[1]S. R. Maynez, L. Pelavin, and G. Erker, *J. Org.*, **40**, 3302 (1975).

3β-Acetoxy-17β-chloroformylandrostene-5 (1).



(1)

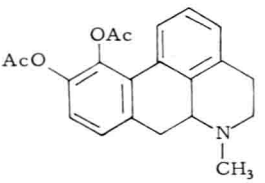
This sterol[1] has been used to resolve squalene-2,3-diol by way of the diastereoisomeric esters.[2]

[1]J. Staunton and E. J. Eisenbraun, *Org. Syn.*, **42**, 4 (1962).
[2]R. B. Boar and K. Damps, *Tetrahedron Letters*, 3731 (1974).

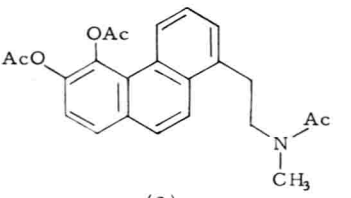
Acetyl bromide, CH_3COBr. Mol. wt. 122.95, b.p. 75–77°. Suppliers: Aldrich, Eastman, others.

Selective O-acetylation with AcBr and CF_3COOH. Hydroxyl groups can be selectively acetylated in the presence of primary and secondary amino groups with acetyl bromide and trifluoroacetic acid.[1]

This system was used successfully to obtain diacetylapomorphine (1) in 70% yield. Acetylation of apomorphine with acetic anhydride catalyzed by a base



(1)



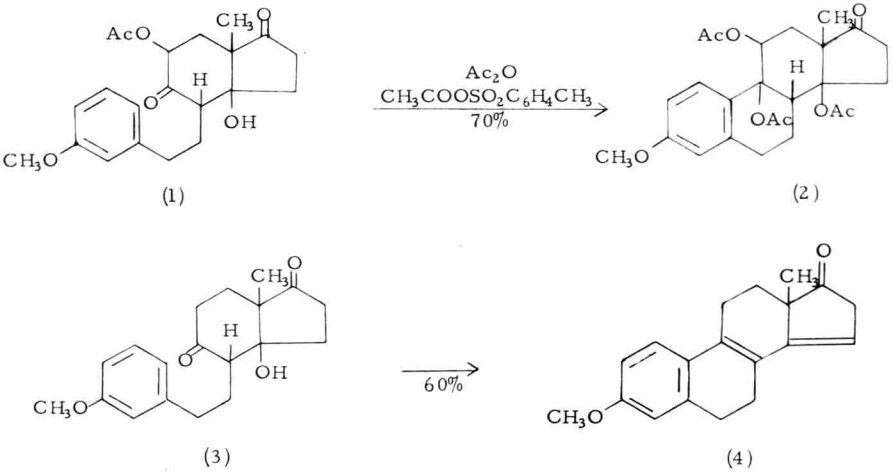
(2)

(NaOAc, pyridine, triethylamine) or with acetic anhydride and acetic acid results mainly or exclusively in formation of the ring-opened product (2).[2] Success with the new system is attributed to the weak basicity of trifluoroacetate anion.

[1]R. J. Borgman, J. J. McPhillips, R. E. Stitzel, and I. J. Goodman, *J. Medicin. Chem.*, **16**, 663 (1973); R. J. Borgman, M. R. Baylor, J. J. McPhillips, and R. E. Stitzel, *ibid.*, **17**, 427 (1974).
[2]R. J. Borgman, R. V. Smith, and J. E. Keiser, *Synthesis*, 249 (1975).

Acetyl *p*-toluenesulfonate, 2, 14–15; 4, 8.

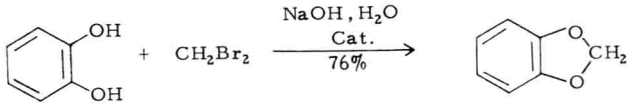
Cyclization.[1] The dione (1) is converted into the estrane (2) by acetyl *p*-toluenesulfonate in acetic anhydride. Cyclization of (1) by the usual reagents is accompanied by dehydration. Thus cyclization of (3), which lacks a C_{11}-keto group, gives (4).



[1] A. R. Daniewski, *J. Org.*, **40**, 3124 (1975); A. R. Daniewski and M. Kocor, *ibid.*, **40**, 3136 (1975).

Adogen 464. This is a methyltrialkylammonium chloride, in which the alkyl groups are a mixture of C_8–C_{10} straight chains. Adogen is a trade name registered by Ashland Chemical Co. Supplier: Aldrich.

Methylenation of catechols. Bashall and Collins[1] have converted various *o*-dihydroxyphenols into the methylenedioxy derivative by addition of a solution of the phenol in aqueous NaOH to a mixture of dibromomethane, water, and this phase-transfer catalyst. Reported yields are 76–86%. Classical methods require anhydrous conditions and aprotic solvents.



[1] A. P. Bashall and J. F. Collins, *Tetrahedron Letters*, 3489 (1975).

β-Alanine, 1, 16.

Knoevenagel condensation. Use of β-alanine as catalyst markedly improves the yield in the condensation of ethyl pyruvate and malononitrile. Potassium sulfide is much less effective.[1]