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THE PFITZINGER REACTION. (REVIEW)

M. G.-A. Shvekhgeimer

Published data on the Pfitzinger reaction and its modifications, leading to quinoline-4-carboxylic acids, are reviewed, analyzed, and classified.

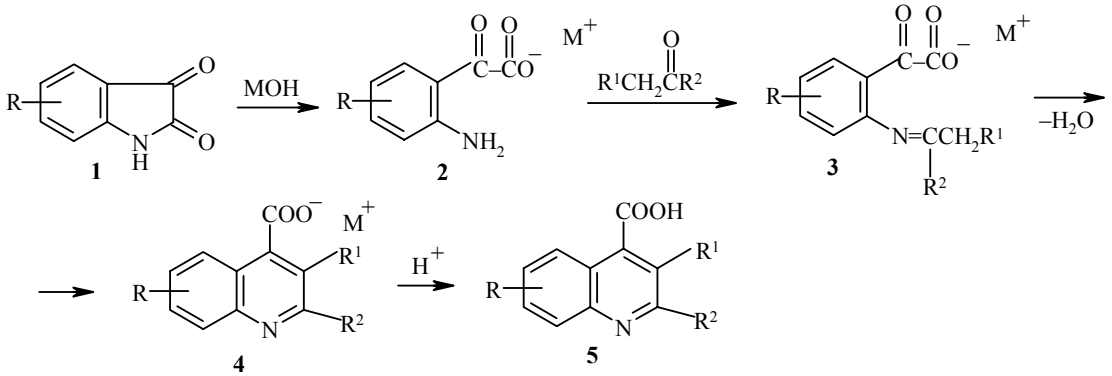
Keywords: isatin, isatin derivatives, ketones, 4-quinolinecarboxylic acid derivatives, condensation, cyclization, Pfitzinger reaction, recyclization.

The formation of derivatives of 4-quinolinecarboxylic (cinchoninic) acid as a result of the reaction of isatin or its derivatives with ketones containing the $–CH_2CO–$ group in the presence of sodium hydroxide or potassium hydroxide was first discovered at the end of the nineteenth century by Pfitzinger [1] and is known in organic chemistry as the Pfitzinger reaction. In the ensuing years this reaction, in which isatin and its derivatives on the one hand and various ketones on the other were used, has attracted the attention of many authors. The interest in this reaction was due to the possibility of synthesizing prospective biologically active substances simply and with good yields from readily available materials.

In spite of numerous papers in this field the literature does not contain any publications summarizing the enormous amount of data that has accumulated over more than a century. Individual and poor-quality data on the Pfitzinger reaction have only appeared in monographs [2-4] and in a review [5].

The present review covers all the available published data on the Pfitzinger reaction beginning from the time of its discovery. The investigated material has been classified on the basis of the structure of the initial ketones; separate sections cover the reactions of isatins with dialkyl ketones, keto acids, alkyl aryl ketones, and alkyl hetaryl ketones and also with cyclic ketones. Papers describing the synthesis of 4-quinolinecarboxylic acids by methods related to the Pfitzinger reaction are discussed in a separated section.

The reaction of isatins with ketones leading to 4-quinolinecarboxylic acids is carried out in the presence of strong nucleophiles (sodium hydroxide or potassium hydroxide). For this reason the generally accepted mechanism of the process is the following. The isatins **1** are converted by the action of alkalis into the salts of



A. N. Kosygin Moscow State Textile University, Moscow 117918, Russia; e-mail: office@msta.ac.ru.
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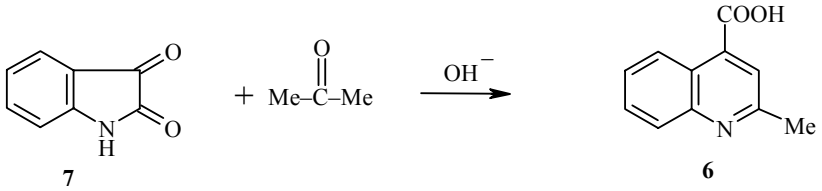
isatoic acids **2**, which condense with ketones with the release of water, forming the salts **3**. The latter undergo cyclization through the CO and CH_2 groups and are converted into the salts of 4-quinolinecarboxylic acids **4**, the treatment of which with acids (usually acetic) gives the required compounds **5**.

Subsequently only the initial isatins and ketones and also the final products will be presented in the texts and in the schemes without mention of the intermediate formation of the salts **2**-**4**. As a rule the conditions and the yields of the reactions will be indicated in the schemes and in the tables.

1. REACTIONS WITH DIALKYL KETONES

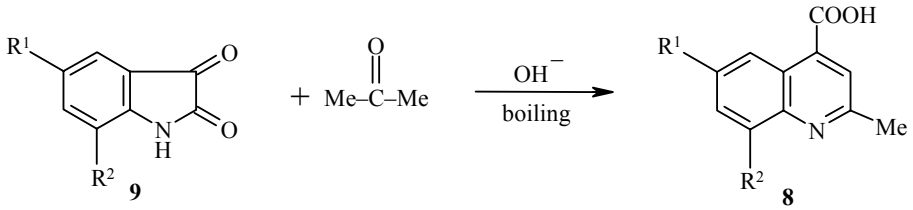
Pfitzinger first reported the synthesis of 2-methyl-4-quinolinecarboxylic acid (**6**) as a result of the reaction of isatin (**7**) with acetone in the presence of an aqueous solution of alkali in a paper published in 1886 [1].



7 **6**

In subsequent papers [6, 7] he refined the reaction conditions (33% NaOH, 100°C, 8 h) and reported that the acid **6** can be obtained with a yield of up to 80% while with more dilute sodium hydroxide solutions the yield was reduced to 50-53% [8-11].

Pfitzinger also studied the reaction of 5-methylisatin with acetone in the presence of a 5% aqueous solution of sodium hydroxide (boiling for several hours) and obtained 2,6-dimethyl-4-quinolinecarboxylic acid with a yield of 80% [6, 7]. The acids **8** substituted in the benzene ring were synthesized by condensation of the appropriately substituted isatins **9** with acetone in the presence of a dilute aqueous solution of sodium hydroxide [12], a 33% alcohol solution of potassium hydroxide [13], a 3.2% aqueous solution of sodium hydroxide [14], a 10% aqueous solution of sodium hydroxide [15], an 18% alcohol solution of potassium hydroxide [16], and a 20% water–alcohol solution of potassium hydroxide [17].

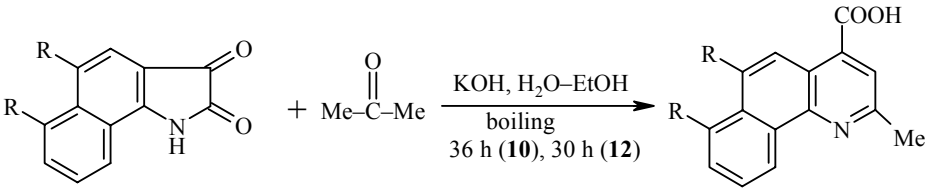


9 **8**

R^1, R^2 (time, h), yield, %: OMe, H (6), n/d [12]; H, H (72), 70; H, Br (72), 75; Br, Br (72), 70 [13]; F, H (12), n/d [14]; H, Br (16), 51 [15, 16]; H, I (24), 87 [17]

The reaction of α-naphthisatin **10** with acetone in a boiling water–alcohol solution of potassium hydroxide gave a 70% yield of the benzo[*f*]quinoline derivative **11** [18].

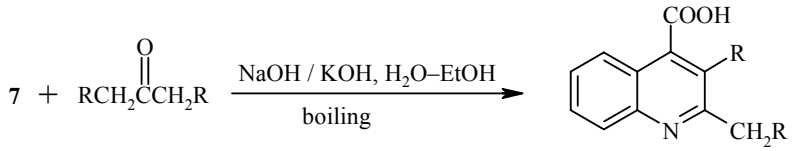
The tetracyclic compound **13** was obtained from acetone and α-acenaphthisatin **12** under analogous conditions (yield 81%) [19].



10, **12** **11**, **13**

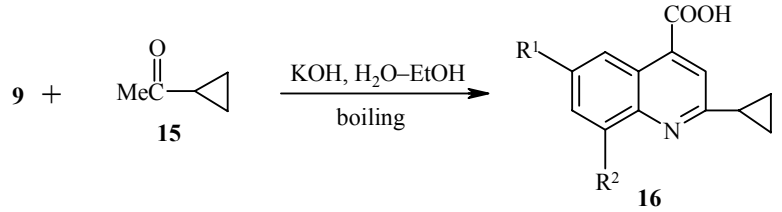
10, **11** R = H [18]; **12**, **13** R+R = CH_2CH_2 [19]

As in the reactions with acetone, in the reaction of isatin **7** with symmetrical ketones in the presence of sodium hydroxide [20] or potassium hydroxide [21, 22] in a water–alcohol medium only one product of type **14** is formed each time.



14

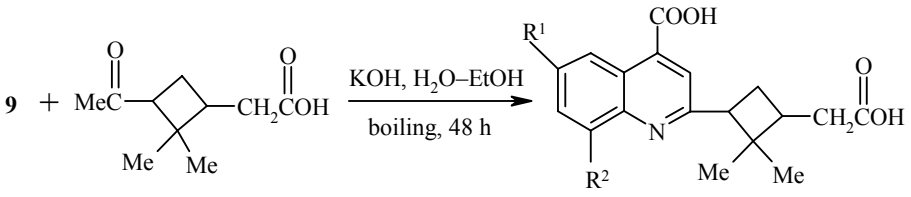
A single product is also formed in the case of unsymmetrical ketones of the $MeCOCHR^1R^2$ or $RCH_2COCHR^1R^2$ type, since for the Pfitzinger reaction to occur the ketone must contain either a methyl group or a methylene group next to the carbonyl group. For example, only one appropriate cyclopropyl-substituted acid **16** is formed from methyl cyclopropyl ketone **15** and isatins **9** [23, 24].



15 **16**

R^1, R^2, time, h: H, H, 5-7, (yield 84%) [23]; H, Me, 24;
Cl, H, 24; Br, H, 24 [25]

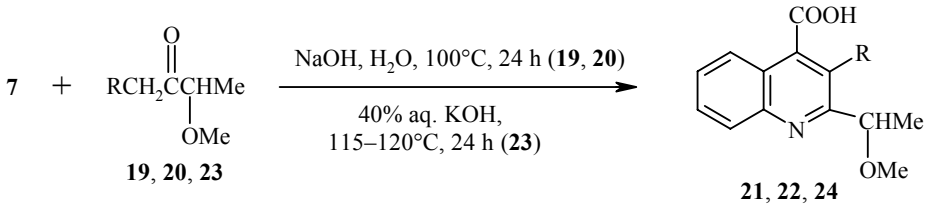
The prolonged action of heat on the isatins **9** with the keto acid **17** gave the diacids **18** [25].



17 **18**

R^1, R^2, yield, %: H, H, 89.0; Me, H, 59.0; H, Me, 76; Br, Br, 42.5

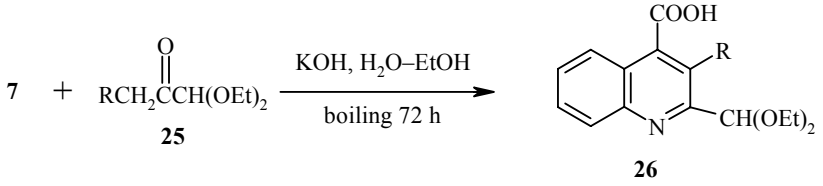
Methyl and ethyl α-methoxyethyl ketones **19** and **20** condense with isatin **7** when heated in the presence of sodium hydroxide in water, and 2-(α-methoxyethyl)-substituted acids **21** and **22** are formed with yields of 74 or 60% respectively [26]. Their analog isopentyl α-methoxyethyl ketone **23** with a bulky substituent does not react with isatin **7** under the same conditions, but under more severe conditions the corresponding derivative of 4-quinolinecarboxylic acid **24** is formed with a yield of 46% [27].



19, **20**, **23** **21**, **22**, **24**

19, **21** R = H; **20**, **22** R = Me; **23**, **24** R = CH_2CHMe_2

As a result of prolonged boiling with the isatin **7** in the presence of potassium hydroxide in water and alcohol the diethoxy-substituted ketones **25** form the acids **26** [28].



25 **26**

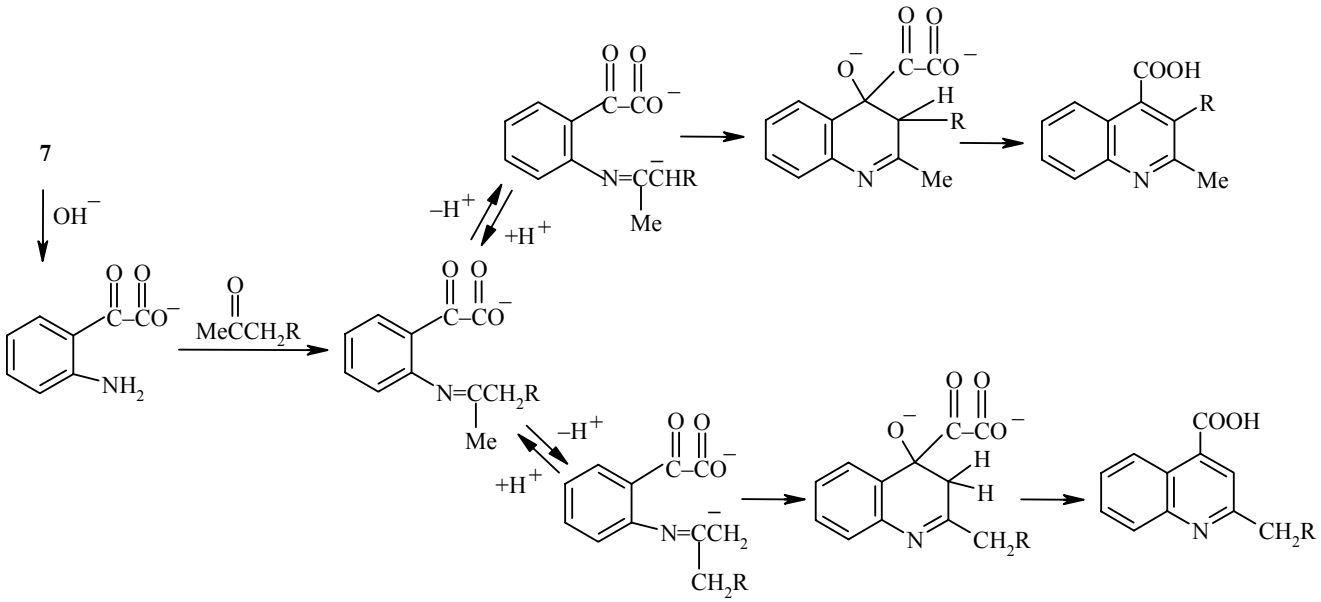
R, yield, %: Et, 25; Bu, 94

The condensation of 5-bromoisatin with methyl β-phenylvinyl ketone in a water–benzene medium in the presence of sodium hydroxide and the phase-transfer catalyst $Et_4N^+Br^-$ takes place readily, and 6-bromo-2-(β-phenylvinyl)-4-quinolinecarboxylic acid is formed with an 85% yield [29].

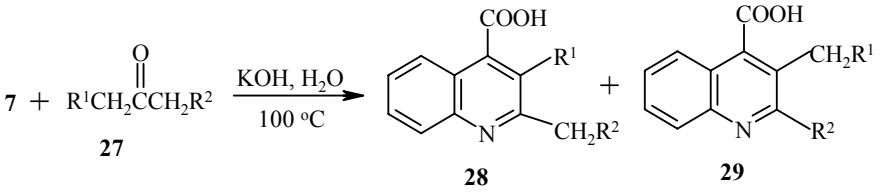
If unsymmetrical ketones of the $RCH_2COCH_2R^1$ type **27** are used in the Pfitzinger reaction, the process may be nonregioselective. Thus, careful study of the products from the reaction of isatin **7** with methyl ethyl ketone showed that 2,6-dimethyl-4-quinolinecarboxylic acid (mainly) and 2-ethyl-4-quinolinecarboxylic acid (and not only the former, as supposed earlier [8]) are obtained [22, 30].

It should be noted that from the halogen-substituted isatins **9** (R = H, R' = Br and R = R^1 = Cl) and methyl ethyl ketone only one product (8-bromo- or 6,8-dichloro-substituted 2,3-dimethyl-4-quinolinecarboxylic acid) was obtained in both cases [16].

A probable mechanism for the formation of the two regioisomers as a result of the condensation of isatin **7** with unsymmetrical ketones of the $MeCOCH_2R$ type was presented in [31].

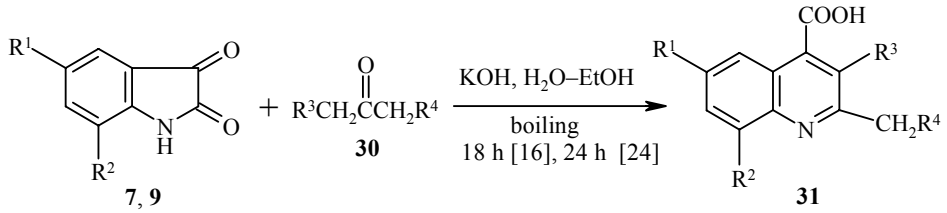


During a systematic study of the reaction of isatin **7** with ketones of type **27** it was shown that either two products **28** and **29** (minor) or only one product **28** are formed depending on the structure of the initial ketone [28].



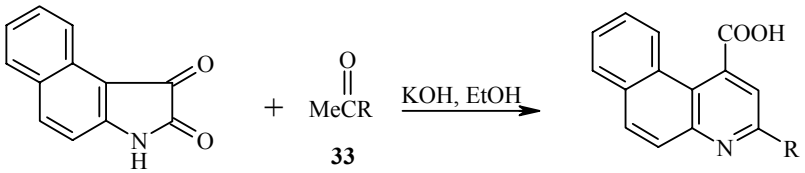
R^1, R^2 (time, h), total yield, %, products: H, Me (7), 85, **28**, **29**;
H, Et (72), 92, **28**; H, Pr (70), 93, **28**; H, Bu (78), 80, **28**; H, C_5H_{11} (96), 92, **28**; H, C_8H_{17} (n/d), n/d, **28**; H, Ph, (n/d), n/d, **28**, **29**; H, CH_2Ph, (n/d), n/d, **28**; Me, Ph, (n/d), n/d, **28**, **29**

It was found that from the ketones $R^3CH_2COCH_2R^4$ **30**, in which $R^3 < R^4$, and the isatins **9** only one compound **31** is formed in each case, i.e., the reaction takes place through the groups with smaller molecular mass CH_2R^3 [16, 24]. Such a reaction path can clearly be explained by steric factors and, to some degree, by the inductive effect of the alkyl radicals.



R^1 = H, Me, Bu, Cl, Br; R^2 = H, Me, Cl; R^3 = H, Me, Et, Pr; R^4 = Alk (C_1–C_6, C_{11}, C_{15}, C_{19}). Yields 37-86%

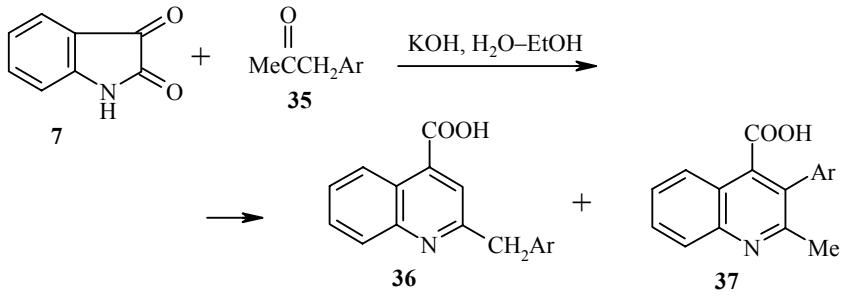
The condensation of β-naphthisatin **32** with the ketones **33** takes place through the methyl group of the latter. Here the tricyclic condensed compounds **34** are formed with almost quantitative yields [24].



R = C_6H_{13}, C_9H_{19}

Unsymmetrical ketones containing Ar and OAr substituents in the alkyl radicals behave differently in the Pfitzinger reaction. Thus, methyl β-phenylethyl ketone reacts with isatin **7** in the presence of potassium hydroxide in water and alcohol through the methyl group – a single product 2-(β-phenylethyl)-4-quinolinecarboxylic acid is formed with a yield of 79% [22, 32].

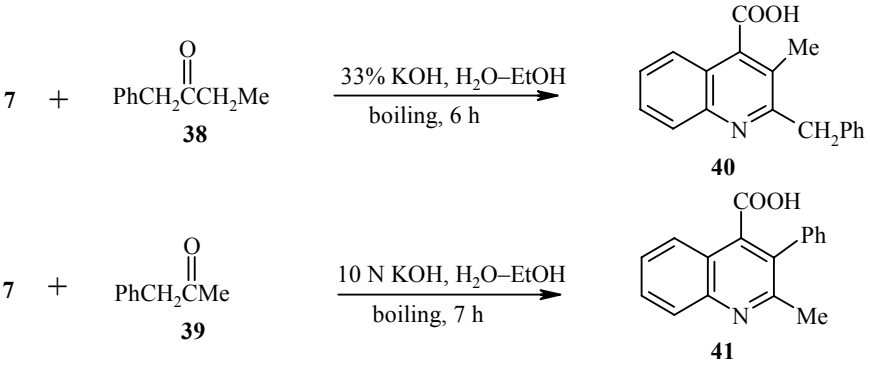
The direction of the reaction of the isatin **7** with ketones of the **35** type under the same conditions depends on the nature of the substituent Ar. Thus, if R = Ph, C_6H_4OMe-4, OPh, or OC_6H_4OMe-4, a mixture of compounds **36** and **37** in ratios of 38:62, 40:60, 38:62, or 29:71 respectively was formed each time. On the other hand, with R = $C_6H_4NO_2$-4 or $OC_6H_4NO_2$-4 only the acids **37** (Ar = $C_6H_4NO_2$-4 or $OC_6H_4NO_2$-4) were obtained [31].



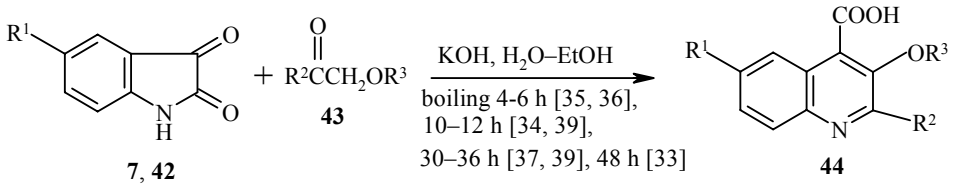
Ar : Ph, C_6H_4OMe-4 (**36**, **37**); $C_6H_4NO_2$-4 (**37**)

The reaction of the isatin **7** with the keto alcohol CH_3COCH_2OH also gave a single product 3-hydroxy-2-methyl-4-quinolinecarboxylic acid [31].

Different regioselectivity was observed in the reaction of isatin **7** with the ketones **38** and **39**, resulting in the synthesis of the acids **40** and **41** with yields of 35 and 41% respectively [22].

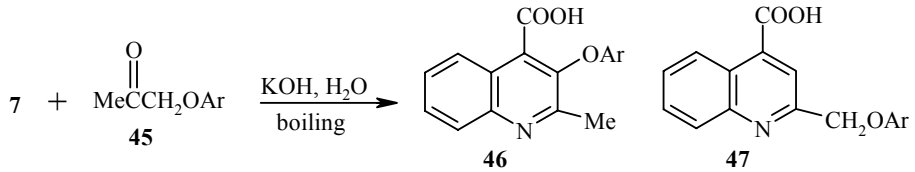


In a series of papers [33-39] it was found that the reaction of isatins **7** and **42** with alkoxy- and aroxy-substituted ketones **43** takes place with the participation of the CH_2 group in CH_2OR^2, leading to compounds **44**.



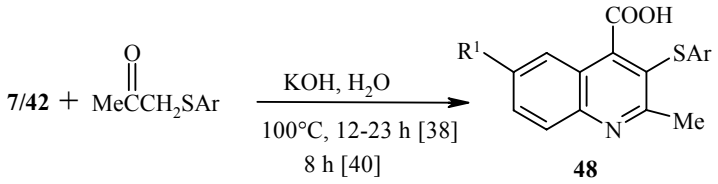
R^1: H, Me; R^2: Alk (C_2–C_5); R^3: Alk (C_2–C_4), $C_6H_4R^4$ (R^4: 4-Me, 3-Me, 2-Me, 4-OMe, 4-OEt, 4-OPr, 4-OBu, 2-OMe), $C_6H_3Me_2$-2,4, 1-naphthyl, 2-naphthyl. Yields 20-93%

It should be noted that other authors later obtained two products each **46** and **47** from methyl aroxymethyl ketones **45** and isatin **7** [31].



Ar, (ratio **46**:**47**): Ph, (62:38); C_6H_4OMe-4, (71:29)

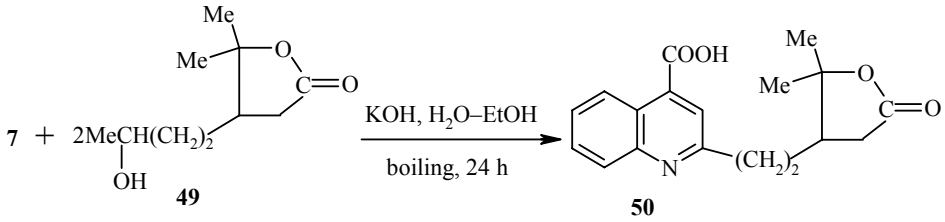
However, only the analogs of compounds **46**, i.e., the acids **48**, were synthesized from the sulfur analogs of the ketones **45** and isatins **11** [38, 40].



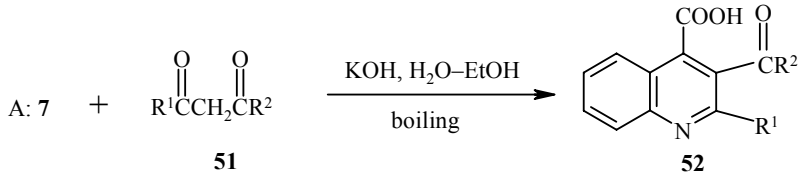
R^1: H, Me; Ar: $C_6H_4R^2$ (R^2: H, 2-Me, 3-Me, 4-Me). Yields 60-90%

Japanese researchers [41] have patented a method for the synthesis of 2,3-dimethyl-4-quinolinecarboxamide (yield 61.8%) by heating the isatin **7** and methyl ethyl ketone with an aqueous solution of ammonia in a tube at 100°C for 8 h.

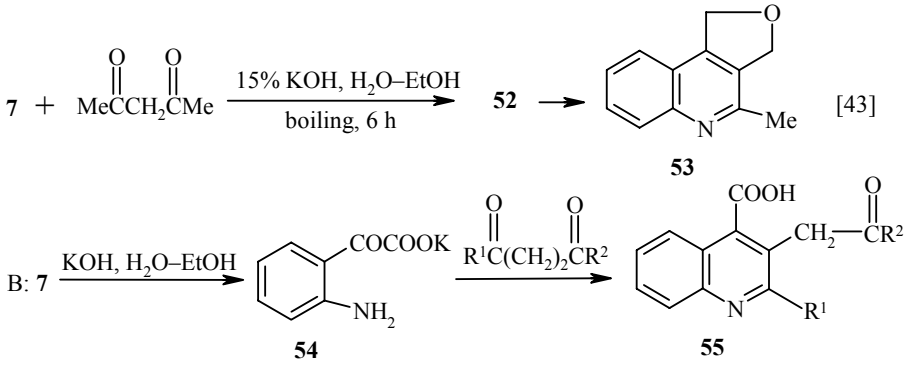
Under the conditions of the Pfitzinger reaction secondary alcohols are capable of being oxidized to ketones and entering into condensation with isatins with the formation of derivatives of 4-quinolinecarboxylic acid. Thus, the product **50** was obtained with a yield of 81% from the hydroxylactone **49** and isatin **7** [25].



The behavior of aliphatic diketones in the investigated reaction has been studied little. Two sets of conditions (A, B) for the reaction of the diketones **51** with isatin **7** were described in [42]. According to method A, a mixture of isatin and the diketone **51** was boiled in the presence of potassium hydroxide in water and alcohol, resulting in the synthesis of the keto acid **52**. From acetylacetone under similar conditions the authors of [43] obtained the product from *in situ* cyclization of the acid **52**, i.e., the lactone **53**. In method B the isatin was first converted by the action of potassium hydroxide into the salt **54**, which was then isolated and brought into reaction with 2,5-hexanedione in the dry form. In this case the reaction product was the acid **55** (yield 33%).

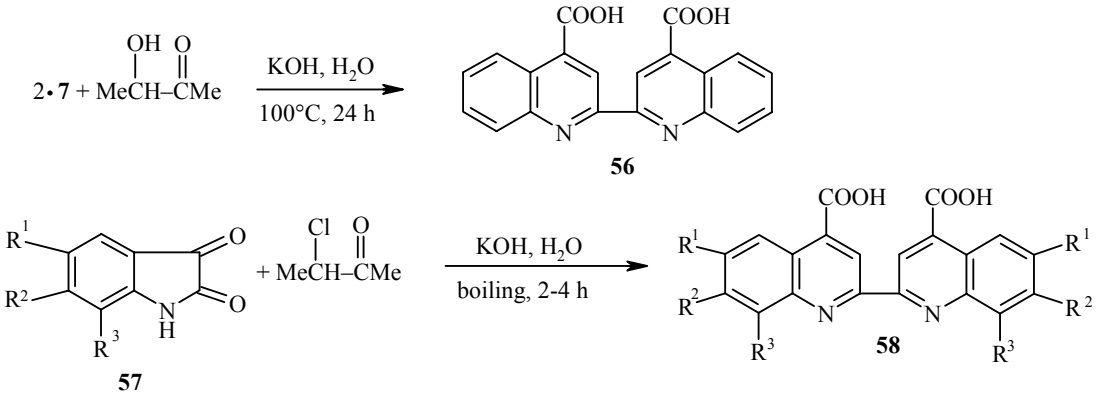


R^1, R^2, (time, h), yield, %: Me, Me, (6), 73; Me, Ph, (8), 67 [42]



R^1, R^2, (time, h, T, °C), yield, %: Me, Me, (3, boiling), 80;
Me, Et, (1, 100°, 20 min, 150°), 67; Me, Ph, (10, 120°), 42; Ph, Ph, (10, 140-150°), 63;
Me, Me, (2, 160-180°), 33 [42]

There are also examples of the use of compounds that are converted into diketones under the conditions of the Pfitzinger reaction and then react with isatins. Thus, the diacid **56** (yield 58%) was obtained from 2-hydroxy-3-butanone and isatin **7** in the presence of potassium hydroxide in water [26], while the dicarboxylic acids **58** were synthesized from 3-chloro-2-butanone and isatins **57** [44]. The initial chloro ketone is clearly saponified to 2-hydroxy-3-butanone under the reaction conditions. As in the reaction with isatin **7**, the product is then oxidized to 2,3-butanedione, which reacts with two molecules of isatin.

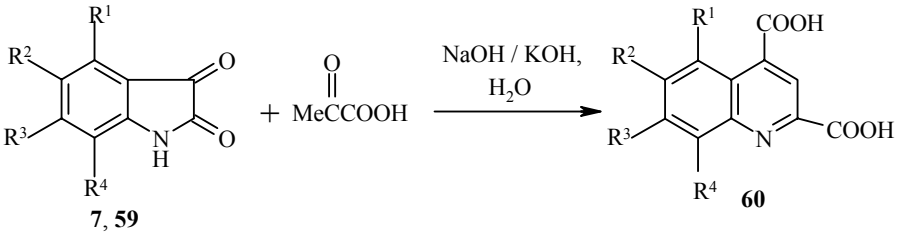


R^1, R^2, R^3: Me, H, H; H, Me, H; H, H, Me

2. REACTIONS WITH KETO ACIDS

In this section we will concentrate on papers in which the reactions of isatins with keto acids having various arrangements of the carbonyl and carboxyl groups, leading to quinolinedicarboxylic and quinolinetricarboxylic acids, are described. Pyruvic acid (an α-keto acid), its derivatives at the methyl group, and its esters in the Pfitzinger reaction have been studied in greatest detail.

In the search for antimalarial products and other biologically active compounds unsubstituted isatin **7** and its derivatives **59** were brought into condensation with pyruvic acid, resulting in the synthesis of the diacids **60** [7, 15, 45-47].

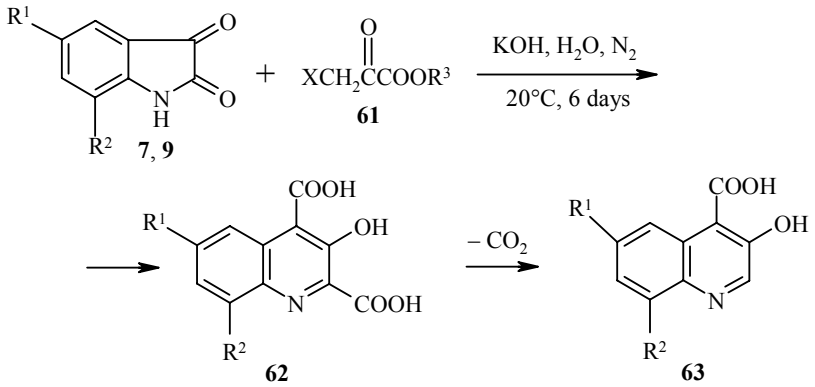


7, **59**

60

R^1, R^2, R^3, R^4, (conditions), yield, %: H, H, H, H, (33% KOH, H_2O, 20°C, 48 h) n/d [7]; H, OMe, H, H, (KOH, K_2CO_3, 20°C, 2 days), n/d [12]; H, OMe, OMe, OMe, (KOH, H_2O, 95°C, 6 ч), n/d [45]; H, Cl, H, H, (KOH, H_2O, 37°C, 48 h), 62 [15, 46]; H, H, Cl, H, (NaOH, H_2O, boiling, 8 h), 95; Cl, H, H, H, (NaOH, H_2O, boiling, 48 h), 30 [47]; H, H, H, Cl, (KOH, H_2O, 37°C, 48 h), 54 [15]; H, Cl, H, Cl, (KOH, H_2O, 37°C, 48 h), 97 [15]

The reaction of isatins **9** with halogen-substituted acids or their esters **61** takes place even at room temperature. The obtained dicarboxylic acids **62** are decarboxylated *in situ*, and the final products are derivatives of 3-hydroxy-4-quinolinecarboxylic acid **63** [48, 49].



7, **9**

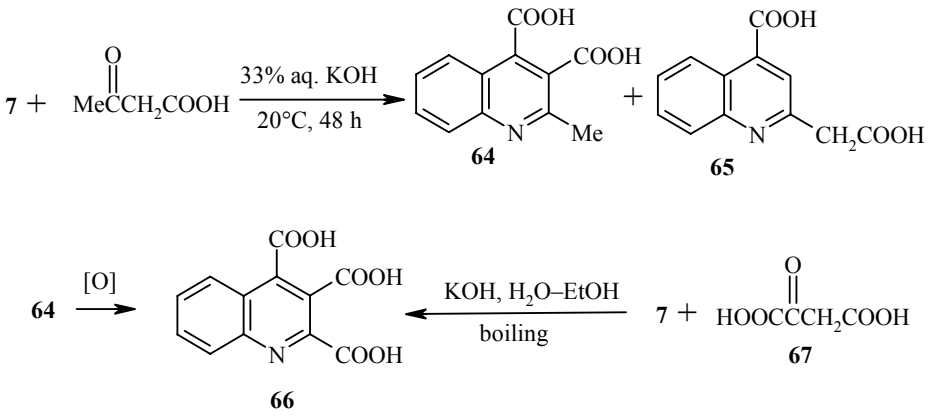
61

62

63

X: Cl, Br; R^1: H, Me, OMe, Cl, Br, I; R^2: H, Cl, COOH; R^3: H, Et. yields, %: 14-79

Structures **64** and **65** were proposed in [7] for the product from the condensation of isatin **7** with acetoacetic acid (a β-keto acid). The first must clearly be preferred, since the CH_2 group must be more active than CH_3 under the conditions of the Pfitzinger reaction. Actually in [21] the structure of the product **64** was proved by its oxidation to the tricarboxylic acid **66**, which was also synthesized from the keto dicarboxylic acid **67** and isatin **7**.



64

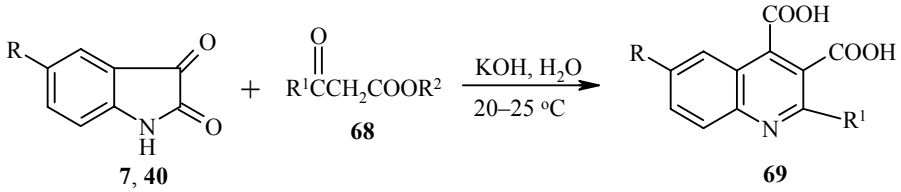
65

66

67

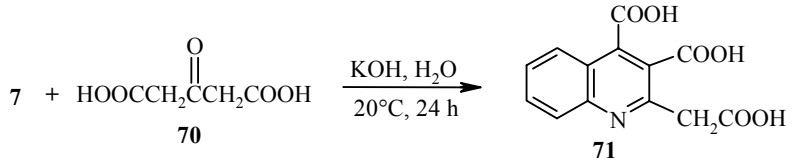
The 6-methoxy derivative of the acid **66** was obtained from the keto diacid **67** and 5-methoxyisatin (potassium hydroxide in water and alcohol, 20°C, 48 h) [12].

The reaction of the isatins **7** and **40** with β-keto acids and their esters **68** under analogous conditions led to the corresponding dicarboxylic acids **69** [21, 50-52]. The tricarboxylic acid **71** was synthesized from acetonedicarboxylic acid **70** and the isatin **7** [21].



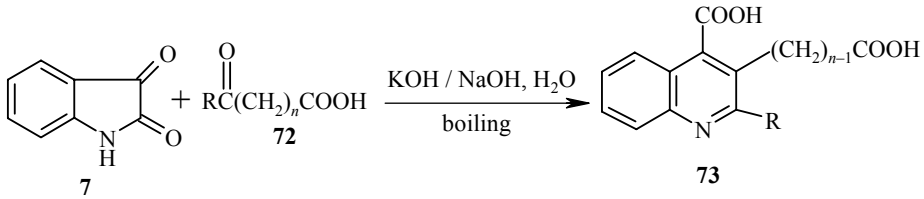
7, **40** **68** **69**

R, R^1, R^2, (time, h), yield, %: H, Ph, H, (24), n/d; Me, Me, H, (24), n/d [21]; Me, Me, Et, (48), 90 [50]; H, Me, Et, (24), 88; Me, Ph, Et, (75), 82; Me, $C_6H_3(OMe)_2$-3, 4, Et, (75), 71; Me, C_6H_4OMe-4, Et, (75), 75 [51]; H, Ph, Et, (48), 44; H, CH_2Ph, Et, (78), 64 [52]



70 **71**

A series of dicarboxylic acids **73** were synthesized as a result of a systematic study of the condensation of isatin **7** with keto acids **72** in the presence of potassium hydroxide or sodium hydroxide (Table 1) [53-59].



7 **72** **73**

TABLE 1

R	*n*	Yield of **73**, %	References	R	*n*	Yield of **73**, %	References
Me	3	62.5	58*	3-Indolyl	2	56.0	56, 57*[5]
Ph	2	65.0	53*[2]	3-Indolyl	3	45.0	56, 57*[5]
Ph	3	93.0	59*[2]	3-Indolyl	4	45.0	57*[5]
4-MeC_6H_4	2	53.0	53*[2]	1-Methyl-3-indolyl	2	55.0	56, 57*[5]
4-ClC_6H_4	2	66.0	53*[2]	1-Methyl-3-indolyl	3	40.0	56, 57*[5]
Ar	2	n/d	54*[3]	2-Methyl-3-indolyl	2	53.0	56, 57*[5]
2-Naphthyl	2	n/d	54*[3]	2-Methyl-3-indolyl	3	41.0	56, 57*[5]
2-Thienyl	2	70.0	55*[4]	2-Methyl-3-indolyl	4	53.0	56, 57*[5]
3-Indolyl	2	n/d	54*[3]	1,2-Dimethyl-3-indolyl	2	53.0	56, 57*[5]

* 33% aq. KOH, 72 h.

*[2] 33% aq. KOH, boiling 12 h.

*[3] Heating.

*[4] KOH, H_2O–EtOH, boiling 12 h.

*[5] 33% aq. NaOH, boiling 50 h.

3. REACTIONS OF ISATINS WITH ALKYL ARYL KETONES

Alkyl aryl ketones are most often used in the Pfitzinger reaction. In view of the large number of publications and the variety of the obtained compounds this material is examined in condensed form and is in a number of cases presented in tabular form.

In one of the first papers [7] it was reported that when isatin **7** was heated (100°C, 6 h) with acetophenone **74** in the presence of potassium hydroxide in water and alcohol 2-phenyl-4-quinolinecarboxylic acid (cinchophen) was formed with a yield of 65%. Later on [60-69] the isatins **59**, containing substituents in the benzene ring, were used in the Pfitzinger reaction with the same ketone, and the similarly substituted quinolinecarboxylic acids **75** were obtained (Table 2) [12, 14, 28, 31, 60-69].

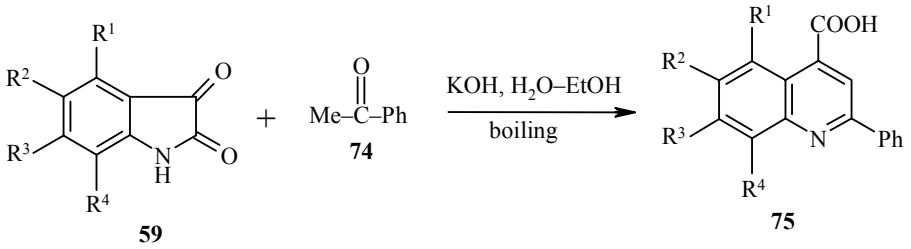
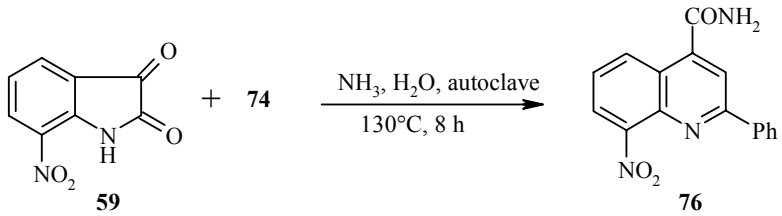


TABLE 2

	Substituent (reaction time, h), yield of product (**72**), % [reference]
R^2, R^3, R^4 = H	R^1 = COOH (n/d), n/d [60]; R^1 = Cl (8), 57 [61]; R^1 = SO_3K (24), 76* [62]
R^1, R^3, R^4 = H	R^2 = Me (n/d), n/d [63]; R^2 = OMe (12*[2]), n/d [12]; R^2 = COOH (7) n/d [64]; R^2 = F (1*[2]), n/d [14]; R^2 = Cl (24), 90 [31]; R^2 = Br (5*[3]), 78 [28]; R^2 = I (n/d), 83 [65, 66]; R^2 = NHAc (4), n/d [67]
R^1, R^4 = H	R^2 = R^3 = Cl (8), 86 [61]; R^2 = R^3 = Me (8), 85 [68]
R^1, R^3 = H	R^2 = R^4 = Br (8), 65 [69]
R^1, R^2, R^3 = H	R^4 = COOH (7), n/d [64]

* The product was 5-hydroxy-4-quinolinecarboxylic acid.
*[2] NaOH, H_2O.
*[3] NaOH, $Et_4N^+Br^-$, H_2O–PhH.

The reaction of 7-nitroisatin with the ketone **74** by heating with a concentrated aqueous solution of ammonia in an autoclave gave the amide **76** (yield 8%) [70].



2-Aryl-4-quinolinecarboxylic acids **78** (Table 3) were synthesized by the condensation of isatin **7** with monosubstituted acetophenones **77** [24, 63, 69, 71-80].

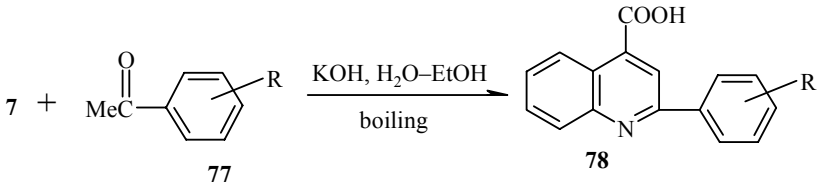


TABLE 3

R	Reaction time, h	Yield of **78**, %	References	R	Reaction time, h	Yield of **78**, %	References
4-Me	48	n/d	63	4-OBu	8	68	75
4-Pr-*i*	48	n/d	71	4-OC_5H_{11}	48	66	75
4-C_7H_{15}	24	95	72	4-SEt	24	n/d	24
4-C_8H_{17}	24	92	72	4-OPh/4-SPh	24	n/d	24
4-C_9H_{19}	24	96	72	4-(C_6H_4OMe-4)	24	n/d	24
4-$C_{12}H_{25}$	24	90	72	4-NEt_2	8	n/d	69
4-Br	8	65	24, 73	4-NO_2	8-10*	7	76
3-Cl	8	n/d	69	3-NO_2	8-10*	8	76
2-OH/4-OH	48	n/d	74	4-Ph	12-15	100	77
2-Cl/4-Cl	48	n/d	24, 74	4-$(CH_2)_2$Ph	12	95	78
3-Me	48	n/d	74	4-(C_6H_3Cl-3, Me-4)	68	85	79
4-OMe	6-8	85.9	75	4-(2,5-Dimethyl-pyrrol-1-yl)	24	98	80
4-OEt	8	70.8	24, 75	4-Et	48	n/d	24
4-OPr	8	67.1	75				

* NH_3 was used instead of KOH.

Data on the reaction of di- and trisubstituted acetophenones with isatin **7** are given in Table 4 [24, 69, 74, 79, 81-83] and with isatins **57** in Table 5 [14, 24, 29, 65, 69, 79, 84, 85].

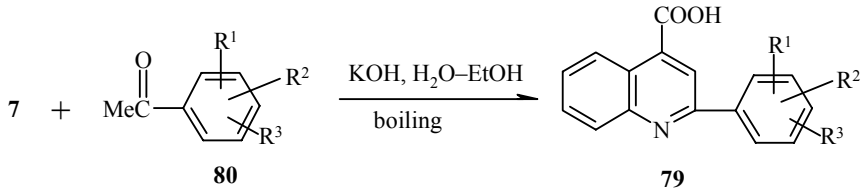


TABLE 4

R^1	R^2	R^3	(Reaction time, h), yield, % [references]	R^1	R^2	R^3	(Reaction time, h), yield, % [references]
2-Me	4-Me	H/5-Me	(24), 53/54 [81]	2-Cl	4-Cl/ 5-Cl	H	(8), n/d [69]
2-Me	5-Me	H	(24, 8, 48) n/d [24, 69, 74 resp.]	3-Cl	4-Cl	H	(24, 19), 82 [24,79]
2-Me	4-Bu-*t*	6-Me	(24), 0 [81]	3-Cl/ 3-Br	4-OMe	H	(24), n/d [82]
2-Me	4-OMe	6-Bu	(24), 0 [81]	3-Cl	4-OEt	H	(24), n/d [82]
3-Me	4-Me	H	(24, 48), n/d [24, 74]	4-Cl	5-Cl	H	(14), 71 [79]
				3-NO_2	4-NHAc	H	(3), n/d [83]

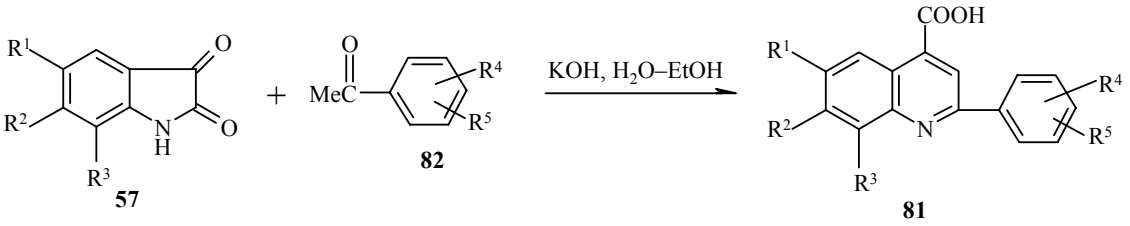
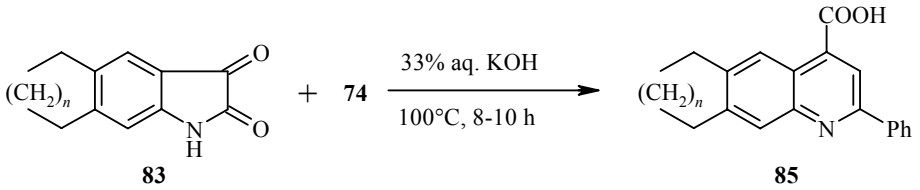


TABLE 5

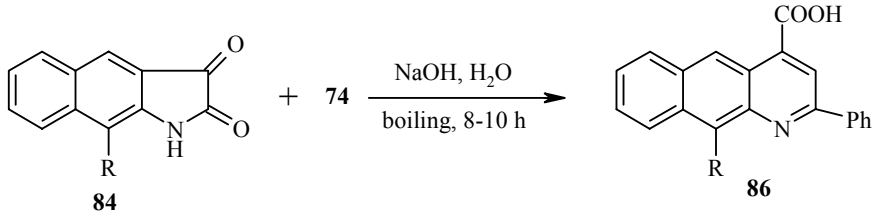
R^1	R^2	R^3	R^4	R^5	(Reaction time, h), yield of **80**, % [references]
H	H	Cl	4-Cl	H	(10), 51 [79]
H	OMe	H	3-Cl	4-Cl	(42.5), 82 [85]
H	Cl	H	4-Cl	H/5-Cl*	(30/28), 86/45 [79]
Me	H	H	4-Cl	H	(24), n/d [24]
Me, Br, I	H	H	3-Me	4-I	(n/d), n/d [65]
F	H	H	4-F	H	(1*[2]), n/d [14]
Cl	H	H	4-Me	H	(24), n/d [24]
Cl	H	H	3-OMe	4-OMe	(22), 95 [85]
Cl	H	Cl	4-Cl	H	(24-48), 85-87 [79, 84]
Cl	H	Cl	3-Cl	4-Cl	(21), 53 [79]
Cl	OMe	H	4-OMe/4-Cl	H	(24/40), 75/76 [85]
Cl	Cl	H	4-OMe	H	(40), 75 [85]
Br	H	H	3-Me/4-OMe*[3]	H	(24/5), n/d /82 [24, 29]
Br	H	H	3-Me, 4-Pr-*i*, 4-Ph, 4-Cl, 4-Br, 4-I	H	(24), n/d [24]
Br	H	H	2-Me	4-Me/5-Me	(24), n/d [24]
Br	H	Br	4-OMe	H	(8), 65 [69]

* There is also a 2-Me substituent in the benzene ring.
*[2] NaOH, H_2O.
*[3] NaOH, $Et_4N^+Br^-$, H_2O–PhH.

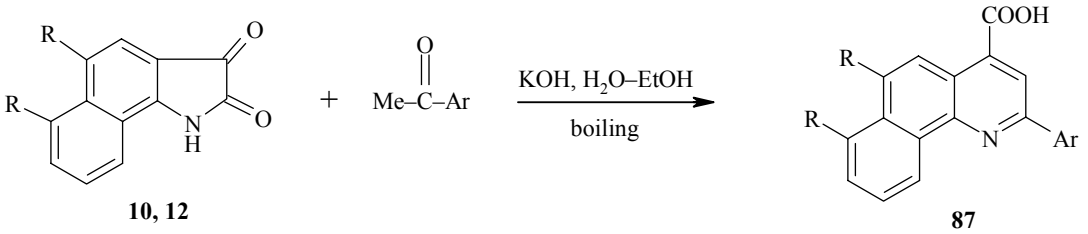
The schemes presented below illustrate investigations into the reaction of acetophenone **74** [18, 19, 68, 86, 87] and more complex methyl aryl ketones [19, 88] with annelated isatins **10**, **12**, **32**, **83**, and **84**, leading to various polycyclic systems **85**-**88**.



n, yield, %: 1, 40; 2, 53 [68]

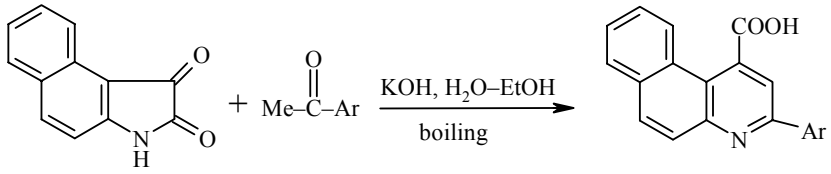


R, yield, %: Cl, 70 [86]; H, n/d [87]



10, 12 **87**

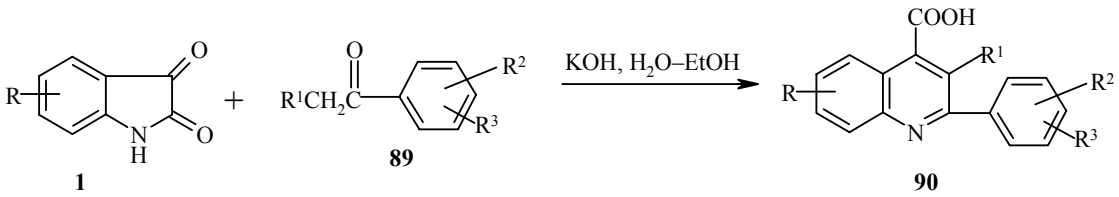
R or R+R, Ar (time, h): H, Ph (36) [18]; CH_2CH_2, Ph (30-36) [19]; C_6H_4Ph-4 (24); H, 2-naphthyl (8); H, 4-methyl-1-naphthyl (8); H, 2-anthracenyl (8); H, 2-acenaphthenyl (8); H, 1-pyrenyl (8) [88]; CH_2CH_2, 2-phenanthrenyl (24) [19]



32 **88**

Ar: C_6H_4Ph-4; 4-methyl-1-naphthyl; 2-fluorenyl; 2-anthracenyl; 5-acenaphthenyl; 1-pyrenyl; 6-benzo(*a*)phenanthrenyl

In [88] it was shown that the ketones **81** and **82** react with the isatins **10** and **32** only if the Ar does not contain substituents at the *o*-position to the carbonyl group; the products **87** and **88** here are obtained with almost quantitative yields. By replacing the methyl group in the acetophenones by RCH_2 [in ketones of type **89**] it is possible to obtain 2,3-disubstituted quinolinecarboxylic acids with structure **90**, many examples of the synthesis of which are summarized in Table 6 [24, 80, 82, 89, 90-97].



1 **89** **90**

TABLE 6

R	R^1	R^2	R^3	References
1	2	3	4	5
H	Me (68), 90; Et, (2), 18; Ph, (100), 80	3-Cl, C_6H_4Me-4	H	89
	Me, Et	3-Cl; 3-Br	4-OMe	82
		3-Cl	4-OEt	82
	Bu (24), 30; C_6H_4Me-4, (48), 37; $C_6H_3Me_2$-2,4, (48), 12; $C_6H_2Me_3$-2,4,6, (48), 0	H	H	90
	OMe, (6-8), 96; NH_2 (6-8), n/d	H	H	92
	α-$C_{10}H_7NH$, (n/d), n/d	H	H	94
	Ph, (12)	4-Me, 65; 4-Et, 55	H	91
		4-CH_2Ph, 44; $CHPh_2$, 68 2-Me, 21; 2-Cl, 24	4-Me	91
6- Me, 65 7- Me, 70 8-Me, 80 8-Me	NH_2, (6-8)	H	H	93
	Ph, (12), 55	5-Me	2-Cl	91

TABLE 6 (continued)

1	2	3	4	5
5-F	Me, (18)	4-Ph, 58	H	96
6-F	Me, (12)	4-C_6H_{13}, 56	H	95
	Me, (n/d)	C_6H_4F-2, n/d	H	97
6-Br	Me, (24)	H; 4-Et, 4-Bu	H	24
	Me, (24)	2-Me	5-Me	24
	Me, Et (24)	4-Pr; 4-Ph	H	24
	Me, Et	6-Tetralinyl (24), n/d	H	24
	Me, Et, Ph, (24)	4-Cl	H	24
	Me, Et, Ph, CH_2COOH (24)	4-Br	H	24
	Et, (24)	3-OMe	4-OMe	24
	Ph, (24)	2-OMe	4-OMe	24
	Ph, (24)	2-Me	5-Me	24
	Me (n/d)	4-(2,5-Dimethyl-1-pyrrolyl), n/d	H	80
	Ph, (12)	2-Me, 46.5	5-Me	91
6-Cl	Ph, (12)	4-Me, 69; 2-Me, 17	H	91
		2-Cl, 43	4-Me	91

It is well known, however, that ketones $Me(CH_2)_nCOAr$ ($n > 2$) hardly react at all with isatin **7** under the usual conditions of the investigated reaction even when boiled for 36 h [24].

On the other hand, in the reaction of the isatins **40** with the ketones **91**, in which the Ar groups are condensed systems, the corresponding acids **92** are as a rule formed with high yields (Table 7) [19, 24, 29, 72, 81, 91, 98].

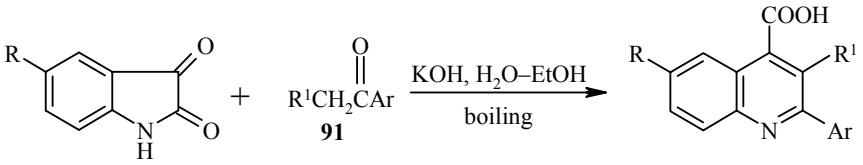


TABLE 7

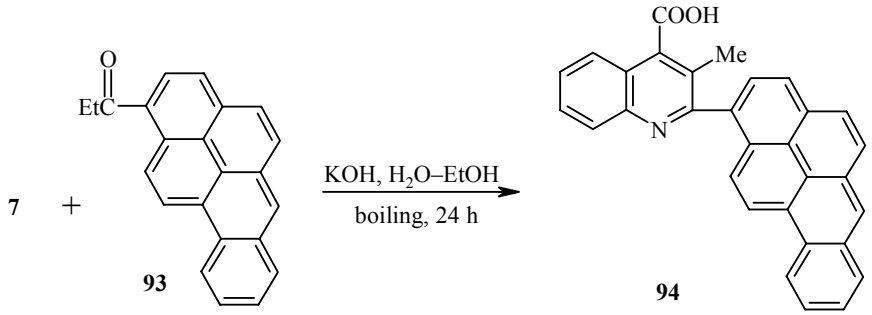
R	R^1	Ar	(Reaction time, h), product yield, % [reference]
1	2	3	4
H	H	2-Naphthyl	(96), 96 [101]
		2-Methyl-1-naphthyl, 4-methyl-1-naphthyl	(24), 90-100 [72*, 81]
		2-Methoxy-1-naphthyl, 2-fluorenyl*	
		5-Indanyl*	(24), 80 [72]
H	Me, Et	2-Naphthyl	(48/96), 90/90, 62 (R^1 = Et) [81, 98]
	Me, Et, Pr	2-Fluorenyl	(24), 0 (Pr), 89 (Me) [81]
	Et	3-Phenanthrenyl	(24), 78 [81]
	Me	1-Benzpyrenyl	(24), 35 [19]
	Me, Et	5-Acenaphthenyl	(48), 78,75 [81]
	Bu-*i*, C_5H_{11}, C_6H_{13}, C_7H_{15}, C_4H_{19}, $C_{11}H_{23}$	2-Naphthyl	(96), 33 (*i*-Bu), 46-56, 28 (C_9H_{19}) 16 ($C_{11}H_{23}$) [98]

TABLE 7 (continued)

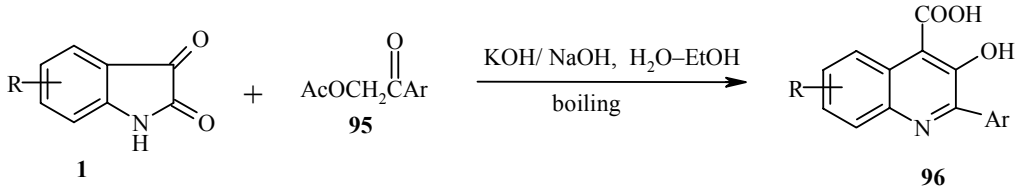
1	2	3	4
H	Ph	2-Naphthyl, 7-methyl-1- and 7-methyl-2-naphthyl	(12), 63-78 [91]
		4-Methoxy-1-naphthyl, 6-chloro-1-naphthyl	(12), 15, 60 [91]
		5-Acenaphthenyl	(12), n/d [91]
Br	H	1-Naphthyl	(5)*[2], 78 [29]
	Me	4-Methyl-1-naphthyl, 5-acenaphthenyl	(24), n/d [24]
	H, Me, Et	3-Pyrenyl	(24), n/d [24]

* At 70-80°C.
*[2] NaOH, $Et_4N^+Br^-$, H_2O–PhH.

Under similar conditions the condensation of isatin **7** with 11-propionyl[3,4]benzpyrene **93** leads to the acid **94** with a yield of 71% [19].

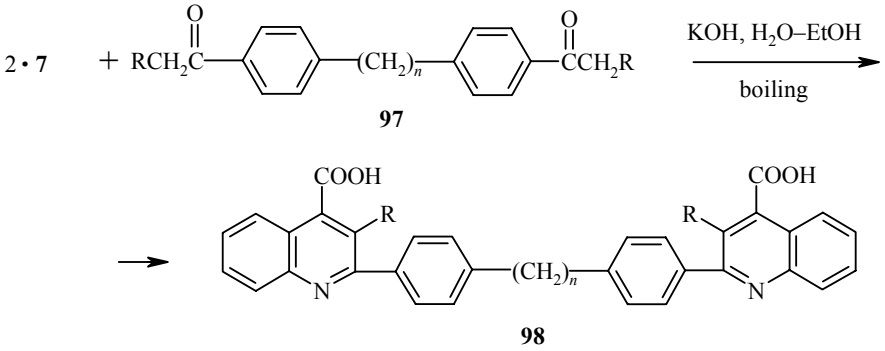


When the isatins **1** and the acetates of α-hydroxy ketones **95** are heated in the presence of potassium hydroxide [99] or sodium hydroxide [100] in water and alcohol, hydrolysis of the OAc group occurs in addition to recyclization, and the reaction products are 2-aryl-3-hydroxy-4-quinolinecarboxylic acids **96**, recommended as antiarhythmic agents and immunodepressants.



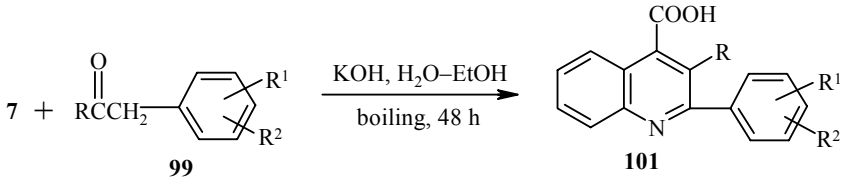
R: H, 8-Me, 6-OMe, 6-Cl; Ar: $C_6H_4R^1$ (R^1: H, 4-Br, 4-OMe, 4-NH_2, 4-Ph), CH_2Ph, $C_6H_3Me_2$-2,4. Time, h: 10 [99]; 4 (for R = 6-OMe, Ar = CH_2Ph [99]; 2.5 [100]. Yields 11-100%

The diketones **97** react with two molecules of isatin **7**, forming the dicarboxylic acids **98** [77, 78].



R, *n*, (time, h), yield,%: H, 0, (3), 41.5 [77]; H, 2, (18), n/d [78];
Me, 2, (18), 20.0 [78]

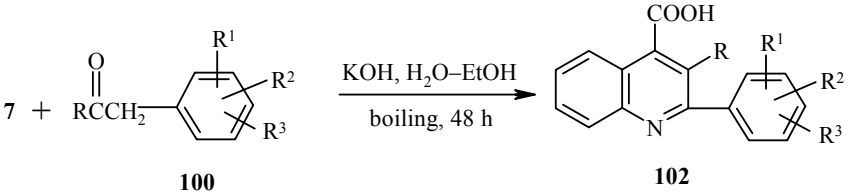
The benzyl CH_2 group takes part in the reaction of isatin **7** with the ketones $RCOCH_2Ar$ **99** and **100**, and the analogs of compounds **90**, i.e., the acids **101** and **102**, are formed. For these reactions the effects of the position and size of substituents in the benzene ring and alkyl radical of the ketone on the formation of the products **101** and **102** were investigated [101, 102]. According to the reactivity in the investigated examples the ketones **99** and **100** were separated into the three groups indicated in the schemes below.



1. Ketones reacting normally with isatin: for R = H, Me, Et, Ph R^1 = 3-Me, R^2 = 4-OMe; then indicated R, R^1, R^2: H, 2-Me, 4-OMe; Me, 2-Me, 4-OMe; Ph, 2-Me, 4-OMe; H, 2-Me, 4-OPr; Me, 2-Me, 4-OPr; Ph, 2-Me, 4-OPr; H, 2-Me, 4-OBu-*i*; Me, 2-OMe, 3-Me; H, 2-OC_5H_{11}-*i*, 3-Me [97]; H, 2-Me, 5-OEt; Me, 2-Me, 5-OEt; H, 2-Me, 4-OBu [98].

2. Ketones reacting with isatin to an insignificant degree: for R = Me, Et, Ph R^1 = 3-Me, R^2 = 4-OC_5H_{11}-*i*; then indicated R, R^1, R^2: 2-Me, 4-OBu; Et, 2-Me, 4-OMe; Et, 2-Me, 4-OPr; Et, 2-Me, 4-OBu; Ph, 2-Me, 4-OBu-*i*; Ph, 2-Me, 4-OBu [97].

3. Ketones not reacting with isatin: R = Et, R^1 = 2-C_5H_{11}, R^2 = Me [97].



1. Ketones reacting normally with isatin: for R = H, Me, Ph R^1 = 2-OMe, 2-OC_5H_{11}-*i*, 4-OPr, R^2 = 2-Me; R^3 = 5-Me; then indicated R, R^1, R^2, R^3: H, 2-Me, 4-OEt, 4-Pr-*i*; Me, 2-Me, 4-OEt, 5-Pr-*i*; Me, 2-Me, 4-OEt, 5-Pr-*i*; Me, 2-Me, 3-Bu-*i*, 4-Me [98].

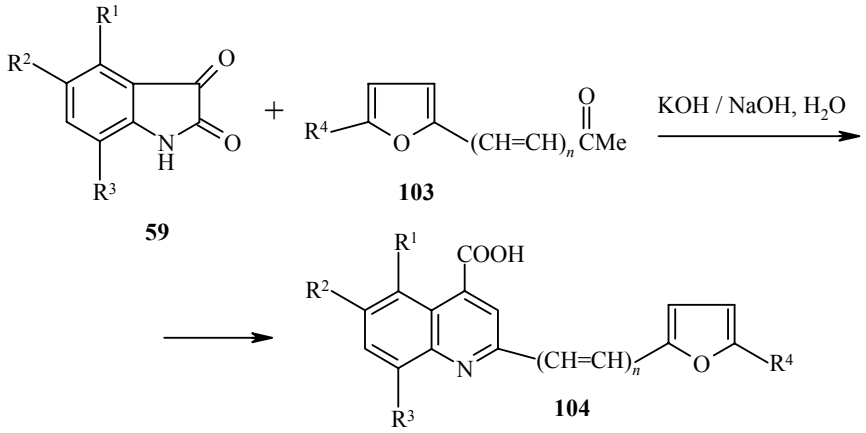
2. Ketones reacting with isatin to an insignificant degree: R, R^1, R^2, R^3: Et, 2-Me, 4-OPr, 5-Me; 2-Me, 4-OBu, 5-Me; Et, 2-Me, 4-OBu, 5-Me; Ph, 2-Me, 4-OBu, 5-Me [98].

3. Ketones not reacting with isatin: R = Me, Ph; R^1 = 2-Me; R^2 = 4-OMe; R^3 = 6-Me [98].

It follows from the data in [101, 102] that the Pfitzinger reaction is sensitive to steric factors arising not only from the effect of substituents at the *ortho* positions of the benzene ring but to some degree also from the size of the substituent at the *para* position.

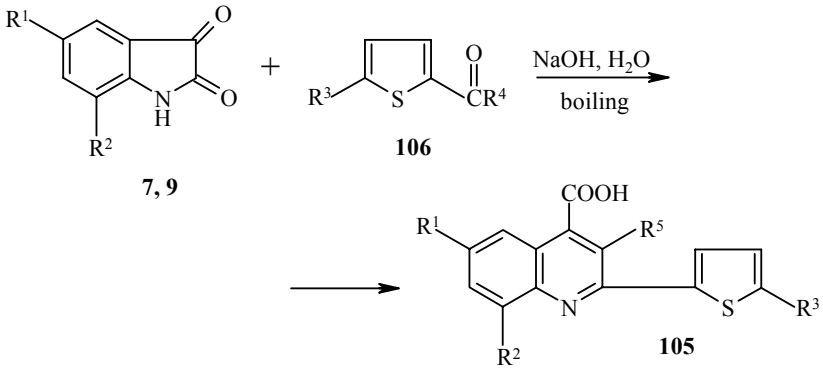
4. REACTIONS OF ISATINS WITH ALKYL HETARYL KETONES

By the reaction of isatins with alkyl hetaryl ketones it is possible to obtain various 2-hetaryl-substituted 4-quinolinecarboxylic acids. Thus, in the presence of aqueous solutions of alkalis ketones of the furan series **103** react with isatins **59** with the formation of acids **104** containing a furyl substituent [12, 103, 104].



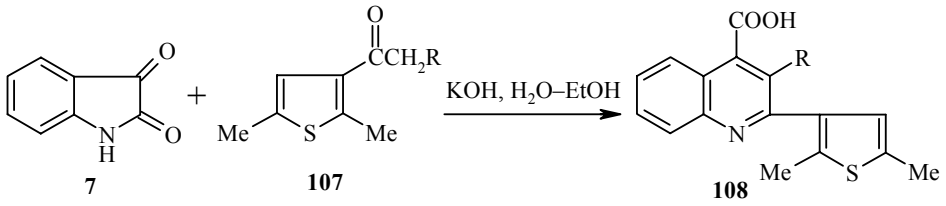
R^1 = H, Cl; R^2 = H, Me, OMe, Cl; R^3 = H, Cl; R^4 = H, NO_2; n = 0, 1. Yields 46-86%

The thienyl-substituted acids **105** were synthesized by the condensation of isatins **9** with acylthiophenes **106** [104-106].



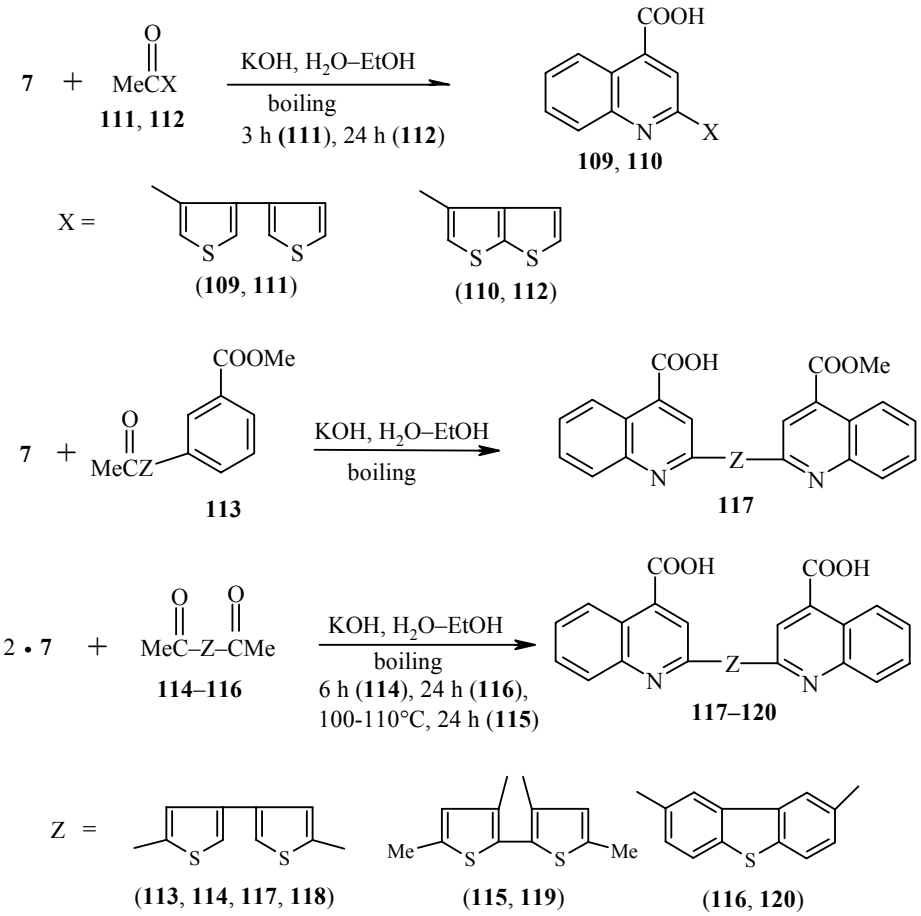
R^1 = H, Me, C_8H_{17}; R^2 = H, Cl, C_7H_{15}; R^3 = H, NO_2, Ph; R^4 = H, Alk (C_1-C_7, C_9-C_{11}), CH_2Ph;
R^5 = H, Alk (C_1-C_6, C_8-C_{10}), Ph. For R^1 = R^2 = R^5 = H, R^3 = R^4 = Me yield 60%

During study of the behavior of alkyl 2,5-dimethylthienyl ketones **107** in the Pfitzinger reaction it was found that their reaction with isatin **7** under normal conditions, leading to compounds **108**, only takes place with R = Me, Ph; with R = Pr, Bu the corresponding products could not be isolated [107]. This is clearly due to steric hindrances brought about by the groups 2-Me and R containing two or more carbon atoms.

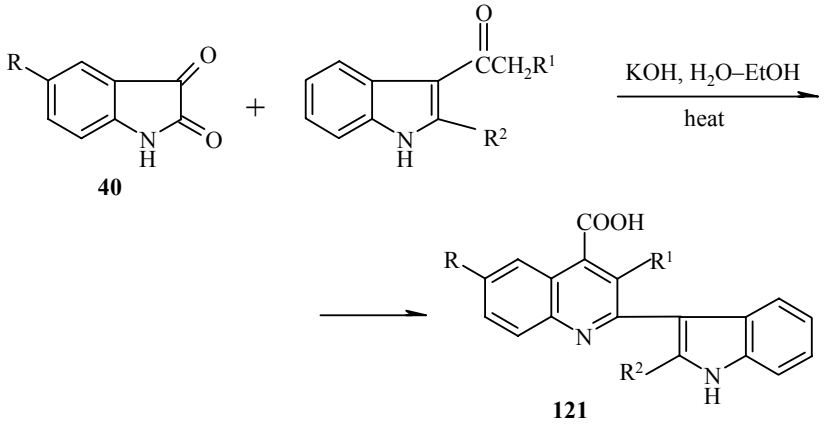


R, yield, %: Me, 50; Ph, 41

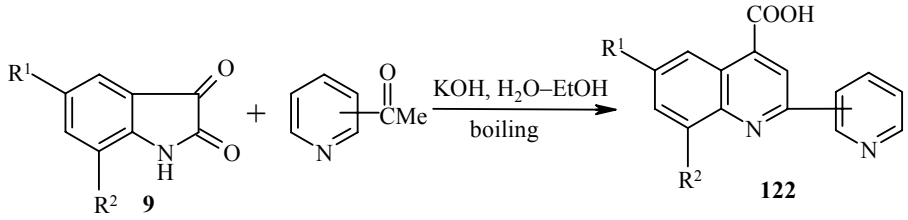
Compounds **109** and **110**, containing two uncondensed or condensed thiophene rings, were synthesized with high yields from the corresponding ketones **111** and **112** and isatin **7** [77, 108]. The bithiophene **117-119** [77, 108] or dibenzothiophene **120** [109] derivatives, containing two 4-quinolinecarboxylic acid residues as substituents, were easily obtained in the same way from the ketone **113** and the diketones **114-116** by condensation with isatin **7**.



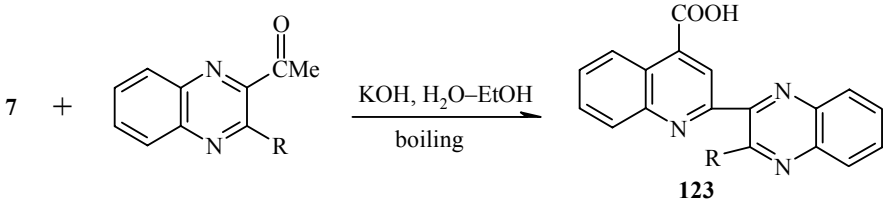
The schemes below give the available data on the synthesis of derivatives of 4-quinolinecarboxylic acid **121-123** with substituted indole [110], pyridine [13, 104, 111, 113], or substituted quinoxaline [113] residues at position 2. It should be noted that compounds **122** with a pyridyl substituent were synthesized in the search for substances having antimalarial activity.



R: H, Me, Br; R^1 = H, Me; R^2 = H, Me, Ph [110]



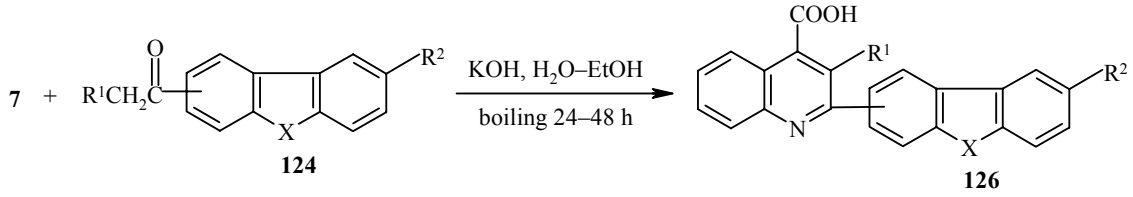
R^1 = H, Cl, Br; R^2 = H, Me, Cl, Br. Time, h: 22/72 [13], 6 [104], 2 [111, 112]. Yields 50-70%



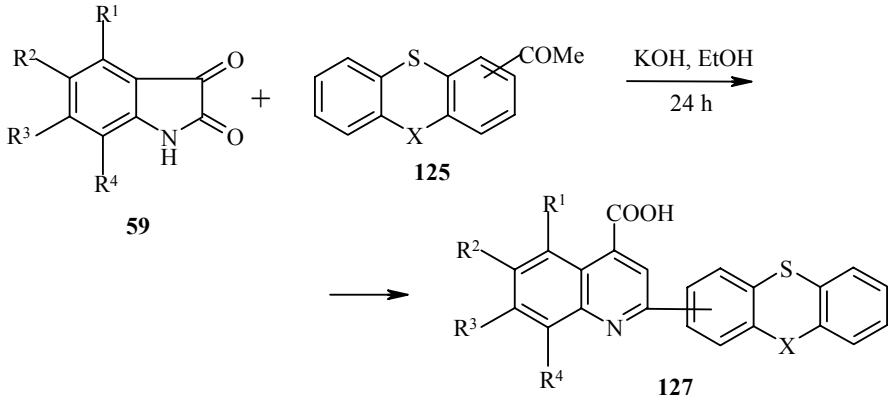
R = H, Me [113]

The condensation of isatin **7** with 2-acetyl-4-phenylquinoline (sodium hydroxide or potassium hydroxide, water, boiling, 1 h) gave an 80% yield of 2-(4-phenyl-2-quinolinyl)quinoline-4-carboxylic acid [114, 115].

The reaction of isatin **7** with acylated dibenzothiophene [81, 109, 116], dibenzofuran [116], and dibenzopyran [72] with the general formula **124** and also the reaction of the isatins **59** with acetylphenothiazine [72] and acetylthianthrene [117] with the general formula **125** gave the corresponding quinolinecarboxylic acids **126** and **127**, having a tricyclic condensed system with a heterocycle as substituent at position 2.



R^1, position of $COCH_2R^1$, R^2, X, yield, %: H, 3, H, NH, (70-80 °C, 24 h), 78 [72];
Me, 2, H, S, 90 [81]; H, 2, H, S, (12 h), 80 [109, 116]; H, 2, H, O, 78; Et, 2, H, O, 31;
Ph, 2, H, O, 68; H, 2, Br, S, 30; Ph, 2, Br, S, 27 [116]

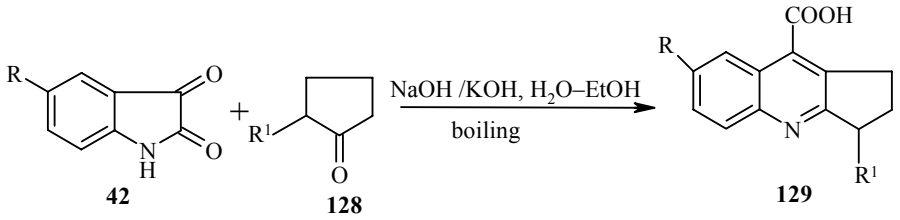


R^1, R^2, R^3, R^4, position of COMe, X, temperature, °C: H, H, H, H, 3, NH, 70-80 (yield 88%) [72]; Me, H, Me, H, 2, S, 100; H, Me, H, Me, 2, S, 100 [117]

5. REACTIONS OF ISATINS WITH CYCLIC KETONES AND DIKETONES

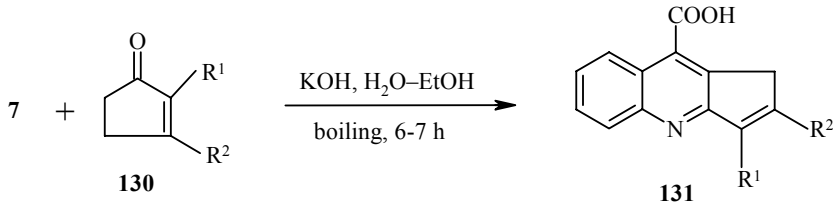
The Pfitzinger reaction provides a simple and convenient method for the synthesis of condensed polycyclic compounds containing a heterocycle from readily obtainable starting materials. Cyclic ketones and, more rarely, diketones are often used as starting compounds.

The condensation of isatins **42** with cyclopentanone and its derivatives **128** has been investigated in a fair amount of detail [13, 19, 118-120]. It was found that the size of the substituent adjacent to the carbonyl group of the ketones has a significant effect on the yield of the condensation products **129**. Thus, in the case of 2-methylpentanone the yield of the acid **129** (R^1 = Me, R = H) amounted to 78%; in the case of 2-ethylcyclopentanone the yield was 1% (R = H, R^1 = Et), and with 2-propylcyclopentanone the reaction did not occur [119].



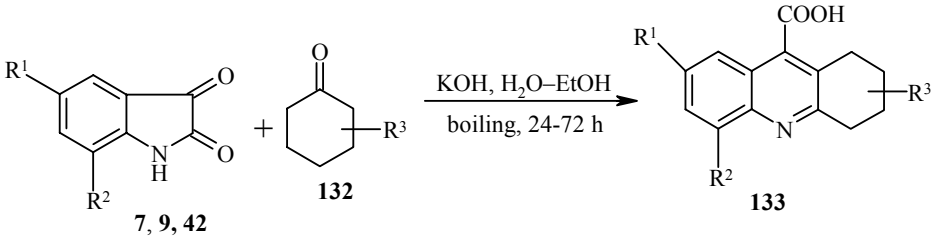
R, R^1, (time, h), yield, %: Br, H, (22), 55 [13]; F, H, (1), n/d [14]; H, Me, (24), 75 [19]; H, H, (5), 57 [13]; H, H, (22), 89 [20]; H, H, (8), 62-87 [118-120]; H, Et, (72), n/d; H, Pr, (72), 0 [119]

Derivatives of 2-cyclopentenone **130** enter readily into reaction with isatin to form the corresponding tricyclic compounds **131** [121, 122].



R, R^1: H, Ph [121]; CH_2COOH, Ph [122]

The reaction of the isatins **9** with cyclohexanones **132** leads to the formation of derivatives of 1,2,3,4-tetrahydro-9-acridinecarboxylic acid **133**. If R = H the yields of the products **133** amount to 75-100% [19, 20, 65, 118, 123-125]. However, it was noticed in [19] that cyclohexanone does not react with α-naphthisatin **10** under the conditions of the Pfitzinger reaction.

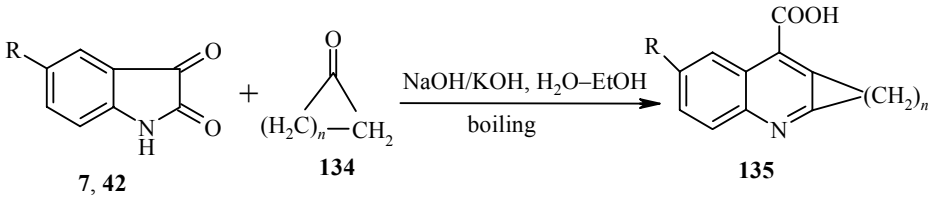


7, **9**, **42** **132** **133**

R^2 = H, R^1, R^3, position of R^3 in **132** and **133**, (time, h), yield, %: H, Me, 2 and 4, (60) [19, 119]; H, Et, 2 and 4, (72), <1; H, Pr, 2 and 4, (72), O; H, $(CH_2)_nMe$ (*n* = 3-7), 2 and 4, (24), 80 [24]; H, Me, 3 and 3, (72), 80; H, Me, 4 and 2, (72), 85; H, C_6H_{11}, 4 and 2, (72), 85 [119]; R^3 = H, R^1, R^2: H, H [20, 118, 123-125]; Cl, Cl; Me, Me [19]; H, H [65]; Br, H; Br, Br [118]; Cl, H; Me, H [123]

The position and size of the substituent R^2 in the cyclohexanone derivatives has a significant effect on their reaction with isatins. Thus, if R^2 is at position 3 or 4, high yields of the products from condensation with isatins **42** are formed. On the other hand, from the ketones with various substituents R^2 at position 2 under the same conditions good yields are only observed with R^2 = Me [13, 19, 24, 119].

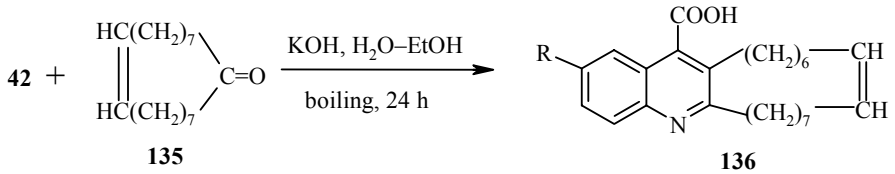
The reactions of isatins **7** [118, 126] and **42** [13, 82, 127-129] with ketones **134** containing seven and 7-17 CH_2 units respectively in the ring have also been described.



7, **42** **134** **135**

R = H, *n* = 6, base, yield, %: NaOH, n/d [126]; KOH, 47 [118]. Base KOH, R, *n*, (time, h): H, 5-6, (72); Br, 5, (24); Br, 6, (72) [13]; H, 5, (72); Br, 5, (24), Br, 6, (72) [13]; H, 11, (24) [82]; Me, 6-8, (24) [127]; H, 6, (15); Cl, 6, (15); Br, 6, (15); Br, 13, (15) [128]; H, 12, (24); H, 15, (24); Me, 13, (24) [129]

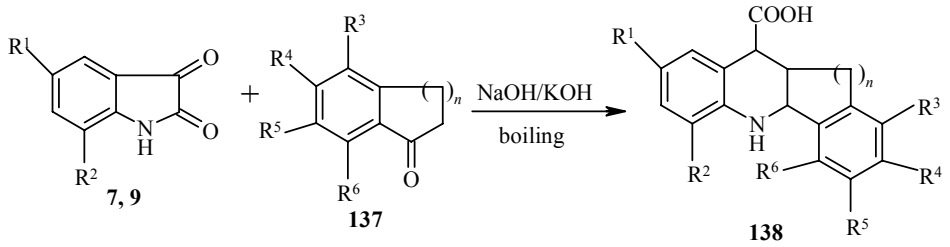
Compounds **136** containing an unsaturated macrocycle were obtained with yields of up to 85% from civetone **135** and isatins **42** [128, 129].



135 **136**

R: Br [128]; H [129]

The reaction of isatins **7** and **9** with substituted benzannelated ketones **137** led to tetracyclic and pentacyclic (with $R^3 + R^4 = CH_2–CH_2$) acids **138** [130-134].

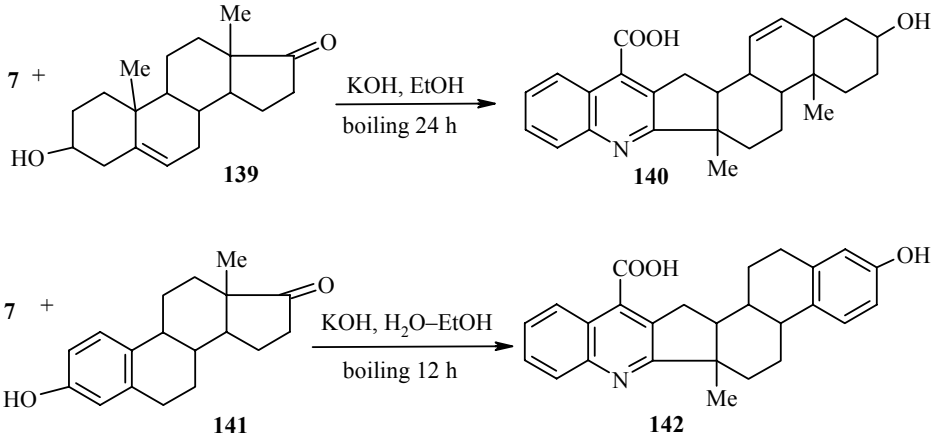


R^3 = H, n = 1, time 12 h, R^1, R^2, R^4, R^5, R^6: H, H, H, H, H, (yield 85%) [130]:
H, H, H, Bu-*t*, H; H, Br, H, Bu-*t*, H; H, OMe, H, H, Me; Br, OMe, H, H, Me; H, Pr-*i*, OMe, Me, H; Me, H, $(CH_2)_4$, H [131];
n = 2, R^1, R^2, R^3, R^4, R^5, R^6, (time, h), yield, %: H, H, H, H, Bu-*t*, H, (12), n/d; H, H, Me, H, OMe, Pr-*i*, (12), n/d;
Me, H, H, H, Bu-*t*, H, (12) n/d [131]; H, H, H, H, H, H, (100), 65; Br, H, H, H, H, H, (100), n/d; Br, Br, H, H, H, H, (100), n/d [132];
F, H, H, Ph, H, H, (12), 78 [133]; F, H, H, Ph, C_6H_4F-4, H, (n/d), 68 [134]

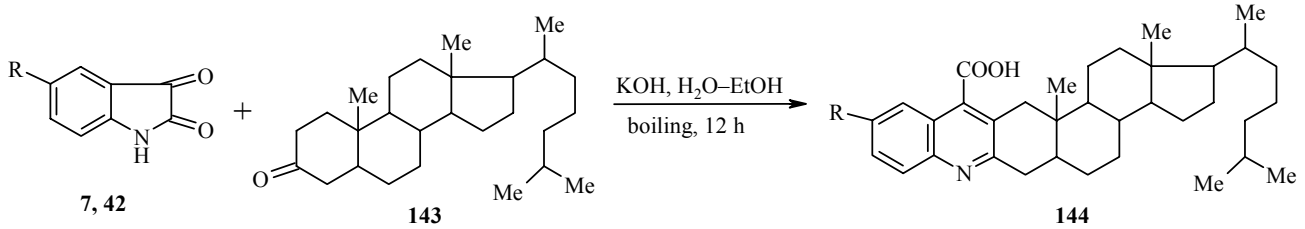
Compound **138** with R = F, R^3 = Ph, and R^1 = R^2 = R^4 = R^5 = H was patented as a product active against leukemia and melanoma [133].

Attempts at the reaction of isatins with menthone, pulegone, camphor [118], isopulegone, dihydroisopulegone, tetrahydrocarvone, or norcamphor [19] were unsuccessful even with prolonged heating (potassium hydroxide, water, ethanol, 100°C, 3 days).

In [135, 136] the behavior of ketones of the steroid series in the Pfitzinger reaction was also studied. From dehydroepiandrosterone **139** and isatin **7** compound **140** was synthesized with a yield of 20%, and the reaction was accompanied by isomerization of the double bond [135]. The reaction of estrone **141** and isatin **7** leads to the acid **142** [136].

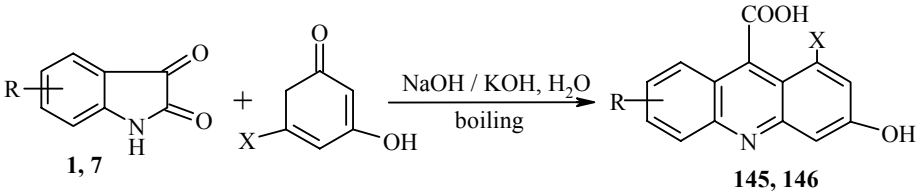


Compounds **144** were synthesized from cholestanone **143** and isatins **7** and **42** under the same conditions, but the reaction of the same isatins with testosterone (with R = H in the isatin) or chlolestenone (with R = Me) could not be realized [136].



R: H [135, 136]; Me (yield 100%) [136]

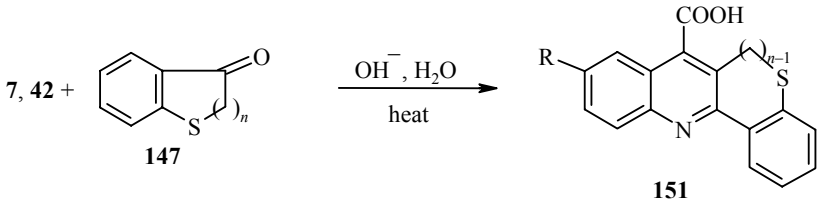
Among the ketones examined in this section it is also possible to include the di- and trihydroxy derivatives of benzene, which are capable under the reaction conditions of forming tautomers containing a keto group. Thus, 3-hydroxy-9-acridinecarboxylic acid **145** was obtained by heating isatin **7** with resorcinol in the presence of alkali in water [137]. Other derivatives of 9-acridinecarboxylic acid **146** were synthesized with yields of 72-92% from phloroglucinol (used in the form of the dihydrate) and isatins **1**. The reactions were conducted in the presence of sodium hydroxide [137, 138] or potassium hydroxide [139] in water.



1, 7 **145, 146**

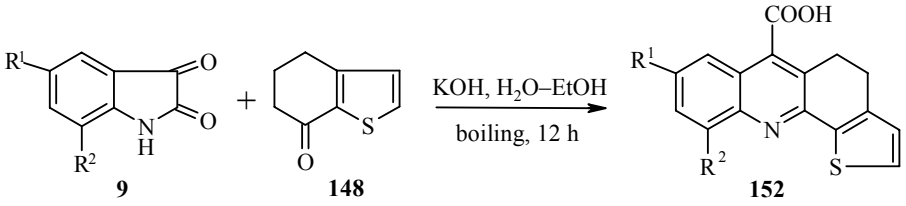
145 X = H [137]; **146** X = OH, time 5 h, R = H [137, 139]; 5-F, 6-F, 7-F [138]

Heterocyclic ketones **147** [130, 140], **148** [52], **149** [141, 142], and **150** [143] have also been studied in the Pfitzinger reaction. Their structure, the structure of the obtained products **151-154**, and the reaction conditions are given in the schemes (see below). Among the obtained the acids **153** (yields ~70%), which inhibit the ignition of cotton induced by oils, should be mentioned.



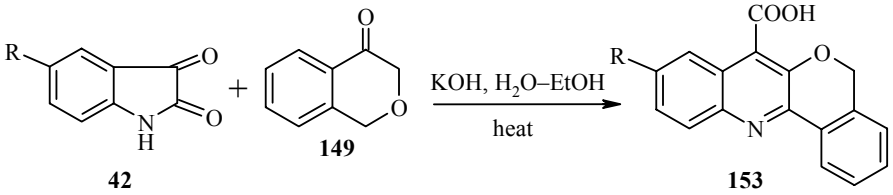
147 **151**

147, **151** *n* = 1, 2, R = H, Me



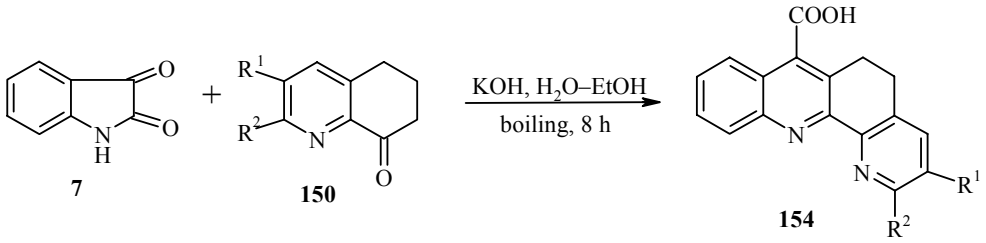
9 **148** **152**

R^1, R^2: H, H; Me, H; Me, Me; Br, H. Yields 90-100%



42 **149** **153**

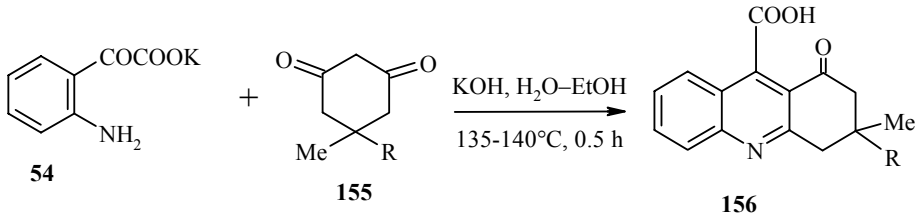
R: H, Cl, Br, Me



7 **150** **154**

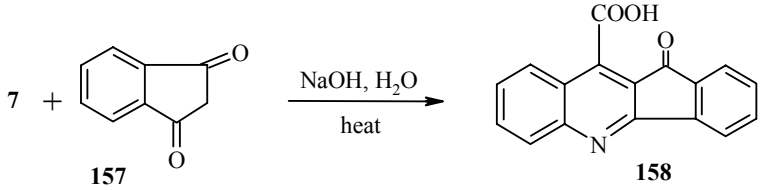
$R^1 + R^2$: $(CH_2)_4$, CH=CH–CH=CH. Yields up to 78%

There are a few examples of the use of cyclic diketones in the Pfitzinger reaction. In all the described cases the products from reaction of only one carbonyl group in these compounds with the isatin were obtained. Thus, the keto acids **156** were formed as a result of the reaction of the salt **54** (previously obtained from the isatin **7**) with the diketones **155** [42].

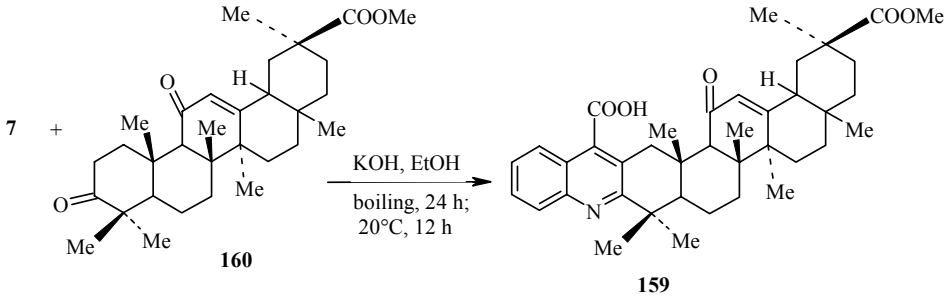


R: H, Me

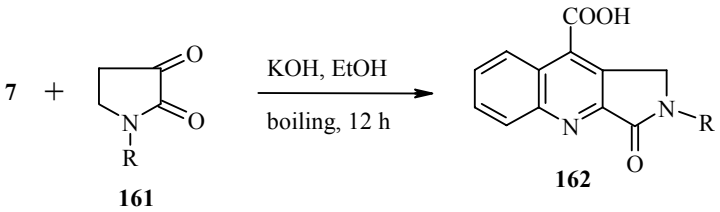
The keto carboxylic acid **158** was obtained from 1,3-indanedione **157** and isatin **7** [130].



A compound of the triterpenoid series, ketomethyl glycyrrhetate **159**, which contains seven condensed six-membered rings, is formed with a yield of 42% as a result of the condensation of isatin **7** with the diketone **160** [144]. If the reaction is carried out in butanol instead of ethanol, the reaction takes place more quickly, but the yield of compound **159** is lower on account of resinification processes.



The condensation product **162** is formed with yields of 71% or 84% [145] when isatin **7** is heated with the N-derivatives of pyrrolidine-2,3-dione **161**.

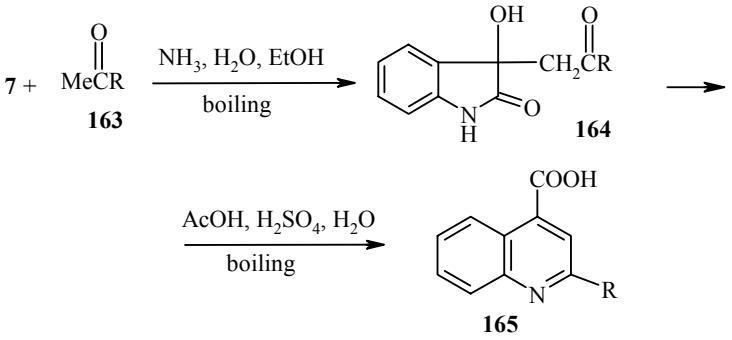


R (yield, %): C_6H_{11} (71), CH_2Ph (84)

6. REACTIONS RELATED TO THE PFITZINGER REACTION

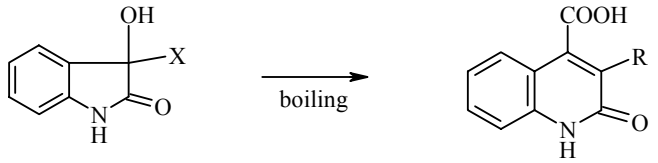
This section reviews the results of investigations on other methods for the synthesis of 4-quinolinecarboxylic acid derivatives, including various 2-quinolone-4-carboxylic acids. The transformations were mostly based on various substituted hydroxyindoles or isatins.

A well-known method for the synthesis of 4-quinolinecarboxylic acid derivatives involves the aldol condensation of isatins with ketones having an activated CH_2 group in the presence of bases, followed by recyclization of the condensation products (or some of their subsequent transformations) to the desired compounds. Thus, the ketols **164** are formed with good yields from the ketones **163** and isatin **7** in the presence of ammonia and are transformed into 2-substituted quinolinecarboxylic acids **165** when heated in an acidic medium [23, 76].



R = $C_6H_4R^1$; R^1 (time, h): H, 3-NH_2 (5), 3-NO_2, 4-NO_2 (16), 4-Ph (20), 4-$C_6H_4NO_2$-*p* (16);
R = R^1, 2-thienyl, R^1 (time, h): H, 2-thienyl (5),
2-thienyl (9), 4-NO_2, 5-NO_2 (12), 1-adamantyl (3-5). Yields 52-92%

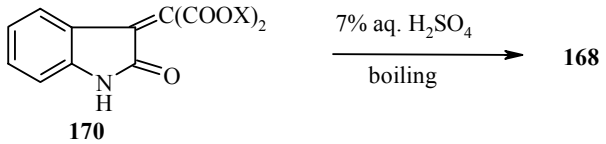
However, the ketols **166** and **167**, which are similar to compounds **164** and are the products from the condensation of isatin **7** with malononitrile or phenylacetic ester respectively, were transformed into 2-quinolone-4-carboxylic acid **168** or its 3-phenyl derivative **169** [146].



166, 167 **168, 169**

166 X = $CH(CN)_2$ (10% aq. NaOH), **168** R = H;
167 X = CH(Ph)COOEt (conc. HCl, EtOH), **169** R = Ph

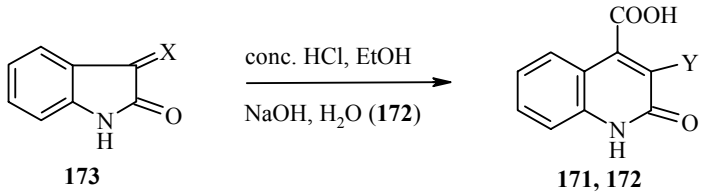
The acid **168** was also obtained by acidification of the diammonium salt **170** (X = NH_4) with HCl or by boiling the silver salt **170** (X = Ag) with sulfuric acid [147].



170

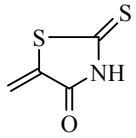
X = NH_4, Ag

Derivatives of compound **168**, i.e., the 3-carboxy- and 3-mercapto-substituted compounds **171** [146] and **172** [148] were synthesized from oxindoles with the general formula **173**.

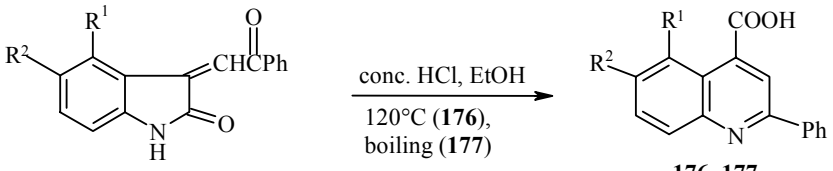


173 **171, 172**

For X = C(R) CN (R = $CONH_2$, CN), Y = COOH (**171**);

For X =  , Y = SH (**172**)

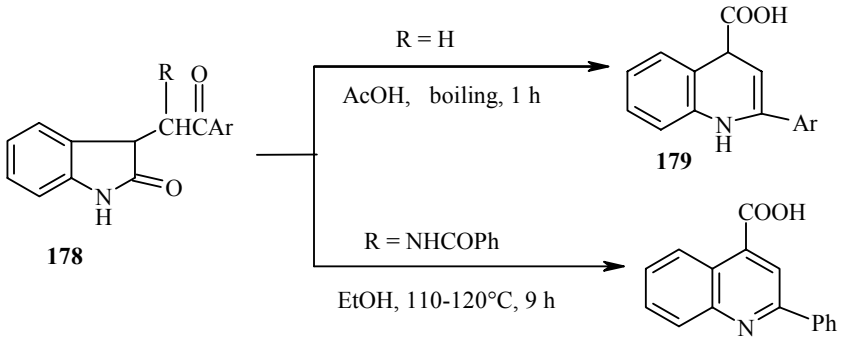
If the substituent at position 3 in the oxindoles **174** or benzoxindole **175** is a CHCOPh group, 2-phenyl-substituted 4-quinolinecarboxylic acids **176** [149] or 4-benzoquinolinecarboxylic acids **177** [150] respectively are formed when they are heated with concentrated hydrochloric acid in alcohol. Compound **174** (R = H) is not transformed into the corresponding acid **176** under the conditions of the Pfitzinger reaction [149].



174, 175 **176, 177**

174, **176** R^1 = H, R^2 (time, h), yield, %: H (2.0), 72; Me (2.0), 95;
Cl (12.5), 65; Br (6.0), 85

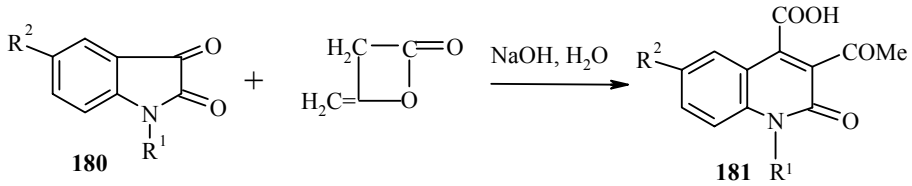
When heated in acidic medium the oxindole derivatives **178** (R = H) undergo recyclization to 2-aryl-1,4-dihydro-4-quinolinecarboxylic acids **179** or to 2-phenyl-4-quinolinecarboxylic acid (cinchophen) [151].



178 **179**

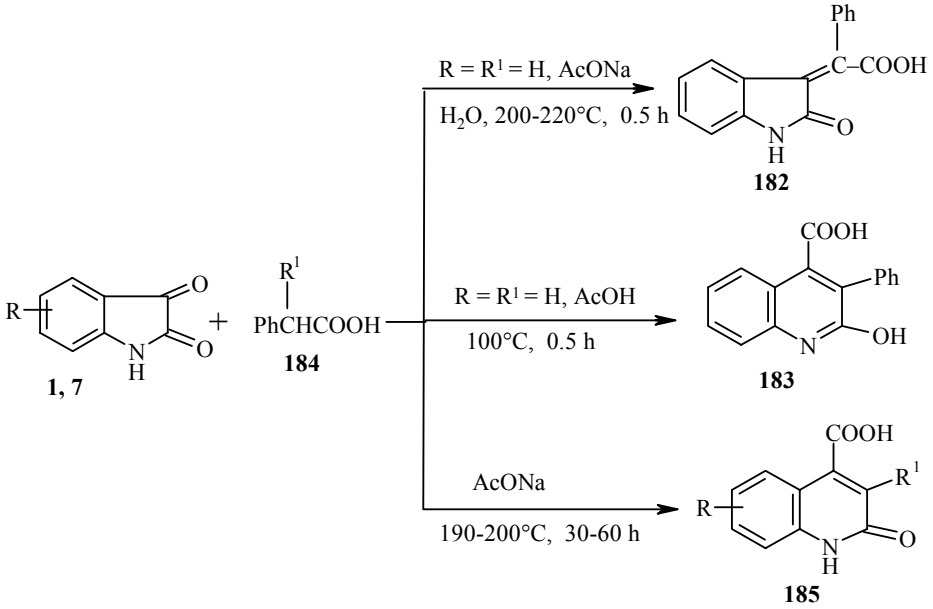
Ar: Ph (yield 98%), $C_6H_4R^1$-4 (R^1 = Me, Cl, Br)

Papers in which the reactions of isatins with various reagents leading mainly to derivatives of 2-quinolone-4-carboxylic acid were studied are discussed below. The condensation of isatins **180** with diketene gave quinolonecarboxylic acids **181** acylated at position 3 [152].



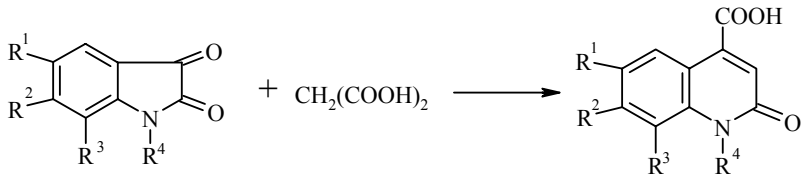
R^1, R^2, yield, %: H, H, 43; H, Me, 47; Me, H, 8

According to existing data, the reaction of isatins with phenylacetic acid under various conditions leads to various products. Thus, the reaction of this acid with isatin **7** in the presence of sodium acetate was first described in 1893 [153], and the product was assigned the formula **182**. The reaction of the same reagents with heat in acetic acid led to 2-hydroxy-3-phenyl-4-quinolinecarboxylic acid **183** [154]. In later papers [155-157] substituted quinolonecarboxylic acids **185** were obtained by heating the isatins **1** or **7** with the above-mentioned acid or its derivatives in the presence of sodium acetate.



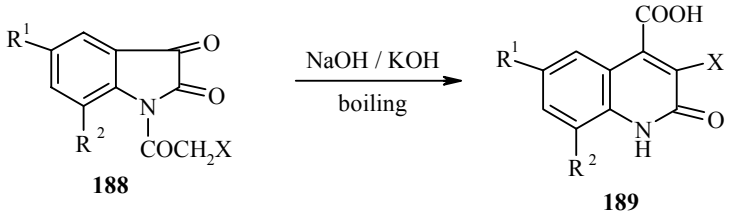
185, R, R^1, yield, %: 5-I, H, n/d [155]; H, OMe, 52 [156]; 5-F, OMe, 49; 5-Cl, OMe, 47; 5-Br, OMe, 35; 5-I, OMe, 26; 6-F, OMe, 58; 6-Cl, OMe, 54; 6-Br, OMe, 81; 6-I, OMe, 81 [157]

In the reaction of the isatins **7** [154, 155], **54** [17, 154, 155], or **186** [155, 158, 159] with malonic acid in the presence of sodium acetate [155, 158] or in acetic acid [17, 154, 155, 159] the reaction products were 2-hydroxy-4-quinolinecarboxylic acids, which usually exist in the form of the 2-quinolone derivatives **187**, as a result of decarboxylation of the initially formed dicarboxylic acids. Compound **187** with R = R^1 = R^2 = H and R^3 = Me was patented as a plant growth regulator (Aureorysin) [158].



R^4 = H, R^1, R^2, R^3, yield, %: I, H, H, 100 [17]; H, H, H, 100; Br, H, H, 100; Br, H, Br, 100; Br, H, Br, 88 [154]; I, H, H (boiling, 5 h), 65 [155]; R^1 = R^2 = R^3 = H, R^4 = Me [155]; R^4 = CH_2CH_2CN [159]

The recyclization of N-acylisatins is often used for the transformation of isatins into derivatives of 4-quinolinecarboxylic acid. The N-acylisatins are obtained by the treatment of the isatins with carboxylic acid chlorides or anhydrides. Published data on the transformation of acyl derivatives with the general formula **188** into quinolonecarboxylic acids **189** are summarized below [12, 14, 155, 160-168].

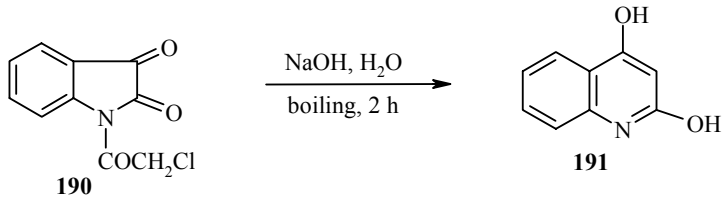


188 **189**

X, R^1, R^2, (time): H, H, H, (1-4 h) [160-163]; H, F, H, (1 h);
H, OMe, H, (1 h); H, H, OMe, (1 h) [12, 14, 155, 164]; Ph, H, H, (5 min) [155];
$CH{=}CH_2$, H, H, (30 min) [165-167]; Me, H, H, (1 h) [170]

The described recyclization was used for the synthesis of 2-quinolone-4-carboxylic acid labeled with the ^{13}C isotope at position 2 or 3 from the products of the acylation of isatin **7** by the acid chlorides $CH_3{}^{13}COCl$ or $H_3{}^{13}CCOCl$ respectively [168].

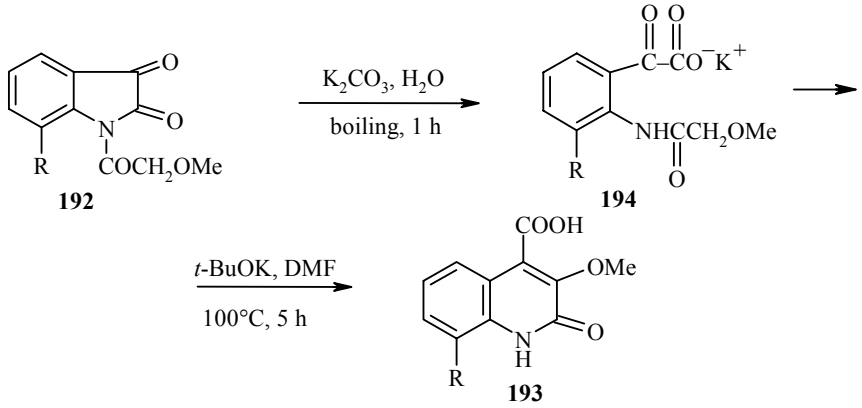
A completely different reaction product is formed from the N-chloroacetyl derivative **190** under the conditions described above. When it was boiled in an aqueous solution of sodium hydroxide, 2,4-dihydroxyquinoline **191** was obtained with a yield of 56-70% [169].



190 **191**

According to data from other authors [170], the reaction results in the formation of a mixture of 3-hydroxy-2-quinolone (15%) and 4-hydroxy-2-quinolone (15%).

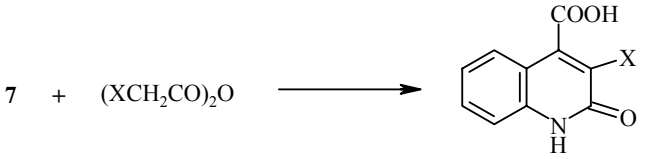
The transformation of the N-acylquinolines **192** (the products from the acylation of isatins with methoxyacetic anhydride) into the 3-methoxy-substituted quinolonecarboxylic acid **193** was realized under different conditions; compounds **192** were converted into the salts **194**, the cyclization of which by heating with potassium *tert*-butoxide in DMF led to compounds **193** [171].



192 **194** **193**

R, yield (%) **192**, **193**: H, 77, 75; Cl, 71, 76

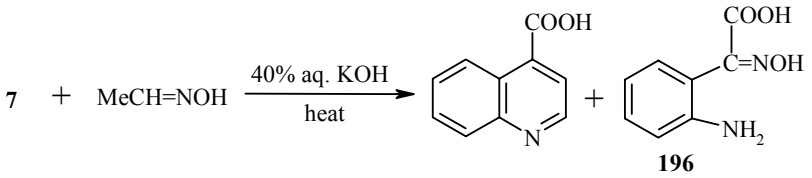
The synthesis of derivatives of quinoline from isatins and carboxylic acid anhydrides can also be realized without isolating the intermediate N-acyl derivatives. Thus, unsubstituted 2-quinolonecarboxylic acid containing the ^{14}C isotope at position 3 was synthesized by the condensation of isatin **7** with the anhydride $(H_3{}^{14}CCO)_2O$ [172]. The unsubstituted acid **168** [163] and its 3-aryl derivatives **195** [173, 174] were obtained by heating the isatin **7** directly with the respective anhydrides.



168, 195

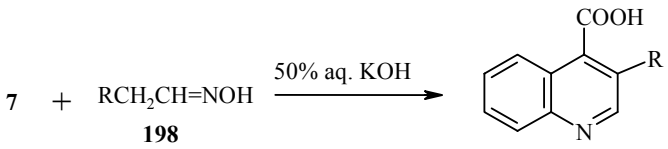
X (reaction conditions): H (NaOAc, autoclave, 180-190°C, 5-10 h, 210-220°C, 1-2 h) [163];
Ph (180-190°C, 3 h) [173]; $C_6H_4NO_2$-4 (180-190°C, 5 h in $PhNO_2$) [174]

Since the Pfitzinger reaction requires a large excess of alkali, aliphatic aldehydes, which readily polymerize under these conditions, cannot be used in the reaction. However, it was possible to overcome these difficulties by using the aldoximes. Thus, Pfitzinger heated the isatin **7** with acetaldehyde oxime in the presence of potassium hydroxide in water and obtained 4-quinolinecarboxylic acid together with the oxime of isatinic acid **196** [175].



196

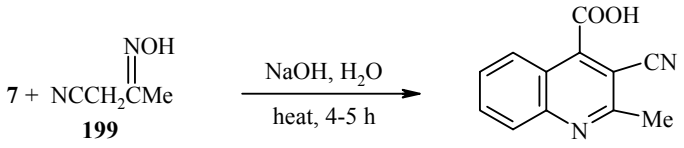
3-Alkyl-substituted 4-quinolinecarboxylic acids **197** were synthesized by the condensation of isatin **7** with the aldoximes **198** [176].



197

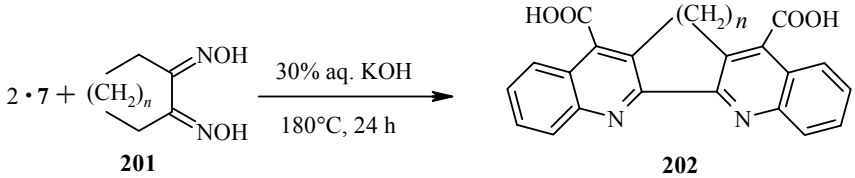
R, temperature, °C, (time, h), yield, %: C_5H_{11}, 105-110, (62), 19;
C_8H_{17}, 115-120, (24), 28

Ketoximes containing a CH_2 group adjacent to the oxime group are also capable of entering into the Pfitzinger reaction. Thus in the reaction of the isatin **7** with the ketoxime **199** 3-cyano-2-methylquinoline-4-carboxylic acid **200** is formed with a 50% yield [177].



200

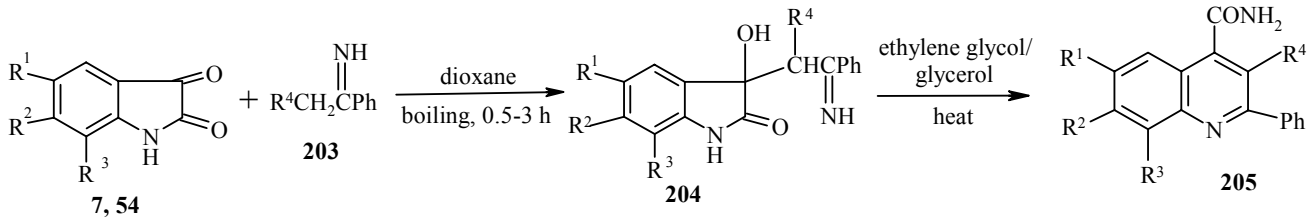
The condensation of isatin **7** with the oximes of cyclic diketones **201** led to the dicarboxylic acids **202** (yields 22-23%) [178].



201 **202**

201, **202:** n = 1, 2

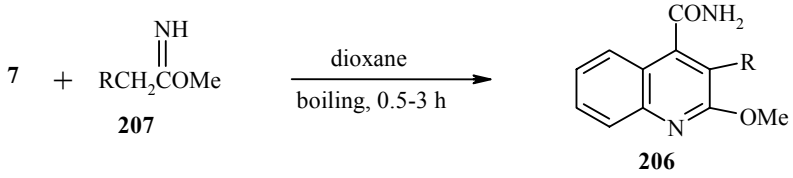
The isatins **7** and **54** react with the imines **203** in boiling dioxane with the formation of the products from aldol condensation **204**, which recyclize when heated in ethylene glycol or glycerol to the amides of 4-quinolinecarboxylic acids **205** [179].



7, 54 **203** **204** **205**

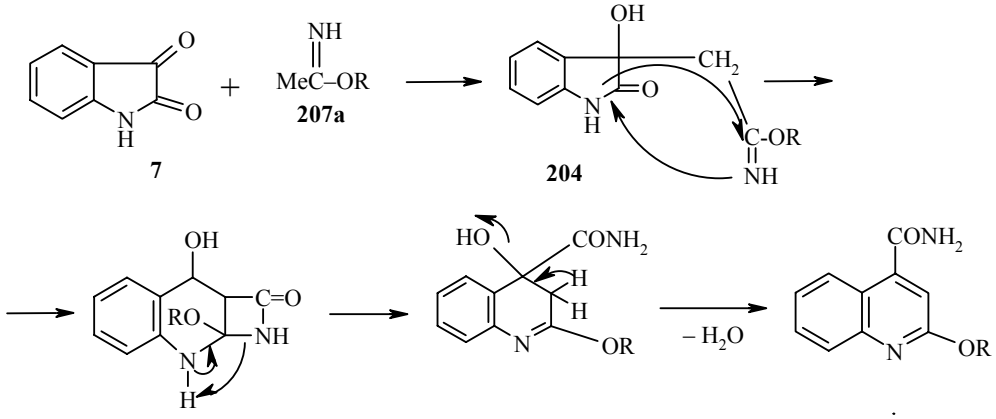
R^1, R^2, R^3, R^4, solvent (temperature, °C), yield of product **205**, %:
H, H, H, Me, ethylene glycol, (197), 82; Cl, H, Cl, Me, glycerol, (290), 65;
H, Cl, Me, Me, glycerol, (230), 81; NO_2, H, H, Me, glycerol, (245), 95; H, H, H, Et, ethylene glycol, (197), 75

The 2-methoxy-substituted amides **206** were synthesized by the reaction of the imidic esters **207** with isatin **7** [179]. A mechanism for the reaction is proposed in the same paper.



207 **206**

R, yield, %: Me, 58; $(CH_2)_3CN$, 44; Ph, 71; 4-$NHC_6H_4CH_2COOH$, 62; 4-$NHC_6H_4SO_3H$; 35;
Cl, 26; CH_2CN, 58; $(CH_2)_2CN$, 29



7 **204**

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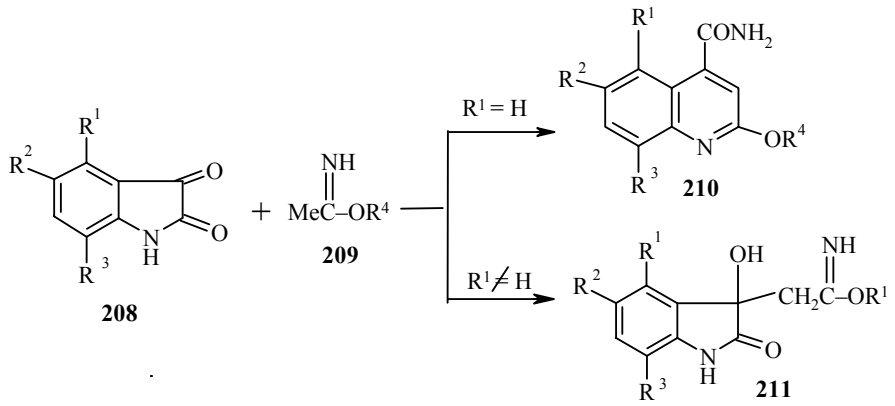
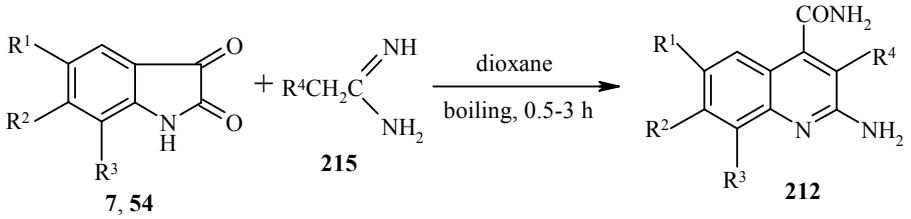
In the case of the condensation of the isatins **208** with the imidic esters **209** with a large excess of the latter it was found that the amides **210** are only formed with isatins not having substituents at position 4 (R = H). If R ≠ H the process stops at the first stage, and compounds **211** are formed [180, 181].

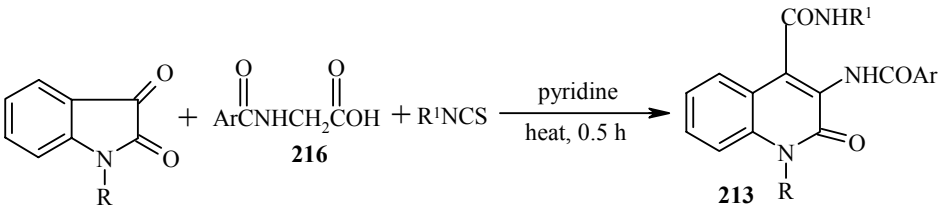


R^1 = H, R^2 = H, Cl, Br, NO_2, Me; R^3 = H, Cl, Br; R^4 = Me, Et. Time, min: 5-10 [180]; 30 [181]. Yield of product **209** 46-71%

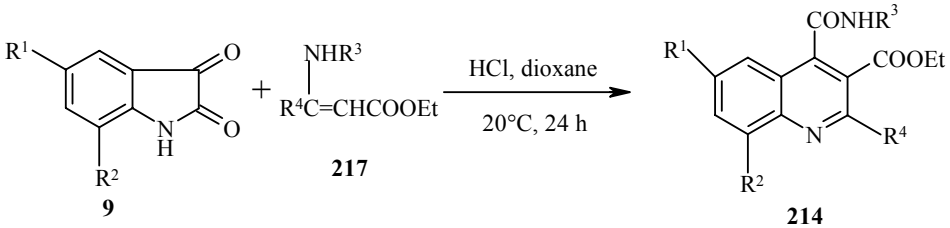
The schemes presented below also illustrate the synthesis of various amides of substituted quinoline- and quinolonecarboxylic acids **212-214** by the reaction of isatins **7**, **9**, **54**, and **180** with amides **215** [179], acylated amino acids **216** and isothiocyanates [182], and enamines **217** [183].



R^1 = H, Cl, Br, NO_2; R^2 = H, Cl; R^3 = H, Cl, Br, Me; R^4 = H, Me, Ph. Yields 46-94%

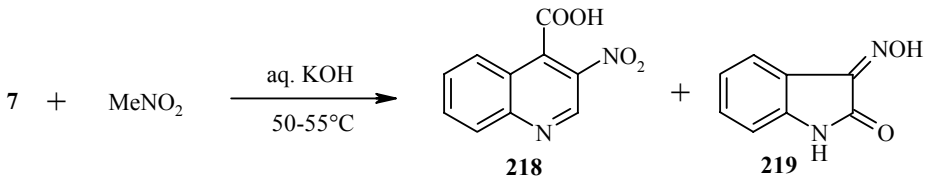


R, R^1, Ar, temperature, °C: H, Me, Ph, 130-140; H, Ph, Ph, 140-150; Me, Ph, Ph, 140-150; H, Ph, C_6H_4Me-4, 140-150. Yields 29-49%

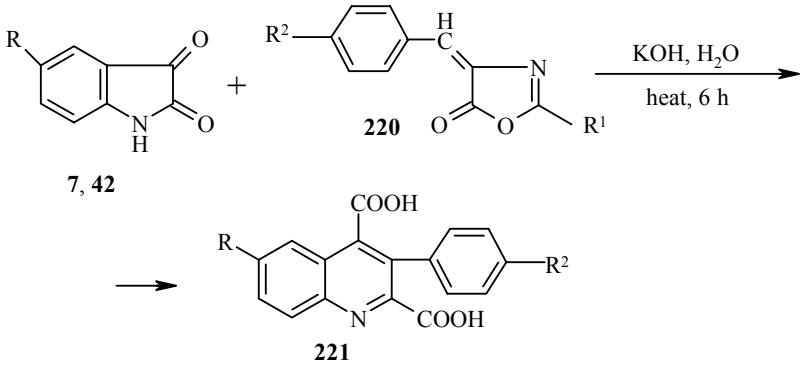


R^1 = Cl, Br, NO_2; R^2 = H, Cl, Br; R^3 = H, Me; R^4 = Me, Ph. Yields 25-85%

The action of 50% aqueous potassium hydroxide on equimolar amounts of isatin and nitromethane leads to the formation of the acid **218** and the oxime **219**. With a twofold excess of nitromethane only **219** is obtained [184].

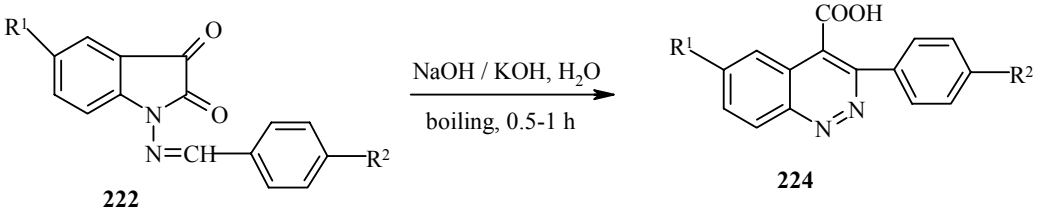


The condensation of isatins **7** and **42** with derivatives of oxazolone **220** in the presence of potassium hydroxide in water gave the dicarboxylic acids **221** (yields 55-88%) [185].

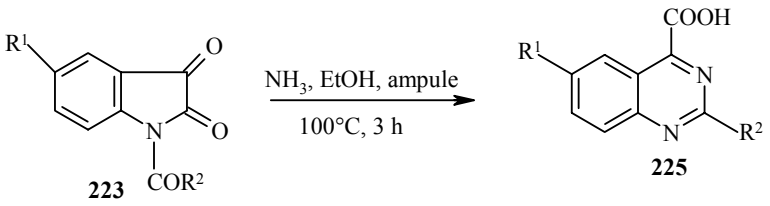


R = H, Me, Br; R^1 = Me, Ph; R^2 = H, Me, OMe

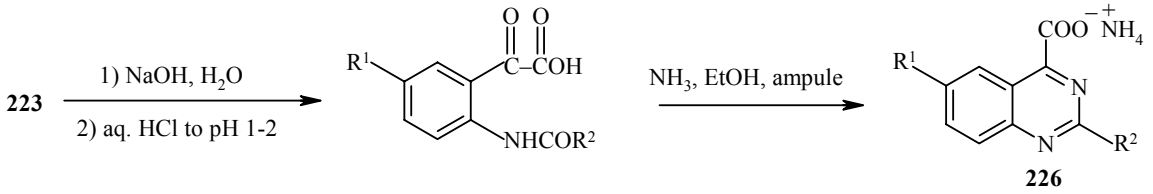
In conclusion it is necessary to mention papers in which the recyclization of isatin derivatives **222** and **223** to 4-cinnolinecarboxylic [186-188] or 4-quinazolinecarboxylic [189] acids **224**, **225**, and **226** was studied. These transformations are presented in the schemes below.



R^1, R^2: H, H, (yield 75-80%); Me, H, (5 h, yield 100%) [186]; H, Me; H, OMe; H, F; Me, Cl; OMe, H [187]; H, Cl [188]



R, R^1 (yield, %): H, H, (70); F, H, (80)



R, R^1 (yield, %): H, H (85); F, Me (70)

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