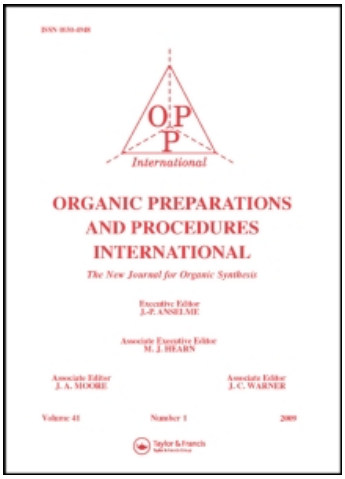

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RECENT STUDIES ON THE MODIFIED NIEMENTOWSKI 4-QUINAZOLONE SYNTHESIS. A REVIEW

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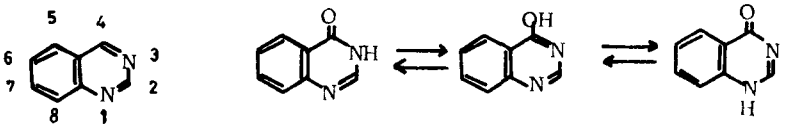
INTRODUCTION

Several reviews[1-5] dealing with the quinazolone ring system have been published. Numerous 4-quinazolones, particularly those with 2,3-disubstituents, have been prepared for biological activity screening. This review summarizes the synthesis of such 4-quinazolones by the modified Niementowski reaction for the period 1964-1971.

I. STRUCTURE AND NOMENCLATURE

The quinazolines having a hydroxy group in the 2 or 4 position are tautomeric[4] with the corresponding ketodihydroquinazolines. Various data[6,7] indicate that 4-hydroxyquinazolines exist as an equilibrium mixture of 2, 3, and 4, with the lactam 4 being the least favored,[8] and form 2 the most favored.



1 quinazoline; 2 4-quinazolone; 3 4-hydroxyquinazoline; 4

Thus 4-hydroxyquinazoline, tautomeric with 4-keto-3,4-dihydroquinazoline, is commonly named 4(3)-quinazolone, or simply 4-quinazolone. Although other names, such as 4-oxo-quinazoline, 4(3H)-quinazolinone and various systems of numbering have previously been used, the name 4-quinazolone which is today universally accepted to denote 4-keto-3,4-dihydroquinazoline, will be utilized throughout this review.

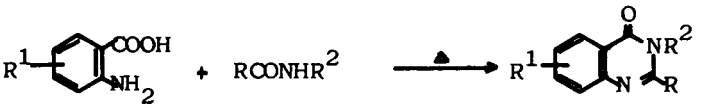
II. PREPARATION OF 4-QUINAZOLONES

The majority of the syntheses of 4-quinazolones essentially proceed from anthranilic acids or derivative thereof. The most common route to 4-quinazolone is the thermal condensation of anthranilic acid with amides, a reaction originally described by Niementowski[9] in 1895 which today bears his name. Since a study of modifications and extensions of the Niementowski synthesis by Meyer and Wagner,[10] this reaction has undergone many adaptations and has been used extensively. A mechanism proposed by Bogert and Gotthelf[11] has had some experimental support[10] but it is still not completely clear. The numerous variants which have been reported may be classified into eight categories according to the types in the components undergoing condensation.

1. Reaction of Anthranilic Acids with Amides, Thioamides, and Amidines

This is Niementowski's reaction in a limited sense. This procedure has been applied to numerous substituted anthranilic acids (5) with amides,[9,10] thioamides[12,13] or amidines[10] to afford the corresponding 4-quinazolones (6) substituted on the benzene ring. Thus, 2-ethyl-4-quinazolones

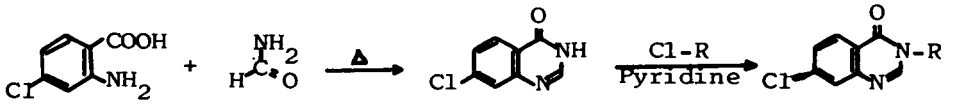
were prepared[13,14] by the similar procedure from propionamide with anthranilic acid.



5 6

By heating anthranilic acid (5) (R^1 = H) in a open container with excess formamide (R = R^1 = R^2 = H) at 120°, water is expelled and 4-quinazolone (6) (R = R^1 = R^2 = H) is produced in 90% yield. It is inadvisable to use more than a 4-fold excess of formamide; best results are obtained when the mixture is heated at 120-130° for 2 hrs followed by additional heating at 170-180° for 2 hrs.[4]

3-Substituted derivatives of 7-chloro-4-quinazolone (9) were prepared[15] by cyclization of 4-chloroanthranilic acid (7) with formamide at 130-177° and subsequent treatment of 8 with p-bromobenzyl chloride, p-methoxycinnamoyl chloride, or benzenesulfonyl chloride in pyridine or sodium ethylate.

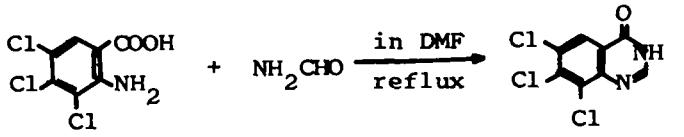


7 8 9

R: acyl, aralkyl

In a similar procedure, Maillard and his co-workers[16] reported that various 4-quinazolone derivatives substituted on the benzene ring were synthesized. Compounds 11 and 12 were similarly prepared.[17] Thus, a solution of 3,4,5-trichloroanthranilic acid (10) and formamide dissolved in dimethylformamide (DMF) is refluxed for 16 hrs to yield

6,7,8-trichloro-4-quinazolone (11) in 30% yield.



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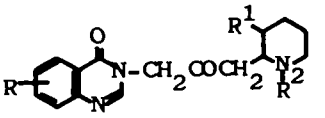
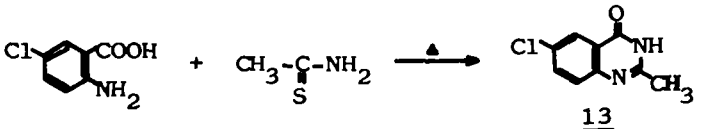


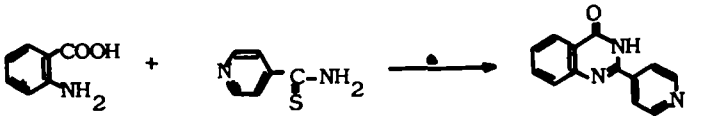
12

The condensation of anthranilic acids with thioacetamide at 180° gave 2-methyl-4-quinazolone (13).[13]



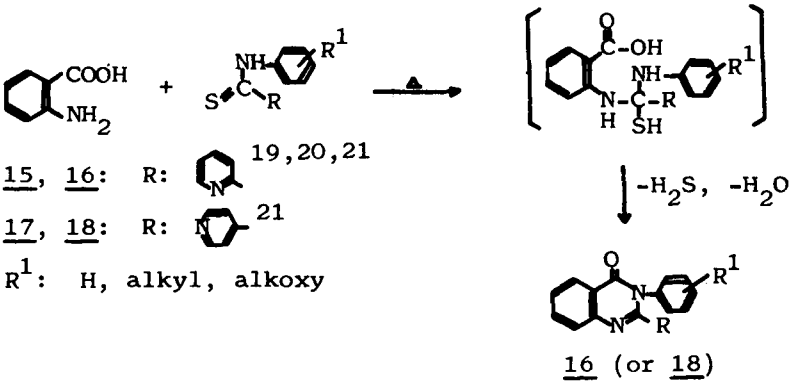
13

Similarly, anthranilic acid and thioisonicotinamide upon heating at 150-160° for 1 hr, gave 2-(4-pyridyl)-4-quinazolone (14).[18]

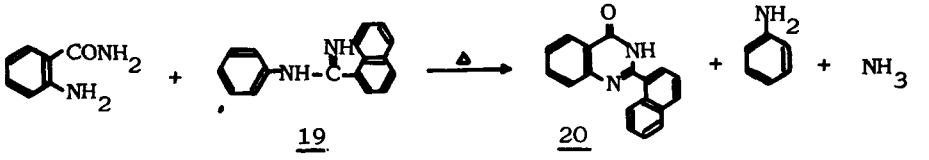


14

Anthranilic acid heated with 2-thiopicolino-R-substituted anilides (15) in the presence of methyl anthranilate gave the corresponding 2-(2-pyridyl)-3-R^1-substituted 4-quinazolones (16).[19,20,21] In a similar procedure, 4-thiopicolino-R^1-substituted anilides (17) gave corresponding 4-quinazolones (18).[21] In certain cases, acid amides can be replaced by the more reactive amidines.

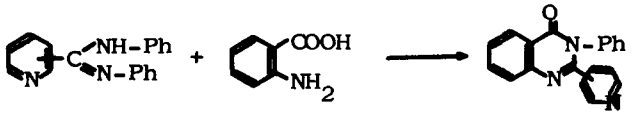


Condensation of N-phenylamidines with o-aminobenzamides yields 4-quinazolones.[22] Thus, N-phenyl-α-naphthamidine (19) and o-aminobenzamide when heated at 200-220° for 11 hrs afforded 2-(α-naphthyl)-4-quinazolone (20).



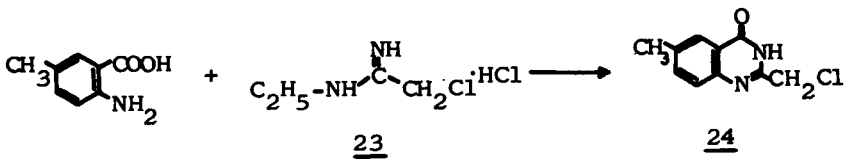
19 20

Similarly, N,N'-diphenyl-picolylamidine (21) and anthranilic acid gave the corresponding 4-quinazolone (22) in nearly the same yield[21] as with the procedure using thiopicolinoanilide (15) (see above).



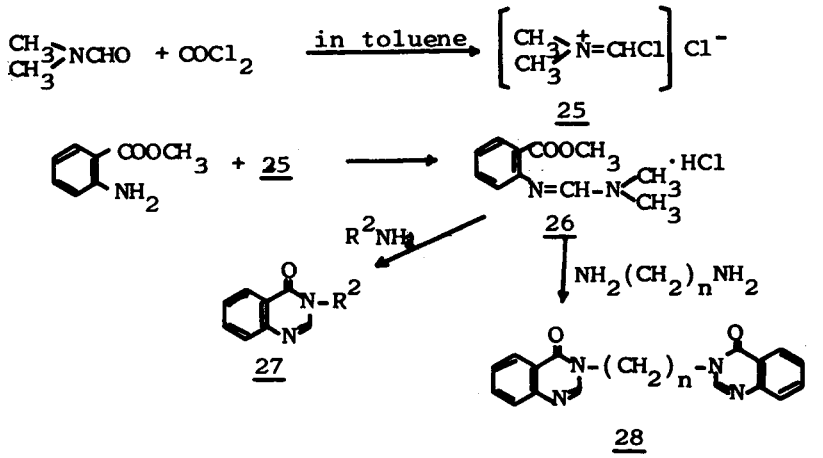
21 22

2-Chloromethyl-6-methyl-4-quinazolone (24) is prepared[23] in a 36% yield by treatment of 5-methylanthranilic acid with hydrochloride of N-ethylchloroacetamidine (23) in ethanol at 0°.



23 24

Similarly, the hydrochloride of N,N-dialkyl-N'-(2-alkoxycarbonylphenyl)formamidine (26) was treated with amine or diamine to give 27 or 28, respectively.[24] Thus, a solution of methyl anthranilate in chloroform was added to dimethylformiminum chloride (25) (obtained[24] in quantitative yield from DMF with phosgene in toluene) in chloroform at 40° and the solution was evaporated to give 26 in 98% yield. Treatment of 26 with amines in methanol at 20° gave 27 and 28 with diamines.[24]



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26

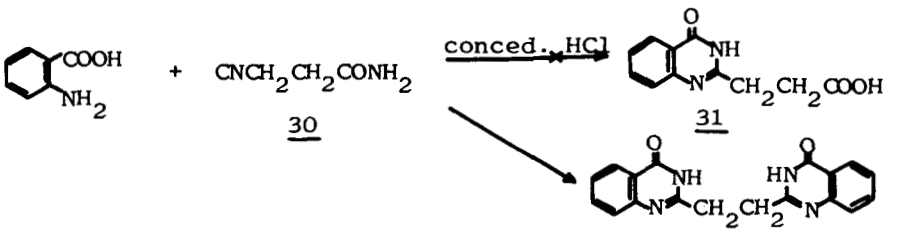
27

28

Heating anthranilic acid with a nitrile resulted also in the formation of 4-quinazolones. Bogert and co-workers[25] determined the relative amount of each product obtained using several combinations of acyl groups and have postulated that the reaction proceeds via the corresponding amide intermediates (29) as shown.

29

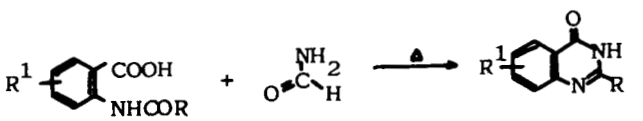
Yanai and his group[26] have reported that attempts to obtain 4-quinazolone-2-propionic acid (31) directly by the reaction of anthranilic acid and 3-cyanopropionamide (30) were unsuccessful and the product obtained being instead 2,2'-ethylenedi-4-quinazolone (32).



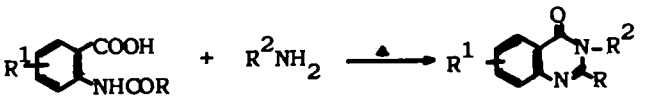
30 31 32

2. Reaction of N-Acyl Anthranilic Acids with Amines

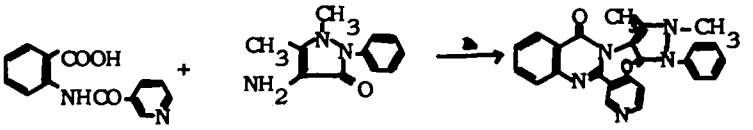
A modified Niementowski 4-quinazolone synthesis involves heating N-acylanthranilic acids with an excess of formamide at various temperature to yield the corresponding 2-substituted 4-quinazolones.[27,28] A mechanism for this reaction has been proposed.[27]



2,3-Disubstituted 4-quinazolones may also be obtained directly from the corresponding N-substituted anthranilic acids by heating with various amines.[29,30]

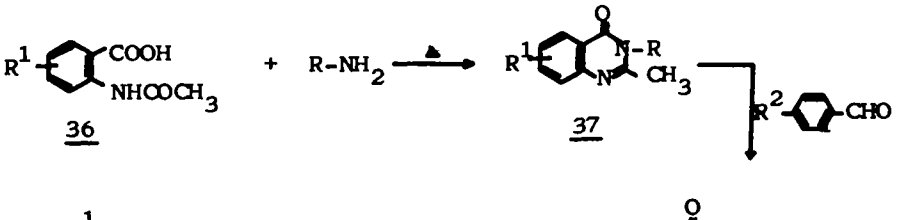


Dory and Duklics[31] reported that the thermal condensation of 4-aminoanthipyrine (34) with N-nicotinoylanthranilic acid (33) gave 2-(3-pyridyl)-3-(4-anthpyrinyl)-4-quinazolone (35).



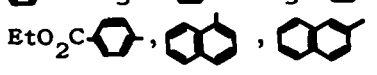
33 34 35

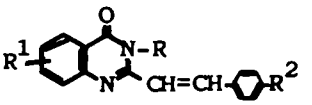
Similarly, 4-quinazolones (37) were prepared by heating substituted N-acetylanthranilic acid (36) with various amines; the effect of substituents on the intensity and position of the fluorescence of 4-quinazolones (37 and 38) was investigated.[32] The appropriate 37 was condensed with aromatic aldehyde to give 38.[32]



36 37

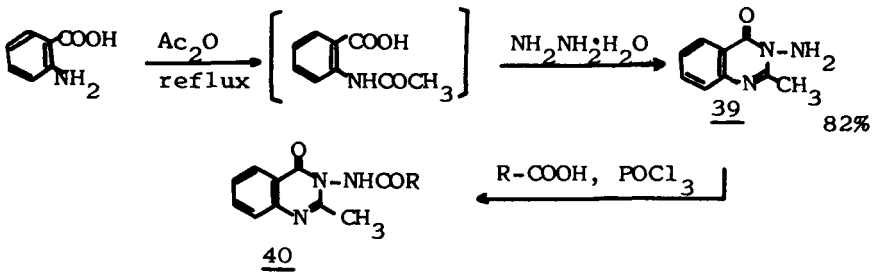
R^1: 6-NO_2, 7-NO_2, H

R : 

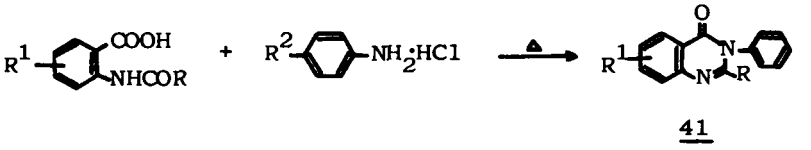


38

A new and simple "one-pot" method[33] for the preparation of 3-amino-4-quinazolones is outlined in the equation below.

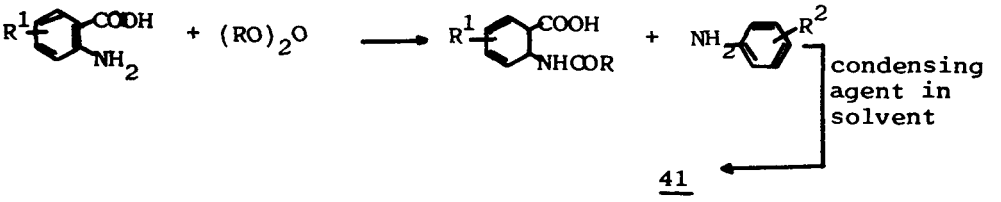


2-Methyl- or 2-phenyl-3-substituted 4-quinazolones (41) were prepared by heating N-acetyl- or N-benzoylanthranilic acid with the hydrochloride of various aromatic primary amines[34] at 170° for 5 min.

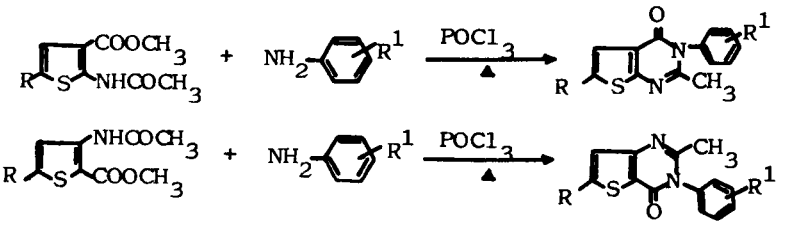


In most cases, this reaction was carried out in the presence of condensing agents such as phosphorus trichloride, phosphorus oxychloride, thionyl chloride or phosgene.

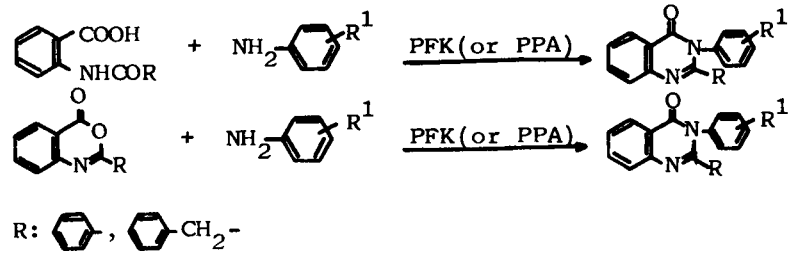
N-Substituted anthranilic acids in xylene or toluene could be made to react with substituted anilines in the presence of condensing agent to afford the corresponding 4-quinazolones.[35-54]



Methyl acetylaminothiophenecarboxylate and a substituted aniline in toluene were refluxed with phosphorus oxychloride for 0.75-24 hrs to give thiophene analogs of 4-quinazolone-like compounds.[55]



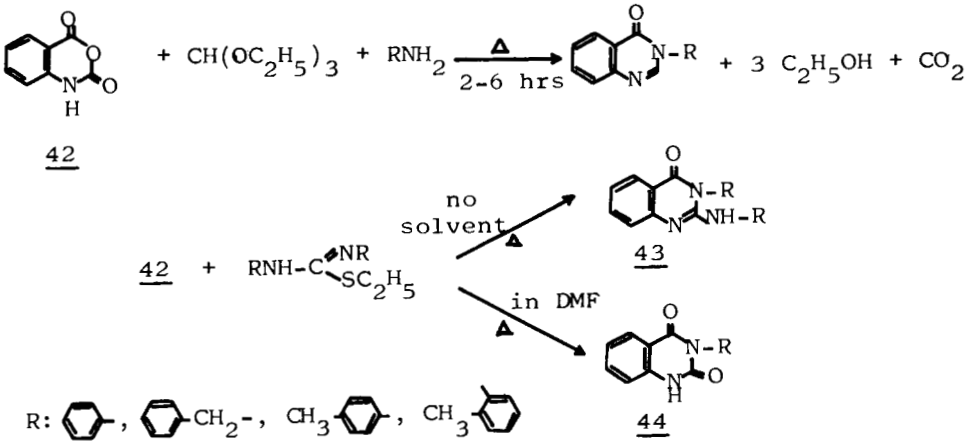
Petyunin and Kozhevnikov[56] have reported the synthesis of 2-methyl-3-(o-tolyl)-4-quinazolone using PFK (a blend of 85% phosphoric acid with phosphorus pentoxide) as a condensing agent for the cyclization of N-acetylanthranilic acid and o-toluidine. In this reaction, polyphosphoric acid[57] could also be used as condensing agent for the condensation and the cyclization steps.



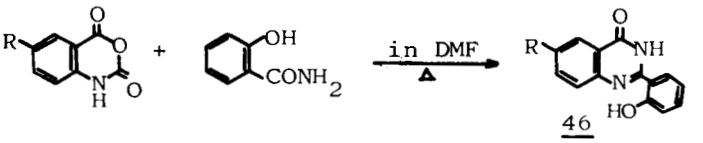
3. Reaction of Isatoic anhydride with Primary Amines

In specific cases, anthranilic acid can be replaced by the more reactive isatoic anhydride (42). Clark and Wagner[58] have reported the use of 42 for the synthesis of 3-substituted 4-quinazolones. When heated with ethyl orthoformate and primary amine, 42 gave 3-substituted 4-quinazolones;[59] upon

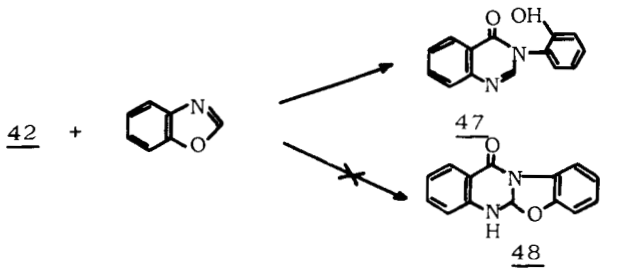
treatment with isothiourea in the absence of solvent, 42 afforded the 2-anilino compound (43);[60] however, a similar reaction in boiling DMF gave 44.



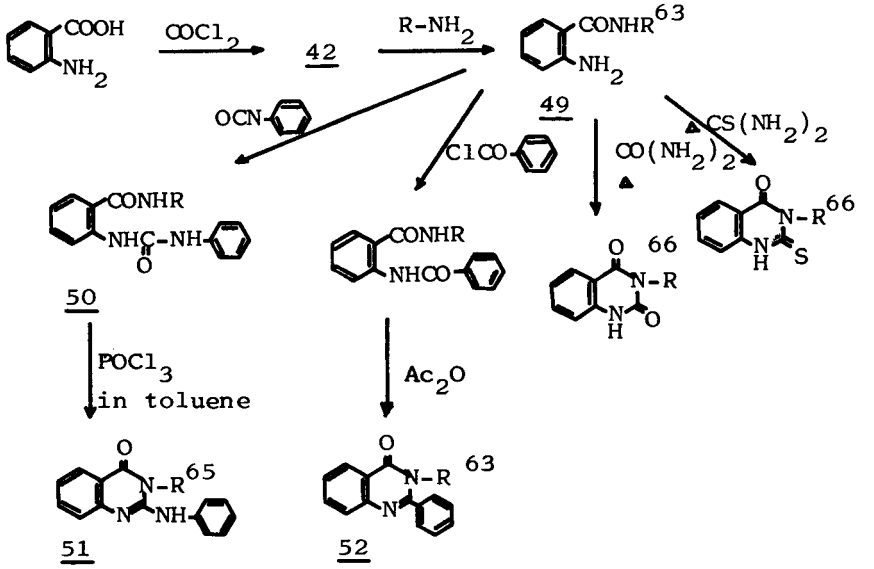
2-(o-Hydroxyaryl)-4-quinazolone (46)[61] was prepared from 5-substituted isatoic anhydride (45) with o-hydroxybenzamide in DMF as solvent at 90-100° in 81% yield (when R = H).



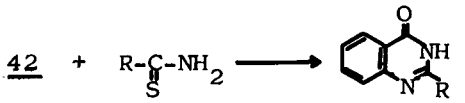
Reaction of 42 with benzoxazole gave 3-phenyl-4-quinazolone (47),[62] and not the expected adduct (48)



Reaction of 42 with amines afforded o-amino-N-substituted benzamides (49)[63] by a procedure described by Clark and Wagner[58] and by Klosa.[64] Compound 49 condensed readily with phenylisocyanate to give 50.[65] The corresponding 2-anilino-3-aryl-4-quinazolone (51) on cyclization of 50 with phosphorus oxychloride in toluene. Similarly, benzoylation of 49 with benzoyl chloride followed by cyclization with acetic anhydride gave 2,3-disubstituted 4-quinazolones (52).[63]

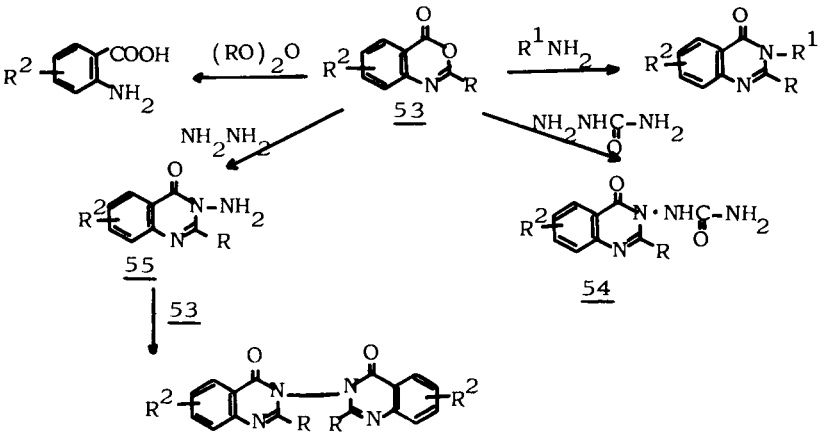


Reaction of 42 with thioamides afforded 2-substituted 4-quinazolones.[67] Extensions of this method to other 4-quinazolones have been reported.[47]



4. Reaction of Acylanthranils with Amines

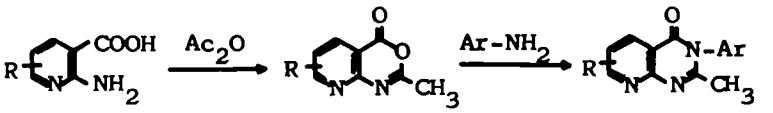
2-Substituted 4-oxo-4H-3,1-benzoxazine (53: the so-called acylanthranil) can easily be prepared by heating anthranilic acid or a substituted anthranilic acid with an acid anhydride. Bogert and his co-workers[68,69] have studied the reaction of 53 with amines and have shown it to proceed through the N-acylanthranilamides. In this reaction, a wide variety of amines has been successfully employed: these include aromatic,[29,47,57,70-75,84,85] aliphatic,[63,71,72,75-80,88-90] and heterocyclic amines,[29,81-83] semicarbazide and hydrazine.[79] Reaction of 53 with semicarbazide gave a 3-quinazolonyl urea (54); with hydrazine, the reaction can be controlled to involve either one (55) or two (56) equivalents of 53.



56 3,3'-bis(2-R-4-quinazolonyl)

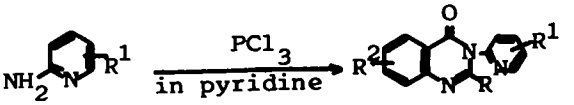
8-Aza-4-quinazolone (pyrido[2,3-d]pyrimidine) (59) was prepared[86] by condensation of 8-aza-acetanthranil (58) generated from 2-amino-nicotinic acid (57) and acetic anhydride)

with the appropriate amine.



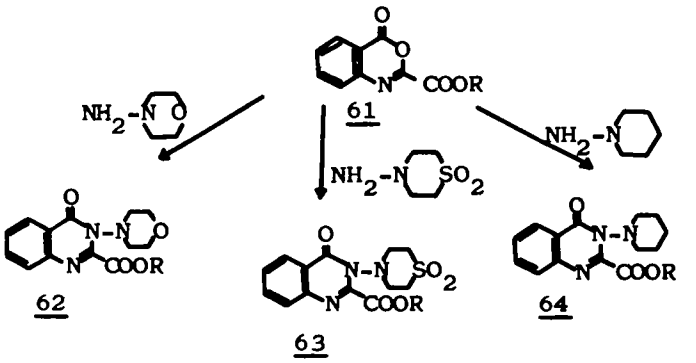
57 58 59

Reaction of 53 with substituted 2-aminopyridine in phosphorus trichloride and pyridine afforded 60.[87]



60 60% (when R : CH_3, R^1 : 3-CH_3, R^2 : H)

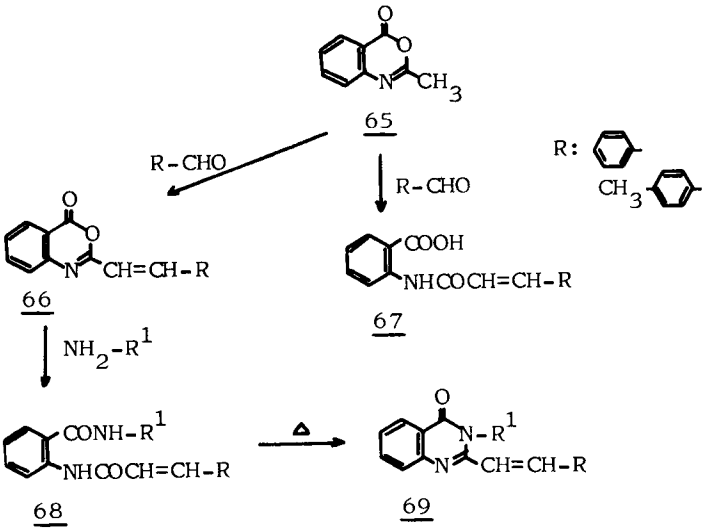
2-Carboalkoxy-4-oxo-4H-3,1-benzoxazinines (61) react with various heterocyclic amines to afford 2-carboalkoxy-3-substituted 4-quinazolones (62-64).[91]



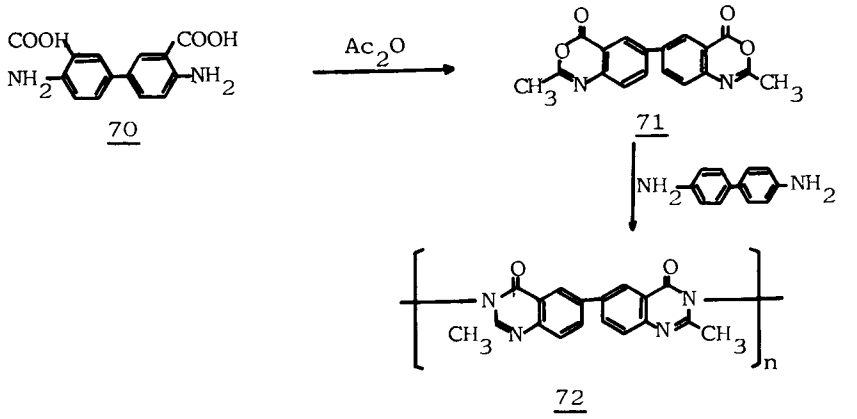
62 63 64

Thermal condensation[92] of acetylanthranil (65) with aromatic aldehydes gives the corresponding styryl derivatives (66) on heating for 30 min. by using a free flame. However, refluxing the same reagents for 10 min. gives N-substituted anthranilic acids (67). When refluxed for 6 hrs with amines in ethanol, 66 gave the o-arylaminobenzamide derivatives (68),

which could be cyclized to the corresponding 2-styryl-3-alkyl-4-quinazolones (69) by heating for 20 min. above their mp.



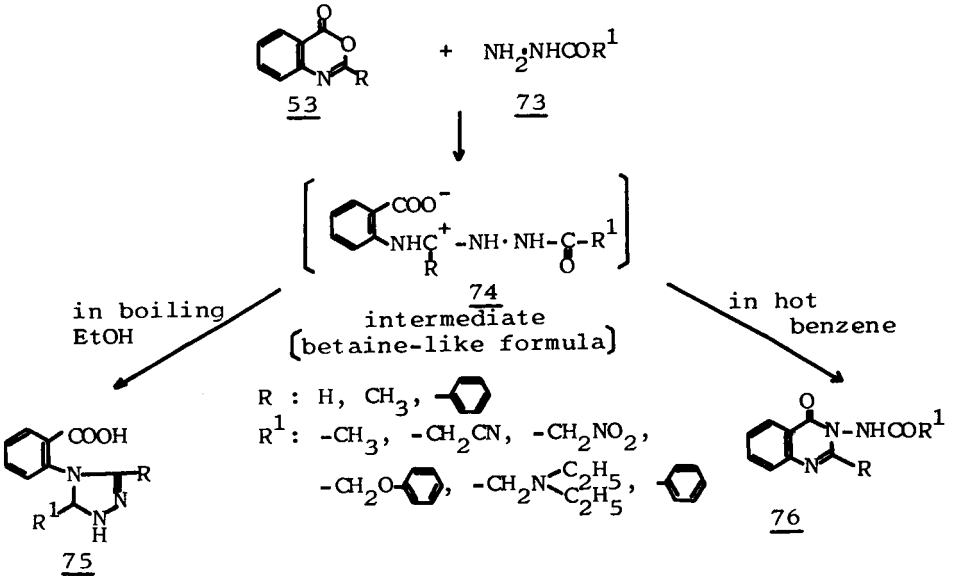
Poly(2-methyl-4-quinazolones) (72) are thermostable polymers which could be synthesized[93] from 71 and aromatic diamines; 71 was generated from 4,4'-diamino-3,3'-biphenyl-dicarboxlic acid (70) with acetic anhydride.



Froemmel and Foken[94] have reported a convenient synthesis of 3-substituted 2-methyl-4-quinazolones. Their method does not

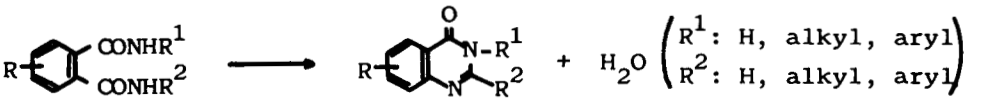
require the use of phosphorus chlorides or phosphorus pentoxide as condensing agent and avoids excessive loss of acetylanthranil (65) by saponification. The reaction can be controlled by regulation of the pressure and temperature. Thus, 65 is melted, allowed to solidify, and covered with desired amine; the mixture is then heated to 60-70° at 10-15 mm of Hg. The water produced is steadily removed. The temperature is maintained below 80° until the solid is used up, whereupon the mixture is heated slowly to 100° to complete the reaction; excess amine is removed by slow heating to 150° to yield 2-methyl-3-substituted 4-quinazolone.

Ried and Peters[95] have reported that the reaction of 2-substituted 4H-3,1-benzoxazines (53) with acylhydrazines (73) in boiling ethanol gave the 4-(2-carboxyphenyl)-4H-1,2,4-triazoles (75), but similar reaction in hot benzene yielded the 4-quinazolones (76); both reactions were postulated as proceeding via betaine-like intermediate (74).



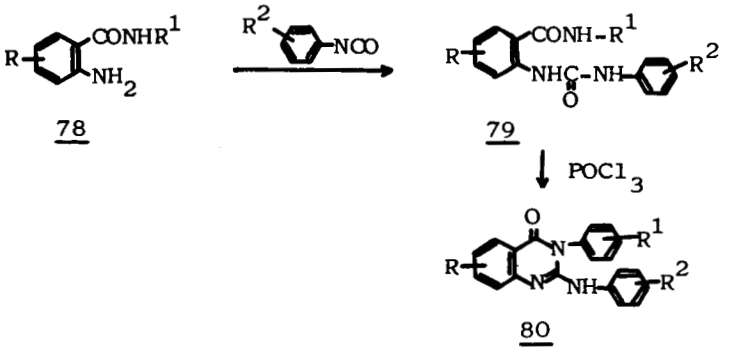
5. Pyrolysis of o-Acylaminobenzamides

A method of wide applicability for preparation of 4-quinazolones involves the direct synthesis and isolation of the desired N-substituted anthranilamides (77). When heated above their melting points, 77 lose water with formation of 4-quinazolones in one operation. These amides are thought to be intermediate in the Niementowski synthesis.[10]



From appropriately substituted o-aminobenzamides, 4-quinazolones with substituents in any position can be obtained.

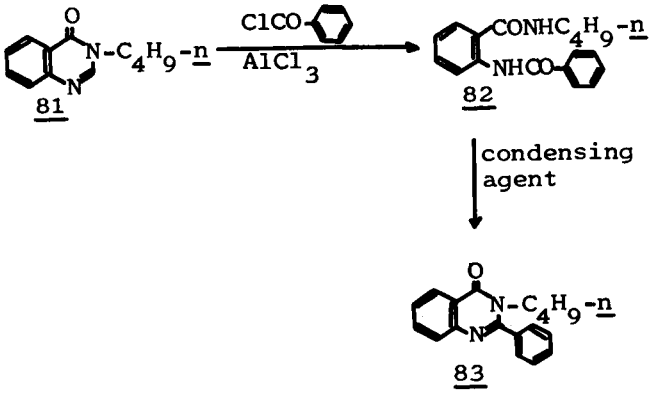
Anthranilamides (78) are readily condensed with phenyl isocyanate to give o-(3-phenylureido)-benzamides (79), and 79 is converted to 2-anilino-4-quinazolones (80) on cyclization with phosphorus oxychloride in toluene as the condensing agent.[65]



78 79 80

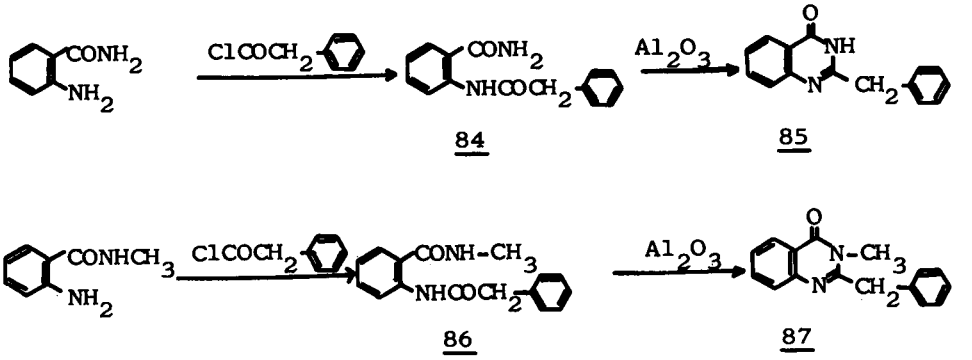
In certain cases, o-acylaminocarboxylic amides have been prepared[96] from 4-quinazolones. Thus, a mixture of 3-n-butyl-4-quinazolone (81), benzoyl chloride, and aluminum chloride

refluxed 6 hrs in chloroform gave 2-(N-benzoyl)-N'-(n-butyl)-benzamide (82) in 40% yield.



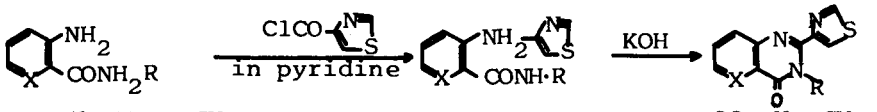
81 82 83

Pakrashi and his co-workers[97] have reported a convenient synthesis of glycosminine (75) and arborine (87)--the alkaloids of Glycosmis arborea--from acetylated anthranilamides. Thus, N-(phenylacetyl)-anthranilamide (84), prepared by the condensation of anthranilamide and phenylacetyl chloride, upon chromatography on neutral alumina (but not on silica gel) gave glycosminine (85); arborine (87) was similarly obtained from N-phenylacetyl-N'-methylanthranilamide (86).



84 85 86 87

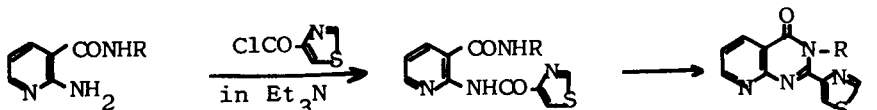
2-(4-Thiazolyl)-4-quinazolones (88) and -8-aza-4-quinazolones (89) were similarly prepared,[98] the cyclization to the quinazolone being carried out with potassium hydroxide.



X: N or CH
R: H or NH_2

88: X: CH
89: X: N

Similarly, 90 prepared from 2-aminonicotinamide with 4-chlorocarbonylthiazole in the presence of triethylamine was cyclized to 91.

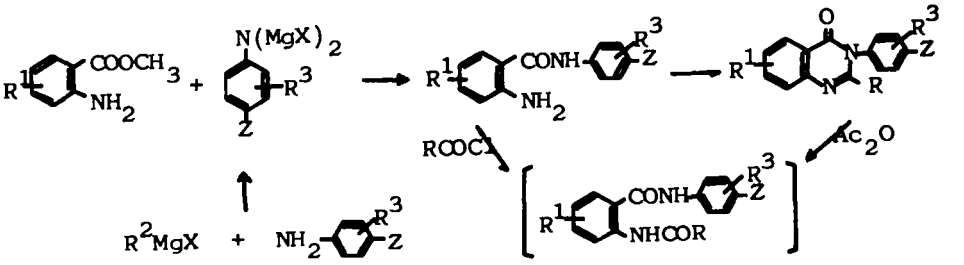


90

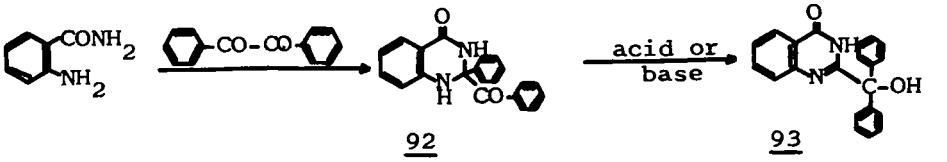
91

A wide variety of condensing agents such as pyridine,[98,99] aluminum chloride,[96] triethylamine,[98] phosphorus trichloride,[100] or merely heating [101] at high temperature has been investigated. The condensing agents used for the cyclization step have included phosphorus oxychloride,[65] alumina,[97] potassium hydroxide,[98,101] sodium hydroxide,[99] zinc chloride,[102,103] or merely heating[104] at high temperature. As noted above, a number of 4-quinazolones, such as those with 2-alkyl-3-aryl,[99,100,103,105,107,108] 2-hydroxy-3-aryl-,[101] 3-alkyl or aryl 2-aminoalkyl-,[104,106] and 2-aryl-3-aryl-[102] substituents in the benzene ring synthesized.

Petyunin and his co-workers[105,109,110] have prepared halogen containing 4-quinazolones as follows.

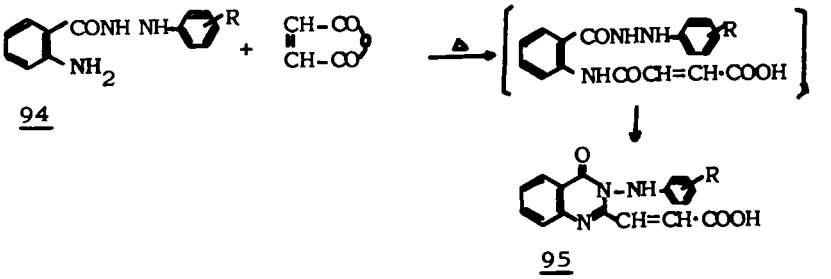


A dihydroquinazolone (92) was obtained [111] from anthranilamide and benzil and rearranged to α,α-diphenyl-2-quinazolonemethanol (93) in acid or base.



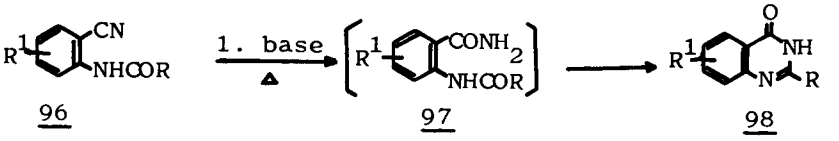
92 93

3-Anilino-2-(2-carboxylvinyl)-r-quinazolones (95) were obtained[112] by melting N-anthraniloyl-N'-phenylhydrazines (94) with maleic anhydride at 150° for 1 hour.



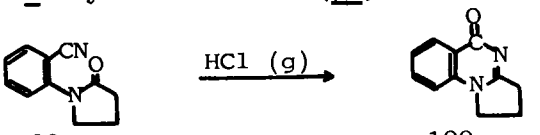
94 95

A reaction similar to that described above may be occurring in the base-catalyzed reaction of N-substituted anthranilonitrile (96). Two processes may be involved in this case: hydrolysis of 96 with alkali to the N-substituted anthranilamide (97) followed by the dehydration of 97 to the corresponding 4-quinazolone (98).[113]



96 97 98

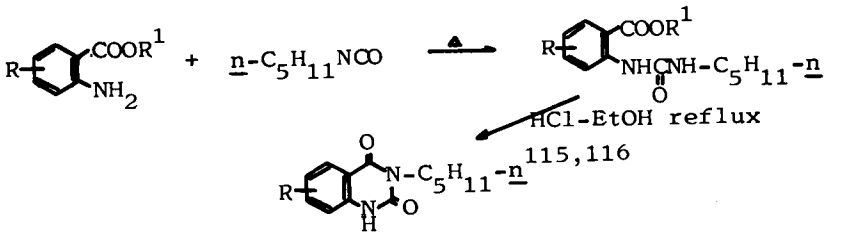
Taylor and Shvo[114] have reported 4-quinazolone (100) ring formation from o-acylaminonitrile (99).



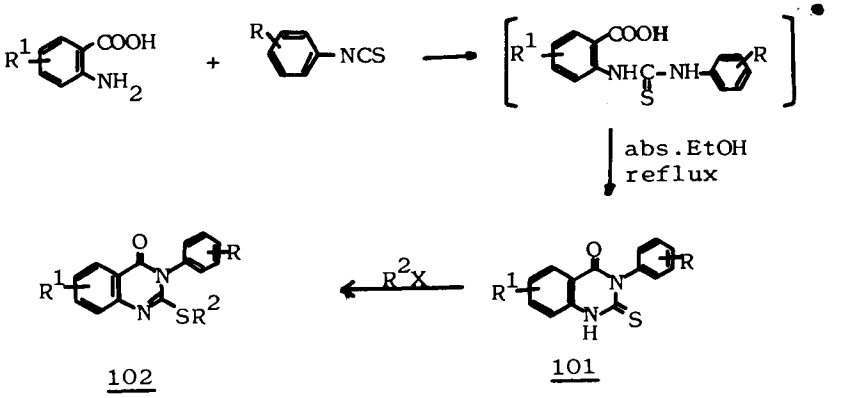
99 100

6. Cyclization of Urea Derivatives of Anthranilic Acids

Quinazolone formation can be brought about under more moderate conditions by heating an anthranilic acid with an isocyanate[13] and cyclization of the resulting urea with acid or alkali.

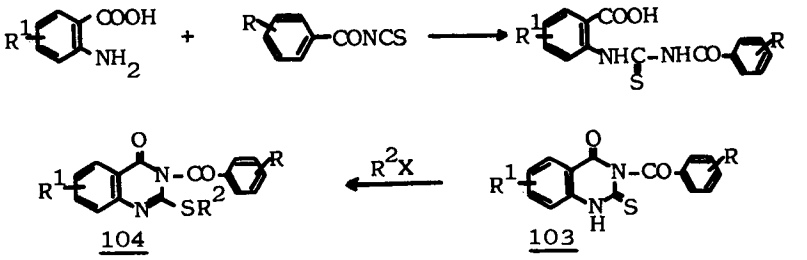


Similarly, anthranilic acids with phenyl isothiocyanate in abs. ethanol yielded 101 directly.[116-128]

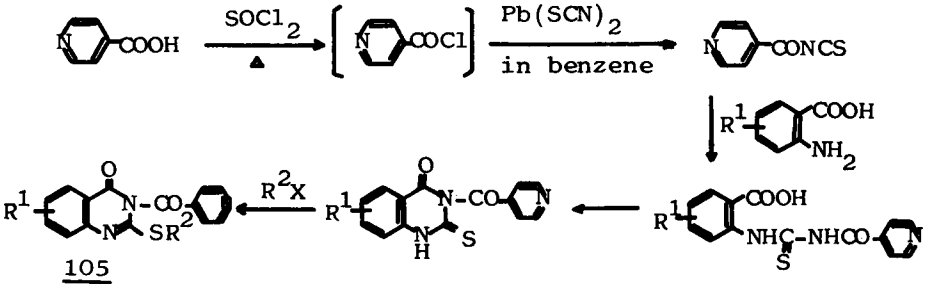


102 101

On addition, 103 were obtained[124] by condensation of anthranilic acids with benzoyl isothiocyanates in abs. ethanol.



3-Isonicotinoyl-4-quinazolones (105) were prepared by the following route.[129]

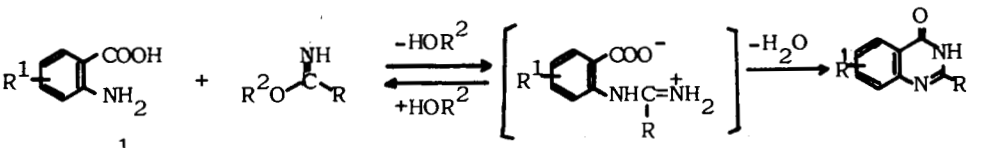


Mehta and Patel[130] have investigated the condensation of various N-acylanthranilic acids with urea and urethane derivatives in an attempt to establish possible mechanisms for the condensation reactions. The experimental results suggest that the condensation proceeds via the intermediate formation of a N-acyl anthranilamide derivative which could be easily cyclodehydrated to a 4-quinazolone derivative.

7. Reaction of Imidates with Anthranilic Acids

Imidates react with substituted anthranilic acids to give substituted 4-quinazolones.[131] Reid and Valentin[132] have postulated that the mechanism for this reaction proceeds

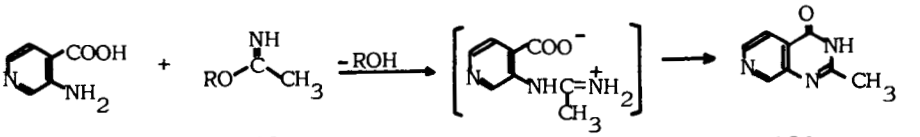
through a betaine (106) which could be easily cyclodehydrated to a 4-quinazolone (107).



R^1: H, R^2: CH_3 } yield 47%

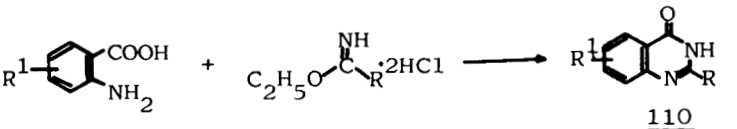
106 107

Thus, the reaction between 2-aminoisonicotonic acid and acetimidates (108) affords 7-aza-2-methyl-4-quinazolone (109).

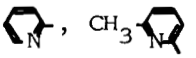


108 109

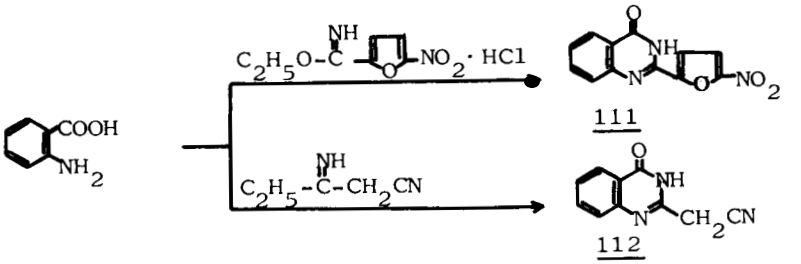
Similarly, pyridyl derivatives of 4-quinazolone (110) were obtained[133] from substituted anthranilic acid with imidate hydrochlorides in the presence of sodium ethylate about pH 7.2-8.



110

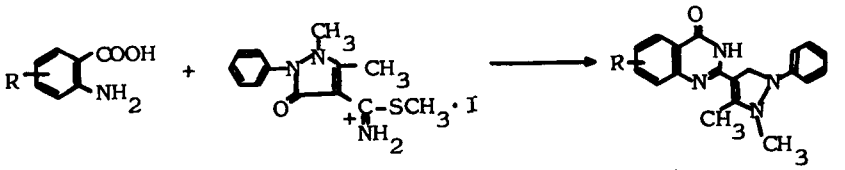
R: 

Similarly, 2-(5-nitro-furyl)-4-quinazolone (111)[134] and 4-quinazolyl-2-acetonitrile (112)[135] were prepared from anthranilic acid and 5-nitro-2-furimidate and theyl cyano-acetimidate respectively in 89% and 80% yields.



111 112

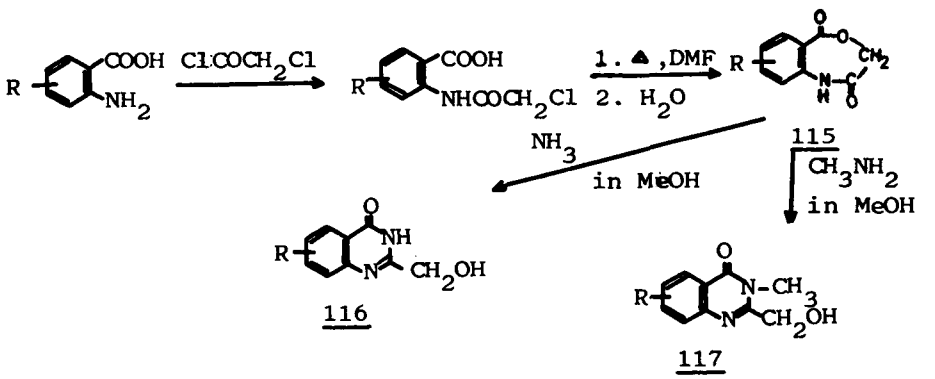
Antipyrine derivatives of 4-quinazolone (114)[136] were obtained by condensation of its 4-thioimidomethiodide (113) with a substituted anthranilic acids.



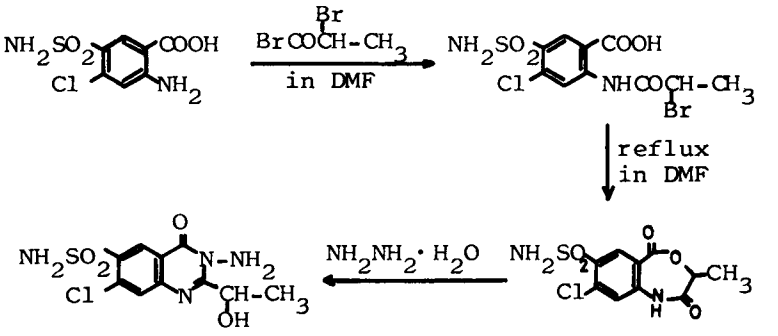
113 114

8. Other Synthetic Methods

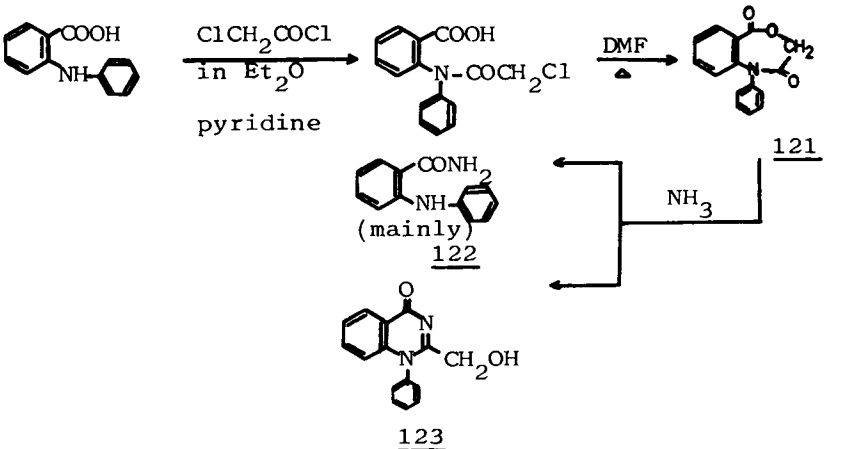
Uskokovic and Wenner[137] have reported that a number of 2-hydroxymethyl-4-quinazolones (116 and 117) are prepared from 4,1-benzoxazepine-2,5(1H,3H)-diones (115) with amines. A hot solution of 115 in methanol saturated with the amine and kept overnight gave 116 or 117.



3-Amino-2-(1-hydroxyethyl)-4-quinazolones (119) were obtained[138] from 1,4-benzoxazepine-2,5-(1H,3H)-diones (118) with hydrazine hydrate.

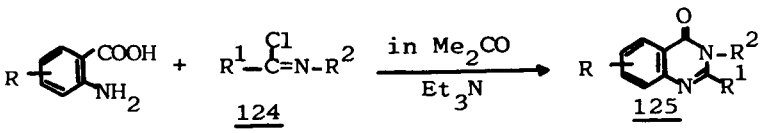


Jacobelli and his co-workers[139] have reported that condensation of o-anilinobenzoic acid and chloroacetyl chloride in dry ether-pyridine yielded o-(N-chloroacetyl-N-phenylamino)-benzoic acid (120). When refluxed for 4 hrs in DMF 120, gave 121 which, when treated in methanol for 3 hrs at 40-50° with dry ammonia, was converted to a mixture consisting of mainly o-anilinobenzamide (122) and some 1-phenyl-2-(2-hydroxymethyl)-4-quinazolone (123).



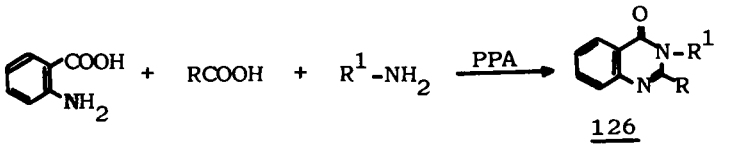
2,3-Disubstituted 4-quinazolones (125) have also been prepared[140] from anthranilic acid and imino chlorides (124) in

acetone or N-methyl-pyrrodidone and in the presence of triethylamine at 0-50°; the reaction is then completed to 125 by heating or by a condensing agent.



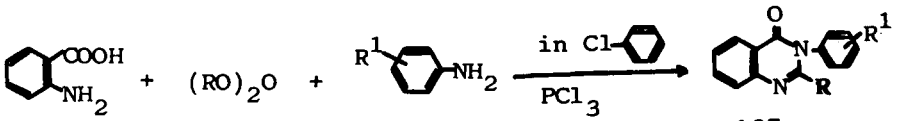
124 125

A one-step operation for the preparation of 4-quinazolones has been reported.[20,21,141-144] Starke has claimed[141] that 4-quinazolones (126) were also obtained by direct condensation of anthranilic acid, a carboxylic acid, and primary amines in the presence of at least a 3-fold amount of PPA without isolation of the intermediate N-acetylanthranilic acid.



126

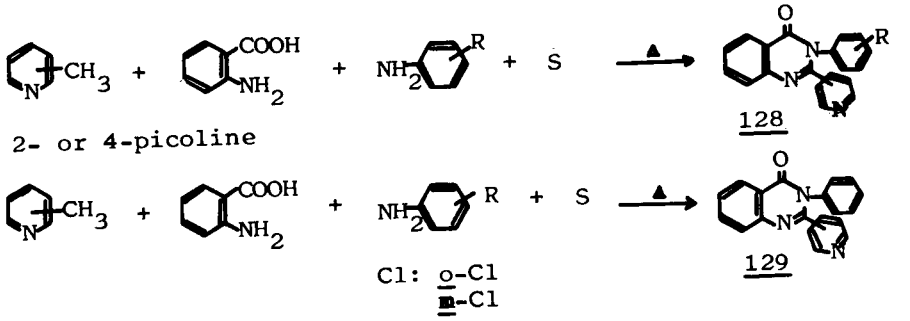
Morgan and Simmons[142] have described a related one-step process for the preparation of 4-quinazolones (127) from the condensation of anthranilic acid, acetic anhydride, and aromatic amines in the presence of phosphorus trichloride in chlorobenzene.



127

Active methyl compounds such as 2-picoline or 4-picoline, aromatic primary amines, and anthranilic acid in the presence of sulfur (modified Willgerodt-Kindler reaction) afforded 2-pyridyl-3-substituted 4-quinazolones (128) in 30-50% yield.[20,21]

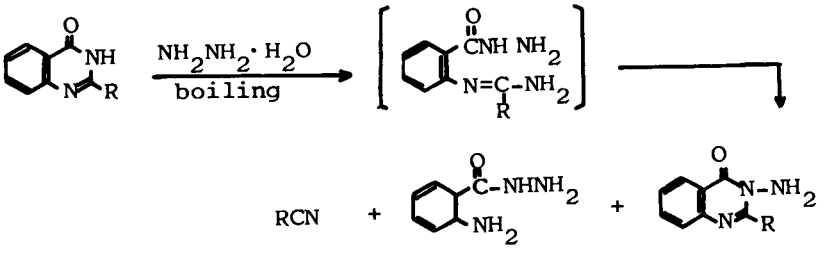
In this procedure, o-(or m-)chloroaniline used as aromatic primary amine is dechlorinated in the course of the reaction to give 2-pyridyl-3-phenyl-4-quinazolone (129).[20]



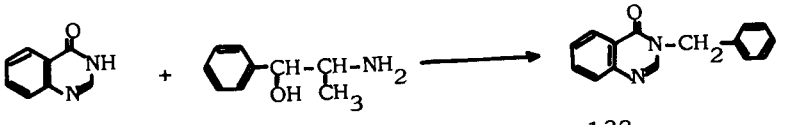
128

129

2-(R-substituted)-4-quinazolones are hydrazinolyzed[145] by boiling with 10-15-fold excess hydrazine hydrate for 5-12 hrs.

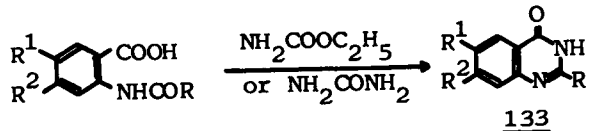


Chinn[146] has reported the formation of 3-benzyl-4-quinazolone (132) from 4-quinazolone (130) and 2-amino-1-phenylpropanol (131) as a novel reaction.



130 131 132

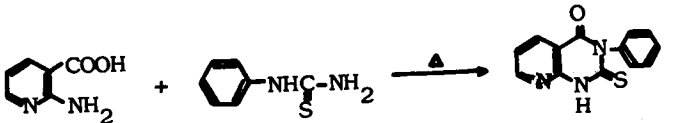
The condensation of N-substituted anthranilic acids with urethane and urea gave 2-substituted 4-quinazolones (133).[28]



133

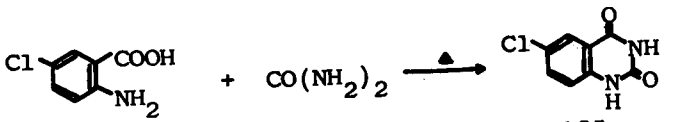
R: CH_3,  ; R^1: H, Cl, NO_2; R^2: H, Cl, NO_2

A mixture of 2-aminonicotinic acid and N-phenylthiourea, heated for 1.5 hrs at 200°, yielded 134.[86]



134

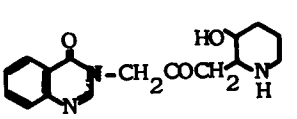
Similarly, the condensation of anthranilic acids with urea afforded 135.[13]



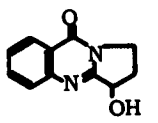
135

III. 4-QUINAZOLONES OF BIOLOGICAL SIGNIFICANCE

Diverse biological activities have been in compounds having a 4-quinazolone ring system. For example, the quinazolone alkaloids, febrifugine (136)[147] and vacisinone (137),[148] are reputed to elicit antimalarial and bronchodilator activity, respectively.

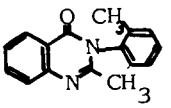


136



137

Gujral and his co-workers[149] found that some 4-quinazolones exhibited a potent hypnotic action in experiments with animals. 2-Methyl-3-o-tolyl-4-quinazolone (138)[150] (Methaquazone; MTQ) and 2-methyl-3-o-chlorophenyl-4-quinazolone (139)[64,151] (Mecloqualone) have been utilized in therapy as a hypnotic.



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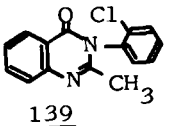


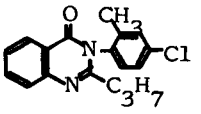
139

A large number of 2-substituted, 3-substituted, and 2,3-disubstituted 4-quinazolones, in particular those possessing 2-alkyl-3-alkyl, 2-alkyl-3-aryl, and 2-alkyl-3-amino substitutions, have been prepared to investigate structure-activity relationship of these 4-quinazolones with respect to their biological activity, such as a sedative, hypnotic, anticonvulsive, muscle relaxant, antiinflammatory, antimiotic, antihistaminic, diuretic, and antihypertensive activity. Breuer and Roesch[152] have studied the structure-activity relationship of amino substituted 3-aryl-4-quinazolones.

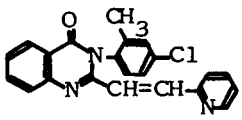
1. Hypnotic Activity

The effect of the 4-quinazolones on the central nervous system (CNS) was also confirmed by Boissier and his group[153] and its clinical use as fast-acting hypnotic was described by Ravina[150] and Arvers.[154] A number of 4-quinazolones substituted in the 2 position with alkyl or aliphatic groups, was screened for their pharmacological effects.[149a,151,155] Boltze and his co-workers[29] have synthesized a number of 2,3-disubstituted 4-quinazolones in order to investigate the role of the substituents on the hypnotic action. Leszkovszky

and his group[156] have reported that 4-quinazolones with aromatic substituents in the 3 position were mainly hypnotic, sedative, and anticonvulsive; MTQ (138) was the most potent representative and even slight modifications of its structure weakened its potency. For example, replacement of the 2-methyl group eliminated anticonvulsive activity; however 140 and 141 exhibited anticonvulsive effects.



140



141

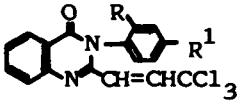
Compounds containing aliphatic substituents in the 3 position had analgesic, antiphlogistic and antipyretic effect. Of these compounds, 2-methyl-3-butyl-4-quinazolone and 2-methyl-3-isobutyl-4-quinazolone were most effective. 4-Quinazolones had no antiphlogistic effect in adrenalectomized animals, indicating dependency on the mobilization of adrenocortical hormones to produce its effect.

Lietz and Matthies[157] have prepared some quinazolones that had particularly favorable effective quotients with regard to their sedative-hypnotic and anticonvulsive effect. Gupta and his co-workers[158] have reported that a variety of 3-substituted 4-quinazolones with and without a substituent in the 2 position, exhibit CNS-depressant activity.

Grishina[159] investigated the relation between chemical structure and biological activity in a series of halogen-substituted derivatives of 4-quinazolone. A necessary condition for high hypnotic action in the halogen derivatives of

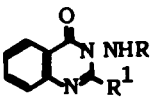
4-quinazolones is believed to be the presence of a methyl group in the 2 position and o-Cl- or o-Br-substituted phenyl group in the 3 position of the primary ring. Substitution of a Cl atom or of phenyl, benzyl, or styryl group for a H atom of the methyl group in 2 position and also the introduction of a halogen into the benzyl ring of the quinazolone structure result in a sharply decreased hypnotic action.

Chlorine-containing derivatives (142)[160] of 4-quinazolones, have longer lasting sedative and hypnotic activity than MTQ, are less toxic and are tasteless.

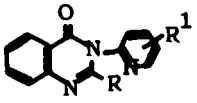


142 R, R^1: H, CH_3 or Cl

Compounds of type 143 have a potentiating effect on barbiturates and have anticonvulsant properties.[112]



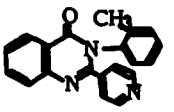
143



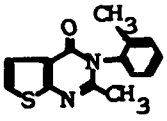
144

A number of pyridyl-substituted 4-quinazolones in 2 or 3 position were synthesized and screened for hypnotic-sedative and anticonvulsive activity. The acute toxicity, hypnotic, and anticonvulsive actions of 144[161] were established and compared with those of MTQ. As a rule,[161] the introduction of substituent (R^1) in the pyridine ring led to a decrease in hypnotic activity.

The author has reported[20,21] a convenient synthesis of 4-quinazolones with heterocyclic substituents in the 2 position. Studies on the structure-activity relationship demonstrated that 2-pyridyl, 3-pyridyl, and 4-pyridyl substitution at 2 position of 4-quinazolone ring, o-, m-, and p-substitution of the aromatic ring at 3 position exhibit hypnotic activity. The order of potency produced by the difference in the substituents at 2 and 3 position decreased in the order of 4-pyridyl, o-tolyl>3-pyridyl, o-tolyl>2-pyridyl, o-tolyl. A maximum hypnotic effect accompanied with other potent pharmacological properties was observed[20] in 2-(4-pyridyl)-3-o-tolyl-4-quinazolone (145), the potency of which was equal to or stronger than MTQ in mice. The effect of the presence of a thiophen substituent on their hypnotic effect has also been studied;[55] 2-methyl-3-o-tolyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine (146) was almost as active as MTQ.



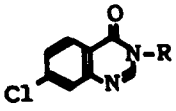
145



146

2. Antiinflammatory Activity

Compound 147[15] showed antiinflammatory effect at 50-200 mg/Kg.i.p. in rats. Similarly, Maillard and his co-workers[16] obtained 4-quinazolones substituted on the benzene ring and compared their antiinflammatory activity in rats.

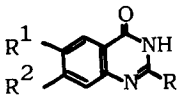


147

R: acyl, aralkyl

3. Antihypertensive Activity

Some of 4-quinazolones have been reported[162,163] to have antihypertensive effect when administered orally to conscious hypertensive dogs. Particularly active compounds were derivatives with two methoxt groups at 6 and 7 positions and dimethylamino, diethylamino, diallylamino, or N-methylpiperazino substituents at 2 position of the quinazolone ring (148).



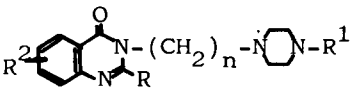
148

R: $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N\langle\rangle N-CH_3$

$R^1 = R^2$: OCH_3

4. Antihistaminic Activity

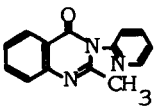
Some compounds of 3-ω-(4-aryl-1-piperazinyl)alkyl-2-methyl-(or 2-phenyl)-4-quinazolones displayed moderate antihistaminic effect;[63] 149 (R = CH_3, n = 6, R^1 =  , R^2 = H) was the most potent antihistaminic agent.



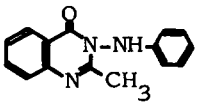
149

5. Antitussive Activity

Dua and his co-workers[164] reported that 2,3-disubstituted 4-quinazolones were tested for the antitussive activity in anestetized cats by the method of electrical stimulation of the superior laryngeal nerve; 150 and 151 exhibited an antitussive effect at a dose of 16 mg/Kg. However, 150 and 151 were less active than codeine phosphate and MTQ as antitussive agents; the advantage with 151 is the absence of any CNS-depressant activity.



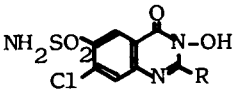
150



151

6. Diuretic Activity

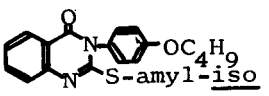
2-Ethyl-6-sulfonamido-7-chloro-1,2-dihydro-4-quinazolone (Quinethazone)[165] has been utilized in therapy as a diuretic. A series of 3-substituted-amino- and 3-hydroxy-7-chloro-3,4-dihydro-4-oxo-6-quinazolinesulfonamides (e.g. 152) were prepared and evaluated for diuretic activity.[166] The introduction of an amino or a dimethylamino group in the 3 position has little effect, but the introduction of a hydroxy group enhanced diuretic activity. The corresponding 1,2,3,4-tetrahydro derivatives proved to be the most active compounds in this series.



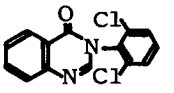
152

7. Antibacterial Activity

4-Quinazolones were found to possess broad in vitro antibacterial activity against a veriety of organisms. Several compounds were also active Staphylococcus aureus infections. 153[124] had the highest in vitro tuberculostatic activity of the compounds tested; 154[59] was specifically active against Ersiphe cichoracearum and Podosphaera leucotricha.

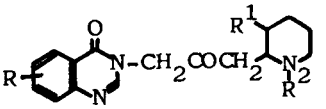


153



154

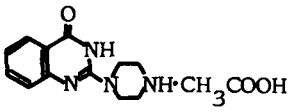
Compounds of type 155 prepared by Waletzky and his group,[11] are used for treatment of coccidiosis.



155

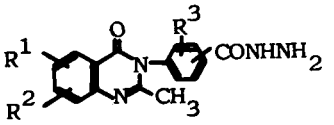
8. Other Activities

Hypoglycaemic activity has not so far been reported in any 4-quinazolones. Gupta and his co-workers[167] have found that 2-piperazino-4-quinazolone monoacetate (156) is an effective blood sugar lowering agent

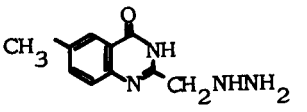


156

Antispasmodic activity of 2-methyl-3-aryl-4-quinazolones was evaluated[168] on small intestine portions of rabbit. MTQ was the most effective antispasmodic agent on tissue portions treated with acetylcholine and $BaCl_2$. Several substituted 4-quinazolone hydrazides (157) were synthesized[84,169,170] to investigate their ability to inhibit rat liver mitochondrial monoamine oxidase (MAO). 158 showed 5.5% MAO inhibition at 1 millimolar concentration in vitro.[23]



157



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