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# (Het)aroylpyruvic acids and their derivatives as promising building blocks for organic synthesis†

S G Perevalov, Ya V Burgart, V I Saloutin, O N Chupakhin

## Contents


| | | |
|---|---|---|
| I. | Introduction | 921 |
| II. | Methods of synthesis and tautomerism of (het)aroylpyruvates | 921 |
| III. | Chemical properties of (het)aroylpyruvates | 923 |
| IV. | Biological activities of (het)aroylpyruvates and the products of their heterocyclisation | 935 |
| V. | Conclusion | 936 |


**Abstract. Methods of synthesis of (het)aroylpyruvic acids and their acyclic derivatives (esters, amides and hydrazides), and their reactions with various C-, N-, O-, S-nucleophiles are described. Problems of tautomerism and biological activity of (het)aroylpyruvates and products of their transformation are briefly considered. The bibliography includes 191 references.**

## I. Introduction

(Het)aroylpyruvic acids [(H)APA] and their derivatives, (het)aroylpyruvates, [(H)AP] were discovered back in the XIX century.[1, 2] They proved to be interesting and useful synthons permitting the preparation of a very broad spectrum of products, in particular, diverse heterocyclic compounds many of which possess biological activities. At present, this class of compound still remains attractive for researchers.[3 – 9] The chemistry of (H)AP is fairly extensive but the current state of investigations in this field is not covered in the world literature. This review is meant to fill this gap.

Cyclic APA derivatives, 5-aryl-2,3-dihydrofuran-2,3-diones have been considered in reviews[7, 10] and will not be discussed here in detail. A review has been devoted to the chemistry of perfluoroaroylpyruvates;[3] therefore we note below only specific features of these compounds not found for non-fluorinated analogues.

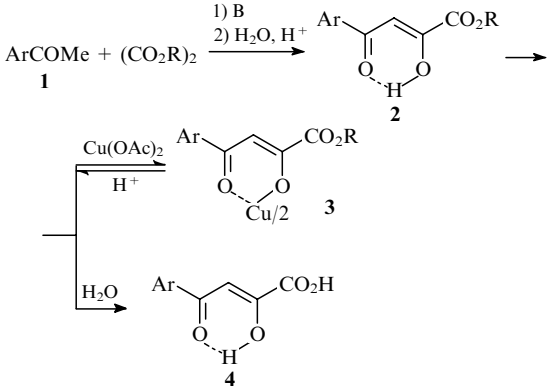
## II. Methods of synthesis and tautomerism of (het)aroylpyruvates

### 1. Methods of synthesis of (het)aroylpyruvates

The Claisen condensation of the corresponding (het)aryl methyl ketones **1** with dialkyl oxalates in the presence of sodium metal or sodium (potassium) alkoxides is the main and the most convenient method for synthesis of (H)APA esters **2** (Scheme 1). Alcohols, diethyl ether, benzene or toluene are used as solvents.[1, 2, 11 – 23] Pentafluorobenzoylpyruvates are prepared from pentafluoroacetophenone in the presence of lithium hydride.[3, 5, 24, 25] It is convenient to isolate and purify labile AP as their copper(II) chelates **3**.[1, 13, 14, 16] This is especially required in the case of pentafluorobenzoylpyruvates,[5, 24, 25] which cyclise very easily to chromone derivatives due to the presence of *ortho*-fluorine atoms in the benzoyl substituent. Hydrolysis of the esters **2** to the corresponding acids **4** is normally carried out in an acid medium,[1, 23, 26, 27] although examples of alkaline hydrolysis are also documented.[2, 11]

A method for the preparation of ethyl 4-(1,2-diaryl-4-hydroxy-5-oxo-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoates **5**

Scheme 1



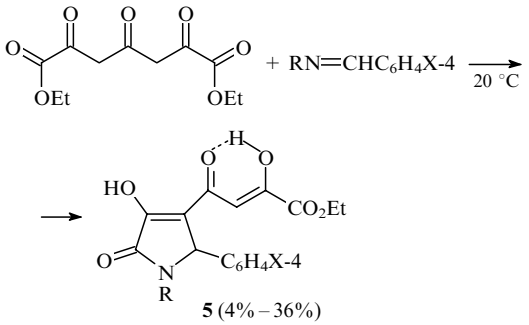

**1 – 4**: Ar = Ph, 2-$XC_6H_4$ (X = $NO_2$, OH), 4-$XC_6H_4$ (X = NHAc, Br, Cl, Ph, OH, OMe), 2-OH-4-OMe-$C_6H_3$, 2-OH-4-OEt-$C_6H_3$, 2,4-$(OEt)_2C_6H_3$, 2,5-$(OEt)_2C_6H_3$, 2,4-$Me_2C_6H_3$, 2,4,6-$(OMe)_3C_6H_2$, 2-OH-4,6-$(OMe)_2C_6H_2$, $C_6F_5$, 2-naphthyl, 1-hydroxy-2-naphthyl, 3-phenanthryl, 2-pyrrolyl, 2,5-dimethyl-3-pyrrolyl, 2,3-dimethyl-4-pyrrolyl, 2-thienyl, 5-methyl-2-thienyl, methyl(phenyl)-2-thienyls, 2-furyl, Py, 5-X-indol-3-yls (X = H, OMe, Cl), 2-methyl-5-methoxy-3-benzo[*b*]-furyl, substituted 5-oxazolyls, 2,4-dimethyl-5-thiazolyl, 3-X-4-sydnonyls (X = Me, Ph), cymantrenyl.
B = Na, NaOR, KOR, LiH; R = Et, Me, Pr, Ph.

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† Dedicated to Academician O M Nefedov with appreciation and on the occasion of his seventieth birthday.

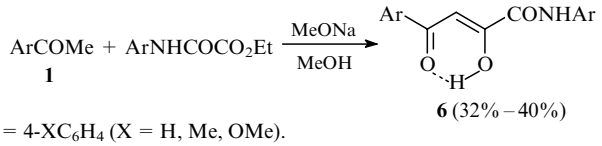
by the reaction of diethoxalylacetone with diarylazomethines was proposed not long ago.[28]



**5** (4% – 36%)

R = Me, 4-YC$_6$H$_4$ (Y = H, Me, OMe, Br); X = H, OMe, Br, Cl.

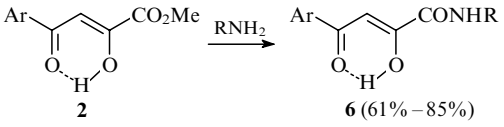
The condensation of acetophenones **1** with esters of oxanilic acids is used for the synthesis of APA amides **6**.[29]



**6** (32% – 40%)

Ar = 4-XC$_6$H$_4$ (X = H, Me, OMe).

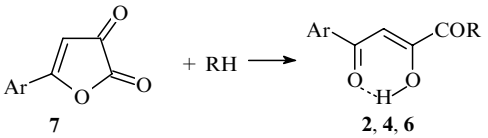
Preparation of the amides **6** from the APA methyl esters **2** and *N*-phenylethylenediamine[30] or 2-aminopyridine has been described.[31]



**6** (61% – 85%)

Ar = 4-XC$_6$H$_4$ (X = H, Me, OMe, Br); R = (CH$_2$)$_2$NHPh, 2-pyridyl.

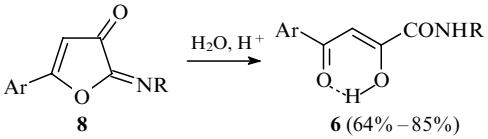
Methods for the synthesis of APA **4**,[32] the esters **2**,[32–37] the amides **6**,[30, 31, 37–64] and hydrazides [65–74] based on the reaction of the corresponding 5-aryl-2,3-dihydrofuran-2,3-diones **7**[38] with diverse nucleophiles have now become significant practically. The range of reagents used includes water,[32] alcohols,[32] oximes [33–36] and amides of 2-hydroxy acids;[37] amines,[30, 31, 37–39, 41–44, 48, 51–64] 2-aminophenol,[37] ethanolamine,[37] amino acids,[40, 49] thiols,[44, 45] mercaptoethanolamine,[44] amides of thioacids,[50] acyl- and aroyl-hydrazides,[65, 67–69, 72, 73] hydrazine,[66] and hydrazones.[70, 71, 74]



**2**, **4**, **6**

**2**: R = OAlk, OPh, ON = CR$^1_2$; **4**: R = OH;
**6**: R = NH$_2$, NHAlk, NHAr, NHHet.

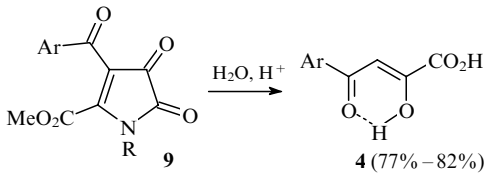
The APA amides and hydrazides **6** have been prepared by acid hydrolysis of 5-aryl-2-imino-2,3-dihydrofuran-3-ones **8**.[75–78]



**6** (64% – 85%)

Ar = 4-YC$_6$H$_4$ (Y = H, Me, OMe, Cl, Br); R = CH$_2$SO$_2$C$_6$H$_4$Me-4, 1-adamantyl, N = CHCOPh.

Extensive hydrolysis of 1-aryl-4-aroyl-5-methoxycarbonyl-2,3-dihydropyrrole-2,3-diones **9** affords the APA **4**.[79]

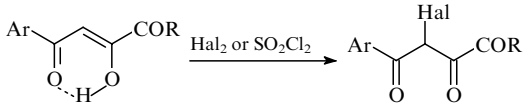


**4** (77% – 82%)

Ar = 4-XC$_6$ H$_4$ (X = H, Me, OMe), R = Ar (X = H, Me, OMe, NO$_2$), *etc*.

3-Halogen-substituted esters **10** (R = OEt, OMe) and amides **11** (R = NHPh) of APA are prepared by halogenation of the corresponding AP **2** (see papers [18, 80–84]) and **6**[39, 85, 86] (Scheme 2).

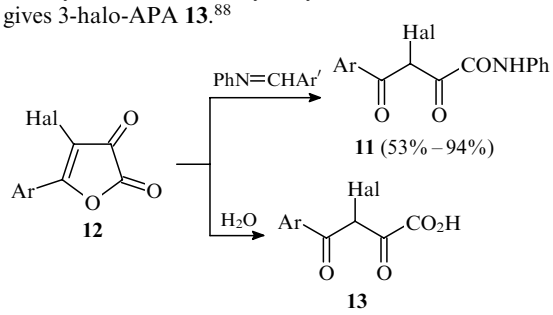
Scheme 2



**10**, **11** (83% – 98%)

Ar = 4-YC$_6$H$_4$ (Y = H, Me, OMe, F, Cl, Br), 2,4,6-Me$_3$C$_6$H$_2$, 2-naphthyl; Hal = Cl, Br; R = OEt, OMe, NHPh.

The amides **11** can also be synthesised from 5-aryl-4-halo-2,3-dihydrofuran-2,3-diones **12** by introducing them into a reaction with diarylazomethines.[87] Hydrolysis of the furandiones **12** readily gives 3-halo-APA **13**.[88]



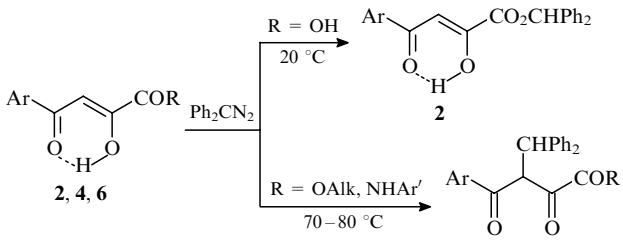
**11** (53% – 94%)

**13**

Hal = Cl, Br; Ar = 4-YC$_6$H$_4$ (Y = H, Me, OMe, Cl).

The reaction of the APA esters **2** and amides **6** with diphenyldiazomethane gives rise to 3-diphenylmethyl-substituted AP **14**[81, 89] and **15**.[90] It should be noted that APA **4** are esterified in this reaction to give the esters **2** (Scheme 3).

Scheme 3

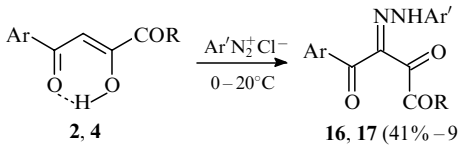


**2**, **4**, **6**

**14**, **15** (7% – 87%)

Azo coupling of the APA **4** [91–93] and the esters **2** [94–96] with aryldiazonium salts is used to prepare 3-arylhydrazones of 4-aryl-2,3,4-trioxobutanoic acids **16** and their esters **17** (Scheme 4).

Scheme 4



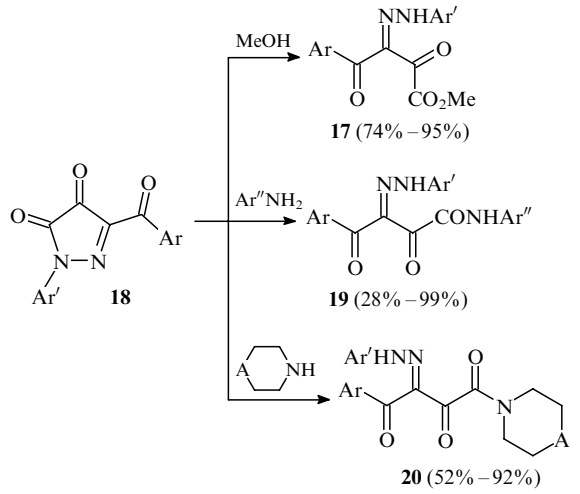
**2**, **4**

**16**, **17** (41% – 91%)

**2**, **17**: R = OMe, OEt; **4**, **16**: R = OH.

The esters **17** are also formed in the alcoholysis of 1-aryl-3-aroyl-4,5-dihydropyrazole-4,5-diones (**18**).[92] Treatment of the

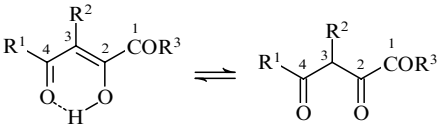
pyrazolediones **18** with amines yields 4-aryl-2,3,4-trioxobutyramide 3-arylhydrazones **19**[97,98] and **20**.[98]




## 2. Tautomerism of (het)aroylpyruvates

Tautomeric equilibrium has been studied for a series of (H)AP (Scheme 5). According to $^1$H NMR data, the 3-unsubstituted (H)APA **4**, their esters **2** and amides **6** exist in solution as enols.[81,99,100] The enol structure of the benzoylpyruvic acid **4a** has also been confirmed by X-ray diffraction analysis.[101] Only ethyl 4-(3-indolyl)-2,4-dioxobutanoate in DMF-$d_7$ is a mixture of ketone and enol tautomers in a ratio of $\sim 1:1$.[20]

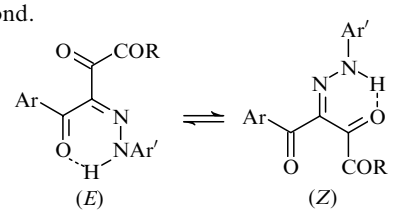
Scheme 5



$R^1$ = Ar, Het; $R^2$ = H, Cl, Br, N=NAr, Alk, Ar; $R^3$ = $OR^4$, $NR^4_2$, $NR^1NR^4_2$ ($R^4$ = H, Alk, Ar, COAlk).

In the case of 3-alkyl- and 3-halo-substituted AP **10**, **11**, and **13**–**15**, the ketone form predominates.[102–105] Apparently, the hampered formation and energetic destabilisation of the enol form are caused by the presence of bulky substituents at the 3-position.

The spectral data for the AP **16**, **17**, **19** and **20** available to date indicate that 3-arylhydrazone-substituted acids **16**,[92] esters **17**[92,96] and amides **19** and **20**[97,98] occur as equilibrium mixtures of *Z*- and *E*-tautomers of the ketone form relative to the C=N bond.



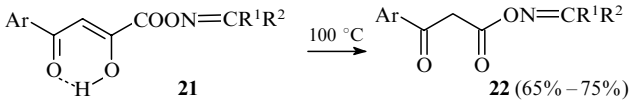

# III. Chemical properties of (het)aroylpyruvates

(Het)aroylpyruvates contain three electrophilic centres, namely, the C(1) atom of the ester group and the C(2) and C(4) carbonyl atoms, and one nucleophilic centre, namely, the *meso*-position of the β-dicarbonyl fragment, *i.e.*, the C(3) atom (see Scheme 5). Therefore, the (H)APA **4**, their esters **2** and the amides **6** tend to react with nucleophilic reagents at the C(1), C(2) and C(4) atoms. In addition, (H)AP enter into reactions with electrophiles at the C(3) centre. These transformations are mainly considered in the previous Section concerned with the methods of synthesis of (H)AP (see Schemes 2–4). A typical feature of (H)AP is the susceptibility to thermal transformation. Some (H)AP are able to undergo intramolecular cyclisations.

## 1. Thermal transformations and intramolecular cyclisations of (het)aroylpyruvates

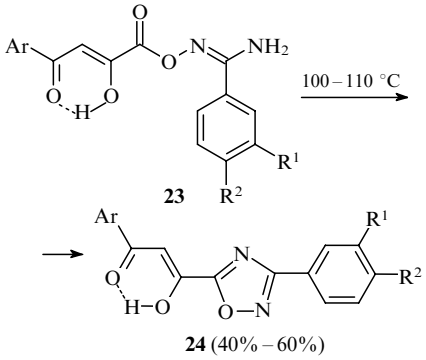
### a. Thermal transformations

Virtually all (H)AP are fairly labile compounds. *O*-Aroylpyruvoyl oximes **21** undergo decarbonylation at 100°C giving rise to *O*-aroylacetyl oximes **22**.[34]



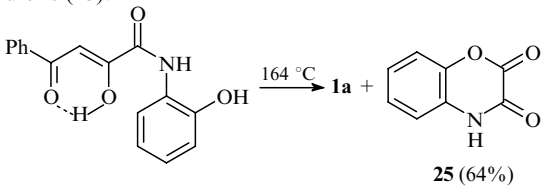

Ar = 4-$XC_6H_4$ (X = H, Me, Et, Cl); $R^1$ = H, Me; $R^2$ = Ph, 2-$HOC_6H_4$, 1-adamantyl.

Under similar conditions, *O*-aroylpyruvoyl oximes **23**, containing an amino group, cyclise to 3-aryl-5-(3-aroyl-1-hydroxypropenyl)-1,2,4-oxadiazoles **24**.[35]

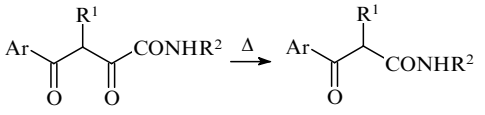



Ar = 4-$XC_6H_4$ (X = H, Me): $R^1$ = $R^2$ = H, OMe; $R^1$ = H, $R^2$ = $NO_2$.

Arylamides of the 3-unsubstituted APA **6** are stable even at 220 °C.[81,106] *N*-(2-Hydroxyphenyl)-3-benzoylpyruvoylamide is an exception; on refluxing in mesitylene, this compound decomposes into acetophenone **1a** and 3,4-dihydro-2*H*-1,4-benzoxazine-2,3-dione (**25**).[37]



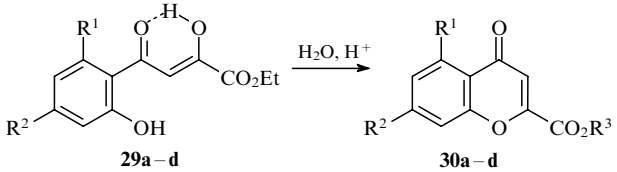

Meanwhile, 3-methyl- (**26**)[106] and 3-diphenylmethyl-substituted (**15**)[90] arylamides are decarbonylated on heating giving rise to *N*-aryl-2-methyl- (**27**) and *N*-aryl-2-diphenylmethyl-3-phenyl-3-oxopropanamides **28**.




**26**, **27**: Ar = Ph, $R^1$ = Me, $R^2$ = $YC_6H_4$ (Y = H, 3-OMe, 4-OMe); **15**, **28**: Ar = 4-$YC_6H_4$ (Y = H, Me); $R^1$ = $CHPh_2$, $R^2$ = Ph, 4-$MeOC_6H_4$.

### b. Intramolecular cyclisations

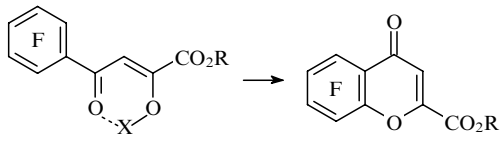
On refluxing in aqueous HCl, ethyl aroylpyruvates **29a**–**d**, containing a hydroxy group in the *ortho*-position of the benzene ring cyclise to give 4-oxachromene-2-carboxylic acids **30a**–**d**.[16]




$R^3$ = Et: $R^1$ = $R^2$ = H (**a**), OEt (**b** ); $R^3$ = H, $R^1$ = H (**c** ), OMe (**d**), $R^2$ = OMe.

Pentafluorobenzoylpyruvates **31a**,**b** cyclise either over a period of one month at 20 °C or rapidly on heating to give 2-alkoxycarbonyl-5,6,7,8-tetrafluoro-4*H*-chromen-4-ones **32a**,**b**.[3, 6, 24] Acid **31c** (R = H) is stable under these conditions.[27] It cyclises to be converted into chromone-2-carboxylic acid (**32c** ) only after treatment with anhydrous ammonia or triethylamine in dioxane at 20 °C. The copper(II) chelates **31d**,**e** are also converted into chromones **32a**,**b** on heating in DMSO at 80 – 90 °C[3, 4, 6, 24] (Scheme 6).

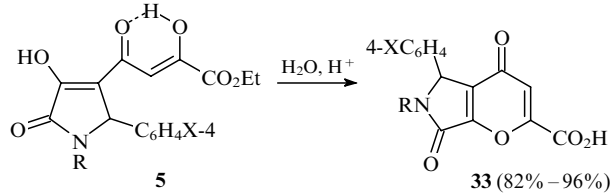
Scheme 6



**31a – e** **32a – e**

**31**: X = H: R = Et (**a**), Me (**b**), H (**c**); X = Cu/2, R = Et (**d**), Me (**e**);
**32**: R = Et (**a**), Me (**b**), H (**c**).

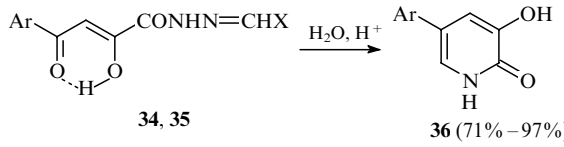
Under conditions of acid hydrolysis, the ethyl pyrrolylpyruvates **5** undergo cyclisation which involves the hydroxy group of the pyrrole fragment and gives 5,6-diaryl-2-carboxypyrano[2,3-*c*]pyrrole-4,7(4*H*,5*H*)-diones **33**.[107]



**5** **33** (82% – 96%)

R = Me, Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$; X = H, NO$_2$, Br.

Acid hydrolysis of APA *N*-benzoylmethylene- (**34**)[78] and APA *N*-benzimidenehydrazides **35**[108] results in the formation of the same 6-aryl-4-hydroxy-2,3-dihydropyridazin-3-ones **36**.

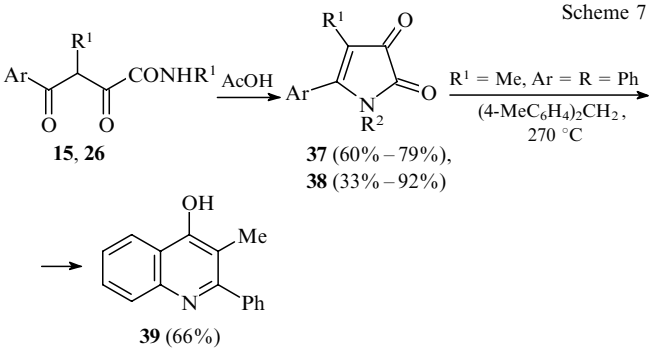


**34**, **35** **36** (71% – 97%)

Ar = 4-YC$_6$H$_4$ (Y = OMe, Cl, H, Me); X = COPh (**34**), Ph (**35**).

The amides **15** and **26** cyclise in boiling AcOH being thus converted into the corresponding 1,5-diaryl-4-diphenylmethyl-(methyl)-2,3-dihydropyrrole-2,3-diones **37**[90, 109] and **38**[110] (Scheme 7). The compound **37** (X = Me, Ar = R = Ph) recyclises on refluxing in ditolylmethane to afford 4-hydroxy-3-methyl-2-phenylquinoline (**39**).[110]

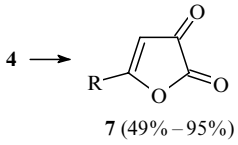
Scheme 7



**15**, **26** **37** (60% – 79%), **38** (33% – 92%) **39** (66%)

**15**, **37**: Ar = 4-YC$_6$H$_4$ (Y = H, Me), R$^1$ = CHPh$_2$, R$^2$ = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$;
**26**, **38** : Ar = Ph, R$^1$ = Me, R$^2$ = YC$_6$H$_4$ (Y = H, 3-OMe, 4-OMe, 4-Me, 4-OH, 2-OH, 4-Br).

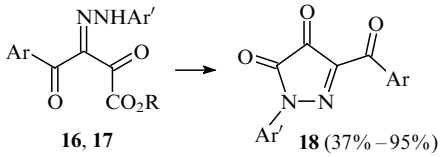
When heated in benzene with thionyl chloride (65 – 70 °C)[38] or acetic anhydride (60 – 70 °C),[111, 112] the acids **4** undergo dehydration to the furandiones **7**. The two methods provide similar yields of the compounds **7**.



**7** (49% – 95%)

R = Ar, Het.

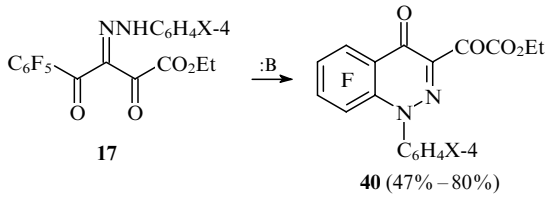
The APA 3-arylhydrazones **16** cyclise on treatment with thionyl chloride to give pyrazolediones **18**.[92, 93] The same compounds are produced on prolonged refluxing of the methyl esters **17** in acetic anhydride.[113]



**16**, **17** **18** (37% – 95%)

Ar = 4-YC$_6$H$_4$ (Y = H, Me, OMe, NO$_2$, Br, Cl); Ar′ = 4-YC$_6$H$_4$ (Y = H, OMe, Cl).

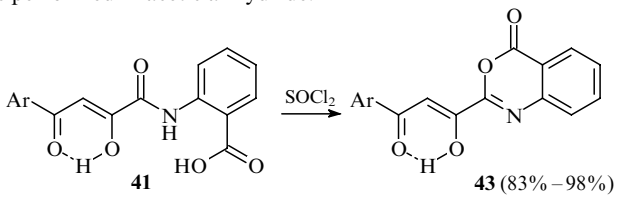
A distinctive feature of pentafluorophenyl-substituted arylhydrazones (**17**, Ar = C$_6$F$_5$) is their ability to undergo cyclisation either on heating with DMSO in the presence of potassium carbonate or in a mixture of triethylamine with chloroform; the reaction furnishes 1-aryl-5,6,7,8-tetrafluoro-3-ethoxalyl-1,4-dihydrocinnolin-4-ones **40**.[95, 96]



**17** **40** (47% – 80%)

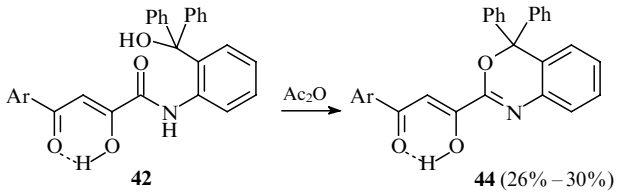
X = H, Me, OMe.

Cyclodehydration of APA arylamides **41**[49] and **42**[64] with participation of the amide group capable of enolisation gives benzoxazines **43**, **44**. In the case of the amide **41**, the reaction was carried out by heating the compound in benzene with thionyl chloride (with DMF as the catalyst),[49] and for the compound **42**, it was performed in acetic anhydride.[64]



**41** **43** (83% – 98%)

Ar = 4-XC$_6$H$_4$ (X = OMe, OEt, Br, Cl).



**42** **44** (26% – 30%)

Ar = 4-XC$_6$H$_4$ (X = H, Me, OMe).

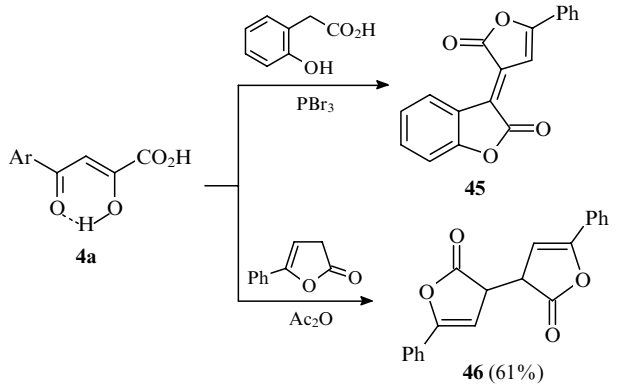
## 2. Reactions of (het)aroylpyruvates with mononucleophiles

Reactions with some C-, N- and O-mononucleophiles are known for the (H)APA **4** and their esters **2** and amides **6**.

**a. Reactions with C-mononucleophiles**

The reported reactions of AP with C-mononucleophiles are few in number because AP tend to decompose under conditions where nucleophiles are generated and/or are sufficiently reactive and heterocyclisation is precluded.

Mention should be made of condensations of **4a** with 2-hydroxyphenylacetic acid in the presence of $PBr_3$ resulting in the product **45** and with 5-phenyl-2,3-dihydrofuran-2-one in the presence of acetic anhydride to give the compound **46**.[114]

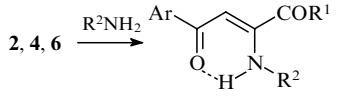



**b. Reactions with O-mononucleophiles**

Of the transformations of (H)AP in reactions with alcohols, only transesterification of the esters **2** is known. Most of the APA esters **2** (Ar is substituted phenyl) are unstable under conditions of alkaline hydrolysis and decompose yielding the corresponding acetophenone **1**, alcohol and oxalate.[1] The HPA esters **2** are more stable to this cleavage because the acids **4** [Ar = 2-thienyl,[2] 3-(2,4-dimethylpyrrolyl) [11]] can be prepared by alkaline hydrolysis of the corresponding esters **2**. However, ethyl 3-indolyl- and 3-(5-methoxyindolyl)pyruvates are readily cleaved by alkalis and are even partially cleaved during recrystallisation from ethanol.[20] Recently, ethyl pentafluorobenzoylpyruvate copper(II) chelate **31d** was reported to undergo transesterification into the chelate of the methyl ester **31e**. For the free AP **2**, this reaction is unknown.

**c. Reactions with N-mononucleophiles**

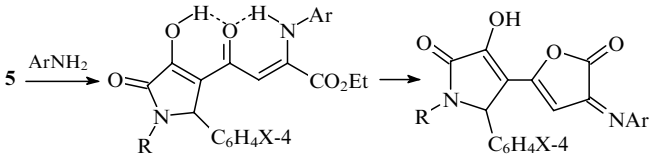
The esters **2** are known [115] to react with ammonium acetate on refluxing in an AcOH – benzene mixture; the reaction involves the carbonyl group at the C(2) atom and gives ethyl 2-amino-4-arylbut-2-en-4-onoates **47** in ~80% yield. Under mild conditions (at 20 – 50 °C), both the (H)APA **4** and their esters **2** add aniline and its derivatives at the carbonyl group giving rise to 2-arylamino-4-aryl-4-oxobut-2-enoates **48** (the yields vary from 9% to 83%).[79, 102, 116] Electron-withdrawing substituents and steric hindrance in the reactants result in lower yields of the products **48**. The structure of the compounds **48**, stabilised by an intramolecular hydrogen bond (IMHB) in the β-amino vinyl ketone fragment, was confirmed by NMR spectroscopy.[117] The APA arylamides **6** behave in a similar way in reactions with aniline, giving rise to arylamides of 4-aryl-4-oxo-2-phenylaminobut-2-enoic acids **49** in 60% – 93% yields.[29, 118]




**47**, **48**, **49**

**2**, **47**: $R^1$ = OEt; $R^2$ = H; **2**, **4**, **48**: $R^1$ = OH, OMe; $R^2$ = Ar′; **6**, **49**: $R^1$ = NHAr′; $R^2$ = Ph.

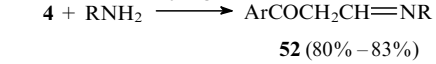
The pyrrolylpyruvates **5** are also converted into amino esters **50b – e** when heated with arylamines to 60 °C.[107] However, on stronger heating (150 – 220 °C), these products cyclise to give compounds **51b – e**.[107] The cyclisation is facilitated by electron-withdrawing substituents in the pyrrole ring of **5**. Indeed, 1-methylpyrrolylpyruvate **5a** readily cyclises with aniline at 20 °C giving rise to heterocycle **51a**; the intermediate compound **50a** cannot be isolated.[107]




**50b – e** (87% – 97%) **51a – e** (29% – 58%)

Ar = Ph, R = Me, X = H (**a**); Ar = R = Ph (**b – d**): X = H (**b**), Br (**c**), $NO_2$ (**d**); Ar = R = 4-$BrC_6H_4$, X = Br (**e**).

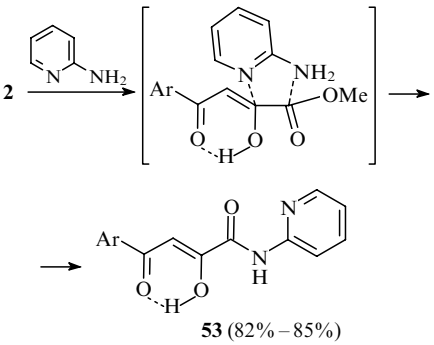
It has been reported that salts decarboxylated on refluxing in mesitylene (164 °C) to give 3-aryl-3-oxopropanal monoanils **52** can be isolated from the products of reaction between the APA **4** and aromatic amines at 20 °C.[119]




**52** (80% – 83%)

Ar = 4-$XC_6H_4$ (X = H, Me, OMe, Cl, Br); R = 4-$XC_6H_4$ (X = H, OMe, Cl, Br).

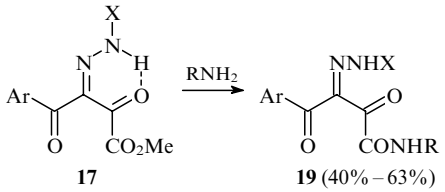
It is of interest that refluxing of methyl aroylpyruvates **2** in benzene with 2-aminopyridine results in APA 2-pyridylamides **53** instead of the 2-amino-derivatives such as **48**, **49**.[31] The unusual pathway of 2-aminopyridine addition to AP is due, apparently, to the fact that in the transition state, the highly basic pyridine nitrogen atom of the nucleophile is coordinated to the C(2) carbonyl atom of the AP and the amino group is coordinated to the C(1) atom.




**53** (82% – 85%)

Ar = 4-$XC_6H_4$ (X = H, Me, OMe, Br).

Unlike 3-unsubstituted esters **2**, 3-arylhydrazones **17**, which are efficiently stabilised by an IMHB, react with arylamines on refluxing in benzene; the reaction involves the ester group and gives the arylamides **19**.[98]

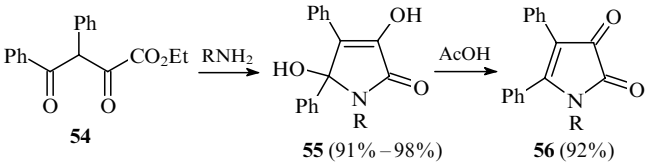



**17** **19** (40% – 63%)

Ar = Ph, 4-$EtOC_6H_4$; R = 4-$YC_6H_4$ (Y = H, Me, Cl); X = Ph.

It is known [120] that APA arylamides containing a bulky group at the 3-position readily cyclise yielding 4-substituted 1,5-diaryl-2,3-dihydropyrrole-2,3-diones **37**, **38** (see Scheme 7).[90, 109, 110] The tendency toward cyclisation is sometimes so pronounced that it is not always possible to isolate arylamides formed in the reaction of APA esters with amines.[121] Indeed, the reaction of ethyl 3-phenylbenzoylpyruvate (**54**) with methyl- or benzylamine in chloroform at 20 °C yields immediately the products of cyclisation of intermediate amides, 1-alkyl-4,5-diphenyl-3,5-dihydroxy-2,5-dihydropyrrol-2-ones **55**. It is noteworthy that in this case, as for arylhydrazones **17**, it is the ester group that is involved in the

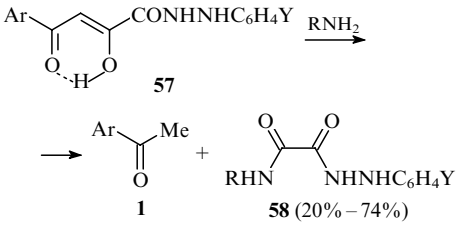
reaction with the amine. The products **55** are dehydrated to give 1-alkyl-4,5-diphenyl-2,3-dihydropyrrole-2,3-diones **56**.[103]



**54** **55** (91% – 98%) **56** (92%)

R = Me, $CH_2Ph$.

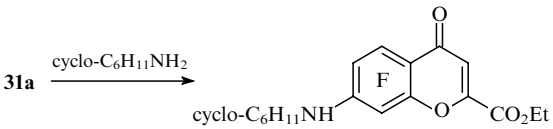
Unlike the amides **6**, APA β-aroylhydrazides **57** are cleaved by aromatic amines when fused together (160 – 165 °C); this gives rise to acetophenones **1** and mixed amidohydrazides of oxalic acid **58**.[67] Benzylamine splits the hydrazides **57** even at 60 – 65 °C.



**57** **1** **58** (20% – 74%)

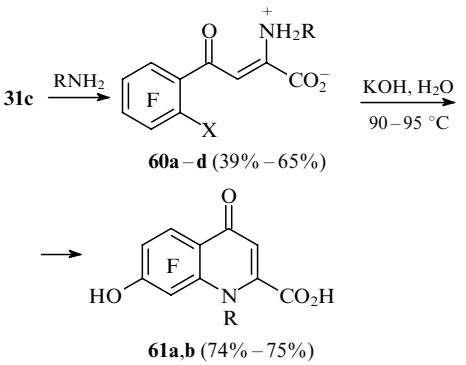
Ar = 4-$XC_6H_4$ (X = H, Me, OMe); R = 4-$XC_6H_4$ (X = H, Me, OEt), $CH_2Ph$; Y = H, 3-$NO_2$, 4-OMe.

Fluorine-containing AP behave quite differently in reactions with amines. Thus the pentafluorobenzoylpyruvates **31a**,**b** rapidly cyclise to the chromones **32a**,**b** when made to react with aqueous ammonia at 20 °C[3, 121] (see Scheme 6); the reaction of the pyruvate **31a** with cyclohexylamine on heating in DMSO does not stop at the cyclisation stage but proceeds as nucleophilic substitution with removal of the fluorine atom at the 7-position of the aromatic ring, thus yielding 5,6,8-trifluoro-7-cyclohexylamino-2-ethoxycarbonylchromen-4(4*H*)-one (**59**).[121]



**59** (63%)

As noted above, the reaction of pentafluorobenzoylpyruvic acid (**31c**) with anhydrous ammonia or triethylamine in dioxane at 20 °C leads to chromone-2-carboxylic acid (**32c**) (see Scheme 6). Heating of the acid **31c** with aqueous ammonia and primary amines affords 2-(alkyl)amino-4-oxo-4-polyfluoroaryl-2-butenoic acids **60**.[26, 27] The acid **60a** cyclises reversibly into the chromone **32c** on heating in an acid medium. On treatment with aqueous alkali, the acids **60b**,**c** undergo cyclisation to give 1-alkyl-2-carboxy-7-hydroxy-5,6,8-trifluoroquinolin-4(4*H*)-ones **61**.[26, 27] The structure of the quinolone **61b** as DMSO adduct has been determined by X-ray diffraction analysis.[104]



**60a** – **d** (39% – 65%)

**61a**,**b** (74% – 75%)

**60**: X = OH, R = H (**a**); X = F: R = $Pr^i$ (**b**), cyclo-$C_6H_{11}$ (**c**), Ph (**d**);
**61**: R = $Pr^i$ (**a**), cyclo-$C_6H_{11}$ (**b**).

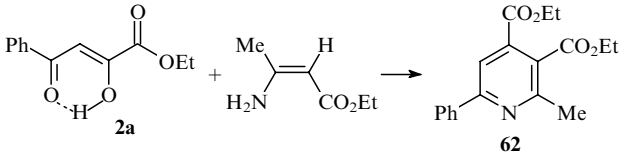
Thus, the reactions of APA **4**, their esters **2** and amides **6** with N-mononucleophiles mainly involve the oxo group at the C(2) atom, although in the case of esters having bulky substituents at the 3-position, the ester group becomes more reactive.

## 3. Reactions of (het)aroylpyruvates with dinucleophiles

The reactions of (H)AP with bifunctional nucleophiles are widely used in organic synthesis to prepare five-, six-, and seven-membered heterocycles and their fused derivatives.

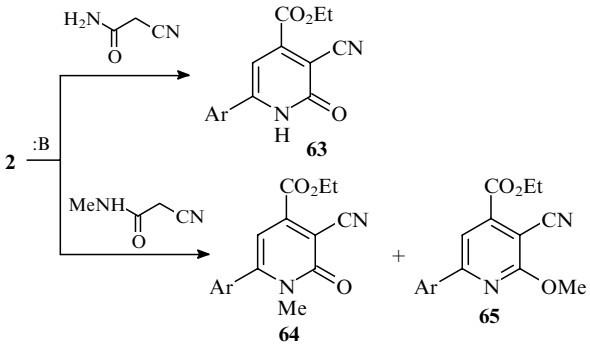
### a. Reactions with C,N-dinucleophiles

Reactions with C,C-dinucleophiles are unknown. Of transformations of (H)AP on treatment with C,N-dinucleophiles, the reactions with ethyl 3-aminocrotonate and cyanoacetamide are documented. Under mild conditions (at 20 °C in the absence of bases), the pyruvate **2a** adds ethyl 3-aminocrotonate at the β-diketone fragment to give 3,4-bis(ethoxycarbonyl)-2-methyl-6-phenylpyridine (**62**).[105] The most electrophilic centre of AP [the C(2) atom] reacts with the C-nucleophilic centre of the crotonate and the C(4) atom reacts with the amino group.



**2a** **62**

The reaction of the (H)AP **2** with cyanoacetamide proceeds in a similar way giving rise to 6-aryl-3-cyano-4-ethoxycarbonyl-2-pyridones **63**.[13,14, 122] The reaction was carried out by refluxing the reactants in ethanol in the presence of piperidine[122] or diethylamine.[13, 14] The use of *N*-methylcyanoacetamide affords not only 6-aryl-3-cyano-4-ethoxycarbonyl-1-methyl-2-pyridones **64**, but also 6-aryl-3-cyano-4-ethoxycarbonyl-2-methoxypyridines **65** as side products.[13, 14]



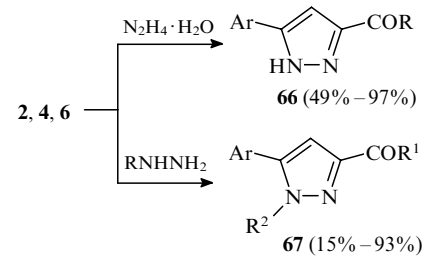
**63** **64** **65**

**2**, **63**: R = Et, Ar = Ph, 2-furyl, 4-diphenylyl;
**64**, **65**: Ar = 2-furyl, 4-diphenylyl.

### b. Reactions with N,N-dinucleophiles

The reactions of (H)AP with N,N-dinucleophilic reagents possess the highest synthetic value; these reactions have been the best studied.

**Reactions with hydrazine and its derivatives**. The acids **4**, the esters **2** and the amides **6** react selectively with hydrazine at the β-dicarbonyl fragment [C(2) and C(4) atoms] to give 5-(het)arylpyrazole-3-carboxylic acid derivatives **66** in good yields.[3 – 5, 11, 13, 14, 16, 17, 20, 21, 23, 31, 53, 59, 62, 67, 72, 73, 123 – 126] The solvents used in these reactions are acetic acid, 1,4-dioxane, alcohols or water. The (H)AP **2**, **4** and **6** react with monomethyl and arylhydrazines in a similar way, the reaction proceeding regioselectively to give exclusively 1-methyl-[13, 14] and 1-aryl-5-(hetero)arylpyrazole-3-carboxylic acid derivatives **67**.[1 – 5, 13, 14, 20, 23, 67, 124, 127]

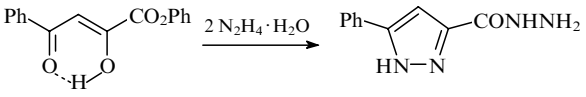



**66**: Ar = $XC_6H_4$ (X = H, 4-OH, 4-Me, 4-OMe, 4-OEt, 4-Br, 3-Br, 4-F, 4-Cl), 2,4-$Me_2C_6H_3$, 4-diphenylyl, 3-phenanthryl, $C_6F_5$, 2-furyl, 3-indolyl, cymantrenyl, 3-methyl-5-phenyl-2-thienyl, 4-methyl-5-oxazolyl, 2,4-dimethyl-5-oxazolyl, 5-(2,4-dimethylthiazolyl); R = OEt, OH, NHPh, $NH(CH_2)_2NHAc$, 2-pyridylamino, 3-pyridylamino, 2-bromo-5-pyridylamino, 2-thiazolylamino, 2-pyrimidylamino, 3-cyano-4,5-tetramethylene-2-thienylamino, NHNHCOAr′ (Ar′ = Ph, 4-$MeOC_6H_4$), $NHNHCOCO-CH=PPh_3$, $NHNHCOC_6H_4Y$ (Y = 2-methylphenylamino, 2-methyl-4-quinolyl);

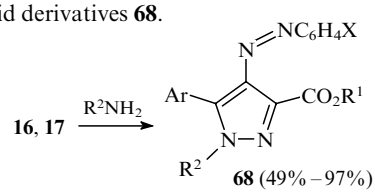
**67**: Ar = Ph, 4-$MeC_6H_4$, 4-diphenylyl, $C_6F_5$, 2-pyrrolyl, 2-furyl, 2-thienyl, 5-methyl-2-furyl, 3-methyl-2-phenyl-5-thienyl, 2,4-dimethyl-5-oxazolyl, 2,4-dimethyl-5-thiazolyl, 3-indolyl; $R^1$ = OH, OEt, $OPr^i$; 2(3)-pyridylamino, 5-bromo-2-pyridylamino, $NHNHCOC_6H_4Y$-4 (Y = H, OMe); $R^2$ = Ph, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, Me.

For the synthesis of pyrazoles **66**, the use of equimolar amounts of (H)AP and hydrazine hydrate or dihydrochloride is recommended.[14] Some examples of cleavage of (H)AP upon the use of excess hydrazine have been reported.[13, 20] In addition, under these conditions, the ester group in the final pyrazoles **66** is usually converted into a hydrazide group.[11, 13, 17] Thus the reaction of 2-furoylpyruvate **2c**[13] with excess hydrazine gives 5-(2-furyl)pyrazole-3-carbohydrazide together with the target pyrazole **66** (Ar = 2-furyl, R = OEt) even under mild conditions.

Note that the reaction of phenyl benzoylpyruvate with hydrazine involves both the β-dicarbonyl fragment and the phenoxycarbonyl group, resulting in 5-phenylpyrazole-3-carbohydrazide.[16]



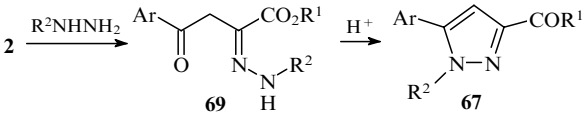

3-Arylhydrazono-APA **16**[128] behave in reactions with hydrazine and phenylhydrazine similarly to 3-unsubstituted analogues giving rise to 4-arylazo-(1-phenyl)-5-arylpyrazole-3-carboxylic acid derivatives **68**.




Ar = $C_6H_4Y$ (Y = H, 4-Me, 4-OMe, 4-Cl); $R^1$ = H, Et; $R^2$ = H, Ph.

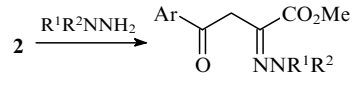
Conversely, the 3-chloroaroylpyruvates **10** are cleaved by hydrazine even under mild conditions without giving pyrazoles.[80]

Reactions of some esters of the (H)APA **2** with arylhydrazines at 20 °C catalysed by AcOH involve the C(2) = O group and result in the corresponding arylhydrazones **69** in good yields (87% for Ar = $R^2$ = Ph).[127] Upon heating in an acid medium (AcOH, AcOH + HCl), these products cyclise almost quantitatively (93% for Ar = $R^2$ = Ph)[127] to give pyrazoles **70**.[11, 20, 124, 127]




Ar = Ph, 3-indolyl, 2,4-dimethyl-3-pyrrolyl; $R^1$ = Et, $Pr^i$; $R^2$ = 2,4-$(NO_2)_2C_6H_3$, Ph.

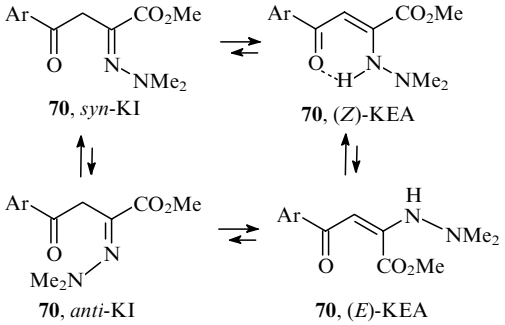
The reactions of methyl aroylpyruvates **2** with *N*,*N*-dimethyl-,[129] *N*-alkyl-*N*-arylhydrazines[130] and benzophenone and 9-fluorenone hydrazones[131] involve exclusively the C(2) centre and give AP *N*,*N*-dimethyl- (**70**) and *N*-alkyl-*N*-arylhydrazones **71** and AP *N*-(di)arylmethylenehydrazones **72**, respectively.




**70**–**72** (27% – 69%)

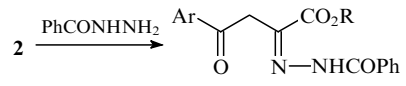
**70**: Ar = $XC_6H_4$ (X = H, 4-Me, 4-OMe, 4-Br, 4-Cl, 3-$NO_2$, 4-$NO_2$); $R^1$ = $R^2$ = Me; **71**: Ar = Ph; $R^1$ = Me, Et, $Pr^i$; $R^2$ = 4-$XC_6H_4$ (X = OMe, Me, H, Br, $NO_2$); **72**: Ar = $XC_6H_4$; $R^1$ + $R^2$ = $CPh_2$, 9-fluorenylidene.

It was shown by $^1$H NMR spectroscopy[129] that the dimethylhydrazones **70** exist in solutions as equilibrium mixtures of β-ketoimine (*syn*-KI, *anti*-KI) and ketoenamine [(*Z*)-KEA, (*E*)-KEA] tautomers. In low-polarity aprotic solvents, the content of the KEA tautomer is higher. Electron-donating substituents X in the aromatic nucleus of the compounds **70** and an increase in the solvent polarity result in a higher content of the KI forms. The *syn*-KI form predominates in the KI pair, while in the KEA pair, the preferred form is (*Z*)-KEA, which is stabilised by an IMHB. The hydrazone **70** (X = H) was isolated from a solution as a mixture of the *syn*-KI and (*Z*)-KEA isomers, whereas other hydrazones **70** were obtained only as (*Z*)-KEA.




The *N*-alkyl-*N*-arylhydrazones **71** are isolated as the (*Z*)-KEA tautomers. However, they exist in chloroform and pyridine solutions as equilibrium mixtures of the (*Z*)-KEA and *syn*-KI forms.[130] In DMSO, the (*E*)-KEA form was also found. The influence of the nature of the solvent and the substituent X in the $R^2$ group on the tautomeric equilibria has been elucidated. On passing from chloroform to pyridine, the content of the tautomer (*Z*)-KEA increases, while in DMSO, the total content of the KEA isomers increase, the (*E*)-KEA form being the preferred one. The content of (*Z*)-KEA increases with the enhancement of the −M-effect of the group X on passing from OMe to $NO_2$.

The AP **2** react with benzoylhydrazine at the α-carbonyl group to give the corresponding hydrazones **73a**–**h**.[132]

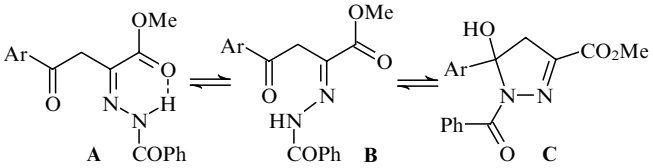



**73a**–**h** (70% – 86%)

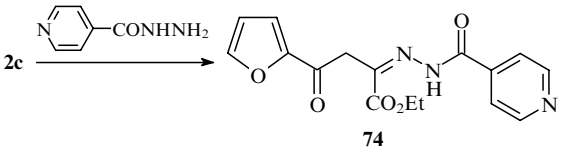
R = Me; Ar = $XC_6H_4$ (X = H (**a**), 4-Me (**b**), 4-OMe (**c**), 4-$NMe_2$ (**d**), 4-Cl (**e**), 3-$NO_2$ (**f**), 4-$NO_2$ (**g**)); R = Et, Ar = Ph (**h**).

A $^1$H NMR study of the tautomerism in the series of benzoylhydrazones **73** has shown[133] that these compounds exist in solutions as equilibrium mixtures of three tautomers, namely, *Z*-(**A**) and *E*-(**B**) ketohydrazones and 5-hydroxypyrazoline (**C**). Their proportions depend on the nature of the hydrazone **73** and the solvent. The electron-donating substituent X in the aryl group of the hydrazone **73** promotes an increase in the content of ketohydrazone. In $CDCl_3$, *Z*-form **A** stabilised by IMHB is preferred, while in DMSO-$d_6$, *E*-form **B** predominates. The

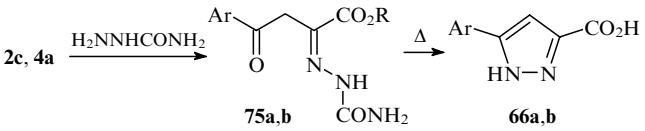
hydrazones **73e–g** with electron-withdrawing groups X predominantly exist in solutions as cyclic form **C**. The content of tautomer **C** is higher in DMSO than in $CDCl_3$. The benzoylhydrazones **73a–d** were isolated from methanol in form **A**, while **73e–g**, in form **C**.



The synthesis of 2-isonicotinoylhydrazone **74** from ethyl 2-furoylpyruvate **2c** and isonicotinic acid hydrazide has been reported.[33]

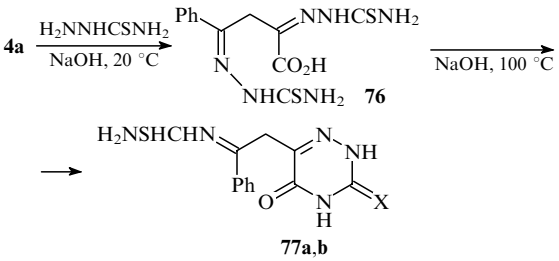


The reaction of the ester (H)AP **2c** [13] and the acid **4a** [134] with semicarbazide or its hydrochloride results in the formation of monosemicarbazones, which have, in our opinion, the structure **75a,b**. These semicarbazones undergo thermal decomposition giving the corresponding pyrazoles **66a,b**. On short-term refluxing in an aqueous solution of potassium carbonate, semicarbazone **75b** is converted into 5-(2-furyl)-3-carboxypyrazole **66b**.[33]



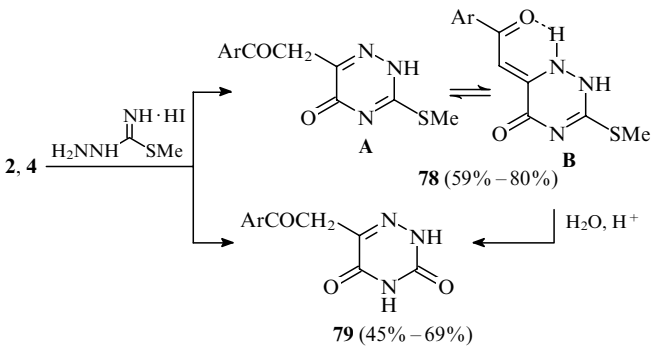
Ar = Ph, R = H (**4a**, **75a**, **66a**); Ar = 2-furyl, R = Et (**2c**, **75b**, **66b**).

The acid **4a** reacts with thiosemicarbazide with participation of both carbonyl groups to give bis(thiosemicarbazone) **76**. The alkaline hydrolysis of this product affords 1,2,4-triazine derivatives **77a,b**.[134]



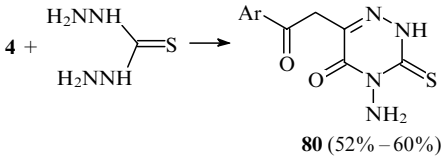
X = S (**a**), O (**b** ).

The reaction of the APA **4** and their methyl esters **2** with *S*-methylisothiosemicarbazide hydroiodide involves the α-dicarbonyl fragment and affords 6-aroylmethyl-3-methylthio-1,2,4-triazin-5(2*H*)-ones **78** or 6-aroylmethyl-1,2,4-triazine-3,5(2*H*,4*H*)-diones **79**, depending on the nature of the aryl substituent and the reaction duration.[135, 136] Thus refluxing in ethanol for 2 h gives 3-methylthio-1,2,4-triazinones **78**; when the reaction time increases to 10 h, the products of their hydrolysis, 1,2,4-triazinediones **79**, are formed.[136] The compounds **78** are converted into the triazinediones **79** upon short-term refluxing in aqueous dioxane in the presence of catalytic amounts of HCl. According to the $^1H$ NMR spectra, the compounds **78** in DMSO-$d_6$ are mixtures of the imine (**A**) and enamine (**B**) tautomers in 4 : 1 ratio.[135, 136]



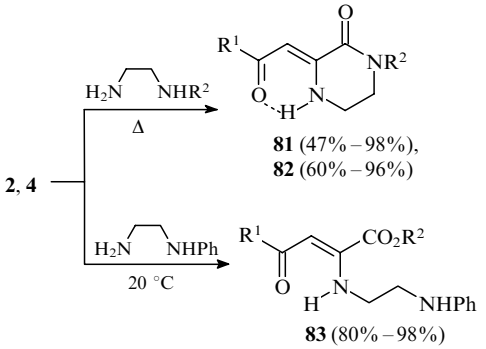
Ar = 4-$XC_6H_4$ (X = H, Me, OMe, Cl, Br, I, $NO_2$), 2,4-$Me_2C_6H_3$.

On refluxing in dioxane, the acids **4** add selectively thiocarbohydrazide at the α-ketocarboxyl fragment to give 4-amino-6-aroylmethyl-3-thioxo-2*H*,4*H*-1,2,4-triazin-5-ones **80**.[136]



Ar = 4-$XC_6H_4$ (X = H, Me, Cl).

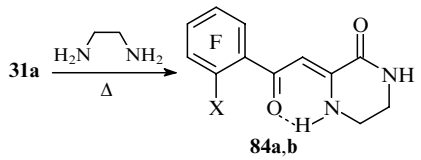
**Reactions with 1,2-diaminoethane and its derivatives**. Both the APA **4** [30, 137] and their esters **2** (see [21, 30, 137–141]) add 1,2-diaminoethane [21, 30, 138–140] or its mono-*N*-methyl-,[141] *N*-benzyl- [137] and *N*-phenyl-substituted [30, 141] derivatives in chemo- and regioselective reactions involving the α-dicarbonyl fragment [the C(1) and C(2) atoms] giving rise to 3-aroylmethylidenepiperazin-2-ones **81** or their 1-alkyl(aryl) derivatives **82**. The reactions are normally carried out on heating in toluene, ethanol or acetic acid. The piperazin-2-ones **81** can also be prepared by heating the sodium enolates of H(AP) **2** with 1,2-diaminoethane in glacial AcOH.[140] Under mild conditions (ethanol, 20 °C) the AP **2** and **4** react with *N*-phenyl-1,2-diaminoethane at the α-carbonyl group to give acyclic 4-aryl-4-oxo-2-(2-phenylamino)ethylamino-2-butenoic acids or their esters **83**.



**81**: $R^1$ = Ar, Het, ferrocenyl, $R^2$ = H; **82**: $R^1$ = Ar, Het, $R^2$ = Me, Ph, $CH_2Ph$; **83**: $R^1$ = Ar, Het, $R^2$ = H, Me, Et.

However, on refluxing in ethanol, the pyruvate **2b** reacts with *N*-phenyl-1,2-diaminoethane at the ester fragment [the C(1) atom] to give benzoylpyruvic acid 2-phenylaminoethylamide in 61% yield.[30] 1,2-Diphenylaminoethane does not react with AP.[30]

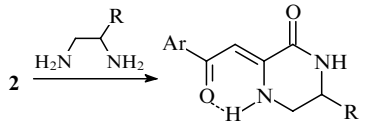
It is noteworthy that the reaction of pentafluorobenzoylpyruvate **31a** with 1,2-diaminoethane gives, depending on the conditions, either 3-pentafluorobenzoyl- (**84a**) or 3-(2-hydroxy-3,4,5,6-tetrafluoro)benzoyl-methylidenepiperazin-2-ones (**84b**).[3, 5] The piperazinone **84a** is formed when the pyruvate **31a** is treated with a large excess of ethylenediamine at 20 °C in a MeOH–AcOH mixture, and the product **84b** is produced on refluxing equimolar amounts of the reactants in methanol.



**84a**,**b**

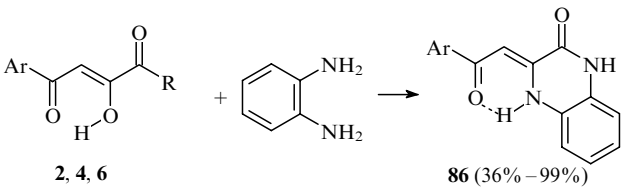
X = F (**a**, 43%), OH (**b**, 18%).

Non-symmetric 1-methyl- and 1-phenyl-1,2-diaminoethanes have been shown [142] to react selectively with the APA esters **2** on refluxing in an ethanol–acetic acid mixture to give the corresponding 6-methyl- or 6-phenyl-3-aroylmethylenepiperazin-2-one **85** as the only reaction product.



**85** (58%–93%)

**Reactions with 1,2-phenylenediamine and other arylenediamines**. The major process involved in the reaction of the (H)APA **4**, their esters **2**, and the amides **6** with 1,2-phenylenediamine (PDA) is cyclocondensation at the α-dicarbonyl fragment [the C(1) and C(2) atoms] giving rise to the corresponding 3-aroylmethylidene-1,2,3,4-tetrahydroquinoxalin-2-ones (**86**).[3, 5, 8, 12, 21, 44, 46, 58, 62, 67, 107, 115, 123, 126, 143–149]



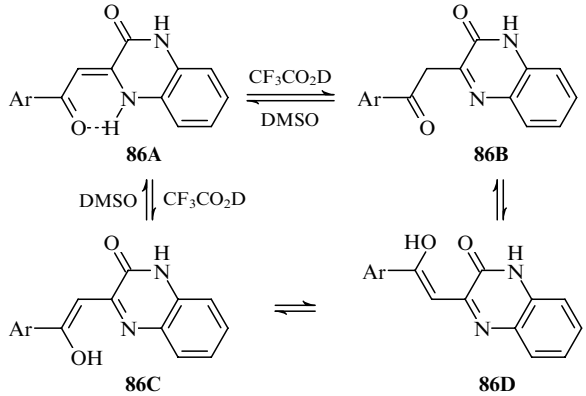
**2**, **4**, **6** **86** (36%–99%)

Ar = $XC_6H_4$ (X = H, 4-Me, 4-Et, OH, OMe, 4-Ph, 4-$NO_2$, 3-$NO_2$, 4-F, 4-Cl, 4-Br), 2,5-$Me_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, $C_6F_5$, 1-naphthyl, 3-phenanthryl, 2-furyl, 2-thienyl, 4-pyridyl, 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydroxypyrrol-3-yl, cymantrenyl;

**2**: R = OMe, OEt, $OBu^t$, $SCH_2Ph$; **4**: R = OH;

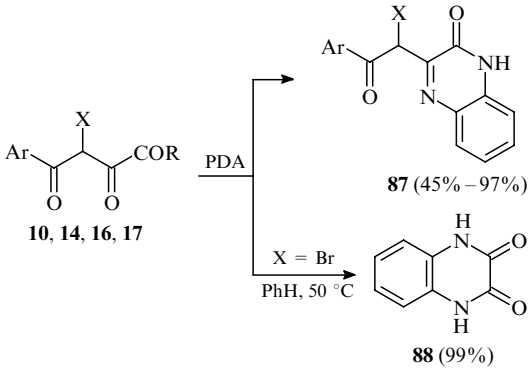
**6**: R = N(Ar′)C(Ph)=$CH_2$, $NH_2$, NHNHAr′, NHAr′, 3-pyridylamino, 2-pyridylamino.

Tautomerism of 2-quinoxalones **86** has been studied by spectroscopy.[145, 146] It was found that these compounds exist as IMHB-stabilised form **A** in the solid state and in solutions in DMSO-$d_6$. Noticeable amounts of forms **B**–**D** are found only in solutions in $CF_3CO_2D$.[145]



**86A** **86B** **86C** **86D**

3-Substituted APA and their esters react with PDA similarly to unsubstituted analogues to yield 3-(1-X-aroylmethyl)-1,2-dihydroquinoxalin-2-ones **87**.[80, 83, 89, 147] For instance, the 3-arylhydrazones **16**,[91] **17**[94–96] and 3-alkyl-substituted APA esters **14**[89, 147] readily react with PDA on refluxing in ethanol. The 3-halogen-containing AP **10** are more reactive and are converted into quinoxalinones **87** on treatment with PDA at 20 °C.[80, 83, 147] Heating of the reactants induces resinification [80] or formation of quinoxaline-2,3(1*H*,4*H*)-dione (**88**).[83]

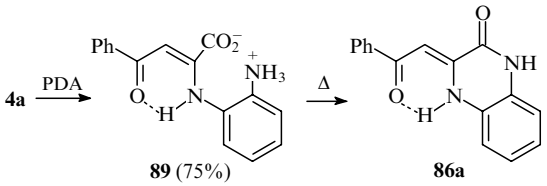


**10**, **14**, **16**, **17** **87** (45%–97%) **88** (99%)

**10**: X = Cl, Br; Ar = 4-$YC_6H_4$ (Y = H, Me, Br, OMe, F, Cl); R = OMe, OEt; **14**: X = Me, Et, $CHPh_2$; Ar = 4-$YC_6H_4$ (Y = H, Me, Br, Cl, $NO_2$); R = OMe, OEt; **16**, **17**: X = N = NAr′; R = OMe, OEt, OH; Ar = $C_6H_4Y$ (Y = H, 4-Cl, 4-Br), $C_6F_5$; **87**: X = Me, Et, $CHPh_2$, Cl, Br, N = NAr′; Ar = 4-$YC_6H_4$ (Y = H, Me, Br, OMe, F, Cl, $NO_2$), $C_6F_5$.

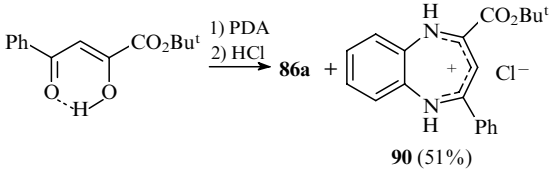
However, prolonged refluxing in ethanol of 3-bromo-substituted ethyl benzoylpyruvate **10a** (Ar = Ph, R = Et, X = Br) with PDA furnishes 3-benzoylmethylidenequinoxalinone **86a** containing no bromine.[150]

When the acid **4a** has been made to react with PDA under mild conditions ($Pr^iOH$, 20 °C), a labile intermediate, 2-(2-ammoniophenylamino)-4-oxo-4-phenyl-2-butenoate (**89**), has been isolated. On heating, this compound is quantitatively converted into quinoxalinone **86a**.[148]



**89** (75%) **86a**

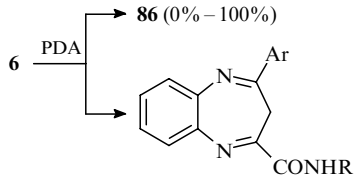
It is notable that *tert*-butyl benzoylpyruvate prepared *in situ* from the acid **4a** and isobutylene in the presence of $H_2SO_4$ reacts with PDA to give, apart from the quinoxalinone **86a**, 2-*tert*-butoxycarbonyl-4-phenylbenzo[*b*]-1,4-diazepine isolated as hydrochloride **90**. The product **90** results from the competing cyclocondensation of PDA at the β-dicarbonyl fragment of the pyruvate **4a**. The diazepine **90** easily recyclises into the quinoxalinone **86a** upon dissolution.[149]



**90** (51%)

Unlike the APA **4** and their esters **2**, the APA arylamides **6** react with PDA to give, depending on the reaction conditions, 4-arylbenzo[*b*]-1,4-diazepine-2-carboxylic acid arylamides **91**[29, 151] instead of the expected quinoxalinones **86**,[115] or a mixture of these products.[62, 149] The formation of the quinoxalinones **86** is promoted by performing the reaction in EtOH–AcOH–$H_2O$–HCl mixtures at pH 2.4–4.6 and temperatures of 20–65 °C.[115] Meanwhile, short-term fusion of the reactants at 115–130 °C furnishes predominantly the benzodiazepines **91**.[29, 115, 149] It was noted that electron-donating substituents in the aryl group of the initial amide **6** lead to higher yields of the benzodiazepines **91**, while electron-withdrawing groups promote the formation of the quinoxalinones **86**.[149] The reaction of the 3-pyridylamide **6b** with PDA on refluxing in a $Pr^iOH$–AcOH

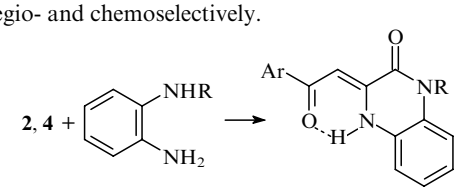
mixture affords both the quinoxalinone **86a** and the benzodiazepine **91** (R = 3-pyridyl).[62]




**91** (39% – 99%)

**86**: Ar = $XC_6H_4$ (X = H, 4-Me, 4-OMe, 4-Cl, 4-Br, 4-$NO_2$, 3-$NO_2$);
**91**: Ar = 4-$XC_6H_4$ (X = H, Me, OMe, Br); R = 4-$YC_6H_4$ (Y = H, Me, OMe, Br), 3-pyridyl.

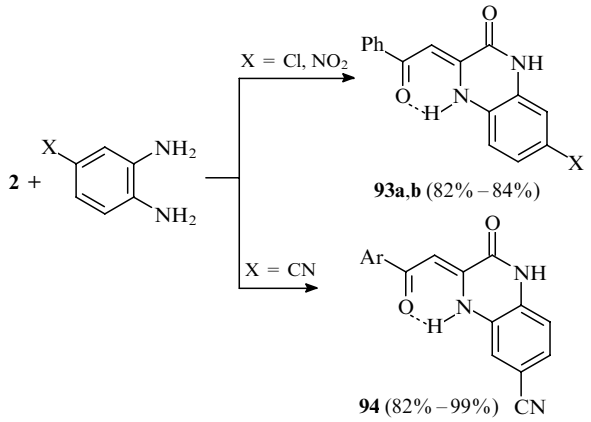
*N*-Monoalkyl(aryl)-1,2-phenylenediamines react with the AP **2** and **4** similarly to PDA giving rise to 1-alkyl(aryl)-3-aroylmethylidene-1,2,3,4-tetrahydroquinoxalin-2-ones **92** [8, 143, 152, 153] stabilised by an IMHB.[153] Note that these reactions proceed regio- and chemoselectively.




**92** (40% – 84%)

Ar = 4-$XC_6H_4$ (X = H, Cl); R = Me, 4-$XC_6H_4$ (X = H, Me, OEt, Cl).

Heterocyclisations of the AP **2** with 1,2-phenylenediamines containing various substituents in the benzene ring have been described. The addition pattern depends on the nature of the substituent in the benzene ring of the nucleophile. 1,2-Diamino-chlorobenzene [145] and 1,2-diamino-4-nitrobenzene [8] provide 3-benzoylmethylidene-7-chloro- (**93a**) and 3-benzoylmethylidene-7-nitro-1,2,3,4-tetrahydroquinoxalin-2-ones (**93b**), whereas 3,4-diaminobenzonitrile forms 3-aroylmethylidene-6-cyano-1,2,3,4-tetrahydroquinoxalin-2-ones **94**.[51]

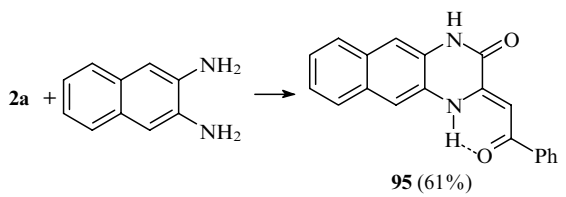



**93a**,**b** (82% – 84%)

**94** (82% – 99%)

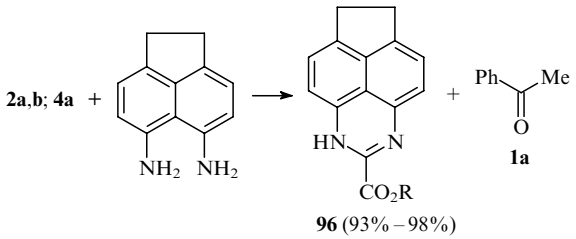
X = Cl (**a**), $NO_2$ (**b**); Ar = 4-$YC_6H_4$ (Y = H, Me, Cl).

2,3-Diaminonaphthalene reacts with the AP **2a** similarly to PDA to give 3-benzoylmethylene-1,2,3,4-tetrahydrobenzo[*g*]quinoxalin-2-one (**95**).[145]




**95** (61%)

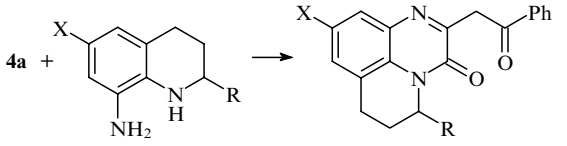
On treatment with 5,6-diaminoacenaphthene, the AP **2a**,**b** and **4a** are cleaved even under mild conditions (at 18 °C) to give 6,7-ethanoperimidine-2-carboxylic acid **96**.[154]




**96** (93% – 98%)

R = H, Me, Et.

When the acid **4a** is refluxed with 2(6)-substituted 8-amino-1,2,3,4-tetrahydroquinolines **97a**,**b** in ethanol, 2-benzoylmethyl-4,5,6,7-tetrahydropyrido[1,2,3-*d*,*e*]quinoxalin-3(4*H*)-one derivatives **98a**,**b** are formed.[155]

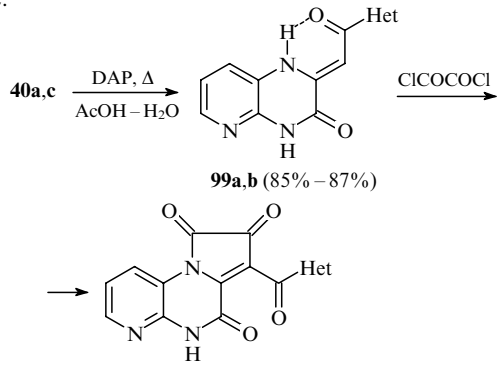



**97a**,**b** **98a**,**b** (39% – 68%)

R = Me, X = H (**a**); R = H, X = OMe (**b**).

**Reactions with heterocyclic diamines**. Known reactions of the (H)APA **4** and their esters **2** with heteroaromatic *ortho*-diamines result in the preparation of annelated pyrazin-2-one derivatives [156 – 162] (the products of addition at the α-dicarbonyl fragment of the AP) or [*b*]annelated 1,4-diazepines [160] (the products of cyclocondensation at the β-dicarbonyl part of the AP), depending on the nature of the reactants. In the case of non-symmetric diamines, these reactions proceed regioselectively. Moreover, in some cases, both possible series of regioisomers can be prepared.[157, 162]

It has been reported [156] that refluxing the HPA **4b**,**c** with 2,3-diaminopyridine (DAP) in an AcOH – $H_2O$ mixture results in the formation of (*Z*)-2-heteroaroylmethylidene-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-3-ones **99b**,**c**. The researchers cited [156] confirmed the structure of the heterocycles **99** by converting them into 3-heteroaroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]pyrido[2,3-*b*]pyridazine-1,2,4-triones **100** upon condensation with oxalyl chloride.[156]

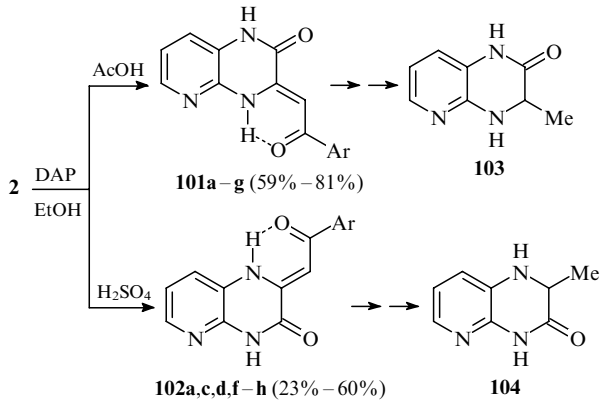



**99a**,**b** (85% – 87%)

**100a**,**b** (69% – 72%)

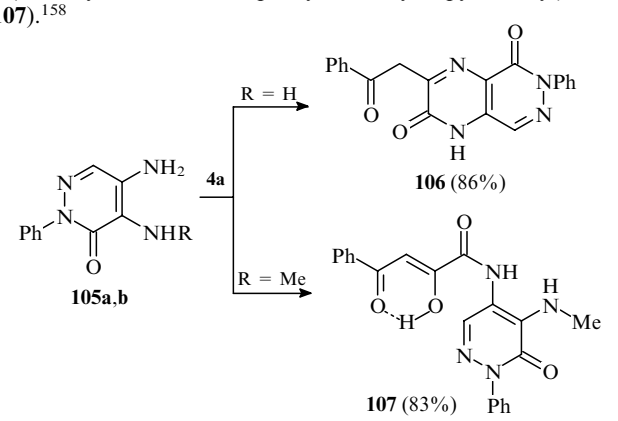
Het = 2-furyl (**4b**, **99a**, **100a**), 5-thiazolyl (**4c**, **99b**, **100b**).

Unlike the APA **4**, the esters **2** can yield two regioisomeric products, depending on the conditions, in the cyclocondensation with DAP. Thus 3-aroylmethylidene-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-2-ones **101** were prepared in an AcOH – EtOH – $H_2O$ solvent mixture, whereas the use of an $H_2SO_4$ – EtOH – $H_2O$ mixture gave 2-aroylmethylidene-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-3-ones **102**.[157] The structure of the heterocycles **101** and **102** was confirmed by hydrolysis of the compounds **101a** and **102a** followed by reduction to give the known methyltetrahydropyrido[2,3-*b*]pyrazinone **103**, **104** isomers.[163]



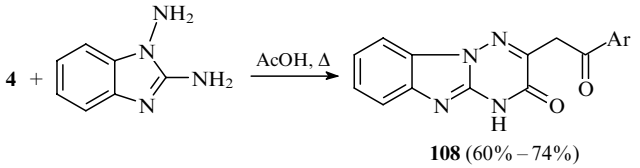

Ar = $XC_6H_4$ (X = H (**a**), 4-Me (**b**), 4-OMe (**c**), 3-OMe (**d**), 2-OMe (**e**), 4-OH (**f** ), 4-Br (**g**), 2-OH (**h**)).

The reaction of the acid **4a** with 4,5-diamino-1-phenyl- (**105a**) and 4-amino-5-methylamino-1-phenyl-1,6-dihydropyridazin-6-ones (**105b**) in boiling ethanol has been described.[158] In the case of the diamine **105a**, the reaction gives the product of cycloaddition at the α-oxocarboxy group of the acid, 3-benzoylmethyl-6-phenyl-1,2,5,6-tetrahydropyrazino[2,3-*d*]pyridazine-2,5-dione (**106**), while the reaction with **105b** gives benzoylpyruvic acid *N*-(5-methylamino-6-oxo-1-phenyl-1,6-dihydropyridazinyl)amide (**107**).[158]



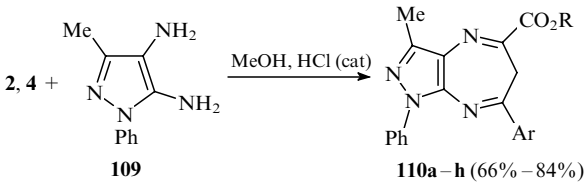

R = H (**a**), Me (**b**).

The reaction of the APA **4** with 1,2-diaminobenzimidazole in boiling AcOH occurs chemo- and regioselectively to yield 2-aroylmethyl-3,4-dihydro-1,2,4-triazino[2,3-*a*]benzimidazol-3-ones **108**.[159] Refluxing of the same reactants in methanol affords salts, which are formed, apparently, at the pyridine N(3) atom of the diamine (yields 80%–85%). When refluxed in AcOH, the salts cyclise to give heterocycles **108** in 80%–87% yields.[159]



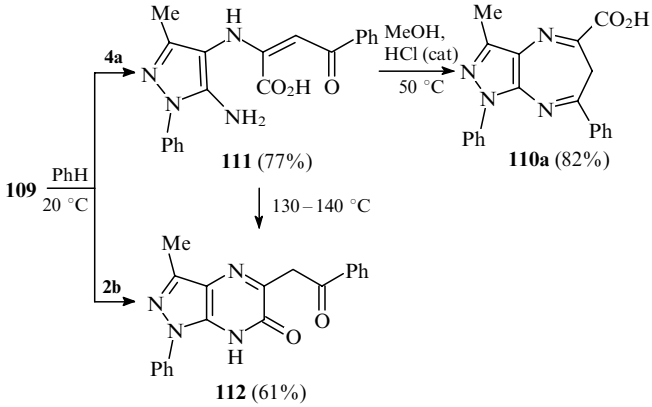

Ar = 4-$XC_6H_4$ (X = H, Me, OMe, Cl, Br).

The direction of the reactions of the AP **2**, **4** with 4,5-diamino-3-methyl-1-phenylpyrazole (**109**) depends on the conditions and on the nature of the α,β-tricarbonyl compound.[160] At 20 °C in methanol, in the presence of a catalytic amount of HCl, both the APA **4** and their esters **2** add selectively the diamine **109** at the β-dicarbonyl fragment giving rise to 7-aryl-5-carboxy(methoxycarbonyl)-3-methyl-1-phenyl-6*H*-pyrazolo[5,4-*b*]-1,4-diazepines **110**.

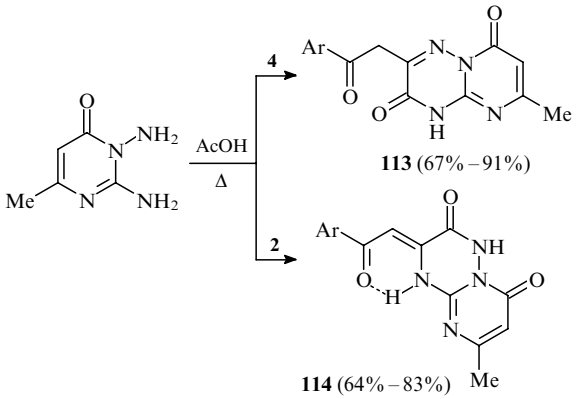



R = H (**a**–**c**), Me (**d**–**h**); Ar = 4-X $C_6H_4$ [X = H (**a**, **d**), Me (**b**, **e**), Cl (**c**, **f**), $NO_2$ (**g**)], 2,4-$Me_2C_6H_3$ (**h**).

When the reaction is carried out in benzene at 20 °C, the APA **4a** and diamine **109** form 2-(5-amino-3-methyl-1-phenylpyrazol-4-yl)amino-4-oxo-4-phenylbut-2-enoic acid (**111**), which cyclises to give pyrazolodiazepine **110a** when heated to 50 °C in methanol in the presence of HCl. Unlike the acid **4a**, the methyl ester **2b** adds selectively the diamine **109** at the α-oxoester fragment under similar conditions; this furnishes 5-benzoylmethyl-3-methyl-1-phenyl-6,7-dihydropyrazolo[4,5-*b*]pyrazin-6-one (**112**). The product **112** can also be obtained by heating the acid **111** without a solvent at 130–140 °C.[160]



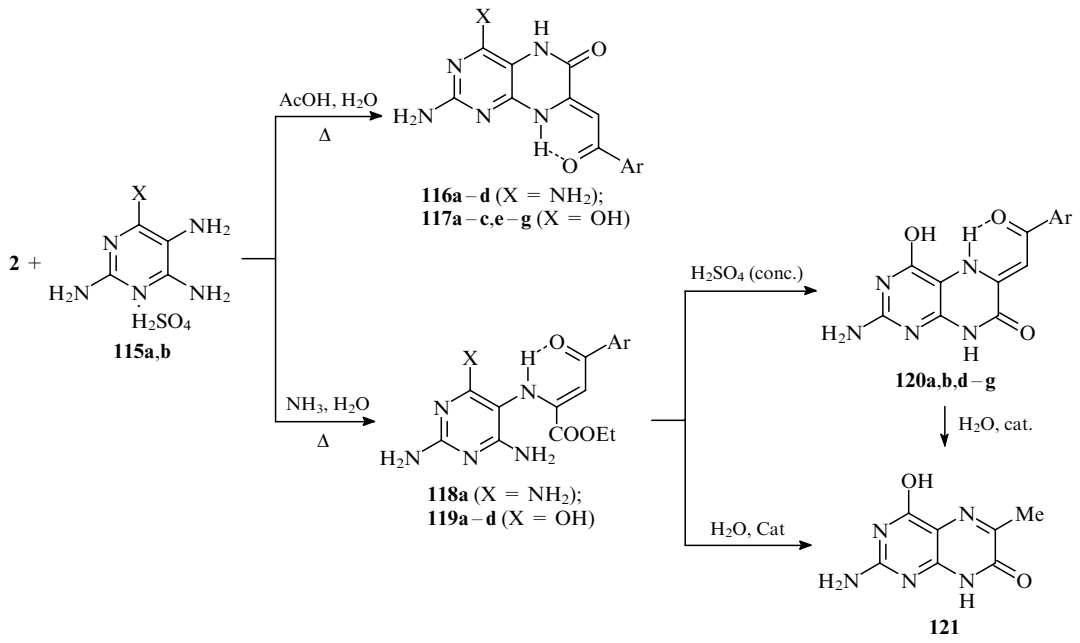

Although cyclocondensation at the α-dicarbonyl fragment is the major process in the reaction of both the APA **4** and the methyl ester **2** with 1,2-diamino-4-methyl-1,6-dihydropyrimidin-6-one on refluxing in AcOH, this process yields different regioisomers for these two types of substrate, namely, 2-aroylmethyl-6-methyl-4,8-dihydro-4*H*-pyrimido[1,2-*b*]-1,2,4-triazine-3,8-diones **113** and (*Z*)-3-aroylmethylidene-6-methyl-2,3,4,8-tetrahydro-1*H*-pyrimido[1,2-*b*]-1,2,4-triazine-2,8-diones **114**, respectively.[161]




Ar = 4-$XC_6H_4$ (X = H, Me, OMe, Cl, OEt, Br, $NO_2$).

Heterocyclic amines such as 2,4,5,6-tetraamino- (**115a**) and 4-hydroxy-2,5,6-triaminopyrimidines (**115b** ) condense with the AP **2** similarly to *o*-diamines. When refluxed in a solution of AcOH, both amines react selectively with the AP **2** or with the corresponding sodium enolates at the α-oxoester fragment to give 2,4-diamino-7-aroylmethylidene-5,6,7,8-tetrahydropteridin-6-ones

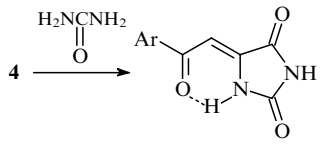
Scheme 8




**116**, **117**, **119**: Ar = 4-$YC_6H_4$ [Y = H (**a**), Me (**b**), CN (**c**), OH (**d**), Cl (**e**), Br (**f**), $CO_2H$ (**g**)]; **118a**: Ar = 4-$OHC_6H_4$ .

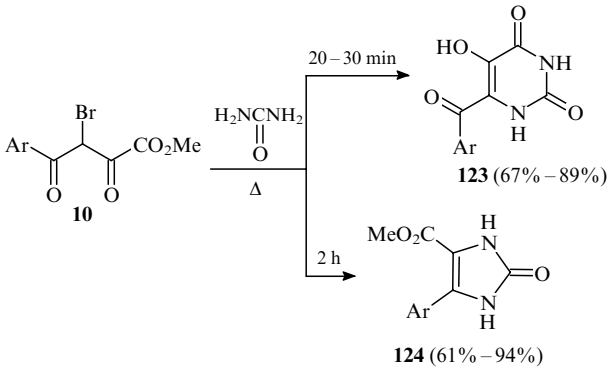
**116** in the case of the amine **115a** or 2-amino-7-aroylmethylidene-4-hydroxy-5,6,7,8-tetrahydropteridin-6-ones **117** in the case of **115b**.[162] When the reaction is conducted in aqueous $NH_3$ (1 mol litre$^{-1}$, pH 8), derivatives of 4-aryl-2-(5-heteroaryl)-amino-4-oxobut-2-enoic acids **118a** and **119a–d**, respectively, can be isolated.[162, 164] In concentrated $H_2SO_4$, the compounds **119** cyclise into 2-amino-6-aroylmethylidene-4-hydroxy-5,6,7,8-tetrahydropteridin-7-ones **120**, which are isomers of the pteridines **117**. The structures of the products **119** and **120** were proved by hydrolysis, which gave rise to known 2-amino-4-hydroxy-6-methyl-7,8-dihydropteridin-7-ones (**121**) and benzoic acids (Scheme 8).[162]

**Reactions with urea and sulfamides**. The aroylpyruvic acids **4** react with urea at the α-oxocarboxyl fragment on fusion (120–130 °C); this affords 5-aroylmethylidene-2,3,4,5-tetrahydroimidazole-2,4-diones **122**.[165]



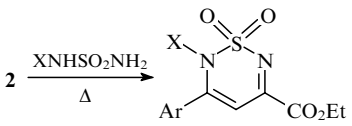

Ar = 4-$XC_6H_4$ (X = H, Me, $Bu^t$, OMe, F, Cl, Br).

The direction of reactions of methyl 3-bromoaroylpyruvates **10** (X = Br) with urea is determined by the reaction conditions. Fusion of equimolar amounts of the reactants for 20–30 min at 105–120 °C results in the formation of 6-aroyl-5-hydroxy-1,2,3,4-tetrahydropyrimidine-2,4-diones **123**, whereas the use of a great excess of urea and a longer reaction time (2 h) gives 5-aryl-4-methoxycarbonyl-2,3-dihydro-1*H*-imidazol-2-ones **124**.[166–168] The researchers proposed a mechanism for the formation of the heterocycles **123** and **124**, according to which the common first stage of the reaction is nucleophilic substitution of urea for the bromine atom in the initial AP **10**.[166]




R = Me, X = Br; Ar = 4-$YC_6H_4$ (Y = H, Me, OMe, F, Cl, Br).

The APA esters **2** react with sulfamide on refluxing in HCl-saturated ethanol at the β-dicarbonyl fragment to give 5-aryl-3-ethoxycarbonyl-2*H*-1,2,6-thiadiazine 1,1-dioxides (**125**).[169] Similarly, *N*-methylsulfamide cyclocondenses selectively with the AP **2** giving rise to only one series of regioisomers, the position of the methyl group in which is not indicated in the study cited.[133] The most probable structure is, apparently, **126**, *i.e.*, the structure of 6-methyl-substituted 1,2,6-thiadiazine dioxides **125**. The products of reactions of the compounds **125**, **126** with ammonia, primary amines and hydrazine possess biological activities.[133, 169]

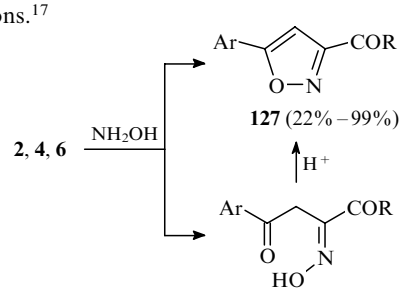



Ar = 4-$YC_6H_4$ (Y = H, Cl, Me).

**c. Reactions with N,O-dinucleophiles**

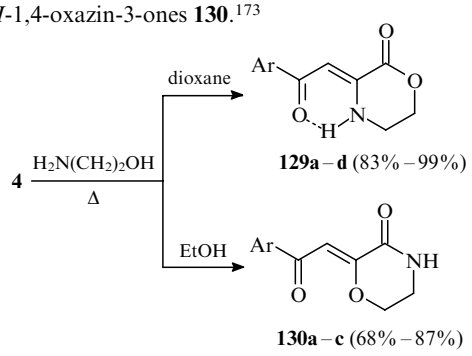
**Reactions with hydroxylamine**. The acids **4** and their esters **2** react with hydroxylamine hydrochloride at the β-dicarbonyl fragment to give isoxazoles of only one of the two possible regioisomer classes — 5-arylisoxazole-3-carboxylic acids **127**. The reactions are usually carried out by refluxing in aqueous ethanol [13–15, 123, 170, 171] or at 20 °C in the presence of $Na_2CO_3$ with subsequent short-term heating with either strong acids [15] or acetyl chloride.[2] Less reactive arylamides AP **6** are converted into the corresponding amides **127** (R = NHAr) on refluxing with hydroxylamine hydrochloride in ethanol in the presence of KOH,[62] while the AP hydrazides **58** produce hydrazides **127** (R = NHNHAr) in boiling dioxane.[67]

Under mild conditions (EtOH – $H_2O$, $Na_2CO_3$, 20 °C), it is sometimes possible to isolate 2-oximes **128** formed as intermediates in the reactions of the (H)AP **2**, **4** with hydroxylamine hydrochloride.[2, 13, 15] The oximes **128** readily cyclise into isoxazoles **127** on heating or on treatment with strong acids [13, 15] or with dehydrating agents such as acetyl chloride.[2] The formation of ethyl 3-pyridoylpyruvate (**128h**) requires more drastic conditions.[17]



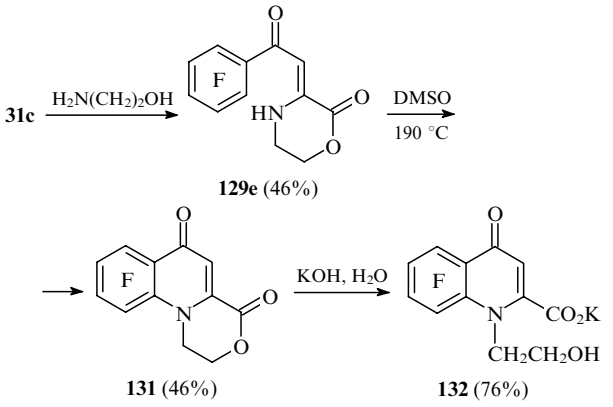

**127**: Ar = Ph, $YC_6H_4$ (Y = 4-Me, 4-Cl, 2-OMe, 4-AcNH), $C_6F_5$, 4-diphenyl, 3-phenanthryl, 2-pyrrolyl, 2-furyl, 2-thienyl, 5-methyl-2-thienyl; R = OH, OEt, 3-pyridylamino, $NHNHCOC_6H_4Z$ (Z = H, 4-OMe);
**128**: Ar = $YC_6H_4$ [Y = H (**a**), 2-$NO_2$ (**b**, **c**), 4-AcNH (**d**)], 2-furyl (**e**), 2-thienyl (**f**), 5-methyl-2-thienyl (**g**), 3-pyridyl (**h**); R = OH (**a**, **b**), OEt (**c** – **g**), OMe (**h**).

**Reactions with 2-aminoethanol**. The acids **4** add 2-aminoethanol at the α-oxocarboxyl fragment to give oxazine derivatives, the regiodirectivity of the reaction being dependent on the reaction conditions. The refluxing of the APA **4** with potassium 2-aminoethoxide in anhydrous dioxane yields 3-aroylmethylidene-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-ones **129**;[172] the reaction in anhydrous ethanol affords 2-aroylmethylidene-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-3-ones **130**.[173]

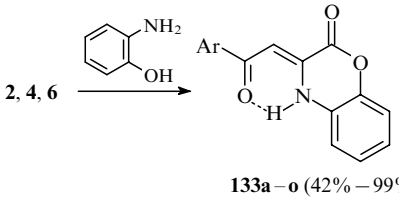



Ar = 4-$XC_6H_4$ [X = H (**a**), F (**b**), Br (**c**), Cl (**d**)].

The acid **31c** reacts with 2-aminoethanol in boiling dioxane also to give 3-pentafluorobenzoylmethylidene-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (**129e**). The structure of the compound **129e** was confirmed by the fact that on heating in DMSO, it cyclises to yield 7,8,9,10-tetrafluoro-1,2-dihydro-1,4-oxazino[4,3-*a*]quinoline-4,6(4*H*,6*H*)-dione (**131**). On treatment with aqueous KOH, this product undergoes opening of the lactone ring, which gives potassium 1-(2-hydroxyethyl)-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline-2-carboxylate (**132**).[26, 27]

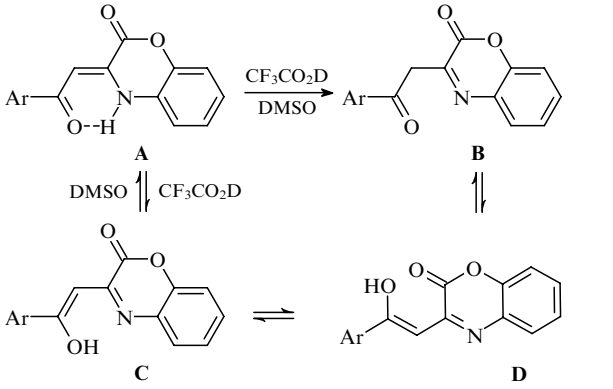



**Reactions with 2-aminophenol and its derivatives**. The reactions of 2-aminophenol with the APA **4**, their esters **2** and anilides **6** also involve the α-dicarbonyl fragment and give 3-aroylmethylidene-3,4-dihydro-1,4-benzoxazin-2(2*H*)-ones **133**.[3, 5, 9, 21, 29, 37, 44, 45, 53, 174–177]




**2**: R = OMe, OEt; **4**: R = OH; **6**: R = NHPh.
Ar = $XC_6H_4$ [X = H (**a**), 4-Me (**b**), 4-OMe (**c**), OH (**d** – **f**), 4-F (**g**), 4-Cl (**h**), 4-Br (**i**), 4-$NO_2$ (**j**)], 2,4,6-$Me_3C_6H_2$ (**k**), 2-furyl (**l**), 2-thienyl (**m**), 4-pyridyl (**n**), cymantrenyl (**o**);

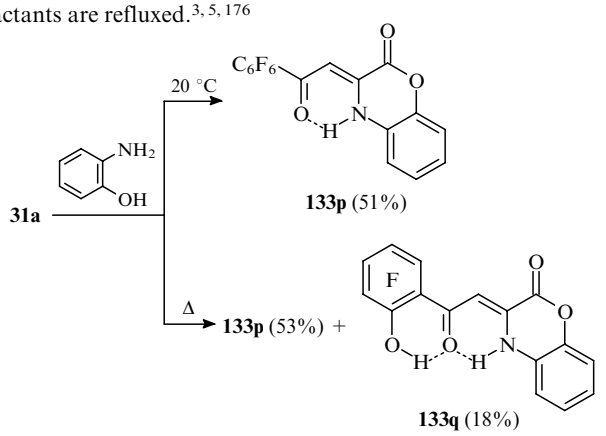
The tautomerism of benzoxazines **133** has been studied by spectroscopy.[145, 146] It was shown that in the solid state and in DMSO-$d_6$ solutions, they exist as form **A** stabilised by an IMHB. Noticeable amounts of forms **B** – **D** are present only in $CF_3CO_2D$.[145]



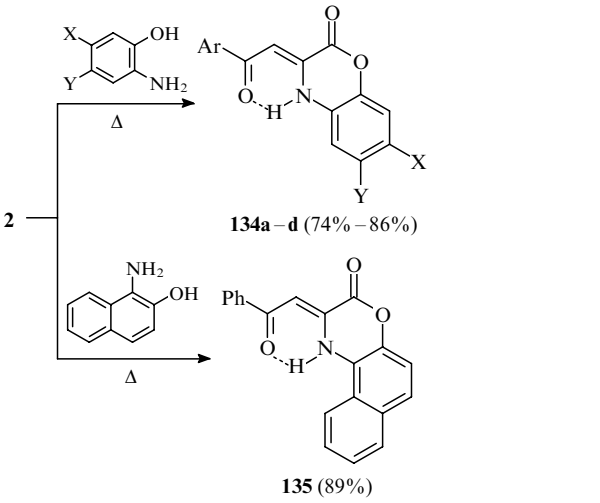

When the reaction of the acid **4a** with 2-aminophenol was carried out under mild conditions (ethanol, 20 °C), a salt was isolated. On heating, this salt readily cyclised to benzoxazin-2-one **133a**.[37] It has been shown [37] that benzoxazinones **133** are thermodynamically less stable than quinoxalones **86**. Thus the compound **133a** is converted into the quinoxalone **86a** almost quantitatively when fused with PDA; in solutions, this transformation occurs even at 20 °C.

Pentafluorobenzoylpyruvate **31a** can react with 2-aminophenol to give, unlike non-fluorinated analogues, not only 3-pentafluorobenzoylmethylidene-3,4-dihydro-1,4-benzoxazin-2(2*H*)-one (**133p**), but also its mixture with 2-hydroxy-3,4,5,6-tetrafluorobenzoylmethylidene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (**133q**). The compound **133p** is formed under mild conditions (at 20 °C)

in alcohol, while the product mixture is produced when the reactants are refluxed.[3, 5, 176]

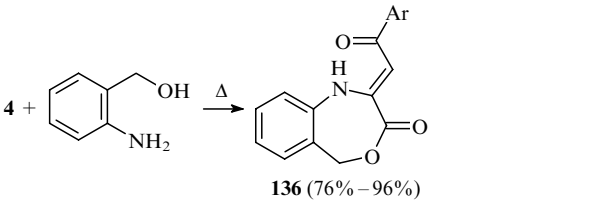



4(5)-Monosubstituted 2-aminophenols and 1-amino-2-naphthol react with the AP **2** similarly to 2-aminophenol yielding 6(7)-derivatives of 3-aroylmethylidene-3,4-dihydro-1,4-benzoxazin-2(2*H*)-ones **134a**–**d** and 3-benzoylmethylidene-3,4-dihydronaphtho[2,1-*b*]-1,4-benzoxazin-2(2*H*)-one (**135**), respectively.[145, 175, 177]

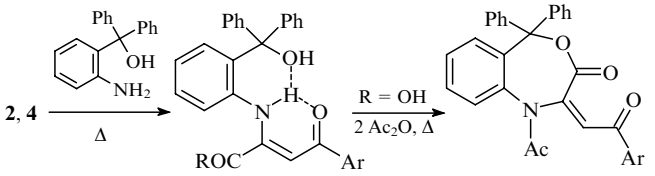



Ar = Ph (**a**–**c**), 4-MeC$_6$H$_4$ (**d**); X = H (**a**–**c**), Me (**d**); Y = Me (**a**), Cl (**b**), NO$_2$ (**c** ), H (**d**).

The reaction of the APA **4** with 2-aminobenzyl alcohol carried out by refluxing in toluene gives 4-aroylmethylidene-3,4-dihydro-1*H*,5*H*-benzo[*e*]-1,4-oxazepin-3-one **136**.[178]



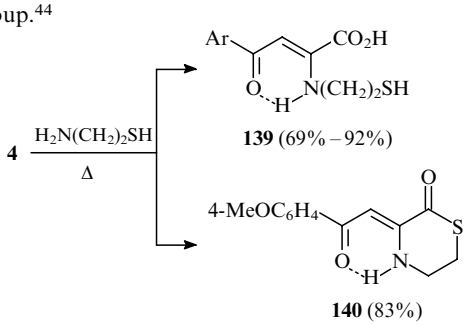

The reactions of the APA **4** and their methyl esters **2** with 2-aminophenyldiphenylmethanol carried out by refluxing in benzene do not result in cyclisation products but give instead 4-aryl-2-[2-(1-hydroxydiphenylmethyl)phenylamino]-4-oxo-4-but-2-enoic acids and their esters **137**. Unlike the ester **137d**, the acids **137a**,**b** cyclise when refluxed in acetic anhydride to 5-acetyl-4-aroylmethylidene-1,1-diphenyl-3,4-dihydro-1*H*,5*H*-benzo[*e*]-1,4-oxazepin-3-ones **138**.[64, 179]




Ar = 4-XC$_6$H$_4$ [X = H (**a**), Me (**b**, **d**), Cl (**c**)]; R = OH (**a**–**c**), OMe (**d**).

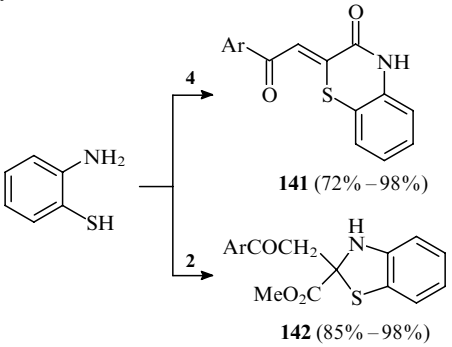
**d. Reactions with N,S-dinucleophiles**

**Reaction with 2-mercaptoethylamine**. The acids **4** react with 2-mercaptoethylamine in boiling ethanol to give acyclic 4-aryl-2-(2-mercaptoethylamino)-4-oxobut-2-enoic acids **139**, except for the APA having a methoxy group in the aryl substituent. In this case, the reaction yields cyclic 3-(4-methoxybenzoylmethylidene)-2,3,5,6-tetrahydro-1,4-thiazin-2(4*H*)-one (**140**), which is due, apparently, to the strong electron-donating effect of the methoxy group.[44]



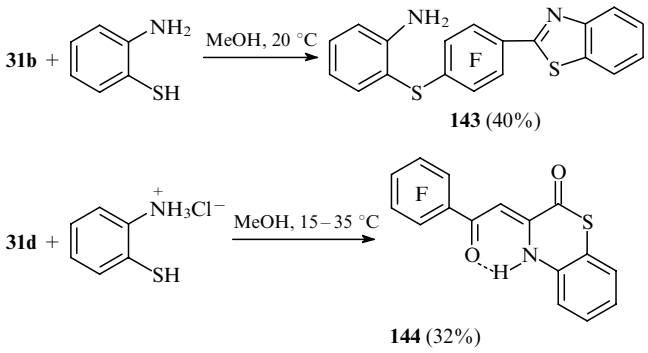

Ar = 4-XC$_6$H$_4$ (X = H, Me, Cl, Br, NO$_2$).

**Reaction with 2-mercaptoaniline**. The aroylpyruvic acids **4** react with 2-mercaptoaniline on refluxing in toluene; the reaction involves the α -oxocarboxyl fragment and affords 2-aroylmethylidene-3,4-dihydro-1,4-benzothiazin-3(2*H*)-ones **141**.[180] Unlike the acids **4**, their methyl esters **2** react with 2-mercaptoaniline on fusion to give the products of addition at the carbonyl group attached to C(2), *i.e.*, 2-aroylmethyl-2-methoxycarbonyl-2,3-dihydrobenzothiazoles **142**.[180, 181]




Ar = 4-XC$_6$H$_4$ (X = H, Me, OMe, Cl, Et, F, Br).

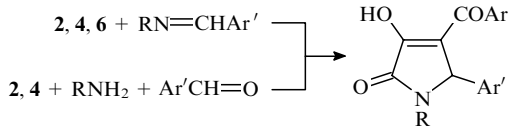
It is of interest that pentafluorobenzoylpyruvates **31b**,**d** behave in a different way towards 2-mercaptoaniline. The pyruvate **31b** is cleaved by the nucleophile under mild conditions (methanol, 15–25 °C) to give ultimately 2-[4-(2-aminophenylthio)-2,3,5,6-tetrafluorophenyl]benzothiazole (**143**). Under similar conditions, the copper(II) chelate **31d** reacts with 2-mercaptoaniline hydrochloride to give the product of selective cyclocondensation at the α-oxoester fragment, 3-pentafluorobenzoylmethylidene-3,4-dihydro-1,4-benzothiazin-2(2*H*)-one (**144**).[3, 6]




## 4. Miscellaneous reactions

A specific feature of the APA **4** and their esters **2** in the formation of heterocycles is the ability to react simultaneously at the nucleophilic C(3) atom and one electrophilic center.

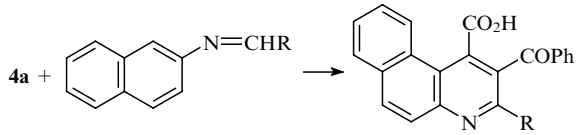
Fusion of ethyl benzoylpyruvate **2a** with benzylideneaniline is known [182] to result in the formation of 4-benzoyl-3-hydroxy-1,5-diphenyldihydropyrrol-2(5*H*)-one (**145**, Y = H, Ar = R = Ph). Borsche has shown [183] that the same pyrrol-2-ones **145** can be prepared from the APA **4** if an equimolar mixture of arylamine and aldehyde is used instead of *N*-arylaldimine. In subsequent studies dealing with the synthesis of pyrrolediones **145**, all the three components, namely, (H)AP, aldehydes and amines were varied over wide limits.[13, 184–187] These reactions are usually carried out in alcohol, AcOH or dioxane at 20–60 °C. The yields of the target products **145** can be increased by using an aldehyde – amine mixture, instead of the corresponding aldimine, and in the case where the AP **2**, **4** contain electron-withdrawing substituents. It is of interest that pyrrolediones **145** are easily (AcOH, 20 °C) formed also from benzoylpyruvic acid 2-pyridylamide **6** (Ar = Ph, R = 2-Py) and diarylaldimines.[187]




Ar = Ph, 4-$XC_6H_4$ (X = Me, OMe, OEt, Cl, Br, $NO_2$), 2-furyl;
R = Ph, 2-naphthyl, 4-$MeC_6H_4$, $CH_2CO_2H$, $(CH_2)_2NMe_2$;
Ar′ = $C_6H_4Y$ (Y = H, 4-OMe, 4-I, 4-Cl, 4-Br, 4-OH, 2-OMe, 2-F, 2-Cl).

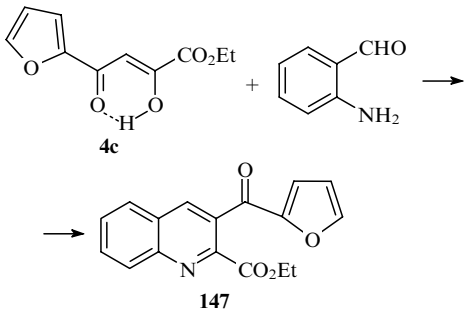
In the given reactions, the aldimine acts as an N-nucleophile and a C-electrophile with respect to AP. The enolysed structure of **145** has been confirmed by NMR spectroscopy.[184–186]

It is notable that when 2-aminonaphthalene (or the corresponding aldimines) are used as the amine component, the acid **4a** is not converted into pyrrolones **145** in boiling ethanol but forms (according to the Doebner condensation pattern) 2-substituted 3-benzoyl-4-carboxybenzo[*f*]quinolines **146**.[183, 188] In this case, the Schiff base acts as a C-nucleophile [the C(1) atom of the 2-naphthyl group] and a C-electrophile with respect to the AP.

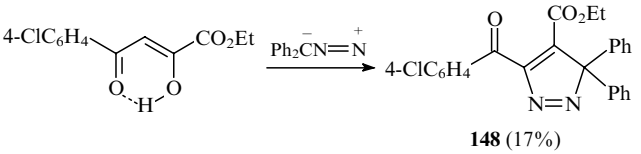



R = H, Me, Ph, 4-$MeOC_6H_4$, piperonyl.

The reaction of ethyl 2-furoylpyruvate **4c** with 2-aminobenzaldehyde gives 3-(2-furoyl)-2-ethoxycarbonylquinoline (**147**).[13]




It has been reported [89] that refluxing of ethyl 4-chlorobenzoylpyruvate with diphenyldiazomethane in benzene induces cycloaddition of the ester at the C(2) and C(3) atoms without elimination of nitrogen to give 3,3-diphenyl-5-(4-chlorobenzoyl)-4-ethoxycarbonyl-3*H*-1,2-pyrazole (**148**).




# IV. Biological activities of (het)aroylpyruvates and the products of their heterocyclisation

The interest in the (H)AP chemistry is related, first of all, to the broad spectrum of biological activities exhibited by representatives of this group of compounds and the products of their heterocyclisation.

Thus sodium enolates derived from ethylbenzoyl- and 4-chlorobenzoylpyruvates possess an antimicrobial activity *in vitro*.[189] Hetaroylpyruvic acids [23] and their esters [22, 33, 34, 36] have been found to display antiaggregation,[23] antibacterial,[23, 33, 34] antiviral,[22] antiinflammatory [34] and analgesic [36] activities. 3-Halogenated esters of APA showed antibacterial [80, 84] and antifungal [18, 80] effects. The most diverse and the highest biological activities were found for (H)APA amides and hydrazides. Substances with analgesic,[31, 54, 59, 61, 62, 73, 94, 179, 190] antiinflammatory,[31, 42, 50, 54, 57–60, 62, 69, 70, 72, 73, 85, 94, 179] anticonvulsant,[43, 61] antiviral [69–71] and antibacterial [50, 51, 57, 58, 61, 62, 66, 69, 70, 73, 77, 86, 179, 190] activities have been found among this group.

Many heterocyclic compounds obtained from (H)AP possess various types of physiological activities. The pyrazoles **66** ($R^1$ = $NHR^2$) exhibit antiinflammatory,[31, 59, 62, 73] analgesic [59, 73] and antibacterial [62, 69, 128] activities with low toxicity. 5-(3-Pyridyl)-3-hydrazinocarbonylpyrazole (**66**, Ar = 3-pyridyl, R = $NHNH_2$) has been patented as an antitumour agent.[17] Antibacterial action has been discovered for a number of 1-phenyl-5-hetarylpyrazole-3-carboxylic acids **67**.[23] 3-Aroylmethylenepiperazin-2-ones **81** [137, 139, 191] and their 1-methyl- and 1-phenyl- **82**[141, 191] or 6-methyl- and 6-phenyl-substituted **85** [142] derivatives show antiinflammatory, anticonvulsant and analgesic activities in combination with low toxicity. Antiinflammatory [94] and analgesic [91, 94] effects of 3-(1-phenylazoaroylmethylene)-1,2,3,4-tetrahydroquinoxalin-2-ones **87** (X = N = NPh) have been reported. *N*-Aryl-4-arylbenzo[b]diazepine-2-carboxamides **91** were patented as analgesics.[151] Antibacterial and antiinflammatory activities have been found for 3-aroylmethylene-6-cyano-2-quinoxalinones **94**.[51] The tetrahydropyridoquinoxalinones **98** exhibited a tuberculostatic activity *in vitro*.[155] It was found that 4-aryl-2-(5-heteroaryl)amino-4-oxobut-2-enoic acid **119** stimulates the cell growth of some microorganisms.[162, 164] Some 5-aroylmethyleneimidazolidine-2,4-diones **122** possess an anticonvulsant activity while having low toxicity; they depress the central nervous system and, possibly, the activity of the microsomal liver enzymes.[165] A series of 5-aryl-1,2,6-thiadiazine-3-

carboxylic acid 1,1-dioxide derivatives **125**, **126** demonstrated antiviral and sedative activities.[133] The benzoxazepinones **136** show antimicrobial action.[178] An antibacterial activity has been noted for 4-aryl-2-[2-(1-hydroxydiphenylmethyl)phenylamino]-4-oxo-4-but-2-enoic acids and their esters **137**.[179] The benzothiazoline **142** (Ar = Ph) has an antiinflammatory activity.[181] In the case of some pyrrolones **145**, antibacterial[185, 186] and nootropic activities have been found.[185]

## V. Conclusion

Analysis of the published data demonstrates that (H)AP represent an ample class of organic compounds containing carboxyl, ester, or amide functional groups. An indispensable structural feature of these substances is the presence of the β-dicarbonyl fragment. The structure of (H)AP accounts for their great synthetic potential. The availability of a wide range of (H)AP is ensured by facile and convenient procedures for their preparation, the main of them being the Claisen condensation or hydrolysis (alcoholysis) of 2,3-dihydrofuran-2,3-diones and -pyrrole-2,3-diones.

When comparing the reactivity of the APA **4**, the esters **2** and the amides **6**, one cannot but note that the amides **6** are somewhat less reactive. Indeed, similar reactions require more drastic conditions in the case of the APA amides **6**. In all the (H)AP **2**, **4** and **6**, the C(2) centre, *i.e.*, the α-carbonyl group, is the site of choice for the primary attack in the reactions with both mono- and dinucleophilic reagents (see Scheme 5). However, when a bulky substituent has been introduced at the 3-position of (H)AP, some reactions involve the ester group. The transformations of (H)AP on treatment with dinucleophiles arouse the greatest interest because these reactions serve as the basis for the synthesis of various heterocyclic systems. The reaction can involve either the α- or β-dicarbonyl fragment. In the reactions with α-dinucleophiles (hydrazines, hydroxylamine), the β-dicarbonyl moiety of (H)AP is involved in the process, while for most of other nucleophiles, the addition at the α-dicarbonyl residue is preferred. In the majority of cases, these processes are regio- and chemoselective, which allows (H)AP to be used for targeted synthesis of heterocycles.

Nevertheless, the chemistry of (H)AP is far from being exhausted. Further research into the properties of these compounds and into the prospects for using them in organic synthesis appears quite topical. These may be related, for example, to investigation of fluoro-containing (H)AP the chemistry of which has essential distinctive features. In addition, (H)AP with organometallic aryl groups are still unknown. The authors hope that this review will be favourable for the development of research into the biological activity of (H)AP and their heterocyclic derivatives, which has been studied only cursorily and fragmentarily.

Thus, (H)AP are readily available and convenient building blocks for the design of diverse acyclic and heterocyclic structures. They can be considered to be promising for further investigations in the fields of heterocyclic and medical chemistry.

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## References

1. C Beyer, L Claisen *Berichte* **20** 2178 (1887)
2. S Salvatori *Gazz. Chim. Ital.* **21** (2) 268 (1891)
3. V I Saloutin, Y V Burgart, C O Kappe, O N Chupakhin *Heterocycles* **52** 1411 (2000)
4. V I Saloutin, Ya V Burgart, O N Chupakhin *Usp. Khim.* **68** 227 (1999) [*Russ. Chem. Rev.* **68** 203 (1999)]
5. V I Saloutin, S G Perevalov *J. Fluor. Chem.* **96** 87 (1999)
6. V I Saloutin, S G Perevalov, O N Chupakhin *Zh. Org. Khim.* **36** 727 (2000) [a]
7. D D Nekrasov *Khim. Geterotsikl. Soedin.* 291 (2001) [b]
8. I V Mashevskaya, R R Makhmudov, G A Aleksandrova, O V Golovnina, A V Duvalov, A N Maslivets *Khim.-Farm. Zh.* **35** (4) 20 (2001) [c]
9. I A Tolmacheva, I V Mashevskaya, A N Maslivets *Zh. Org. Khim.* **37** 630 (2001) [a]
10. S N Shurov, Yu S Andreichikov, in *Khimiya Pyatichlennykh 2,3-Dioksogeterotsiklov* (The Chemistry of Five-Membered 2,3-Dioxoheterocycles) (Perm': Perm' State University, 1994) p. 5
11. O Piloty, H Will *Berichte* **46** 2607 (1913)
12. S Fatutta, A Stener *Gazz. Chim. Ital.* **88** 89 (1958)
13. C Musante, S Fatutta *Gazz. Chim. Ital.* **88** 879 (1958)
14. S Fatutta, M Balestra *Gazz. Chim. Ital.* **88** 899 (1958)
15. T S Gardner, E Wenis, J Lee *J. Org. Chem.* **26** 1514 (1961)
16. V A Zagorevskii, D A Zykov *Zh. Obshch. Khim.* **33** 2469 (1963) [d]
17. US P. 3 449 350; *Chem. Abstr.* **71** 70 595 (1969)
18. H A Burch, J E Gray *J. Med. Chem.* **15** 429 (1972)
19. USSR P. 345 134; *Chem. Abstr.* **78** 71 485 (1973)
20. V P Gorbunova, N N Suvorov *Khim. Geterotsikl. Soedin.* 1519 (1973) [b]
21. Yu S Andreichikov, Z D Belykh, E V Kalmykova, M D Reshetova, in *4-ya Vsesoyuznaya Konferentsiya po Metalloorganicheskoi Khimii, Kazan' 1988* (The Fourth All-Union Conference on Organometallic Chemistry, Kazan' 1988) Pt. 1, p. 15
22. Russ. P. 2 032 683; *Chem. Abstr.* **124** 106 627 (1996)
23. T N Yanborisov, I A Zhikina, Yu S Andreichikov, A V Milyutin, A N Plaksina *Khim.-Farm. Zh.* **32** (9) 26 (1998) [c]
24. V I Saloutin, Z E Skryabina, I T Bazyl', O N Chupakhin *Izv. Akad. Nauk, Ser. Khim.* 362 (1993) [e]
25. V I Saloutin, Z E Skryabina, I T Bazyl', O N Chupakhin *J. Fluor. Chem.* **65** 37 (1993)
26. V I Saloutin, I T Bazyl', Z E Skryabina, P N Kondrat'ev, O N Chupakhin *Izv. Akad. Nauk, Ser. Khim.* 299 (1994) [e]
27. V I Saloutin, Z E Skryabina, I T Bazyl', P N Kondrat'ev, O N Chupakhin *J. Fluor. Chem.* **69** 119 (1994)
28. Yu S Andreichikov, V L Gein, L O Kon'shina, N N Shapet'ko *Zh. Org. Khim.* **25** 2494 (1989) [a]
29. Yu S Andreichikov, S P Tendryakova, Yu A Nalimova, S G Pitirimova, L A Voronova *Zh. Org. Khim.* **13** 529 (1977) [a]
30. Yu S Andreichikov, T N Tokmakova, L N Voronova, Yu A Nalimova *Zh. Org. Khim.* **12** 1073 (1976) [a]
31. Yu S Andreichikov, A V Milyutin, I V Krylova, R F Saraeva, E V Dormidontova, L P Drovosekova, F Ya Nazmetdinov, V E Kolla *Khim.-Farm. Zh.* **24** (7) 33 (1990) [c]
32. Yu S Andreichikov, S P Tendryakova, Yu A Nalimova, G D Plakhina *Khim. Geterotsikl. Soedin.* 1030 (1977); [b] USSR P. 740 747; *Chem. Abstr.* **93** 185 976 (1980)
33. Yu S Andreichikov, D D Nekrasov, E A Kolevatova, M A Trushule *Khim.-Farm. Zh.* **24** (12) 33 (1990) [c]
34. D D Nekrasov, V G Chizh, Yu S Andreichikov, R R Makhmudov *Khim.-Farm. Zh.* **28** (4) 30 (1994) [c]
35. D D Nekrasov, V G Chizh, Yu S Andreichikov, G A Tul'bovich *Zh. Org. Khim.* **32** 761 (1996) [a]
36. D D Nekrasov, V G Chizh, Yu S Andreichikov, G A Tul'bovich, G A Aleksandrova *Khim.-Farm. Zh.* **31** (3) 34 (1997) [c]
37. Yu S Andreichikov, L A Voronova, A V Milyutin *Zh. Org. Khim.* **15** 847 (1979) [a]
38. Yu S Andreichikov, Yu A Nalimova, G D Plakhina, R F Saraeva, S P Tendryakova *Khim. Geterotsikl. Soedin.* 1468 (1975); [b] USSR P. 476 254; *Chem. Abstr.* **83** 178 796 (1975)
39. Yu S Andreichikov, Yu A Nalimova, S P Tendryakova, Ya M Vilenchik *Zh. Org. Khim.* **14** 160 (1978) [a]
40. USSR P. 727 633; *Chem. Abstr.* **93** 185 792 (1980)
41. USSR P. 727 632; *Chem. Abstr.* **93** 149 825 (1980)
42. USSR P. 686 308; *Chem. Abstr.* **96** 115 968 (1982)
43. USSR P. 769 992; *Chem. Abstr.* **96** 28 651 (1982)
44. Yu S Andreichikov, S P Tendryakova, Yu A Nalimova, I V Krylova *Zh. Org. Khim.* **18** 193 (1982) [a]
45. USSR P. 630 253; *Chem. Abstr.* **90** 87 078 (1979)
46. Yu S Andreichikov, Yu V Ionov *Zh. Org. Khim.* **18** 2430 (1982) [a]
47. USSR P. 956 462; *Chem. Abstr.* **98** 53 435 (1983)
48. Yu S Andreichikov, D D Nekrasov, M A Rudenko, A Yu Konovalov *Khim. Geterotsikl. Soedin.* 740 (1987) [b]
49. Yu S Andreichikov, I V Krylova *Zh. Org. Khim.* **24** 2212 (1988) [a]

50. Yu S Andreichikov, D D Nekrasov, I V Krylova, V I Bachurina *Khim. Geterotsikl. Soedin.* 1461 (1992) [b]
51. Yu S Andreichikov, D D Nekrasov, S G Pitirimova, A S Zaks, M I Korsheninnikova, P N Plaksina, Z N Semenova, V A Kopeikin *Khim.-Farm. Zh.* **23** 946 (1989) [c]
52. A V Milyutin, Yu S Andreichikov, in *Seminar-Soveshchanie 'Potrebiteli i Proizvoditeli Organicheskikh Reaktivov', Erevan, 1991* (Seminar-Meeting 'Users and Producers of Organic Agents', Erevan, 1991) p. 67
53. D D Nekrasov, S V Kol'tsova, Yu S Andreichikov *Khim. Geterotsikl. Soedin.* 173 (1994) [b]
54. Russ. P. 2 021 262; *Chem. Abstr.* **123** 276 022 (1995)
55. D D Nekrasov, S V Kol'tsova, Yu S Andreichikov, G A Tul'bovich *Zh. Org. Khim.* **31** 907 (1995) [a]
56. Z G Aliev, S N Shurov, E Yu Pavlova, Yu S Andreichikov, L O Atovmyan *Izv. Akad. Nauk, Ser. Khim.* 1552 (1995) [e]
57. T N Yanborisov, N N Kasimova, A V Milyutin, Yu S Andreichikov, I P Rudakova, G N Novoselova, V E Kolla, F Ya Nazmetdinov *Khim.-Farm. Zh.* **29** (8) 29 (1995) [c]
58. A V Milyutin, L R Amirova, F Ya Nazmetdinov, R R Makhmudov, A L Golovanenko, Yu S Andreichikov, V E Kolla *Khim.-Farm. Zh.* **30** (5) 47 (1996) [c]
59. A V Milyutin, R R Makhmudov, Yu S Andreichikov, A F Goleneva, G A Tul'bovich, T I Kovina *Khim.-Farm. Zh.* **30** (6) 20 (1996) [c]
60. Russ. Appl. 94 037 753/04; *Ref. Zh. Khim.* 18 O 97 P (1997)
61. N M Igidov, E N Koz'minykh, A V Milyutin, E S Berezina, G A Shavkunova, I B Yakovlev, S A Shelenkova, V E Kolla, E V Voronina, V O Koz'minykh *Khim.-Farm. Zh.* **30** (11) 21 (1996) [c]
62. A V Milyutin, L R Amirova, I V Krylova, F Ya Nazmetdinov, G N Novoselova, Yu S Andreichikov, V E Kolla *Khim.-Farm. Zh.* **31** (1) 32 (1997) [c]
63. M A Tlekhusezh, Yu S Andreichikov, Z I Tyukhteneva, L A Badovskaya *Khim. Geterotsikl. Soedin.* 1422 (1998) [b]
64. N V Kolotova, V O Koz'minykh, E V Dolbilkina, E N Koz'minykh *Izv. Akad. Nauk, Ser. Khim.* 2317 (1998) [e]
65. USSR P. 785 303; *Chem. Abstr.* **94** 208 569 (1981)
66. USSR P. 782 317; *Chem. Abstr.* **97** 127 273 (1982)
67. A N Maslivets, O P Tarasova, I S Berdinskii, Yu S Andreichikov *Zh. Org. Khim.* **25** 1039 (1989) [a]
68. Yu S Andreichikov, Yu V Ionov, O P Tarasova, A N Maslivets *Khim. Geterotsikl. Soedin.* 846 (1990) [b]
69. V O Koz'minykh, N M Igidov, V I Il'enko, A V Milyutin, V E Kolla, Z N Semenova, Yu S Andreichikov *Khim.-Farm. Zh.* **26** (7–8) 28 (1992) [c]
70. V O Koz'minykh, N V Safonova, A V Milyutin, V G Armaginova, V E Kolla, S A Shelenkova, I V Yakovlev, G N Novoselova, Yu S Andreichikov, V I Il'enko *Khim.-Farm. Zh.* **28** (3) 42 (1994) [c]
71. Russ. P. 1 623 134; *Chem. Abstr.* **126** 70 116 (1997)
72. A V Milyutin, N V Safonova, V P Chesnokov, F Ya Nazmetdinov, E V Voronina, I V Krylova, Yu S Andreichikov, V E Kolla, Yu V Kozhevnikov *Khim.-Farm. Zh.* **30** (5) 26 (1996) [c]
73. A V Milyutin, L R Amirova, V E Kolla, F Ya Nazmetdinov, L P Drovosekova, Yu S Andreichikov *Khim.-Farm. Zh.* **32** (8) 24 (1998) [c]
74. S N Shurov, L N Karpova, E Yu Posyagina, Yu V Ionov, T N Somova, N G Shilova, Yu S Andreichikov *Zh. Org. Khim.* **35** 1232 (1999) [a]
75. Yu S Andreichikov, S N Shurov, V V Zalesov, N N Shapet'ko *Zh. Org. Khim.* **22** 857 (1986) [a]
76. T N Yanborisov, S N Shurov, Yu S Andreichikov, in *3-e Vsesoyuznoe Soveshchanie po Khimicheskim Reaktivam, Ashkhabad, 1989* (The Third All-Union Meeting on Chemical Agents, Ashkhabad, 1989) p. 38
77. T N Yanborisov, S N Shurov, Yu S Andreichikov, I P Rudakova, E N Semenova, G N Novoselova *Khim.-Farm. Zh.* **23** 1470 (1989) [c]
78. V V Zalesov, N A Pulina, Yu S Andreichikov *Zh. Org. Khim.* **25** 1054 (1989) [a]
79. Yu S Andreichikov, A N Maslivets, L I Smirnova, O P Krasnykh, A P Kozlov, L A Perevozchikov *Zh. Org. Khim.* **23** 1534 (1987) [a]
80. Yu S Andreichikov, G D Plakhina, S G Pitirimova, E P Oshchepkova, A N Plaksina *Khim.-Farm. Zh.* **12** (1) 76 (1978) [c]
81. L N Kurkovskaya, N N Shapet'ko, Yu S Andreichikov, V L Gein, G D Plakhina, S P Tendryakova *Zh. Strukt. Khim.* **16** 1070 (1975) [f]
82. USSR P. 466 208; *Chem. Abstr.* **83** 43 070 (1975)
83. Yu S Andreichikov, G D Plakhina, S P Tendryakova, Yu A Nalimova, Z D Belykh, in *Khimiya Elementoorganicheskikh Soedinenii II, IV, V, VI Grupp Periodicheskoi Sistemy* (The Chemistry of Organoelement Compounds of Groups II, IV, V and VI of Periodic System (Perm': Perm' State University, 1978) p. 156
84. USSR P. 650 329; *Chem. Abstr.* **96** 68 617 (1982)
85. USSR P. 623 356; *Chem. Abstr.* **96** 28 650 (1982)
86. USSR P. 750 971; *Chem. Abstr.* **96** 46 260 (1982)
87. L N Karpova, N V Kolotova, S N Shurov, Yu S Andreichikov *Zh. Org. Khim.* **28** 779 (1992) [a]
88. Yu S Andreichikov, N V Gel't, A P Kozlov *Zh. Org. Khim.* **20** 1749 (1984) [a]
89. A L Fridman, Yu S Andreichikov, V L Gein *Zh. Org. Khim.* **13** 1422 (1977) [a]
90. E V Brigadnova, A N Maslivets, Yu S Andreichikov *Zh. Org. Khim.* **26** 327 (1990) [a]
91. USSR P. 505 641; *Chem. Abstr.* **85** 41101 (1976)
92. E V Pimenova, Yu S Andreichikov *Zh. Org. Khim.* **28** 376 (1992) [a]
93. E V Pimenova, A N Maslivets, R A Khamatgaleev, Yu S Andreichikov, in *Karbonil'nye Soedineniya v Sinteze Geterotsiklov* (Carbonyl Compounds in the Synthesis of Heterocycles) (Saratov: Saratov State University, 1996) P. 124
94. Yu S Andreichikov, L F Gein, V L Gein, E L Pidemskii *Khim.-Farm. Zh.* **11** (4) 17 (1977) [c]
95. Y V Burgart, A S Fokin, O G Kuzueva, O N Chupakhin, V I Saloutin *J. Fluor. Chem.* **82** 101 (1998)
96. V I Saloutin, A S Fokin, Ya V Burgart *Zh. Org. Khim.* **35** 309 (1999) [a]
97. E V Pimenova, A N Maslivets, S N Shurov, Yu S Andreichikov *Zh. Org. Khim.* **31** 604 (1995) [a]
98. E V Pimenova, R A Khamatgaleev, E V Voronina, Yu S Andreichikov *Khim.-Farm. Zh.* **33** (8) 22 (1999) [c]
99. P Battesti, O Battesti, M Selim *Bull. Soc. Chim. Fr.* 2214 (1974)
100. L N Kurkovskaya, N N Shapet'ko, Yu S Andreichikov, R F Saraeva *Zh. Strukt. Khim.* **13** 1026 (1972) [f]
101. Z G Aliev, S N Shurov, D D Nekrasov, I B Podvintsev, L O Atovmyan *Zh. Strukt. Khim.* **41** 1255 (2000) [f]
102. A N Maslivets, O P Krasnykh, L I Smirnova, Yu S Andreichikov *Zh. Org. Khim.* **25** 1045 (1989) [a]
103. USSR P. 1 608 186; *Chem. Abstr.* **115** 29 111 (1991)
104. V I Saloutin, I T Bazyl', Z E Skryabina, G G Aleksandrov, O N Chupakhin *Zh. Obshch. Khim.* **64** 2054 (1994) [d]
105. O Mumm, O Böhme *Berichte* **54** 726 (1921)
106. D I Sychev *Zh. Org. Khim.* **25** 1341 (1989) [a]
107. V L Gein, L O Kon'shina, Yu S Andreichikov *Zh. Org. Khim.* **28** 2134 (1992) [a]
108. USSR P. 1 441 735; *Chem. Abstr.* **116** 128 947 (1992)
109. Yu S Andreichikov, V L Gein, O I Ivanenko, E V Brigadnova, A N Maslivets *Zh. Org. Khim.* **24** 1115 (1988) [a]
110. Yu S Andreichikov, D I Sychev *Zh. Org. Khim.* **29** 1085 (1993) [a]
111. N M Igidov, E N Koz'minykh, O A Sof'ina, T M Shironina, V O Koz'minykh *Khim. Geterotsikl. Soedin.* 1466 (1999) [b]
112. S N Shurov, I A Zhikina *Zh. Obshch. Khim.* **70** 1890 (2000) [d]
113. E V Pimenova, Yu S Andreichikov, in *Khimiya Pyatichlennykh 2,3-Dioksogeterotsiklov* (The Chemistry of Five-Membered 2,3-Dioxoheterocycles) (Perm': Perm' State University, 1994) p. 188
114. E Klingsberg *Chem. Rev.* **54** 59 (1954)
115. Yu S Andreichikov, A P Kozlov, L N Kurdina *Zh. Org. Khim.* **20** 826 (1984) [a]
116. A P Kozlov, V V Ryabova, G A Kozlova, Yu S Andreichikov *Zh. Org. Khim.* **33** 406 (1997) [a]
117. L N Kurkovskaya, N N Shapet'ko, Yu S Andreichikov, R F Saraeva *Zh. Strukt. Khim.* **16** 139 (1975) [f]
118. Yu S Andreichikov, A P Kozlov, L N Kudrina *Zh. Org. Khim.* **19** 378 (1983) [a]
119. USSR P. 488 811; *Chem. Abstr.* **84** 16 930 (1976)
120. A N Maslivets, Yu S Andreichikov, in *Khimiya Pyatichlennykh 2,3-Dioksogeterotsiklov* (The Chemistry of Five-Membered 2,3-Dioxoheterocycles) (Perm': Perm' State University, 1994) p. 91
121. V I Saloutin, I T Bazyl', Z E Skryabina, O N Chupakhin *Izv. Akad. Nauk, Ser. Khim.* 904 (1994) [e]

122. D Liberman, N Rist, F Grumbach, S Cals, M Moyeux, A Rouaix *Bull. Soc. Chim. Fr.* 687 (1958)
123. C Musante, S Fatutta *Ann. Chim. (Rome)* **49** 1496 (1959)
124. J Elguero, G Guiraud, R Jacquier *Bull. Soc. Chim. Fr.* 619 (1966)
125. Yu S Andreichikov, A N Maslivets, L I Smirnova *Zh. Org. Khim.* **23** 2254 (1987) [a]
126. V I Saloutin, Z E Skryabina, P N Kondrat'ev, S G Perevalov *Zh. Org. Khim.* **31** 266 (1995) [a]
127. E V Pimenova, R A Khamatgaleev, E V Voronina, Yu S Andreichikov *Khim.-Farm. Zh.* **32** (8) 27 (1998) [c]
128. I I Lapkin, Yu S Andreichikov *Zh. Org. Khim.* **2** 2075 (1966) [a]
129. S I Yakimovich, I V Zerova *Zh. Org. Khim.* **14** 42 (1978) [a]
130. S I Yakimovich, I V Zerova *Zh. Org. Khim.* **16** 1633 (1980) [a]
131. O P Krasnykh, A N Maslivets, V R Stukov, Yu S Andreichikov, in *Khimiya Fiziologicheski Aktivnykh Soedinenii. Vsesoyuznyi Seminar, Chernogolovka, 1989* (The Chemistry of Physiologically Active Compounds. All-Union Seminar, Chernogolovka, 1989) p. 137
132. S I Yakimovich, V N Nikolaev *Zh. Org. Khim.* **17** 284 (1981) [a]
133. US P. 3 223 703; *Chem. Abstr.* **64** 8217 (1966)
134. E Cattelain, P Chabrier *Bull. Soc. Chim. Fr.* 1098 (1947)
135. Z G Aliev, L O Atovmyan, Yu S Andreichikov, S V Kol'tsova, D D Nekrasov *Izv. Akad. Nauk, Ser. Khim.* 704 (1998) [e]
136. Yu S Andreichikov, S V Kol'tsova, I A Zhikina, D D Nekrasov *Zh. Org. Khim.* **35** 1567 (1999) [a]
137. A V Milyutin, N V Safonova, R R Makhmudov, G A Tul'bovich, V A Safin, A F Goleneva, in *8-ya Mezhdunarodnaya Konferentsiya po Khimicheskim Reaktivam, Ufa, 1995* (The Eighth International Conference on Chemical Agents, Ufa, 1995) p. 98
138. Yu S Andreichikov, T N Tokmakova, E L Pidemskii, L A Voronova, Ya M Vilenchik *Khim.-Farm. Zh.* **11** (5) 85 (1977) [c]
139. USSR P. 1 544 773; *Chem. Abstr.* **113** 23 949 (1990)
140. A V Milyutin, N V Safonova, A F Goleneva, Yu S Andreichikov, G A Tul'bovich, R R Makhmudov *Khim.-Farm. Zh.* **28** (12) 37 (1994) [c]
141. A V Milyutin, N V Safonova, R R Makhmudov, G N Novoselova, A F Goleneva, Yu S Andreichikov *Khim.-Farm. Zh.* **30** (3) 42 (1996) [c]
142. A V Milyutin, N V Safonova, R R Makhmudov, Yu S Andreichikov, Z G Aliev *Khim.-Farm. Zh.* **32** (1) 27 (1998) [c]
143. G S Predvoditeleva, T V Kartseva, M N Shchukina, T N Zykova, G N Pershin *Khim.-Farm. Zh.* **2** (11) 19 (1968) [c]
144. Yu S Andreichikov, R F Saraeva, A L Fridman *Khim. Geterotsikl. Soedin.* 259 (1973) [b]
145. Y Iwanami, T Seki, T Inagaki *Bull. Chem. Soc. Jpn.* **44** 1316 (1971)
146. Y Iwanami, T Inagaki *J. Heterocycl. Chem.* **13** 681 (1976)
147. Yu S Andreichikov, S G Pitirimova, R F Saraeva, V L Gein, G D Plakhina, L A Voronova *Khim. Geterotsikl. Soedin.* 407 (1978) [b]
148. A N Maslivets, L I Smirnova, O I Ivanenko, Yu S Andreichikov *Khim. Geterotsikl. Soedin.* 697 (1991) [b]
149. Yu S Andreichikov, S G Pitirimova, S P Tendryakova, R F Saraeva, T N Tokmakova *Zh. Org. Khim.* **14** 169 (1978) [a]
150. E V Brigadnova, Yu S Andreichikov *Zh. Org. Khim.* **25** 1169 (1989) [a]
151. USSR P. 611 421; *Chem. Abstr.* **91** 193 345 (1979)
152. G S Predvoditeleva, T V Kartseva, T N Zykova, M N Shchukina, G N Pershin *Khim.-Farm. Zh.* **6** (10) 3 (1972) [c]
153. A N Maslivets, L I Smirnova, Yu S Andreichikov *Zh. Org. Khim.* **28** 2141 (1992) [a]
154. USSR P. 895 983; *Chem. Abstr.* **97** 92 303 (1982)
155. T V Kartseva, G S Predvoditeleva, V I Shvedov, N B Lapaeva, G N Pershin *Khim.-Farm. Zh.* **12** (7) 89 (1978) [c]
156. I V Mashevskaya, I A Tolmacheva, A N Maslivets *Khim. Geterotsikl. Soedin.* 1277 (2000) [b]
157. T Seki, H Sakata, Y Iwanami *J. Heterocycl. Chem.* **32** 347 (1995)
158. G S Predvoditeleva, T V Kartseva, M N Shchukina *Khim.-Farm. Zh.* **8** (9) 7 (1974) [c]
159. V P Kruglenko, V P Gnidets, N A Klyuev, E V Logachev, M A Klykov, M V Povstyanoi *Khim. Geterotsikl. Soedin.* 1402 (1985) [b]
160. T N Yanborisov, I A Zhikina, O A Yanborisova, S N Shurov, Yu S Andreichikov *Zh. Org. Khim.* **28** 2554 (1992) [a]
161. D D Nekrasov, S N Shurov, O I Ivanenko, Yu S Andreichikov *Zh. Org. Khim.* **30** 126 (1994) [a]
162. Y Iwanami, T Seki *Bull. Chem. Soc. Jpn.* **45** 2829 (1972)
163. T Seki, H Sakata, Y Iwanami *J. Heterocycl. Chem.* **32** 703 (1995)
164. Jpn. P. 72-45 752; *Chem. Abstr.* **78** 97 697 (1973)
165. V S Zalesov, Yu S Andreichikov, Yu A Nalimova, S P Tendryakova, S M Starkova, N A Podushkina *Khim.-Farm. Zh.* **12** (7) 93 (1978) [c]
166. Yu S Andreichikov, G D Plakhina *Zh. Org. Khim.* **23** 872 (1987) [a]
167. USSR P. 674 414; *Chem. Abstr.* **93** 150 271 (1980)
168. USSR P. 794 007; *Chem. Abstr.* **95** 25 060 (1981)
169. J B Wright *J. Org. Chem.* **29** 1905 (1964)
170. P G Baraldi, A Barco, S Benetti, S Manfredini, G P Pollini, D Simoni *Tetrahedron* **43** 235 (1987)
171. P G Baraldi, D Simoni, F Moroder, S Manfredini, L Mucchi, F D Vecchia, P Orsolini *J. Heterocycl. Chem.* **19** 557 (1982)
172. USSR P. 621 676; *Chem. Abstr.* **90** 87 478 (1979)
173. USSR P. 910 627; *Chem. Abstr.* **97** 92 298 (1982)
174. Yu S Andreichikov, L A Voronova, A P Kozlov *Zh. Org. Khim.* **15** 520 (1979) [a]
175. A N Maslivets, I V Mashevskaya, O P Krasnykh, S N Shurov, Yu S Andreichikov *Zh. Org. Khim.* **28** 2545 (1992) [a]
176. V I Saloutin, S G Perevalov, Z E Skryabina *Zh. Org. Khim.* **32** 1386 (1996) [a]
177. Z G Aliev, O P Krasnykh, A N Maslivets, L O Atovmyan *Izv. Akad. Nauk, Ser. Khim.* 2080 (2000) [e]
178. USSR P. 666 799; *Chem. Abstr.* **93** 71 822 (1980)
179. N V Kolotova, V O Koz'minykh, E V Dolbilkina, E N Koz'minykh, V E Kolla, S A Shelenkova *Khim.-Farm. Zh.* **32** (9) 32 (1998) [c]
180. Yu S Andreichikov, S P Tendryakova, Yu A Nalimova, L A Voronova *Khim. Geterotsikl. Soedin.* 755 (1977); [b] USSR P. 615 071; *Chem. Abstr.* **89** 129 528 (1978)
181. USSR P. 625 392; *Chem. Abstr.* **95** 150 646 (1981)
182. R Schiff, L Gigli *Berichte* **31** 1306 (1898)
183. W Borsche *Berichte* **42** 4072 (1909)
184. Yu S Andreichikov, V L Gein, I N Anikina *Zh. Org. Khim.* **22** 1749 (1986) [a]
185. V L Gein, L F Gein, N Yu Porseva, E V Voronina, M I Vakhrin, K D Potemkin, V E Kolla, L P Drovosekova, A V Milyutin, N S Shchuklina, G A Veikhman *Khim.-Farm. Zh.* **32** (9) 23 (1998) [c]
186. V L Gein, N N Kasimova, E V Voronina, L F Gein *Khim.-Farm. Zh.* **35** (3) 31 (2001) [c]
187. A V Milyutin, V L Gein, Yu S Andreichikov *Zh. Obshch. Khim.* **62** 2633 (1992) [d]
188. E A Robinson, M T Bogert *J. Org. Chem.* **1** 65 (1936)
189. H Rinderknecht, J L Ward, F Bergel, A L Morrison *Biochem. J.* **41** 463 (1947)
190. E N Koz'minykh, N M Igidov, E S Berezina, G A Shavkunova, I B Yakovlev, S A Shelenkova, V E Kolla, E V Voronina, V O Koz'minykh *Khim.-Farm. Zh.* **30** (7) 31 (1996) [c]
191. Russ. P. 2 067 579; *Chem. Abstr.* **126** 312 261 (1997)


[a] — *Russ. J. Org. Chem. (Engl. Transl.)*
[b] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[c] — *Chem.-Pharm. J. (Engl. Transl.)*
[d] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[e] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*
[f] — *J. Struct. Chem. (Engl. Transl.)*