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REACTIVITY OF PYRROL-2-ONES. (REVIEW)

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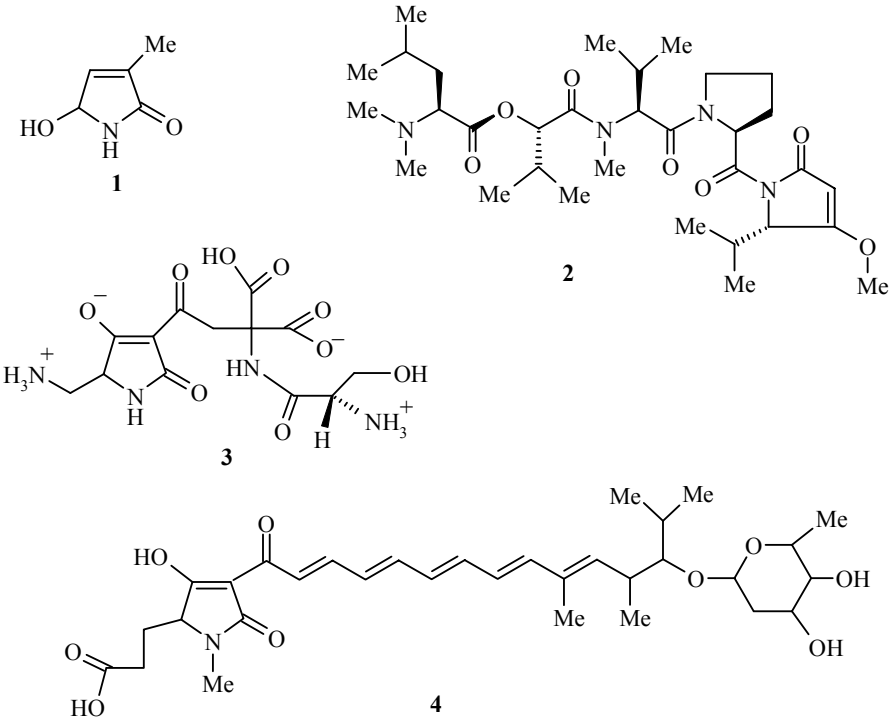
Published data on the chemical transformations of pyrrol-2-ones are reviewed and analyzed. The extensive synthetic possibilities of compounds containing a pyrrolone ring in the synthesis of various heterocyclic compounds with complex structures are demonstrated. The reactions are arranged according to the reaction centers of the pyrrol-2-ones: The methylene unit, the C=C double bond, the electron-deficient carbon atom of the carbonyl group.

Keywords: 3H-pyrrol-2-ones, 5H-pyrrol-2-ones, reaction center.

Five-membered nitrogen heterocycles of nonaromatic type (pyrrol-2-ones) rightly occupy a special position in contemporary organic chemistry in connection with the discovery of their fragments in natural compounds and also with the production of substances with various types of biological activity from them.

In recent years the greatest attention has been paid to the investigation of pyrrol-2-ones and pyrrol-3-ones, which are present in natural biologically active compounds and their analogs [1-47].



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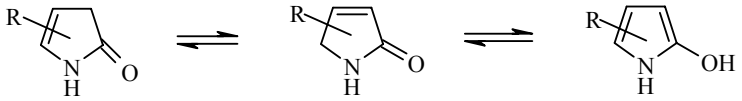
The most important factor that has stimulated development of the chemistry of pyrrol-2-ones is their high chemical potential, which makes it possible to produce from them a whole new series of heterocyclic compounds and technically valuable substances. Their structural fragments are present in such natural substances as porphyrins, bile pigments (biliverdin, phycocyanobilin), natural alkaloids (lilidine **1**, *Jatropha macrorrhiza*, *Mirabimides* A-D **2**) and also in compounds having antibiotic [Malonomicin (**3**)] and pharmacological activity. Among the antimetabolites, antibacterial agents, and enzymes, including inhibitors, there are substances containing a pyrrol-2-one ring: a-Lipomycin **4** and streptolydigin, which inhibits the synthesis of RNA by the bacterium *Bacillus megaterium*, thereby retarding their development [44, 45].

On account of their prototropic tautomerism the pyrrol-2-ones can exist in three isomeric forms **A**, **B**, and **C** [48].

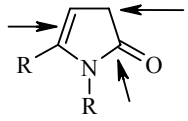


A **B** **C**

It was noted that α-hydroxypyrroles **C** exist in the tautomeric form of pyrrolones with a double bond at the 3H (**A**) or 5H (**B**) positions [49, 50]. Unsubstituted 2-hydroxypyrrole and its 3-alkyl and 3-acetyl derivatives exist predominantly in the form of the 5H isomers **B**, as shown by analysis of the NMR spectra. If, however, the acyl or ether substituents occupy position 4, the 3H isomer **A** predominates.

The review on the chemistry of pyrrol-2-ones published in 1972 [51] is now obsolescent. In the present review we attempted to summarize, analyze, and classify for the first time data from investigations of the reactivity of pyrrol-2-ones at various reaction centers.

Pyrrol-2-ones have several reaction centers that make them attractive subjects for study, i.e., the heteroring, the activated methylene unit, and the C=C and C=O double bonds.

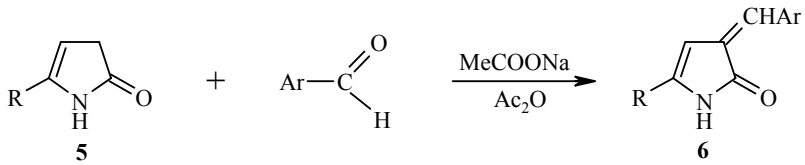


R = H, Alk, Ar

1. Reactions Taking Place at the Methylene Unit of the Heterocycle

The structure of carbonyl-containing pyrrol-2-ones presupposes high mobility for the hydrogen atoms at the position of the heterocycle. This is due to the activating effect of the carbonyl group, which depends on the nature of the heteroatom attached to it. The reactivity of the methylene unit of pyrrol-2-ones has been studied for various condensation reactions – Knoevenagel, Michael, Vilsmeier–Haack, azo coupling.

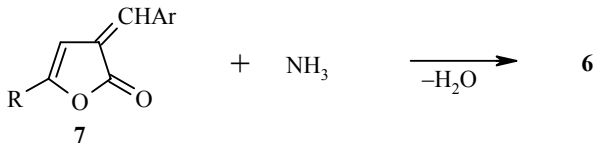
The condensation of N-unsubstituted 5-alkyl(aryl)-3H-pyrrol-2-ones **5** with aldehydes of the benzene and furan series in acetic anhydride in the presence of sodium acetate with prolonged heating leads to compounds **6** with yields of 25-30% [52, 53].



5 **6**

R = Am, C_7H_{15}, Ph; Ar = Ph, $C_6H_4NO_2$-3, C_6H_4OH-2

Arylidene derivatives of pyrrol-2-ones are potential biologically active compounds, and substances possessing herbicidal [11, 40-42] and antimicrobial activity [54] have been found among them. For this reason a synthesis was proposed for this series of compounds based on their oxahetero analogs already containing an arylidene substituent. Ammonolysis of 5-R-3-arylidene-3H-furan-2-ones **7** takes place through opening of the furanone ring and cyclization of the amides of the oxoalkanoic acids to 3-arylidene-3H-pyrrol-2-ones.

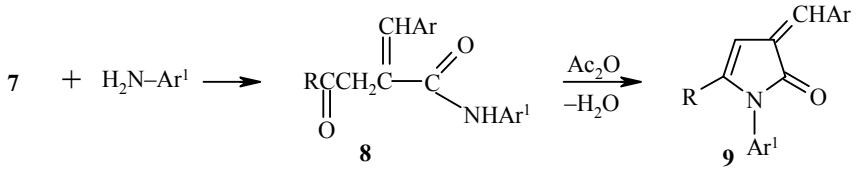


7

R = Am, C_7H_{15}, Ph; Ar = Ph, $C_6H_4NO_2$-3, C_6H_4OH-2

It was shown on the basis of the spectral data of compounds **6** that of the possible isomeric forms (lactam, lactim, iminolactam) the lactam form is actually realized in the series of N-substituted 3-arylidene-3H-pyrrol-2-ones.

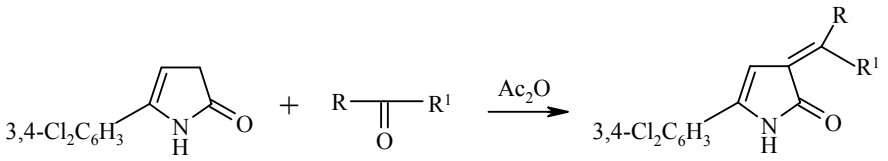
The 3-arylidene derivatives of pyrrol-2-ones containing an aromatic substituent at the nitrogen atom of the heterocycle could not be obtained from 1,5-disubstituted pyrrol-2-ones or compounds **7** in a single stage [54].



R = Ph, C_6H_4Me; Ar = Ph, $C_6H_4NO_2$-3, C_6H_4OMe, C_6H_4OH-2; Ar^1 = Ph, C_6H_4Me

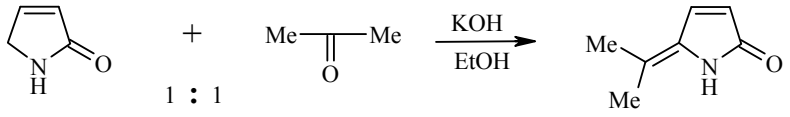
The low nucleophilicity of the nitrogen atom in aromatic amines makes it possible to stop the ammonolysis of the arylidene derivatives of furan-2-ones **7** at the stage of the formation of the substituted amides of 4-oxo acids **8**, which are isolated with quantitative yields. Further intramolecular cyclization of the latter takes place successfully in the presence of dehydrating agents with the formation of compounds **9**.

The reactivity of the methylene group of the pyrrol-2-ones was studied also for the case of the reaction of 5-(3,4-dichlorophenyl)-3H-pyrrol-2-one with acetophenone, fluorenone, and isatin. Reaction with prolonged heating (10 h) in xylene or acetic anhydride led to the formation of 5-aryl-3-arylidene-3H-pyrrol-2-ones **11** [55].



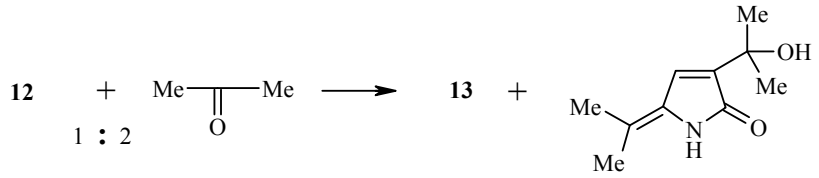
R = Me, Et, Ph; R^1 = Me, Ph, MeCO, PhCO

N-Unsubstituted pyrrol-2-one **12**, which exists 98% in the 5H form, condenses with acetone in an alkaline medium at the methylene unit at position 5 [56]. If equimolar amounts of the reagents are used, 5-isopropylidene-5H-pyrrol-2-one (**13**) is obtained.



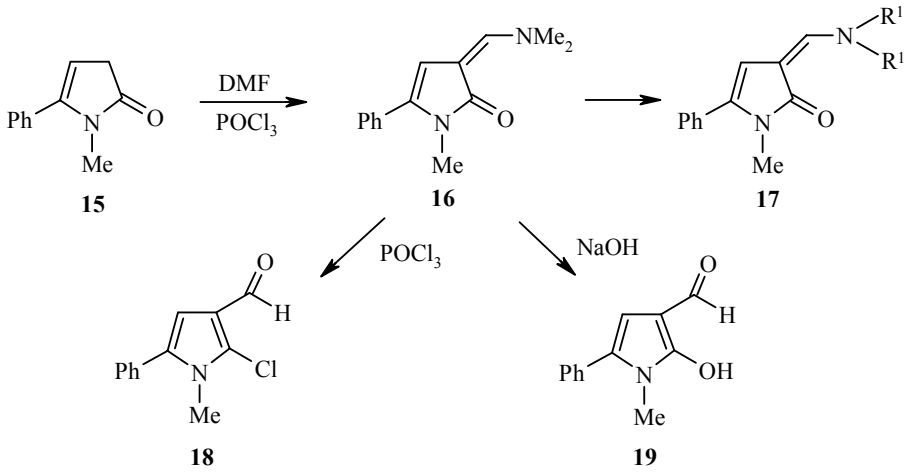
12 **13**

Increase in the concentration of acetone leads to an decrease in the yield of the condensation product and is accompanied by the formation of another condensation product **14** involving position 3 of the ring.



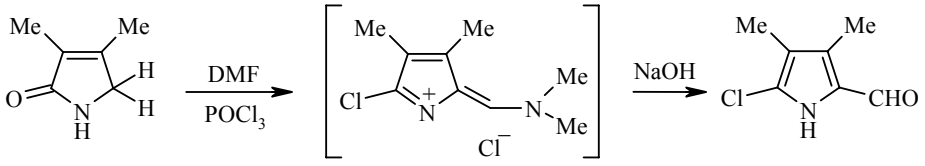
14

In the series of 1,5-disubstituted 3H-pyrrol-2-ones **15** the active methylene group makes it possible to realize Vilsmeier–Haack formylation by the action of the DMF–phosphorus oxychloride complex at -30°C. The authors isolated the aminomethylation product dimethylaminomethylenepyrrol-2-one **16**, from which it was then possible to obtain either the transamination products **17** or the formyl derivatives **18** and **19** [57, 58].



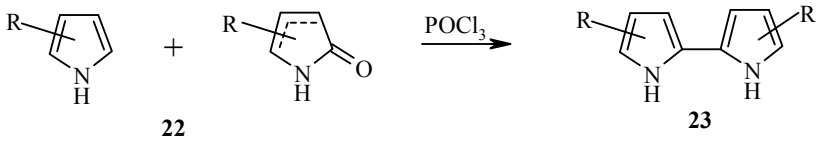
15 **16** **17** **18** **19**

Under the influence of the Vilsmeier complex the N-unsubstituted 3,4-dimethylpyrrol-2-one **20** gives a good yield of the immonium salt **20a**, the alkaline hydrolysis of which gives 2-formyl-5-chloropyrrole **21** [59-61].



20 **20a** **21**

A condensation of the Vilsmeier type in the N-unsubstituted pyrrol-2-ones **22** by the action of phosphorus oxychloride and pyrrole leads to a good yield of the bispyrrole **23** [62].



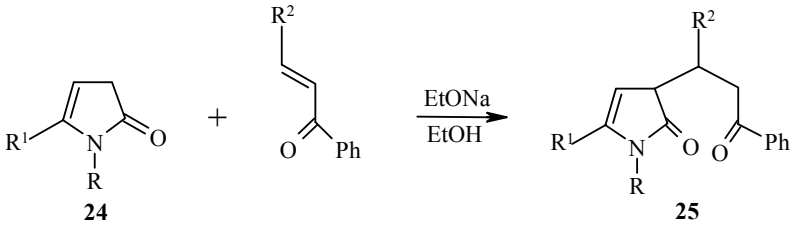
22 **23**

N-Substituted pyrrol-2-ones dimerize with N-R-pyrrolid-2-ones during the action of protic and aprotic acids with yields of up to 79% [63].

The reaction of 4-ethoxycarbonyl-3H-pyrrol-2-one with pyrrole in acetic acid also leads to the bispyrroles [64].

Michael condensation takes place with higher speed the more readily the enolic form is transformed into the ketone form [65]. Pyrrol-2-ones are present entirely in the lactam form, and this determines their ability to participate in the Michael condensation [66]. 5-Aryl(alkyl)-3H-pyrrol-2-ones **24** are capable of acting as methylene component (addend) in the Michael reaction with electron-deficient unsaturated ketones under the conditions of base catalysis [65-75].

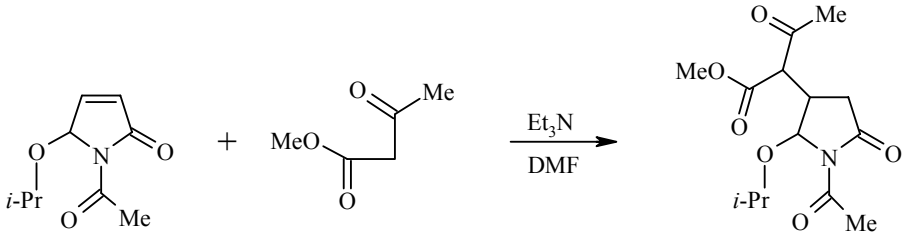
The reaction with benzylideneacetophenone and also with chalcones having an electron-withdrawing substituent leads to good yields of the condensation products, which exist in the stable 1,5-dioxo form **25**.



24 **25**

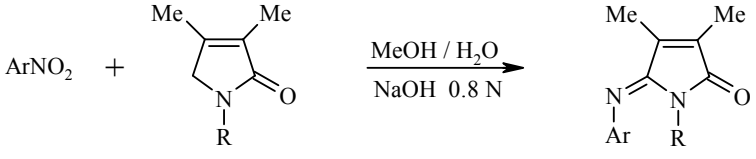
R = H, Ph; R^1 = Bu, C_5H_{11}, Ph; R^2 = Ph, $C_6H_4NMe_2$-4, C_6H_4OMe-4

Under the conditions of alkaline catalysis the 5-alkoxypyrrolone **26**, acting as electron acceptor, gives Michael condensation products **27** with methyl acetoacetate [1].



26 **27**

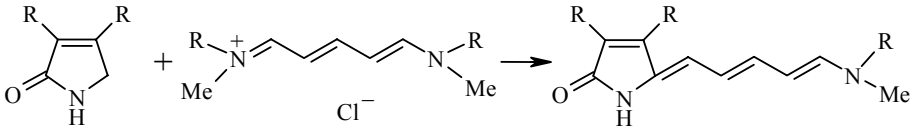
3,4-Dimethyl-5H-pyrrol-2-ones **28** react with aromatic nitro compounds in an water–methanol solution of alkali. If the reaction is carried out in ethanol/2N sodium ethoxide, it is possible to increase the yield of the final product to 55% [76].



28 **29**

R = H, Me; Ar = Ph, C_6H_4CHO-*p*, C_6H_4Me-*p*

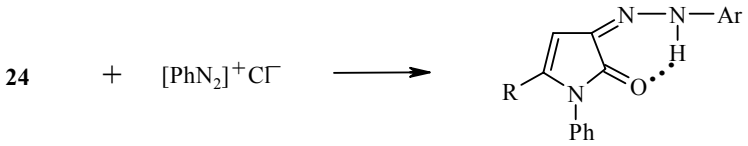
The condensation of 3,4-disubstituted 5H-pyrrol-2-ones **30** with the immonium salt **I** leads to the formation of the enamines **31** with a yield of 35% [77].



30 **I** **31**

R = Me, Ph

In the series of 1,5-disubstituted pyrrol-2-ones azo coupling with arenediazonium salts takes place in alcohol solution under mild conditions at +1 to -5°C.



32

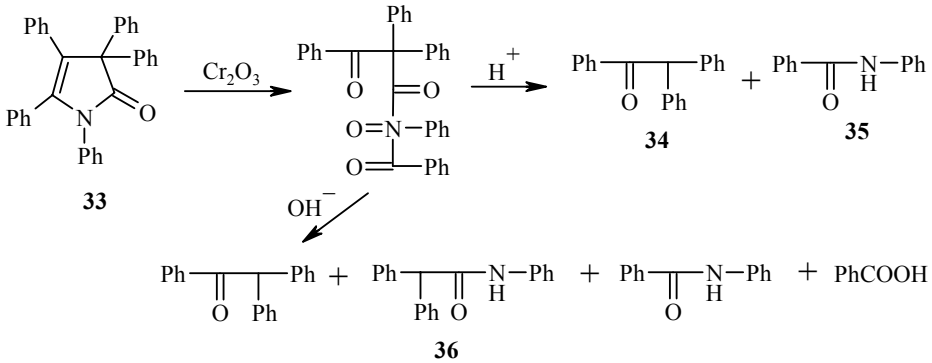
R = Am, Ph

In the investigated compounds **24**, of the two reaction centers capable of reacting with the diazo component the reaction takes place at position 3 with the formation of 5-aryl-3-(4-nitrophenyldiazo)-3H-pyrrol-2-ones **32** as red crystals [54].

2. Reactions Taking Place at the Ethylene Bond of the Heterocycle

Data on research into the reactivity of the ethylene bond in the investigated heterocycles are represented by few papers in the literature. Most of the information concerns reduction reactions using various types of reducing agents.

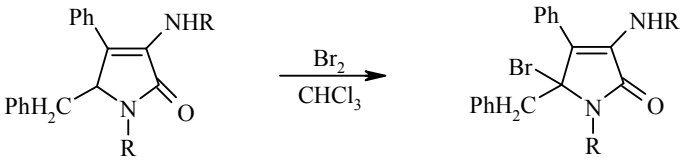
The pentaphenyl-substituted pyrrol-2-one **33** undergoes oxidation by chromic anhydride in acidic and basic media [78]. It was established that the C=C bond of the heterocycle is cleaved during oxidation, and in an acidic medium the decomposition products are diphenylacetophenone **34** and benzoylanilide **35**. In an alkaline medium N-phenylacetamide **36** and benzoic acid are formed in addition to the above-mentioned compounds.



33 **34** **35**

36

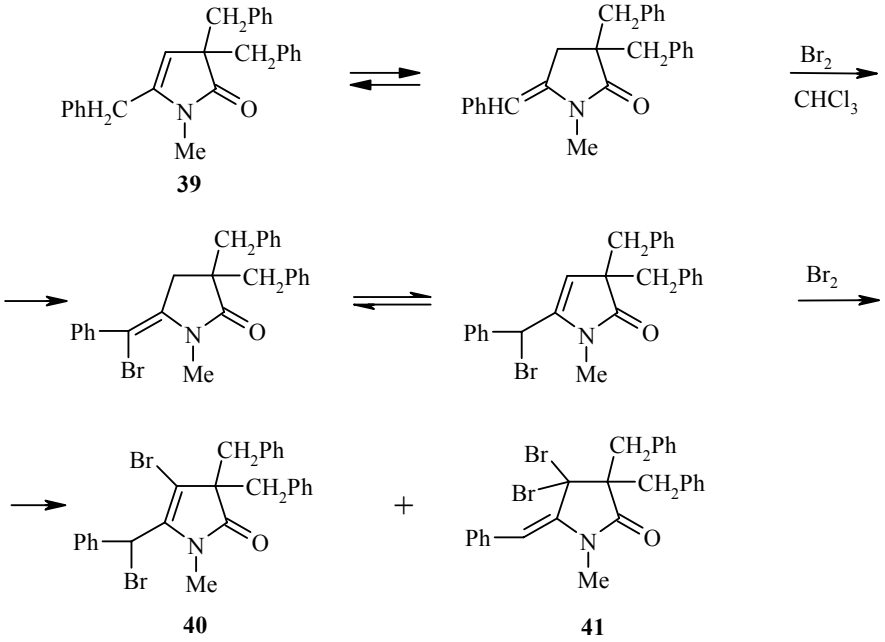
During bromination of the polysubstituted 5H-pyrrol-2-ones **37** with bromine in chloroform in a molar ratio of 1:1 substitution takes place at the allylic position, and the C=C bond is not affected. Amino-substituted pyrrol-2-ones react with the formation of the monobromo-substituted compounds **38** with yields up to 60% [79].



37 **38**

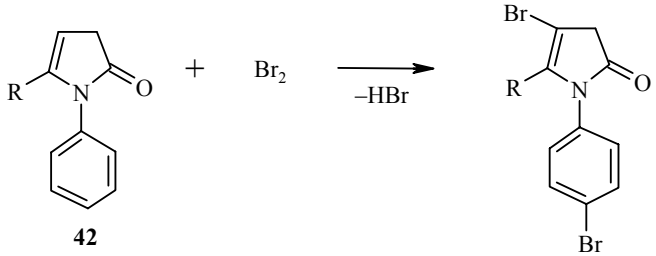
R = *m*-$C_6H_4NO_2$

Brief contact between 3,3,5-tribenzyl-3H-pyrrol-2-one **39** and a solution of bromine in chloroform leads to the isolation of dibromo-substituted derivatives **40** and **41** with the halogen at various positions [80]. The authors proposed a reaction mechanism that explains the preferential attack of the halogen at the exocyclic C=C bond.



39 **40** **41**

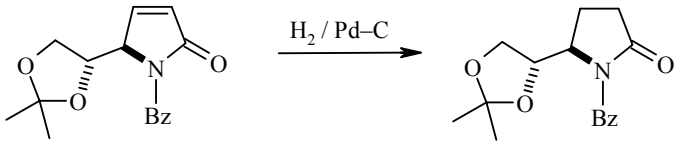
The bromination of 5-substituted 1-phenyl-3H-pyrrol-2-ones [54] using various brominating agents – a solution of bromine in chloroform and also dioxane dibromide under mild conditions at 18-20°C in a equimolar ratio – gave 5-alkyl(aryl)-4-bromo-1-(4-bromophenyl)-3H-pyrrol-2-ones with yields of up to 65%.



42 **43**

R = Bu, Am

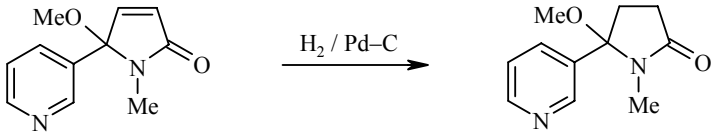
The reduction of the ethylene bond was studied for 1,5-disubstituted 5H-pyrrol-2-ones **44** under conditions of catalytic hydrogenation with palladium on charcoal as catalysis [81].



44 **45**

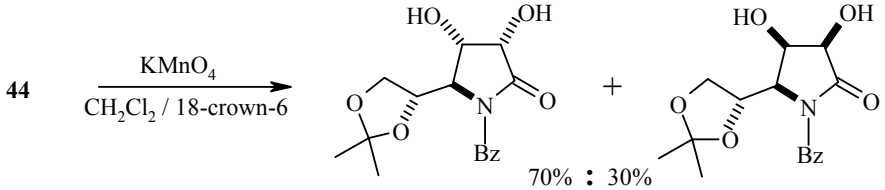
N-Aryl-4-ethoxycarbonyl-3H-pyrrol-2-one is reduced to pyrrolidone in the presence of nickel [82].

5-Pyridyl-substituted 5H-pyrrol-2-one **46** readily reduces the olefinic fragment of the hetero ring during hydrogenation in the presence of Pd/C [83].



46 **47**

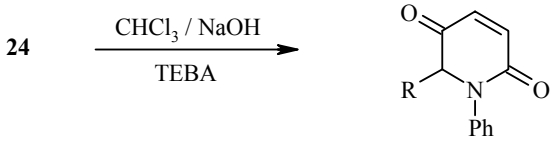
The oxidation of 1,5-disubstituted 5H-pyrrol-2-one with potassium permanganate solution under the conditions of phase-transfer catalysis with crown-18 as catalyst [81] leads to a mixture of isomeric 3,4-dihydro derivatives.



48

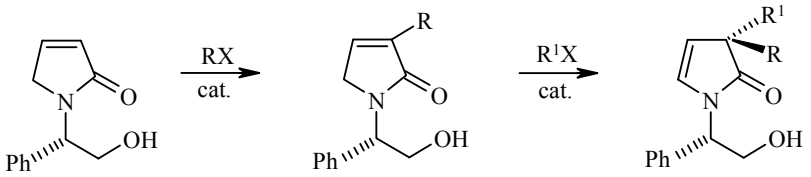
Dichlorocarbene reacts readily with 5-alkyl(aryl)-3H-pyrrol-2-ones **24** in the two-phase water–chloroform system in the presence of TEBA even at 20°C [84, 85]. The reaction products are 6-alkyl(aryl)-5-oxo-1-phenylhydropyridin-2-ones **49**, the structure of which was established on the basis of the data from ^{1}H and ^{13}C NMR spectroscopy. The authors propose a mechanism for the formation of the reaction products.

Of the several reaction centers in the molecule of compound **24** the C=C bonds of the heterocycle are capable of reacting with dichlorocarbene by a [1+2] cycloaddition mechanism with subsequent cyclopropylallylic rearrangement, accompanied by enlargement of the five-membered ring.



R = Bu, Am, Ph **49**

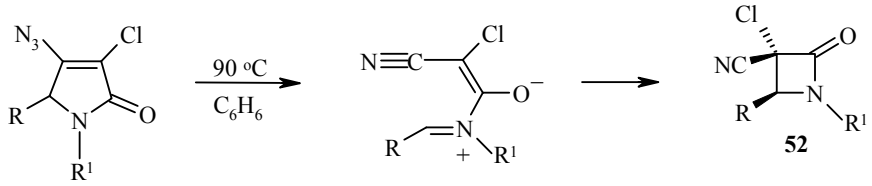
The bisalkylation of the chiral nonracemic (γ-lactam) N-substituted 5H-pyrrol-2-one at the α-position to the carbonyl group results in the formation of a new chiral center in the molecule of the pyrrol-2-one **50** [86-90].



50

R = Et, Pr; R^1 = $PhCH_2$

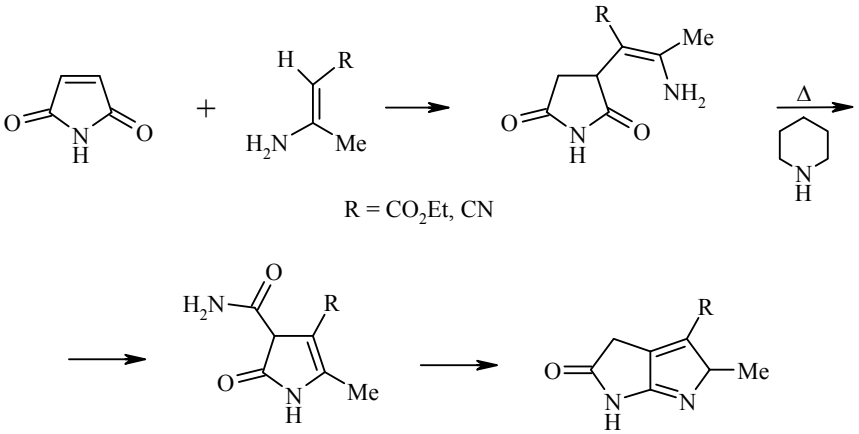
Thermolysis of 4-azidopyrrol-2-ones **51** in benzene leads to ring contraction and to the production of the *E*-isomers of the β-lactams. The yield of the reaction products **52** amounts to between 55 and 90% depending on the substituent in the initial compounds [91, 92].



51 **52**

R^1 = Me, Et, *i*-Pr; R = OMe, OEt, OCH_2Ph

4-Carbamoylmethyl-3H-pyrrol-2-one is produced by the reaction of maleimide with 3-aminocrotonate. When boiled in alcohol solution the 4-carbamoyl-3H-pyrrol-2-ones **53** undergo cyclization to pyrrolo[2,3-*b*]-pyrroles **54** [93].

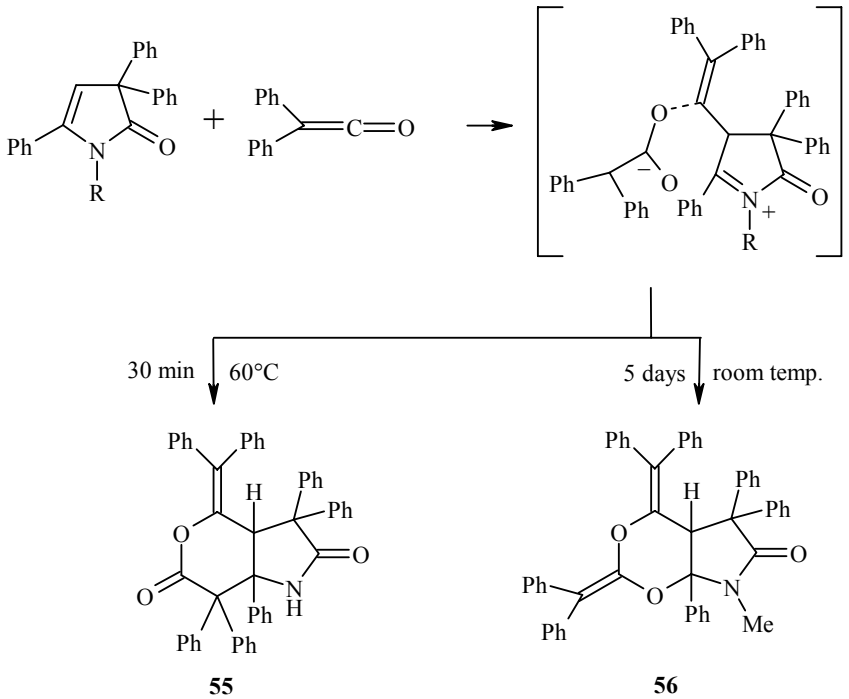


53 **54**

R = CO_2Et, CN

R = CO_2H, $CONH_2$

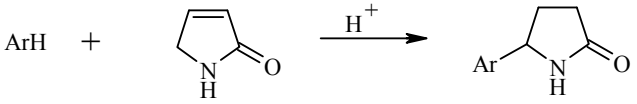
The effect of stereochemical factors on the addition of certain 3H-pyrrol-2-ones to diphenylketene was studied. In the opinion of the authors, the reaction takes place through the formation of the intermediate **A**, and its direction of cyclization is determined by the energy of the immonium ion, by steric factors, and by the reaction conditions. Thus, in reaction with diphenylketene 3,3,5-triphenyl-3H-pyrrol-2-one gives the cyclization product **55** (through the C atom), while N-methyl-3,3,5-triphenyl-3H-pyrrol-2-one gives the cyclization product **56** (through the oxygen atom) [94].



55 **56**

R = H, Me

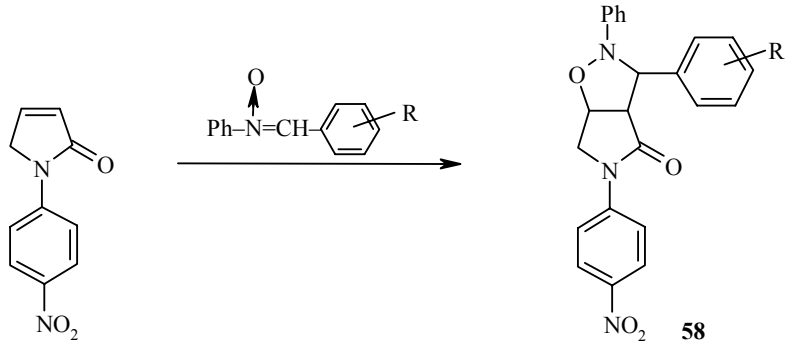
In an acidic medium and in protic solvents pyrrol-2-one is capable of acting as electrophile with respect to activated aromatic and heteroaromatic substrates, and arylation and hetarylation take place at position 5 of the pyrrole ring. Among the obtained compounds **57** there are substances having effective anticonvulsive activity [95, 96].



57 50–90%

Ar = C_6H_4OH, $C_6H_3(OH)_2$, 2-furyl, 2-NR-pyrrolyl, 4-MeEtN–C_6H_4, 2-hydroxynaphthyl

The 1,3-dipolar cycloaddition of diaryl nitrones was investigated for 1-aryl-substituted pyrrol-2-ones and takes place at the double bond of the heterocycle.



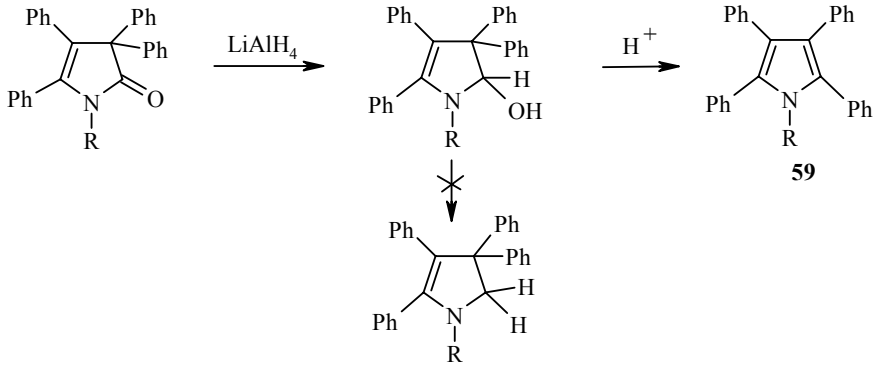
58

R = H, 3-NO_2, 4-Br, 4-Me, 4-OMe, 4-NMe_2

The stereospecificity of the process is due to the *exo* approach of the reagent with *cis*-stereospecific addition of the *trans* form of the N-diaryl nitrones to the double bond of the heterocycle with the formation of the cyclic adduct **58** [97-100].

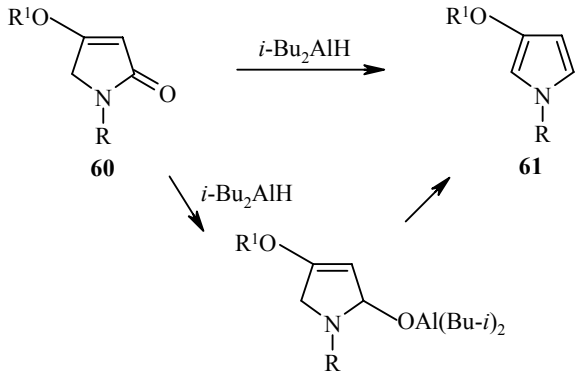
3. Reactions with Participation of the Functional Groups

The authors [101, 102] obtained the substituted pyrrole **59**, which is the product of a skeletal rearrangement taking place during reduction. The formation of a partially saturated structure was not observed here.



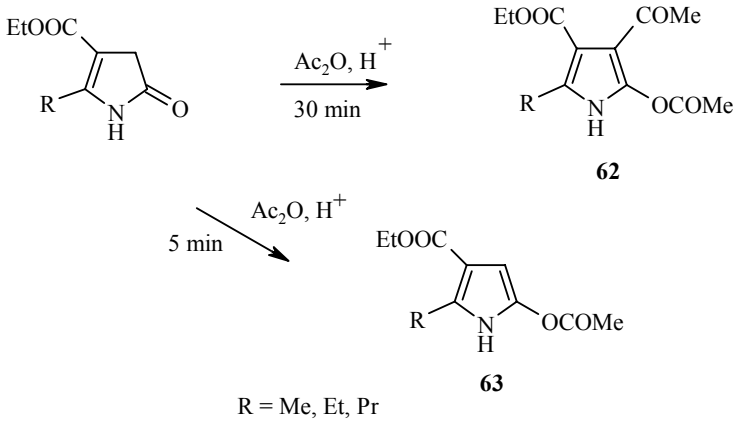
R = Me, H, Ph, $C_6H_4NMe_2$, C_6H_4Me, C_6H_4OMe

Reduction of 4-alkoxypyrrol-2-ones **60** with diisobutylaluminum hydride also takes place at the C=O bond without affecting the heterocycle. The mechanism of the reaction was investigated, the intermediates were isolated, and the method made it possible to obtain preparative yields of the 3-alkoxypyrroles **61** [103].



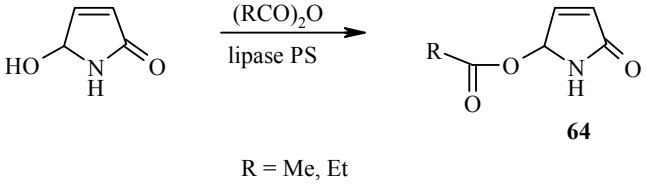
R = H, Me, CH_2Ph; R^1 = Et

Acylation of N-unsubstituted and N-alkyl-substituted pyrrol-2-ones with acetic anhydride leads to the formation of the monoacyl **63** and diacyl **62** derivatives [104].



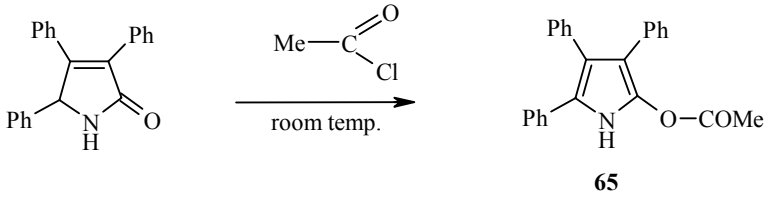
It was noticed that the structure of the final reaction products depended on the length of contact between the reagents and the sulfuric acid used as catalyst. Heating for 5 min led to the O-acylation products **63**, and further increase in the contact time between the reagents led to the products from both O- and C-alkylation **62** [104].

Enzymatic alkylation was studied for the case of 5-hydroxypyrrol-2-ones using acetic and propionic anhydrides. Lipase was used as catalyst [105].

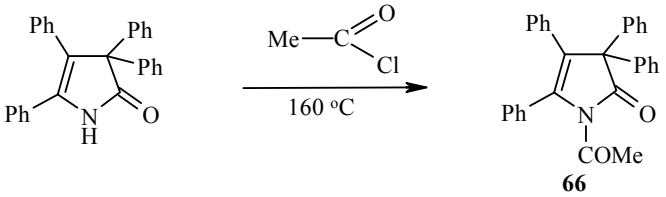


Use of the enzyme makes it possible to conduct the reaction at room temperature and, accordingly, to avoid resin formation from the initial compounds and the reaction products, which is unavoidable with other catalysts.

It was also shown that the direction of acylation depends on the temperature regime and on the substituents. Thus, the O-acylation products **65** were isolated in the reaction of N-unsubstituted 3,4,5-triphenyl- and 3,3,4,5-tetraphenylpyrrol-2-ones with a strong acylating agent (acetyl chloride) at room temperature [106].

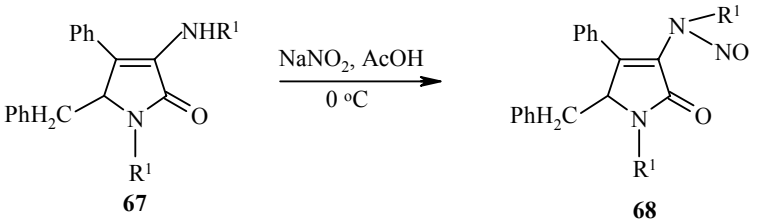


Increase in temperature to 160°C leads to the formation of the products from N-acylation **66**.



The reaction of 3-acyl-5-benzyl-4-hydroxy-5H-pyrrol-2-one with acetic anhydride and tosyl chloride in pyridine leads to tetrasubstituted pyrroles [107].

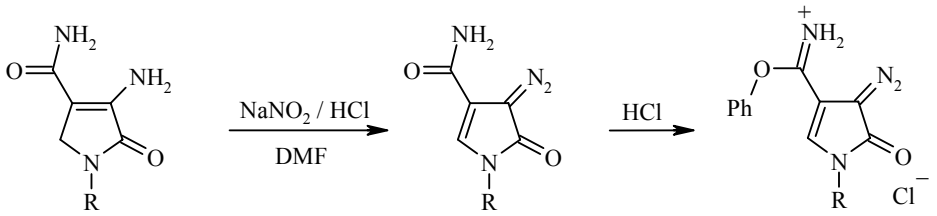
The diazotization of compound **67**, which has a secondary amino group, with sodium nitrite in acetic acid leads to the nitroso derivative **68** with a yield of 64% [79].



67 **68**

$R^1 = C_6H_4NO_2$-3

The diazotization of 3-aminopyrrol-2-ones in DMF gives diazopyrrolones **69**, which exist in the form of salts **70** in a strongly acidic medium [108].

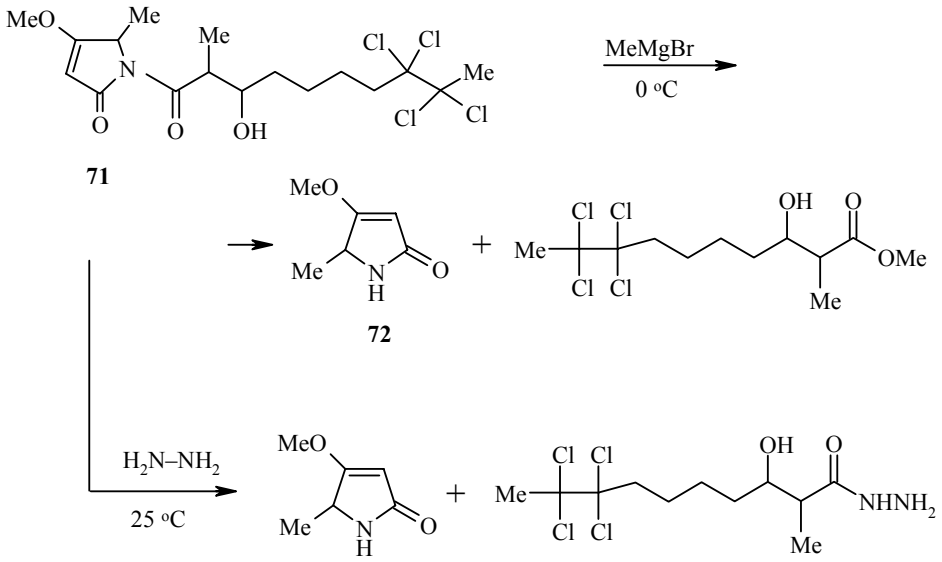


69 **70**

R = CH_2Ph, Bu

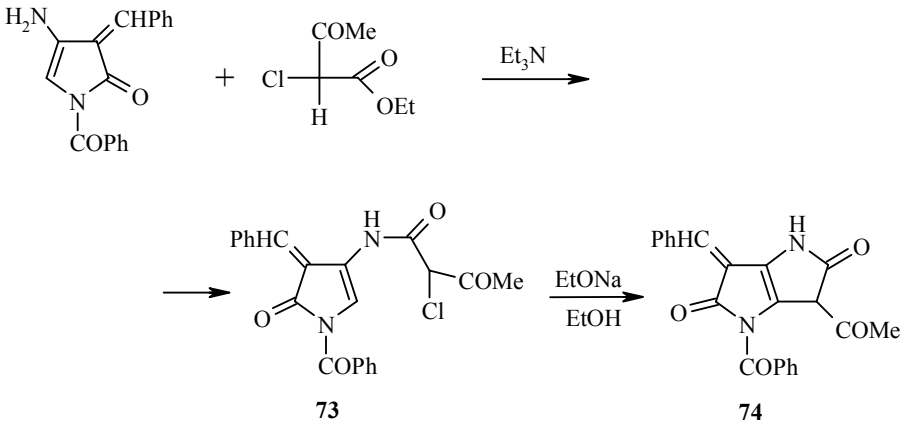
The obtained diazo-substituted pyrrol-2-ones react with triphenylphosphine and with prolonged contact give quantitative yields of phosphazines [108].

Pyrrol-2-ones **71** substituted at the nitrogen atom with a polyfunctional chain underwent degradation during the action of a Grignard reagent and hydrazine, giving NH-pyrrol-2-ones with a yield of 35% [109].



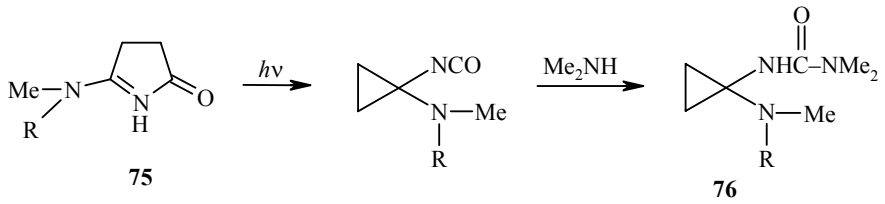
71 **72**

Compounds with condensed pyrrole rings were synthesized in the search for compounds with antibiotic activity. The reaction of 4-amino-3-benzylidene-1-benzoylpyrrol-2-one with ethyl α-chloroacetoacetate in alcohol in the presence of triethylamine led to the formation of the amide **73**, which underwent cyclization in a boiling alcohol solution of sodium ethoxide to form a derivative of pyrrolo[3,2-*b*]pyrrole **74** [33].



73 **74**

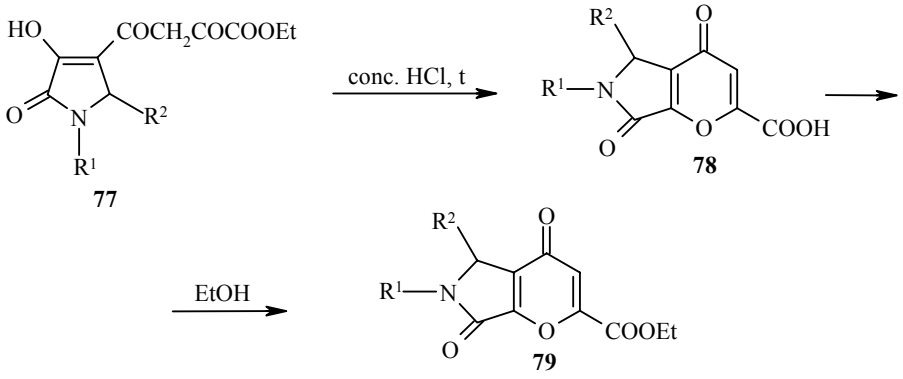
The photochemical rearrangement of 5-dimethyl- and 5-methylphenylaminopyrrol-2-ones **75** has been described. It leads to cyclopropyl isocyanates, which after treatment with dimethylamine give the corresponding cyclopropylureas **76** with yields of 80-90% [110].



75 **76**

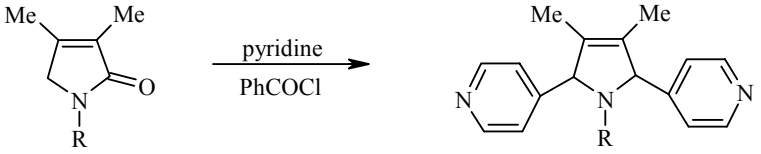
R = Me, Ph

When heated in concentrated hydrochloric acid 1,5-disubstituted 4-ethoxalylacetyltetrahydro-5H-pyrrol-2-ones **77** undergo cyclization to 6-methyl-5-phenyl- and 5,6-diaryl-4,7-dioxo-2-carboxy-5,7-dihydropyrrolo[2,3-*b*]pyrans **78**, which are esterified by treatment with ethanol to the corresponding ethyl esters **79** [111].



77 **78** **79**

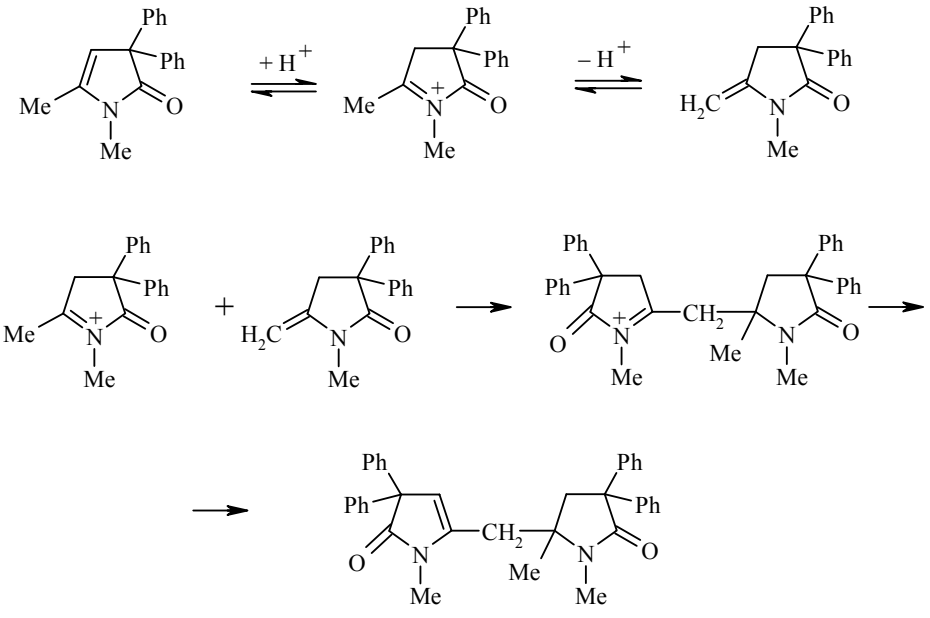
In reaction with pyridine in the presence of benzoyl chloride 3,4-dimethyl-5H-pyrrol-2-ones form 3,4-dimethyl-2,5-dipyridylpyrroline **81** with a yield of 35% [112].



80 **81**

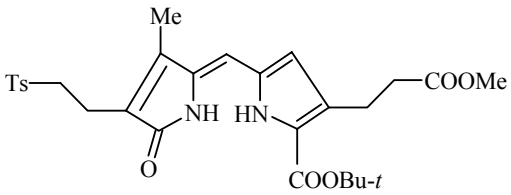
R = H, Me

A dimerization mechanism, taking place during acid catalysis and leading to compounds **82**, was proposed in the series of methyl-substituted pyrrol-2-ones [18].



82

The authors [113] found a new type of Wittig reaction for the production of derivatives of pyrromethenone. Condensation of 4-methyl-5-tosyl-3-(2-tosyl)-5H-pyrrol-2-one with 5-*tert*-butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole in the presence of a catalyst gave compound **83**, which is a potential equivalent to the C/D-ring component of phytochromobilin, with a yield of 73%.



83

The pyrromethene structures based on pyrrol-2-ones were studied in a series of papers [50, 114-119].

Pyrrol-2-ones are also intermediates or final compounds in the synthesis of biologically active materials [1, 5, 6, 120-131].

Thus, in the series of pyrrol-2-ones there are various condensations that take place at the methylene unit. Classical oxidation and reduction with various types of reducing agents are observed.

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