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The chemical reactions of acetoacetanilides are reported and the literature data are discussed.

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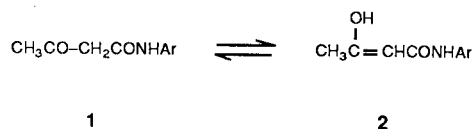
Contents.

- I. Introduction
- II. Chemical Properties and Reactions
 1. Pyrolysis and Photolysis
 2. Metal Complexes
 3. Reduction
 4. Halogenation
 5. Alkylation
 6. Acylation
 7. Reaction with sulfur halides
 8. Mercuration
 9. Reaction with 2,4-Dinitrochlorobenzene
 10. Formation of Sulfonium Ylides
 11. Reaction with Formamidines
 12. Nitrosation
 13. Reaction with Nitrosobenzene
 14. Reaction with Aldehydes
 15. Reaction with Ketonic Compounds
 16. Coupling with Diazonium Salts
 17. Reaction with Quinones and Derivatives
 18. Michael Addition
 19. Action of Boron Trifluoride
 20. Reaction with Carbonyl Reagents
 21. Reaction with Ammonia and Amines
 22. Reaction with Hydroxy Compounds
 23. Reaction with Cyano Compounds
 24. Reaction with Alkali Cyanide
 25. Reaction with Ortho Carboxylic Esters
 26. Reaction with Hydrazonyl Halides
 27. Reaction with Hydrogen Sulfide
 28. Reaction with Isocyanates
 29. Cyclisation Reactions
 - A. Formation of Carbostryrils
 - B. Formation of Pyridones
 - C. Other Cyclisation

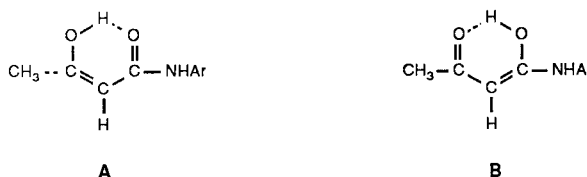
Introduction.

Acetoacetanilides (3-oxobutanilides) are readily available. They have three active centres and find exten-

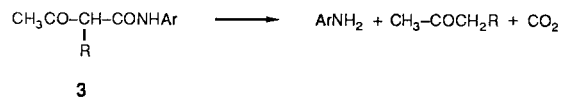
sive utility in the formation of metal-complexes, manufacture of dyes and synthesis of heterocycles. They exhibit keto **1**, enol **2** tautomerism. The enol content of acetoacetanilide is about 9.5% in ethanol and increases to 43% in ether [1-4].



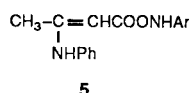
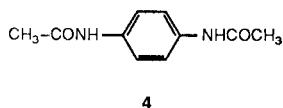
Of the two possible chelate structures, **A** and **B**, the enol structure, **A**, seems to be more stable.



Acetoacetanilide reduces ammoniacal silver nitrate forming a silver mirror [1]. Acetoacetanilides and their α -alkyl derivatives **3** are hydrolyzed by acids, alkalis, or water at 200° to give the amine and decomposition products of acetoacetic acid [1,5,6].



However, α,α -diethyl and α -methyl- α -(*n*-propyl)acetoacetanilides appear to be stable to the action of 30% sulfuric acid; they are recovered unchanged after four days refluxing in this medium [7]. When *p*-acetylaminoacetoacetanilide is fused with alkali, *N,N'*-diacetyl-*p*-phenylenediamine (**4**) is obtained [8]. Acetoacetanilide is partially transformed into ethyl β -anilinoacrylate (**5**) on heating with a dehydrating agent (Drierite) in ethanol [9].

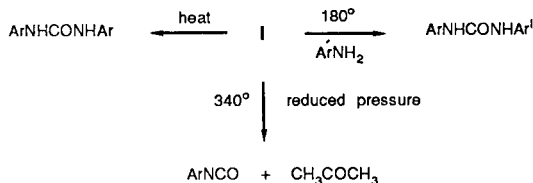


The infrared spectrum of **1** (Ar = C₆H₅) reveals a strong band due to an unconjugated C=O, (OH stretching vibration is absent), thus indicating that under ordinary conditions **1** exists almost entirely in the keto form [10-13]. This is substantiated by its nmr spectrum, which shows the presence of a methylene group, and small signals due to OH and CH groups [10,11-14].

Chemical Properties and Reactions.

1. Pyrolysis and Photolysis.

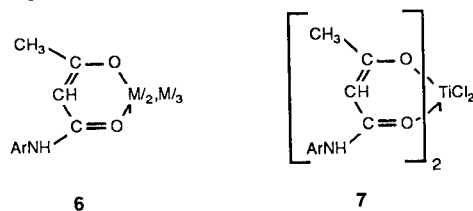
Heat, pressure or ultraviolet radiation are the main three factors affecting the pyrolysis of acetoacetanilides **1**; they decompose on distillation yielding diphenylurea [1,15]. Also, heating **1** at high temperatures (*ca.* 200°) with or without solvent, affords sym-diarylureas [16-19]. Asym-diarylureas are obtained when **1** is heated with primary aromatic amines. When **1** is heated at 180-200° under pressure, aniline is formed as the main product, along with small amounts of acetone and sym-diphenylurea [20,21]. However, pyrolysis of **1** at >340° under reduced pressure provides arylisocyanates and acetone [20,22]. Isocyanates could not be isolated from the pyrolysis of *p*-nitro and *p*-carboxyacetanilides. However, pyrolysis of *N*-*t*-butylacetoacetanilide gave phenylisocyanate. The *N*-ethyl derivative of **1** was recovered unchanged from the pyrolysis reaction [20]. Under ultraviolet irradiation, **1** gives an 18% yield of phenyl isocyanate [23].



Metal Complexes.

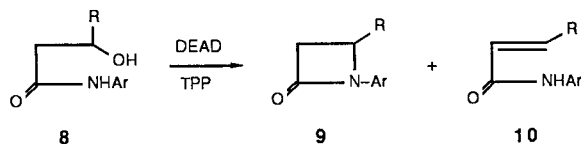
Acetoacetanilides give the metal chelate complexes **6** and **7** with copper [1,24-27,29], beryllium [10,24,28], iron(III) [10], chromium(III) [10,30], niobium [11] tantalum [11], and titanium [31]. The metal atom reacts with the C-3 oxygen of the acyl group in its enol form and with the carbonyl group of the carbamoyl group. The ir, nmr and mass spectroscopy of these complexes have been studied [10,11,25,28,29]. An octahedral structure is suggested for the complexes and conductance measurements indicate nonelectrolytic nature of them [32]. *Cis* and *trans* isomers of Cr(III) complexes were isolated and resolved. Thermogravimetric analysis studies of these isomers show that *trans* compounds are thermally more stable than the *cis*

compounds [30]. Nickel and cobalt bis-acetoacetanilides form adducts with heterocyclic bases as pyridine and picolines [32].



3. Reduction.

Acetoacetanilides are reduced by potassium borohydride/lithium chloride in tetrahydrofuran to give 3-hydroxybutananilides **8** [33,34]. The latter compounds can be converted with diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) to *N*-aryl-β-lactams **9** and crotonanilides **10**.

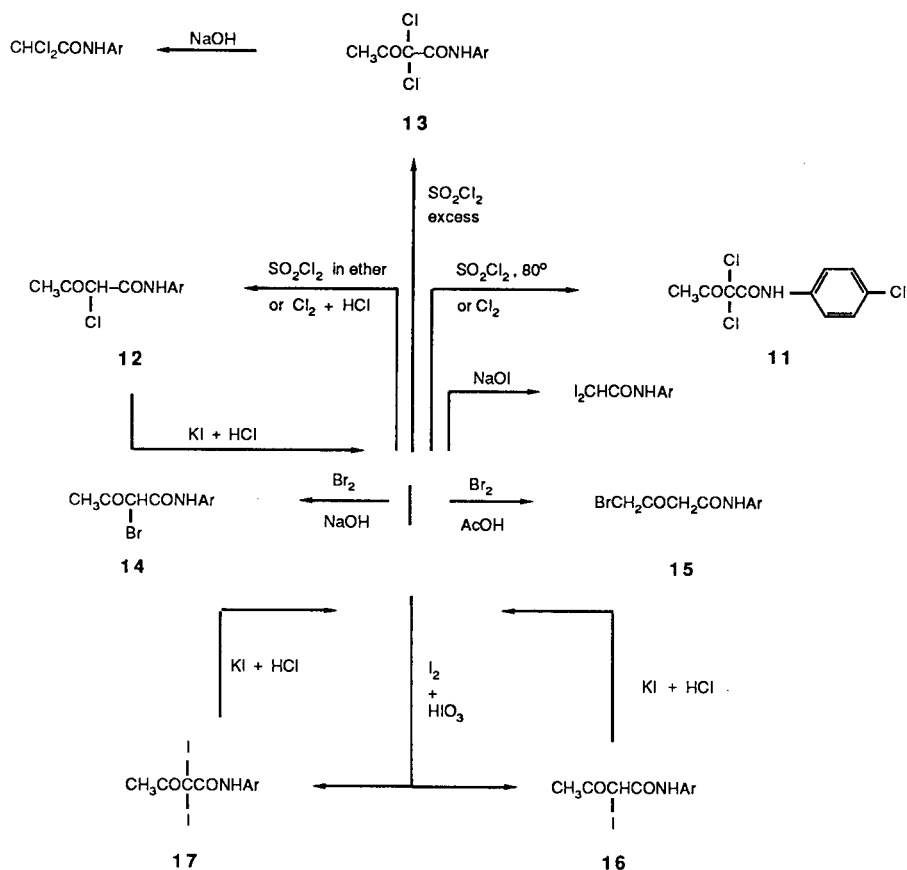


Halogenation.

When **1** is treated with chlorine, a low yield (5%) of the trichloro derivative **11** could be obtained [35]. However, Fragara has found that, treatment of **1** with chlorine in presence of hydrochloric acid at 10° yield α-chloroacetoacetanilides **12** [36]. The latter compounds are readily prepared by the action of equimolecular amounts of sulfuryl chloride on acetoacetanilides in ether [37]. Some reactions of α-haloacetoacetanilides are reported in literature [35,38-41]. Compounds **12** are converted to the original anilides by treatment with potassium iodide in the presence of hydrochloric acid [38], most probably through the α-iodo derivative **16** as an intermediate. Treating **1** with an excess of sulfuryl chloride yields α,α-dichloroacetoacetanilides **13** [35,39]. Compounds **13**, in contrast to **12**, are readily hydrolysed by dilute sodium hydroxide at 20°, to yield the corresponding α,α-dichloroacetanilides [39].

The reaction of sulfuryl chloride with **1** at 80° does not yield 4-methyl-6-chlorosulfonyl-2-quinolone (as reported by Monti and Palmieri) [42] but leads to the formation of the trichloro derivative **11** [43]. Although the reaction of bromine with **1** has been reported to give α-bromoacetoacetanilide **14** [43,44], the product proved to be the γ-bromo derivatives **15** [44-47].

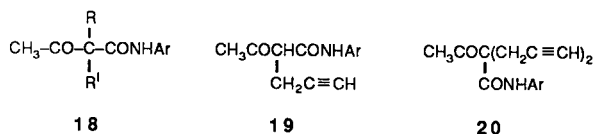
α-Bromoacetoacetanilides **14** are obtained by the reaction of **1** and bromine in alkali medium [40,41]. Some reactions of **15** are reported in literature [48-50]. Acetoacet-



anilides react with iodine in presence of iodic acid to give the α -iodo derivatives **16** and the α,α -diiodo derivatives **17** [51]. The iodo compounds are reduced to the original anilides by the action of potassium iodide and hydrochloric acid. Acetoacetanilides are degraded by sodium hypiodite to give diiodoacetamides [52].

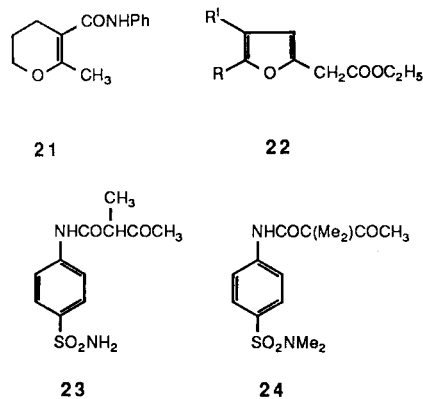
5. Alkylation.

When the sodium salts of **1** are treated with alkyl halides, the α -alkyl derivatives **3** are obtained [6,53-57]. Alkylation of the sodium salt **3** leads to the formation of α,α -dialkyl derivatives **18** [7,41,57]. Reactions of **1** with propargyl bromide lead to the formation of mono- and dialkylated derivatives **19** and **20** [58].



Acetoacetanilides react with propylene bromide to give hydropyran derivatives **21** [59] and with ethyl 3,4-dibromocrotonate to give furan derivatives **22** with some pyrroles as byproducts [60]. When 4-sulfamyl- α -methylacetoacet-

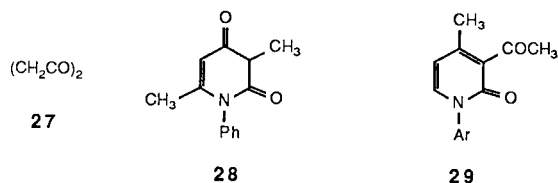
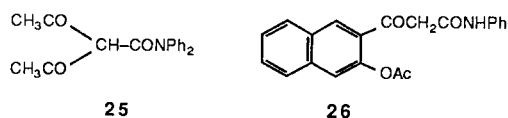
anilide **23**, in aqueous sodium hydroxide, is treated with an excess of dimethyl sulfate, the tetramethyl derivative **24** is obtained [61].



6. Acylation.

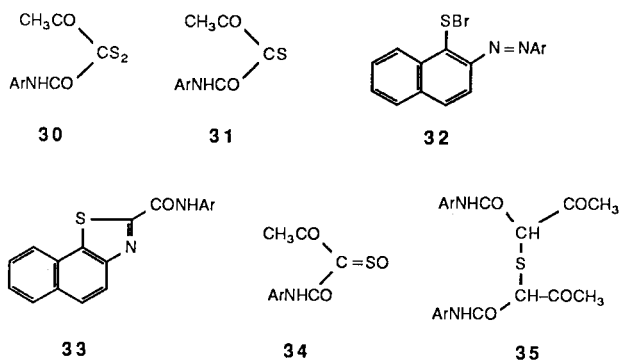
The sodium salt of acetoacetadiphenylamide reacts with acetyl chloride to give the α -acetyl derivative **25** [57]. The acylation of **1** with 3-acetoxy-2-naphthoyl chloride followed by hydrolysis affords the naphthoylacetanilide **26** [62]. Acetoacetanilide reacts with diketene **27** to give the pyridone **28** [63]. However, in the presence of weak bases

like *N,N*-disubstituted anilines, diketene and **1** condense to give **29** [64].



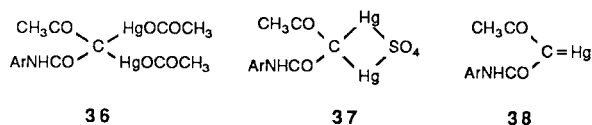
7. Reaction with Sulfur Halides.

Acetoacetanilides react with sulfur monochloride [65] and sulfur dichloride [66] to give **30** and **31**, respectively. Also, they react with 2-arylazaphthalene-1-sulfonyl bromide **32** to yield **33** [67]. The reaction of **1** with thionyl chloride in boiling benzene gives the α -sulfoxide derivative **34** [68]. However, when the reaction between (**1**) and thionyl chloride is carried out in ether at room temperature, thio-bis-acetoacetanilides **35** are formed [69,70].



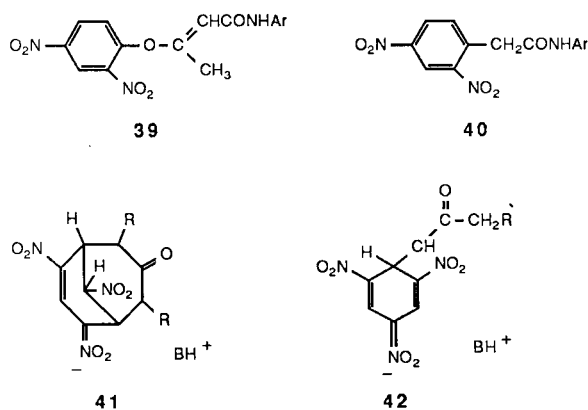
8. Mercuration.

Acetoacetanilides react with mercuric acetate in boiling methanol to give the α,α -diacetoxymercuri derivatives **36** which when heated with 10% sulfuric acid give the sulfato-mercuri compounds **37** [71]. The acetoxymercuri derivatives **36** also can be obtained by the action of aqueous mercuric acetate on the chelates of **1** [72]. However, when **1** are boiled in methanol with mercuric chloride in presence of sodium carbonate, the mercuri derivatives **38** are obtained [73]. All the mercuri derivatives readily regenerate the starting **1** on treatment with *N/4* hydrochloric acid, potassium iodide, or hydrogen sulfide [73].



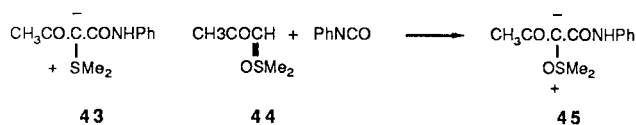
9. Reaction with 2,4-Dinitrochlorobenzene.

Acetoacetanilides react with 2,4-dinitrochlorobenzene in refluxing ethanol to give **39** [74]. However, in presence of equimolecular amounts of sodium hydroxide, they yield 2,4-dinitroacetanilides **40** [75]. The reaction of 1,3,5-trinitrobenzene with carbanions derived from substituted **1** yield a series of new bicyclic anions containing the bicyclo[3.3.1]nonane skeleton **41** *via* Meisenheimer complexes **42** [76].



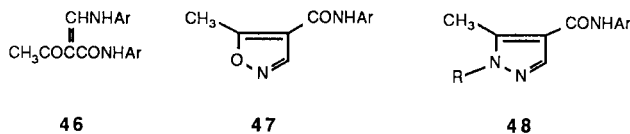
10. Formation of Sulfonium Ylides.

Acetoacetanilide reacts with dimethyl sulfoxide in presence of dicyclohexylcarbodiimide and anhydrous phosphoric acid to give 2-dimethylsulfuranylideneacetoacetanilide **43** [77]. The corresponding sulfoxonium ylide **45** has been obtained by the action of phenyl isocyanate on **44** [78].



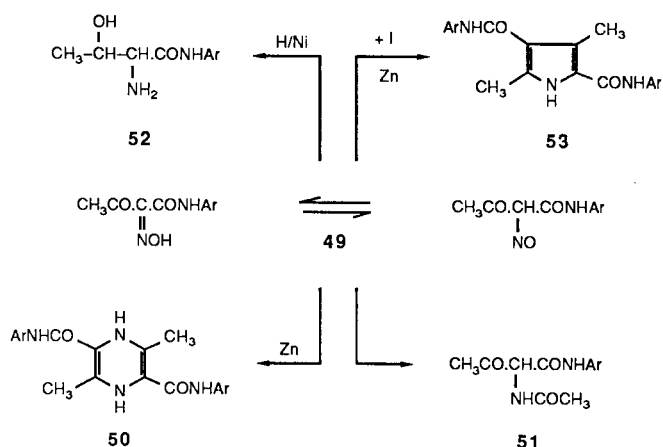
11. Reaction with Formamidines.

Acetoacetanilides react with formamidines at 150° to give α -arylamino-methylene-acetoacetanilides **46** [79-81]. These compounds react with hydroxylamine, hydrazine and phenylhydrazine to give isoxazole **47** and pyrazole **48** derivatives [80-82].



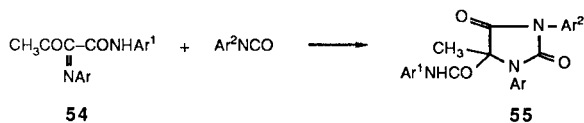
12. Nitrosation.

Acetoacetanilides react with nitrous acid [1,83,87] or with nitrosyl chloride [37] to form the α -oximido(α -isoximido) derivatives **49**. When **49**, in acetic acid, are treated with an excess of zinc dust, dihydropyrazine derivatives such as **50** are obtained [83,84]. On the other hand, reductive acylation affords α -acetylaminoacetoacetanilides **51** [85]. Catalytic hydrogenation of **49**, in presence of nickel and under pressure, gives α -amino- β -hydroxybutyranilides **52** [84,85]. When an equimolecular mixture of **1** and **49**, in acetic acid, is treated with zinc dust, pyrrole derivatives **53** are formed [84,88].



13. Reaction with Nitrosobenzene.

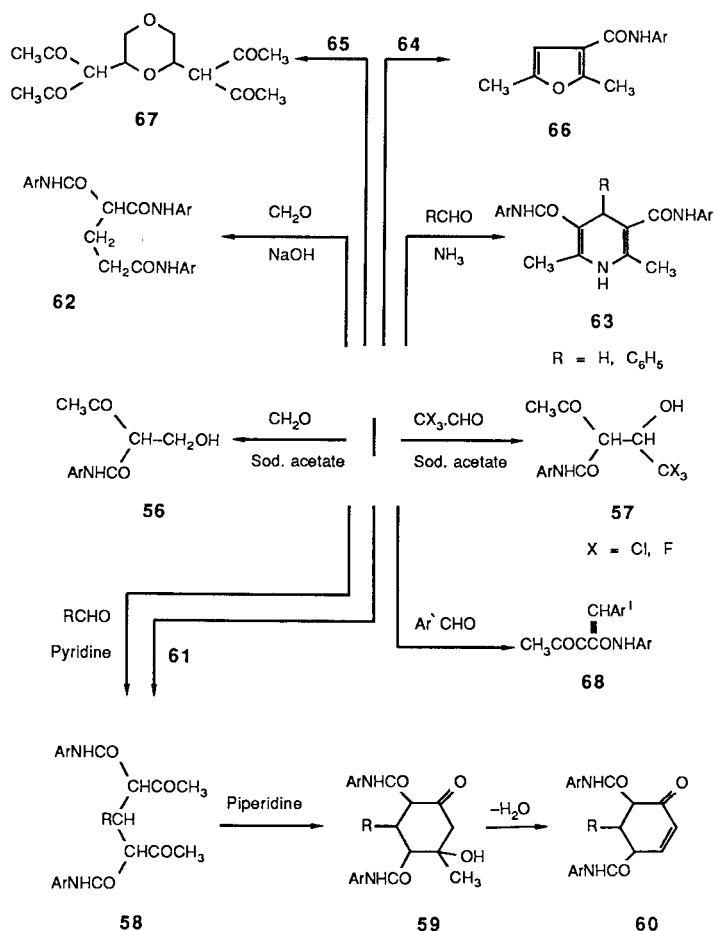
Acetoacetanilides condense with nitrosobenzene to give the α -azomethine derivatives **54** [89,90]. The latter compounds react with arylisocyanates and produce substituted hydantoin derivatives **55** [91]. No condensation (to give hydrazones) takes place between acetoacetadiphenylamide and *N*-nitrosomethylanilines [92].



14. Reaction with Aldehydes.

The reaction of acetoacetanilides **1** with aldehydes is very complicated and leads to different products depending on the reaction conditions and the nature of the aldehyde and catalyst used. Acetoacetanilides react with formaldehyde in presence of sodium acetate to yield the α -methylol derivative **56** [93,94]. A similar reaction with trichloro or trifluoroacetaldehyde leads to compounds of the type **57** [95-97]. Acetoacetanilides condense with aldehydes in presence of pyridine to give the bis-

compounds **58** which in presence of piperidine cyclise to **59**. Compounds **59** can be dehydrated to **60** [97-101]. Methylene-bis-acetoacetanilides **58** (R = H) are also obtained by the reaction of **1** with sodium hydroxymethanesulfonate **61** [102]. In the presence of sodium hydroxide, the reaction between **1** and formaldehyde gives a product formulated as **62** [94]. Acetoacetanilides react with formaldehyde and β -aminocrotonic acid derivatives to give dihydropyridine derivatives **63** [103]. Also, the reaction of **1** with formaldehyde or aromatic aldehydes in presence of ammonia yields derivatives of **63** [104]. Acetoacetanilides

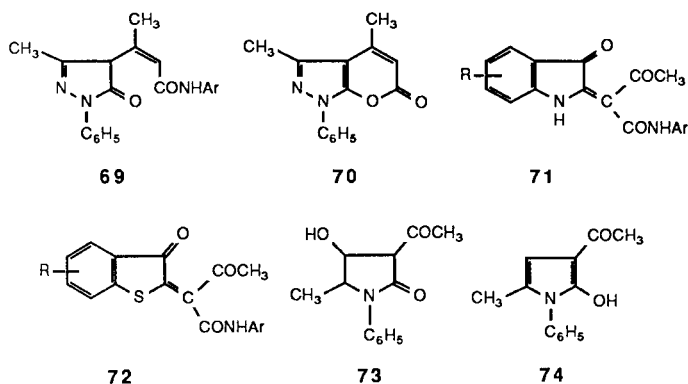


react with α -acetoxypropionaldehyde **64** [105,106] and with diglycolic aldehydes **65** [107] to afford **66** and **67**, respectively. Aromatic aldehydes react with **1** by fusion [108,109] or in presence of a catalyst such as pyridine, hydrogen chloride or $(\text{PdCl}_2)_3$ [6,101,110-113], to give the corresponding α -arylidene derivatives **68**. Some reactions of **68** are given in literature [108,109,114]. Catalytic hydrogenation of benzylideneacetoacetanilide over Pd-catalyst gives α -benzylacetoacetanilide [6].

15. Reaction with Ketonic Compounds.

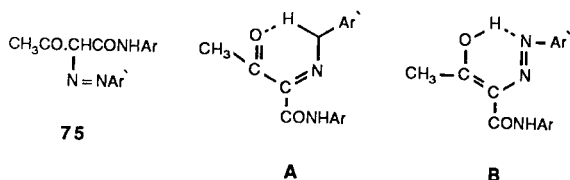
Acetoacetanilides condense with 3-methyl-1-phenyl-

pyrazolone at 100° to give the open structure **69** (or possible tautomers). However, when the reaction is performed at 140°, the pyranopyrazole **70** is formed [115]. Isatin chloride condenses with **1** to give **71** [116]. Compounds **1** also react with anils of 3-hydroxythianaphthene, in acetic acid, to afford **72** [116]. The reaction of **1** with α -halo-ketones, in the presence of potassium carbonate and sodium iodide, yields **73**. Dehydration of **73** by trifluoroacetic acid affords **74** [117].



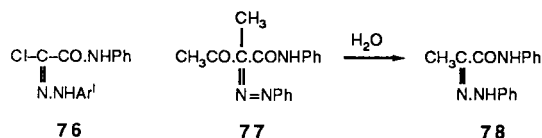
16. Coupling with Diazonium Salts.

The presence of an active methylene group in **1** renders the compounds susceptible to couple with diazonium salts. The azo compounds produced (Hansa Yellows) [118-120] have found use as yellow dyes and pigments. Attempts to improve the color and stability of the dyes has resulted in the preparation of a number of arylazoacetoacetanilides **75** by varying the anilide as well as the coupling components. The dyes are formulated as existing in the hydrazone, **A**, in the solid state or in the azo, **B**, in non-polar solvents [121].



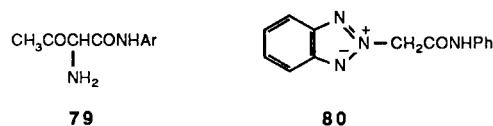
The coupling of diazonium salts with β -keto anilides has been reviewed by Parmeter [122] up to the late 1950's. The main investigations on the same subject are included in references [119,123-136]. The coupling kinetics of benzenediazonium salts with **1** have been studied by Vecera and his collaborators [137]. The molecular structure of α -(2-nitroarylazo)acetoacetanilides has been determined by X-ray diffraction analysis [138]. When α -chloroacetoacetanilide **12** is coupled with diazonium salts it undergoes the Japp-Klingemann reaction [139]; the acetyl group is lost and the corresponding α -chloroglyoxylic acid anilide hydrazones **76** are formed [35]. However, when

coupling of α -methylacetoacetanilide **3** with benzenediazonium chloride is carried out in aqueous pyridine, α -phenylazo- α -methylacetoacetanilide **77** can be isolated [140]. The azo derivative **77** is readily hydrolysed by acid or base to yield pyruvanilide phenylhydrazone **78** [140].



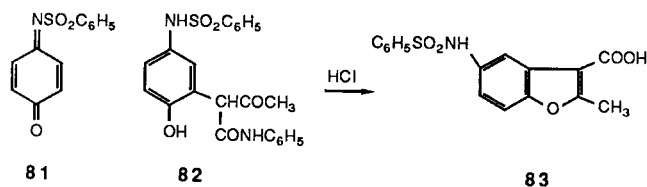
Reductive acetylation of **75** affords the α -acetylamino derivatives **51** [85,141]. When **75** are reduced by reaction with boiling sodium hydrosulfide in ammoniacal solution, the α -amino compounds **79**, first formed, undergo self condensation to give **50** [116]. On the other hand, catalytic hydrogenation by nickel in methanol gives **52** [85].

When compounds **75** ($\text{Ar}' = o$ -nitrophenyl) are reduced by zinc dust in pyridine the 2-substituted benzotriazoles **80** are obtained [136].

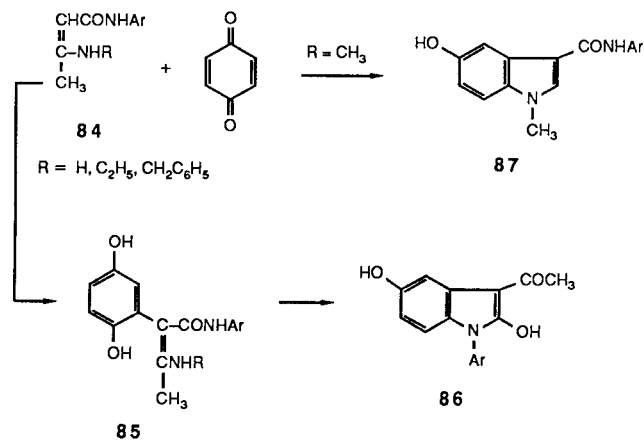


17. Reaction with Quinones and Derivatives.

Acetoacetanilide adds to *p*-quinonemonobenzenesulfonamide **81**, in presence of sodium methoxide, to give the adduct **82** which is transformed by the action of hydrochloric acid into the benzofuran derivative **83** [142].

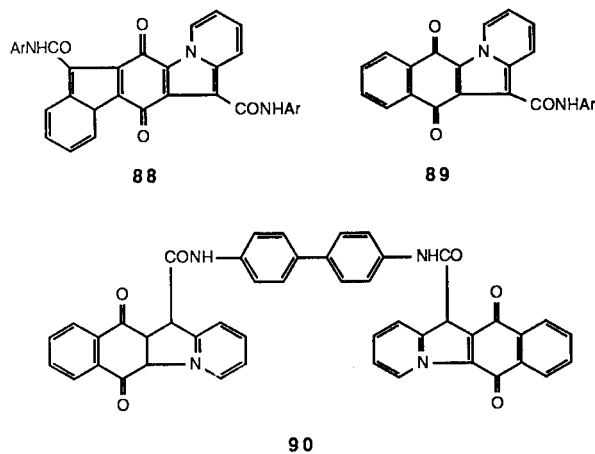


The anils **84** of **1** (β -aminocrotonanilides) add to *p*-benzoquinone to give the adducts **85** which are cyclised



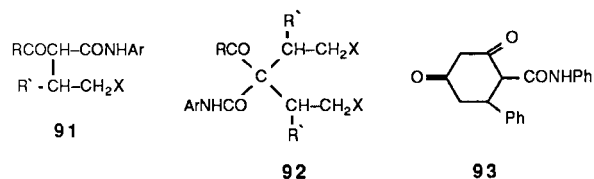
to indole derivatives **86** [143]. However, the reaction between **84** ($R = CH_3$) and *p*-benzoquinone leads directly to the formation of **87** [143].

Acetoacetanilides react with chloranil in pyridine to give vat dyes of the formula **88** [144]. The reaction between **1** and 2,3-dichloronaphthoquinone in pyridine affords compounds such as **89** and **90** [145-148].

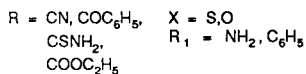
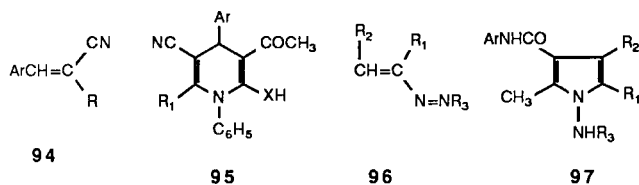


18. Michael Addition.

Acetoacetanilides and benzoylacetoanilides react with activated alkenes to give the mono and di-adducts **91** and **92**, respectively [149-152]. The reaction of **1** ($R = C_6H_5$) with ethyl acrylate, in presence of sodium ethoxide, yields **93** [153].



Recently, Hammouda *et al.* [154] have reported that the reaction of **1** ($Ar = C_6H_5$) with α -substituted cinnamitriles **94** yields the dihydropyridine derivatives **95**. Also, it has been found by Attanasi *et al.* [155-158] that **1** add to activated α -azoalkenes **96** in presence of copper(II) chloride, to give pyrrole derivatives **97**.

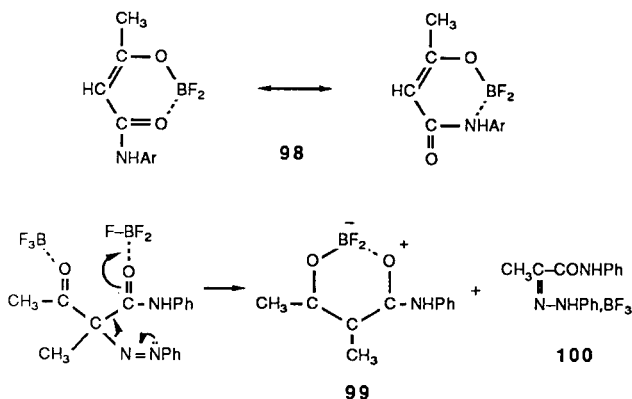


19. Action of Boron Trifluoride.

Acetoacetanilides react with boron trifluoride in ab-

solute ethanol or with boron trifluoride etherate, with the elimination of HF and formation of the difluoroxyborane derivatives **98** [159-161]. These boro compounds are hydrolyzed by water to **1** and are cyclized by concentrated sulfuric acid to the 4-methylcarbostyryl (*cf.* Cyclization reactions).

When compound **77** is treated with boron trifluoride, the difluoroboro α -methylacetoacetanilide salt **99** and pyruvanilide phenylhydrazoneboron trifluoride adduct **100** are obtained [162].

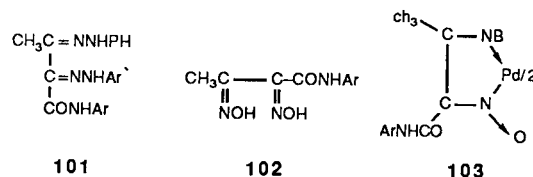


20. Reaction with Carbonyl Reagents.

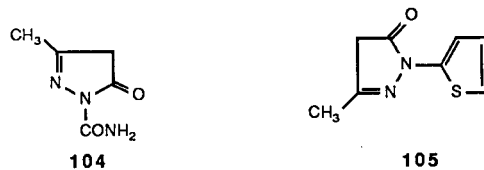
Acetoacetanilides are derivatized to give oximes [163], phenylhydrazones [162], 2,4-dinitrophenylhydrazones [54,164-166], semicarbazones, thiosemicarbazones, aroylhydrazones [167,168], and nitroguanylhazones [169].

The phenylhydrazones couple with diazonium salts to give bis-arylhazones, such as **101**, which are also formed from **75** and phenylhydrazine [170]. α -Oximidoacetoacetanilides **49** react with hydroxylamine to give bis-oximido-compounds **102** which form complexes with a number of metals such as copper, cobalt, nickel and palladium **103** [171-173].

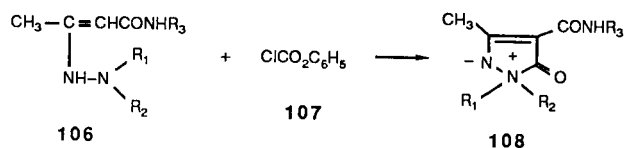
The semicarbazones of **1** are cyclized, in liquid ammonia or by cold sodium hydroxide solution, to give 3-methyl-5-pyrazolone-1-carboxamide **104** [174].



The reaction of **1** with 1-acetyl-1-thienylhydrazine leads to the pyrazolone **105** [175].

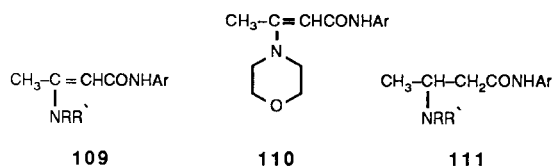


Cycloaddition of the *N*²-dialkyl-substituted enehydrazines **106** with phenyl chloroformate **107** leads to the pyrazolium betaines **108** [176].

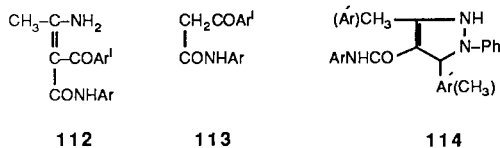


21. Reaction with Ammonia and Amines.

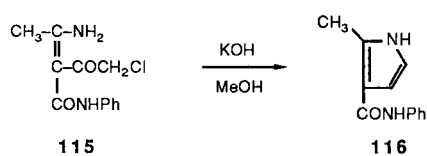
Compounds **1** condense with ammonia, primary and secondary aliphatic amines to give the corresponding β -aminocrotonanilides **109** and **110** [163], [177-182]. Also, compounds **1**, **109** (R and R' = H or alkyl) and **110** react with aromatic amines to yield β -arylamino crotonanilides **109** (R = H, R' = aryl), the reaction being, catalyzed by small amounts of hydrogen chloride or iodine [178,179]. Nilson and Carlson reported a convenient method for the preparation of enamines from ketones functionalized with various groups [183]. Unfortunately, the enamine from acetoacetanilide is obtained in poor yield. Compounds **109** and **110** are readily hydrolyzed to the original **1** by the action of dilute acids [163,178,179,184]. Reduction of **109**, in presence of raney nickel or with Al-Hg, yields 3-aminobutanilides **111** [185].



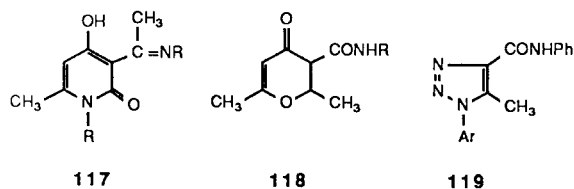
Compounds **109** (R = R' = H) react with benzoyl and with cinnamoyl chlorides to give *C*-acyl derivatives such as **112** which are hydrolyzed by acids to yield aroylacetonilides **113** [89, 186]. The acyl derivatives **112** react with phenylhydrazine to give pyrazole derivatives **114** [186].



Although β -aminocrotonanilide **109** does not react with acetyl chloride, it gives with chloroacetyl chloride, the *C*-acyl derivative **115** which can be cyclized by methanolic potassium hydroxide to give the pyrrole derivative **116** [186].

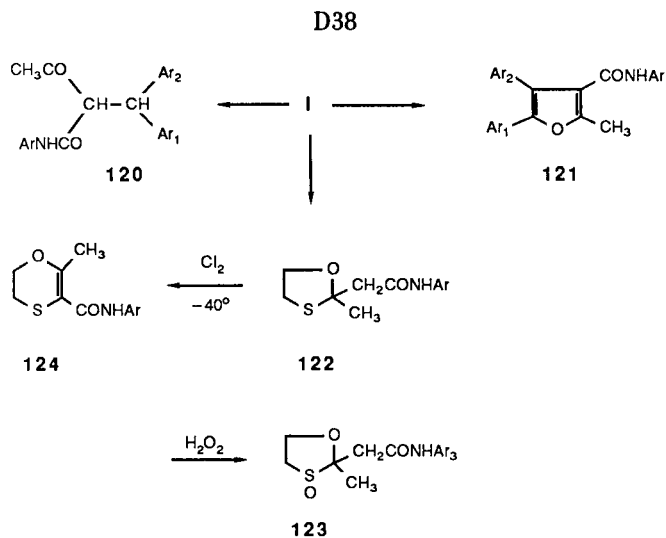


Enamine of acetoacetamides and *N*-alkylacetoacetamides react with diketene to yield the pyridone derivatives **117** whereas the enamines of *N*-arylacetoacetamides **109** give the γ -pyrone derivatives **118** [187]. β -Morpholinocrotonanilide **110** reacts with aryl azides to give the triazole derivatives **119** [180]. However, when **1** is heated with aniline, sym-diphenylurea is obtained [1,184].

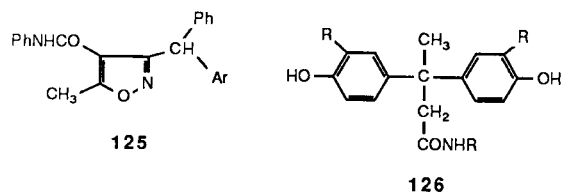


22. Reaction with Hydroxy Compounds.

Acetoacetanilides react with secondary alcohols [188] and with α -hydroxy ketones [189] to give **120** and **121**, respectively. The reaction of **1** with 2-mercaptoethanol affords the oxathiolanes **122** [190-193] which undergo oxidation by hydrogen peroxide to give **123**. Compounds **122**, on treatment with chlorine at -40° , yield **124**, the latter compounds can be also obtained from the reaction of **1** and bis-(β -hydroxyethyl) sulfide [194].

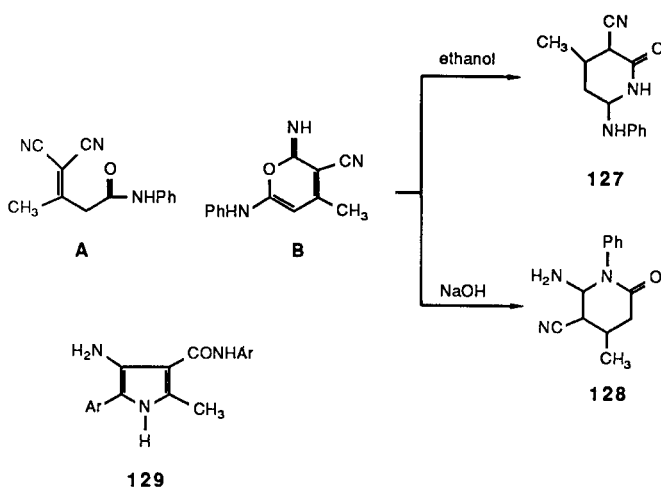


Cyclocondensation of **1** with hydroxyimidoyl chlorides yields the isoxazole derivatives **125** [195,196]. Acetoacetamides undergo condensation with alkylphenols in presence of catalytic amounts of ethanethiol to give **126** [197].



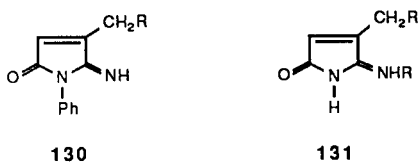
23. Reaction with Cyano Compounds.

The reaction of β -ketoamides with malononitrile affords different products according to the reaction conditions. In presence of alcohol the reaction proceeds through cyano-carbon acid **A** and iminopyran **B** intermediates to yield the pyridone **127**. Cope-Knoevenagel condensation of the reactants in benzene solution gives compound **A** which, on brief heating with aqueous sodium hydroxide, converts into the *N*-phenyl derivative **128**. Some mechanisms explain the formation of **127** and **128** are reported [198,199]. Also, the reaction of **1** with aminophenylacetonitriles yields the pyrrole derivatives **129** [200,201].



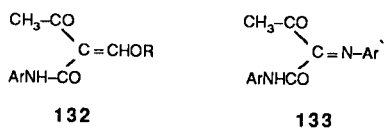
24. Reaction with Alkali Cyanide.

Reaction of **1** and their γ -halo derivatives **15** with sodium cyanide in alcohol gives the pyrrolones **130** and **131** [202,203].



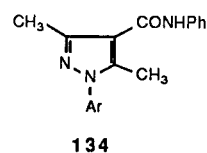
25. Reaction with Ortho Carboxylic Esters.

Acetoacetanilides react with a mixture of primary or secondary amines and orthoformic esters to give the *N*-substituted aminoalkylidene derivatives **133** via the corresponding alkoxymethylene **132** [204,205].



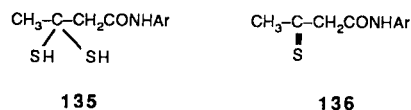
26. Reaction with Hydrazone Halides.

Acetoacetanilides condense with hydrazone halides, and the pyrazole derivatives **134** are obtained [206].



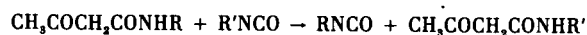
27. Reaction with Hydrogen Sulfide.

Acetoacetanilides give thioacetoacetanilides **136** through β,β -dimercaptobutyranilides **135** on treatment with hydrogen sulfide [207].



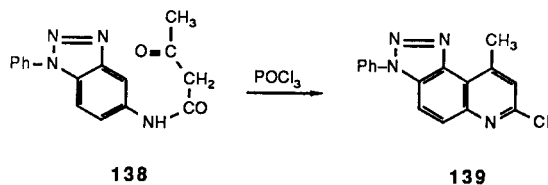
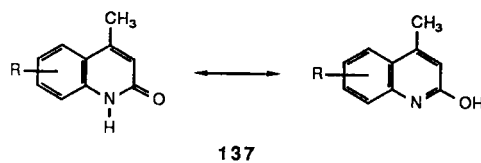
28. Reaction with Isocyanates.

The alkyl or aryl group on *N*-alkyl- or *N*-arylacetoacetanilides undergoes alkyl exchange with alkyl isocyanate [208].

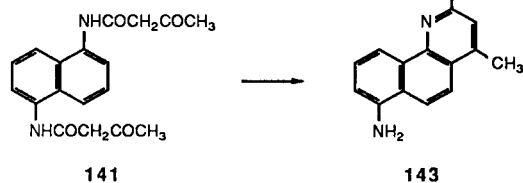
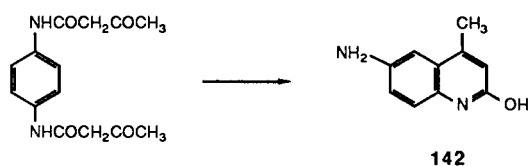


29. Cyclization Reactions. (A) Formation of Carbostyrils.

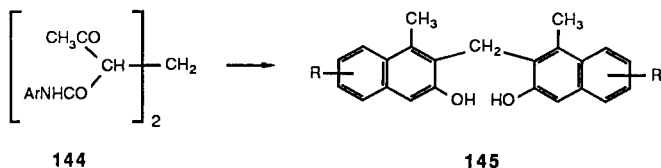
Acetoacetanilides undergo dehydration to give 4-methylcarbostyrils **137** [166,167,209,222]. The agents which effect cyclization include concentrated sulfuric acid, polyphosphoric acid, ...etc. Desai *et al.* separated a mixture of 2-hydroxy and 4-hydroxyquinolines when **1** was heated with polyphosphoric acid [223]. Other compounds, structurally similar to **1**, are cyclized to carbostyril derivatives [224-226]. Compound **138** is hydrolyzed by concentrated sulfuric acid and cyclized by phosphorus oxychloride to give **139**, in a poor yield [227].



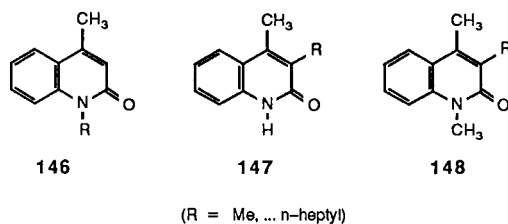
When bis-acetoacetyl derivatives of diamines **140** and **141** are subjected to cyclization, one acetoacetyl amino group is cyclized while the other is hydrolyzed, and **142** and **143** are obtained [228,229]. Methylene bis-acetoacet-



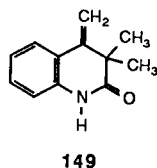
anilides **144** are cyclized by the action of acetic anhydride-sulfuric acid to give 3,3'-methylene bisquinolines **145** [102]. Some acetoacetanilides failed to cyclize (or no cyclized product could be isolated on their dehydration) [230-235].



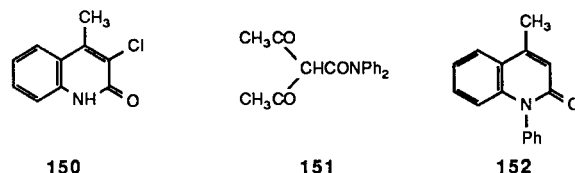
N-Substituted acetoacetanilides are cyclized by concentrated sulfuric acid to give *N*-substituted quinolones **146** [1,164,225]. α -Alkylacetoacetanilides **3** are cyclized by 74% sulfuric acid to give 3-alkyl-4-methyl-2-quinolones such as **147** and **148** [54,56,236,237].



When α,α -dialkylacetoacetanilides **18** are heated with concentrated sulfuric acid, they undergo ring closure with concomitant loss of an α -alkyl group (except when both groups are methyl) to give **147**. When both alkyl groups are primary and normal, the larger group is lost, and when one is isopropyl or benzyl it is lost preferentially to any of the others [7]. The action of concentrated sulfuric acid on α,α -dimethylacetoacetanilide gives 3,3-dimethyl-4-methylene-1,2,3,4-tetrahydro-2-quinolones **149** [7]. Whereas



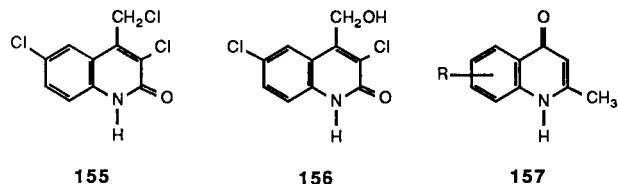
α -chloroacetanilide **12** is cyclized by concentrated sulfuric acid to give the chloroquinolone **150** [35], α -acetylacetoacetadiphenylamide **151** cyclizes by the loss of an acetyl group to give the *N*-phenylquinolone **152** [57].



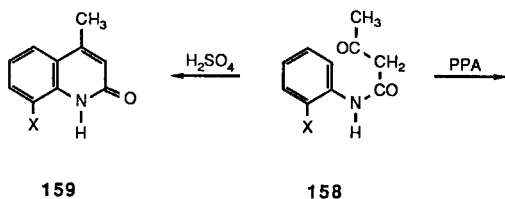
When α,α -dichloroacetoacetanilide **13** is warmed with concentrated sulfuric acid, 3-chloro-4-hydroxymethyl-2-quinolone **153** is formed [39]. Similarly, α,α -4-dichloro- α -methylacetoacetanilide is cyclized in sulfuric acid to give **154** [39]. On the other hand, α,α -dichloro-2,4,6-trimethyl-



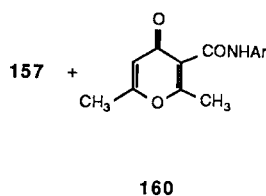
acetoacetanilide is recovered unchanged from sulfuric acid [39]. Pouring the reaction mixture from **11** and sulfuric acid into ice-water, yields 4-chloromethyl-3,6-dichloro-2-quinolone **155** in 22% yield. Addition of water to the same reaction mixture without cooling produces the corresponding 4-hydroxymethylquinolone **156** in 77% yield [39]. When **1** are heated with an excess of polyphosphoric acid, **137** are the only products formed. On the other hand, when **1** was heated together with equimolecular amounts of the corresponding anilines in an excess of polyphosphoric acid, mixtures of **137** and 2-methyl-4-quinolones **157** are obtained [238]. In the case of 4-halogeno- and some other substituted acetoacetanilides, heating with small amounts of polyphosphoric acid, yields the corresponding **157** [238]. Cyclization of 2-fluoro- and 2-chloroacetoacetanilides **158** using concentrated sulfuric



acid gives low yields of the corresponding 8-halo-2-quinolones **159** [16,17,239]. When compounds **158** and 2-substituted aminoacetoacetanilides are heated with polyphosphoric acid, mixtures of **157** and 3-arylcarbamoyl-2,6-dimethyl-4-pyrone **160** are obtained [238-240].

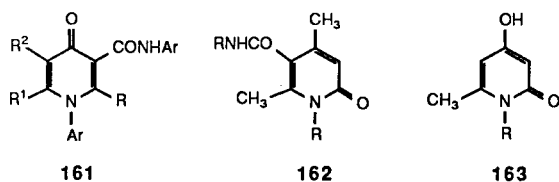


X = Cl, F, NHR



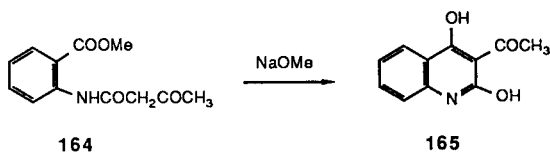
(B) Formation of Pyridones.

γ -Pyridinones **161** are obtained when **1** are dimerized in presence of *p*-toluenesulfonic acid, while dimerization of *N*-alkylacetoacetamides, under the same conditions, yields α -pyridinones **162** [241-243]. Acetoacetanilide is cyclized by sodium bicarbonate into **163** [244].

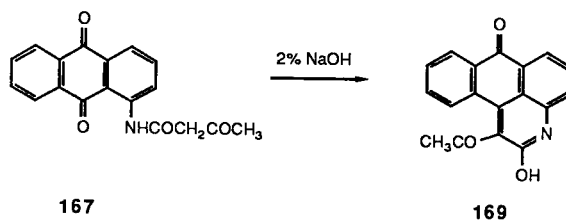
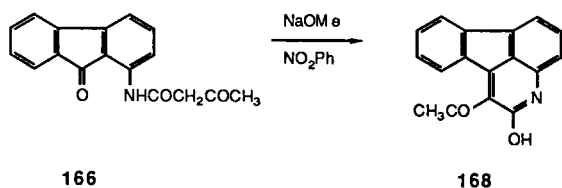


(C) Other Cyclisations.

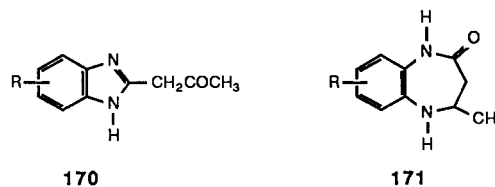
When the *N*-acetoacetyl derivative of methyl anthranilate **164** is treated with methanolic sodium methoxide, it is cyclized to 3-acetyl-2,4-dihydroxyquinoline **165** [235].



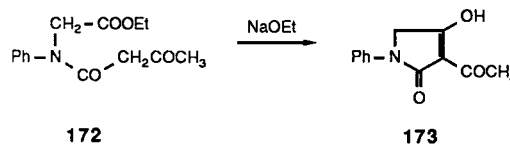
Acetoacetyl derivatives of 1-aminofluorenone **166** and 1-aminoanthraquinones **167** are cyclized by bases to yield compounds **168** and **169**, respectively [245-247].



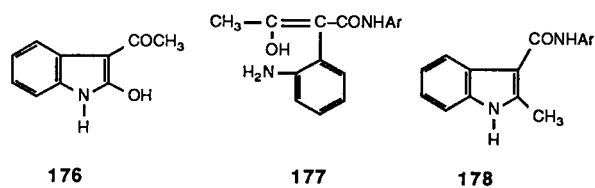
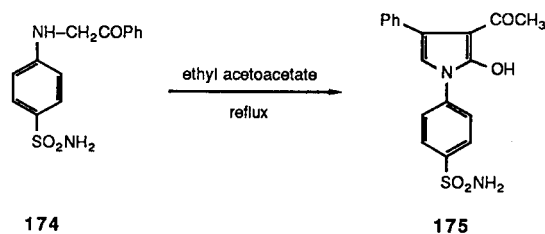
o-Nitroacetoacetanilides are reduced by iron in alcoholic hydrochloric acid to give 2-acetylbenzimidazoles **170** [224,248]. Catalytic hydrogenation of these anilides, in presence of raney nickel, yields the diazepinone derivatives **171** [249].



The *N*-substituted acetoacetanilide **172** is cyclized to give the tetramic acid derivative **173** [250].



Also, when the phenacylamino derivative **174** is heated with acetoacetic ester, compound **175** is formed presumably *via* the cyclization of an intermediate acetoacetyl derivative [251]. *o*-Chloroacetanilide **161** is cyclized by potassium amide in liquid ammonia to give 3-acetyl-2,4-dihydroxyquinoline **176** [252]. α -(*o*-Aminophenyl)acetoacetanilides **177** undergo ring closure to produce indole derivatives **178** [253].



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