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QUINAZOLINONE DERIVATIVES

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The presented review covers applications (especially medical and pharmaceutical), natural occurrence and the synthesis of quinazolin-2-one, quinazolin-4-one and quinazolin-2,4-dione derivatives. The reaction mechanisms of the most interesting reactions are also discussed.

Quinazolin-2-Ones, 4-Ones and Quinazolin-2,4-Diones

Quinazolin-4-ones (Fig. 1) and their substituted derivatives are compounds derived from quinazoline or its derivatives. The name quinazolin is commonly used although it is a trivial name. According to Hantzch–Widman nomenclature system the name benzo[*d*](1,3)diazine should be used.

The first [1] derivative — 2-cyanoquinazolin-4(3*H*)-one — was prepared in 1869 by Griess. The parent non-substituted quinazoline was prepared [2] as late as in 1903 from 3,4-dihydroquinazoline by oxidation with potassium ferricyanide(III) in alkaline medium.

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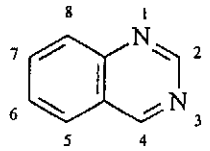
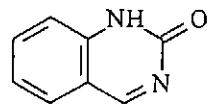
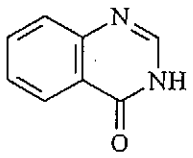


quinazoline
benzo[*d*][1,3]diazine



quinazolin-2(1*H*)-one



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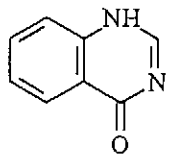
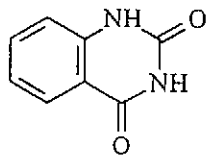


quinazolin-4(1*H*)-one



quinazolin-2,4(1*H*, 3*H*)-dione

Fig. 1

Substituted derivatives of quinazoline can be divided into two sections according to whether the substituent occurs on the benzene or heterocyclic moiety. A special case of substitution of heterocyclic moiety is a substitution by hydroxy group in position 2-, 4- or in both positions. As early [3] as 1895, Niementowski found that there is a tautomeric equilibrium between 4-hydroxyquinazoline and quinazolin-4-one. A completely identical situation is encountered in the case of 2-hydroxyquinazoline and 2,4-dihydroxyquinazoline (Fig. 2). The high melting points, low solubility, good thermal stability, resistance against light, air, oxidisers and reducers observed with the compounds mentioned indicate that the preferred [4] tautomeric form is keto-form. On the other hand, the quinazoline derivatives carrying substituents on the heterocyclic moiety (except hydroxy group) are low melting and low thermostable compounds that readily undergo oxidation and reduction reactions.

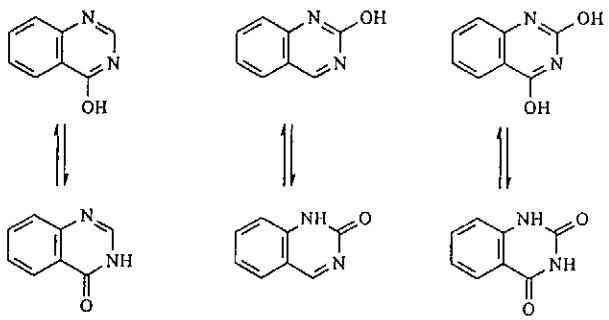


Fig. 2

For example, the direct reduction of quinazolin-4(3*H*)-one to quinazoline does not take place and a multistep [5] synthesis is needed instead .

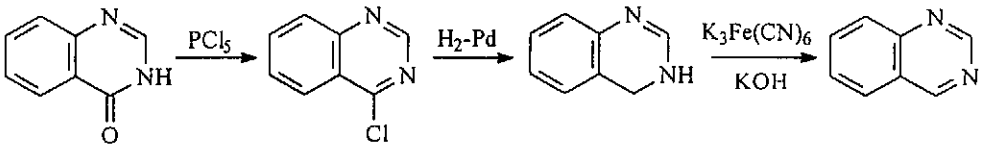


Fig. 3

Quinazolin-2(1H)-one and its Derivatives

Practical Applications

The derivatives of quinazolin-2(1*H*)-one are used in many areas of human activity. Perhaps the most important is application in medicine and pharmacology. At present, five registered preparations based on quinazolin-2(1*H*)-one are known [6]: their generic names, formulas and effects on human organism are summarised in Table I and Fig. 4.

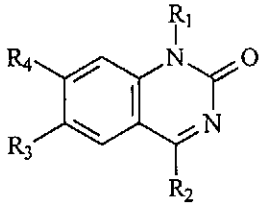


Fig. 4

Table I Registered preparations based on quinazolin-2(1*H*)-one

Generic name	R_1	R_2	R_3	R_4	Effect
Proquazone	$(CH_3)_2CH-$	C_6H_5-	H	CH_3-	anti-inflammatory, analgesic
Fluproquazone	$(CH_3)_2CH-$	$4-F-C_6H_5-$	H	CH_3-	anti-inflammatory, analgesic
Fluquazone	CF_3CH_2-	C_6H_5-	Cl	H	anti-inflammatory
Ciproquazone	▷$-CH_2-$	C_6H_5-	CH_3CO-	H	anti-inflammatory, antirheumatic
SL-512	▷$-CH_2-$	C_6H_5-	H	H	anti-inflammatory

Besides the compounds mentioned in Table I, there also exist derivatives of quinazolin-2(1*H*)-one applicable as oral or intravenous cardiotonics. It can be presumed that these compounds will be adopted into clinical practice in the future. The compounds 4-amino-5,6-dimethoxyquinazolin-2(1*H*)-one [7] or 4-methyl-5,6-dimethoxyquinazolin-2(1*H*)-one are examples to be mentioned. Quinazolin-2(1*H*)-ones have been also described [9] to have anticonvulsive effects. 2,3-Dihydroderivatives of quinazolin-2(1*H*)-one recently started to attract attention because they posses antiviral [10] and HIV-reverse transcriptase [11,12] inhibition effect, or potentiate the effect of another HIV-reverse transcriptase [13] inhibitors (e.g. AZT). For instance we can give 1-methyl-(4*S*)-cyclopropyl-4-(2-pyridyl-ethinyl)-6-chloro-3,4-dihydroquinazolin-2(1*H*)-one, whose enantioselective synthesis was carried out with help of quinine as a chiral catalyst.

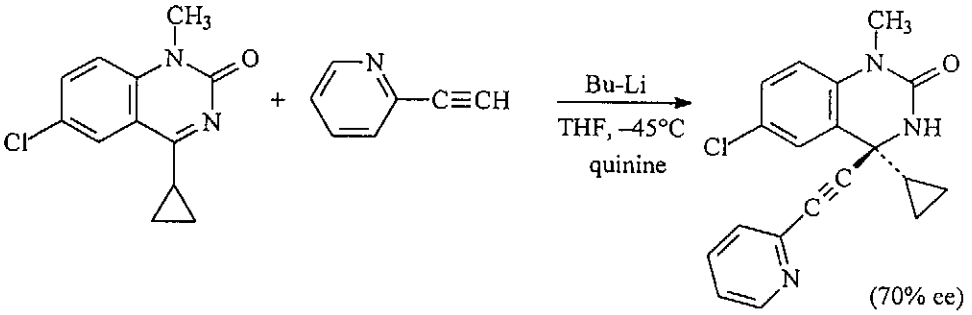
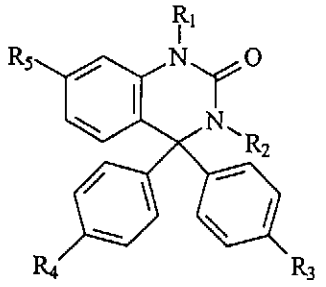


Fig. 5

Quinazolin-2(1*H*)-ones were also identified as metabolic products of 1,4-benzodiazepines [15] and tetrahydro-1,4-benzodiazepines [16].

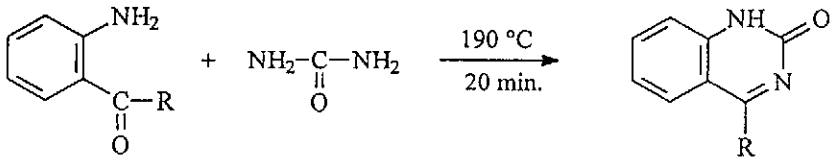
Sporadically it is possible to find some references about other applications outside medicine. Some derivatives of quinazolin-2(1*H*)-one are used as dyes (Fig. 6) for photocopying machines [17] or as a herbicides and pesticides [18].



R_1 = H, alkyl, cycloalkyl, aralkyl, aryl
R_2 = subst. benzoyl
R_3 - R_5 = H, halogen, alkyl, aryl, alkylamin

Fig. 6

The first syntheses of quinazolin-2(1*H*)-one derivatives were carried out as early as 19th century in Germany. First [19] Bischler and later [20] Gabriel and Posner carried out the condensation reaction of 2-aminobenzaldehyde or 2-amino-acetophenone with urea. By heating of reaction mixture at 190 °C for 20 min. they obtained quinazolin-2(1*H*)-one or 4-methylquinazolin-2(1*H*)-one, respectively (Fig. 7). This method was perhaps the only known in the literature until 1970s, although it is now not universal.



R = H, CH_3 (cca 60%)

Fig. 7

After 1970 a lot of synthetic approaches suitable for synthesis of more complex derivatives of quinazolin-2(1*H*)-one was published (especially in patent literature in connection with pharmacological activity mentioned above). In 1970 Sandoz Ltd. patented [21] a method starting from the imino-compound previously prepared from corresponding nitrile and phenyl-lithium. The ring closure was carried out by several ways (Fig 8.), whereas use of phosgene as a reactant was also [22] published later again.

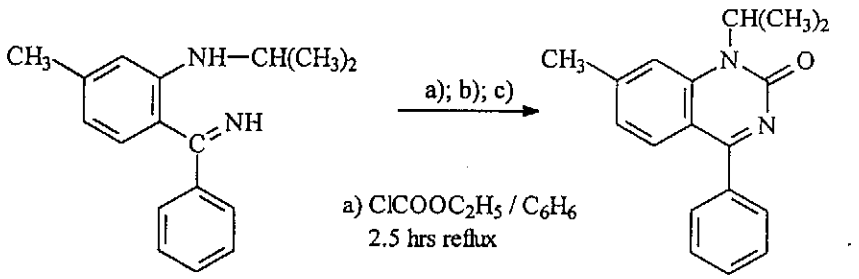
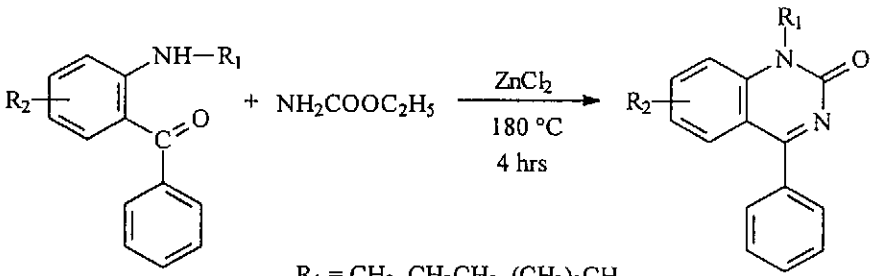


Fig. 8

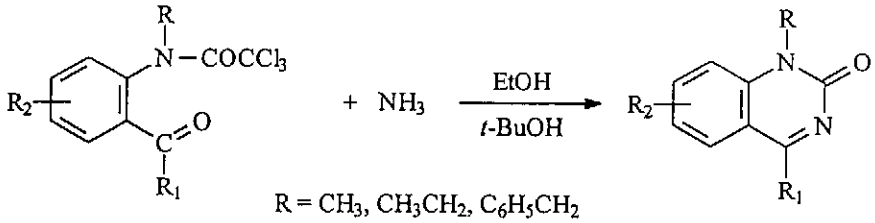
Also it is possible to start from imino-compound instead of corresponding keto-compound. In this case, ethyl-carbamate [23] in the presence of zinc dichloride (Fig. 9) or chlorsulphonylisocyanate [24] in benzene as a solvent must be used.



$R_1 = CH_3, CH_3CH_2, (CH_3)_2CH$
$R_2 = CH_3, NO_2, OCH_3, SCH_3, Cl$

Fig. 9

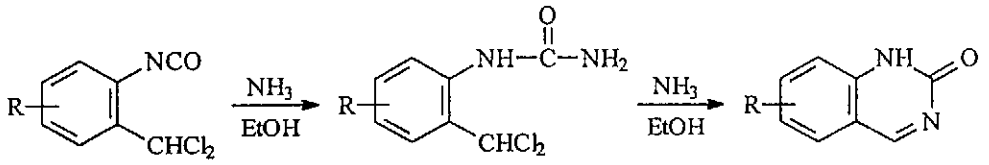
Somewhat different strategy was used by Japanese authors [25,26], who started from keto-compound as well. However in the first step they carried out the acylation of *ortho*-aminogroup with trichloroacetyl chloride. The resulting intermediate was then converted in ethanolic solution of ammonia or ammonium acetate into substituted quinazolin-2(1*H*)-one.



$R = CH_3, CH_3CH_2, C_6H_5CH_2$
R_1 = cycloalkyl, aryl, heteroaryl
$R_2 = H, CH_3S, CH_3SO, CH_3SO_2, Cl, NO_2$

Fig. 10

Another method [27] of preparation consists in reaction of substituted (dichloromethyl)phenyl isocyanates with ammonia to give substituted . (dichloromethyl)-phenylureas. These compounds readily cyclise in the high yield: (~ 90%) into corresponding quinazolin-2(1*H*)-ones.



R = H, Cl

Fig. 11

An elegant method [28] of preparation of 4-phenylquinazolin-2(1*H*)-one applying the so-called *ortho*-lithiation was described by Muchowski in 1980. This method consists in the finding that *N*-(*t*-butoxycarbonyl)aniline readily reacts with butyl-lithium to give the corresponding *ortho*-lithio-derivative, which is very reactive towards electrophiles. If benzonitrile is used as an "electrophile", the corresponding imino-compound formed spontaneously cyclises into product mentioned above.

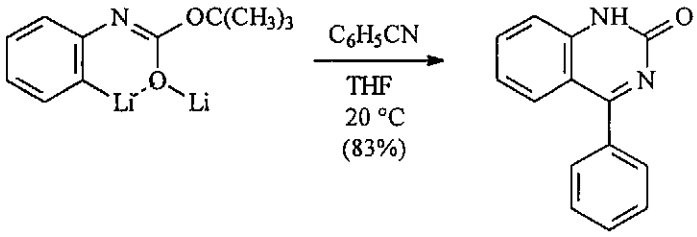
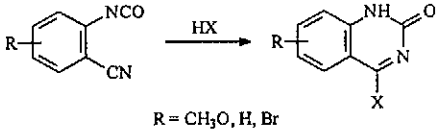


Fig. 12

The methods described in the previous text are suitable for preparation of quinazolin-2(1*H*)-ones substituted at position 4 by alkyl or aryl. There is also a synthetic method suitable [29] for preparation of 4-haloquinazolin-2(1*H*)-ones (Fig. 13). These compounds play an important role in further syntheses. The starting compound, which is substituted 2-cyanophenyl isocyanate, is converted by treatment with hydrogen chloride or hydrogen bromide into the corresponding quinazolin-2(1*H*)-one. 2-Cyanophenyl isocyanate can be prepared *in situ* from aniline or its hydrochloride and phosgene.

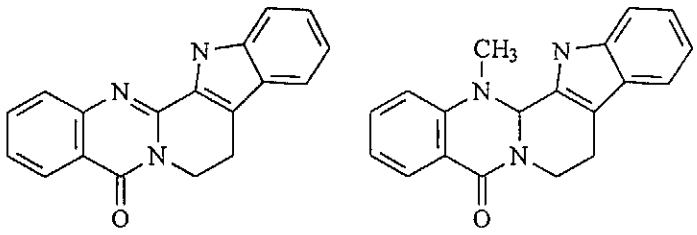


R = CH_3O, H, Br
X = Cl, Br

Fig. 13

Natural Occurrence

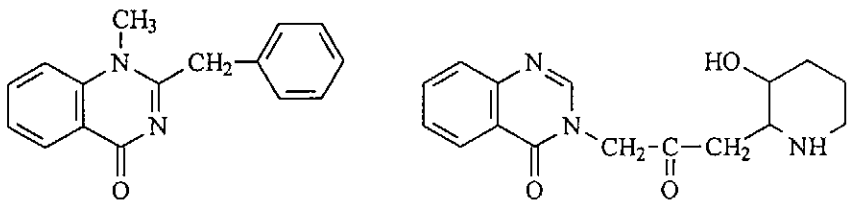
The possibility of natural occurrence of the derivatives of quinazolin-4-one is not too high. Quinazolin-4-one skeleton is incorporated in some alkaloids as for instance [30] Rutaecarpine or Evodiamine (Fig. 14) which can be classified among so-called indole alkaloids.



Rutaecarpin **Evodiamin**

Fig. 14

Alkaloids of somewhat simpler structure were isolated from plants (*Glycosmis arborea*, *Glycosmis pentaphylla* (Arborin) [30]), leaves or especially from roots of *Dichroa Febrifuga* [31] and from leaves of *Hydrangea* [32] (Febrifugin).

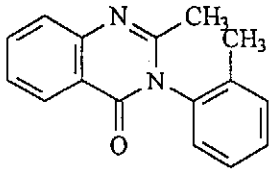


Arborin **Febrifugin**

Fig. 15

It was just extract from roots of *Dichroa Febrifuga* known under the name *Ch'ang- Shan*, which in the middle of the 20th century stimulated great interest in derivatives of quinazolinone. The extract, whose active component is alkaloid Febrifugin, showed high activity against ague incurred by microorganisms of *Plasmodium* Strain. Pure Febrifugin became registered as a drug, but its application is restricted because of relatively high toxicity and side effects (severe nausea).

As already marked above, the derivatives of quinazolin-4-one are potential medical drugs. They started to attract attention after the discovery of antimalarial activity of natural alkaloid Febrifugin, which (although clinically applied to a limited extent only) formed the starting point of further research. As early as 1952, Baker [33] synthesised Febrifugin analogues of as much as 100x higher activity. As active substances appeared 2-methyl-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one [34] and 2-ethyl-6-methyl-3-(2-methoxy-phenyl)quinazolin-4(3*H*)-one [35]. Other derivatives have been inactive against *Plasmodium* Strain. Along with the development of new antimalarials it was found that quinazolin-4-one derivatives show a general calming effect on CNS and possess hypnotic, sedative, analgesic, and antipyretic properties. First antipyretic [36] properties of 3-phenylquinazolin-4(3*H*)-one were discovered, which was found to be equal to aspirin in lowering the temperatures of febrile rats. Afterwards [37], 2,3-disubstituted quinazolin-4(3*H*)-ones were prepared and tested for hypnotic activity. It was found that for clinical application the best derivatives are 2-methyl-3-(2-methylphenyl)quinazolin-4(3*H*)-one – nowadays a well-known hypnotic with the generic name Methaqualone (Fig. 16) — and 2-methyl-3-phenylchinazolin-4(3*H*)-one.

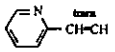
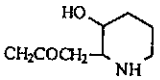
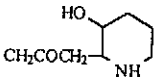
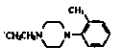


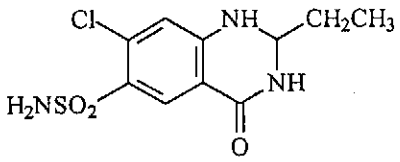
Methachalon

Fig. 16

Unfortunately [38], it was found later that 2-methyl-3-phenylquinazolin-4(3*H*)-one causes great hypothermia, hence its application as hypnotic was restricted. Structure/biological activity was generalised by Leszkovsky *et al.* [39] who found that hypnotic an anticonvulsant effect appears when derivatives are substituted at position 3 with aryl whereas derivatives substituted at position 3 with alkyl show analgesic, antipyretic and antiflogistic effects. In 1959, Cohen *et al.* accomplished an isosteric exchange of sulphuryl group by carbonyl group [40] in popular oral diuretic Chlorothiazide, and they found that newly synthesised compound showed greater diuretic activity than original Chlorothiazide. Further research in this field led to discovery and clinical tests [41] of 7-chloro-6-aminosulphonyl-2-ethyl-1,2,3,4-tetrahydroquinazolin-4-one which was adopted into clinical practice under generic name Quinethazone (Fig. 17).

Table II Registered preparations based on quinazolin-4-one

Generic name	R_1	R_2	R_3	R_4	R_5	Effect
Menilon	CH_3	4-Cl-C_6H_4	H	H	H	Tr
Mecloqualone	CH_3	2-Cl-C_6H_4	H	H	H	Hy, Se
SL-164	CH_3	4-Cl-2-CH_3-C_6H_3	Cl	H	H	Tr
Cloroqualone	CH_3CH_2	2,4-di-Cl-C_6H_3	H	H	H	At
Metolazone	CH_3	2-CH_3-C_6H_4	H	SO_2NH_2	Cl	Di, Ah
Tiacrilast	H	*trans*-CH=CHCOOH	H	CH_3S	H	Aa
Mefequizone	CH_3	4-C_2H_5O-C_6H_4	H	H	H	Tr
Diproqualone	CH_3	$CH_2CH(OH)CH_2OH$	H	H	H	An
EG 1088	CH_3NHCOO	2-Cl-C_6H_4	CH_3	C_2H_5OCO	CH_3	Ah
6-aminomethaqualone	CH_3	2-CH_3-C_6H_4	H	H	NH_2	Sr
HQ-335	CH_2F	2-CH_3-C_6H_4	H	H	H	Hy
Nitromethaqualone	CH_3	4-NO_2-2-CH_3O-C_6H_3	H	H	H	Hy
Methaqualone	CH_3	2-CH_3-C_6H_4	H	H	H	Hy
Piriqualone		2-CH_3-C_6H_4	H	H	H	Ak
QZ 16		2-CH_3-C_6H_4	H	I	H	Af
Febrifugine	H		H	H	H	Am, Ap
Centpiperalone		H	H	H	H	Hg
Halofuginone	H		H	Cl	Br	Apt
Paraquinsin		H	H	CH_3O	CH_3	Ah

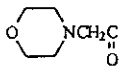
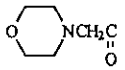


Quinethazone

Fig. 17

Simultaneously with the diuretic effect, antihypertensive effect was discovered and investigated in detail. Then 2-diethylamino-6,7-dimethoxyquinazolin-4(3*H*)-one was found as a very potent antihypertensive [42]. Besides the mentioned pharmacological properties, the derivatives of quinazolin-4(3*H*)-ones were tested with various degrees of success as antituberculotics, antiflogistics, antibacterial, antiviral and antitussic agents. The overall survey about pharmacological properties of quinazolin-4-ones (until 1970) is provided in a rewiew [43]. At present, about 25 preparations based on quinazolin-4-one are registered [6]: their generic names, formulas and effects on human organism are summarised in Tables II and III and Figs 18 and 19.

Table III Registered preparations based on 1,2,3,4-tetrahydroquinazolin-4-one

Name	R_1	R_2	R_3	R_4	R_5	Effect
HQ 275		CH_3	C_6H_5	H	H	Ch
Acemo-quinazone		H	C_6H_5	H	H	Ch
Quinethazone	H	CH_3CH_2	H	SO_2NH_2	Cl	Di, Ah
Fenquizone	H	C_6H_5	H	SO_2NH_2	Cl	Di
Metolazone	H	CH_3	2-CH_3-C_6H_4	SO_2NH_2	Cl	Di, Ah
NSC 145669	H	1-naphthyl	H	H	H	Al

The effect of compounds mentioned in Tables II and III is expressed by the following abbreviations: Aa – antiallergic, Af – antiflogistic, Ah – antihypertensive, Ak – anticonvulsant, Al–antileukemia, Am – antimalarial, An – analgesic, Ap – antineoplastic, Apt – antiprotozoal agent, At – antitussic, Di – diuretic, Hg – hypoglykemic, Ch – choleretic, Hy – hypnotic, Se – sedative, Sr – muscle relaxant, Tr – tranquillizer.

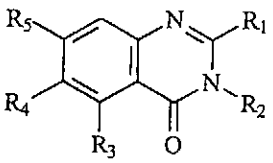


Fig. 18

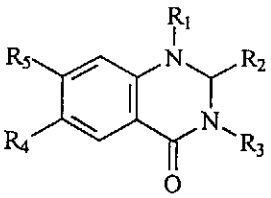


Fig. 19

Besides the pharmaceutical applications the quinazolin-4-one derivatives are also useful dyes and fungicides. In fact, there are azo dyes based on 2-sulphanyl-3-arylquinazolin-4(3*H*)-one carrying amino-group. Passive components used for this purpose could be some substituted naphtols [44]. Another variant [45] of azodyes based on quinazoline-4-one derivatives is depicted in Fig. 20.

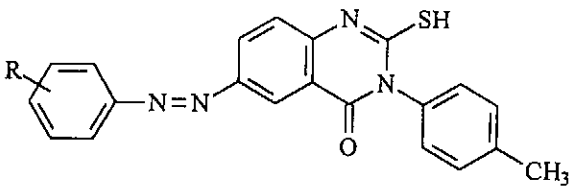


Fig. 20

Practically applied [46] to cornfield protection is Fluquinconazole (produced by AgrEvo-GmbH under trade names Castellan, Vista), which blocks the biosynthesis of ergosterol.

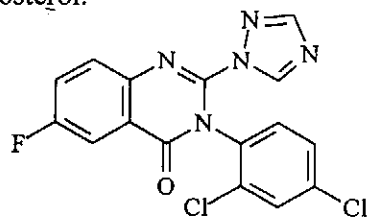


Fig. 21 **Fluquinconazole**

Derivatives of quinazolin-4(3*H*)-one substituted by aroyl- or heterocyclyl -group at position 6 show also fungicidal and bactericidal effects [47,48].

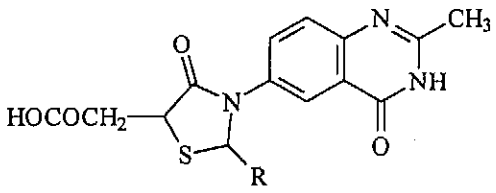
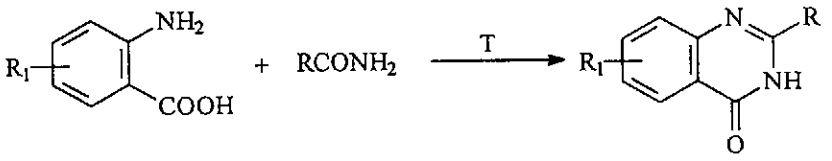


Fig. 22

Synthesis of Quinazolin-4-One Skeleton

The most common and the oldest of them is the synthesis of quinazolin-4(3*H*)-one by a condensation reaction (Niementovski reaction) of substituted anthranilic acids [3,33] or their esters [49] with alkanamides (Fig. 23). The reaction is usually carried out by heating of the reaction mixture at 120 °C.



R = H, alkyl
R_1 = H, alkyl, halogen, NO_2

(R = R_1 = H ; T = 120 °C, 2 hrs, 95%)

Fig. 23

A higher temperature and longer time are necessary for the preparation starting from substituted anthranilic acids than those in the case of formamide as depicted in Fig. 23. This method is useless for preparation [50] of 2-arylquinazolin-4(3H)-ones from the corresponding arylamides. However, when we replace arylamide by corresponding arylthioamide or imidoester (Fig. 24), the required 2-arylchinazolin-4(3*H*)-ones are formed in yields of 50 – 70%. An analogous method starting from imidoformic acid salt instead of imidoester was recently used [51] for instance in synthesis of 7-fluoroquinazolin-4(3*H*)-one. The reaction was carried out in 2-methoxyethanol as a solvent by refluxing for 18 hours. The yield was about 90%, even higher than in the case of the imidoester.

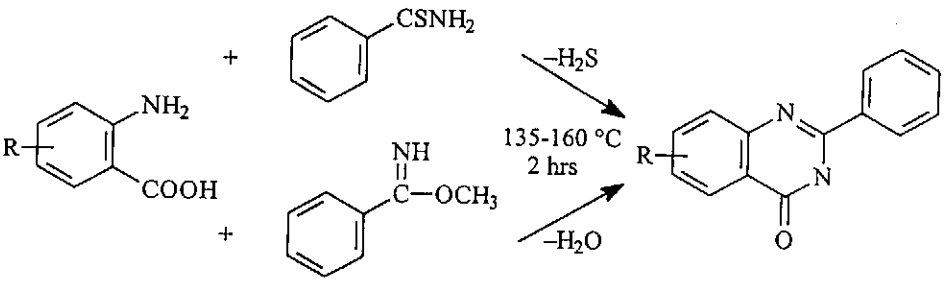


Fig. 24

A somewhat different approach to the synthesis was used by Bogert [52]: although he also started from substituted anthranilic acid, he did not use the direct reaction with amide but prepared the benzo[*d*](1,3)oxazin-4-one derivative by the reaction with acetic anhydride in the first step and then converted this derivative into quinazolin-4(3*H*)-one derivative by the reaction with an amine or ammonia (Fig. 25). Since both the reaction steps proceed with high yields and the realisation is technically simple, this method has been adopted most frequently so far.

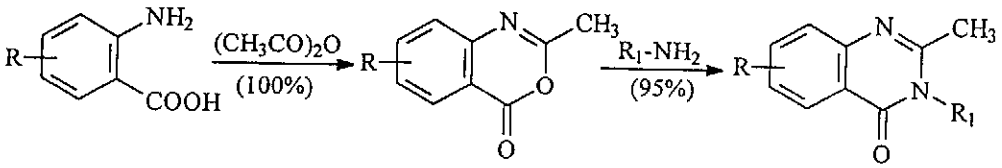
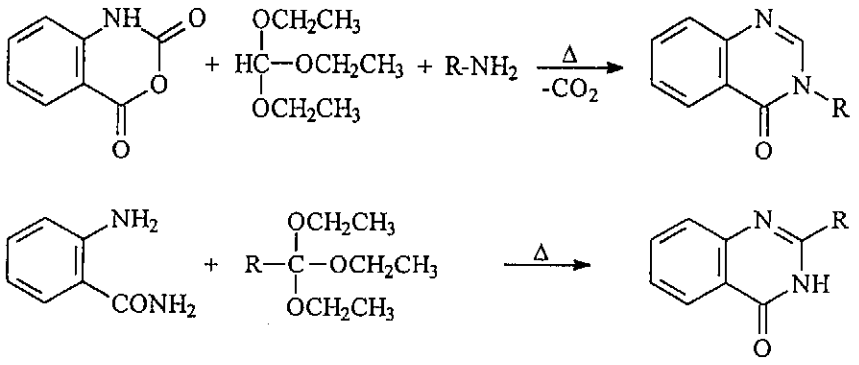


Fig. 25

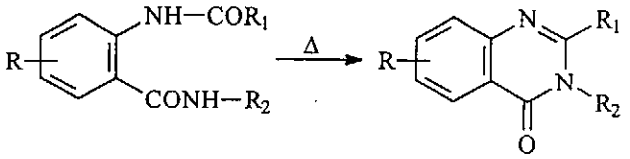
Another variant of synthesis [53] was described by Clark and Wagner. It consists in the reaction of isatoic anhydride (benzo[*d*](1,3)oxazin-2,4-dione) with alkylamines and arylamines in triethylorthoformate (Fig. 26). On heating for 2 – 6 hours, the yields of the reaction are about 65 – 70%. The method can be modified by using of subtituted anthanilamides and triethyl-orthoformate [54] (Fig. 26) or other ortho-esters [55]. Ethanol or ethylenglycol are used as solvents. Unfortunately the yields of this reaction are rather lower, about 50 – 70%.

Suitable starting substances are also *N*-acylanthranilamides [56] or their derivatives, which by heating up to almost their melting point undergo a process of ring closure to give the required derivatives of quinazolin-4(3*H*)-one (Fig. 27). The cyclisation can also be achieved by action of aqueous sodium hydroxide solution [57] or by refluxing with a solution of ammonia in pyridine [58].



R = H, alkyl, aryl

Fig. 26



R = H, alkyl, halogen, NO_2
R_1 = H, alkyl, aryl
R_2 = H, alkyl, aryl

Fig. 27

Another variant of this reaction consists application of nitriles as starting compounds. It is possible to start either from anthranilonitriles or aliphatic/ aromatic nitriles. The first method starting from anthranilonitrile or from its *N*-acyl derivative consists in the reaction with anhydride [59]. The reaction takes place in a sealed tube at 170 – 180 °C, or in the reaction with mixture of hydrogen peroxide and aqueous solution of sodium hydroxide [59] at boiling point or with an aqueous solution of hydrochloric acid [60].

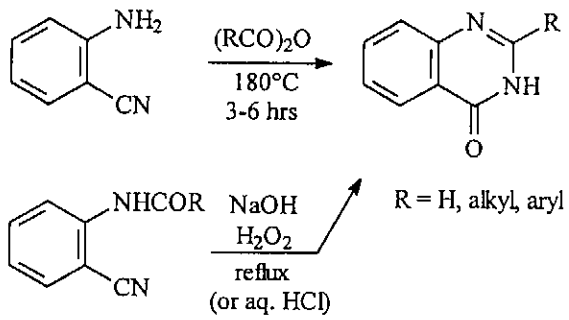


Fig. 28

The second method [61] starts from *N*-acyl-anthranilic acid and aliphatic or aromatic nitrile, which by heating gives the quinazolin-4(3*H*)-one derivatives too (Fig. 29). Generally two products can be formed. Product I is formed in preference, so the synthetic usefulness of this reaction is rather low.

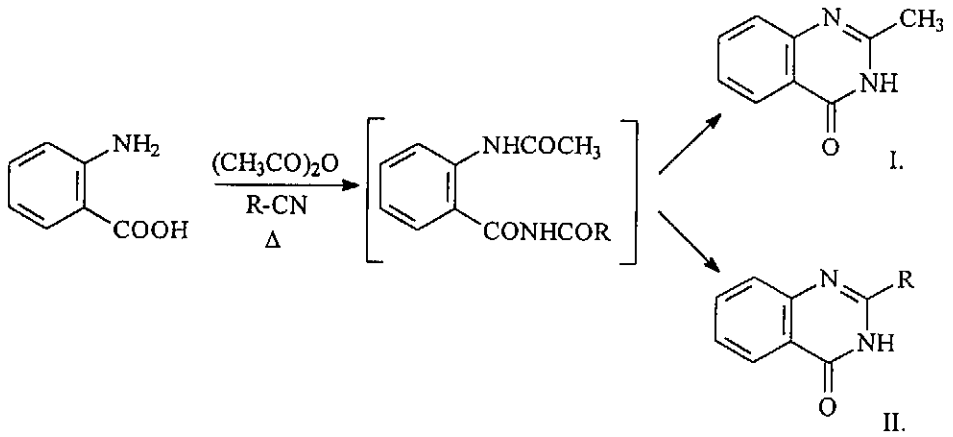
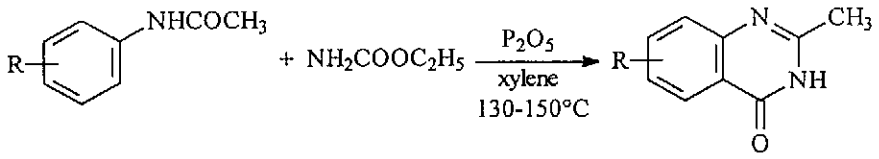


Fig. 29

A generally useful method giving quinazolin-4(3*H*)-one (Fig. 30) derivatives starts from substituted acetanilides and ethyl carbamate [62] in the presence of phosphorus pentoxide in toluene or xylene. Reaction is carried out by three hour's heating at 130 – 150 °C. If we start from aniline instead of acetanilide, it is necessary to use ethyl-*N*-acetyl carbamate for successful cyclisation. However, this variant is less convenient.



R = H, alkyl, halogen

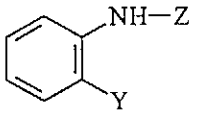
Fig. 30

Also it is possible [63] to prepare 2-phenylquinazolin-4(3*H*)-ones from anthraniloamide and benzaldehyde in *N,N*-dimethylacetamide. The resulting Schiff base is cyclised at 150 °C by treating with sodium hydrosulphite. Another [64] method consists inreaction of anthranilic acid *N,N*-diethylamide with benzonitrile in the presence of butyl-lithium as a base.

At the end of this chapter it must be stated that the enumeration of these methods is not complete, because there are many alternatives to each described method differing in minor details.

Mechanisms of forming Quinazolin-4(3H)-one Cycle

Almost all the depicted methods of preparation quinazolin-4(3*H*)-one derivatives show a common structural feature, namely the presence of groupings (Fig. 31) of substituted amino-group (alkylamino, acylamino) near a functionalised of carboxylic group (single acid, ester, amide, nitrile, anhydride).



Y = COOH, $CONH_2$, CN, COOR
Z = alkyl, aryl, alkanoyl, aroyl

Fig. 31

Therefore, it is obvious that all the cyclisation reactions should show common features. The first two studies [59,65] concerning chemical behaviour of 2-acylaminobenzonitrile in aqueous solutions of sodium hydroxide and in the presence of hydrogen peroxide were carried out at the beginning of the last century. It was found that this reaction involves the formation of anthraniloamide (hydrogen peroxide anion is the attacking agent), which subsequently undergoes a specific base catalysed cyclisation to give quinazolin-4(3*H*)-one (Fig. 32). The mechanism thus formulated was proved in the later communication as well [66].

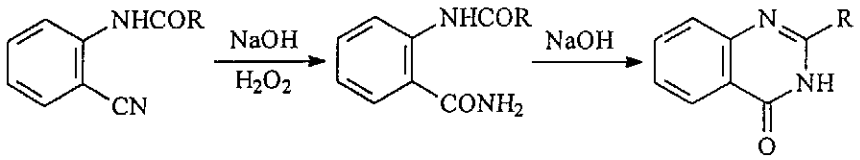


Fig. 32

Another mechanistic study [49] of formation quinazolin-4(3*H*)-ones was published in 1943 and concerned the reaction between anthranilic acid and alkanamides (so-called Niementowski reaction). It was proved that the reaction proceeds *via* intermediates, involving ammonium 2-acylaminobenzoate and 2-acylaminobenzoic acid amide. The amide then undergoes cyclisation reaction.

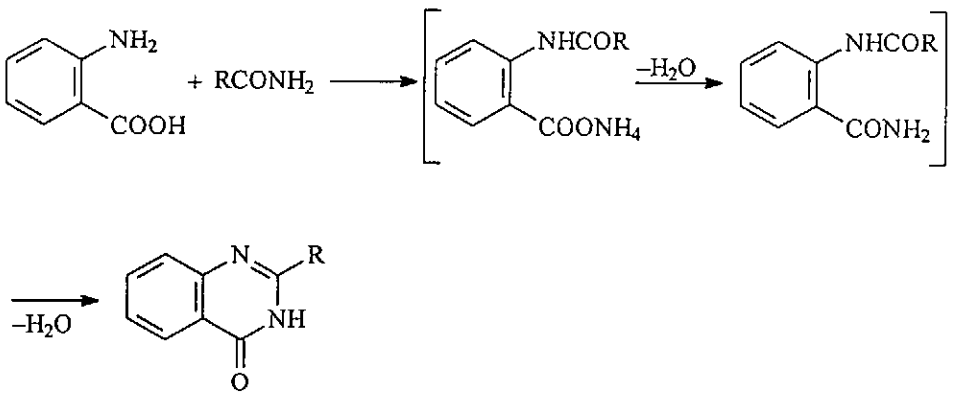


Fig. 33

Recently the problem of cyclisation reaction of substituted 2-benzoylaminobenzamides was solved by Gardner *et al.* [67], who investigated particular parts of the mechanism. On the basis of a kinetic study they suggested the following reaction scheme valid for cyclisation reaction in basic medium (Fig. 34).

It was found that the rate-limiting step consists in a specific base catalysed cyclisation. The observed rate constant non-linearly increases (formation of the reactive anion) to a maximum value and then remains unchanged or slightly decreases (the formation of non-reactive dianion makes itself felt). All the substituents adopted obeyed the Hammett correlation.

Also in the case of the reaction of substituted isatoic anhydrides with amines (Bogert reaction) it was anticipated that 2-acylaminobenzamide occurs in the reaction pathway as an intermediate. However, Errede [68,69] proved that the re-

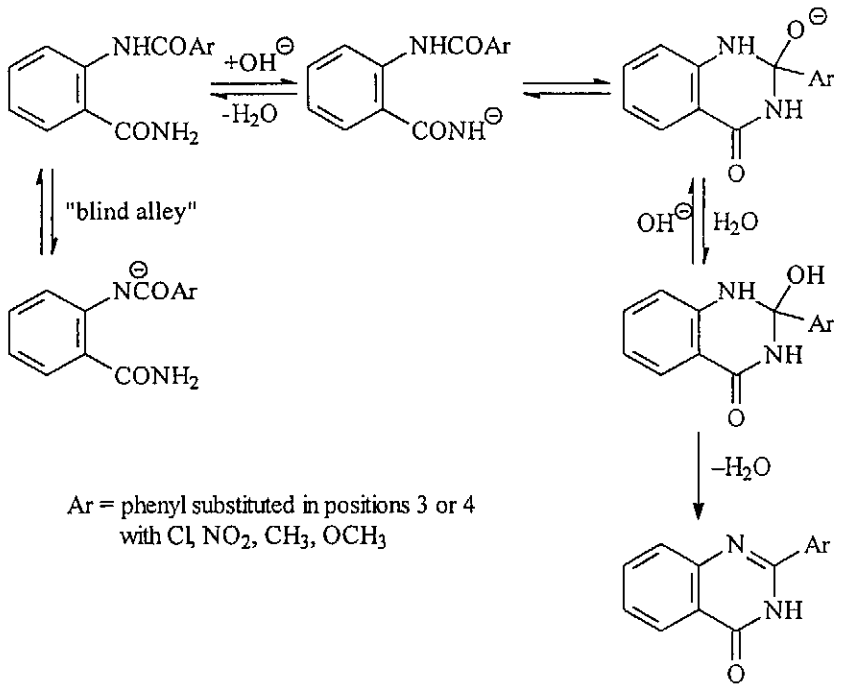


Fig. 34

action does not take place only in terms of formation of 2-acylaminobenzamide but considerable amount of internal amidine salt is formed as well. This salt by heating at 130 °C gives corresponding quinazolin-4(3*H*)-one derivative. For instance, in the case of reaction of 2-methyl-3,1-benzo[*e*]oxazin-4-one with excess aniline (without any solvent), 54% of amidine salt, 30% 2-methyl-3-phenylquinazolin-4(3*H*)-one and 15% anthranilic acid is formed (Fig. 35). On the other hand, in the case of 2-phenyl-3,1-benzo[*e*]oxazin-4-one almost quantitative yield of 2-benzoyl-aminobenzamide was obtained.

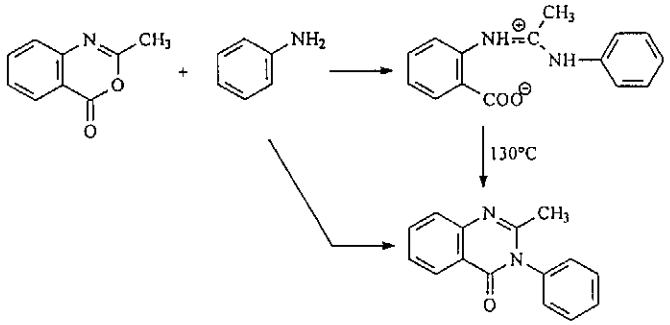
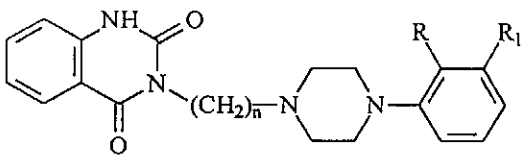


Fig. 35

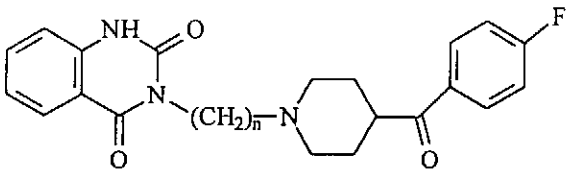
Practical Applications

In analogy to quinazolin-2(1*H*)-one and quinazolin-4(3*H*)-one derivatives, the leading practical application of quinazolin-2,4(1*H*, 3*H*)-diones is in medicine and pharmacology. First in 1965, the antihypertensive and sedative effects of 3-(4-aryl-1-piperazinylalkyl)quinazolin-2,4(1*H*, 3*H*)-diones were found [70], thereafter some of them were adopted into the clinical practice. In some cases, an anti-inflammatory effect was observed as well. Some derivatives show a strong effect to brain receptors (serotonine receptors especially), hence they can be applied in psychotherapy. A survey [6] of quinazolin-2,4(1*H*,3*H*)-dione derivatives used in clinical practice is presented in Fig. 36.



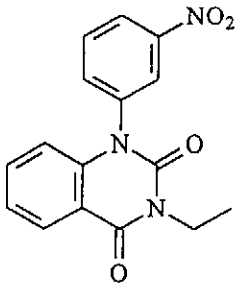
R = H, n = 3 : **Cloperidone**
R_1 = Cl sedative
tranquiliser

R = C_3H_7S, n = 4 : **Tioperidone**
R_1 = H antipsychotic
neuroleptic



n = 2 : **Ketanserin**
antihypertensive
serotonine antagonist

n = 4 : **Butanserin**
antihypertesive



Nitroquazone (antidepressant, antiflogistic)

Fig. 36

Sporadically it is possible to find some references about applications outside medicine. Some quinazolin-2,4(1*H*,3*H*)-diones are used as a azo dyes [71] or herbicides [72].

The classical method of preparation of quinazolin-2,4(1*H*,3*H*)-dione derivatives consists in the reaction of anthranilic acid with urea [73] at melting temperature.

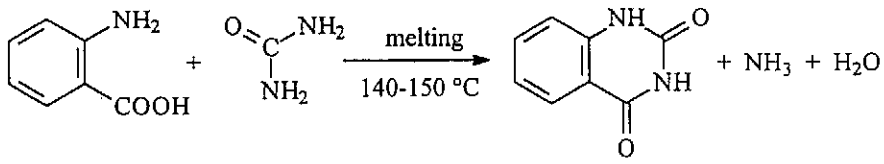
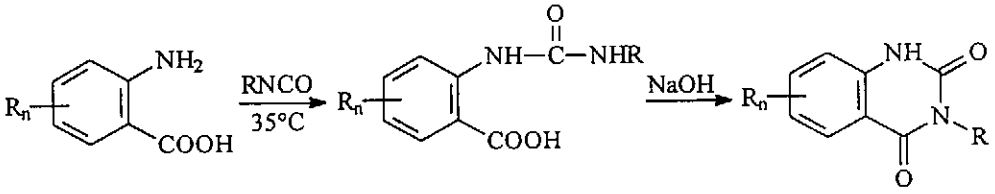


Fig. 37

Another synthetic approach involves substituted anthranilic acid (or its esters, amides and nitriles) and HOCN [74] or alkyl [75] and aryl isocyanates [76]. The reaction takes place in two steps. As an intermediate, the corresponding urea derivative was found, which readily cyclises into substituted quinazolin-2,4(1*H*,3*H*)-dione in basic or acidic medium.



R_n = H, alkyl, alkoxy, halogen
R = H, alkyl, subst. phenyl

Fig. 38

Methyl ester of *N*-methylanthranilic acid also cyclises [77] by treating with dimethyl-(trichloromethyl)amine in dichlorethane as the solvent.

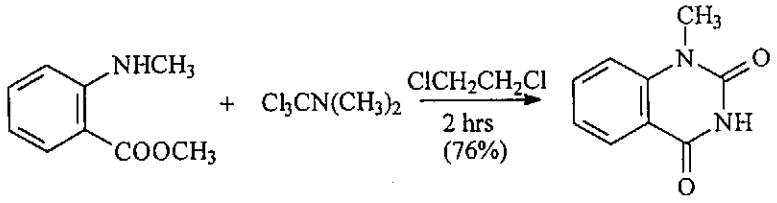


Fig. 39

The starting component can be represented by isatoic anhydride [53] (3,1-benzoxazin-2,4-dione), which reacts with ethylcarbamate to give quinazolin-2,4(1*H*, 3*H*)-dione in low yield (about 35%). When ethylcarbamate is replaced by substituted phenyl isocyanate, a considerably higher yield is obtained (about 80%).

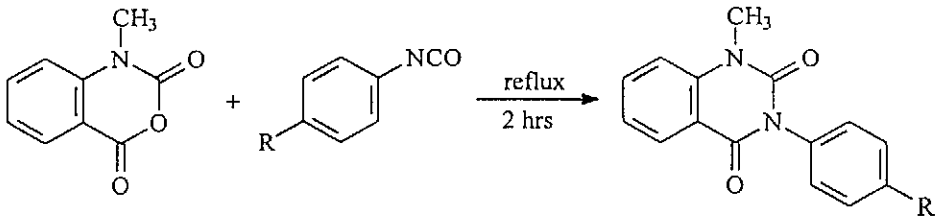


Fig. 40

An interesting reaction consisting in enlargement of five-membered cycle was described by Jacini [79]. The yield of this reaction is about 80% as well.

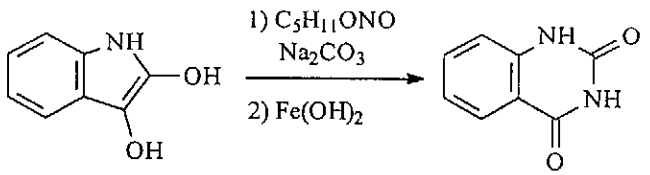


Fig. 41

Another method [80] leading to the enlargement of a cycle was published in 1958: it involves the reaction of *N*-methansulphonyloxyftalimide with aqueous solution of ammonia .

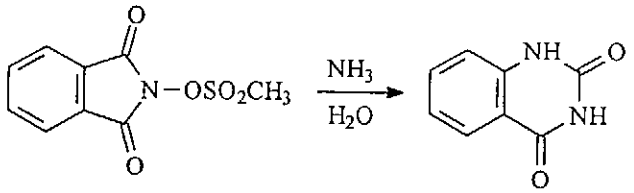


Fig. 42

It is possible to obtain the same product by Hoffmann rearrangement [81] from 1,2-benzendicarboxamide. The corresponding 2-isocyanatobenzamide was found as an intermediate which readily cyclises into quinazolin-2,4(1*H*,3*H*)-dione.

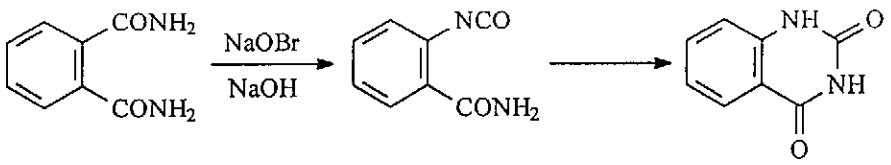


Fig. 43

Acknowledgements

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