Acetic Anhydride as a Synthetic Reagent

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Acetic anhydride has been used widely in synthetic organic chemistry, especially in syntheses and transformations of heterocyclic compounds. These utilities are reviewed under the following classification.

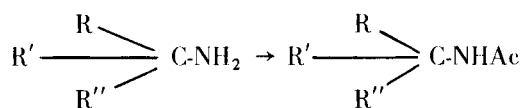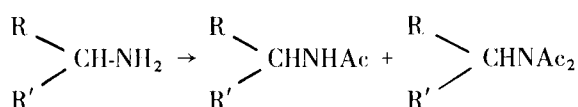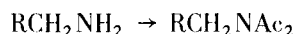|	
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Reaction with amines and alcohols	Molecular rearrangement
Reaction with amino acids	Aromatization
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Introduction.

Acetic anhydride, a representative member of carboxylic acid anhydrides, can be found in every organic laboratory. It has been known to chemists for over a century (1). Although the literature is abundant with examples of its utility in chemical manipulations, heretofore its importance has been strangely unnoticed. It is highly surprising to learn that no single review article devoted to this reagent has yet appeared. This article is prepared to shed some light on this versatile reagent, and thus to create a momentum for further exploration and systematic investigation.

Reaction with Amines and Alcohols.

The acetylation of amines and alcohols is undoubtedly one of the most widely employed uses of acetic anhydride. There are a great many examples in the literature, the first one being acetylation of aniline reported in 1853 by Gerhardt (2). Recent investigations by Mariella and Brown showed that primary amines give mono- or di-acetylated products, depending on the steric nature of the alkyl group, when heated with acetic anhydride at reflux (3) (Scheme 1).

Scheme 1

$$RCH_2NH_2 \rightarrow RCH_2NAc_2$$

$$\begin{array}{c} R \\ \diagdown \\ R' \end{array} CH\text{-}NH_2 \rightarrow \begin{array}{c} R \\ \diagdown \\ R' \end{array} CHNHAc + \begin{array}{c} R \\ \diagdown \\ R' \end{array} CHNAc_2$$

$$\begin{array}{c} R \\ R' \text{---} \\ R'' \end{array} C\text{-}NH_2 \rightarrow \begin{array}{c} R \\ R' \text{---} \\ R'' \end{array} C\text{-}NHAc$$

Certain tertiary amines are known to undergo a displacement reaction with acetic anhydride. At the turn of this century, Tiffeneau and Fuhrer found that benzyl-dimethylamine, on heating with acetic anhydride, was cleaved to give dimethylacetamide and benzyl acetate (4).

$$C_6H_5CH_2NMe_2 \rightarrow AcNMe_2 + AcOCH_2C_6H_5$$
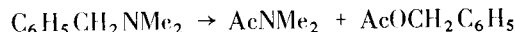
Examples of this type of cleavage reaction are also found in natural product chemistry; e.g., tetrahydro-13H-iso-indolo[1,2-a]-β-carboline (1) gave the indolo[3,2-e][2]-benzazonine derivative (2) in 80% yield when refluxed with acetic anhydride for 3 hours (5). The ring opening reaction of 3 to give 4 on treatment with boiling acetic
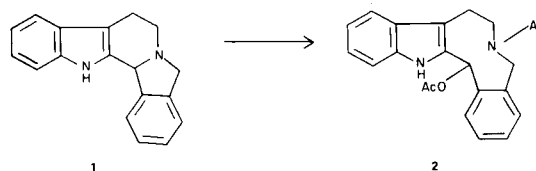

anhydride reported by Freter, et al., is a further example (6). Mariella and Brown investigated this type of tertiary amine reaction in depth and proposed an S_{N_1} type
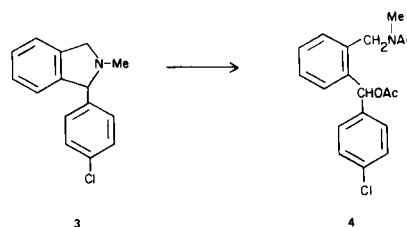

mechanism (7). However, Gol'dfarb and Belen'kii disputed the Mariella and Brown mechanism and instead suggested the S_{N_2} type mechanism catalyzed by acetic acid (8) (Scheme 2).

Scheme 2

RR'R''N + Ac₂O

(Mariella and Brown)

AcNRR' + AcOR'' + AcO⁻

(Gol'dfarb and Belen'kii)

AcO⁻ + AcNRR' +
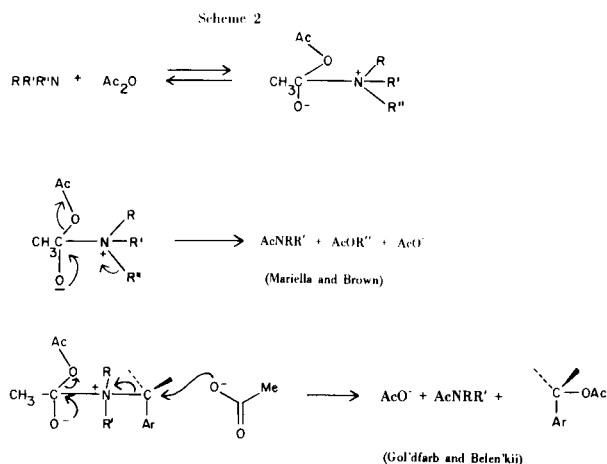
Gerszberg, et al., showed that a quaternary ammonium salt can be bis-dealkylated to give directly acyl derivative of the corresponding secondary amine when heated with a carboxylic acid anhydride. For example, treatment of N,N-dimethylpiperidinium iodide with acetic anhydride at 200° for 24 hours gave N-acetylpiperidine in 47% yield (9).
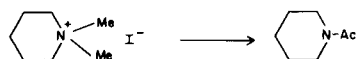

(9). The reaction mechanism proposed by the authors involves an initial removal of an alkyl group by nucleophilic attack on the α-carbon of an N-alkyl group by iodide and/or acetate ion, an equilibrium reaction between the tertiary amine and its acylammonium salt, and the final dealkylation of the acylammonium salt by the acetate and/or iodide nucleophile (9) (Scheme 3).

Scheme 3
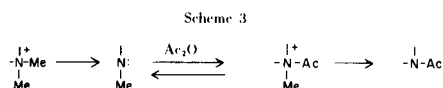
Acetylation of primary and secondary alcohols with acetic anhydride to form esters is a widely used synthetic practice which need not be discussed here in detail (10). Acids, Lewis acids, as well as bases catalyze the reaction. Pyridine has been used most frequently for this type of esterification reaction.

Tertiary alcohols react with acetic anhydride to give olefinic products (11,12). The reaction is facilitated greatly by perchloric acid. Thus an equimolar mixture of acetic anhydride and t-butyl alcohol reacts vigorously when treated with a little perchloric acid, giving isobutene in ca. 25% yield (13). However, when an excess of acetic

Me₃COH $\xrightarrow{Ac_2O}$ Me₂C=CH₂
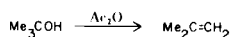
anhydride is used, the reaction does not stop at the dehydration stage, but proceeds further, giving a solid product 2,4,6-trimethylpyrylium perchlorate (5) (11,14).

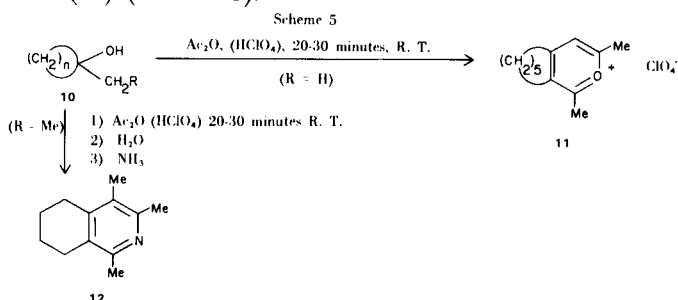Me₃COH + 4 Ac₂O $\xrightarrow{HClO_4}$

5
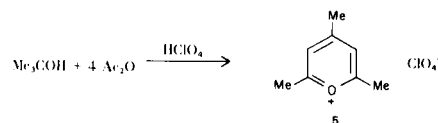
The pyrylium salt is a very versatile and useful starting material for the syntheses of a variety of heterocyclics (14).

It is believed that the isobutene first formed reacts with the acylating agent to form a carbonium ion which then loses a proton preferentially from the terminal position. Normally the β,γ-unsaturated ketone would be expected to isomerize to the α,β-unsaturated compound, but in the presence of excess acylating agent further reaction occurs to form 9. The latter loses water giving the pyrylium salt (11,15) (Scheme 4).

Scheme 4

Me₃C-OH ⟶ Me-C=CH₂

6
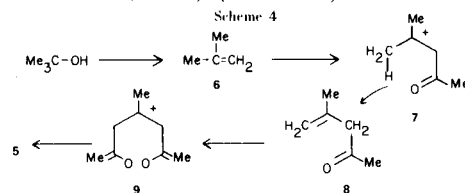
Dorofeenko, et al., obtained the pyrylium salt, 11 from cyclic tertiary alcohol, 10. Treatment of a pyrylium salt with ammonium hydroxide gave the pyridine derivative 12 (17) (Scheme 5).

Scheme 5

Ac₂O, (HClO₄), 20-30 minutes, R. T.

(R = H)

(R = Me) 1) Ac₂O (HClO₄) 20-30 minutes R. T.
          2) H₂O
          3) NH₃

The novel synthesis of the dialkylindene, 15 from diol 13 reported by Parham and Montgomery by the treatment with acetic anhydride in the presence of formic acid can be considered as an application of the reaction of acetic anhydride with tertiary alcohol (16) (Scheme 6).

Scheme 6

MeCOCl
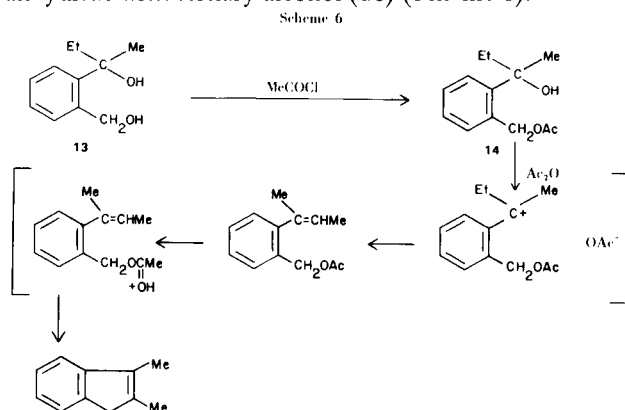
In acetylation reaction of tertiary alcohols, Steglich and Hofle showed that 4-dimethylaminopyridine alone or mixed with triethylamine is a superior catalyst. With this catalyst 1-methylcyclohexanol which resists acetylation by acetic anhydride and pyridine was acetylated at room temperature in 86% yield (18).
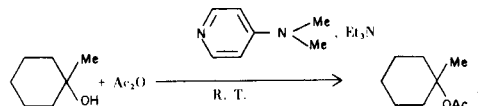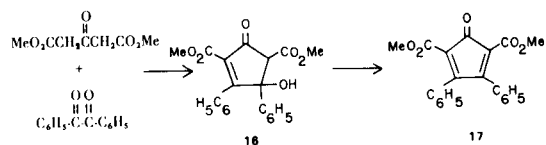

Dehydration Reaction

The utility of acetic anhydride as a dehydration agent may be illustrated with the preparation of veratronitrile which is obtainable from veratraldoxime by a brief treatment with acetic anhydride (19). Dehydration of 16,
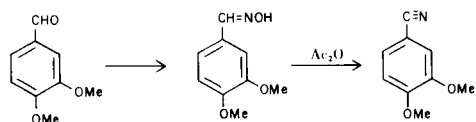

which was obtained from dimethyl acetonedicarboxylate and benzil was effected with acetic anhydride in the presence of an acid, giving 2,5-dicarbomethoxy-3,4-diphenylcyclopentadienone (17) (20).

Acetic anhydride was used as a dehydrating agent in the rearrangement reaction of hydroxamic acids to isocyanates, a reaction commonly called the Lassen rearrangement. For example, Nicolet and Pelc reported that oleoelaidohydroxamic acid rearranged to a mixture of cis- and trans-heptadecylenyl isocyanate on warming with an excess of acetic anhydride (21).

$$CH_3(CH_2)_7CH=CH(CH_2)_7C-NHOH \xrightarrow{Ac_2O} CH_3(CH_2)_7CH=CH(CH_2)_7NCO$$
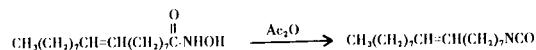
The dehydrative property of acetic anhydride has also been utilized in the structure elucidation of natural products. Thus, in the structure determination of gliotoxin, Woodward and coworkers treated dehydrodethiotoxin (18) with acetic anhydride at 230°, yielding 19 (22).
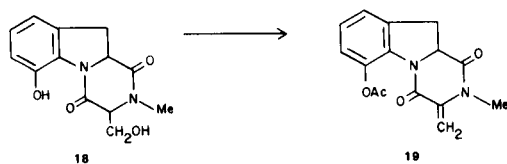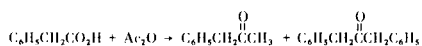

Reaction with Amino Acids

Reaction of α-amino acids with acetic anhydride in the presence of a base gives 2-acetamido ketones (23). This type of reaction is commonly known as the Dakin-West Reaction. Recently Allinger, et al., reviewed critically

$$\underset{NH_2}{RCHCO_2H} \longrightarrow \underset{NHCOCH_3}{RCHCOCH_3}$$
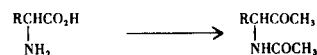
four types of mechanisms which have been proposed since the discovery of this reaction. From the kinetic study made on the decarboxylation of a group of α-acylamino acids, they concluded that the oxazolone mechanism proposed by Dakin and West was the only one in accord with the experimental data. It is suggested that either step 5 or step 7 is a possible rate-determining step (24) (Scheme 7). Decarboxylative acylation of phenylacetic


Scheme 7
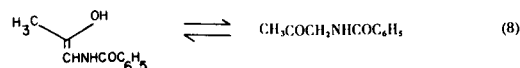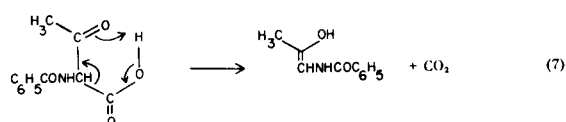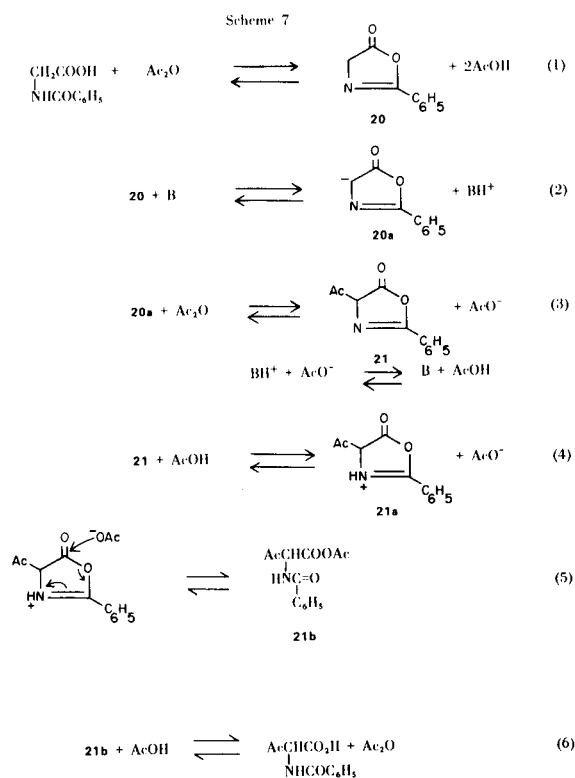
acid by acetic anhydride in the presence of pyridine, also discovered by Dakin and West, is formally analogous to the Dakin-West reaction (25). In this reaction, phenyl-acetone is the major product (56%) and dibenzyl ketone is obtained as a minor product (24%) (26). King and

$$C_6H_5CH_2CO_2H + Ac_2O \rightarrow C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_3 + C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_2C_6H_5$$

McMillan proposed an intermolecular mechanism which involves a transition state such as **22**. This explanation was supported later by an isotope study made by Nakai, et al., (27).
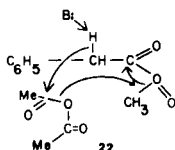
γ- or δ-Dialkylamino acids having primary alkyl groups on the nitrogen were also found to react with acetic anhydride. In these reactions, γ or δ-dialkylamino-ketones were the products (28). When the alkyl on the nitrogen is a secondary group which could form a stable carbonium ion an S_{N_1} type cleavage reaction takes place, resulting in the formation of a lactam (Scheme 8).

Scheme 8
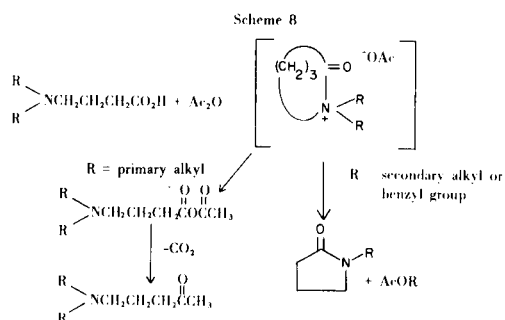
Formation of cevanidane (24), reported by Sheehan, et al., on treatment of 23 with acetic anhydride, is an example of this reaction found in natural product chemistry (29).
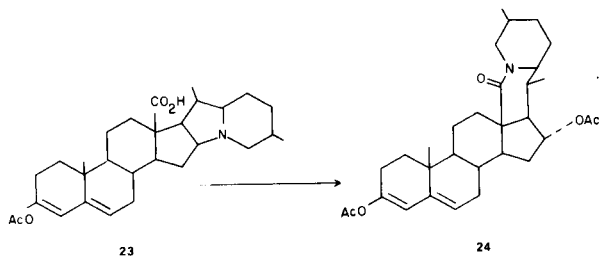

Cyclic β-amino acids rearrange on treatment with acetic anhydride, to α-methylene lactams. This type of rear-rangement was first observed by Stoll, et al., (30) in 1942, and later by Feries (31). Recently Rappaport and co-workers investigated the reaction in detail, and showed that the rearrangement proceeds via the zwitterion of

the amino acid through the protonated amine-mixed anhydride; the latter then undergoes β-elimination by the concurrently generated acetate ion, followed by recycliza-tion (32) (Scheme 9).

Scheme 9
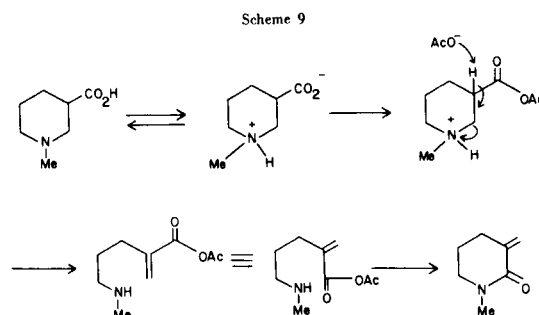
Hippuric acid (25) is known to condense with an aldehyde on treatment with acetic anhydride in the presence of sodium acetate, giving azlactone (27). This reaction, which is commonly referred to as the *Erlenmeyer-Plochl azlactone synthesis* (33), is a special type of the Perkin reaction; and is best suited for aromatic aldehydes. The azlactone thus formed is a versatile intermediate for the synthesis of a variety of different types of compounds, including α-amino acids and α-keto acids as well as pep-tides (34). It is believed that hippuric acid is first con-verted into 2-phenyloxazol-5-one (26) which then con-denses with aldehyde under the reaction conditions (35).
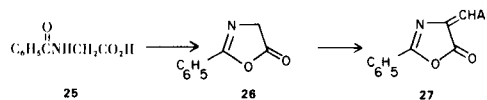

Perkin Reaction

The Perkin reaction is characterized by the formation of α,β-unsaturated carboxylic acids from aromatic alde-hydes and an acid anhydride in the presence of a base (36). m-Nitrocinnamic acid was prepared by heating a mixture of benzaldehyde, acetic anhydride, and sodium acetate at 180° for 13 hours in yield of 74-77% (37). As in an aldol condensation, a carbanion which is derived by proton abstraction on the anhydride, attacks the carbonyl
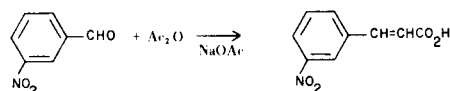
group of the aldehyde. Subsequent dehydration and then hydrolysis results in the product (38). In general, aliphatic aldehydes give low yields or are inert. This lack of reactivity of aliphatic aldehydes appears to be due to the slow elimination of water (39). The synthesis of coumarin from salicylaldehyde and acetic anhydride in the presence of triethylamine is another example of this reaction (40).
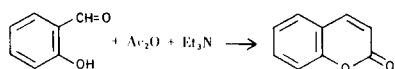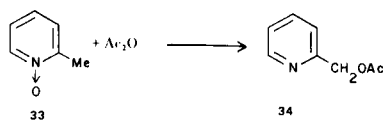
Reaction with N-Oxides

Katada reported in 1947 that the reaction of pyridine 1-oxide with acetic anhydride at 140-150° led to the isolation of 2-pyridone (41). It is now apparent that the product of the reaction was 2-acetoxy-pyridine, which was hydrolyzed during the work up to form 2-pyridone. Subsequently it was found that the reaction is a general type applicable to most N-heterocyclic ring systems (42,43). Kinetic (44) as well as isotopic studies (45) have shown that the reaction involves an intermolecular ionic path, with the rate-determining step being the attack of the acetate ion on the N-acetoxypyridinium ion at the 2-position (Scheme 10).
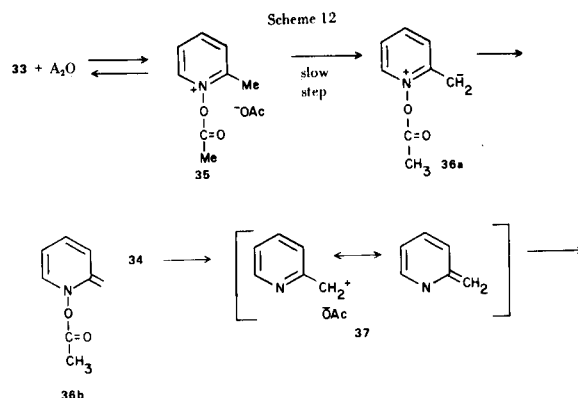
Scheme 10
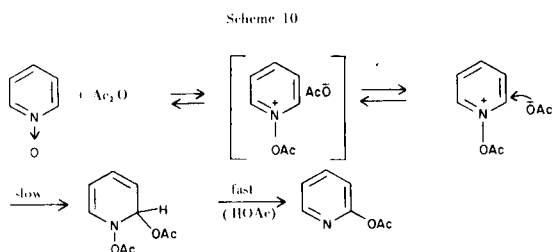
This type of rearrangement can also be found in open chain N-oxides. For example, the nitrone 28 was transformed on treatment with boiling acetic anhydride to 29 which on hydrolysis gave the amide 30. Based on a study made with homogeneously ¹⁸O-labeled acetic anhydride as well as kinetic measurements, Oae and co-workers proposed the following mechanism for this rearrangement (46) (Scheme 11).

Scheme 11
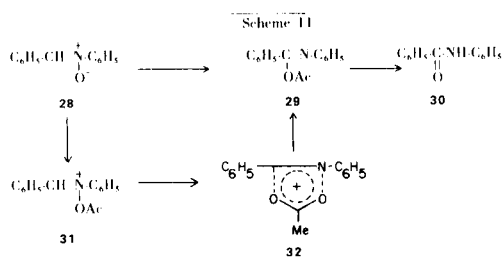
Kobayashi and Furukawa (47) in 1953 and three other groups (48-50) almost simultaneously discovered independently that treatment of 2-picoline 1-oxide (33) with an excess of boiling acetic anhydride gave 2-pyridylmethyl acetate (34). Soon afterwards it was realized that the

side-chain acyloxylation by acetic anhydride is a general reaction for the N-oxides of N-hetero-aromatics with a side-chain (42,43). These types of reactions have found wide utility in synthetic chemistry as a convenient means of obtaining heterocyclic carbinols and aldehydes. The mechanism of the reaction has been the subject of intensive research. A variety of reaction mechanisms, including a radical-chain mechanism, have been proposed in the past. It is now generally thought that the first acylation takes place reversibly followed by slow formation of a zwitterionic species (rate determining step). The anhydro base 36b is considered to be an intermediate. Rupture of the N-O bond of the intermediate and subsequent intramolecular recombination leads to the observed product, 34 (51) (Scheme 12). However, a stereo-

Scheme 12

chemical study recently made by Parham and Olson (52) using isotopically labeled quinoline 1-oxide derivatives precluded the possibility of the anhydro base being an intermediate in the reaction scheme. An analogous rearrangement reaction occurred when 4-alkylpyridine 1-oxides were heated with acetic anhydride. A reaction mechanism which is similar to that for 2-picoline N-oxides is generally accepted for this rearrangement reaction (53,54). A controversy (55,57) which had prevailed concerning the nature of the rapid rearrangement steps of the anhydro base intermediate 37 to 39 appears to have
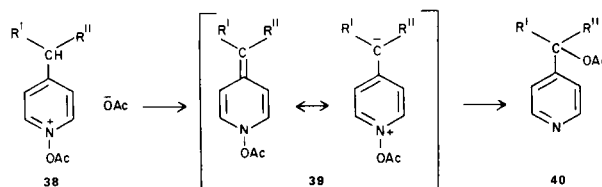

been settled through convincing evidence recently presented by Traynelis and co-workers (54). Traynelis, et al., observed that treatment of 4-neopentylpyridine 1-oxide (41) with acetic anhydride gave 44 (54%) in addition to the expected ester 43 (31%) (54). These results supported an ionic pair intermediate such as 44 for the rearrangement step (Scheme 13). Extension of the Katada reaction
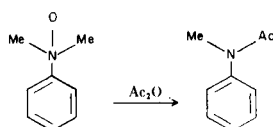
Scheme 13
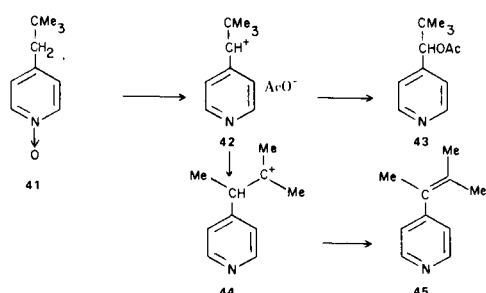
was recently realized by Humana and co-workers. They showed that quinoline 1-oxide reacts readily with active methylene compounds in the presence of acetic anhydride to give 2-substituted quinolines in good yields. For example, treatment of quinoline 1-oxide **46** with ethyl cyanoacetate in acetic anhydride gave **47** in 83% yield (58) (Scheme 14).

Scheme 14
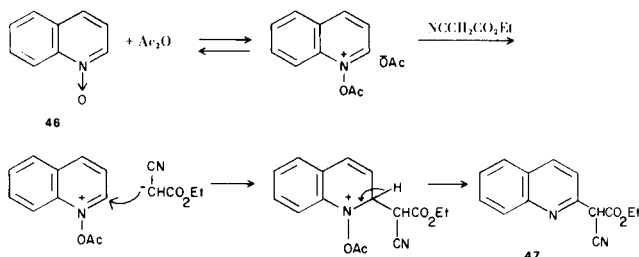
Tertiary amine N-oxides also react with acetic anhydride, resulting in the formation of the acetamide of the corresponding secondary amines. This reaction was


discovered by Polonovski in 1927 (59) and is now referred to as the *Polonovski reaction.* A reaction mechanism which involves an ylide as an intermediate was presented by Hayashi, *et al.*, based on a trapping experiment (60) (Scheme 15).

Scheme 15
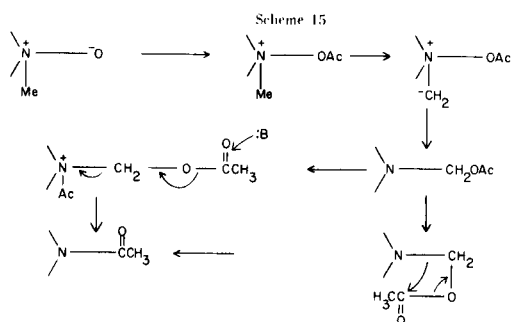
An application of such an N-oxide rearrangement reaction is found in the synthesis of a therapeutically important 2-hydroxybenzodiazepine, **51** (61). The latter compound was prepared by Bell and Childress by treatment of the benzodiazepin-2-one 4-oxide **48** with acetic anhydride, followed by alkaline hydrolysis (62). Using


48 (R = H)
49 (R = Me)   50   51
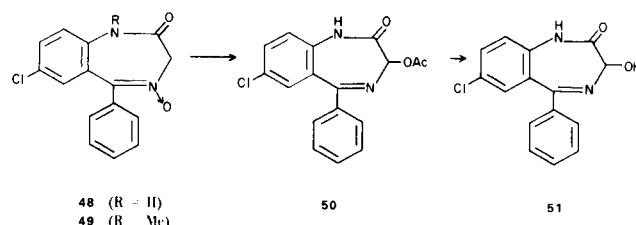
^{18}O-enriched acetic anhydride and mass spectral technique, Castagnoli and Sadee recently showed that the rearrangement of **51** with acetic anhydride occurred in an intramolecular fashion (63). In contrast to the 5-phenyl-benzodiazepine 4-oxides, the 5-methylbenzodiazepine 4-oxide **52** took a different course in the rearrangement, to give the side-chain acetoxylated product **53** (64).


52   53
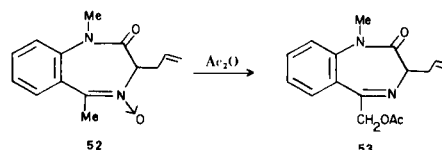
Another type of pyridine N-oxide reaction with acid anhydride was discovered simultaneously by three independent research groups; Cohen, *et al.*, (65), Rüchardt, *et al.*, (66), and Koening (67). In this reaction pyridine N-oxide is reduced to pyridine, with concomitant oxidation of the acid anhydride to a carbonyl compound, carbon dioxide, and carboxylic acid, as illustrated with phenylacetic anhydride. Numerous reaction mechanisms for the
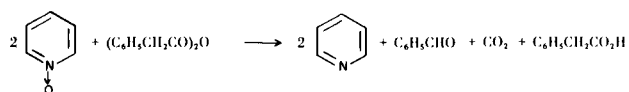
process have been proposed by the three groups (68). Among these proposed mechanisms, one suggested by Cohen, *et al.*, appears to account for the experimental facts best, although not completely satisfactorily (69). The first step is a reversible acylation of the N-oxide to give the cation **54**. The reversible formation of an enol species **55** precedes the rate-determining step in which **55** loses pyridine to form a cationic intermediate, **56**. The latter intermediate combines with a second pyridine N-oxide molecule to give **57**. Decarboxylative fragmentation of **57** with the loss of pyridine gives the observed products (69) (Scheme 16).

Scheme 16

56

57
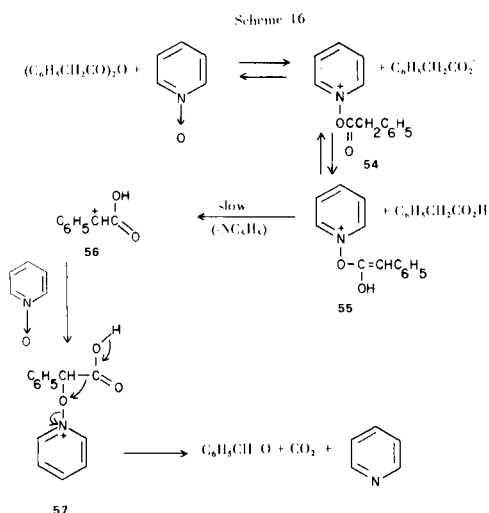
When the α or β-positions of the N-oxides are blocked, the acetate ion finds an electrophilic center elsewhere. Thus when 58 was treated with acetic anhydride, 59 was obtained (70). A mechanism for the reaction was proposed by Livingstone and Tennant (71). It is interesting
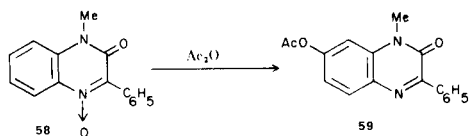
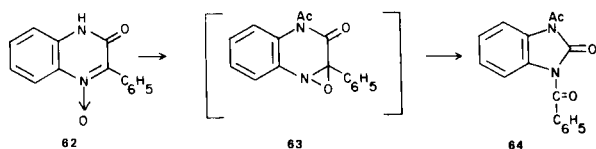to note that under similar conditions 3-(o-hydroxy-phenyl)quinoxalin 1-oxide (60) took a cyclization reaction path, giving 61 in 70% yield (72). In the case of 62,
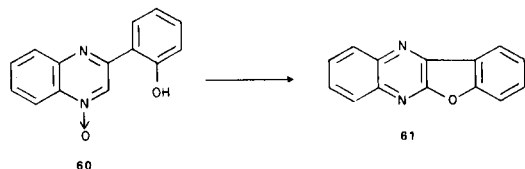

where the 4-position was unsubstituted, a rearrangement reaction occurred, giving 64. An oxaziridine intermediate (63) was proposed for the rearrangement reaction (70).


This type of ring contraction-rearrangement reaction was also observed with pteridine N-oxide by Hutzenlaub, et al., (73). 1,3-Dimethyluric acid (66) was isolated in 84% yield when 65 was refluxed with acetic anhydride for 20 minutes.
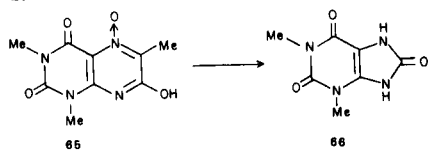
Acetic anhydride caused 6-aminopurine 1-oxide to cleave its pyrimidine nucleus when heated under reflux for 5 minutes. The initial N-acetoxy acetate salt 68 suffered cleavage of the pyrimidine ring by the acetate group. The 6-amino and 1-acetoxy groups of 68 reacted to form the 1,2,4-oxadiazole ring. Subsequent reaction of 69 with acetic anhydride (see the reaction of acetic anhydride with Schiff bases) led to the isolated product 70 (74) (Scheme 17).

Scheme 17
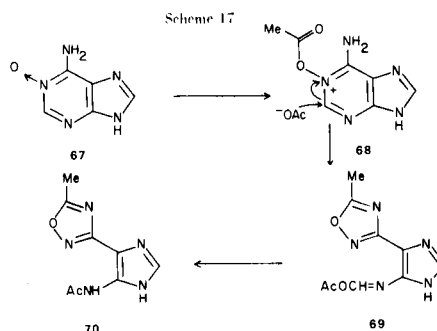
Heterocyclic N-hydroxides were also reported to react with acetic anhydride in a similar manner. Thus treatment of 71 (X = S) with acetic anhydride gave the 2-acetoxy derivative 72 (75). Interestingly, 71 (X = O) gave the 6-acetoxy derivative 74 (75). However, under similar conditions, benzothiazin 1,1-dioxide (75) formed only the 4-acetoxy derivative 76 (75) (Scheme 18).

Scheme 18
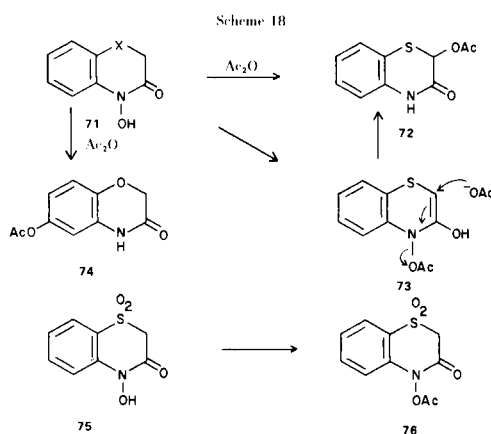
Reaction with Sulfoxides

The reaction of sulfoxides with acetic anhydride is formally analogous to that of N-oxides of tertiary amines. Pummerer observed in 1910 that treatment of sulfoxides with boiling acetic anhydride gave 2-acetoxy sulfoxides (76). A reaction of this type is now called the *Pummerer reaction* (77). The mechanism of this reaction has been
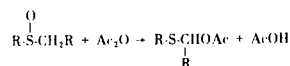
a subject of intensive research and it is now generally
agreed that it involves an initial acetylation of the
sulfoxides and subsequent formation of a sulfur-stabilized
carbonium ion intermediate (78) (Scheme 19).

Scheme 19

The synthesis of **78** from the sulfoxide **77** by treatment
with boiling acetic anhydride is an example which demon-
strates the value of the Pummerer reaction for heterocyclic
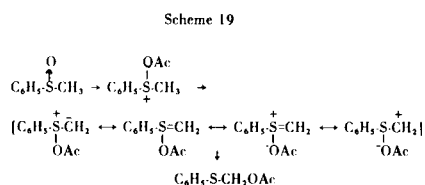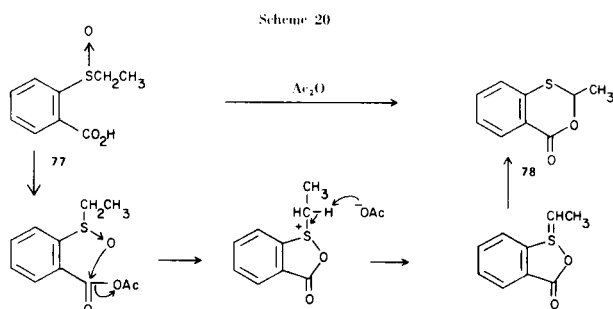synthesis (79). A likely mechanism for the reaction is
given below (79, 80) (Scheme 20). In the case of the

Scheme 20

corresponding carbamoyl sulfoxides, the mode of cycliza-
tion was changed by a slight modification in structure.
Thus o-methylcarbamoyl sulfoxide (**79**) was cyclized to
give **84**, and the corresponding N-unsubstituted sulfoxide
80 gave **83** on treatment with refluxing acetic anhydride
(79). For both reactions the involvement of a cyclic
aminosulfonium salt **82** has been suggested (80) (Scheme
21).

Scheme 21
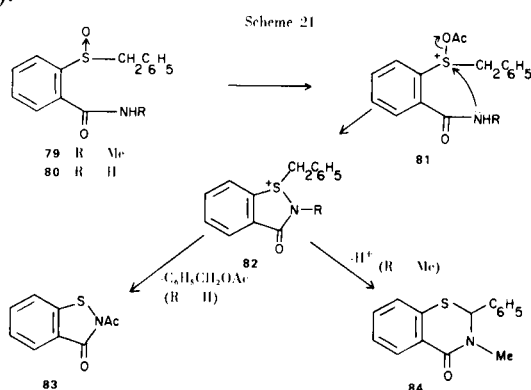
Morin, et al., discovered in 1963 that when the penicil-
lin sulfoxide **85** was treated with refluxing acetic anhyd-
ride, an unusual type of Pummerer rearrangement reaction
occurred to give a ring expansion product, **86** along with
87 (81). This observation eventually led Chauvette, et al.,
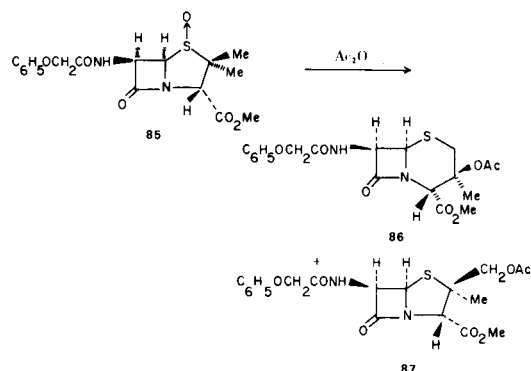
at Eli Lilly and Co. to the successful discovery of an
economically feasible chemical means of converting peni-
cillin V (**88a**) and G (**88b**), which are available cheaply
from fermentation, to cephalexin (**89**), a broad spectrum,
orally active antibiotic (82). The reaction mechanism of
this interesting sulfoxide rearrangement reaction has been
investigated in great detail and has recently been reviewed
(83).

88a: R = C₆H₅O
88b: R   C₆H₅   89
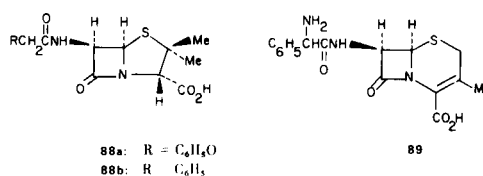
Ring Closure Reaction

A wide variety of cyclization reactions were brought
about by acetic anhydride resulting in many different
classes of heterocyclic compounds. The following reac-
tions have been arbitrarily chosen to illustrate the delicate
but versatile nature of this reagent for ring closure
reactions.

Distillation of dibasic carboxylic acids with acetic
anhydride yields either cyclic anhydrides or cyclic ketones,
depending on the length of carbon chain. Dibasic acids
with n ⩽ 3 give cyclic anhydrides and those with n ⩽ 4
form cyclic ketones. This is generally known as the
Blanc reaction (84). Ruzicka and co-workers utilized
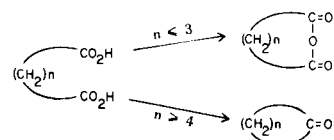
this type of reaction in their synthesis of A-*nor*-androstan-
one (**91**) from the dicarboxylic acid **90** (85).
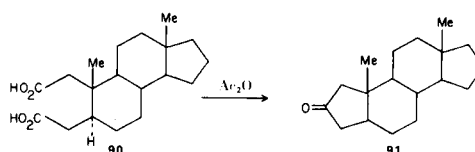
The preparation of homophthalic acid anhydride (93) exemplifies anhydride formation form a dibasic carboxylic acid with a three carbon atom chain on treatment with acetic anhydride (86).

N-Acylanthranilic acids are known to cyclize when heated with acetic anhydride to give 3,1,4-benzoxazones. For example, Zentmyer and Wagner reportedly obtained 2-phenyl-3,1,4-benzoxazone (95) in 81% yield when N-benzoylanthranilic acid (94) was refluxed with an excess of acetic anhydride with slow distillation of the acetic acid formed (87).

Treatment of 4-(N-substituted-2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid (96) with acetic anhydride gave the corres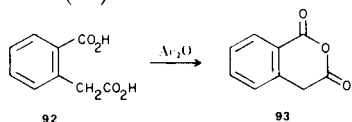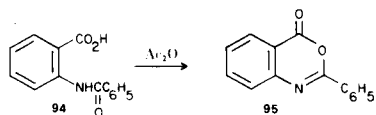ponding lactone 97 (88). However, when the hydroxyethylamino group is unsubstituted at the nitrogen, the reaction takes a different path, giving oxazolo[2,3-b]pyrimido[4,5-d][1,3]oxazine (99) under similar conditions. An explanation given by Kim and Santilli involves an intermediate such as 98, which is generated by acetylation on both the carboxylic acid and hydroxy groups (88) (Scheme 22). A further
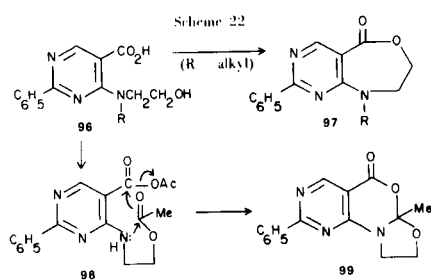
variation in the cyclization course was noted when the hydroxy group in the substituent at the 4-position of the pyrimidine became a tertiary carbinol. Thus 100, on refluxing with an excess of acetic anhydride, gave 101. A proposed reaction mechanism is given below (88) (Scheme 23). Introduction of a π-bond between the amino nitrogen and the hydroxy oxygen as in 102 gave the lactone 103 (89). Extension of the above reaction to an athranilic acid derivative (104) resulted in a novel type of cyclization reaction, giving 105 in one step (90) (Scheme 24). The difference in the mode of cyclization between 102 and its phenyl analog 104 may possibly be due to the difference in the basicities of the amino groups.
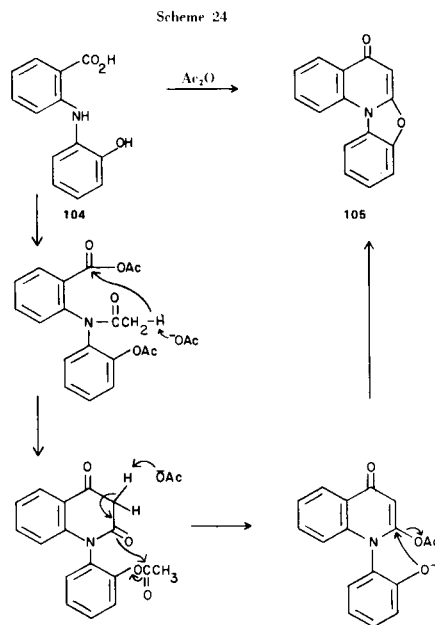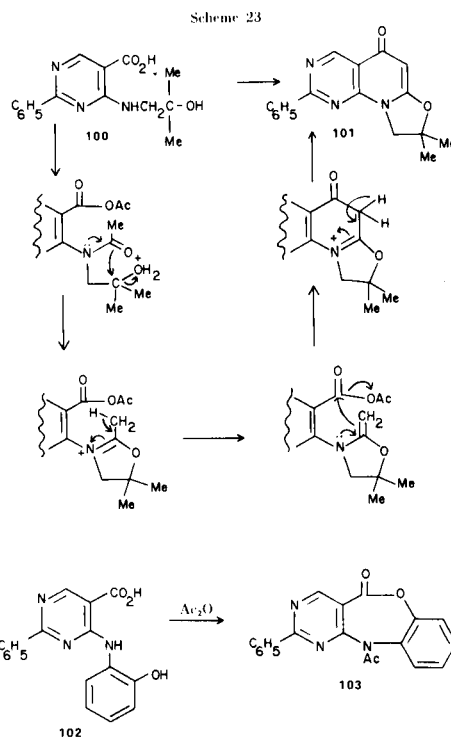
o-Formylphenoxyacetic acid cyclizes on heating with acetic anhydride in the presence of sodium acetate to give coumaritic acid (91). Modification of the reaction by addition of acetic acid gave coumarone directly (92). Rodionov, et al., prepared the benzothiophene 108 from thiosalicylic acid 106 by effecting the ring closure of 107 with acetic anhydride (93).
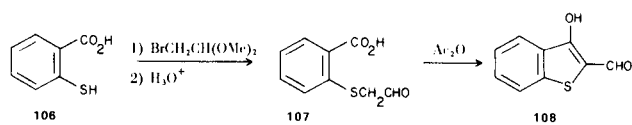
The operation of demethylative lactam formation was noted by Teitel, *et al.*, in their synthesis of "Schopf's base VI" (111) (94). Treatment of 109 with a large excess of acetic anhydride under reflux for 1 hour gave 110 in 64% yield. Reduction of 110 with diborane gave the base.
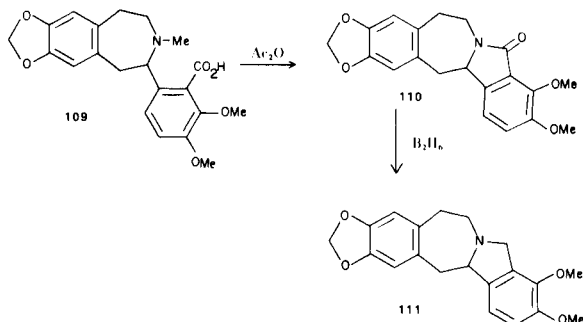
Sugihara, *et al.*, showed that 112 cyclizes to give 113 in 76% yield on treatment with acetic anhydride and acetid acid (95).

Certain enamines are known to undergo a ring closure reaction when treated with acetic anhydride. For example, enamine 114, derived from proline and dihydroarcinol, experienced cyclization when heated with acetic anhydride, leading to 116. A mixed anhydride 115 was speculated as an intermediate which then cyclized with displacement of acetate ion (96) (Scheme 25).

Scheme 25

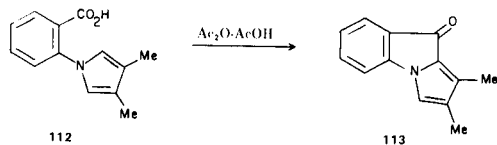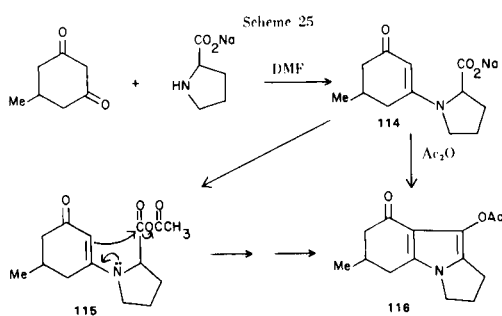Pinnow observed as early as 1894 that treatment of o-aminodimethylaniline (117) with acetic anhydride formed 1,2-dimethylbenzimidazole (118) instead of the expected acetylation product (97). An explanation for this unusual cyclization reaction was given recently by Meth-Cohn and Suschitzky (98) as shown below (Scheme 26).

Scheme 26
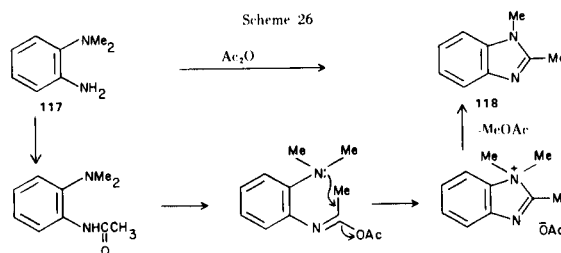
Nitrogen-bridged [12] annulene (121) was prepared by Awaya, *et al.*, by allowing acetic anhydride to react with 120 which was obtained from the reaction of 119 wtih ethoxymethylene malononitrile (99).
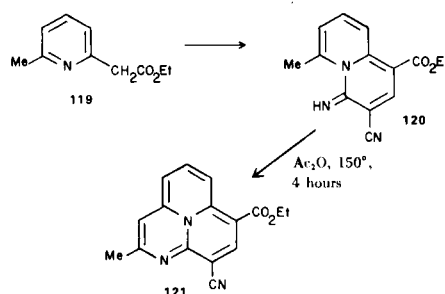
Woodward and Singh elegantly utilized acetic anhydride in their total synthesis of an antibiotic, patulin (126). Treatment of 122, obtained from the reaction of tetrahydro-γ-pyrone and diethyl ketomalonate followed by hydrolysis, with a mixture of acetic anhydride and acetic acid generated a lactal acetate (123) with the basic skeleton of patulin. Bromination of 123 with NBS and subsequent treatment with silver acetate gave the acetoxy acetate 124. The latter was then briefly treated with a warm mixture of acetic anhydride, acetic acid and sulfuric acid to give patulin acetate (125). Hydrolysis of 125 gave patulin (126) (100) (Scheme 27).

Scheme 27
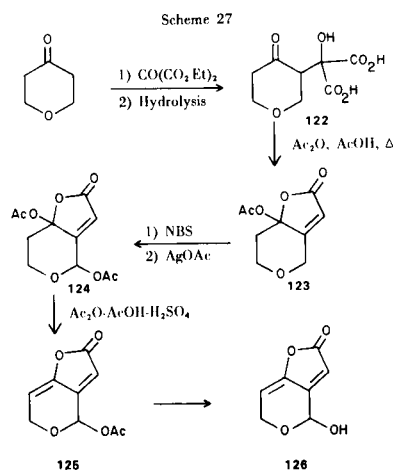
N-Nitroso-N-phenylglycine (127) reacts smoothly with acetic anhydride to give a meso-ionic compound, sydnone (128) (101). This reaction was first discovered by Earl

and Mackney (102) in 1935 at the University of Sydney (from which the name sydnone came), and the current meso-ionic structure was invoked by Baker, Ollis and Poole in 1949 (103). A kinetic study on the formation of sydnone was made recently by Ogata, et al., (104). The

127 **128**
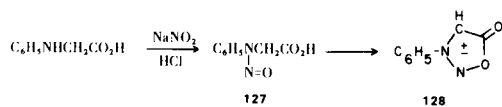
following reaction mechanism was suggested by them on the basis of the kinetic data (104). An intramolecular nucleophilic attack by the nitroso oxygen on the carbonyl carbon (activated by hydrogen-bonded acetic acid) of a mixed anhydride leading to the cyclized product is believed to be the rate-determining step (Scheme 28).

Scheme 28
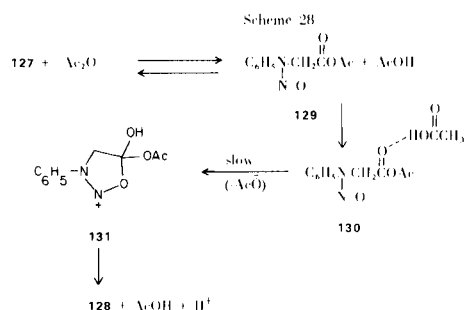
The preparation of N-arylmaleimide (136) from N-arylmaleamic acid (132) by means of acetic anhydride has been the subject of many studies (105). The reaction is known to be catalyzed by base such as sodium acetate. Several contradicting reports have appeared in the past. An extensive study made by Sauers suggested that the reaction path which involves N-arylmaleisoimide (134) as an intermediate, constitutes the major route to the imide. Direct formation of the imide appears to take place to a lesser extent (105) (Scheme 29).

Scheme 29

Acetic anhydride has also been used to cause an inter-molecular cyclization reaction ot occur. Taylor and co-workers showed that 1,3-dimethyl-6-aminouracil (137) undergoes a cyclic condensation reaction with nitroso-benzene in acetic anhydride, resulting in the formation of 1,3-dimethylalloxazine (139) (106). Acetic anhydride is
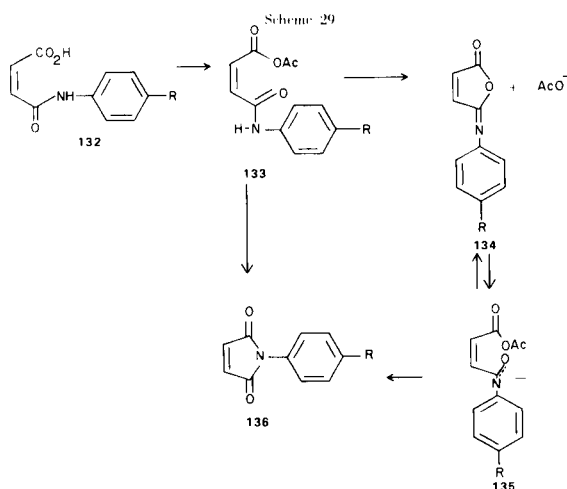

137 **138** **139**
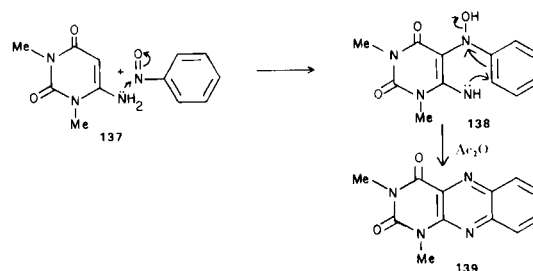
thought to be involved in the dehydration of the inter-mediate hydroxylamine. In the case of 1,3-dimethyl-6-alkylaminouracil, (140) the reaction took a different course under similar conditions, giving the 7-phenyltheo-phylline 141 (107) (Scheme 30).

Scheme 30

140 **141**
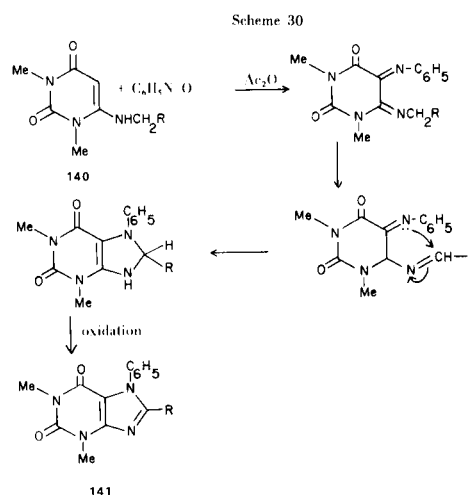
Molecular Rearrangement

Many novel types of molecular rearrangement reactions have been brought about by acetic anhydride. The following are illustrative examples which demonstrate the intriguing nature of acetic anhydride for such purposes.

Fryer, et al., reported that 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (142) (unsubstituted at the 1-position) rearranges to 1-acetylisoindole (143) when heated with acetic anhydride in the presence of pyridine (108) (Scheme 30). The reaction mechanism proposed by the authors involves an initial acetylation at the 1-position followed by a double ring contraction brought about by the acetate anion. Contrastingly, the reaction of 142 with acetic anhydride, when carried out in the presence of a catalytic amount of sulfuric acid,

Reviews

Scheme 31
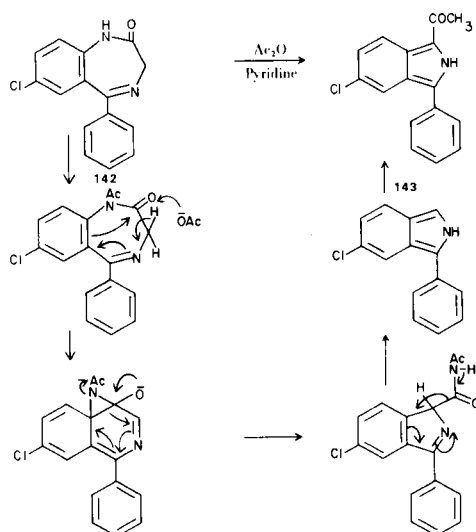
look an entirely different path, leading to the formation of **144** and **145**. Under these conditions, an acetylation at the N-4 position is believed to be the initial reaction. The following mechanism was suggested by Fryer and Sternbach (109). The formation of the anilide **145** was explained with the postulation of an addition product which reacts with another molecule of the starting material resulting in the ring cleavage (109) (Scheme 32).

Scheme 32
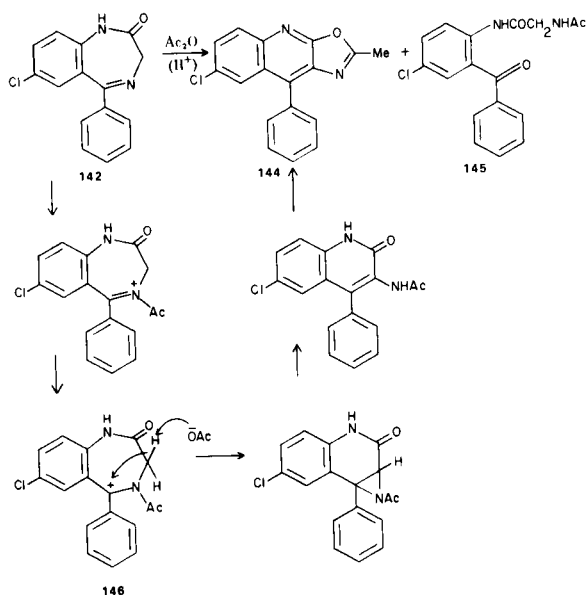
Still another interesting rearrangement reaction was observed with compounds in this series. When the 3-allyl-1,4-benzodiazepine 4-oxide **147** was allowed to react with boiling acetic anhydride, the reaction proceeded beyond the N-oxide rearrangement stage, resulting in the formation of pyrrolo[2,1-c][1,4]benzodiazepine **148**. The

suggested reaction mechanism involves the N-oxide rearrangement, dehydration, and nucleophilic attack by the acetate anion at the 5-position, with a concomitant pyrrole ring formation (110) (Scheme 33).

Scheme 33
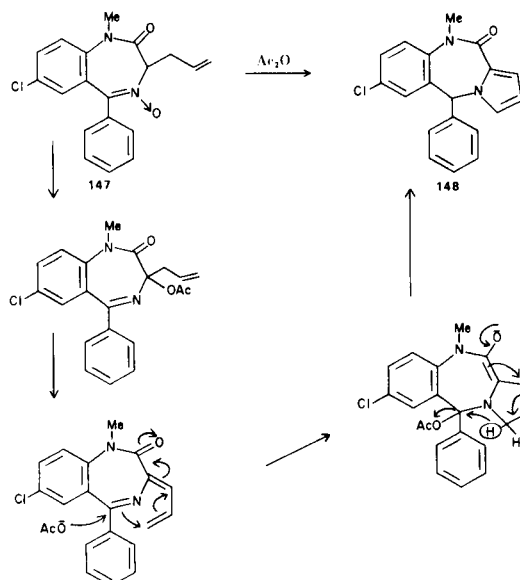
Jones, et al., reported that brief treatment of tetrahydro-4-oxoisoazolo[2,3-a]pyridinium bromide **(149)** with boiling acetic anhydride did not cause the expected aromatization to occur (see latter part of this article), but instead caused a rearrangement reaction, giving the furopyridone **150** in 49% yield (111). A ketene **(151)** was invoked as a possible intermediate in this reaction. The assumption that the reaction is initiated by a proton abstraction from the 2-position was supported by the observation that the corresponding 2-methyl derivative failed to undergo the rearrangement reaction, whereas the 3-methyl derivative did (111). Under similar conditions,
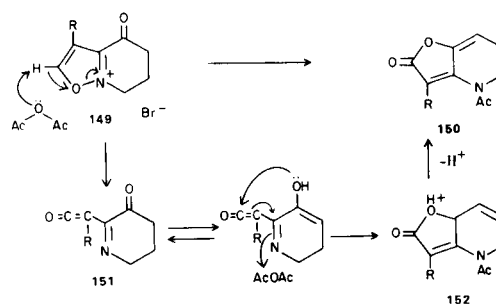
however, the 5-bromo derivative **153** underwent only a ring fission reaction, giving two products, **154** and **155**, the former being the major product (111) (Scheme 34). A
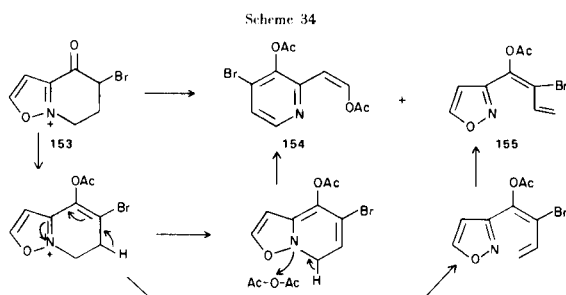
Scheme 34

similar type of rearrangement reaction was observed with the corresponding oxime (156) when heated with acetic anhydride, giving 157 (112) (Scheme 35). The suggested mechanism (Scheme 34) involves a ketene intermediate. However, an alternative explanation which postulates a mixed anhydride as an intermediate could not be ruled out (112).

Scheme 35
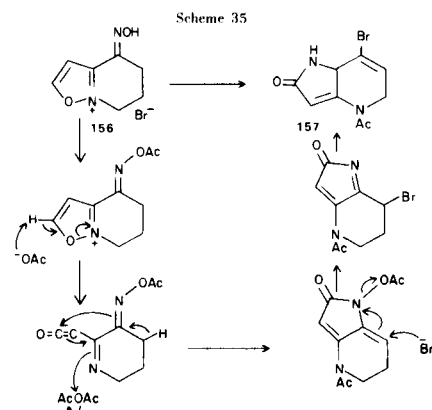
Aromatization

Jones and Jones reported that boiling acetic anhydride aromatized quinolizinium ketone (158) to give 159 in high yield (113). An explanation given by the authors involves a double bond isomerization of the enol acetate, a protonation at the 1-position and subsequent 1,4-elimination (113) (Scheme 36). While 160 was aromatized under

Scheme 36
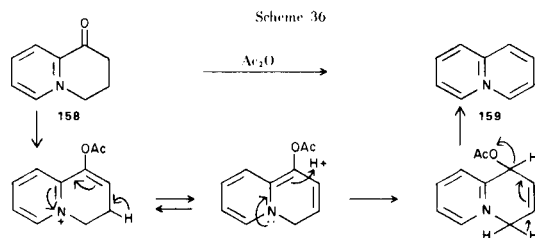
similar conditions, its isomer 161 failed to react. These facts appear to be in agreement with the suggested mechanism.
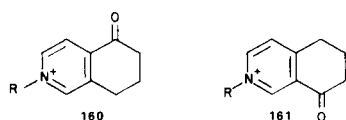
An efficient one-step aromatization of cyclohexanediones to the corresponding diacetoxybenzenes, reported by Kablaoui uses an acetic anhydride-acetic acid mixture in the presence of sulfuric acid. Thus, the aromatization of 1,4-(162) and 1,2-cyclohexanediones 164 with the reagent gave, after hydrolysis, 163 and 165, respectively, in over 90% yield (114).
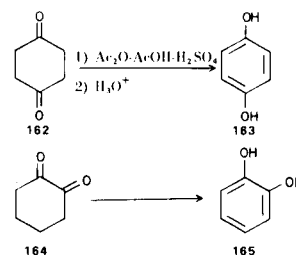
Miscellaneous Reactions

Passerini and Macentelli discovered in 1929 that Schiff base, when heated under reflux with acetic anhydride, gave an unstable addition product (166) which decomposed readily on treatment with aqueous base or acid, yielding the corresponding aldehydes and acetylated amines (115).
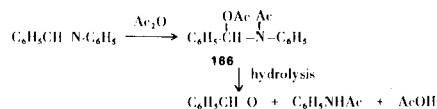
Acetic anhydride in combination with DMSO is used to oxidize primary and secondary alcohols to the corresponding carbonyl compounds at room temperature (116). Thus, Albright and Goldman oxidized yohimbine (167) to yohimbinone (168) in 80-85% yield with that mixture (116). A reaction mechanism suggested by Albright and
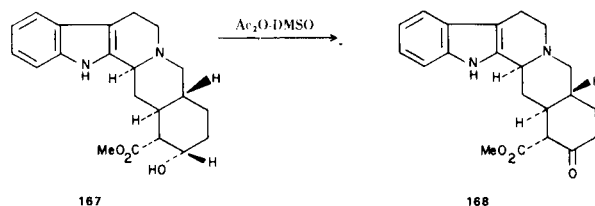
Goldman involves an acyloxysulfonium salt such as 169 as an intermediate (116) (Scheme 37).

Scheme 37
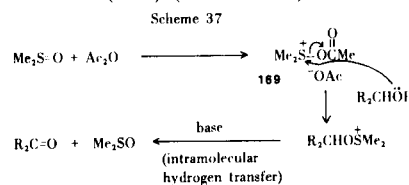
Organomagnesium halides (Grignard reagents) react with acid anhydrides in much the same way as acyl halides. The reaction of acetic anhydride with a molecular equivalent of alkylmagnesium bromide results, after hydro-

lysis of the magnesium complex, in the formation of methyl ketones (117). Newman and Smith showed that the best yields were obtained when the reaction was carried out at 70° (118,119).

$$RMgBr + Ac_2O \longrightarrow R\overset{O}{\underset{\parallel}{C}}CH_3 + BrMgOAc$$
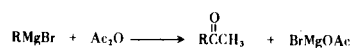
Acetic anhydride has been used in the Friedel-Crafts reaction as an acylating agent (120). For example, 2-acetylfluorene was prepared from fluorene using acetic anhydride as a acetylating agent in 55-63% yield (121).

Acetic anhydride reasts with isocyanates. The reaction, which was discovered by Wurtz as early as 1854, gives N-ethyldiacetimide when ethyl isocyanate is heated with acetic anhydride (122). Hurd and Prapas investigated the reaction in depth and proposed the following reaction mechanism (123) (Scheme 38).
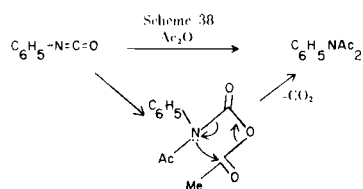
Thioureas give isothiocyanates on heating with acetic anhydride. This reaction was also discovered before the turn of the century by Kalckhoff (124). p-Acetoxyphenyl isothiocyanate was prepared from the reaction of 1,3-bis-(p-hydroxyphenyl)thiourea with acetic anhydride (125).
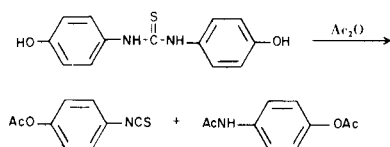
Reaction of 2-dimethylamino-1,3-dioxolans with acetic anhydride affords alkenes. Eastwood, et al., used this reaction in converting 1,2-diols into alkenes (126). Racemic 1,2-diphenylethane-diol (170) was first treated with N,N-dimethylformamide dimethylacetal to give the dioxolan 171. Heating the intermediate 171 with acetic anhydride at 180° for 2 hours gave trans-diphenyl-ethene (172) in 80% yield (126).

Many other interesting reactions and uses of acetic anhydride have been reported, especially in the last several years. Limitation of space, however, precludes inclusion of these in this review. Many of the reactions discussed here are believed to be applicable to other carboxylic acid anhydrides, and some to acid chlorides.
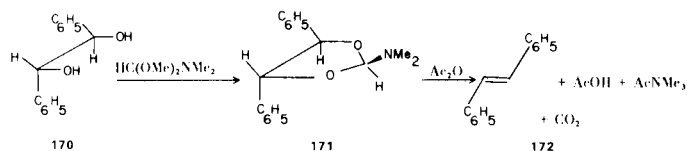
Conclusion

Acetic anhydride has unique and versatile chemical properties which no other reagent can match. It can function as a nucleophile, electrophile, and dehydrating agent. In addition, the acetate ion which is generated in situ by a nucleophilic reaction on acetic anhydride brings about a wide variety of intriguing molecular reorganizations (127).

The acetate group formed initially may serve as a leaving group at a later stage of the reaction. The versatility of the compound is widened further when it is used in combination with a base, an acid, or an oxidizing agent.

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